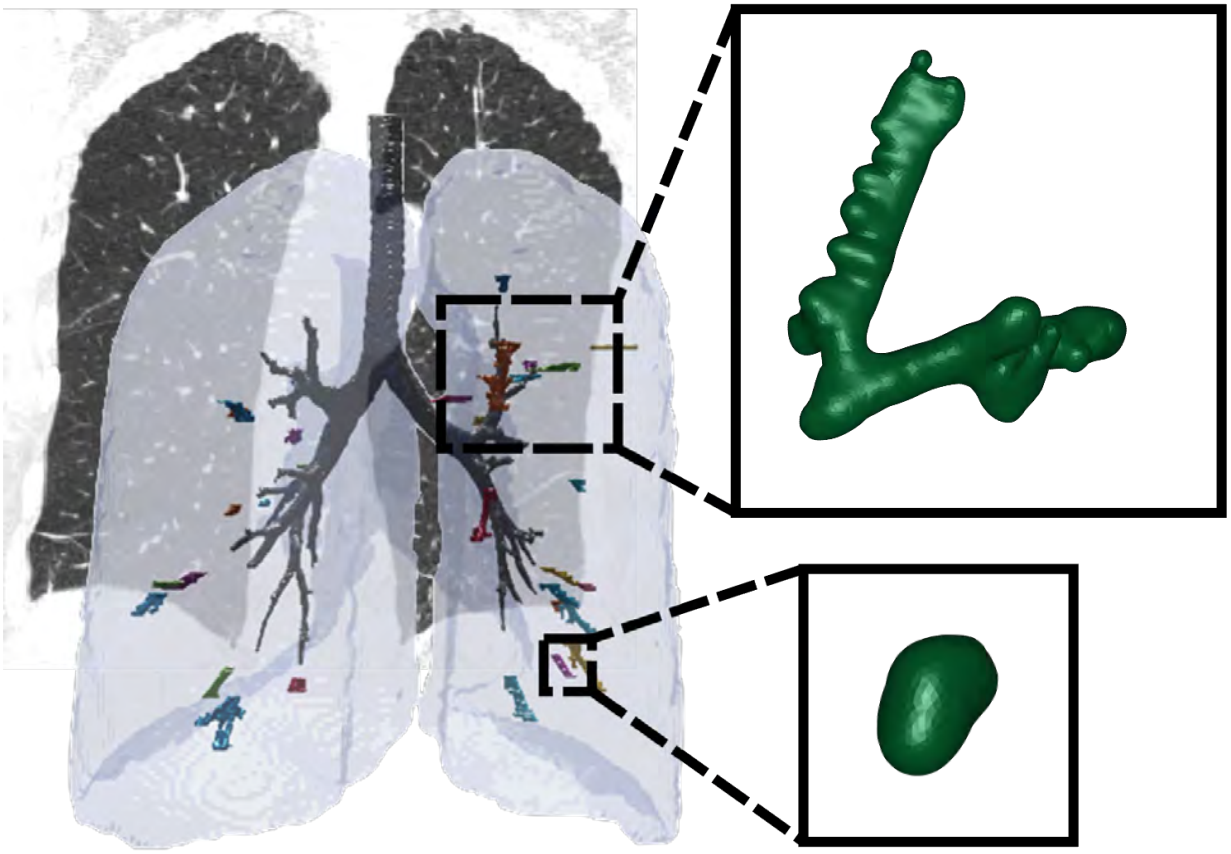
Sandler Asthma Basic REsearch Center

University of California, San Francisco



Progress Report

Year 22

July 2021

Figure Legend: Multi-detector computed tomography (MCTD) lung scan of a patient with poorly controlled asthma revealed occlusive mucus plugs of varying size and shape, which has been shown to correlate with worse lung function (technique developed and refined in the Fahy SABRE Center lab with UCSF Radiology). Therapeutic dissolution of plugs remains a priority in the Fahy lab. (Image contributed by Brendan Huang).

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Mission Statement

The Sandler Asthma Basic Research Center (SABRE Center) is an investigative unit dedicated to basic research discovery in asthma. Founded in 1999, the SABRE Center is nucleated by basic scientists supported by advanced technology cores and linked with the greater scientific community through Center Grants and Program Projects focused around asthma research. The SABRE Center aligned in 2014 with the Airway Clinical Research Center (ACRC) at UCSF to facilitate increased focus on and integration with asthma patient studies. Our mission remains to be a progressive, nimble, transformative scientific group that pioneers basic discovery in asthma research, a platform made possible by the generous support of the Sandler Foundation.

Summary of Accomplishments over the Past Year

The past year has imposed unprecedented difficulties on academic life, research and the health care system. SABRE labs were shuttered in March, 2020, and only achieved 75% occupancy with spacing in late May, 2021. Animal breeding, sequencing studies, core activities, in-person conferences and seminars were suspended to minimize human contact and to redirect resources to COVID-19-related activities, generating opportunity that could only be met by the flexibility provided through SABRE funding. Thus, SABRE Center investigators could continue to make contributions to the understanding of asthma and allergic disease, while pivoting to address the impact on COVID-19 on patients with asthma, an emphasis that continues with the ongoing pandemic.

Notable accomplishments from SABRE Center members since the prior Report:

(1) The COMET consortium was mobilized quickly to confront the pandemic and organized by Prescott Woodruff, David Erle, Mark Ansel, John Fahy and others on the Leadership team to rapidly phenotype COVID patients for immune studies to uncover mechanisms driving severe disease. Key findings included dysregulated anti-viral interferon pathways mediated by aberrant autoantibodies that interfere with immune control and active neutrophils that foment tissue damage, creating strategies for intervention. Of note, patients with asthma were relatively protected from severe disease.
(2) Despite the pandemic, Esteban Burchard continued to enroll mother-infant pairs in the NIH-awarded PRIMERO study to follow asthma development in a prospective cohort of 3000 mother-newborn pairs in Puerto Rico, where the prevalence and severity of asthma are among the highest in the world, promising a rich dataset already being leveraged to additional SABRE investigators with collaborative grants in progress.
(3) The Locksley lab leveraged SABRE-targeted single-cell RNA sequencing efforts to contribute to studies identifying ILC2 precursors in tissues and to define the trajectories by which these cells become pathologic during inflammatory and allergic reactions in the skin and lung.
(4) The Allen lab discovered the role of IL-21 in inhibiting IgE class switch recombination in mouse and human B cells, and the Shin lab continued to probe the role of MARCH1 regulation in dendritic cells and its contributions to allergic T cell differentiation.

Overview – 2021

Richard M. Locksley, M.D.

The SABRE Center continues with its discovery-oriented mission towards deeper understanding of asthma that will guide innovative therapeutics. Comprised of four basic scientists, a population geneticist, two pulmonary basic/translational scientists, a bioinformatics specialist, and young associate members, the Center has networked across the greater UCSF research and national research organizations to establish increasing recognition for contributions to asthma research.

The onset of the COVID-19 pandemic in late February began an unprecedented disruption of American society, including research, with non-essential research and clinical research activities suspended at UCSF in March, 2020. Efforts were made to pivot to COVID-19-related activities, as permitted at 25% effort, and here the flexibility of SABRE support allowed a number of labs to move quickly to assess interactions between the virus, lung tissues, and among patients with asthma. These activities became unified to form COMET, a spontaneous integration of scientists across disciplines with clinicians to bring cutting-edge technologies to bear on understanding this new infectious disease. Boosted by our early commitment to single-cell RNAseq and related platforms, SABRE labs were able to contribute quickly to studies of viral receptors, cell phenotypes and transcriptomic signatures among patients, including those with airways disease, and these studies continue. With the successful rollout of vaccines, labs expanded to 50% occupancy in late 2020 and to 75% capacity in late May, 2021, although still with spacing and masking. With essentially 100% vaccination rates, we anticipate complete opening by July. Clinical research activities were impacted most due to necessity to stop all patient visits except those related to COVID or dangers to health. Planned scientific conferences, including the 2020 Keystone Symposium on Asthma Immunobiology by the former American Asthma Foundation Scientific Board assembled by the Sandler Foundation to be held in Utah, and the 4th International Conference on Innate Lymphoid Cells to be held in San Francisco were postponed until 2022.

Investigators

The SABRE Center consists of the Director, Dr. Locksley; core basic science faculty - Drs. Allen, Ansel, and Shin; and core translational scientists - Drs. Fahy and Woodruff, who direct the Airway Clinical Research Center (ACRC) at Parnassus, and Dr. Burchard, who directs the Asthma Collaboratory Genetics Consortium at the Mission Bay campus. Dr. Hal Chapman, whose interests in lung fibrosis and inflammation complement those of investigators in the SABRE Center, works in contiguous space with the core SABRE laboratories and is a member of the Executive Board. Associate Investigators with active laboratories on the SABRE Center floor include Drs. Erin Gordon, Mallar Bhattacharya, and Apurna Sundaram, who engage in collaborative work with SABRE investigators in addition to their primary research in aspects of lung biology, asthma, and inflammation.

Last year we hired a Bioinformatics Specialist, Andrew Schroeder, MPH, to help with large datasets and the need for novel analytic tools generated by next-gen sequencing efforts. Their CVs are included in this report.

The SABRE Center is integrated with the Airway Clinical Research Center (ACRC) under the leadership of Dr. John Fahy and Dr. Prescott Woodruff. SABRE investigators share quarterly lab and research meetings, and attend monthly research conferences that also include outside guest investigators. The fruits of this collaborative effort resulted in an NIH Program Project Grant awarded to SABRE investigators in 2012, with a major focus centered on human patients and tissues as organized through the ACRC. The competitive renewal was renewed in 2019 for an additional 5 years, one of the few Program Projects elected for continued funding by the National Heart, Lung and Blood Institutes of the NIH. The SABRE Center remains an active research constituent on the UCSF campus with a role in generating new basic understanding with potential therapeutic approaches to asthma. Despite the pandemic, over 75 manuscripts were published over the last 2 years, many in high-impact journals, emphasizing the productive output of this collaborative Center. We briefly review the Core Principal investigators and their progress, followed by an overview of the components of the Center, a brief discussion of achievements and finally a listing of extramural grants and other resources that have been obtained to support these activities.

Chris Allen, Ph.D., joined the SABRE center thirteen years ago as a UCSF Fellow. He was the first member of the UCSF Sandler Fellows Program (http://fellows.ucsf.edu/) who was selected to work on a specific human disease, in this case, asthma. This program enabled Dr. Allen to develop an independent research program combining his skills in cellular and molecular immunology with optical imaging capacities that have powered new insights in allergic inflammation. His primary research focuses on understanding the mechanisms that regulate the generation and fate of IgE-producing B cells and plasma cells. Surprisingly, this remains a poorly understood pathway of fundamental importance to the pathogenesis of allergy and asthma. Dr. Allen published his initial findings in *Immunity,* reporting his discovery that IgE heavy chains inherently drive plasma cell differentiation and the movement of B cells out of germinal centers, a process that may serve to limit somatic hypermutation and thus affinity. He followed up this work showing that the unusual properties of IgE-switched B cells are due to constitutive activity of the IgE B cell receptor, which he published in *eLife*. These findings will drive new hypotheses regarding mechanisms by which some allergic individuals develop high-affinity IgE, and these continue to be a major effort of his laboratory. More recently, Dr. Allen published a paper in the *Journal of Experimental Medicine* regarding cytokine regulation of IgE responses, showing that IL-21 is a major factor limiting the generation of IgE B cells. Dr. Allen is revising a manuscript on how antigen is captured and presented to T cells in the lung by macrophages proximal to the bronchial airway epithelium, as well as preparing two manuscripts on the activation and function of basophils, which are IgE effector cells. Dr. Allen's generation of an IgE reporter mouse that permits the efficient tracking of IgE-switched B cells constitutes an important technical advance for the field and has been shared with numerous investigators, and Dr. Allen has published detailed protocols on how to use this reporter mouse to study IgE in

the *Methods in Molecular Biology* book series. Dr. Allen also developed methodology to characterize human IgE+ B cells. To facilitate mechanistic studies of human B cells, Dr. Allen optimized approaches to genetically manipulate primary human B cells with CRISPR-Cas9 technology, which was published in the *Journal of Immunological Methods*. Dr. Allen also published a letter in *The Journal of Allergy and Clinical Immunology* showing how an antibody to the IgE receptor, FcepsilonRI, actually recognizes multiple Fcgamma receptors, which has led to significant confusion in the field regarding the functions of basophils, a type of IgE effector cell. Dr. Allen also published a review on recent advances in IgE biology for *Current Opinion in Immunology* and a comprehensive review on B cells in *Cell*. He continues to work closely with other investigators in the SABRE Center as he optimizes lung and immune cell imaging technologies that are applicable to broader use by other investigators on campus.

Dr. Allen continues to attract substantial extramural funding to support his studies. He has an R01 focusing on the role of B cell receptor signaling in the regulation of IgE responses, and an R21 to elucidate the molecular basis for the regulation of IgE class switch recombination by IL-21 and STAT3. He completed another R21 characterizing a population of lung macrophages involved in antigen capture that may trigger inflammation in asthma. This is Dr. Allen's second R01 award, and he was previously awarded an NIH Director's New Innovator Award focused on asthma. In 2016, Dr. Allen was recognized as a Pew Scholar in the Biomedical Sciences, a highly competitive national award that attests to the outstanding quality of his science and his stature as a young investigator.

Dr. Allen is a member of the Cardiovascular Research Institute (CVRI) at UCSF since 2012, when he joined the UCSF faculty as an Assistant Professor in the Department of Anatomy. Dr. Allen moved his laboratory to the Smith Cardiovascular Research Building on the Mission Bay campus in 2013, putting him in close proximity to other researchers working on the lung as well as advanced optical imaging techniques. Dr. Allen remains an active member of SABRE and participates in monthly and quarterly meetings with SABRE investigators on the Parnassus site. Dr. Allen has contributed his imaging expertise and advanced microscopy capabilities to Dr. Sundaram's research on how airway smooth muscle tethering contributes to bronchoconstriction in asthma, with a paper recently accepted to the *Journal of Clinical Investigation*. Dr. Allen has also contributed significantly to Dr. Bhattacharya's imaging studies of macrophage-fibroblast crosstalk in lung injury, with a manuscript in preparation. In addition, Dr. Allen contributed his expertise on IgE B cells to a study on microRNA regulation of B cell class switch recombination in Dr. Ansel's lab, which has been resubmitted to the *Journal of Experimental Medicine*. Dr. Allen has also joined the team led by Dr. Burchard in the longitudinal study of asthma, starting at birth, in the Puerto Rican Infant Metagenomic and Epidemiologic study of Respiratory Outcomes (PRIMERO), for which Dr. Allen will contribute RNAseq and functional studies on lymphocytes from blood samples.

Dr. Allen is currently mentoring a PhD student and a postdoc in his lab, and has recruited three undergraduates from UC Berkeley to work on summer projects. The PhD

student is following up on work from a previous postdoc regarding the generation of IgE B cells in mouse models of asthma, and the postdoc is working on the IgE-mediated functions of basophils in allergic inflammation. Dr. Allen mentored a medical student who worked for five years in his laboratory on the properties of human IgE B cells. This student began as a volunteer, and then was awarded UCSF Resource Allocation Program, Pathways to Explore summer fellowship, and then was recognized with a 2016-17 HHMI Medical Research Fellows award for a full year of research, followed by extended study through the Pathways program. In recognition of his significant contributions, his maintenance of extramural funding, and his service to UCSF, Dr. Allen was promoted to Associate Professor in 2018.

K. Mark Ansel, Ph.D., is an RNA immunologist working to understand the molecular and cellular underpinnings of the chronic tissue inflammation and dysfunction that manifest in allergic diseases, particularly asthma. RNA is a messenger molecule, tasked with carrying information about the state of a cell and its genome so that internal and external cues can be translated into action. The BioNTech/Pfizer and Moderna SARS-CoV-2 RNA vaccines are a powerful demonstration of the potential of harnessing RNA for the prevention and treatment of human diseases. The Ansel lab has developed novel biochemical and computational techniques to discover the regulatory information encoded in RNA molecules. They use human and mouse genetics to interrogate the function of novel RNA modules in the programming of cell fate and function, with a focus on the lymphocytes and epithelial cells that are central to the pathogenesis of asthma. Since it is now clear that RNA can be delivered safely and effectively to cells, engineering these modules for cell reprogramming is a viable and exciting new path to development of therapeutics and customized cell therapies.

Dr. Ansel also pursues related research to improve and expand the characterization of airway infiltrating inflammatory cells in asthma. He works closely with SABRE investigators and others in the Airway Clinical Research Center to improve and apply high-dimensional cytometry and single cell RNA sequencing to human airway biospecimens. During the past year and a half, the Ansel lab used this experience to contribute to the rapid mobilization of research to understand and combat COVID-19. As part of the COMET consortium, the Ansel lab investigated the cellular heterogeneity and signaling status of immune and epithelial cells recovered from the airways of COVID-19 patients. This work has directly benefited Dr. Ansel's ongoing asthma research by providing access to airway biospecimens, closer collaboration with CyTOF expert Dr. Matt Spitzer, and the opportunity to develop and empirically test new technical and computational analysis pipelines.

Dr. Ansel is an established leader in his field. He contributed to 9 published manuscripts this year, and 8 others are in review or revision for publication. He has recently renewed funding from R01 and P01 grants from NHLBI, as well as Fastgrants and NIAID supplemental funding for his COVID-19 research. The Ansel laboratory is currently populated by three graduate students, two postdoctoral fellows, two technicians, and one undergraduate researcher. Marlys Fassett is supported by a K08 Career Development Award, graduate student Didi Zhu was awarded a Hooper Foundation Fellowship, and Priscila Muñoz-Sandoval is supported by a prestigious Howard Hughes

Medical Institute Gilliam Fellowship. Dr. Ansel's departed trainees have moved successfully into the next phases of their careers as postdoctoral fellows, scientists at biotechnology companies, MD/PhD residents, fellows in research career tracks, and in four cases, as principal investigators of independent laboratories in the US and Germany where they have continued their work on cell programming in asthma.

Dr. Ansel is active in University service and leadership. He co-founded ImmunoX and remains a key member of its leadership. He is the co-director of the UCSF Biomedical Sciences (BMS) graduate program and the principal investigator of its recently awarded NIH T32 training grant. He has championed and in some cases spearheaded initiatives to enhance diversity, equity and inclusion in the UCSF research community. He successfully organized faculty efforts to advocate for university investment in a new research building on the Parnassus campus, and continues to work with university leadership and campus stakeholders to ensure that these investments move forward with maximum benefit. He teaches medical, dental and graduate students, and designed the immunology curriculum for the UCSF Doctor of Pharmacy program.

Esteban G. Burchard, M.D., M.P.H., directs the UCSF *Asthma Collaboratory*, which contains the largest annotated gene biorepository of minority children with asthma in the world. The Collaboratory shares data with over 80 collaborators and has participated in more than 300 publications. These data have led the way in contributing understanding racial/ethnic differences in asthma and drug response across minority children in the U.S.

Puerto Ricans have the highest asthma prevalence and mortality in the world and experience a disproportionate amount of early-life respiratory illnesses. In 2018, the NIH funded the *Puerto Rican Infant Metagenomic and Epidemiologic study of Respiratory Outcomes* (**PRIMERO**, U01HL138626) birth cohort study, which is designed to study the complex relationship between early-life respiratory viral infections and the development of recurrent respiratory wheeze and asthma in children. In February, 2020, the first of 3,000 Puerto Rican mother-infant dyads across socioeconomic strata was recruited. PRIMERO will prospectively follow the infants through their first 5 years of life, collecting breast milk, maternal and neonatal cord blood, neonatal/infant nasal epithelium swabs for viral etiologies (at birth and during respiratory illnesses), and blood and nasal swabs (at yearly health-child clinical evaluations). PRIMERO offers the opportunity to study how genetic ancestry and socio-environmental factors such as race, family structure, and socioeconomic status affect the immunological profiles of mothers and infants and further affect the child's respiratory health. These prospective measures will establish the etiology of recurrent wheeze by identifying pathogenic trajectories and biomarkers that may predict lower respiratory tract illnesses, recurrent wheeze, and asthma. PRIMERO will uncover novel biological insights that can guide vaccine strategies and drug targets for recurrent wheeze and asthma.

PRIMERO is a natural progression and culmination of the research that the team has been conducting over the past 20 years. The buy-in and support from local institutions and authorities were also critical to funding and establishing the birth cohort study. Despite Puerto Rico's shelter-in-place mandate, recruitment and specimen collection has continued during the COVID-19 pandemic. To date, the PRIMERO team have

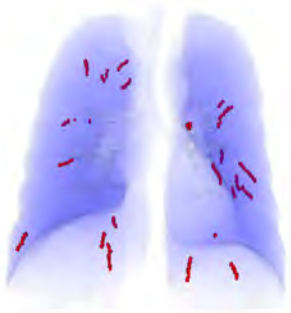
successfully recruited almost 700 mother-infant dyads and maintained a participant retention rate of 99.7%. Biological samples have been collected from the majority of participants while operating under COVID-19 constraints, including cord blood (90%), maternal blood (99%), and nasal swabs (99%). We were awarded additional NIH funds in late 2020 to expand PRIMERO to examine the epigenetic inheritance of maternal exposures during pregnancy and how they may impact the child's risk for respiratory disease. We have received methylation data on 200 exposed and unexposed mother-infant dyads and have begun analysis. We received further funding in 2021 to study how maternally derived antibodies resulting from maternal SARS-CoV-2 infection or vaccination impact the child's risk for COVID-19 disease and other clinical sequala. We have enlisted collaborators across the university (George Rutherford, Alan Wu and Elad Ziv) to help us examine the impact of SARS-CoV-2. This study is a realization of Dr. Burchard's goal to make PRIMERO a university-wide resource.

Outside of PRIMERO, the *Asthma Collaboratory* has led efforts to identify genetic variants associated with lung function in Puerto Rican and African American children with asthma. Here, differences in the proportion of genetic ancestry can partially explain disparities in asthma susceptibility and lung function; Native American ancestry was associated with lower odds of asthma, while African ancestry was associated with higher odds of asthma. Importantly, since exposure to risk factors is so varied across minority populations, genetic variance may help us untangle why some children develop asthma while others do not.

Dr. Burchard and his team moved to the forefront of the debate on the use of race/ethnicity in clinical decisions. In a widely read NEJM paper, the team advocated for the epidemiological importance of race/ethnicity never disappearing and for inclusion of genetic ancestry in clinical prediction to reduce the error in current clinical standards. To follow this up, the team submitted an NIH grant to recruit a healthy cohort of Puerto Rican individuals with admixture of African, Native American, and European ancestries. Lung function and genetic ancestry testing will be used to generate personalized ancestry-adjusted lung function predictive equations, which will be validated in independent healthy cohorts.

John Fahy, M.D. is a longstanding participant in SABRE research and a formal faculty member in the SABRE Center for the past 8 years. He is a physician scientist with a primary appointment in the Division of Pulmonary and Critical Care Medicine (Department of Medicine and Cardiovascular Research Institute). He directs a mechanism-oriented clinical research program in airways disease that emphasizes studies in humans and in human-derived tissues and cells. For asthmatics with prominent airway type 2 inflammation ("type 2-high asthma"), his current research focuses on mechanisms underlying regional variation in type 2 inflammation in the lung and airway epithelial cell dysfunction in patients with "ultra-high" type 2 inflammation who are steroid-resistant and have mucus plugs and severe airflow obstruction. Dr Fahy's lab is a leader in

developing methods, applicable in humans that advance understanding for how pathologic mucus gels form in asthma (Figure). He leads a PO1 program in type 2 airway inflammation in asthma (with Drs. Locksley, Ansel and Woodruff) and the UCSF center in the NHLBI-funded PrecISE program (biomarker driven clinical trials in severe asthma). In addition, Dr Fahy leads a translational PO1 program in academic drug discovery that aims to advance thiol-saccharide mucolytics to the clinic. In response to the COVID19 emergency, Dr Fahy and colleagues have also been exploring the utility of thiol-based drugs – including inhaled thiol-saccharides - as treatments that could have anti-viral and anti-inflammatory effects in COVID19. Initial data from these studies - including data from COVID19 animal models - are very promising.



PID	80-811-005
Total CT Slices	588
Mucus Plug Score	28
Mucus-Slice Score	514
Mucus-Segment Score	11
Length (mm)	8.5 [.5, 22.36]
Diameter	4.84 [1.8, 14.03]
Total Volume (mL)	9.05
FEV1 % Predicted	39.8
Blood Eos	Not measured
Sputum Eos	0.9 (0.4%)
Sputum EPO	1448
Daily OCS	No
Biologic	No

Figure: Left: Mucus plug and lung visualizations in a patients with severe asthma informed by radiology annotations of an MDCT lung scan. Right; Detailed metrics of mucus plugs in the same severe asthma patient. Note the multiple metrics made possible with this technology including length and diameter and the total volume of mucus. These methods are very powerful enabling research in mucus plug biology and in treatments for mucus plugs.

Dr. Fahy is a frequent advisor to the National Heart, Lung and Blood Center regarding research needs in asthma. His recent honors include election to the American Association of Physicians in 2016, a Recognition Award for Scientific Accomplishments from the American Thoracic Society in 2017, the European Respiratory Society Gold Medal in Asthma in 2019, and the inaugural K. Frank Austen Bench to Bedside Plenary Lectureship from the American Academy of Allergy, Asthma, and Immunology (AAAAI) in 2020. UCSF honored Dr Fahy by naming him the 10th Annual Faculty Research Lecture in Translational Science in 2021.

Richard Locksley, M.D., is Director of the SABRE Center, an immunologist and infectious diseases-trained physician who pursues basic studies of allergic immunity and asthma. His laboratory focuses on deeper understanding of the role for allergic cytokines in basal homeostasis, with a particular emphasis on group 2 innate lymphoid cells, or ILC2s, that have become of increasing interest in not only basic immune functions, but also in our understanding of human asthma. These studies have revealed previously unknown links with basal tissue health, metabolic homeostasis, and local regulation of cytokine expression by adaptive Th2 cells. His laboratory discovered the association of allergic immune responses by the environmental polysaccharide chitin, a constituent of fungi and insects associated with human allergic sensitivity, and has explored the role of mammalian chitinases in regulating enzymatic breakdown of environmental chitins at mucosal barriers. He directs an active laboratory effort with 8 peer-reviewed publications, 2 open repository contributions in active review, 3 invited commentaries,

and 3 invited comprehensive reviews during 2019-2021,with 3 manuscript in revision after positive review.

Dr. Locksley's laboratory pioneered the use of reagents that facilitate identification of cytokine-producing cells in vivo, and contributed to the discovery of ILC2s, previously unappreciated cells that contribute to allergic inflammation, in 2010. In 2016, his laboratory was among 3 reports to identify an important role for tuft cells, rare epithelial cells in the nose, lung and gut, in allergic immunity. Despite their description for over 60 years, tuft cell function was unknown until these pioneering studies that implicate these cells as the source of IL-25 and leukotrienes that mediate crosstalk between epithelia and ILC2s associated with allergic immunity. Ongoing studies are examining the role of these cells in the nasal epithelium, including in humans, where allergic nasal polyposis is highly associated with severe asthma in adults. His laboratory contributed to some of the initial single-cell RNAseq studies of ILC2s to define their tissue-specific transcriptomic signatures as these cells first enter tissues during fetal development. He is a Professor in the Departments of Medicine and Microbiology & Immunology, and an Investigator in the Howard Hughes Medical Institute. Dr. Locksley is a member of the Lasker Foundation Jury and the National Advisory Committee for the Pew Scholars Program in Biomedical Sciences. He moderated the 2019 NIH Workshop on the role of ILC2s in allergy and asthma. He is a member of the American Academy of Arts & Sciences and the National Academy of Sciences. He received the first annual William Paul Award for contributions to cytokine research from the International Cytokine & Interferon Society in 2016 and was recognized as a Distinguished Fellow of the American Association of Immunologists Inaugural Class. His laboratory is supported by HHMI and by grants from the NIH, and he directs Subproject 1 for the SABRE Center Program Grant, 'Exploring the biology of persistent type 2 airway niches in asthma'. Recent postdoctoral trainees in his laboratory include recipients of a Cancer Research Institute Fellowship, a Fulbright Fellowship, a Giannini Fellowship, an American Dermatology Research Fellowship, an NIH F32 and a pending NIH K22 award. Recent postdoctoral graduates have moved into academic faculty positions at UCSF, University of Washington, Washington University St. Louis, and ETH Zurich (Swiss Federal Institute of Technology). He is active in teaching graduate and medical students in immunology and infectious diseases. Dr. Locksley and SABRE organized the 4th International Conference on Innate Lymphoid Cells to be held in San Francisco in October 2020, although this was delayed due to the pandemic and is scheduled to be held in Hawaii in late 2022.

Jeoung-Sook Shin, Ph.D., seeks to understand the molecular mechanisms by which dendritic cells contribute to immune homeostasis and diseases. The research goal of Dr. Shin's laboratory is to better understand the molecular mechanisms underlying antigen presenting function of dendritic cells and apply that understanding to the development of therapeutics for treatment of human diseases. In particular, Dr. Shin is interested in understanding the contribution of membrane trafficking to dendritic cell function in allergic asthma. Dr. Shin has previously found that the high affinity IgE receptor, which mediates activation of mast cells in allergic asthma, mediates endocytosis of IgE in dendritic cells contributing to IgE clearance, thus potentially mitigating allergy. Dr. Shin

also discovered that the endocytic pathway of the IgE receptor could be exploited to establish immune tolerance against the IgE-bound antigens.

Recently, Dr. Shin has investigated the role of the ubiquitin ligase MARCH1 in dendritic cell function in allergic asthma. She and others had found that MARCH1 ubiquitinates the antigen presenting molecule MHCII and the costimulatory molecule CD86. Her recent studies indicate that ubiquitination of these molecules by MARCH1 conditions dendritic cells to prime allergen-specific naïve T cells for IL-4 production and drive development of IgE responses, airway inflammation, and airway hyper-reactivity to house dust mite allergens. More recently, she found that MARCH1 also contributes to the chronic phase of allergic asthma by supporting expansion of cytokine-producing effector T cells upon repetitive exposure to allergens thus augmenting chronic inflammation in the airway. Finally, she found that MARCH1 is significantly associated with asthma in Puerto Ricans, a population with extremely high asthma prevalence and mortality. This study was undertaken in collaboration with another SABRE investigator, Dr. Burchard. Taken together, these new findings represent a major advancement to our understanding of the molecular mechanisms underlying the pathogenesis of asthma and offer a potential therapeutic target for treatment of this disease.

Dr. Shin contributed 5 peer-reviewed publications in 2018-2020. She submitted two new manuscripts reporting the role of MARCH1 in asthma in 2021 each to *Science Immunology* and to the *Journal of Clinical Investigation.* Dr. Shin was awarded a R35 Outstanding Investigator Award from NIGMS in 2019, which will support her continuously until 2025.

Dr. Shin is active in teaching pharmacy and dentistry students in immunology. Dr. Shin is mentoring two minority students in her laboratory. One has been selected to give an oral presentation during the 2020 Keystone Symposia as well as the 2020 annual meeting of the American Association of Immunologists. The other student received an NIH diversity training program award. Dr. Shin serves as organizer of the UCSF ImmunoX faculty research-in-progress seminar program and also serves a grant reviewer for HAMI (Hypersensitivity, allergy, and mucosal immunology) study section on the NIH.

Prescott Woodruff, M.D., is Associate Director of the Airway Clinical Research Center, has been an integral member of the SABRE Center for the past 7 years and is a longstanding collaborator with other SABRE investigators. He is a physician-scientist with a primary appointment in the Department of Medicine, Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, where he is Vice-Chief for Research and in which he was awarded the Mentoring Award for 2020. His research interests are in asthma pathogenesis, genomics and translational studies, particularly in the field of precision medicine. His discoveries were among the earliest to identify biomarkers that permit segregation of asthma patients into categories likely to benefit from specific types of therapies that target type 2 inflammation mediated by the IL-4/IL-13 pathway. More recently, he has focused on non-type 2 inflammation in severe asthma and mechanisms of pathological mucus production in asthma. In particular, he identified a micro-RNA (miR-

141) that regulates airway epithelial mucus production and which can be therapeutically targeted using an inhaled synthetic oligonucleotide. At the start of the COVID-19 pandemic, Dr. Woodruff organized the UCSF COMET Study (https://www.comet-study.org/) which has immunophenotyped 441 patients with COVID-19 to date. The multi-investigator COMET team recently published novel data on antibody-mediated dysregulation of interferon-driven inflammation that characterizes severe COVID-19. Dr. Woodruff is PI or multiple-PI of (1) the NHLBI Severe Asthma Research Program (4th iteration which started in 2019), (2) the NHLBI SPIROMICS study of COPD, (3) the NHLBI RETHINC clinical trial in COPD, and (4) a NHLBI study of obstructive lung disease in patients living with HIV (the NIH "I AM GOLD") Study and (5) a NHLBI K24 award which supports his mentoring of junior faculty and trainees. He is a co-investigator and/or project leader on three NIH-funded asthma grants, the NHLBI PRECISE adaptive clinical trial study in severe asthma, a NHLBI P01 directed by Dr. Fahy and a NIAID U19 directed by Dr. Erle. He serves on the Scientific Advisory Board for the NIAID Inner City Asthma Consortium. Finally, he was co-Chair the Keystone Symposium on Asthma in 2020. Dr. Woodruff's honors include election to membership in the American Society for Clinical Investigation.

Core Activities and Technology Development

An integral component of the SABRE Center includes support and guidance for advanced technology cores. In the past, these included cores in Mouse Physiology (which provides acute and chronic mouse models of allergic lung inflammation, including challenge with model antigens, fungal antigens and house dust mite antigens), Functional Genomics, Genetics, Flow Cytometry and Microscopic Imaging, including video, two-photon, confocal and total internal reflection instruments. Due to the success of the cores in attracting matching funds from alternative sources and the initiation of a campus payback system that successfully linked cores with a system-wide reimbursement policy, we phased out some of these activities and re-directed resources to individual technology-enhancing procurements on an as-needed basis. This policy reflects both recommendations from our outside Scientific Advisory Board as well as initiatives reflected in the Strategic Plan. We continue to direct leveraged support to the Microscopy Core, under the guidance of Dr. Krummel, and have moved into novel areas of technology to facilitate their use in SABRE labs and across the campus. The Microscopy Core continues to lead applications of *in situ* microscopy of the lung and more powerful approaches for visualizing chemistry in single cells using lattice-sheet microscopy, Clarity, and other cutting-edge technologies. Their updated report is included. We made major efforts to support next-generation deep-sequencing efforts, including single-cell RNAseq and epigenetic analyses, such as ATACseq methods, which were accelerated by providing funds for sequencing and bioinformatics as part of our sincle-cell RNAseq consortia. To this end, SABRE hired Dr. Andrew Schroeder to coordinate bioinformatics needs across SABRE labs and to integrate databases more completely with public and in-house databases from BioHub and ImmunoX. Creation of this infrastructure was essential in enabling the pivot to the crisis of the COVID pandemic, to which these advanced technical and analytical tools were rapidly embraced in confronting the need for human-based study at previously unprecedented scale. We

continue to embrace new technologies with current interest in working with others to secure a multilaser CyTECK instrument and for enhancing technology in spatial transcriptomics.

The Genetics Asthma Collaboratory under Dr. Burchard remains the largest collection of annotated genomes among defined ethnic groups, representing a key data base for analytics. The Collaboratory has leveraged SABRE support with NIH support to sequence over 16,000 minority children with asthma to define genetic contributions to disposition, severity and treatment response. Dr. Burchard's work has focused the potential for illuminating genetic/environmental aspects underlying asthma on Puerto Rico, where the prevalence of asthma is almost 24% among children, a risk that has initiated efforts to understand the admixture effects of Native Ancestry, African American and European genomes in this unique culture. With this in mind, Dr. Burchard obtained a $10 million grant from National Heart, Lung and Blood Institute at the NIH in 2019, named PRIMERO, to prospectively study 3,000 newborn/parental family units with cutting-edge repeated evaluations over time to define asthma risk in relationship to genome. This has already spawned several leveraged NIH applications from UCSF to monitor the mother-child microbiota and collect environmental data that will be integrated with deep sequencing and cell analysis to provide an unprecedented resource evaluating the evolution of asthma in humans as it develops. Despite the COVID-19 pandemic and its havoc on Puerto Rico and travel, the team has enrolled over 700 infant-mother pairs while instituting rigorous methods for sample collection, storage and both on-site in Puerto Rico and. at UCSF for analytical studies, for which SABRE has provided funding to obtain pre-submission materials to facilitate collaborative grants from SABRE investigators. This is a momentous study that has the potential to open up tremendous understanding of the wide prevalence and penetrance of asthma into human populations worldwide.

As part of the nimble nature of our technology support, SABRE contributed as part of leveraged equipment requests that contribute broadly to research efforts across the campus, including to investigators in SABRE labs. A number of instruments supported by SABRE matching funds, including CyTOF, liquid mass spectrophotometers and flow units remain in widespread use among many labs at UCSF. We are currently exploring contributions to an Aurora CyTECK multi-laser spectroscopy unit with the capacity to rapidly fill the space between flow cytometry and single-cell sequencing at substantial cost saving once antibody profiles are optimized. The dedication of a Microbiota Center under the leadership of Dr. Susan Lynch has created need for expansion of the gnotobiotic core supporting maintenance of germfree mice under the direction of Dr. Peter Turnbaugh. SABRE investigators, including Drs. Locksley, Allen and Ansel have all used the gnotobiotic core and capitalized on its value in controlling and isolating microbiota that have profound effects on metabolism and organ function. With this in mind, SABRE has made a contribution to developing the gnotobiotic core to facilitate work in allergic and asthma diseases in a highly leveraged way that will work well for our access while supporting greater use of this technology across UCSF.

SABRE Associate Support

We contributed pilot funds to enhance collaborative interactions between SABRE Associates – Drs. Gordon, Battacharya and Sundaram – to create discovery opportunities in asthma research. These three young scientists have also generated terrific data with these resources and are already procuring independent grants and contributing to the SABRE Mission. Dr. Gordon, who is on a grant with Drs. Locksley and Fahy, obtained her own grants to further her interests in epithelial responses in asthma. She works closely with Dr. Locksley and surgical colleagues in understanding the mechanisms driving allergic nasal polyposis that emerge among patients with severe poorly controlled asthma. Dr. Battacharya investigates lung injury, pivoted rapidly to address mechanisms by which COVID-10 mediates lung destruction, and just received an NIH R01 to study pathways resulting in lung fibrosis. Lastly, Dr. Sundaram studies smooth muscle and its role in asthma pathogenesis, an incompletely studied area of research of much relevance to SABRE. We look forward to continue support with matching Innovative Grants to allow these talented young scientists to continue their outstanding trajectories. Their CVs has been included.

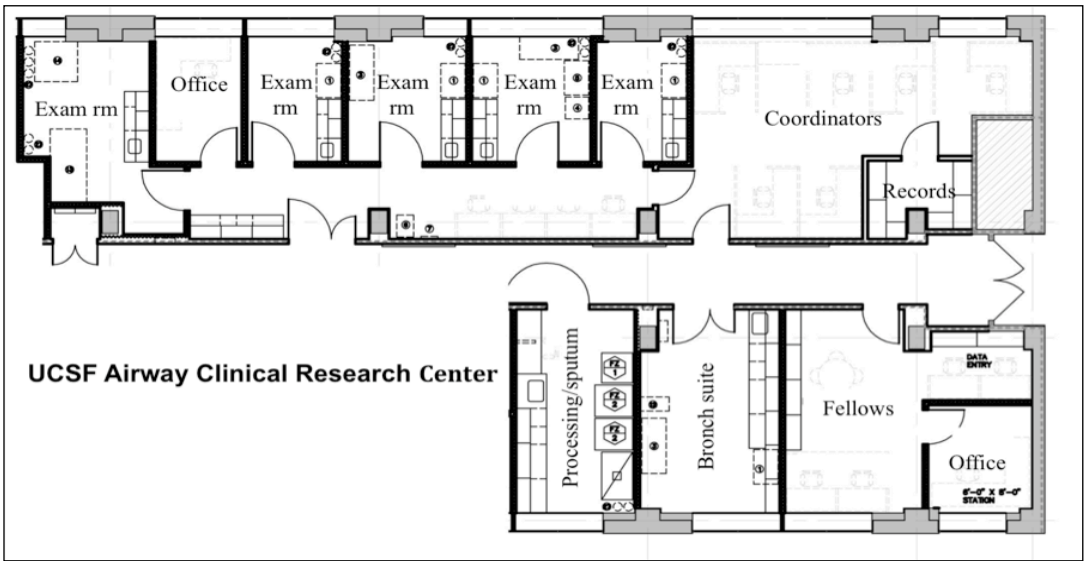
SABRE RNA-seq Consortia

Based on discussions hatched at the 2017 SABRE Retreat, we designated commitments to core labs for use in bulk and single-cell RNA-sequencing of airway tissues in order to create a tissue bank for core use and dissemination among labs across UCSF and wider after publication. Initial requests included studies of mouse nasal and lung ILC2s and epithelial tuft cells (Locksley lab), human airway brushes (Fahy lab), human airway epithelial monolayers under various conditions (Woodruff lab), human nasal polyp tissues from patients with allergic polyposis (Gordon/Locksley/Fahy labs), Ig-E-switched allergen-specific B cells in the mouse (Allen lab), human and mouse micro-RNA and RNA comparators (Ansel lab), and human drug-response outliers (Burchard lab). These data resulted in over 15 manuscripts and have yielded valuable information for comparisons between the mouse and human as well as biologic insights that will continue to drive hypothesis-driven exercises. With the pandemic, these platforms contributed to the rapid pivot to COVID-directed research among cohort data in the SABRE consortium, which have contributed to 9 manuscripts with others pending. All of these data are established in the public science space with proper masking of human data. Based on the success of these studies, SABRE hired a 50% bioinformatics specialist, Andrew Schroeder, and helped purchase a 10X single-cell sequencing platform to speed acquisition and access to this technology, which remains a continued priority.

Airway Clinical Research Center

The Airway Clinical Research Center (ACRC) is a customized space of 3500 sq ft. located on the 13th floor of the UCSF Medical Center. The ACRC comprises 5 separate testing rooms for history and physical examination, phlebotomy, allergen skin tests, spirometry and methacholine challenge (Figure). This center has a research

bronchoscopy suite, a sample processing lab, and administrative space for twelve research coordinators and six research fellows. The space is dedicated to clinical research in airway disease; there is no clinical patient care activity in this space. The ACRC has fully equipped exam rooms for conducting pulmonary function testing, research bronchoscopy, participant interviews and specimen collection and processing.



The ACRC is equipped to see patients and collect tissue specimens and to do so in a manner that ensures compliance with all regulatory requirements. The ACRC has 2 research managers, 10 research coordinators a data manager and a special project manager. The model for coordinators is that each take ownership of specific research studies and manage their study in terms of recruitment, study visits, and biospecimen handling. Weekly meeting of ACRC staff and faculty involve presentations of specific projects and administrative and quality assurance meeting focused on compliance with local, state, and federal regulations governing research in human subjects.

ACRC Faculty: John Fahy, Prescott Woodruff, Erin Gordon, Stephen Lazarus, Michael Peters, Stephanie Christenson, and Nirav Bhakta are research faculty in the ACRC. They have robust grant support from NIH, nearly all of which leveraged SABRE support and activities. (see grant list below).

ACRC Trainees: The ACRC has provided a successful training environment for multiple trainees in the past, including Drs Woodruff, Gordon, Peters, Christenson, Dunican, and Bhakta. Current trainees include Anita Oh, M.D., Aartik Sarma, M.D., Elizabeth Yu, M.D., Brendan Huang, M.D., William McKleroy, M.D. and Aaron Baugh, M.D. A new trainee (Clarus Leung, M.D.) joins the ACRC in July 2021.
ACRC Research: The ACRC supports research programs that involve human-centered study of asthma and other airway diseases. Most of this research is funded by NIH grants (below), but ACRC investigators have a strong track record of successful engagement in research alliances with biotech and pharmaceutical companies. Examples include collaborations that Drs Fahy and Woodruff have had with Genentech (GNE) to assist

GNE with its therapeutic antibody programs in asthma that target IgE, IL4R, IL33R (ST2) and tryptase. In addition, Dr Fahy has secured funding from NIH for a drug development program that is advancing thiol-modified carbohydrates as novel inhaled mucolytic drugs. This mucolytic program is augmented by biomarker discovery research that has developed and validated an image (CT lung)-based score as a predictive and monitoring biomarker for airway mucus plugs in asthma and COPD. In the past year, Dr Fahy's team has applied its expertise in thiol-based medicines to uncover a vulnerability of SARS-CoV2 to thiol drugs and to develop *in vitro* and *in vivo* data for the antiviral effects and anti-inflammatory effects of these drugs that supports consideration of their use as treatments for COVID-19. Dr. Woodruff has been pursuing another novel therapeutic approach to reducing pathological mucus production, the inhaled delivery of oligonucleotides which target epithelial miRNAs. This work is based on his recent demonstration that the miR-141/200 family of micro-RNAs (small regulatory RNAs) regulates airway epithelial mucin production in human and murine airway epithelial cells and that inhaled delivery of a synthetic oligonucleotide that antagonizes miR-141 reduces airway mucus production and resistance in a murine asthma model. UCSF has submitted a patent application based on this work. In other very recent work, Dr. Woodruff has leveraged the existing asthma U19 grant (Understanding Asthma Endotypes) to fund the COMET Study which is performing deep immunophenotyping of patients with severe COVID-19 at UCSF and has demonstrated that severe COVID-19 is associated with antibody-mediated defects in interferon driven anti-viral host responses (Combes A, Nature 2021). This study has led to a Genentech collaboration that Dr. Woodruff directs to match COVID-19 immunophenotypes to existing biological therapies that may be repurposed. Finally, Dr. Peters has been exploring mechanisms of asthma that do not involve type 2 inflammation pathways and he has been focusing on how metabolic dysfunction contributes to lung dysfunction in severe forms of asthma. Dr Peters' work in this area has led to the identification of an "IL-6-high" subtype of asthma that is orthogonal to type-2 high asthma. All this work has led him to propose IL-6 inhibition as a novel strategy to treat "IL-6-high" asthma, and the steering committee for the NHLBI Precise Network (severe asthma clinical trials network) has selected clazakizumab (anti IL-6 ligand) as one of the drugs to be tested in the Precise platform trial. Dr. Peters now leads the clazakizumab trial for asthma in Precise and the study has enrolled its first patients. The activities of ACRC illustrate how the human centered and mechanism-oriented research of the Center are being translated into treatment programs that have potential to address the unmet needs of patients.

Current NIH Funding

1. P01 HL107202 (7/01/2012 – 6/31/2024): *Exploring the biology of persistent type 2 airway niches in asthma.* Dr Fahy is overall PI and a project leader and Drs. Locksley and Ansel lead subprojects. Dr Woodruff leads a core and is co-PI on Dr Ansel's project 2.

2. UG1 HL139106 (9/23/2017 - 6/30/2023): *Sequential, Multiple Assignment, Randomized Trial in Severe Asthma Protocol.* Dr Fahy is PI; Dr Woodruff is co-I. UCSF leads a consortium that is one of 10 centers in the NHLBI's Precision Interventions for Severe and/or Exacerbation Prone Asthma ("PrecISE") program. The UCSF consortium includes a subsite at UC Davis and at the University of Leicester in the UK).

3. U10 HL109146 (07/01/2011 – 07/01/24): **:** *Immunometabolic phenotypes in adult severe asthma and disease progression*. Severe Asthma Research Program (SARP). Dr Woodruff is PI and Dr Fahy is co-I. This multicenter grant is exploring molecular subtypes of asthma in a cohort of patients with severe asthma. The focus is on assessments focused on underlying genetic, inflammatory mechanisms and metabolic dysfunction that enable, promote and/or predict disease progression.

4. U19 AI 077439 (4/01/2018 - 3/31/2023) *Understanding Asthma Endotypes*. Dr David Erle is PI and Dr Woodruff directs 1 of the 2 projects while Dr Fahy is a co-I on Dr Erle's grant. This NIAID/AADCRC grant is focused on understanding how airway epithelial cells are involved in causing different forms of asthma.

5. U19 AI077439 – 13S2 (05/08/20-03/31/22) *UCSF COVID-19 Immunophenotyping clinical study and core laboratories.* Dr David Erle is PI and Dr Woodruff is co-I and Executive Committee Member. The goal of this project is to identify causes of severe COVID-19 through detailed immunophenotyping in a multi-center longitudinal clinical study (The UCSF COMET Study).

6. Genentech TSK-020586 (12/15/20-12/15/23) *The COMET+ Study: Deep phenotyping study of COVID+ and COVID- ARDS.* Dr. Woodruff is PI. The goal of this study is identify biological pathways associated with severe COVID-19 using deep immunophenotyping.

7. R01 AI136962 (1/15/2018 – 12/31/2022). *Understanding the Molecular Genetic Mechanisms of Asthma Risk Loci: IL33, IL1RL1, and GSDMB*. This is Dr Gordon's first RO1 and marks her successful transition from K to R funding.

8. R01 HL080414 (04/07/2016 - 03/31/2021). *Mechanisms of mucus pathology in acute severe asthma*. Dr Fahy is PI. This RO1 focuses on mechanism of mucus pathology occurring during episodes of acute severe asthma.

9. PO1 HL128191 (09/01/2016 – 06/30/2021): *Carbohydrate-based Therapy for Lung Disease.*
Dr Fahy is PI. This translational PPG (tPPG) is developing a novel mucolytic drug for asthma and other mucus-associated lung diseases using an approach based on thiol modification of carbohydrate backbones and using CT imaging as a biomarker to identify asthma subgroups with mucus impaction as a cause of airflow limitation.

10. U01 HL137880 (09/15/17-5/30/22) *SPIROMICS II: Biological underpinnings of COPD heterogeneity and progression.* Dr. Woodruff is PI. The goal of this grant is to establish the biological underpinnings of COPD heterogeneity, progression and exacerbations using the SPIROMICS cohort.

11. K24 HL137013 04/28/17-3/31/22) *Mentoring Research in Precision Medicine for Lung Disease.* Dr. Woodruff is PI. The goal of this grant is to enable Dr. Woodruff

mentor students, fellows and junior faculty in patient oriented precision medicine related research in respiratory disease.

12. R35 HL138424 (08/01/17-06/30/21) *Airway Epithelial Cell Gene Regulation: New Mechanisms and Therapeutic Strategies.* Dr. Erle is PI, Woodruff co-I. This grant is designed to identify genomic elements that are important in airway epithelial cell differentiation in asthma and to develop approaches for targeting these elements.

13. R01 HL143998 (09/15/19-07/31/23) *Integrated Analysis of Microbial and Genomic data in Obstructive Lung Disease (I AM GOLD) Study.* MPI Woodruff, Contact PI Huang. This study investigates mechanisms underlying the increased risk of COPD with HIV infection in an ongoing international longitudinal multi-center study of HIV-associated COPD in Uganda and San Francisco.

14. R01 HL146002 (07/01/19-06/30/24) *SPIROMICS II Heart Failure* Dr Woodruff is co-I, PI is RG Barr. This study is designed to define the heart failure phenotypes associated with COPD using 4D MRI and exercise echo by leveraging the SPIROMICS study.

15. R01HL128156-05A1 05/01/20-4/30/25 *Inflammation, Aging, Microbes, Obstructive Lung Disease, and Diffusion Abnormalities (I AM OLD-DA) Study.* Dr. Huang is PI and Dr. Woodruff is co-I. This grant tests the hypothesis that asymptomatic CMV co-infection and chronic inflammation are associated with lung function abnormalities in patients with HIV/AIDS.

16. R01 HL144718 (05/01/20-04/30/25) *Understanding the Origins of Early COPD*. Dr Woodruff is co-I, PI is Fernando J. Martinez. This grant will establish a longitudinal cohort of patients with "early COPD" and identify the pathophysiologic changes in the lung that predispose smokers to develop *bona fide* COPD that is associated with overt airflow obstruction.

Communications, Training and Leadership Initiatives

SABRE is involved with ImmunoX leadership council at Parnassus, with Mark Ansel sitting as a representative on the council. John Fahy is involved with research and clinical planning on the Space Committee at Parnassus. Richard Locksley organizes the basic immunology research seminars and is a Co-PI on the Gnotobiotic Initiative. Prescott Woodruff organized the COMET NIH-Genentech-UCSF Consortia for rapid acquisition and study of COVID patients, and has re-organized the second generation request recently submitted, which includes SABRE support for airway specimen collection and patient study.

SABRE Center core scientists and the Director meet quarterly with translational scientists to further communication, planning and collaborative investigations of human asthma patients. Each of the core scientists is involved in ongoing or planned investigations with translational scientists in the ACRC, confirming that this serves as an

important integrative unit for translational interests of the SABRE Center. We hold monthly research conferences for SABRE/ACRC investigators at the Parnassus site to promote interactions and collaborations.

National and International Meetings

Dr. Locksley and SABRE Center investigators participated in the organization and content of the 2020 Keystone meeting on Asthma and in the 4th International Conference on Innate Lymphoid Cells, planned for San Francisco, although both were postponed due to the pandemic. The fourth International ILC Meeting, organized by Dr. Locksley, has been rescheduled for September 2022 in Hawaii.

Human Upper Respiratory Tract Analysis

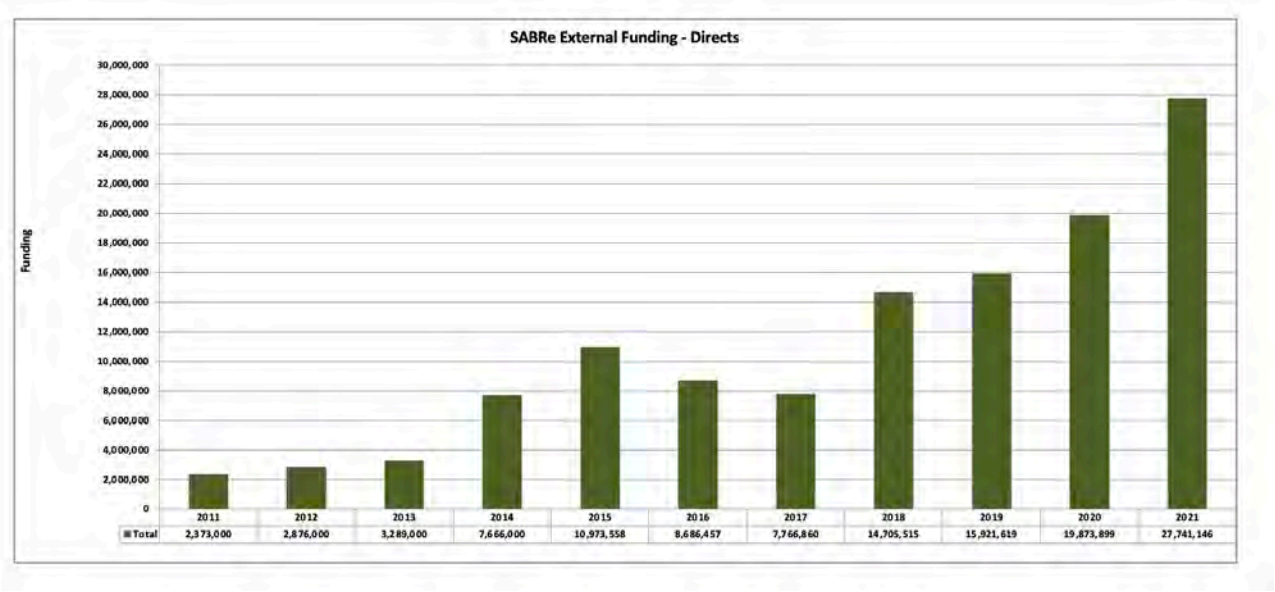
The SABRE Center is working with a UCSF surgical practice located at Mt. Zion campus with large numbers of patients with allergic nasal polyposis. These investigators, Drs. Andrew Goldberg and Steven Pletcher, faculty in the Department of Otolaryngology and Head and Neck Surgery at UCSF, have been examining the interactions of the nasal microbiome and allergy-associated immune cells in excised nasal polyps. We have worked through planning meetings, human use forms and other regulatory issues in order to establish formal collaborative relationships with these investigators and their research group. These nasal polyps provide a rich source of human epithelia, macrophages, eosinophils and ILC2s that collect in these tissues. A substantial number of these recurrent allergic nasal polyposis patients have severe asthma, thus establishing a patient base for further study, including in clinical intervention trials. While the working relationship continues to evolve, we continue to strengthen basic and clinical research interactions with this surgical group. A postdoc, Benjamin Terrier, a Fulbright Scholar in the Locksley lab, worked regularly with this group investigating nasal upper airway epithelial cells involved in sensory perception to allergens, and this is now continued by Maya Kotas, a postdoc in the Locksley lab. Dr. Erin Gordon is involved in all of these studies while working as an Associate Investigator in the SABRE Center. The biosketches of Dr. Goldberg, Pletcher and Gordon are appended.

Successful competition for extramural support

Evidence-based metrics for success are important in leveraging continuing support in the future, including from philanthropic entities. Fund-raising will require evidence for metrics of success, including our capacity to attract extramural research dollars to the community, to contribute high-impact papers that establish novel paradigms in the asthma research arena, to attract new investigators into the field and, ultimately, to drive the discovery of new therapies that affect the disease. Although therapeutic discoveries will take time, we believe we can point to successes in evidence-based metric achievements over the past year.

We have maintained substantial procurement of external funds by the core SABRE investigators in support of their research efforts. This has occurred despite the difficult

funding climate, and attests to the capacity of the Center to serve as a nidus for successful asthma basic research. We believe that building multicomponent research teams to take on difficult problems associated with asthma will prove a successful strategy for maintaining this funding momentum.



Growth in accumulated extramural funds by SABRE investigators – ACRC investigators Fahy and Woodruff joined in 2014.

SABRE Center activities resulted in publication of numerous manuscripts and contributed to many successful grants and fellowships of various types to investigators at UCSF. Despite our successes in competing for extramural resources, the flexibility enable by Sandler Foundation support is not matched by these types of grant monies.

<u>Highlighted SABRE Center-supported manuscripts impacting asthma-related and lung COVID research in 2020-21</u>

Kasela S, VE Ortega, M Martorella, *et al*. 2021. Genetic and non-genetic factors affecting the expression of COVID-19-relevant genes in the airway epithelium. Genome Med 13:66.

Large consortia study of mild and severe asthma and COPD patients to uncover disease-modifying genes and nongenomic environmental contributors to COVID disease severity. Prior inflammatory-associated chronic conditions like smoking, obesity and hypertension predicted poor outcomes, whereas asthma alone did not, suggesting that organism-wide inflammatory states alter the acute antiviral state of the lung, thus contributing to adverse outcomes in COVID, and in part explained by upregulation of viral lung receptors and impaired early interferon responses. Investigators Fahy and Woodruff were key participants.

Van der Wijst MGP, SE Vazquez, GC Hartoularos, *et al*. 2021. Longitudinal singlc-cell epitope and RNA-sequencing reveals the immunological impact of type 1 interferon autoantibodies in critical COVID-19. bioRxiv doi.org/10.1101/2021.03.09.434529
Combes AJ, T Courau, NF Kuhn, *et al*. 2021. Global absence and targeting of protective immune states in severe COVID-19. Nature 591:124-130.

Examples of UCSF COMET consortia study with SABRE investigators (Ansel, Fahy, Woodruff, etc) using next-generation single-cell sequencing and serum analytic platforms to reveal key role of subverted type 1 interferon response underlying cases of severe COVID lung disease. Direct neutralization by auto-antibodies, and immunosuppressing Fc antibody effects on myeloid cells represented common mechanisms underlying virus-induced blockade of an effective antiviral response, resulting in devastating lung injury.

Borrell LN, JR Elhawary, E Fuentes-Afflick,…, EG Burchard. 2021. Race and genetic ancestry in medicine – a time for reckoning with racism. New Engl J Med 384:474-480.

Widely ready discourse on underpinning of genetic ancestry and overt effects of race identity.

Yang Z, CA Wu, S Targ, CDC Allen. 2020. IL-21 is a broad negative regulator of IgE class switch recombination in mouse and human B cells. J Exp Med 217:e20190472.

The Allen lab continues to uncover novel details regarding IgE, a class of immunoglobulins central to allergic diseases, including airways disease and asthma. Although IL-21, a key cytokine produced by follicular T cells, was known to be a key B cell growth factor, its role in class switching remained controversial. Using reagents previously engineered in the lab, the Allen lab overturned the currently Th1-Th2 cytokine regulation of IgE class switching to show that IL-21, in both mouse and human B cells, is a critical negative regulator of IgE class switching and independent of previously claimed regulators like IL-10 and IFNγ. Unexpectedly, limiting doses of IL-4 with IL-21 promoted IgG1 class-switching, potentially creating a pool of memory B cells with the potential for re-selection for IgE in future immunizations. Taken together, these findings substantially revise our understanding of cytokine-regulated immunoglobulin class switching, and open up new areas for intervention in blocking IgE generation in vivo.

Peters MC, S Sajuthi, P Deford, S Christenson, CL Rios, MT Mongomery PG Woodruff, DT Mauger, SC Erzurum, MW Johansson, LC Denlinger, NN Jarjour, M Castro, AT Hastie, W Moore, VE Ortega, ER Bleecker, SE Wenzel, E Israel, BD Levy, MA Seibold, JV Fahy. 2020. COVID-19-related genes in sputum cells in asthma in relationship to demographic features and corticosteroids. Am J Respir Crit Care Med 202:83-90.

The Fahy lab used patient samples from the NIH SARP-3 (Severe Asthma Research Program-3) repository to assess which cells from airway samples expressed receptors critical for infection by SARV-CoV-2, the etiologic agent of COVID-19. Analyzing 330 SARP-3 asthma patient samples and 79 healthy controls, the authors used next generation sequencing to reveal significantly higher levels of the viral spike protein receptor, ACE2, and the trimming protease necessary for permissive entry, TMPRSS2, among asthma patients who were male, African American, and with diabetes, consistent with known risk factors for exacerbated disease. Levels in the remainder of samples did not differ from healthy controls, and patients on inhaled corticosteroids had lower

transcripts, presaging later studies showing protection by glucocorticoids among patients with severe COVID-19. Although these studies are early and remain incomplete, they suggest that asthma alone may not constitute significant risk for severe disease, and inhaled steroids may offer some protection by regulating the levels of receptors and proteases on host cells.

Jackson ND, JL Everman, M Chioccioli, L Feriani, KC Goldfarbmuren, SP Sajuthi, CL Rios, R Powell, M Armstrong, J Gomez, C Michel, C Eng, SS Oh, J Rodriguez-Santana, P Cicuta, N Reisdorph, EG Burchard, MA Seibold. 2020. Single-cell and population transcriptomics reveal pan-epithelial remodeling in type 2-high asthma. Cell Reports 32:107872.

This manuscript constitutes a rich resource of transcriptomic data generated from next generation sequencing of air-liquid interfaces of human airway epithelia grown under increasing days of IL-13, a key biomarker of type 2-high asthma, followed by supportive comparisons from nasal epithelia populations from children with type 2-high asthma. Increasing IL-13 drove major metaplastic changes characterized by increasing secretory mucus phenotypes, even in club-like cells, leading to loss of innate immune genes and defensins at the expense of secretory phenotypes in association with increased ER stress and emergence of a partial type 1 interferon signature. The data reveal the major impact of IL-13 on epithelial homeostasis and provide a deep resource for interrogating novel pathways that might interdict the massive remodeling induced by the asthmatic state.

Lee EY, ACY Mak, D Hu, S Sajuthi, MJ White, KL Keys, W Eckalbar, L Bonser, S Huntsman, C Urbanek, C Eng, D Jain, G Abecasis, HM Kang, S Germer, MC Zody, DA Nickerson, D Erle, E Ziv, J Rodriguez-Santana, MA Seibold, E. Burchard. 2020. Whole genome sequencing identifies novel functional loci associated with lung function in Puerto Rican Youth. Am J Resp Crit Care Med, in press.

The high asthma prevalence, approaching 25%, and severity of disease in Puerto Rican youths is known to reflect the underlying admixture of European, Native Ancestry and African American genes in the relevant environment. Using whole genome sequencing, RNA-seq and ChIP-Seq, the authors were able to uncover rare variants of TMEM9 and MROH3P in epithelia of upper airways and esophagus. The involvement of TMEM9 in integrating Wnt-regulated control of inflammatory cytokine secretion could lead to novel interventional strategies in this poorly controlled population.

Bielecki P, SJ Riesenfeld, J-C Hutter,…,RM Locksley, A Regev, RA Flavell. 2020. Skin-resident innate lymphoid cells converge on a pathogenic effector state. *Nature* 592:128-132.

Zeis P, M Lian, X Fan,…, RM Locksley,…, G Gasteiger. 2020. In situ maturation and tissue adaptation of type 2 innate lymphoid progenitors. *Immunity* 53:775-792.

Leveraging large data sets among several labs, these two studies describe the presence of tissue-resident ILC2 skin and lung progenitors, which repopulate expanded effector ILC2 in situ in response to inflammatory stimuli. ILC2s in lung assume multiple effector states across the spectrum of allergic and inflammatory disease, whereas skin ILC2s transit to an ILC3-like inflammatory state characterized by production of IL-17

and IL-22 that drive myeloid cell infiltration and keratinocyte proliferation to establish barrier homeostasis. Together, these studies reveal new aspects of ILC2 biology that increases our understanding of these foundational contributors to allergic immunity.

Organization of the body of this Annual Report

We organized this report as in the past to review SABRE Center activities and update the core and leveraged technologies that focus on asthma-related research. We summarize our interactions with other campus asthma-oriented research projects and provide listings of the seminar speakers of conferences to which we lend support. We summarize the Financial Report for the Program. Finally, we outline the strategies for the coming years and append the current biographical summaries of the members, awardees and participants in the SABRE Center at UCSF.

We thank the Sandler family for their vision and support in creating and sustaining the SABRE Center. Support for high-risk, open-ended, basic science is difficult to procure in the current funding and fiscal climate. As noted as examples here, the ability of SABRE labs to pivot quickly and decisively has allowed our investigators to add to the understanding of COVID-19 and its impact on patients with asthma, and these studies continue while the world responds to this unprecedented pandemic. We are most grateful for the continued support of the Sandler Foundation and the Jewish Community Federation.

Executive Committee

Richard M. Locksley, M.D.

The goals of the SABRE Center are to drive innovation in basic asthma research. We pursue this goal from a core scientific group dedicated to the study of asthma, by promoting access to state-of-the-art technologies required to drive the research, and by facilitating opportunities for interactions with translational and clinical investigators studying asthma patients. The Executive Committee is constituted to provide the Director with counsel regarding issues of scope, direction and execution. The Executive Committee plays a role in overseeing progress of SABRE Center faculty and provides oversight in sustaining progress towards the overall goals of the Center.

SABRE Center Executive Committee Members

Richard Locksley, M.D., Professor
Director, SABRE Center
Departments of Medicine and Microbiology/Immunology

Homer Boushey, M.D., Professor *
Department of Medicine

Hal Chapman, M.D., Professor
Department of Medicine

John V. Fahy, M.D., Professor
Department of Medicine

Dean Sheppard, M.D., Professor
Department of Medicine

Art Weiss, M.D., Ph.D., Professor
Departments of Medicine and Microbiology/Immunology

**ex officio*

SCIENTIFIC ADVISORY BOARD

Susan Kaech, Ph.D.
Director of the Nomis Center for Immunobiology and Microbial Pathogenesis
The Salk Institute

Susan Kaech is a Salk Institute Professor, Director of the NOMIS Center for Immunobiology and Microbial Pathogenesis, and holder of the NOMIS Chair. Prior to this she was a Waldemar Von Zedtwitz Professor at Yale University in the Department of Immunobiology (2004-2018). Dr. Kaech did her postdoctoral work with Dr. Rafi Ahmed at Emory University (1999-2004) and received her PhD in Developmental Biology at Stanford University. She received her BS in Cellular and Molecular Biology at the University of Washington.
Dr. Kaech aims to understand how memory T cells are produced during infection and vaccination, how they function and why they can fail to induce long-term immunity during immunization. Her lab has been a leader in using genetic and molecular tools to identify the genes and signaling molecules involved in generating two specific types of memory T cells, CD4 and CD8, from precursor cells during both acute and chronic viral infections. She and her team discovered more than half a dozen important regulatory genes, as well as several types of key molecules called cytokines, which influence memory T cell development.
Dr. Kaech is also interested in how T cells are metabolically regulated, and how their differentiation and function can be altered by nutrient availability during infection and in tumors. In particular, she seeks to learn how T cell behavior is suppressed by tumors, in order to create better therapies for cancer using the body's own immune system—an innovative and rapidly moving field called cancer immunotherapy.
Dr. Kaech has been the recipient of numerous awards including the Damon Runyon-Walter Winchell Cancer Research Fellowship (1999), the Burroughs-Wellcome Foundation Award in Biomedical Sciences (2003), the Presidential Early Career Award for Scientists and Engineers (PECASE) (2007) and the Howard Hughes Medical Institute Early Career Scientist (2009).

Mitchell Kronenberg, Ph.D.
President and Scientific Director
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Dr. Kronenberg received his Ph.D. from the California Institute of Technology in 1983 and stayed on to complete postdoctoral work before joining the faculty of the UCLA School of Medicine in 1986. At UCLA, he became a full professor in 1997. The same year, he joined the La Jolla Institute for Allergy and Immunology (LJI) to head the Division of Developmental Immunology. Dr. Kronenberg was appointed President of LJI in 2003.

In addition to his executive duties, Dr. Kronenberg conducts a vigorous research program. His research interests include antimicrobial responses, mucosal immunity, immune system differentiation, and the study of chronic inflammatory conditions. Dr. Kronenberg's scientific accomplishments include authorship of more than 340 publications and numerous honorary lectureships around the world. Dr. Kronenberg has served on the scientific advisory boards of numerous organizations, including the Japan-U.S. Cooperative Medical Board for Immunology and Sanford Consortium for Regenerative Medicine. His awards include an NIH Merit Award a Burroughs Wellcome Fund Visiting Professor at Harvard University. He has served in numerous editorial positions including deputy editor for *The Journal of Immunolog*y. In 2015, he was elected to be a fellow of the American Association for the Advancement of Science and in 2016 he received the American Association of Immunologists (AAI) public service award after serving on the AAI Council.

Ruslan Medzhitov, Ph.D.
Professor of Immunobiology
Yale School of Medicine

Ruslan M. Medzhitov, Ph.D., is a Professor of Immunobiology at Yale School of Medicine, a member of Yale Cancer Center, and a Howard Hughes Medical Institute investigator. His research focuses on the innate immune system, inflammatory responses, including allergy, the innate control of adaptive immunity, and host-pathogen interactions.

He was born in Tashkent, Uzbekistan, and earned a Bachelor of Science at Tashkent State University before going on to pursue a PhD in biochemistry at Moscow State University. Before coming to Yale, Ruslan was a fellow in the laboratory of Russell Doolittle at the University of California, San Diego. His post-doctoral training was with Charles Janeway at Yale University School of Medicine from 1994 to 1999.

In 2000, Ruslan Medzhitov was selected as a Searle Scholar. He has received the William Coley Award for Distinguished Research in Basic and Tumor Immunology from the Cancer Research Institute, a Master of Arts Privatum at Yale University, the Emil von Behring Award, AAI-BD Biosciences Investigator Award, a doctorate honoris Causa at the University of Munich, the Blavatnik Award for Young Scientists from the New York Academy of Arts and Sciences, the Howard Taylor Ricketts Award from the University of Chicago, and the Lewis S. Rosenstiel Award for Distinguished Work in Basic Medical Research in 2010.

In recognition of his many contributions to the field of immunological research, he was elected to the National Academy of Sciences and in 2011 he was a co-recipient of the Shaw Prize in Life Science and Medicine. In 2013, Medzhitov received the Vilcek Prize in Biomedical Science.

SABRE CENTER INVESTIGATORS

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Dr. Locksley is the Director of the Sandler Asthma Basic Research Center (SABRE) and a Howard Hughes Medical Institute Investigator. He is a Professor in the Departments of Medicine and Microbiology & Immunology. He received his undergraduate degree in biochemistry from Harvard and his M.D. from the University of Rochester. After completing his residency at UCSF, he trained in infectious diseases at the University of Washington. Prior to his position as director of the SABRE Center, Dr. Locksley served 18 years as the Chief of the Division of Infectious Diseases at UCSF Medical Center. He is a member of the Pew Scholars Program Advisory Committee and the Lasker Basic Medical Research Awards Jury. Dr. Locksley is an elected member of the American Academy of Arts and Sciences and the National Academy of Sciences.

Dr. Locksley's laboratory addresses the immune cells and tissue responses that occur during allergic, or type 2, immunity. This includes the processes by which naïve helper T cells differentiate to become allergy-supporting Th2 cells, but also the interactions of these cells with eosinophils, basophils, mast cells and alternatively activated macrophages that mediate activities in peripheral tissues. The laboratory increasingly focuses on innate immunity, particularly since the discovery of Group 2 innate lymphoid cells, or ILC2s, which are prominently involved in allergy. Importantly, the discovery of ILC2s initiated efforts to uncover the 'ground state' of allergy by investigating homeostatic pathways involving these cells that might provide insights regarding their primary function in the immune system and in homeostasis.

Dr. Locksley's laboratory pioneered the use of mice genetically engineered to report cytokines expressed during allergic immune responses. Using these methods, the laboratory participated in the discovery of innate lymphoid type 2 cells, or ILC2s, and tuft cells, enigmatic epithelial cells of mucosal surfaces which activate tissue ILC2s and neural regulatory circuits, thus opening up entirely new avenues for discovery.

Representative Publications

1. **Locksley RM**. 2010. Asthma and allergic inflammation. *Cell* 140:777-83.
2. Wu D, AB Molofsky, HE Liang, RR Ricardo-Gonzalez, HA Jouihan, JK Bando, A Chawla, **RM Locksley**. 2011. Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. *Science* 332:243-7.
3. Nussbaum JC, SJ Van Dyken, J von Moltke, LE Cheng, A Mohapatra, AB Molofsky, EE Thornton, MF Krummel, A Chawla, H-E Liang, **RM Locksley**. 2013. Type 2 innate lymphoid cells control eosinophil homeostasis. *Nature* 502:245-8.
4. Lee M-W, JI Odegaard, L Mukundan, Y Qui, AB Molofsky, JC Nussbaum, K Yun, **RM Locksley**, A Chawla. 2015. Activated type 2 innate lymphoid cells regulate beige fat biogenesis. *Cell* 160:74-87.
5. von Moltke J, M Ji, H-E Liang, **RM Locksley**. 2016. Tuft cell-derived IL-25 regulates an intestinal ILC2-epithelial response circuit. *Nature* 529:221-5.
6. Van Dyken SJ, JC Nussbaum, J Lee, AB Molofsky, H-E Liang, JL Pollack, RE Gate, GE Haliburton, CJ Ye, A Marson, DJ Erle, **RM Locksley**. 2016. A tissue checkpoint regulates type 2 immunity. *Nat Immunol* 17:1381-7.
7. Van Dyken SJ, H-E Liang, R Naikawadi, P Woodruff, P Wolters, D Erle, **RM Locksley**. 2017. Spontaneous chitin accumulation in airways and age-related fibrotic lung disease. *Cell* 169:497-509.
8. Sui P, DL Wiesner, X Jinhao, Y Zhang, J Lee, SJ Van Dyken, A Iashua, C Yu, BS Klein, **RM Locksley**, G Deutsch, X Sun. 2018. Pulmonary neuroendocrine cells amplify allergic asthma responses. *Science* 360: eean8546. DOI: 10.1126/science.aan8546..
9. Miller CN, I Proekt, J von Moltke, KL Wells, AR Rajpurkar, H Wang, K Rattay, IS Khan, TC Metzger, JL Pollack, AC Fries, WW Lwin, EJ Wigton, AV Parent, B Kyewski, DJ Erle, KA Hogquist, LM Steinmetz, **RM Locksley**, MS Anderson. 2018. Thymic tuft cells promote an IL-4-enriched medullary microenvironment and shape thymocyte development. *Nature* 559:627-631.
10. Schneider C, CE O'Leary, J von Moltke, H-E Liang, Q Yan Ang, PJ Turnbaugh, S Radhakrishnan, Michael Pellizzon, A Ma, **RM Locksley**. 2018. A metabolite-triggered tuft cell-ILC2 circuit drives small intestinal remodeling. *Cell* 174:271-284.
11. Kotas ME, **RM Locksley**. 2018. Why Innate Lymphoid Cells? *Immunity* 48:1081-1090.
12. Vivier E, D Artis, M Colonna, A Diefenbach, JP Di Santo, G Eberl, S Koyasu, **RM Locksley**, ANJ McKenzie, RF Mebius, F Powrie, H Spits. 2018. Innate lymphoid cells: 10 years on. *Cell* 174:1054-1066.
13. Ricardo-Gonzalez RR, SJ Van Dyken, C Schneider, J Lee, JC Nussbaum, H-E Liang, D Vaka, WL Eckalbar, AB Molofsky, DJ Erle, **RM Locksley**. 2018. Tissue signals imprint ILC2 identity with anticipatory function. *Nature Immunol* 19:1093-1099.
14. O'Leary CE, C Schneider, RM Locksley. 2019. Tuft cells – systemically dispersed sensory epithelia integrating immune and neural circuitry. Annu Rev Immunol 37:47-72.
15. Schneider C, J Lee, S Koga, R Ricardo-Gonzalez, JC Nussbaum, LK Smith, SA Villeda, H-E Liang, RM Locksley. 2019. Tissue-resident group 2 innate lymphoid cells differentiate by layered ontogeny and in situ perinatal priming. *Immunity* 50:1425-1438.
16. Bielecki P, SJ Riesenfeld, JC Hutter,…,RM Locksley, A Regev, RA Flavell. 2021. Skin-resident innate lymphoid cells converge on a pathogenic effector state. *Nature* 592:128-132.

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Dr. Allen is an Investigator of the Cardiovascular Research Institute and an Assistant Professor in the Department of Anatomy at UCSF. He completed his B.S. in Biology at MIT, and then his Ph.D. at UCSF in the Biomedical Sciences Graduate Program in the laboratory of Jason Cyster, with the support of a Howard Hughes Medical Institute Predoctoral Fellowship. Dr. Allen was then selected as the first Sandler-Newman Foundation UCSF Fellow in Asthma Research, giving him the opportunity to attain principal investigator status and to develop an independent research program in asthma immediately after obtaining his Ph.D. He was then recruited into a tenure-track Assistant Professor position in the Smith Cardiovascular Research Building on the UCSF Mission Bay campus and promoted to Associate Professor in 2018.

Dr. Allen's research in the SABRE center focuses on the cellular immune response in asthma. He is using his expertise in cutting-edge two-photon microscopy to visualize interactions among cells in the lungs as well as in lymphoid organs that 'prime' cells for immune responses in the respiratory tract. A particular emphasis of his research is on the development and function of IgE antibodies that contribute to allergic responses. IgE has been shown to be important in human asthma, yet little is known about the events leading to IgE production after inhaling allergen. The major goals of the research are to:

1) Develop innovative new mouse models of asthma that will be useful for studies of IgE antibody responses to inhaled allergens.
2) Define the early events leading to allergic sensitization and IgE antibody production after inhalation of allergen.
3) Characterize the interactions among inflammatory cells in the lung in asthma and define the features of the microenvironments in which these interactions occur.

Selected Publications

1. **Allen C.D.C.**, Ansel K.M., Low C., Lesley R., Tamamura H., Fujii N. Cyster J.G. (2004). Germinal center dark and light zone organization is mediated by CXCR4 and CXCR5. *Nature Immunology*, 5(9), 943-952.
2. **Allen C.D.C.**, Okada T., Tang H.L., Cyster J.G. (2007). Imaging of germinal center selection events during affinity maturation. *Science*, 315(5811), 528-531.

3. ***Allen C.D.C.**, *Okada T., *Cyster J.G. (2007). Germinal-center organization and cellular dynamics (Review). *Immunity* 27(2), 190-202. *co-corresponding author. PMCID: PMC2242846.
4. Haynes N.M., **Allen C.D.C.**, Lesley R., Ansel K.M., Killeen N., and Cyster J.G. (2007). Role of CXCR5 and CCR7 in follicular Th cell positioning and appearance of a programmed cell death gene-1^{High} germinal center-associated subpopulation. *The Journal of Immunology*, 179(8), 5099-5108.
5. ***Allen C.D.C.**, *Cyster J.G. (2008). Follicular dendritic cell networks of primary follicles and germinal centers: phenotype and function (Review). *Seminars in Immunology* 20(1), 14-25. *co-corresponding author PMCID: PMC2366796.
6. Beltman J.B., **Allen C.D.C.**, Cyster J.G., de Boer R.J. (2011). B cells within germinal centers migrate preferentially from dark to light zone. *Proceedings of the National Academy of Sciences*, 108(21), 8755-8760. PMCID: PMC3102384
7. Sullivan B.M., Liang H.E., Bando J.K., Wu D., Cheng L.E., McKerrow J.K., ***Allen C.D.C.**, *Locksley R.M. (2011). Genetic analysis of basophil function *in vivo*. *Nature Immunology*, 12(6), 527-535. *co-corresponding author. PMCID: PMC3271435.
8. Steiner D.F., Thomas M.F., Hu J.K., Yang Z., Babiarz J.E., **Allen C.D.C.**, Matloubian M., Blelloch R., Ansel K.M. (2011). MicroRNA-29 Regulates T-Box Transcription Factors and Interferon-γ Production in Helper T Cells. *Immunity*, 35(2), 169-181. PMCID: PMC3361370.
9. Yang Z., Sullivan B.M., **Allen C.D.C.** (2012). Fluorescent *in vivo* detection reveals that IgE^{+} B cells are restrained by an intrinsic cell fate predisposition. *Immunity*, 36(5), 857-872.
10. Yang Z., Robinson M.J., **Allen C.D.C.** (2014). Regulatory Constraints in the Generation and Differentiation of IgE-Expressing B Cells (Review). *Current Opinion in Immunology,* 28, 64-70. PMCID: PMC4069329
11. Cheng L.E., Sullivan B.M., Retana L.E., **Allen C.D.C.**, Liang H.E., Locksley R.M. (2015). IgE-activated basophils regulate eosinophil tissue entry by modulating endothelial function. *The Journal of Experimental Medicine*, 212(4):513-24. PMCID: PMC2213179
12. Yang Z., Robinson M.J., Chen X., Smith G.A., Taunton J., Liu W., **Allen C.D.C.** (2016). Regulation of B cell fate by chronic activity of the IgE B cell receptor. *eLife*, 5:e21238. PMCID: PMC5207771
13. Robinson M.J., Prout M., Mearns H., Kyle R., Camberis M., Forbes-Blom E.E., Paul W.E., **Allen C.D.C.**, Le Gros G. (2017). IL-4 Haploinsufficiency Specifically Impairs IgE Responses against Allergens in Mice. *The Journal of Immunology*, 198(5):1815-1822. PMCID: PMC5886363
14. Yang Z., **Allen C.D.C.** (2018). Expression of Exogenous Genes in Murine Primary B Cells and B Cell Lines Using Retroviral Vectors. *Methods in Molecular Biology* 1707:39-49. PMID: 29388098
15. Yang Z., Jung J.B., **Allen C.D.C.** (2018) Study of IgE-Producing B Cells Using the Verigem Fluorescent Reporter Mouse. *Methods in Molecular Biology*. 1799:247-264. PMID: 29956157
16. Wu C.M., Roth T.L., Baglaenko Y., Ferri D.M., Brauer P., Zuniga-Pflucker J.C., Rosbe K.W., Wither J.E., Marson A., **Allen C.D.C.** (2018). Genetic engineering in primary

K. Mark Ansel, Ph.D.
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Mark Ansel is a Professor in the Department of Microbiology & Immunology. He completed a B.S. in biochemistry at Virginia Tech, a Ph.D. in Biomedical Sciences at UCSF, and postdoctoral training at the Immune Disease Institute at Harvard Medical School. He is a co-founder of the Bakar ImmunoX Initiative, a new UCSF initiative to harness immunology to improve human health. In addition, he serves as Faculty Director of the UCSF Biomedical Sciences Graduate Program. His laboratory in the Sandler Asthma Basic Research Center focuses on the regulation of gene expression in the immune system.

MicroRNAs (miRNA), RNA binding proteins (RBP), transcription factors, and epigenetic regulation shape the gene expression programs that determine cell identity and function. The Ansel lab studies how these molecular mechanisms work together to control lymphocyte development, differentiation, and function in immunity. We use in vitro cell differentiation systems, biochemistry, mouse genetics, disease models, and gene expression analyses in cells from human clinical samples to unravel the regulatory networks that underlie immunity and immune pathology, especially allergy and asthma.

Lymphocyte lineage decisions and the deployment of their effector functions are critical for the development of protective immunity against a great diversity of pathogens. Improper or exaggerated responses underlie the pathogenesis of autoimmune diseases, chronic inflammation, allergy, and asthma. Our primary experimental system is the differentiation of helper T cells, the central coordinators of adaptive immune responses. Upon immune activation, naïve CD4+ T cells can differentiate into several different helper T cell effectors subtypes defined by characteristic gene expression programs and distinct immune functions. These programs are controlled by external factors that derive from other cells or the environment, signaling-induced and lineage-specific transcription factors, epigenetic regulation of transcriptional responses, and posttranscriptional mechanisms directed by RBPs and miRNAs. The depth of our knowledge about the networks that control helper T cells makes them an attractive model for studying basic mechanisms of gene regulation.

Active projects in the laboratory focus on cellular and molecular analysis of allergic inflammation in asthma and atopic dermatitis, and the post-transcriptional regulatory networks that program immune cells involved in these diseases. We pioneered the study of miRNAs in immune cell differentiation and effector functions, and continue that work to leverage miRNA biology to uncover gene networks that program the cells that drive allergic airway inflammation in asthma. We also study the fate of miRNAs and other regulatory

RNAs in activated T cells and airway epithelial cells, as they are specifically regulated by transcription, processing, degradation and even secretion within extracellular vesicles. Recently, we developed a biochemical method for broadly interrogating the cis-regulatory transcriptome in living cells by mapping protein occupancy genome-wide at near-nucleotide resolution. We hypothesized that RBP occupancy in transcripts would be a marker of cis-regulatory activity, and this prediction was supported by a massively parallel reporter assay testing each of these site in primary T cells. We are now using GCLiPP together with other biochemical and genetic data to guide experimental dissection of transcripts involved in airway inflammation and allergic disease.

Lab Objectives

1) To characterize the function of RBPs and miRNAs that regulate the pathogenic properties of T cells and other immune cells in asthma.
2) To map the cis-regulatory activity of the transcriptome and reveal the trans-acting RNA binding proteins and miRNA mediators of post-transriptional regulation.
3) To decode the immunologic regulatory networks that control sustatined type 2 airway inflammation in asthma.

Selected Publications

1. Gagnon JD, Kageyama R, Shehata HM, Fassett MS, Mar DJ, Wigton EJ, Johansson K, Litterman AJ, Odorizzi P, Simeonov D, Laidlaw BJ, Panduro M, Patel S, Jeker LT, Feeney ME, McManus MT, Marson A, Matloubian M, Sanjabi S, Ansel KM. miR-15/16 Restrain Memory T Cell Differentiation, Cell Cycle, and Survival. *Cell Rep*. 2019 Aug;28(8):2169-2181.e4
2. Wigton EJ, DeFranco AL, Ansel KM. Antigen Complexed with a TLR9 Agonist Bolsters c-Myc and mTORC1 Activity in Germinal Center B Lymphocytes. *Immunohorizons*. 2019 Aug 19;3(8):389-401
3. Litterman AJ, Kageyama R, Le Tonqueze O, Zhao W, Gagnon JD, Goodarzi H, Erle DJ, Ansel KM. A massively parallel 3' UTR reporter assay reveals relationships between nucleotide content, sequence conservation, and mRNA destabilization. *Genome Res.* 2019 Jun;29(6):896-906
4. Gagnon JD, Ansel KM. MicroRNA regulation of CD8(+) T cell responses. *Noncoding RNA Investig*. 2019 Aug;3. pii: 24
5. Das S; Extracellular RNA Communication Consortium, Ansel KM, Bitzer M, Breakefield XO, Charest A, Galas DJ, Gerstein MB, Gupta M, Milosavljevic A, McManus MT, Patel T, Raffai RL, Rozowsky J, Roth ME, Saugstad JA, Van Keuren-Jensen K, Weaver AM, Laurent LC. The Extracellular RNA Communication Consortium: Establishing Foundational Knowledge and Technologies for Extracellular RNA Research. *Cell*. 2019 Apr 4;177(2):231-242
6. Pua HH, Happ HC, Gray CJ, Mar DJ, Chiou NT, Hesse LE, Ansel KM. Increased Hematopoietic Extracellular RNAs and Vesicles in the Lung during Allergic Airway Responses. *Cell Rep.* 2019 Jan 22;26(4):933-944
7. Fassett MS, Pua HH, Simpson LJ, Steiner DF, Ansel KM. Identification of Functionally Relevant microRNAs in the Regulation of Allergic Inflammation. *Methods Mol Biol.* 2018;1799:341-351
8. Durack J, Huang YJ, Nariya S, Christian LS, Ansel KM, Beigelman A, Castro M, Dyer AM, Israel E, Kraft M, Martin RJ, Mauger DT, Rosenberg SR, King TS, White SR, Denlinger LC, Holguin F, Lazarus SC, Lugogo N, Peters SP, Smith LJ, Wechsler ME,

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Esteban González Burchard, M.D., M.P.H., is a physician-scientist with formal training and expertise in pulmonary medicine, epidemiology, molecular genetics, genetic and clinical research. He has led a large research program focusing on minority children and gene-environment interactions since 2001. Dr. Burchard served as an advisor to the National Academy of Sciences of the U.S. Congress on gene-environment interactions. Dr. Burchard has expertise in the field of precision medicine and served on the Expert Panel for President Obama's Precision Medicine Initiative. He initiated and now directs four independent asthma studies in minority children. He has assembled a collaborative team of co-investigators on several projects with specific expertise in genetics, social and environmental epidemiology. Dr. Burchard is the lead PI of the NIH/NHLBI funded **PRIMERO**, the *Puerto Rican Infant Metagenomic and Epidemiologic study of Respiratory Outcomes* birth cohort study (U01HL138626), which is designed to study early-life respiratory viral infections.

Dr. Esteban Burchard directs the UCSF Asthma Genetics Core Facility, now named the *Asthma Collaboratory*, which is now the largest biorepository from minority populations with asthma in the world. The Asthma Biobank is open to reputable scientists seeking to assess genetic risk for variants in populations of interest or to extend findings made in animal models to suggest potential mechanistic involvement in human asthma. The Asthma Collaboratory has met continued goals to expand the numbers of patient samples; to extend the numbers of collaborators both nationally and internationally who use the database; and to continue to spearhead genetic studies in minority populations with asthma. The Burchard lab has led efforts to identify genetic modifiers of drugs used in asthma that might contribute to the poorer response in a number of ethnic populations and more recently is leading efforts to find biomarkers for different subsets of asthma as defined by presentation or response to therapy. These efforts have contributed to over 300 publications with more than 90 collaborators. Dr. Burchard served on President Obama's Precision Medicine Initiative and has begun efforts to prepare a US-wide Asthma Genetics Consortium grant funded by the NIH.

Dr. Burchard's team is taking a comprehensive approach to studying asthma and related phenotypes in minority children by focusing on genetic, social and environmental risk factors with the goal of creating innovative therapies and identifying targets for public health inventions. Dr. Burchard's team was the first to leverage genetic ancestry to identify novel genetic and environmental risk factors for disease and drug response. Dr. Burchard's laboratory recently completed the largest genome-wide association studies (GWAS) and

admixture-mapping scans of asthma in minority children and total IgE in the United States. Dr. Burchard and his team published the largest air pollution and genome-wide study of asthma in minority children. His research has been seminal in elucidating the pathogenesis of asthma and asthma related traits in minority populations.

Lab Objectives

1. Focus on the interplay between genes and their social and physical environments to determine the root causes of asthma health disparities among different populations locally and globally.
2. Identify risk factors associated with poor drug response, which we hope will lead the way to better therapies for all populations.
3. Collaborate with other researchers in the field and share our results and strengths.

Selected Publications

1. Thakur N, Borrell LN, Ye M, Oh SS, Eng C, Meade K, Avila PC, Farber HJ, Serebrisky D, Brigino-Buenaventura E, Rodriguez-Cintron W, Kumar R, Bibbins-Domingo K, Thyne S, Sen S, Rodriguez-Santana JR and **Burchard EG**. Acculturation is associated with asthma burden and pulmonary function in Latino youth: The GALA II study. *J Allergy Clin Immunol*. 2019 May; 143(5):1914-1922. PMID: 30682453.
2. Neophytou AM, Oh SS, Hu D, Huntsman S, Eng C, Rodríguez-Santana JR, Kumar R, Balmes JR, Eisen EA and **Burchard EG**. In utero tobacco smoke exposure, DNA methylation, and asthma in Latino children. *Environ Epidemiol*. 2019 Jun; 3(3):e048. PMID: 31342008.
3. Mak ACY, Sajuthi S, Joo J, Xiao S, Sleiman PM, White MJ, Lee EY, Saef B, Hu D, Gui H, Keys KL, Lurmann F, Jain D, Abecasis G, Kang HM, Nickerson DA, Germer S, Zody MC, Winterkorn L, Reeves C, Huntsman S, Eng C, Salazar S, Oh SS, Gilliland FD, Chen Z, Kumar R, Martínez FD, Wu AC, Ziv E, Hakonarson H, Himes BE, Williams LK, Seibold MA and **Burchard EG**. Lung Function in African American Children with Asthma Is Associated with Novel Regulatory Variants of the KIT Ligand KITLG/SCF and Gene-By-Air-Pollution Interaction. *Genetics*. 2020 Jul; 215(3):869-886. PMID: 32327564.
4. Lee EY, Mak ACY, Hu D, Sajuthi S, White MJ, Keys KL, Eckalbar W, Bonser L, Huntsman S, Urbanek C, Eng C, Jain D, Abecasis G, Kang HM, Germer S, Zody MC, Nickerson DA, Erle D, Ziv E, Rodriguez-Santana J, Seibold MA and **Burchard EG**. Whole-Genome Sequencing Identifies Novel Functional Loci Associated with Lung Function in Puerto Rican Youth. *Am J Respir Crit Care Med*. 2020 Oct 1; 202(7):962-972. PMID: 32459537.
5. Borrell LN*, Elhawary JR*, Fuentes-Afflick E, Witonsky J, Bhakta N, Wu AB, Bibbins-Domingo K, Rodriguez-Santana JR, Gavin J, Kittles R, Zaitlen NA, Wilkes DS, Powe N, Ziv E, **Burchard EG***. Race and Genetic Ancestry -- A time for reckoning with racism. *N Engl J Med*. 2021 Feb 4;384(5):474-480. PMID: 33406325.
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John Fahy, M.D. is a longstanding supporter of SABRE research and a formal faculty member in the SABRE Center for the past 6 years. He is a physician scientist with a primary appointment in the Division of Pulmonary and Critical Care Medicine (Department of Medicine and CVRI). He directs a mechanism-oriented clinical research program in airways disease that emphasizes studies in humans and in human-derived tissues and cells. For asthmatics with prominent airway type 2 inflammation ("type 2-high asthma"), his current research focuses on mechanisms underlying regional variation in type 2 inflammation in the lung and airway epithelial cell dysfunction in patients with "ultra-high" type 2 inflammation who are steroid-resistant and have mucus plugs and severe airflow obstruction. Dr Fahy's lab is a leader in advancing understanding for how pathologic mucus gels form in asthma and other mucus-associated airway diseases. He leads a PO1 program in type 2 airway inflammation in asthma (includes Drs. Locksley, Ansel and Woodruff), a translational PO1 program in academic drug discovery that aims to advance mucolytic to the clinic, and an RO1 program investigating mechanisms of airway inflammation and mucus pathology in acute severe asthma. In addition, he leads the UCSF center in the NHLBI funded PrecISE program (biomarker driven clinical trials in severe asthma). Recent honors include election to AAP in 2016 and a Recognition Award for Scientific Accomplishments from the ATS in 2017.

Dr. Fahy directs a research program in asthma and other airway diseases that is human centered and focused on uncovering abnormalities in airway epithelial cell function that contribute to abnormal type 2 immune responses in asthma, exploring mechanisms of formation of pathologic mucus gels in the airway, and investigating the heterogeneity of molecular mechanisms in asthma to improve prospects for personalized treatments.

ABNORMAL TYPE 2 IMMUNE RESPONSES IN HUMAN ASTHMA: The airway epithelium has emerged as an important regulator of innate and adaptive immune responses that result in type 2 allergic airway inflammation. My lab is specifically investigating epithelial mechanisms that contribute to upregulation of Th2 cytokines in the asthmatic airway. Our experimental approaches include gene and protein expression analysis of airway

epithelial brushings, biopsies, and secretions, and cell culture studies in airway epithelial cells from human donors. We collaborate with multiple other UCSF labs, including the Locksley, Ansel, and Woodruff labs, and the Seibold lab at National Jewish Healthy is a key non-UCSF collaborator.

PATHOLOGIC MUCUS GELS: The formation of pathologic mucus is a feature of multiple lung diseases and has multiple consequences for lung health, including airflow obstruction and infections. My lab is investigating how pathologic mucus gels form. Our experimental approaches include detailed analyses of sputum samples using rheology-, imaging- and biochemistry-based approaches. We use the data from analysis of pathologic mucus to inform strategies for development of novel mucolytics. Dr Stefan Oscarson at University College Dublin and Dr Anne Marie Healy at Trinity College Dublin are important collaborators for our mucolytic drug development program.

HETEROGENEITY OF MOLECULAR MECHANISMS IN ASTHMA: Many asthmatics do not respond well to currently available treatments and one reason is that current medications assume a one size fits all approach. My lab is applying a variety of targeted and unbiased approaches to investigate disease mechanism in large numbers of asthmatics with a view to improving understanding of the range and frequency of disease mechanisms that underlie asthma. Our experimental approaches include detailed analysis of the differential expression of genes and proteins in airway biospecimens collected from highly characterized patients with asthma and healthy controls. We also simultaneously explore how simpler tests in blood might reveal specific disease mechanisms and serve as biomarkers for personalizing treatment. Our work in this area is done in collaboration with the Woodruff lab at UCSF and with investigators in the NIH Severe Asthma Research Program (SARP).

Lab Objectives

(i) To define abnormalities in airway epithelial cell function that contribute to abnormal type 2 immune responses in asthma.
(ii) To explore mechanisms of formation of pathologic mucus gels in the airway so that novel mucolytics can be developed.
(iii) To explore the heterogeneity of molecular mechanisms in asthma to improve prospects for treatment approaches that are patient specific.

Selected Publications

1. **Fahy JV**, Fleming HE, Wong HH, Liu JT, Su JQ, Reimann J, Fick RB, Boushey HA. The effect of an anti-IgE monoclonal antibody-E25 on the early and late phase responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med* 1997; 155:1828-1834.
2. **Fahy JV**, Cockcroft DW, Boulet LP, Wong HH, Deschesnes F, Davis EE, Ruppel J, Su JQ, Adelman DC. Effect of aerosolized anti-IgE (E25) on airway responses to inhaled allergen in asthmatic subjects. *Am J Resp Crit Care Med* 1999; 160:1023-27
3. Longpre M, Li D, Matovinovic E, Ordoñez C, Redman T, **Fahy JV**, Basbaum C. Allergen-induced IL-9 directly stimulates mucin transcription in respiratory epithelial cells. *J Clin Invest* 1999; 104: 1375-1382.

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The Shin laboratory is interested in understanding the molecular mechanisms by which dendritic cells shape and control T cell immunity. The current research is focused on understanding the role of a membrane-anchored ubiquitin ligase named MARCH1 (membrane-associated RINC-CH1). MARCH1 is highly expressed in dendritic cells, attaches ubiquitin chains to the cytoplasmic tail of MHCII, CD86, and possibly other membrane proteins, and mediates endocytosis, lysosomal sorting, and degradation of the substrates. Through this activity, MARCH1 promotes surface turnover of specific immune-associated molecules in dendritic cells. However, its functional role is not clearly understood.

The specific objectives are as following.

1. **Determine the role of MARCH1 in dendritic cell function of establishing T cell tolerance**. Dendritic cells play a significant role in establishing T cell tolerance through their ability to present self-antigens to developing T cells in the thymus. When antigen-presenting DCs make a cognitive interaction with antigen-specific thymocytes, this interaction leads the engaged thymocytes to apoptotic cell death or regulatory T cell differentiation. Whether MARCH1 is involved in any of these processes is being investigated.

2. **Determine the role of MARCH1 in dendritic cell function of driving T cell immunity.** Dendritic cells play an essential role in the development of specific T cell immunity to various antigens. Dendritic cell subset 1 drives cytotoxic T lymphocyte and T helper type 1 (Th1) immunity against virus, cancer, and intracellular bacteria or parasite whereas dendritic cell subset 2 drives Th17 immunity to fungi and extracellular bacteria and Th2 immunity to intestinal hookworm and allergens. The Shin laboratory is interested in finding out whether MARCH1 plays an important role in the development and maintenance of any specific types of T cell immunity.

3. **Determine the role of MARCH1 in immune-stimulatory diseases.** Many of immune-stimulatory diseases are associated with unregulated T cell immunity. Allergic diseases including allergic asthma are associated with strong Th2 immunity while certain autoimmune diseases such as multiple sclerosis are associated with strong Th1 and Th17 immunity. The Shin laboratory is interested in determining whether MARCH1 is involved in the development and exacerbation of these T cell-dependent immune-stimulatory diseases and if so, whether MARCH1 could serve as a therapeutic target for treatment of these diseases.

Selected Publications

1. **Shin, JS**, Gao, Z, Abraham, SN. Involvement of cellular caveolae in bacterial entry into mast cells. *Science*. 289:785-8, 2000.
2. **Shin JS**, Abraham SN. Cell biology. Caveolae--not just craters in the cellular landscape. *Science*. 293:1447-8, 2001.
3. **Shin, JS**, Shelburne, CP, Jin, C, LeFurgey, EA, Abraham, SN. Harboring of particulate allergens within secretory compartments by mast cells following IgE/FcεRI-lipid raft mediated phagocytosis, *J Immunol*. 177:5791-5800, 2006
4. **Shin, JS**, Ebersold, M, Pypaert, M, Delamarre, L, Hartley, A, and Mellman, I. Surface expression of MHC class II in dendritic cells is controlled by regulated ubiquitination, *Nature*. 444:115-8, 2006
5. Bloom, O, Unternaehrer, JJ, Jiang, A, **Shin, JS**, Delamarre, L, Allen, P, and Mellman, I. Spinophilin participates in information transfer at immunological synapses, *J Cell Biol*. 181:203-11, 2008
6. Baravalle, G, Park, H, McSweeney, M, Ohmura-Hoshino, M, Matsuki, Y, **Shin**, **JS.** Ubiquitination of CD86 is a key mechanism in regulating antigen presentation by dendritic cells, *J Immunology*. 187:2966, 2011
7. Ma, JK, Platt, MY, Eastham-Anderson, J, **Shin, JS***, and Mellman, I*. MHC class II distribution in dendritic cells and B cells is determined by ubiquitin chain length, *PNAS*. 109:8820, 2012 ***Shin, JS** and Mellman, contributed equally to this work
8. Oh, J, Wu, N, Baravalle, G, Cohn, B, Ma, J, Lo, B, Mellman, I, Ishido, S, Anderson, M, and **Shin, JS**. MARCH1-mediated MHCII ubiquitination promotes dendritic cell selection of natural regulatory T cells*, J Exp Med*. 210:1069, 2013
9. Greer, A, Wu, N, Putnam, A, Woodruff, P, and **Shin, JS.** Serum IgE clearance is facilitated by human FceRI internalization. *J Clin Inves*. 124:1187, 2014
10. Baravalle, G, Greer, A, LaFlam, TN, and **Shin, JS**. Antigen-conjugated human IgE induces antigen-specific T cell tolerance in a humanized mouse model, *J Immunology*. 192:3280, 2014
11. Greer, AM, Matthay, MA, Kukreja, J, Bhakta, NR, Nguyen, CP, Wolters, PJ, Woodruff, PG, Fahy, JV, and **Shin, JS**. Accumulation of BDCA1$^+$ dendritic cells in interstitial fibrotic lung diseases and Th2-high asthma. *PLoS ONE*, Jun 9(6): e99084, 2014
12. Greer, AM and **Shin, JS**. The Role of FceRI expressed by dendritic cells and monocytes. *Cellular and Molecular Life Sciences.* 72:2349, 2015
13. Oh J, **Shin, JS**. Molecular mechanism and cellular function of MHCII ubiquitination. *Immunological reviews*. 266:134, 2015.

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Prescott Woodruff is a Professor of Medicine, Vice Chief for Research in the Division of Pulmonary, Critical Care, Sleep and Allergy and Associate Director of the UCSF Airway Clinical Research Center. He completed a B.A. at Wesleyan University, an M.D. at the Columbia College of Physicians and Surgeons, and an M.P.H. at the Harvard School of Public Health. He trained in Internal Medicine at the Massachusetts General Hospital, in Pulmonary and Critical Care Medicine at UCSF and completed post-doctoral research training at the Brigham and Women's Hospital and UCSF.

Dr. Woodruff's research comprises a program of NIH-funded clinical and translational research into a range of lung diseases including asthma, chronic obstructive pulmonary disease (COPD), and granulomatous lung diseases (e.g. sarcoidosis and hypersensitivity pneumonitis). His laboratory is in HSE13 and focuses on functional genomics in asthma, COPD and granulomatous lung disease, mechanisms of airway mucus production and biomarker development. His clinical studies are undertaken in the UCSF Airway Clinical Research Center, which is located on the 13th floor of Moffitt Hospital and serves as a shared and highly equipped resource for human studies in airway disease, including those contributing to SABRE projects. He is also the co-director (with John Fahy) of the UCSF Airway Tissue Bank. The primary function of this bank is to preserve human samples for ongoing research in the Woodruff and Fahy Laboratories, but this bank can also contribute human samples to SABRE projects contingent on a review of scientific need and adherence to formal sharing procedures.

Dr. Woodruff's major contribution has been in the field of personalized pulmonary medicine through the identification of specific proteins expressed in human airway epithelial cells in response to canonical Th2 stimuli (Woodruff PNAS 2007). These bioresponse markers, including periostin, have been widely validated and used to identify patient subgroups responsive to anti-Th2 therapy (Woodruff AJRCCM 2009, Corren NEJM 2011, Hanania AJRCCM 2013). This work has led to the development of a blood biomarker that is being used to develop personalized asthma treatment strategies and is considered a model for a new era of "precision" drug development for lung diseases.

Lab Objectives

These studies fall into three specific categories:

1) The identification of distinct molecular sub-phenotypes of asthma, chronic obstructive pulmonary disease (COPD), and granulomatous lung diseases (e.g. sarcoidosis and hypersensitivity pneumonitis),

2) The elucidation of disease-relevant mechanisms of airway inflammation and remodeling in the lung in these diseases and

3) Clinical trials of novel therapeutic approaches.

Selected Publications

1. Siddiqui S, Johansson K, Joo A, Bonser LR, Koh KD, Le Tonqueze O, Bolourchi S, Bautista RA, Zlock L, Roth TL, Marson A, Bhakta NR, Ansel KM, Finkbeiner WE, Erle DJ, **Woodruff PG**. Epithelial miR-141 regulates IL-13-induced airway mucus production. *JCI Insight*. 2021 Mar 8;6(5): e139019. doi: 10.1172/jci.insight.139019. PMID: 33682796.
2. An airway epithelial IL-17A response signature identifies a steroid-unresponsive COPD patient subgroup. Christenson SA, van den Berge M, Faiz A, Inkamp K, Bhakta N, Bonser LR, Zlock LT, Barjaktarevic IZ, Barr RG, Bleecker ER, Boucher RC, Bowler RP, Comellas AP, Curtis JL, Han MK, Hansel NN, Hiemstra PS, Kaner RJ, Krishnanm JA, Martinez FJ, O'Neal WK, Paine R 3rd, Timens W, Wells JM, Spira A, Erle DJ, **Woodruff PG**. *J Clin Invest*. 2019 Jan 2;129(1):169-181.
3. Godoy PM, Bhakta NR, Barczak AJ, Cakmak H, Fisher S, MacKenzie TC, Patel T, Price RW, Smith JF, **Woodruff PG**, Erle DJ. Large Differences in Small RNA Composition Between Human Biofluids. *Cell Rep*. 2018 Oct 30;25(5):1346-1358.
4. Wells JM, Parker MM, Oster RA, Bowler RP, Dransfield MT, Bhatt SP, Cho MH, Kim V, Curtis JL, Martinez FJ, Paine R 3rd, O'Neal W, Labaki WW, Kaner RJ, Barjaktarevic I, Han MK, Silverman EK, Crapo JD, Barr RG, **Woodruff P**, Castaldi PJ, Gaggar A, Investigators TSAC. Elevated circulating MMP-9 is linked to increased COPD exacerbation risk in SPIROMICS and COPDGene. *JCI Insight*. 2018 Nov 15;3(22).
5. Giraldez MD, Spengler RM, Etheridge A, Godoy PM, Barczak AJ, Srinivasan S, De Hoff PL, Tanriverdi K, Courtright A, Lu S, Khoory J, Rubio R, Baxter D, Driedonks TAP, Buermans HPJ, Nolte-'t Hoen ENM, Jiang H, Wang K, Ghiran I, Wang YE, Van Keuren-Jensen K, Freedman JE, **Woodruff PG**, Laurent LC, Erle DJ, Galas DJ, Tewari M. Comprehensive multi-center assessment of small RNA-seq methods for quantitative miRNA profiling. *Nat Biotechnol*. 2018 Sep;36(8):746-757.
6. Dunican EM, Elicker BM, Gierada DS, Nagle SK, Schiebler ML, Newell JD, Raymond WW, Lachowicz-Scroggins ME, Di Maio S, Hoffman EA, Castro M, Fain SB, Jarjour NN, Israel E, Levy BD, Erzurum SC, Wenzel SE, Meyers DA, Bleecker ER, Phillips BR, Mauger DT, Gordon ED, **Woodruff PG**, Peters MC, Fahy JV; National Heart Lung and Blood Institute (NHLBI) Severe Asthma Research Program (SARP). Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. *J Clin Invest*. 2018 Mar 1;128(3):997-1009.
7. Bhakta NR, Christenson SA, Nerella S, Solberg OD, Nguyen CP, Choy DF, Jung KL, Garudadri S, Bonser LR, Pollack JL, Zlock LT, Erle DJ, Langelier C, Derisi JL, Arron JR, Fahy JV, **Woodruff PG**. IFN-stimulated Gene Expression, Type 2 Inflammation, and Endoplasmic Reticulum Stress in Asthma. *Am J Respir Crit Care* Med. 2018 Feb 1;197(3):313-324.

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The Bhattacharya laboratory is interested in understanding lung macrophage function under acute inflammatory conditions. The current research is focused on how monocyte-derived macrophages activate adjacent fibroblasts. Using mouse lung slice imaging and genetically-encoded calcium indicators, the lab is testing the role of macrophage-derived factors on fibroblast cytosolic calcium-dependent activation responses after injury. A second focus is cellular senescence: specifically, its role in human lung aging and how it is regulated by immune lineages, including iNKTs and macrophages, during lung injury and infection.

Selected Publications

1. Sigle RO, Gil SG, **Bhattacharya M**, Ryan MC, Yang TM, Brown TA, Boutaud A, Miyashita Y, Olerud J, Carter WG. (2004) Globular domains 4/5 of the laminin alpha3 chain mediate deposition of precursor laminin 5. *Journal of Cell Science*. 117(Pt 19): 4481-94. PMID: 15316072.
2. **Bhattacharya M**, Su G, Su X, Oses-Prieto JA, Li JT, Huang X, Hernandez H, Atakilit A, Burlingame AL, Matthay M, Sheppard D. (2012) IQGAP1 is necessary for pulmonary vascular barrier protection in murine acute injury and pneumonia. *Am J Physiol Lung Cell Mol Physiol.* 303(1):L12-19. PMID: 22561460.
3. Su G, Atakilit A, Li JT, Wu N., **Bhattacharya M**, Zhu J, Shieh JE, Li E, Sheppard D. (2012) Absence of integrin αvβ3 enhances vascular leak in mice by inhibiting endothelial cortical actin formation. *Am J Respir Crit Care Med*. 185(1):58-66. PMID: 21980034.
4. Su G, Atakilit A, Li JT, Wu N, Luong J, Chen R, **Bhattacharya M**, Sheppard D. (2013) Effective treatment of mouse sepsis with an inhibitory antibody targeting integrin αvβ5. *Crit Care Med.* Feb;41(2):546-53. PMID: 23263571.
5. **Bhattacharya M**, Sundaram A, Kudo M, Farmer J, Ganesan P, Khalifeh-Soltani A, Arjomandi M, Atabai K, Huang X, Sheppard D. (2014) IQGAP1-dependent scaffold suppresses RhoA and inhibits airway smooth muscle contraction. *The Journal of Clinical Investigation.* 124(11):4895-8. PMID: 25271629.

6. **Bhattacharya M**, Kallet RH, Ware LB, Matthay MA. (2016) Negative-Pressure Pulmonary Edema. Chest. 150(4):927-933. PMID: 27063348.
7. **Bhattacharya M.** (2016) Macrophages build a wall and the host pays for it. *Sci Transl Med.* 8(364):ec178.
8. **Bhattacharya, M**. (2016) Mesenchymal metamorphosis. *Sci Transl. Med.* 8(370):370ec202. PMID: 28003541.
9. **Bhattacharya, M**. (2017) Could a coffee a day keep the inflammasome away? *Sci Transl. Med.* 9(376). PMID: 28179502.
10. Fong V, Hsu A, Wu E, Looney AP, Ganesan P, Ren X, Sheppard D, Wicher SA, Thompson MA, Britt Jr. RD, Prakash YS, **Bhattacharya M**. (2018) Arhgef12 drives IL17A-induced airway contractility and airway hyperresponsiveness in mice. *JCI Insight*. Nov 2;3(21). pii: 123578. PMID: 30385725.
11. Aran D, Looney AP, Liu L, Wu E, Fong V, Hsu A, Chak S, Naikawadi RP, Wolters PJ, Abate A, Butte AJ, **Bhattacharya M**. (2019) Reference-based analysis of lung single cell RNA-seq reveals a transitional profibrotic macrophage. *Nature Immunology*. Feb;20(2):163-172. PMID: 30643263.
12. Alam Z, Devalaraja S, Li M, To TKJ, Folkert IW, Mitchell-Velasquez E, Dang MT, Young P, Wilbur CJ, Silverman MA, Li X, Chen YH, Hernandez PT, Bhattacharyya A, **Bhattacharya M**, Levine MH, Haldar M. (2020) Counter Regulation of Spic by NF-kB and STAT Signaling Controls Inflammation and Iron Metabolism in Macrophages. *Cell Reports.* Jun;31(13):107825. PMID: 32610126.
13. Arora S, Thompson PJ, Wang Y, Bhattacharyya A, Apostolopoulou H, Hatano R, Naikawadi R, Shah A, Wolters PJ, Koliwad S, **Bhattacharya M**, Bhushan A. Invariant Natural Killer T cells coordinate removal of senescent cells. *Med.* In press.
14. Lee J, Islam MI, Boostanpour K, Aran D, Christenson S, Matthay MA, Eckalbar W, DePianto DJ, Arron JR, Magee L, Bhattacharya S, Matsumoto R, Kubota M, Farber DL, Bhattacharya, Wolters PJ, **Bhattacharya M.** Molecular programs of fibrotic change in aging human lung. Biorxiv 427195. [Preprint]. January 18, 2021. Available from: https://doi.org/10.1101/2021.01.18.427195.

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The Gordon laboratory is a translational research lab focused on understanding how genetics influence disease heterogeneity in asthma. Our laboratory is particularly focused on understanding the molecular mechanisms that underlie the asthma risk conferred by asthma-associated genes: *IL-33, IL1RL1, and GSDMB.* IL-33 is an epithelial derived cytokine and both it and its receptor ST2 (encoded by the *IL1RL1* gene) are among the most replicated genome wide association study hits for asthma. We have discovered polymorphisms in these genes that influence gene expression in airway epithelial cells and we are using CRISPR based gene editing to determine the causal polymorphism. We have also found that polymorphisms in these genes are associated with the type 2 high asthma endotype. The *GSDMB* locus is also among the most replicated asthma genetic loci and the gene encodes a membrane pore forming protein. We have discovered that the gasdermin family of proteins is involved in the secretion of IL-33 from airway epithelial cells. Finally, we have been studying the role of type 2 inflammation and basal cell differentiation in the epithelium of patients with chronic rhinosinusitis with nasal polyps, a disease closely related clinically to severe asthma.

Selected Publications

Lachowicz-Scroggins ME, **Gordon ED**, Wesolowska-Andersen A, Jackson ND, MacLeod HJ, Sharp LZ, Sun M, Seibold MA, Fahy JV. Cadherin-26 (CDH26) regulates airway epithelial cell cytoskeletal structure and polarity. Cell Discov. 2018; 4:7. PMID: 29449961.

a. **Gordon ED**, Simpson LJ, Rios CL, Ringel L, Lachowicz-Scroggins ME, Peters MC, Wesolowska-Andersen A, Gonzalez JR, MacLeod HJ, Christian LS, Yuan S, Barry

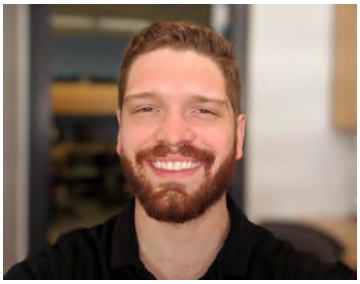
L, Woodruff PG, Ansel KM, Nocka K, Seibold MA, Fahy JV. Alternative splicing of IL-33 and type 2 inflammation in asthma. PNAS, 2016; 113(31):8765-70. PMCID: PMC4978244

b. **Gordon ED**, Locksley RM, Fahy JV. Cross-Talk between Epithelial Cells and Type 2 Immune Signaling. The Role of IL-25. Am J Respir Crit Care Med. 2016 May 1;193(9):935-6. PMCID: PMC4872659

c. **Gordon ED**, Palandra J, Wesolowska-Andersen A, Ringel L, Rios CL, Lachowicz-Scroggins ME, Sharp LZ, Everman JL, MacLeod HJ, Lee JW, Mason RJ, Matthay MA, Sheldon RT, Peters MC, Nocka KH, Fahy JV, Seibold MA. *IL1RL1* Asthma Risk Variants Regulate Airway Type 2 Inflammation. JCI Insight. 2016;1(14):287871. PMCID: PMC5033813

d. Sweerus K*, Lachowicz-Scroggins ME*, **Gordon ED**, LaFemina M, Huang X, Parikh M, Fahy JV, Frank JA. Claudin-18 deficiency is associated with airway epithelial barrier dysfunction and asthma. J Allergy Clin ImmunoI, 2016 Apr 20. pii: S0091-6749(16)30089-6. PMCID: PMC5073041

e. **Gordon ED,** Sidhu SS, Wang ZE, Woodruff PG, Yuan S, Solon MC, Conway SJ, Huang X, Locksley RM, Fahy JV. A protective role of periostin and TGF-β in IgE-mediated allergy and airway hyperresponsiveness. Clinical and Experimental Allergy, 2012. PMCID: PMC3271792



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Andrew Schroeder is a Bioinformatics Scientist in the UCSF Genomics CoLab & Dept. of Pulmonology recruited to his position to build computational pipelines for next-generation sequencing analysis (e.g. RNA-seq and scRNA-seq). He is responsible for transcript quality, cell quality, differential gene expression analysis, single-cell developmental trajectory analysis, receptor-ligand analysis, pathway and gene ontology analysis. His background as a Research Data Analyst in the UCSF Medical Center was in analysis of high-throughput-omics and clinical data for biomarket discovery, outcome prediction and statistical inference. Statistical methods applied using R: FDR, Regression, Random Forests, support vector machines, neural networks, LASSO, t-SNE, and PCA.

Prior to coming to UCSF, Andrew was a Graduate Intern in Biostatistics and Machine Learning at the NASA Langley Research Center in Hampton, Virgina where he trained machine learning algorithms on repeated measures human subject data using R to predict human response to sound. His work was published in the Journal of Acoustical Society https://asa.scitation.org/doi/abs/0.1121/1.5035683.

Additionally, Andrew held an previous internship in Biostatistis and Machine Learning at the National Human Genome Research Institute of the NIH in Baltimore, Maryland and was a Graduate Research Assistant at Washington University, St. Louis Institute for Public Health, St. Louis, Missouri where he compared neoadjuvant chemotherapy drug regimens using statistical methods.

Andrew holds a Master of Public Health (MPH) from St. Louis University, St. Louis, MO and is certified in Public Health by the National Board of Public Health Examiners. He received his undergraduate degree from Southern Illinois University, Edwardsville, IL.

Publications: https://scholar.google.com/citations?user=8HoBVHEAAAAJ&hl=en

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The Sundaram laboratory is interested in understanding the molecular mechanisms by which airway smooth muscle cells respond to allergic inflammation and regulate force transmission in chronic airways disease. Current research is focused on understanding the role of cell-matrix and cell-cell tethering in regulating force in smooth muscle. Using a combination of in vitro screening, ex vivo contraction assays, in vivo disease-modeling, and advanced microscopy, the Sundaram lab aims to establish a pipeline for academic drug discovery to advance novel inhibitors of cellular tethering into the clinical setting. We are aided in these efforts by ongoing collaborations with the Sheppard, DeGrado, and Agarwal (Baylor) labs.

Selected Publications

1. Dual antagonists of a5ß1/avß1 integrin for airway hyperresponsiveness. Bioorg Med Chem Lett. 2020 11 15; 30(22):127578. **Sundaram A**, Chen C, Isik Reed N, Liu S, Ki Yeon S, McIntosh J, Tang YZ, Yang H, Adler M, Beresis R, Seiple IB, Sheppard D, DeGrado WF, Jo H. PMID: 33007395.
2. G protein-regulated endocytic trafficking of adenylyl cyclase type 9. Elife. 2020 Jun 09; 9. Lazar AM, Irannejad R, Baldwin TA, **Sundaram AB**, Gutkind JS, Inoue A, Dessauer CW, Von Zastrow M. PMID: 32515353
3. A disease-associated mutation in fibrillin-1 differentially regulates integrin-mediated cell adhesion. J Biol Chem. 2019 11 29; 294(48):18232-18243. Del Cid JS, Reed NI, Molnar K, Liu S, Dang B, Jensen SA, DeGrado W, Handford PA, Sheppard D, **Sundaram AB**. PMID: 31640988.
4. IL-17A Recruits Rab35 to IL-17R to Mediate PKCa-Dependent Stress Fiber Formation and Airway Smooth Muscle Contractility. J Immunol. 2019 03 01; 202(5):1540-1548. Bulek K, Chen X, Parron V, **Sundaram A**, Herjan T, Ouyang

S, Liu C, Majors A, Zepp J, Gao J, Dongre A, Bodaszewska-Lubas M, Echard A, Aronica M, Carman J, Garantziotis S, Sheppard D, Li X. PMID: 30683702.

5. Targeting integrin a5ß1 ameliorates severe airway hyperresponsiveness in experimental asthma. J Clin Invest. 2017 01 03; 127(1):365-374. **Sundaram A**, Chen C, Khalifeh-Soltani A, Atakilit A, Ren X, Qiu W, Jo H, DeGrado W, Huang X, Sheppard D. PMID: 27918306.
6. G Protein-Coupled Receptor Endocytosis Confers Uniformity in Responses to Chemically Distinct Ligands. Mol Pharmacol. 2017 Feb; 91(2):145-156. Tsvetanova NG, Trester-Zedlitz M, Newton BW, Riordan DP, **Sundaram AB**, Johnson JR, Krogan NJ, von Zastrow M. PMID: 27879340.
7. IQGAP1-dependent scaffold suppresses RhoA and inhibits airway smooth muscle contraction. J Clin Invest. 2014 Nov; 124(11):4895-8. Bhattacharya M, **Sundaram A**, Kudo M, Farmer J, Ganesan P, Khalifeh-Soltani A, Arjomandi M, Atabai K, Huang X, Sheppard D. PMID: 25271629.
8. The phosphatase CD148 promotes airway hyperresponsiveness through SRC family kinases. J Clin Invest. 2013 May; 123(5):2037-48. Katsumoto TR, Kudo M, Chen C, **Sundaram A**, Callahan EC, Zhu JW, Lin J, Rosen CE, Manz BN, Lee JW, Matthay MA, Huang X, Sheppard D, Weiss A. PMID: 23543053.
9. The avß6 integrin modulates airway hyperresponsiveness in mice by regulating intraepithelial mast cells. J Clin Invest. 2012 Feb; 122(2):748-58. Sugimoto K, Kudo M, **Sundaram A**, Ren X, Huang K, Bernstein X, Wang Y, Raymond WW, Erle DJ, Abrink M, Caughey GH, Huang X, Sheppard D. PMID: 22232213.

CORE REPORTS

Microscopy Core

Managing Director: Kyle Marchuk, Ph.D.
Faculty Director: Matthew Krummel, Ph.D.

Objective/Mandate

The objective of the SABRE Microscopy Core is to facilitate access to highly sophisticated light-based microscopy equipment and to continue to develop technologies to advance imaging of the lung and associated tissues. Our core operates under the premise that a critical understanding of diseased tissues and organs such as the asthmatic lung will come with the study of the activities of component players (cell types, effector molecules) in their native environment. Lung biology represents a unique set of challenges for imaging and many powerful existing methods require additional development or elaboration in order to be successfully applied in the study of asthma. We act as a resource for imaging technologies and expertise, working with researchers to develop novel approaches to imaging. We represent an emerging and evolving example of a 'co-laboratory' in which expertise in this active area of scientific progress is shared rather than arbitrarily monetized.

COVID-19 non-essential research shutdown and long-term reduced campus density has delayed some projects and initiatives, but 2020 still held many scientific successes.

Strategic Goals

The efforts of this center are being directed toward improving imaging technologies for the normal and allergic lung. In 2021, the core will focus on expanding use of new technologies, and continue to develop and elaborate custom built tools for image acquisition and analysis that have direct and indirect benefits to the lung imaging community.

1. To extend the usage and utility of mouse lung imaging through continued development of minimally invasive intravital imaging methods and instrumentation.
2. To provide ongoing technical and instrumentation support to the UCSF (and beyond) asthma community in order to put existing and emerging imaging technologies to practical use in the study of asthma.
3. To make available the nearly completed homebuilt ZipSeq spatialtransciptomics microscope built in collaboration with the Krummel lab.
4. To make available XYZeq, a spatrialtransciptomics technology complementary to ZipSeq, to the great BIDC and CoLab community.
5. To incorporate the newly released Micro-Manager (open-source and UCSF based) Python extension Pycro-Manager into our 'Gen3' and 'Gen4' homebuilt 2-photon microscopes.
6. To formalize the Multiplexed Ion Beam Imaging (MIBI) microscope data analysis pipeline utilizing DeepCell.
7. To expand the BIDC's 3D cell surface morphology analysis program to include a larger set of standard data input for "common" feature comparisons.
8. To continue to develop in collaboration with Ophir Klein (UCSF) and Jeremy Green (King's College, London) an automated epithelial cell identification and

morphological characterization pipeline for cells undergoing the invagination process during organ development.

9. To upgrade and extend the capabilities of the selective-plane imaging microscope (SPIM) to include more simultaneous fluorophore imaging capabilities while increasing the overall speed and flexibility of the microscope.

Organization

The SABRE Microscopy Core is contained within the Biological Imaging Development CoLab (BIDC). The larger BIDC is an interdisciplinary center configured to assemble, test, and apply emerging light microscopy techniques and technologies. The BIDC is designed to serve as a conduit for new optical imaging technology at UCSF and as a site for new technology development. In its role as a conduit for new optical imaging technology, the BIDC also runs an incubator program, which provides support to investigators to acquire, maintain, and share equipment with other investigators, allowing a broader access to these valuable instruments. The SABRE center is currently one of the major supporters for this campus-wide imaging initiative and holds major stakes in confocal and 2-photon instruments in addition to driving key development initiatives. SABRE-affiliated labs and investigators enjoy privileged access to both the SABRE microscopy core and the larger BIDC. This center is managed by a Director (Kyle Marchuk) under the supervision of a Faculty Director (Max Krummel) and an oversight committee representing many of the key stakeholders on campus.

Current Usage

In 2020, there were 138 unique users of the BIDC. Many users are trained on multiple instruments. These users represent 68 principal investigators or labs. These labs are drawn from 22 departments or organizational units.

The BIDC performed 146 new user trainings in 2020. All users received comprehensive training on Center instruments or image processing stations. Training is done on an individual basis and reflects the differences in each user's experience, aptitude, and project needs. After initial training, BIDC staff continues to consult and assist with projects on an individual basis. The BIDC does not charge assisted time through recharges, and thus encourages users to ask questions and request assistance as needed. Many projects evolve into collaborations. Within the past year we have specifically worked with users from the following labs.

Alliston	Laird	Sarwal
Anderson	Looney	Schneider
Ashworth	Lowell	Schrepfer
Baskin	Ma	Schurman
Bhattacharya	Marcucio	Shin
Bhushan	Marshall	Shum
Brack	Marson	Smith
Bush	Matthay	Sneddon
Chang	McManus	Tang

Chapman	Molofsky	Thompson
Cyster	Nystul	Tlsty
Deuse	OFarrell	Tward
Gardner	Okimoto	Vaisse
Gartner	Paredes	Valdearcos Contreras
Gordon	Parent	Vasquez
Gould	Peng	Waterfield
Hebrok	Perera	Weaver
Hervey-Jumper	Pollen	Werb
Klein	Rajkovic	Wolters
Koliwad	Reiter	Xu
Kornberg	Roose	Yu
Krummel	Rosenblum	Zhang
Ku	Roybal	

Recent Accomplishments

In 2020, scientifically:

1. John Eichorst (BIDC, Bioinformatics Programmer) in collaboration with the Krummel Lab automated a microscope built around the ZipSeq spatialtransciptomics technology. The system will be available to SABRe and the UCSF microscopy community summer 2021.
2. John Eichorst (BIDC, Bioinformatics Programmer) in collaboration with the Krummel Lab developed user-friendly software to study t-cell surface membrane protrusions commonly referred to as microvilli. The program was expanded in the past year to include the co-localization of geometric features across channels using kernel scanning.
3. Austin Edwards (BIDC, Bioinformatics Programmer), Su-Yang Liu (Werb Lab) Stanley Tamaki (Flow CoLab), Mohammad Naser (BIOS), Maha Rahim and Matt Spitzer (Spitzer Lab) have been collaborating to develop an image acquisition, processing, and analysis pipeline regarding the newly functional MIBI operating within the Flow CoLab. The working group has identified DeepCell to develop the image analysis pipeline around.
4. Austin Edwards (BIDC, Bioinformatic programmer) in collaboration with Zoltan Laszik's lab has developed a data analysis pipeline for high-dimensional CODEX data utilizing QuPath. The pipeline utilized pixel classification to identify tissue regions of interest to which cell populations can be associated.
5. Kyle Marchuk (BIDC, Director) in collaboration with the labs of Ophir Klein (UCSF) and Jeremy Green (King's College, London) has developed a data analysis program with a graphical user interface (GUI) to analyze the morphology of cells within the context of tissue development. The morphological traits of individual cells associated with tissue specific regions reveals sub-populations of cells.
6. We continued to provide ongoing technical and instrumentation support to the asthma community at UCSF and beyond, in order to put existing and emerging imaging technologies to practical use in the study of asthma.

Space

The primary residence of the BIDC is Medical Sciences S11 at Parnassus Heights, which includes an office for staff of 4 employees with an attached Analysis Suite fostering a collaborative environment; a wetlab space outfitted for sample preparation including a vibratome, compresstome, incubator, biosafety cabinet, and fume hood which has allowed comprehensive training of new and inexperienced users from start to finish; and three core microscopy rooms housing some of the more advanced instrumentation. The BIDC also maintains additional microscopes at eight other sites throughout campus including behind the animal barrier.

Plans for the Coming Year

1. The ZipSeq spatrialtransciptomics homebuilt microscope is nearing completion and will be available to SABRe and the greater UCSF microscopy community Summer 2021. The microscope currently supports manually specifying regions of interest to tag with region specific oligonucleotides. Written in Python, the control software will be expanded upon to include increased automation and feature requests crowd-sourced from the ZipSeq community.
2. XYZeq uses in-situ reverse transcription of cells from fixed tissue sections in a microwell array combined with combitorial split-pool indexing to map single cell transciptomes to the microwell position. UCSF PBBR grant money has been awarded to the BIDC and Genomics CoLab to open the technology to our community. Austin Edwards and John Eichorst (Both BIDC, Bioinformatics Programmers) will work alongside the Genomic CoLab is developing analysis pipelines for upcoming projects.
3. Pycro-Manager, a recently released Python interface for the UCSF developed open-source software Micro-Manager, will be integrated into our existing homebuilt microscope platforms. Pycro-Manager allows for n-dimensional acquisitions with user defined hooks and feedback loops (including machine learning and inline data analysis) as well as the interface with non-microscopy related hardware. This software can greatly increase the opportunity for “smart-acquisitions” resulting in smaller files size and increased temporal resolution for events of interest.
4. The Multiplexed Ion Beam Imaging (MIBI) system is now online and producing high-dimensional images. The BIDC is continuously working alongside our collaborators in developing and evaluating analysis pipelines. A data analysis pipeline currently centered around DeepCell is continued to be refined and made more user friendly to the growing MIBI community.
5. John Eichorst (BIDC, Bioinformatic Programmer) has developed a user-friendly interface for his software that evaluates the morphology of cell surfaces in the 3D. The software can identify and measure morphological surface features as well as quantify areas of colocalization of said features between channels. The program will be increasingly generalized in the upcoming year to work on more input data structures and work with a larger variety of geometrical features of interest.
6. Kyle Marchuk (BIDC, Director), Ophir Klein (UCSF) and Jeremy Green (King’s College, London, UK) will continue working in collaboration on an automated pipeline

for the 3D segmentation and morphological evaluation of epithelial cells undergoing tissue invagination during tissue development. The next steps are a focus on increased automation and parameter optimization for higher throughput.

7. As part of the ImmunoX equipment RFA, money was allocated to improve the functionality and performance of the selective-plane imaging microscope (SPIM). This microscope will gain additional excitation and emission options for increasing the number of simultaneous fluorophores imaged while increasing the acquisition speed per channel. Custom software and acquisition modes will be written in Pycro-Manager.

Training and Integration with Sandler Program

As noted in previous updates, the BIDC's mission is to provide technical imaging expertise, support, and instrumentation to the UCSF asthma community. We continue to train and collaborate with researchers; this close relationship has allowed us to stay in tune with the current specific needs of a large number of users. Our goal is to continually improve and adapt both existing and emerging technologies to further the study of asthma. With the addition of the wet lab space, the BIDC has launched an "in residence" program for post-docs. This is an immersive training experience, designed to train researchers in every aspect of imaging, from experimental design, to sample preparation, troubleshooting, and analysis. We have hosted hands-on analysis workshops that focus on a particular aspect of analysis, such as creating FIJI macros for automation, allowing users to follow along and build their own skills.

Current Equipment

Permanent Equipment:

1. *Gen3 custom built 2-photon: 6 color/2 lasers
2. *Gen4 custom built 2-photon: 6 color/2 lasers
3. * Nikon C1si spectral laser scanning confocal microscope
4. Nikon spinning-disk confocal with TIRF and photo-ablation (Wittman)
5. Nikon A1R Multiphoton and laser scanning confocal microscope
6. Nikon AZ100 MacroConfocal microscope
7. Zeiss large field of view spinning disk microscope (Yokogawa CSU-X1)
8. Zeiss TIRF microscope with IRM
9. Zeiss Cell Observer with Apotome (Nystul)
10. Zeiss AxioImager2 with Apotome
11. Zeiss AxioImagerA1 brightfield microscope
12. Leica SP5 laser scanning confocal microscope
13. Leica SP8 laser scanning confocal microscope with white light laser
14. IVIS Spectrum live animal imager (animal colony)
15. Selective-plane imaging microscope (SPIM) custom built: 3 lasers
16. Lattice Light-Sheet Microscope
17. *FormLabs 3D printer
18. Alveole PRIMO Micropatterning System
19. *Precisionary Compresstome VF 310-02 Vibrating Microtome
20. Leica VT1000S Vibratome
21. *Analysis stations: 4 custom built computers

* Indicates SABRE is a partial owner of this instrument.

Analysis Computers and Software Platforms:
The BIDC maintains a suite of analysis stations equipped with high-end CPUs, GPUs, RAM, and large dual-monitor displays. The stations have a mix of proprietary and open-source image/data analysis software such as recently released Imaris 9.6, Matlab, NIS-Elements, Zen, GraphPad Prism, FIJI, R, and Python. Additionally, the BIDC has two Autodesk Inventor Academic Licenses for prototyping and manufacturing purposes.

We would like to acknowledge:

- Nikon for supplying a software key for the full image analysis version of NIS-Elements.
- Bitplane ‘Imaris’ for subsidizing the purchase of software and bestowing a ‘developer’ license.

ASTHMA RELATED RESEARCH PROJECTS

Birth Cohort Profile: the Puerto Rican Infant Metagenomics and Epidemiologic study of Respiratory Outcomes (PRIMERO)

PRIMERO is a longitudinal birth cohort study actively recruiting pregnant mothers in Puerto Rico and following their newborns over the first 5 years of life (target recruitment goal: 3000 mother-child dyads). Non-invasive swabs are collected from the baby's nostrils at birth, during respiratory illnesses identified via active and passive surveillance during the first 2 years of life, and at healthy visits for the child's first 5 birthdays. These swabs will be analyzed via whole transcriptome gene expression profiling to determine the children's airway responses to different viral species. Quantifying virus and host genes with high precision in PRIMERO samples will provide the first insights into how the airway of children with asthma is altered prior to disease development.

Introduction

Respiratory viral infections in early life cause minor illnesses in most children but some develop more severe illnesses that involve lower respiratory symptoms such as wheeze.[1] Decades of well-designed epidemiological studies have made clear the strong relationship between severe early-life viral respiratory illnesses and development of asthma.[2] Asthma is the most racially and ethnically disparate common chronic disease.[3] In the US, asthma prevalence is highest among Puerto Ricans (23.0%), followed by African Americans (15.6%), Whites (12.9%), and Mexican Americans (9.6%).[4] Asthma mortality is 4 times higher among Puerto Ricans and African Americans compared with Whites.[5]

The occurrence and severity of lower respiratory tract illnesses (LRI) in early life, especially when caused by respiratory syncytial virus (RSV)[6] or human rhinovirus (HRV), are associated with higher risk for recurrent wheezing and asthma later in childhood.[7] While early-life respiratory infections increase the odds of subsequent asthma in children, Puerto Rican children are at higher risk of asthma after these infections relative to other groups.[8] Despite the dramatic increase in risk associated with severe viral respiratory tract illnesses, it is also clear that most people affected by respiratory viruses are resilient to severe illness, recurrent wheezing, and asthma development.

To determine why some children with respiratory viral infections experience severe lower airway symptoms, and why they are at higher risk for childhood wheezing and asthma, the National Heart, Lung, and Blood Institute (NHLBI) funded creation of the Puerto Rican Infant

[1] Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2017. Available from: http://www.ginasthma.org/. PMID: 27286779; PMID: 11029352.
[2] PMID: 22444510; PMID: 23782528; PMID: 11254543; PMID: 10806145; PMID: 7700748; PMID: 15516534; 18565953; PMID: 17353039
[3] PMID 26871667
[4] National Center for Health Statistics. National Health Interview Survey, 2018. https://www.cdc.gov/asthma/nhis/2018/table2-1.htm
[5] PMID 21634072
[6] PMID: 22444510; PMID: 23782528; PMID: 11254543; PMID: 10806145; PMID: 7700748; PMID: 15516534
[7] PMID: 18565953; PMID: 17353039
[8] PMID 32369487

Metagenomics and Epidemiologic study of Respiratory Outcomes (PRIMERO, U01HL138626). PRIMERO is a partnership between the NHLBI and principal investigators from the University of California, San Francisco (UCSF), National Jewish Health (NJH) in Denver, CO, and Centro de Neumología Pediátrica (CNP) in Caguas, Puerto Rico. The purpose of this paper is to detail the design, aims, and profile of the PRIMERO birth cohort.

Methods

PRIMERO is a longitudinal birth cohort study actively recruiting pregnant mothers in Puerto Rico and following their newborns over the first 5 years of life (target recruitment goal: 3000 mother-child dyads). Non-invasive swabs are collected from the baby's nostrils at birth, during respiratory illnesses identified via active and passive surveillance during the first 2 years of life, and at healthy visits for the child's first 5 birthdays. These swabs will be analyzed via whole transcriptome gene expression profiling to determine the children's airway responses to different viral species. Quantitating virus and host genes with high precision[9] in PRIMERO samples will provide the first insights into how the airway of children with asthma is altered prior to disease development.

Population

Pregnant women receiving obstetric/gynecologic services and giving birth at Hospital Interamericano de Medicina Avanzada-San Pablo (HIMA) constitute the source population for recruitment. HIMA is in the municipality of Caguas, Puerto Rico, which neighbors San Juan, Puerto Rico's capital and most populous municipality. Most babies born at HIMA (>95%) come from families residing in the San Juan-Caguas-Carolina metropolitan area, which covers the northeast portion of the island and is home to 63% of Puerto Rico's population. HIMA is located near the geographic center of this metropolitan area. Demographically, the San Juan-Caguas-Carolina metropolitan area is similar to the entire island in terms of median age (41 years), marital status (38% married), birth rate (2.8%), and educational attainment (78% high school graduate or higher).[10] Based on the most recent urban-rural Census data, a higher proportion of Puerto Ricans (94%) live in urban areas compared to those in the mainland US (81%).[11] Elective cesarean births are common in Puerto Rico. During the first quarter of 2019, 60% of babies at HIMA were born by cesarean section.

Recruitment

Physicians and nurses from obstetrics/gynecology (OB/GYN) services at HIMA were informed of PRIMERO and invited to participate in recruitment efforts through brochures, presentations and information sessions from PRIMERO staff. Collaborating OB/GYN offices are provided with brochures and information packets about PRIMERO for distribution to pregnant women during routine scheduled prenatal care visits. OB/GYN office staff record the mother's name, phone number, and expected date of birth in a tracking log for PRIMERO staff. This information is entered into a custom-developed electronic database (PRIMERO-DB, see **Supplemental Text**). PRIMERO recruiters are hired from the pool of registered nurses (RNs) working in HIMA's labor and delivery (L&D) as well as the pediatric and neonatal intensive care units. The

[9] PMID 28103897

[10] U.S. Census Bureau. San Juan-Carolina-Caguas, PR Metro Area [cited 2019]. Available from: https://censusreporter.org/profiles/31000US41980-san-juan-carolina-caguas-pr-metro-area/.

[11] https://www.census.gov/programs-surveys/geography/guidance/geo-areas/urban-rural/ua-facts.html

recruiters wear identification badges, white coats, and shirts that have the PRIMERO logo on them to distinguish themselves from hospital staff. Recruiters do not provide clinical care while working as PRIMERO recruiters.

Recruitment in PRIMERO occurs in two stages. In the first stage, PRIMERO recruiters place phone calls to potential participants from the tracking log to assess their interest in participating in PRIMERO. Phone calls are made several days after information packets have been distributed to allow women sufficient time to review the information without pressure from PRIMERO or OB/GYN staff. Potential participants are informed that medical care for them and their child will not be affected regardless of their decision to participate in PRIMERO. Women expressing interest are consented by PRIMERO staff, followed by determination of eligibility; signed consent is obtained via DocuSign. PRIMERO recruiters stationed in HIMA's L&D use PRIMERO-DB to cross-reference admitted women to identify and assign study IDs to consented study participants. A bag containing pre-printed barcoded study IDs is placed with each participant's hospital bed to aid collection of biological samples. The second stage of consent occurs one day after the child has been born, in which mothers are given the opportunity to re-affirm their consent to continue participating in PRIMERO.

Eligibility criteria

Eligibility criteria were chosen to ensure the quality and integrity of collected data, reduce potential confounding, increase internal study validity, and improve generalizability to the target population of healthy Puerto Rican newborns. Pregnant women who are at least 18 years old and plan to deliver at the recruitment hospital are eligible to participate in PRIMERO (**Table 1**). Women must also have an SMS-capable phone or email address. Infants born to consenting mothers are assessed for eligibility on the day of their birth (**Table 1**). Newborns meeting eligibility criteria but weighing within 10% of the 2,500g cutoff (i.e., 2,250g) may be included if an obstetrician or pediatrician determines by physical examination that they are otherwise healthy.

Study visits and procedures

Table 2 summarizes the study visits and procedures. Cord blood is obtained immediately after the child is born. On the child's second day of life, peripheral blood is obtained from the mother, a nasal swab is obtained from the child, and a detailed interviewer-assisted questionnaire is administered to the mother. The questionnaire assesses demographic characteristics, mother's and family's medical history, environmental exposures, and other factors associated with development of childhood asthma and wheeze. Prior to discharge, mothers are provided with written and verbal instructions to inform PRIMERO staff when their child has onset of respiratory-related symptoms. These symptoms and instructions are summarized in the PRIMERO Action Plan (**Supplemental Text**). Children with respiratory illnesses are assessed via in-person visits at CNP during their first two years of life. These clinic visits involve a physical examination, a nasal swab, and characterization of illness history and current severity. Annual follow-up visits for the child's first five birthdays are conducted at CNP and involve a physical exam, a nasal swab, collection of blood, and a detailed questionnaire to assess environmental, demographic, social, and clinical risk factors for recurrent wheeze and asthma. When children are 3 years old, study participants will be assessed for lung function using

impulse oscillometry, which measures nearly effort-independent tidal breathing. Traditional spirometry will be performed among children on their fourth birthday.

Respiratory illness surveillance

Surveillance for respiratory illnesses begins once mother and child are discharged home from HIMA and lasts for the first two years of a child's life. Passive surveillance for respiratory illness relies on participants contacting PRIMERO staff when their child is ill. While the PRIMERO Action Plan has been a valuable decision-making tool for parents in this regard, the majority of incident respiratory illnesses have been detected through active surveillance. PRIMERO-DB sends weekly automated SMS texts or email messages to the child's mother to identify children with respiratory illnesses. The message provides a link to indicate whether the child has signs of respiratory illness. PRIMERO-DB uses the participants' responses to create a daily follow-up call list. Text and email messages that are unanswered or have an affirmative response are followed up by phone call from project staff. An over-the-phone screening tool is used to determine whether a child likely has an upper respiratory illness (URI) or a lower respiratory illness (LRI). All likely LRIs occurring during the first two years of life are assessed via in-person clinic visits. The PRIMERO study protocol originally planned for one in-clinic URI assessment per child per year, but URI visits have been postponed under current pandemic study protocol modifications. Visits for LRIs are continuing regardless of study protocol because they are considered medically necessary.

The respiratory illness visits take place at CNP. To delineate clinical care from study-related procedures, activities related to the study are conducted after providing clinical care to the ill child and are performed in a defined examination room. Once the clinical portion is completed, participants are told that the clinical portion of the visit has ended and that activities related to their participation in PRIMERO will begin. Participants are then walked by PRIMERO staff from the clinical examination room to the research examination room. The Pediatric Respiratory Assessment Measure (PRAM)[12] and the Respiratory Severity Score (RSS)[13] are administered as part of the illness visit to obtain a clinically standardized measure of the child's illness severity. A final determination of upper versus lower respiratory tract illness is recorded based on the physician's assessment of the child's symptoms and PRAM and RSS scores (**Table 3**). The choice of these cut points for the PRAM and RSS assures that individuals with a higher probability of LRI based on these scores will be coded as LRI.

Following the respiratory illness surveillance visit, PRIMERO staff conduct weekly follow-up phone calls to document the trajectory of the illness that precipitated the respiratory illness surveillance visit. These calls are used to determine the current state of the illness, presence and severity of symptoms, and whether various clinical events occurred as a result of the illness (e.g., diagnosis of bronchiolitis; prescription of albuterol or oral steroids; illness-related hospitalizations). Another in-person clinic visit is scheduled at CNP if mothers report worsening of the following symptoms: cough that interferes with daily activities; wheezing; difficulty breathing; disturbances in sleep due to cough, wheeze, or difficulty breathing. Once an illness is determined to have resolved, the child is returned to the regular weekly SMS/email surveillance messaging.

[12] Ducharme. PRAM. J Peds 2008

[13] Feldman RSS Red Allerg Immun Pulm 2015

Core facilities

PRIMERO staff from all three sites (UCSF, NJH, and CNP) have weekly conference calls to assess and discuss recruitment and follow-up, and to coordinate the transfer of clinical, biologic and phenotypic data. The conduct of PRIMERO activities is coordinated through three core facilities: (1) recruitment and follow-up core; (2) data coordinating core; and (3) laboratory core.

Recruitment and follow-up core. CNP serves as the recruitment and follow-up core. CNP coordinates activities between recruiters, data collectors, and follow-up staff and houses the text messaging and call center for respiratory illness surveillance and scheduling of study visits. CNP is equipped with a biosafety level 2 laboratory for processing of nasal and blood samples prior to shipment.

Data coordinating core. The UCSF Asthma Collaboratory serves as the data coordinating center (DCC). The DCC helps collect, monitor, integrate, and distribute information for PRIMERO. Data collection forms and protocols are generated by and distributed through the DCC, which maintains a coded data set stored on UCSF servers.

Laboratory cores. Biological samples are distributed to two laboratory cores. Coded nasal swab samples are sent to the NJH Nasal Biobank and coded blood samples are sent to the UCSF Pediatric Asthma Specimen Bank. These two laboratory cores track and manage the inventory of their respective biological samples. The laboratory cores extract RNA/DNA, produce cell cultures, and perform other analyses from nasal swabs and blood.

Data collection and management

PRIMERO uses the Research Electronic Data Capture (REDCap) system to collect, transfer, store, and manage recruitment, surveillance, and annual follow-up visit data. PRIMERO data collectors use electronic tablets installed with REDCap software to directly enter data into eligibility forms and questionnaires for each participant they encounter. Data are stored locally on tablets if there is no internet connection during time of data collection. REDCap software automatically uploads data to the DCC once an internet connection is re-established. Recruiters use the tablet's camera to scan a participant's barcoded subject ID into the baseline questionnaire, reducing the probability of entering the wrong subject ID number. Automated data uploads from PRIMERO-DB to the DCC's REDCap system occur on a regular basis. Data from clinical encounters at CNP (e.g., illness surveillance visits and annual follow-up visits) are entered by physicians and staff in real-time into CNP's electronic medical records system (EMR). Selected data are extracted from CNP's EMR by PRIMERO-DB and sent to the UCSF DCC as part of the regular data upload.

Primary outcomes

PRIMERO is designed to document the natural history of early-life respiratory illnesses and to determine the genetic, environmental, and molecular airway determinants of these illnesses. The primary endpoints include (1) early-life respiratory illness outcome; (2) gene expression and viral infection assay; and (3) assessment of the modified asthma predictive index (mAPI).

Early-life respiratory illness outcome. Participants' LRIs in the first two years of life will be dichotomized as mild/moderate or severe. LRI events will be classified as severe if any one of the following criteria is met: (1) the illness requires the participant to be hospitalized, (2) the participant is prescribed oral steroids for the illness, or (3) the illness PRAM score assigned is in the severe category (8 to 12). Each participant will be classified at the end of their 2-year surveillance period based on the severity of LRI(s) experienced as follows: Group 1 – did not experience an LRI; Group 2 – experienced at least one mild/moderate LRI (PRAM score = 0 to 7), but not a severe LRI (PRAM score = 8 to 12); and Group 3 - experienced at least one severe LRI.

Gene expression and viral infection assay. We will use RNA-seq technology to measure whole transcriptome gene expression patterns of nasal airway cells sampled at birth, during respiratory illness, and at annual follow-up visits. Metagenomic analysis of RNA-seq data and viral species-specific qPCR assays will allow us to determine if a participant has been infected with a respiratory virus.

mAPI. Children undergo clinical assessment for asthma risk at 2 years of age via the modified asthma predictive index (mAPI). The mAPI is an updated iteration of the asthma predictive index (API) and provides a dichotomous (positive or negative) assessment for future asthma risk.[14] The mAPI has greater sensitivity than the API and has been included in the National Asthma Education and Prevention Program guidelines as a criterion for institution of long-term therapy to decrease asthma morbidity and exacerbations.

Planned primary analyses

Analyses of data from the first 5 years of PRIMERO will investigate a number of questions, which can be classified into several topics (see **Supplemental Text**). The first group of questions concerns viral and genetic risk factors for susceptibility to respiratory illnesses, as well as factors that determine illness timing, type (URI or LRI), and severity (analyses 1-3 and 13-14). The majority of questions fall into a grouping that investigates gene expression, both as an outcome (due to the passage of time, viral infection, respiratory illness characteristics, and genetics) and as a predictor of future illness (analyses 4-12). The last group of questions examines how LRI occurrence and severity in the first two years of life predict the mAPI, which will be determined at age 2 (analyses 15-16).

OSMB oversight

An independent Observational Study Monitoring Board (OSMB) was appointed by the Director of the NHLBI to act in an advisory capacity to the NHLBI. The OSMB (1) provides oversight of data and safety monitoring of participants, (2) evaluates the progress of the study, and (3) reviews procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses. Reports on study participant recruitment are sent on a regular basis, and reports of participant safety sent as they arise. The OSMB meets twice yearly with study investigators and the NHLBI program officer to ensure that the study is appropriately monitored.

Results

Recruitment

[14] PMID 24187656

PRIMERO began recruitment in March 2020, as the first cases of COVID-19 were being reported in Puerto Rico. With only one child born into the cohort, Puerto Rico's governor ordered an island-wide curfew and closure of non-essential businesses in mid-March.[15] Additional pandemic control measures have followed but PRIMERO continues to recruit and is one of few studies actively recruiting during the pandemic.

More than 500 mother-child dyads have been enrolled into PRIMERO as of February 4, 2021 (**Table 4**), representing 55.6% of the pregnant women who were invited to participate in PRIMERO. An additional 133 women have consented to participate and are awaiting the birth of their child. On average, mothers in PRIMERO were 26.1 years of age and self-identified as Black or African American (50.6%) or White (48.7%); nearly all mothers identified as Puerto Rican (98.8%). Baseline questionnaires were obtained from 100% of enrolled mothers, and maternal blood was drawn from 98.8% of women. Most newborns were male (51.8%), and cesarean delivery was common among all enrolled infants (69.6%). Average gestational age at birth was 38.7 weeks and birth weight was 3,174 grams; mean Apgar score was 8.9. Cord blood and birth nasal swabs were collected among 88.8% and 99.3% of infants, respectively. Recruitment remains ongoing and is expected to be complete by XX.

Illness surveillance and follow-up

The majority (97.9%) of weekly SMS/email messages have been answered on the first attempt. Non-response was highest during the first quarter of the study (3.4%) and has steadily decreased (1.5%, most recent quarter). Among the ## children in the respiratory illness surveillance phase of PRIMERO, 22 URIs and 17 LRIs have been reported, leading to 17 respiratory illness visits and 17 respiratory illness nasal swabs. We had projected to accrue 148.75 person-years of follow-up time by the end of 2020. As of December 31, 2020, PRIMERO had accrued 142.45 cumulative person-years of follow-up time, representing 95.8% of our target. To date, only one dyad has been lost to follow-up after a mother requested to drop out of the study. The first set of healthy annual follow-up visits are scheduled to occur in March 2021.

Discussion

Asthma represents a significant and growing public health disparity and is the most common chronic disease among children.[16] While viral respiratory illnesses are a well-documented risk factor for childhood asthma, what remains to be determined is how viral respiratory infections and illnesses alter normal airway biological function and resilience. PRIMERO will provide the first insights into how the airway of children is altered prior to asthma development. Analyzing prospectively collected nasal swabs in the same participants will allow a first-of-its-kind investigation of how the airway evolves in early childhood, under a range of viral exposure scenarios. PRIMERO will help us understand normal airway biological function and resilience, as well as factors that account for individual- and population-level differences in determinants of health. Since 80% of Puerto Rican children with asthma in our prior studies had respiratory symptoms by age 3,[17] our prospective design will identify biomarkers that may predict asthma

[15] https://www.faegredrinker.com/en/insights/topics/coronavirus-covid-19-resource-center/government-actions-covid-19/puerto-rico-covid-resources#!#tab-Overview

[16] WHO | Asthma. WHO [Internet]. World Health Organization. Retrieved from: http://www.who.int/respiratory/asthma/en/

[17] 23750510, 22552109

status. PRIMERO's birth cohort design will provide the basis for studies of pathobiological mechanisms important to the onset and progression of asthma and related outcomes.

PRIMERO addresses the growing realization of the schism between the representativeness of study populations in biomedical science and the American taxpayers who fund that science.[18] Despite the attention and resources allocated to genetic research in the past decade, globally diverse populations are severely underrepresented. Most genetic discoveries (72%) have been estimated to have come from studies that recruited participants from the US, UK and Iceland, while over three-quarters of the world's population resides in Africa and Asia.[19] Among the largescale genetic studies involving non-European populations, most have unfortunately been performed using genotyping arrays designed for European populations.[20] We and others have found substantial evidence for ethnic-specific or population-specific differences in the frequency and composition of genetic variants associated with common diseases, including asthma.[21] *Primero* means "first" in Spanish. Fittingly, PRIMERO is Puerto Rico's first birth cohort study of asthma. Recruitment and follow-up take place entirely within Puerto Rico in close collaboration with investigators, clinicians, and other Puerto Rican personnel. This work will greatly develop and sustain a strong diverse biomedical workforce. Expansive research in diverse genomes will help bridge the gap and produce better science and medicine. PRIMERO represents a strategic investment in diversity and embodies NHLBI's Strategic Vision and overarching objectives.[22]

The strengths of the PRIMERO study include weekly surveillance for respiratory illnesses and well-characterized illness assessments. Participant recruitment and follow-up occur within a closed healthcare system—medical care is provided through the same health care system in which infants are born, increasing the likelihood of ascertaining that an illness event has occurred. The study has also received strong support and buy-in from HIMA administrators and staff. PRIMERO was one of few studies allowed by HIMA to continue recruitment during the pandemic. Study staff have also arranged an agreement with HIMA whereby hospital staff transport the placenta from the operating room and labor suite to a separate room dedicated for PRIMERO staff to perform cord blood extractions.

Transcriptomic analysis of prospectively collected nasal swabs at birth, during respiratory illnesses, and at healthy birthday visits will allow us to determine (1) airway dysfunction that exists at birth prior to exposures, (2) molecular responses to mild and severe viral illnesses, and (3) airway dysfunction that exists in early childhood before asthma is clinically apparent. These swabs analyzed together in the same participants with allow novel investigation of early childhood airway development. Another strength of PRIMERO is its study design. Creating a birth cohort is an extremely rare opportunity and uniquely positions us to answer questions about the early-life origins of health and disease. While our initial focus is on respiratory disease, we hope to leverage this rare opportunity to study the broader health of children over the next

[18] 26671224
[19] 30623105
[20] 27734877
[21] 21804549
[22] NHLBI. Strategic Resource Priorities [Internet]. [cited 2018 Mar 1]. Retrieved from: https://www.nhlbi.nih.gov/sites/default/files/media/docs/020316DSRPPublicCommentVersion-FINALB.pdf

decades, chronicling their exposures and health outcomes in real-time. Long-term prospective follow-up of PRIMERO participants will provide the basis for studies of numerous exposures and outcomes, including diabetes, childhood obesity, neurological development, hematologic conditions (e.g., Zika), childhood cancers, and cardiovascular disease. Our prospective design will allow us to identify biomarkers that may predict outcomes well before they are traditionally diagnosed. These biomarkers can inform development of therapeutics for early intervention and prevention of disease.

One of the main challenges in PRIMERO was the lack of available software to manage the recruitment, surveillance, and follow-up of 3,000 mother-child dyads progressing their way through each stage of the study. A key innovation in PRIMERO was the creation of PRIMERO-DB to address this need (**Supplemental Text**). PRIMERO-DB has the same HIPAA securities as electronic medical record data and is available from any web-enabled device, allowing authorized users to log in with user-specific permissions. Another major challenge has been the COVID-19 pandemic. Since the start of recruitment was nearly coincident with the arrival of the pandemic in Puerto Rico, the PRIMERO team briefly paused recruitment to deliberate suspending the study or continuing with modifications. With social distancing measures in place and OB/GYN offices limiting the number of people who could be indoors, recruiters would lack the advantage of building the kind of rapport provided through face-to-face interactions. After considering the risks of viral exposure to staff and participants and developing a risk mitigation plan in conjunction with the NHLBI and the OSMB, the team was approved to proceed with some modifications (e.g., using enhanced respiratory precautions; limiting research activities to visits that are medically necessary; separating laboratory staff by space and time to reduce workplace density, **Supplemental Text**).

Operating a study site in Puerto Rico can amplify the challenges of conducting a research study. We have relied on our experience working in Puerto Rico since the early 2000s to obviate some of these challenges. For example, blood samples from an individual are divided into two separate shipments and the second shipment is not sent until the first shipment has been received. In the event that a shipment is delayed while in transit and samples are lost because they were not maintained at the proper temperature (e.g., ice packs have fully melted), the second batch will not be sent until the reasons for the delay have been addressed. Past solutions have included switching couriers, adding more ice packs, and re-training staff. We have also learned to keep abreast of current events, including civil disturbances and weather phenomena. For instance, we will delay shipment of study samples if we anticipate that a significant weather event has the potential to affect their safe delivery. We have also expanded our product procurement network and been acquiring and maintaining an inventory that will allow operations to continue for at least 2 months.

PRIMERO is an outgrowth of the realization that the complexities of asthma require integration of multiple disciplines, including clinical medicine, cell biology, genetics, genomics, and epidemiology. This landmark study will prospectively trace the airway mechanisms that precede early-life respiratory illnesses and the development of childhood asthma. PRIMERO presents an unprecedented opportunity to better understand the link between viral infections, airway dysfunction, and development of asthma. This ongoing study will be able to answer (1) why some children get sicker when infected by a respiratory virus, (2) how viral infection increases

risk for childhood respiratory conditions like asthma, and (3) whether childhood respiratory conditions can be diagnosed and treated earlier than what is currently possible.

Acknowledgements
The authors acknowledge the families for their participation and thank the numerous data collectors, recruiters, technicians, and hospital administrators for their support and participation in PRIMERO. In particular, the authors thank …

Single Cell Sequencing in Nasal Polyp Patients

Erin Gordon, M.D.
Maya Kotas, M.D., Ph.D.

Severe asthma accounts for approximately 10% of the disease burden, but nearly 50% of asthma costs. Understanding the molecular pathways that promote severe disease is critical to the development of novel therapeutics. One strategy is to study extreme phenotypes or outliers. In severe asthma, one extreme phenotype is **nasal polyposis (NP).** NP affects only 2-4% of the general population (1), but among patients with NP, 30-70% carry a diagnosis of asthma (2). While not all patients who have chronic sinus inflammation (chronic rhinosinusitis; CRS) have NP, the presence of NP (CRS with NP; CRSwNP) is strongly associated with tissue **type 2 inflammation.** In 386 asthmatics enrolled in the Severe Asthma Research Program (SARP), we find that 19% of asthmatics suffer from NP. Asthmatics with NP have **lower lung function** (FEV1% 77.9±20.4 vs 71.3±17.9, p=0.011) and **more exacerbations than asthmatics without NP (Fig 1).** Understanding the relationship between upper and lower airway responses in patients with asthma and NP may hold the key to understanding the mechanisms that underlie airflow obstruction and exacerbations in severe asthma.

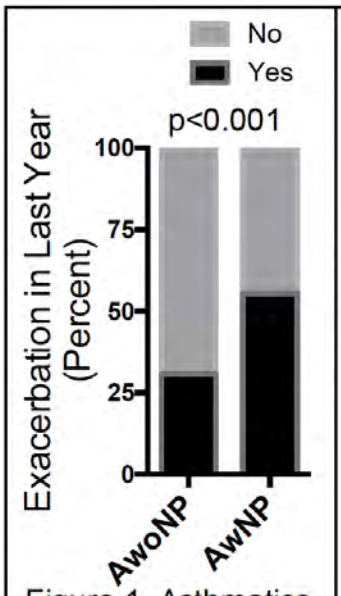

Figure 1. Asthmatics with nasal polyps (AwNP) have a higher rate of asthma exacerbation than those without polyps (AwoNP)

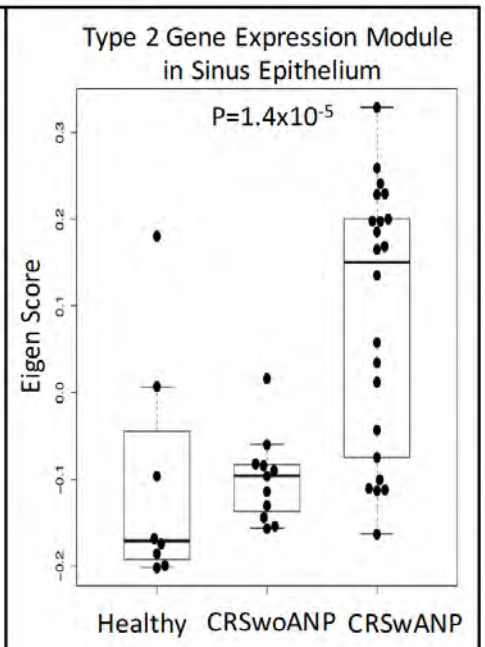

Figure 2. Type 2 Gene Signature is increased in the sinus epithelium of CRS with asthma and nasal polyps (CRSwANP) compared to health and CRS without asthma and polyps (CRSwoANP).

To explore this relationship between the upper and lower airway in nasal polyposis, we performed whole genome RNA sequencing in upper and lower airway brushes from patients undergoing endoscopic surgery for CRS. We collected epithelial brushes from patients with CRS without polyps or asthma, CRS with polyps and asthma, and subjects without CRS undergoing pituitary surgery (healthy). Our data demonstrates a type 2 gene expression

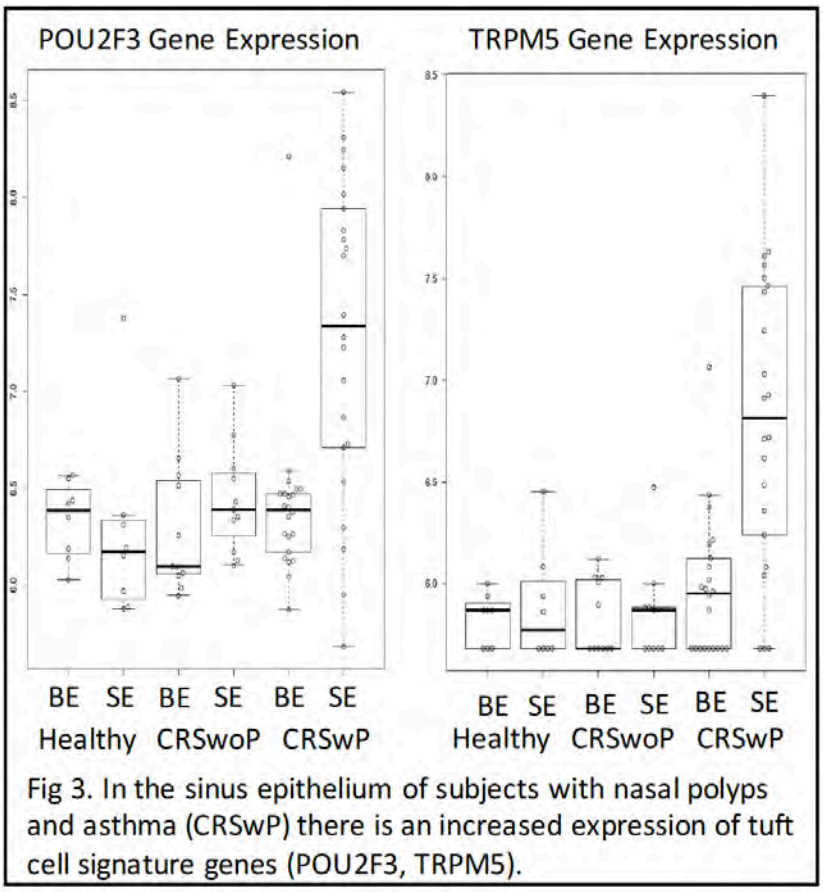

Fig 3. In the sinus epithelium of subjects with nasal polyps and asthma (CRSwP) there is an increased expression of tuft cell signature genes (POU2F3, TRPM5).

signature which is increased in the **sinus epithelium** in subjects with **NP and asthma (Fig 2).** This gene expression module is characterized by increased IL13 signature genes (CDH26, SERPINB2, POSTN, CLCA1, SPDEF), basophil/mast cell genes (CPA3, GATA2, KIT) and the IL-33 and IL-25 receptors (IL1RL1, IL17RB).

Recent studies in mice (3) demonstrate that master epithelial cytokines IL-33, TLSP, and IL-25, are critical upstream drivers of type 2 inflammation. These cytokines stimulate mast cells, basophils, ILC2, and Th2 cells to produce type 2 cytokines. The expression of these cytokines in human disease has been difficult to detect, likely due to a low level of basal expression and transient increases in expression. Our inability to characterize the timing and context of their expression in relationship to disease has hampered drug development efforts. Recently, restricted expression of IL-25 has been demonstrated in a rare chemosensory cell population called tuft cells (4). We hypothesize that tuft cells act as sensors of environmental insults at the respiratory epithelial barrier. Characterizing these cells in humans has been limited by lack of consensus about markers and antibodies as well as their rarity. Indeed, we find a robust gene expression signature of tuft cells (POU2F3, TRPM5) **(Fig 3)** coincident with the type 2 gene expression signature. These genes are increased markedly in the sinus epithelium only in patients with NP. Interestingly, augmented tuft cell-associated transcripts were not observed in the bronchial epithelium of these same patients; this may be explained by distal airway sampling (as tuft cells may be restricted to larger airways), and suggests a unique role of tuft cells in type 2 inflammation in the sinus versus the lower airways.

In order to further study tuft cells in the context of NP we performed single cell RNA sequencing on brushes obtained from 5 subjects with nasal polyps and 4 healthy control subjects. From this data, we identified 15 clusters of epithelial cells encompassing the spectrum of basal (cluster 0, 1, 2 8, 9), secretory (3, 4, 6), goblet (6), and ciliated cells (11,12,13,14) **(Fig 4)**. The cell type percentages in each of these clusters was surprisingly similar between polyp and health with the exception of an expected increase in goblet cells.

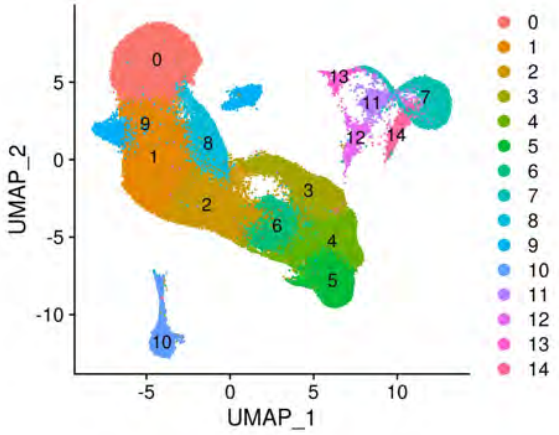

Figure 4: Single cell RNA sequencing reveals 15 clusters of epithelial cells in the sinus epithelium in healthy and nasal polyposis.

Within the initial clustering, we were further able to identify a population of rare cells in cluster 10 which contained markers of tuft cells and ionocytes, and further dissected this population to identify *bona fide* tuft cells using accepted markers that included LRMP, KIT, AVIL, POU2F3, TRPM5. Though tuft cells had previously been observed in sinus tissue using immunofluorescence, transcriptional characterization of this fascinating population has thus far been lacking, presumably due to their relative rarity. Further, we found that these cells were increased in number 2.5 fold in the polyp epithelium compared to healthy epithelium. Moreover, close examination of polyp and healthy tuft cells identified the emergence of a new population of tuft cells only in polyps and absent the healthy controls which were strongly expressing BMX, GNG13, IL17RB, and PTGS1: a key biosynthetic enzyme for the production of prostaglandins **(Fig 5)**. Curiously, many of the genes have been described as consensus tuft cells markers in mice, which suggests a key difference in tuft cell tone in mice and humans that could contribute to the propensity towards type 2 inflammation.

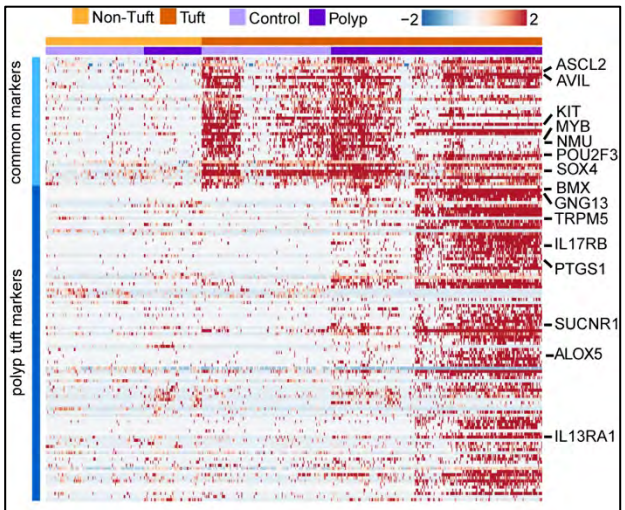

Figure 5: Polyp tuft cells exhibit a unique inflammatory signature, enriched in prostaglandin biosynthetic enzymes

Mouse tuft cells have been reported to produce various prostaglandin species (in addition to leukotrienes, acetylcholine, and IL-25), which may in turn have wide-ranging effects on immune cells and the tissue in which they reside. We observed a novel transcriptional signature across all cell types within the NP epithelium that was not seen in healthy controls, and which we found could be replicated by stimulation with prostaglandin E2 (PGE2). These data suggested that tuft cells in human NP may be producing PGE2 to stimulate the neighboring epithelium. To test this hypothesis, we employed a mouse model of type 2 airway inflammation imparted by treatment with IL-13, and found that this could recreate

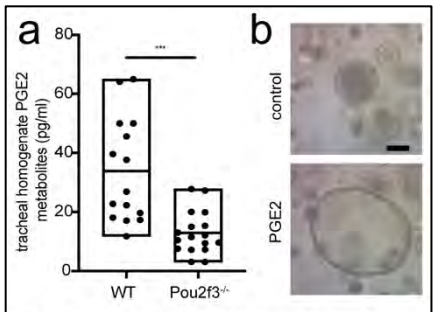

Figure 6: (a) Airway PGE2 production is partially dependent on tuft cells. (b) PGE2 contributes to epithelial organoid remodeling.

expansion of tuft cells with a similar inflammatory profile to those observed in NP patients. And while we could detect PGE2 in airway tissues from wildtype mice treated with IL-13 to expand and activate tuft cells, Pou2f3$^{-/-}$ mice that are genetically deficient in tuft cells had dramatically decreased PGE2 production *in vivo* and *in vitro*. Further, we find that PGE2 treatment of human airway organoids causes architectural remodeling that mimics some aspects of NP formation **(Fig 6)**. These findings point to the tuft cell as the primary source of PGE2 in the respiratory epithelium and suggest a link to the development of polypoid epithelial remodeling in type 2 inflammation.

REFERENCES:

1. Langdon C, Mullol J. Nasal polyps in patients with asthma: prevalence, impact, and management challenges. J Asthma Allergy. 2016; 9:45-53. doi: 10.2147/JAA.S86251. PubMed PMID: 27042129; PMCID: PMC4798207.
2. Larsen K. The clinical relationship of nasal polyps to asthma. Allergy Asthma Proc. 1996;17(5):243-9. PubMed PMID: 8922143.
3. Fahy JV, Locksley RM. The airway epithelium as a regulator of Th2 responses in asthma. American journal of respiratory and critical care medicine. 2011;184(4):390-2. Epub 2011/08/17. doi: 10.1164/rccm.201107-1258ED. PubMed PMID: 21844510.
4. von Moltke J, Ji M, Liang HE, Locksley RM. Tuft-cell-derived IL-25 regulates an intestinal ILC2-epithelial response circuit. Nature. 2016;529(7585):221-5. doi: 10.1038/nature16161. PubMed PMID: 26675736; PMCID: PMC4830391.

CONTRIBUTIONS TO RELEVANT SCIENTIFIC ACTIVITIES

Immunology Seminar Series 2020-2021
Mondays, 9 am

Dates	Speaker	Institution
9/7/20	Labor Day	
9/14/20	Betty Diamond (Wofsy Guest)	*Feinstein Institutes for Medical Research*
9/21/20	Ansuman Satpathy (Gladstone)	*Stanford University*
9/28/20	Jason D. Buenrostro	*Broad Institute/Harvard*
10/5/20	Shane Crotty	*La Jolla Institute for Immunology*
10/12/20	Michael Lenardo (Weiss Guest)	*NIH: NIAID*
10/19/20	Marc K. Jenkins	*University of Minnesota*
10/26/20	Barbara Rehermann	*NIH: NIDDK*
11/2/20	Hongbo Chi	*St. Jude Children's Hospital*
11/9/20	Ivy Dambuza	*University of Exeter*
11/16/20	Joshua Milner	*Columbia University*
11/23/20	Avery August	*Cornell University*
11/30/20	Thanksgiving	
12/7/20	Jessica A. Hamerman	*Benaroya Research Institute*
12/14/20	Sara Suliman	*Brigham and Women Hospital/Harvard Medical School*
12/21/20	Christmas	
12/28/20	Christmas	
1/4/21	New Years	
1/11/21	Christopher K. Glass	*UCSD*
1/18/21	MLK Day	
1/25/21	Anthony Shum	*UCSF*
2/1/21	Boris Reizis	*NYU*
2/8/21	De'Broski R. Herbert	*University of Pennsylvania*
2/15/21	Presidents Day	
2/17/21	Aviv Regev (Gladstone)	*Broad Institute*
2/22/21	David Masopust	*University of Minnesota*
3/1/21	Jose Ordovas-Montanes	*Broad Institute/Boston's Children*
3/8/21	Erin Adams	*University of Chicago*
3/15/21	Lydia Lynch	*Brigham and Women Hospital/Harvard Medical School*
3/22/21	Steffen Jung	*Weizmann Institute of Science*
3/29/21	Alex K. Shalek	*MIT*
4/5/21	Susan Kaech	*Salk Institute*
4/12/21	Sarah L. Gaffen	*University of Pittsburgh*
4/19/21	Tamia A. Harris-Tryon	*UT Southwestern*
4/26/21	Olivia M. Martinez	*Stanford University*
5/3/21	John O'Shea	*NIH: NIAMS*
5/10/21	Vishva Dixit	*Genentech*
5/17/21	Katherine Fitzgerald	*University of Massachusetts*
5/24/21	Michellle Hermiston	*UCSF*
5/31/21	Memorial Day	

2020-21 Clinical and Research Conference Schedule

Clinical Conference 3-4pm, Research Conference 4-5pm

Date	Talk 1	Talk 2	Research	Research	Moderator
09/07/20	**HOLIDAY - LABOR DAY**				
09/14/20	BYANOVA	SUEN	Michael Matthay	Aaron Baugh	Prescott Woodruff
09/21/20	CASILLAS	LEBA	John Fahy	Lekshmi Santhosh	Prescott Woodruff
09/28/20	MCLAFFERTY	BYANOVA	Adithya Cattamanchi	Neeta Thakur	Prescott Woodruff
10/05/20	SULLIVAN	SCHRAUFNAGEL	David Erle	Jonathan Budzik	Dean Shepard
10/12/20	CASILLAS	MCLAFFERTY	Dean Sheppard	Erin Gordon	Mehrdad Arjomandi
10/19/20	SCHRAUFNAGEL	SULLIVAN	Brian Block	Stephanie Christenson	Jon Singer
10/26/20	SUEN	CASILLAS	Payam Nahid	Maya Kotas	Prescott Woodruff
11/02/20	**PULMONARY RESEARCH RETREAT**				
11/09/20	LEBA	MCLAFFERTY	Soledad Reyes De Mochel	Rahul Kumar	Erin Gordon/Nirav Sub
11/16/20	SUEN	BYANOVA	Anthony Shum	Chaoqun Wang	Michael Matthay
11/23/20	Start at 3:30 PM	LEBA	Alyssa Perez	Carlos Castellanos	Neeta Thakur
11/30/20	CASILLAS	SUEN	High Impact Professor: Hal Chapman		Prescott Woodruff
12/07/20	LEBA	SCHRAUFNAGEL	Josh Adler	Survey Results on Diversity	Nirav Bhakta
12/14/20	**F2/F3 FELLOW FEEDBACK SESSION #1**				
12/21/20	**F1 FELLOW FEEDBACK SESSION #1**				
12/28/20	**HOLIDAY - WINTER BREAK**				
01/04/21	MCLAFFERTY	BYANOVA	Paul Wolters	Walter Eckalbar	Neeta Thakur
01/11/21	**FACULTY EXPERT TALK: DAVID CLAMAN**		**Visiting Professor: Renda Wiener (12-1 pm)**		Yaron Gesthalter
01/18/21	**HOLIDAY - MLK JR. DAY**				
01/25/21	SCHRAUFNAGEL	LEBA	Carolyn Calfee	Nicholas Arger	Jon Singer
02/01/21	SULLIVAN	SCHRAUFNAGEL	**CANCELLED: Visiting Professor: Victor Thannickal (1-2 pm)**		Paul Wolters
02/08/21	**FACULTY EXPERT TALK: IRIS OTANI**		Claude Le Saux	Richard Wang	John Fahy
02/15/21	**HOLIDAY - PRESIDENTS' DAY**				
02/22/21	**FACULTY EXPERT TALK: MARY ELLEN KLEINHENZ**		Mallar Bhattacharya	Michael Peters	Prescott Woodruff
03/01/21	**ACGME SURVEY SESSION**		Juan Caraballo	Jonathan Singer	Mehrdad Arjomandi
03/08/21	CASILLAS	BYANOVA	**Visiting Professor: Lisa Young (1-2 pm)**		Hal Chapman
03/15/21	LEBA	MCLAFFERTY	Bhavika Kaul	Aparna Sundaram	Mallar Bhattacharya
03/22/21	SUEN	CASILLAS	**Visiting Professor: Rachel Zemans (1-2 pm)**		Meshell Johnson
03/29/21	**FACULTY EXPERT TALK: LEAH WITT**		Tatsuya Tsukui	John Greenland	Prescott Woodruff
04/05/21	SULLIVAN	SCHRAUFNAGEL	**Visiting Professor: Rosalind Wright (12-1 pm)**		Neeta Thakur
04/12/21	SUEN	BYANOVA	Daniel Calabrese	Vaibhav Upadhyay	Mallar Bhattacharya
04/19/21	MCLAFFERTY	SULLIVAN	Alison Dedent	Michael Podolsky	Mallar Bhattacharya
04/26/21	SCHRAUFNAGEL	CASILLAS	**Visiting Professor: Jay Rajagopal (1-2 pm)**		Tien Peng
05/03/21	SULLIVAN	BYANOVA	Max Krummel	George Hartoularos	Prescott Woodruff
05/10/21	**F2/F3 FELLOW FEEDBACK SESSION #2**				
05/17/21	**ATS**				
05/24/21	**F1 FELLOW FEEDBACK SESSION #2**				
05/31/21	**HOLIDAY - MEMORIAL DAY**				
06/07/21	**FACULTY FEEDBACK & APPRECATION**				
06/14/21	SUEN	LEBA	Luke Bonser	Aartik Sarma	Jon Singer
06/21/21	MCLAFFERTY	SULLIVAN	Jinyoung Lee	Melia Magnen	Jon Singer

SABRE Asthma Research Conference Schedule 2021

Location: all conferences held on Zoom		
Time: 9:00- 10:00AM		
Day: 4th Wednesday of each month (**except Wednesdays that fall on a UCSF holiday*)		
Date	Presenter	Title
2/24/21	Kristina Johansson	*"MicroRNA regulation of airway mucus production".*
3/24/20	K. Mark Ansel, Ph.D.	*Preempted by the Chancellor's Townhall on race*
4/28/20	Jonathan Witonsky	"*Racial/ethnic-based spirometry reference equations: Are they accurate for admixed populations?"*
5/27/20	John Fahy, M.D.	*cancelled*
6/23/21	Allen Lab	
		Summer Break
9/22/20	Richard Locksley, M.D.	
10/27/21	Erin Gordon, M.D.	
11/24/21	Mallar Bhattacharya	

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Harnessing Immunology
To Improve Human Health

ImmunoX Inaugural ECO Seminar

A component of the ImmunoX Seminar Series
Monday 10/12/2020, 9 AM, via Zoom

"Insights into human immune function from a new genetic immunodysregulatory disease"

Michael Lenardo, M.D.

NIH: NIAID

RECENT AND NEW PUBLICATIONS SUPPORTED BY THE SANDLER ASTHMA BASIC RESEARCH CENTER (2019-2021)

Christopher D.C. Allen, Ph.D.

Yang Z, Wu CM, Targ S, **Allen CDC**. IL-21 is a broad negative regulator of IgE class switch recombination in mouse and human B cells. *J Exp Med*. 2020 May 4;217(5): e20190472. doi: 10.1084/jem.20190472. PMID: 32130409

Tang XZ, Jung JB, **Allen CDC**. A case of mistaken identity: The MAR-1 antibody to mouse FcεRIα cross-reacts with FcγRI and FcγRIV. *J Allergy Clin Immunol*. 2019 Apr;143(4):1643-1646.e6. doi: 10.1016/j.jaci.2018.11.045. Epub 2019 Jan 10. PMID: 30639345

Cyster JG, **Allen CDC**. B Cell Responses: Cell Interaction Dynamics and Decisions. *Cell.* 2019 Apr 18;177(3):524-540. doi: 10.1016/j.cell.2019.03.016. Review. PMID: 31002794

Tang XZ, Jung JB, **Allen CDC**. A case of mistaken identity: The MAR-1 antibody to mouse FcεRIα cross-reacts with FcγRI and FcγRIV. *J Allergy Clin Immunol*. 2019 Apr;143(4):1643-1646.e6. doi: 10.1016/j.jaci.2018.11.045. Epub 2019 Jan 10. No abstract available. PMID: 30639345

K. Mark Ansel, Ph.D.

Sarma A, Christenson S, Mick E, Deiss T, DeVoe C, Pisco A, Ghale R, Jauregui A, Byrne A, Moazed F, Spottiswoode N, Sinha P, Zha B, Neff N, Tan M, Serpa PH, **Ansel KM**, Wilson J, Leligdowicz A, Seigel E, Sirota M, DeRisi J, Matthay M, Consortium C, Hendrickson C, Kangelaris K, Krummel M, Woodruff P, Erle D, Calfee C, Langelier C. COVID-19 ARDS is characterized by a dysregulated host response that differs from cytokine storm and is modified by dexamethasone. *Res Sq*. 2021 Jan 14: rs.3.rs-141578. doi: 10.21203/rs.3.rs-141578/v1. Preprint. PMID: 33469573

Wigton EJ, **Ansel KM**. Noncoding RNAs in B cell responses. *RNA Biol*. 2021 Feb 15:1-7. doi: 10.1080/15476286.2021.1885876. Online ahead of print. PMID: 33586605

Taylor KE, **Ansel KM**, Marson A, Criswell LA, Farh KK. PICS2: Next-generation fine mapping via probabilistic identification of causal SNPs. *Bioinformatics*. 2021 Feb 24: btab122. doi: 10.1093/bioinformatics/btab122. Online ahead of print. PMID: 33624747

Durack J, Christian LS, Nariya S, Gonzalez J, Bhakta NR, **Ansel KM**, Beigelman A, Castro M, Dyer AM, Israel E, Kraft M, Martin RJ, Mauger DT, Peters SP, Rosenberg SR, Sorkness CA, Wechsler ME, Wenzel SE, White SR, Lynch SV, Boushey HA, Huang YJ; National Heart, Lung, and Blood Institute's "AsthmaNet". Distinct associations of sputum and oral microbiota with atopic, immunologic, and clinical features in mild asthma. *J Allergy Clin Immunol*. 2020 Nov;146(5):1016-1026. doi: 10.1016/j.jaci.2020.03.028. Epub 2020 Apr 13. PMID: 32298699

Hines MJ, Coffre M, Mudianto T, Panduro M, Wigton EJ, Tegla C, Osorio-Vasquez V, Kageyama R, Benhamou D, Perez O, Bajwa S, McManus MT, **Ansel KM**, Melamed D, Koralov SB. miR-29 Sustains B Cell Survival and Controls Terminal Differentiation via Regulation of PI3K Signaling. *Cell Rep*. 2020 Dec 1;33(9):108436. doi: 10.1016/j.celrep.2020.108436. PMID: 33264610

Mandric I, Rotman J, Yang HT, Strauli N, Montoya DJ, Van Der Wey W, Ronas JR, Statz B, Yao D, Petrova V, Zelikovsky A, Spreafico R, Shifman S, Zaitlen N, Rossetti M, **Ansel KM**, Eskin E, Mangul S. Author Correction: Profiling immunoglobulin repertoires across multiple human tissues using RNA sequencing. *Nat Commun*. 2020 Sep 4;11(1):4499. doi: 10.1038/s41467-020-18509-2. PMID: 32887888

Mandric I, Rotman J, Yang HT, Strauli N, Montoya DJ, Van Der Wey W, Ronas JR, Statz B, Yao D, Petrova V, Zelikovsky A, Spreafico R, Shifman S, Zaitlen N, Rossetti M, **Ansel KM**, Eskin E, Mangul S. Profiling immunoglobulin repertoires across multiple human tissues using RNA sequencing. *Nat Commun*. 2020 Jun 19;11(1):3126. doi: 10.1038/s41467-020-16857-7. PMID: 32561710

Hines MJ, Coffre M, Mudianto T, Panduro M, Wigton EJ, Tegla C, Osorio-Vasquez V, Kageyama R, Benhamou D, Perez O, Bajwa S, McManus MT, **Ansel KM**, Melamed D, Koralov SB. miR-29 Sustains B Cell Survival and Controls Terminal Differentiation via Regulation of PI3K Signaling. *Cell Rep*. 2020 Dec 1;33(9):108436. doi: 10.1016/j.celrep.2020.108436. PMID: 33264610

Mandric I, Rotman J, Yang HT, Strauli N, Montoya DJ, Van Der Wey W, Ronas JR, Statz B, Yao D, Petrova V, Zelikovsky A, Spreafico R, Shifman S, Zaitlen N, Rossetti M, **Ansel KM**, Eskin E, Mangul S. Author Correction: Profiling immunoglobulin repertoires across multiple human tissues using RNA sequencing. *Nat Commun*. 2020 Sep 4;11(1):4499. doi: 10.1038/s41467-020-18509-2. PMID: 32887888

Chatrikhi R, Mallory MJ, Gazzara MR, Agosto LM, Zhu WS, Litterman AJ, **Ansel KM**, Lynch KW. RNA Binding Protein CELF2 Regulates Signal-Induced Alternative Polyadenylation by Competing with Enhancers of the Polyadenylation Machinery. *Cell Rep*. 2019 Sep 10;28(11):2795-2806.e3. doi: 10.1016/j.celrep.2019.08.022. PMID: 31509743

Wigton EJ, DeFranco AL, **Ansel KM**. Antigen Complexed with a TLR9 Agonist Bolsters c-Myc and mTORC1 Activity in Germinal Center B Lymphocytes. *Immunohorizons*. 2019 Aug 19;3(8):389-401. doi: 10.4049/immunohorizons.1900030. PMID: 31427364

Litterman AJ, Kageyama R, Le Tonqueze O, Zhao W, Gagnon JD, Goodarzi H, Erle DJ, **Ansel KM**. A massively parallel 3' UTR reporter assay reveals relationships between nucleotide content, sequence conservation, and mRNA destabilization. *Genome Res*. 2019 Jun;29(6):896-906. doi: 10.1101/gr.242552.118. Epub 2019 May 31. PMID: 31152051

Gagnon JD, **Ansel KM**. MicroRNA regulation of CD8+ T cell responses. Noncoding RNA Investig. 2019 Aug;3. pii: 24. doi: 10.21037/ncri.2019.07.02. Epub 2019 Aug 26. PMID: 31844841

Krummel M, Blish C, Kuhns M, Cadwell K, Oberst A, Goldrath A, **Ansel KM**, Chi H, O'Connell R, Wherry EJ, Pepper M; Future Immunology Consortium. Universal Principled Review: A Community-Driven Method to Improve Peer Review. *Cell*. 2019 Dec 12;179(7):1441-1445. doi: 10.1016/j.cell.2019.11.029. PMID: 31835023

Chatrikhi R, Mallory MJ, Gazzara MR, Agosto LM, Zhu WS, Litterman AJ, **Ansel KM**, Lynch KW. RNA Binding Protein CELF2 Regulates Signal-Induced Alternative Polyadenylation by Competing with Enhancers of the Polyadenylation Machinery. *Cell Rep*. 2019 Sep 10;28(11):2795-2806.e3. doi: 10.1016/j.celrep.2019.08.022. PMID: 31509743

Gagnon JD, Kageyama R, Shehata HM, Fassett MS, Mar DJ, Wigton EJ, Johansson K, Litterman AJ, Odorizzi P, Simeonov D, Laidlaw BJ, Panduro M, Patel S, Jeker LT, Feeney ME, McManus MT, Marson A, Matloubian M, Sanjabi S, **Ansel KM**. miR-15/16 Restrain Memory T Cell Differentiation, Cell Cycle, and Survival. *Cell Rep*. 2019 Aug 20;28(8):2169-2181.e4. doi: 10.1016/j.celrep.2019.07.064. PMID: 31433990

Wigton EJ, DeFranco AL, Ansel KM. Antigen Complexed with a TLR9 Agonist Bolsters c-Myc and mTORC1 Activity in Germinal Center B Lymphocytes. Immunohorizons. 2019 Aug 19;3(8):389-401. doi: 10.4049/immunohorizons.1900030. PMID: 31427364
Litterman AJ, Kageyama R, Le Tonqueze O, Zhao W, Gagnon JD, Goodarzi H, Erle DJ, **Ansel KM**. A massively parallel 3' UTR reporter assay reveals relationships between nucleotide content, sequence conservation, and mRNA destabilization. *Genome Res.* 2019 Jun;29(6):896-906. doi: 10.1101/gr.242552.118. Epub 2019 May 31. PMID: 31152051
Das S; Extracellular RNA Communication Consortium, **Ansel KM,** Bitzer M, Breakefield XO, Charest A, Galas DJ, Gerstein MB, Gupta M, Milosavljevic A, McManus MT, Patel T, Raffai RL, Rozowsky J, Roth ME, Saugstad JA, Van Keuren-Jensen K, Weaver AM, Laurent LC. The Extracellular RNA Communication Consortium: Establishing Foundational Knowledge and Technologies for Extracellular RNA Research. *Cell*. 2019 Apr 4;177(2):231-242. doi: 10.1016/j.cell.2019.03.023. Review. PMID: 30951667
Das S; Extracellular RNA Communication Consortium, **Ansel KM**, Bitzer M, Breakefield XO, Charest A, Galas DJ, Gerstein MB, Gupta M, Milosavljevic A, McManus MT, Patel T, Raffai RL, Rozowsky J, Roth ME, Saugstad JA, Van Keuren-Jensen K, Weaver AM, Laurent LC. The Extracellular RNA Communication Consortium: Establishing Foundational Knowledge and Technologies for Extracellular RNA Research. *Cell*. 2019 Apr 4;177(2):231-242. doi: 10.1016/j.cell.2019.03.023. Review. PMID:30951667
Pua HH, Happ HC, Gray CJ, Mar DJ, Chiou NT, Hesse LE, **Ansel KM.** Increased Hematopoietic Extracellular RNAs and Vesicles in the Lung during Allergic Airway Responses. *Cell Rep*. 2019 Jan 22;26(4):933-944.e4. doi: 10.1016/j.celrep.2019.01.002. PMID:30673615
Krummel M, Blish C, Kuhns M, Cadwell K, Oberst A, Goldrath A, **Ansel KM**, Chi H, O'Connell R, Wherry EJ, Pepper M; Future Immunology Consortium Universal Principled Review: A Community-Driven Method to Improve Peer Review. *Cell*. 2019 Dec 12;179(7):1441-1445. doi: 10.1016/j.cell.2019.11.029. PMID: 31835023
Pua HH, Happ HC, Gray CJ, Mar DJ, Chiou NT, Hesse LE, **Ansel KM**. Increased Hematopoietic Extracellular RNAs and Vesicles in the Lung during Allergic Airway Responses. *Cell Rep*. 2019 Jan 22;26(4):933-944.e4. doi: 10.1016/j.celrep.2019.01.002. PMID: 30673615
Pua HH, Happ HC, Gray CJ, Mar DJ, Chiou NT, Hesse LE, **Ansel KM**. Increased Hematopoietic Extracellular RNAs and Vesicles in the Lung during Allergic Airway Responses. *Cell Rep*. 2019 Jan 22;26(4):933-944.e4. doi: 10.1016/j.celrep.2019.01.002. PMID: 30673615

Nirav Rati Bhakta, M.D., Ph.D.

Bunis DG, Bronevetsky Y, Krow-Lucal E, **Bhakta NR**, Kim CC, Nerella S, Jones N, Mendoza VF, Bryson YJ, Gern JE, Rutishauser RL, Ye CJ, Sirota M, McCune JM, Burt TD. Single-Cell Mapping of Progressive Fetal-to-Adult Transition in Human Naive T Cells. *Cell Rep*. 2021 Jan 5;34(1):108573. doi: 10.1016/j.celrep.2020.108573.PMID: 33406429
Fortis S, Comellas A, Bhatt SP, Hoffman EA, Han MK, **Bhakta NR**, Paine R 3rd, Ronish B, Kanner RE, Dransfield M, Hoesterey D, Buhr RG, Barr RG, Dolezal B, Ortega VE, Drummond MB, Arjomandi M, Kaner RJ, Kim V, Curtis JL, Bowler RP, Martinez F, Labaki WW, Cooper CB, O'Neal WK, Criner G, Hansel NN, Krishnan JA, Woodruff P, Couper D,

Tashkin D, Barjaktarevic I. Ratio of Forced Expiratory Volume in 1 second /Slow Vital Capacity (FEV1/SVC)<0.7 is associated with clinical, functional, and radiologic features of obstructive lung disease in smokers with preserved lung function. *Chest*. 2021 Feb 1: S0012-3692(21)00229-4. doi: 10.1016/j.chest.2021.01.067. Online ahead of print. PMID: 33539837

Borrell LN, Elhawary JR, Fuentes-Afflick E, Witonsky J, **Bhakta N**, Wu AHB, Bibbins-Domingo K, Rodríguez-Santana JR, Lenoir MA, Gavin JR 3rd, Kittles RA, Zaitlen NA, Wilkes DS, Powe NR, Ziv E, Burchard EG. Race and Genetic Ancestry in Medicine - A Time for Reckoning with Racism. *N Engl J Med.* 2021 Feb 4;384(5):474-480. doi: 10.1056/NEJMms2029562. Epub 2021 Jan 6. PMID: 33406325

Vempilly JJ, Abejie BA, Rashidian A, Jain VV, **Bhakta N.** Air Trapping Correlates with Increased Frequency of Albuterol Use and Severity of Wheeze in Persistent Asthma. *Respir Care.* 2020 Feb 4. pii: respcare.07288. doi: 10.4187/respcare.07288. [Epub ahead of print] PMID: 32019852

Bodduluri S, Nakhmani A, Reinhardt JM, Wilson CG, McDonald ML, Rudraraju R, Jaeger BC, **Bhakta NR**, Castaldi PJ, Sciurba FC, Zhang C, Bangalore PV, Bhatt SP. Deep neural network analyses of spirometry for structural phenotyping of chronic obstructive pulmonary disease. *JCI Insight*. 2020 Jul 9;5(13): e132781. doi: 10.1172/jci.insight.132781.PMID: 32554922

Vempilly JJ, Abejie BA, Rashidian A, Jain VV, **Bhakta N**. Air Trapping Correlates with Increased Frequency of Albuterol Use and Severity of Wheeze in Persistent Asthma. *Respir Care*. 2020 Jul;65(7):994-1000. doi: 10.4187/respcare.07288. Epub 2020 Feb 4. PMID: 32019852

Wilson KC, Kaminsky DA, Michaud G, Sharma S, Nici L, Folz RJ, Barjaktarevic I, **Bhakta NR**, Cheng G, Chupp GL, Cole A, Dixon AE, Finigan JH, Graham B, Hallstrand TS, Haynes J, Hankinson J, MacIntyre N, Mandel J, McCarthy K, McCormack M, Patil SP, Rosenfeld M, Senitko M, Sethi S, Swenson ER, Stanojevic S, Teodorescu M, Weiner DJ, Wiener RS, Powell CA. Restoring Pulmonary and Sleep Services as the COVID-19 Pandemic Lessens. From an Association of Pulmonary, Critical Care, and Sleep Division Directors and American Thoracic Society-coordinated Task Force*Ann Am Thorac Soc*. 2020 Nov;17(11):1343-1351. doi: 10.1513 . *AnnalsATS*.202005-514TH. PMID: 32663071

Durack J, Christian LS, Nariya S, Gonzalez J, **Bhakta NR**, Ansel KM, Beigelman A, Castro M, Dyer AM, Israel E, Kraft M, Martin RJ, Mauger DT, Peters SP, Rosenberg SR, Sorkness CA, Wechsler ME, Wenzel SE, White SR, Lynch SV, Boushey HA, Huang YJ; National Heart, Lung, and Blood Institute's "AsthmaNet". Distinct associations of sputum and oral microbiota with atopic, immunologic, and clinical features in mild asthma. *J Allergy Clin Immunol*. 2020 Nov;146(5):1016-1026. doi: 10.1016/j.jaci.2020.03.028. Epub 2020 Apr 13. PMID: 32298699

Barjaktarevic IZ, Buhr RG, Wang X, Hu S, Couper D, Anderson W, Kanner RE, Paine Iii R, Bhatt SP, **Bhakta NR**, Arjomandi M, Kaner RJ, Pirozzi CS, Curtis JL, O'Neal WK, Woodruff PG, Han MK, Martinez FJ, Hansel N, Wells JM, Ortega VE, Hoffman EA, Doerschuk CM, Kim V, Dransfield MT, Drummond MB, Bowler R, Criner G, Christenson SA, Ronish B, Peters SP, Krishnan JA, Tashkin DP, Cooper CB; Clinical Significance of Bronchodilator Responsiveness Evaluated by Forced Vital Capacity in COPD: SPIROMICS Cohort Analysis. NHLBI SubPopulations and InteRmediate Outcome Measures in COPD Study (SPIROMICS). *Int J Chron Obstruct Pulmon Dis*. 2019 Dec 20; 14:2927-2938. doi: 10.2147/COPD.S220164. eCollection 2019. PMID: 31908441

Nakada EM, **Bhakta NR**, Korwin-Mihavics BR, Kumar A, Chamberlain N, Bruno SR, Chapman DG, Hoffman SM, Daphtary N, Aliyeva M, Irvin CG, Dixon AE, Woodruff PG, Amin S, Poynter ME, Desai DH, Anathy V. Conjugated bile acids attenuate allergen-induced airway inflammation and hyperresponsiveness by inhibiting UPR transducers. *JCI Insight.* 2019 May 2;4(9). pii: 98101. doi: 10.1172/jci.insight.98101. eCollection 2019 May 2. PMID: 31045581

Bhatt SP, Bodduluri S, Raghav V, **Bhakta NR**, Wilson CG, Kim YI, Eberlein M, Sciurba FC, Han MK, Dransfield MT, Nakhmani A; COPDGene Investigators. The Peak Index: Spirometry Metric for Airflow Obstruction Severity and Heterogeneity. *Ann Am Thorac Soc*. 2019 Mar 13. doi: 10.1513/AnnalsATS.201811-812OC. [Epub ahead of print]. PMID: 30865842

Christenson SA, van den Berge M, Faiz A, Inkamp K, **Bhakta N,** Bonser LR, Zlock LT, Barjaktarevic IZ, Barr RG, Bleecker ER, Boucher RC, Bowler RP, Comellas AP, Curtis JL, Han MK, Hansel NN, Hiemstra PS, Kaner RJ, Krishnanm JA, Martinez FJ, O'Neal WK, Paine R 3rd, Timens W, Wells JM, Spira A, Erle DJ, Woodruff PG. An airway epithelial IL-17A response signature identifies a steroid-unresponsive COPD patient subgroup. *J Clin Invest.* 2019 Jan 2;129(1):169-181. doi: 10.1172/JCI121087. Epub 2018 Nov 26. PMID: 30383540

Christenson SA, van den Berge M, Faiz A, Inkamp K, **Bhakta N**, Bonser LR, Zlock LT, Barjaktarevic IZ, Barr RG, Bleecker ER, Boucher RC, Bowler RP, Comellas AP, Curtis JL, Han MK, Hansel NN, Hiemstra PS, Kaner RJ, Krishnanm JA, Martinez FJ, O'Neal WK, Paine R 3rd, Timens W, Wells JM, Spira A, Erle DJ, Woodruff PG. An airway epithelial IL-17A response signature identifies a steroid-unresponsive COPD patient subgroup. *J Clin Invest*. 2019 Jan 2;129(1):169-181. doi: 10.1172/JCI121087. Epub 2018 Nov 26. PMID: 30383540

Barjaktarevic IZ, Buhr RG, Wang X, Hu S, Couper D, Anderson W, Kanner RE, Paine Iii R, Bhatt SP, **Bhakta NR**, Arjomandi M, Kaner RJ, Pirozzi CS, Curtis JL, O'Neal WK, Woodruff PG, Han MK, Martinez FJ, Hansel N, Wells JM, Ortega VE, Hoffman EA, Doerschuk CM, Kim V, Dransfield MT, Drummond MB, Bowler R, Criner G, Christenson SA, Ronish B, Peters SP, Krishnan JA, Tashkin DP, Cooper CB; NHLBI SubPopulations and InteRmediate Outcome Measures in COPD Study (SPIROMICS). Clinical Significance of Bronchodilator Responsiveness Evaluated by Forced Vital Capacity in COPD: SPIROMICS Cohort Analysis. *Int J Chron Obstruct Pulmon Dis.* 2019 Dec 20; 14:2927-2938. doi: 10.2147/COPD.S220164. eCollection 2019. PMID: 31908441

Bhatt SP, Bodduluri S, Raghav V, **Bhakta NR**, Wilson CG, Kim YI, Eberlein M, Sciurba FC, Han MK, Dransfield MT, Nakhmani A. The Peak Index: Spirometry Metric for Airflow Obstruction Severity and Heterogeneity. *Ann Am Thorac Soc*. 2019 Aug;16(8):982-989. doi: 10.1513/AnnalsATS.201811-812OC. PMID: 30865842

Nakada EM, **Bhakta NR**, Korwin-Mihavics BR, Kumar A, Chamberlain N, Bruno SR, Chapman DG, Hoffman SM, Daphtary N, Aliyeva M, Irvin CG, Dixon AE, Woodruff PG, Amin S, Poynter ME, Desai DH, Anathy V. Conjugated bile acids attenuate allergen-induced airway inflammation and hyperresponsiveness by inhibiting UPR transducers. *JCI Insight*. 2019 May 2;4(9): e98101. doi: 10.1172/jci.insight.98101. eCollection 2019 May 2. PMID: 31045581

Mallar Bhattacharya, M.D., MSc.

Aran D, Looney AP, Liu L, Wu E, Fong V, Hsu A, Chak S, Naikawadi RP, Wolters PJ, Abate A, Butte AJ, **Bhattacharya M**. (2019) Reference-based analysis of lung single cell RNA-seq reveals a transitional profibrotic macrophage. *Nature Immunology*. Feb;20(2):163-172. PMID: 30643263.

Alam Z, Devalaraja S, Li M, To TKJ, Folkert IW, Mitchell-Velasquez E, Dang MT, Young P, Wilbur CJ, Silverman MA, Li X, Chen YH, Hernandez PT, Bhattacharyya A, Bhattacharya M, Levine MH, Haldar M. Counter Regulation of Spic by NF-κB and STAT Signaling Controls Inflammation and Iron Metabolism in Macrophages. *Cell Rep.* 2020 Jun 30;31(13):107825. doi: 10.1016/j.celrep.2020.107825.PMID: 32610126

Looney AP, **Bhattacharya M**., Fibroblast Gap-closure Assay-Microscopy-based in vitro Assay Measuring the Migration of Murine Fibroblasts. *Bio Protoc*. 2019 Aug 20;9(16). pii: e3333. doi: 10.21769/BioProtoc.3333. PMID: 31531389

Aran D, Looney AP, Liu L, Wu E, Fong V, Hsu A, Chak S, Naikawadi RP, Wolters PJ, Abate AR, Butte AJ, **Bhattacharya M**. Reference-based analysis of lung single-cell sequencing reveals a transitional profibrotic macrophage. *Nat Immunol*. 2019 Feb;20(2):163-172. doi: 10.1038/s41590-018-0276-y. Epub 2019 Jan 14.
PMID: 30643263

Homer Boushey, M.D.

Ober C, McKennan CG, Magnaye KM, Altman MC, Washington C 3rd, Stanhope C, Naughton KA, Rosasco MG, Bacharier LB, Billheimer D, Gold DR, Gress L, Hartert T, Havstad S, Khurana Hershey GK, Hallmark B, Hogarth DK, Jackson DJ, Johnson CC, Kattan M, Lemanske RF, Lynch SV, Mendonca EA, Miller RL, Naureckas ET, O'Connor GT, Seroogy CM, Wegienka G, White SR, Wood RA, Wright AL, Zoratti EM, Martinez FD, Ownby D, Nicolae DL, Levin AM, Gern JE; Environmental Influences on Child Health Outcomes-Children's Respiratory Research Workgroup. Expression quantitative trait locus fine mapping of the 17q12-21 asthma locus in African American children: a genetic association and gene expression study. *Lancet Respir Med*. 2020 May;8(5):482-492. doi: 10.1016/S2213-2600(20)30011-4. PMID: 32380068

Durack J, Christian LS, Nariya S, Gonzalez J, Bhakta NR, Ansel KM, Beigelman A, Castro M, Dyer AM, Israel E, Kraft M, Martin RJ, Mauger DT, Peters SP, Rosenberg SR, Sorkness CA, Wechsler ME, Wenzel SE, White SR, Lynch SV, **Boushey HA**, Huang YJ; National Heart, Lung, and Blood Institute's" AsthmaNet ". Distinct associations of sputum and oral microbiota with atopic, immunologic, and clinical features in mild asthma. *J Allergy Clin Immunol*. 2020 Nov;146(5):1016-1026. doi: 10.1016/j.jaci.2020.03.028. Epub 2020 Apr 13.
PMID: 32298699

Mitchell JP, Berlinski A, Canisius S, Cipolla D, Dolovich MB, Gonda I, Hochhaus G, Kadrichu N, Lyapustina S, Mansour HM, Darquenne C, Clark AR, Newhouse M, Ehrmann S, Humphries R, **Boushey H**. Urgent Appeal from International Society for Aerosols in Medicine (ISAM) During COVID-19: Clinical Decision Makers and Governmental Agencies Should Consider the Inhaled Route of Administration: A Statement from the ISAM Regulatory and Standardization Issues Networking Group. *J Aerosol Med Pulm Drug Deliv*. 2020 Aug;33(4):235-238. doi: 10.1089/jamp.2020.1622. Epub 2020 Jun 23.
PMID: 32589076

Zhou Y, Jackson D, Bacharier LB, Mauger D, **Boushey H**, Castro M, Durack J, Huang Y, Lemanske RF Jr, Storch GA, Weinstock GM, Wylie K, Covar R, Fitzpatrick AM, Phipatanakul W, Robison RG, Beigelman A. The upper-airway microbiota and loss of asthma control among asthmatic children. *Nat Commun*. 2019 Dec 16;10(1):5714. doi: 10.1038/s41467-019-13698-x. PMID: 31844063

Levan SR, Stamnes KA, Lin DL, Panzer AR, Fukui E, McCauley K, Fujimura KE, McKean M, Ownby DR, Zoratti EM, **Boushey HA**, Cabana MD, Johnson CC, Lynch SV. Author Correction: Elevated faecal 12,13-diHOME concentration in neonates at high risk for asthma is produced by gut bacteria and impedes immune tolerance. *Nat Microbiol.* 2019 Nov;4(11):2020. doi: 10.1038/s41564-019-0574-7. PMID: 31492948

Levan SR, Stamnes KA, Lin DL, Panzer AR, Fukui E, McCauley K, Fujimura KE, McKean M, Ownby DR, Zoratti EM, **Boushey HA**, Cabana MD, Johnson CC, Lynch SV. Elevated faecal 12,13-diHOME concentration in neonates at high risk for asthma is produced by gut bacteria and impedes immune tolerance. *Nat Microbiol*. 2019 Nov;4(11):1851-1861. doi: 10.1038/s41564-019-0498-2. Epub 2019 Jul 22. Erratum in: *Nat Microbiol*. 2019 Sep 6;. PMID: 31332384

Cardet JC, Jiang X, Lu Q, Gerard N, McIntire K, **Boushey HA**, Castro M, Chinchilli VM, Codispoti CD, Dyer AM, Holguin F, Kraft M, Lazarus S, Lemanske RF, Lugogo N, Mauger D, Moore WC, Moy J, Ortega VE, Peters SP, Smith LJ, Solway J, Sorkness CA, Sumino K, Wechsler ME, Wenzel S, Israel E; AsthmaNet Investigators. Loss of bronchoprotection with ICS+LABA, beta-receptor dynamics, and the effect of alendronate. *J Allergy Clin Immunol*. 2019 Mar 11. pii: S0091-6749(19)30347-1. doi: 10.1016/j.jaci.2019.01.049. [Epub ahead of print]. PMID: 30872116

Bacharier LB, Beigelman A, Calatroni A, Jackson DJ, Gergen PJ, O'Connor GT, Kattan M, Wood RA, Sandel MT, Lynch SV, Fujimura KE, Fadrosh DW, Santee CA, **Boushey H**, Visness CM, Gern JE; NIAID sponsored Inner-City Asthma Consortium. Longitudinal Phenotypes of Respiratory Health in a High-Risk Urban Birth Cohort. *Am J Respir Crit Care Med*. 2019 Jan 1;199(1):71-82. doi: 10.1164/rccm.201801-0190OC.

Lazarus SC, Krishnan JA, King TS, Lang JE, Blake KV, Covar R, Lugogo N, Wenzel S, Chinchilli VM, Mauger DT, Dyer AM, **Boushey HA**, Fahy JV, Woodruff PG, Bacharier LB, Cabana MD, Cardet JC, Castro M, Chmiel J, Denlinger L, DiMango E, Fitzpatrick AM, Gentile D, Hastie A, Holguin F, Israel E, Jackson D, Kraft M, LaForce C, Lemanske RF Jr, Martinez FD, Moore W, Morgan WJ, Moy JN, Myers R, Peters SP, Phipatanakul W, Pongracic JA, Que L, Ross K, Smith L, Szefler SJ, Wechsler ME, Sorkness CA; National Heart, Lung, and Blood Institute AsthmaNet. Mometasone or Tiotropium in Mild Asthma with a Low Sputum Eosinophil Level. *N Engl J Med*. 2019 May 23;380(21):2009-2019. doi: 10.1056/NEJMoa1814917. Epub 2019 May 19. PMID: 31112384

McCauley K, Durack J, Valladares R, Fadrosh DW, Lin DL, Calatroni A, LeBeau PK, Tran HT, Fujimura KE, LaMere B, Merana G, Lynch K, Cohen RT, Pongracic J, Khurana Hershey GK, Kercsmar CM, Gill M, Liu AH, Kim H, Kattan M, Teach SJ, Togias A, **Boushey HA**, Gern JE, Jackson DJ, Lynch SV; National Institute of Allergy and Infectious Diseases–sponsored Inner-City Asthma Consortium. Distinct nasal airway bacterial microbiotas differentially relate to exacerbation in pediatric patients with asthma. *J Allergy Clin Immunol*. 2019 Nov;144(5):1187-1197. doi: 10.1016/j.jaci.2019.05.035. Epub 2019 Jun 13. PMID: 31201890

Bacharier LB, Beigelman A, Calatroni A, Jackson DJ, Gergen PJ, O'Connor GT, Kattan M, Wood RA, Sandel MT, Lynch SV, Fujimura KE, Fadrosh DW, Santee CA, **Boushey H**, Visness CM, Gern JE; NIAID sponsored Inner-City Asthma Consortium. Longitudinal Phenotypes of Respiratory Health in a High-Risk Urban Birth Cohort. *Am J Respir Crit Care Med.* 2019 Jan 1;199(1):71-82. doi: 10.1164/rccm.201801-0190OC.PMID: 30079758
Boushey H, Gonda I. Comment on Increased Risk of COVID-19 Among Users of Proton Pump Inhibitors. *Am J Gastroenterol*. 2020 Nov;115(11):1921. doi: 10.14309/ajg.0000000000001014.PMID: 33156117
Cardet JC, Jiang X, Lu Q, Gerard N, McIntire K, **Boushey HA**, Castro M, Chinchilli VM, Codispoti CD, Dyer AM, Holguin F, Kraft M, Lazarus S, Lemanske RF, Lugogo N, Mauger D, Moore WC, Moy J, Ortega VE, Peters SP, Smith LJ, Solway J, Sorkness CA, Sumino K, Wechsler ME, Wenzel S, Israel E; AsthmaNet Investigators. Loss of bronchoprotection with ICS plus LABA treatment, β-receptor dynamics, and the effect of alendronate. *J Allergy Clin Immunol*. 2019 Aug;144(2):416-425.e7. doi: 10.1016/j.jaci.2019.01.049. Epub 2019 Mar 11. PMID: 30872116

Esteban G. Burchard, M.D., M.P.H.
Reiner AP, Raffield LM, Franceschini N, Auer PL, Lange EM, Nickerson DA, Zakai NA, Correa A, Olson N; National Heart, Lung, and Blood Institute Trans-Omics for Precision Medicine Consortium; National Heart, Lung, and Blood Institute Trans-Omics for Precision Medicine Consortium. Effect of Sickle Cell Trait and APOL1 Genotype on the Association of Soluble uPAR with Kidney Function Measures in Black Americans. *Clin J Am Soc Nephrol*. 2021 Feb 8;16(2):287-289. doi: 10.2215/CJN.12100720. Epub 2020 Dec 2. PMID: 33268503
Gui H, Levin AM, Hu D, Sleiman P, Xiao S, Mak ACY, Yang M, Barczak AJ, Huntsman S, Eng C, Hochstadt S, Zhang E, Whitehouse K, Simons S, Cabral W, Takriti S, Abecasis G, Blackwell TW, Kang HM, Nickerson DA, Germer S, Lanfear DE, Gilliland F, Gauderman WJ, Kumar R, Erle DJ, Martinez FD, Hakonarson H, **Burchard EG**, Williams LK. Mapping the 17q12-21.1 Locus for Variants Associated with Early-Onset Asthma in African Americans. *Am J Respir Crit Care Med*. 2021 Feb 15;203(4):424-436. doi: 10.1164/rccm.202006-2623OC.PMID: 32966749
Taliun D, Harris DN, Kessler MD, Carlson J, Szpiech ZA, Torres R, Taliun SAG, Corvelo A, Gogarten SM, Kang HM, Pitsillides AN, LeFaive J, Lee SB, Tian X, Browning BL, Das S, Emde AK, Clarke WE, Loesch DP, Shetty AC, Blackwell TW, Smith AV, Wong Q, Liu X, Conomos MP, Bobo DM, Aguet F, Albert C, Alonso A, Ardlie KG, Arking DE, Aslibekyan S, Auer PL, Barnard J, Barr RG, Barwick L, Becker LC, Beer RL, Benjamin EJ, Bielak LF, Blangero J, Boehnke M, Bowden DW, Brody JA, **Burchard EG**, Cade BE, Casella JF, Chalazan B, Chasman DI, Chen YI, Cho MH, Choi SH, Chung MK, Clish CB, Correa A, Curran JE, Custer B, Darbar D, Daya M, de Andrade M, DeMeo DL, Dutcher SK, Ellinor PT, Emery LS, Eng C, Fatkin D, Fingerlin T, Forer L, Fornage M, Franceschini N, Fuchsberger C, Fullerton SM, Germer S, Gladwin MT, Gottlieb DJ, Guo X, Hall ME, He J, Heard-Costa NL, Heckbert SR, Irvin MR, Johnsen JM, Johnson AD, Kaplan R, Kardia SLR, Kelly T, Kelly S, Kenny EE, Kiel DP, Klemmer R, Konkle BA, Kooperberg C, Köttgen A, Lange LA, Lasky-Su J, Levy D, Lin X, Lin KH, Liu C, Loos RJF, Garman L, Gerszten R, Lubitz SA, Lunetta KL, Mak ACY, Manichaikul A, Manning AK, Mathias RA, McManus DD, McGarvey ST, Meigs JB, Meyers DA, Mikulla JL, Minear MA, Mitchell BD, Mohanty

S, Montasser ME, Montgomery C, Morrison AC, Murabito JM, Natale A, Natarajan P, Nelson SC, North KE, O'Connell JR, Palmer ND, Pankratz N, Peloso GM, Peyser PA, Pleiness J, Post WS, Psaty GR, Rotter BM, Rao DC, Redline S, Reiner AP, Roden D, Rotter JI, Ruczinski I, Sarnowski C, Schoenherr S, Schwartz DA, Seo JS, Seshadri S, Sheehan VA, Sheu WH, Shoemaker MB, Smith NL, Smith JA, Sotoodehnia N, Stilp AM, Tang W, Taylor KD, Telen M, Thornton TA, Tracy RP, Van Den Berg DJ, Vasan RS, Viaud-Martinez KA, Vrieze S, Weeks DE, Weir BS, Weiss ST, Weng LC, Willer CJ, Zhang Y, Zhao X, Arnett DK, Ashley-Koch AE, Barnes KC, Boerwinkle E, Gabriel S, Gibbs R, Rice KM, Rich SS, Silverman EK, Qasba P, Gan W; NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium, Papanicolaou GJ, Nickerson DA, Browning SR, Zody MC, Zöllner S, Wilson JG, Cupples LA, Laurie CC, Jaquish CE, Hernandez RD, O'Connor TD, Abecasis GR. Sequencing of 53,831 diverse genomes from the NHLBI TOPMed Program. *Nature*. 2021 Feb;590(7845):290-299. doi: 10.1038/s41586-021-03205-y. Epub 2021 Feb 10. PMID: 33568819

Contreras MG, Keys K, Magaña J, Goddard PC, Risse-Adams O, Zeiger AM, Mak ACY, Samedy-Bates LA, Neophytou AM, Lee E, Thakur N, Elhawary JR, Hu D, Huntsman S, Eng C, Hu T, **Burchard EG**, White MJ. Native American Ancestry and Air Pollution Interact to Impact Bronchodilator Response in Puerto Rican Children with Asthma. *Ethn Dis*. 2021 Jan 21;31(1):77-88. doi: 10.18865/ed.31.1.77. eCollection 2021 Winter.PMID: 33519158

Herrera-Luis E, Espuela-Ortiz A, Lorenzo-Diaz F, Keys KL, Mak ACY, Eng C, Huntsman S, Villar J, Rodriguez-Santana JR, **Burchard EG**, Pino-Yanes M. Genome-wide association study reveals a novel locus for asthma with severe exacerbations in diverse populations. *Pediatr Allergy Immunol*. 2021 Jan;32(1):106-115. doi: 10.1111/pai.13337. Epub 2020 Sep 14. PMID: 32841424

Borrell LN, Elhawary JR, Fuentes-Afflick E, Witonsky J, Bhakta N, Wu AHB, Bibbins-Domingo K, Rodríguez-Santana JR, Lenoir MA, Gavin JR 3rd, Kittles RA, Zaitlen NA, Wilkes DS, Powe NR, Ziv E, **Burchard EG**. Race and Genetic Ancestry in Medicine - A Time for Reckoning with Racism. *N Engl J Med*. 2021 Feb 4;384(5):474-480. doi: 10.1056/NEJMms2029562. Epub 2021 Jan 6. PMID: 33406325

Herrera-Luis E, Lorenzo-Diaz F, Samedy-Bates LA, Eng C, Villar J, Rodriguez-Santana JR, **Burchard EG,** Pino-Yanes M. A deoxyribonuclease 1-like 3 genetic variant associates with asthma exacerbations. *J Allergy Clin Immunol*. 2020 Oct 6: S0091-6749(20)31393-2. doi: 10.1016/j.jaci.2020.09.027. Online ahead of print. PMID: 33035569

Sajuthi SP, DeFord P, Li Y, Jackson ND, Montgomery MT, Everman JL, Rios CL, Pruesse E, Nolin JD, Plender EG, Wechsler ME, Mak ACY, Eng C, Salazar S, Medina V, Wohlford EM, Huntsman S, Nickerson DA, Germer S, Zody MC, Abecasis G, Kang HM, Rice KM, Kumar R, Oh S, Rodriguez-Santana J, **Burchard EG**, Seibold MA. Type 2 and interferon inflammation regulate SARS-CoV-2 entry factor expression in the airway epithelium. *Nat Commun*. 2020 Oct 12;11(1):5139. doi: 10.1038/s41467-020-18781-2.PMID: 33046696

Jackson ND, Everman JL, Chioccioli M, Feriani L, Goldfarbmuren KC, Sajuthi SP, Rios CL, Powell R, Armstrong M, Gomez J, Michel C, Eng C, Oh SS, Rodriguez-Santana J, Cicuta P, Keys KL, Mak ACY, White MJ, Eckalbar WL, Dahl AW, Mefford J, Mikhaylova AV, Contreras MG, Elhawary JR, Eng C, Hu D, Huntsman S, Oh SS, Salazar S, Lenoir MA, Ye JC, Thornton TA, Zaitlen N, **Burchard EG**, Gignoux CR. On the cross-population generalizability of gene expression prediction models. *PLoS Genet*. 2020 Aug 14;16(8): e1008927. doi: 10.1371/journal.pgen.1008927. eCollection 2020 Aug.PMID: 32797036

Reisdorph N, **Burchard EG**, Seibold MA. Single-Cell and Population Transcriptomics Reveal Pan-epithelial Remodeling in Type 2-High Asthma. *Cell Rep*. 2020 Jul 7;32(1):107872. doi: 10.1016/j.celrep.2020.107872.PMID: 32640237

Ioannidis AG, Blanco-Portillo J, Sandoval K, Hagelberg E, Miquel-Poblete JF, Moreno-Mayar JV, Rodríguez-Rodríguez JE, Quinto-Cortés CD, Auckland K, Parks T, Robson K, Hill AVS, Avila-Arcos MC, Sockell A, Homburger JR, Wojcik GL, Barnes KC, Herrera L, Berríos S, Acuña M, Llop E, Eng C, Huntsman S, **Burchard EG**, Gignoux CR, Cifuentes L, Verdugo RA, Moraga M, Mentzer AJ, Bustamante CD, Moreno-Estrada A. Native American gene flow into Polynesia predating Easter Island settlement. *Nature*. 2020 ul;583(7817):572-577. doi: 10.1038/s41586-020-2487-2. Epub 2020 Jul 8. PMID: 32641827

Abel HJ, Larson DE, Regier AA, Chiang C, Das I, Kanchi KL, Layer RM, Neale BM, Salerno WJ, Reeves C, Buyske S; NHGRI Centers for Common Disease Genomics, Matise TC, Muzny DM, Zody MC, Lander ES, Dutcher SK, Stitziel NO, Hall IM. Mapping and characterization of structural variation in 17,795 human genomes. *Nature*. 2020 Jul;583(7814):83-89. doi: 10.1038/s41586-020-2371-0. Epub 2020 May 27. PMID: 32460305

Bick AG, Weinstock JS, Nandakumar SK, Fulco CP, Bao EL, Zekavat SM, Szeto MD, Liao X, Leventhal MJ, Nasser J, Chang K, Laurie C, Burugula BB, Gibson CJ, Lin AE, Taub MA, Aguet F, Ardlie K, Mitchell BD, Barnes KC, Moscati A, Fornage M, Redline S, Psaty BM, Silverman EK, Weiss ST, Palmer ND, Vasan RS, **Burchard EG**, Kardia SLR, He J, Kaplan RC, Smith NL, Arnett DK, Schwartz DA, Correa A, de Andrade M, Guo X, Konkle BA, Custer B, Peralta JM, Gui H, Meyers DA, McGarvey ST, Chen IY, Shoemaker MB, Peyser PA, Broome JG, Gogarten SM, Wang FF, Wong Q, Montasser ME, Daya M, Kenny EE, North KE, Launer LJ, Cade BE, Bis JC, Cho MH, Lasky-Su J, Bowden DW, Cupples LA, Mak ACY, Becker LC, Smith JA, Kelly TN, Aslibekyan S, Heckbert SR, Tiwari HK, Yang IV, Heit JA, Lubitz SA, Johnsen JM, Curran JE, Wenzel SE, Weeks DE, Rao DC, Darbar D, Moon JY, Tracy RP, Buth EJ, Rafaels N, Loos RJF, Durda P, Liu Y, Hou L, Lee J, Kachroo P, Freedman BI, Levy D, Bielak LF, Hixson JE, Floyd JS, Whitsel EA, Ellinor PT, Irvin MR, Fingerlin TE, Raffield LM, Armasu SM, Wheeler MM, Sabino EC, Blangero J, Williams LK, Levy BD, Sheu WH, Roden DM, Boerwinkle E, Manson JE, Mathias RA, Desai P, Taylor KD, Johnson AD; NHLBI Trans-Omics for Precision Medicine Consortium, Auer PL, Kooperberg C, Laurie CC, Blackwell TW, Smith AV, Zhao H, Lange E, Lange L, Rich SS, Rotter JI, Wilson JG, Scheet P, Kitzman JO, Lander ES, Engreitz JM, Ebert BL, Reiner AP, Jaiswal S, Abecasis G, Sankaran VG, Kathiresan S, Natarajan P. Inherited causes of clonal haematopoiesis in 97,691 whole genomes. *Nature*. 2020 Oct;586(7831):763-768. doi: 10.1038/s41586-020-2819-2. Epub 2020 Oct 14. PMID: 33057201

Montgomery MT, Sajuthi SP, Cho SH, Everman JL, Rios CL, Goldfarbmuren KC, Jackson ND, Saef B, Cromie M, Eng C, Medina V, Elhawary JR, Oh SS, Rodriguez-Santana J, Vladar EK, **Burchard EG**, Seibold MA. Genome-Wide Analysis Reveals Mucociliary Remodeling of the Nasal Airway Epithelium Induced by Urban PM2.5. *Am J Respir Cell Mol Biol*. 2020 Aug;63(2):172-184. doi: 10.1165/rcmb.2019-0454OC.PMID: 32275839

Li X, Li Z, Zhou H, Gaynor SM, Liu Y, Chen H, Sun R, Dey R, Arnett DK, Aslibekyan S, Ballantyne CM, Bielak LF, Blangero J, Boerwinkle E, Bowden DW, Broome JG, Conomos MP, Correa A, Cupples LA, Curran JE, Freedman BI, Guo X, Hindy G, Irvin MR, Kardia SLR, Kathiresan S, Khan AT, Kooperberg CL, Laurie CC, Liu XS, Mahaney MC, Manichaikul AW, Martin LW, Mathias RA, McGarvey ST, Mitchell BD, Montasser ME,

Moore JE, Morrison AC, O'Connell JR, Palmer ND, Pampana A, Peralta JM, Peyser PA, Psaty BM, Redline S, Rice KM, Rich SS, Smith JA, Tiwari HK, Tsai MY, Vasan RS, Wang FF, Weeks DE, Weng Z, Wilson JG, Yanek LR; NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium; TOPMed Lipids Working Group, Neale BM, Sunyaev SR, Abecasis JI, Willer CJ, Peloso GM, Natarajan P, Lin X. Dynamic incorporation of multiple in silico functional annotations empowers rare variant association analysis of large whole-genome sequencing studies at scale. *Nat Genet*. 2020 Sep;52(9):969-983. doi: 10.1038/s41588-020-0676-4. Epub 2020 Aug 24. PMID: 32839606

McGeachie MJ, Sordillo JE, Dahlin A, Wang AL, Lutz SM, Tantisira KG, Panganiban R, Lu Q, Sajuthi S, Urbanek C, Kelly R, Saef B, Eng C, Oh SS, Kho AT, Croteau-Chonka DC, Weiss ST, Raby BA, Mak ACY, Rodriguez-Santana JR, **Burchard EG**, Seibold MA, Wu AC. Expression of SMARCD1 interacts with age in association with asthma control on inhaled corticosteroid therapy. *Respir Res.* 2020 Jan 28;21(1):31. doi: 10.1186/s12931-020-1295-4. PMID: 31992292

Kessler MD, Loesch DP, Perry JA, Heard-Costa NL, Taliun D, Cade BE, Wang H, Daya M, Ziniti J, Datta S, Celedón JC, Soto-Quiros ME, Avila L, Weiss ST, Barnes K, Redline SS, Vasan RS, Johnson AD, Mathias RA, Hernandez R, Wilson JG, Nickerson DA, Abecasis G, Browning SR, Zöllner S, O'Connell JR, Mitchell BD; National Heart, Lung, and Blood Institute Trans-Omics for Precision Medicine (TOPMed) Consortium; TOPMed Population Genetics Working Group, O'Connor TD. De novo mutations across 1,465 diverse genomes reveal mutational insights and reductions in the Amish founder population. *Proc Natl Acad Sci U S A*. 2020 Feb 4;117(5):2560-2569. doi: 10.1073/pnas.1902766117. Epub 2020 Jan 21. PMID: 31964835

Yan Q, Forno E, Herrera-Luis E, Pino-Yanes M, Qi C, Rios R, Han YY, Kim S, Oh S, Acosta-Pérez E, Zhang R, Hu D, Eng C, Huntsman S, Avila L, Boutaoui N, Cloutier MM, Soto-Quiros ME, Xu CJ, Weiss ST, Lasky-Su J, Kiedrowski MR, Figueiredo C, Bomberger J, Barreto ML, Canino G, Chen W, Koppelman GH, **Burchard EG**, Celedón JC. A genome-wide association study of severe asthma exacerbations in Latino children and adolescents. *Eur Respir J.* 2020 Oct 22:2002693. doi: 10.1183/13993003.02693-2020. Online ahead of print. PMID: 33093117

Espuela-Ortiz A, Lorenzo-Diaz F, Baez-Ortega A, Eng C, Hernandez-Pacheco N, Oh SS, Lenoir M, **Burchard EG**, Flores C, Pino-Yanes M. Bacterial salivary microbiome associates with asthma among african american children and young adults. *Pediatr Pulmonol*. 2019 Dec;54(12):1948-1956. doi: 10.1002/ppul.24504. Epub 2019 Sep 9. PMID: 31496123

Wohlford EM, Borrell LN, Elhawary JR, Plotkin B, Oh SS, Nuckton TJ, Eng C, Salazar S, LeNoir MA, Meade K, Farber HJ, Serebrisky D, Brigino-Buenaventura E, Rodriguez-Cintron W, Kumar R, Thyne S, Seibold MA, Rodríguez-Santana JR, **Burchard EG**. Differential asthma odds following respiratory infection in children from three minority populations. *PLoS One*. 2020 May 5;15(5): e0231782. doi: 10.1371/journal.pone.0231782. eCollection 2020.PMID: 32369487

Yan Q, Forno E, Herrera-Luis E, Pino-Yanes M, Yang G, Oh S, Acosta-Pérez E, Hu D, Eng C, Huntsman S, Rodriguez-Santana JR, Cloutier MM, Canino G, **Burchard EG**, Chen W, Celedón JC. A genome-wide association study of asthma hospitalizations in adults. *J Allergy Clin Immunol.* 2020 Sep 2: S0091-6749(20)31224-0. doi: 10.1016/j.jaci.2020.08.020. Online ahead of print. PMID: 32890573

Hernandez-Pacheco N, Vijverberg SJ, Herrera-Luis E, Li J, Sio YY, Granell R, Corrales A, Maroteau C, Lethem R, Perez-Garcia J, Farzan N, Repnik K, Gorenjak M, Soares P, Karimi L, Schieck M, Pérez-Méndez L, Berce V, Tavendale R, Eng C, Sardon O, Kull I, Mukhopadhyay S, Pirmohamed M, Verhamme KM, **Burchard EG**, Kabesch M, Hawcutt DB, Melén E, Potočnik U, Chew FT, Tantisira KG, Turner S, Palmer CN, Flores C, Pino-Yanes M, Maitland-van der Zee AH; PiCA and SysPharmPedia consortia. Genome-wide association study of asthma exacerbations despite inhaled corticosteroids use. *Eur Respir J*. 2020 Dec 10:2003388. doi: 10.1183/13993003.03388-2020. Online ahead of print. PMID: 33303529

Goddard PC, Keys KL, Mak ACY, Lee EY, Liu AK, Samedy-Bates LA, Risse-Adams O, Contreras MG, Elhawary JR, Hu D, Huntsman S, Oh SS, Salazar S, Eng C, Himes BE, White MJ, **Burchard EG**. Integrative genomic analysis in African American children with asthma finds three novel loci associated with lung function. *Genet Epidemiol*. 2021 Mar;45(2):190-208. doi: 10.1002/gepi.22365. Epub 2020 Sep 29. PMID: 32989782

Verdugo RA, Di Genova A, Herrera L, Moraga M, Acuña M, Berríos S, Llop E, Valenzuela CY, Bustamante ML, Digman D, Symon A, Asenjo S, López P, Blanco A, Suazo J, Barozet E, Caba F, Villalón M, Alvarado S, Cáceres D, Salgado K, Portales P, Moreno-Estrada A, Gignoux CR, Sandoval K, Bustamante CD, Eng C, Huntsman S, **Burchard EG**, Loira N, Maass A, Cifuentes L. Development of a small panel of SNPs to infer ancestry in Chileans that distinguishes Aymara and Mapuche components. *Biol Res*. 2020 Apr 16;53(1):15. doi: 10.1186/s40659-020-00284-5.PMID: 32299502

Mak ACY, Sajuthi S, Joo J, Xiao S, Sleiman PM, White MJ, Lee EY, Saef B, Hu D, Gui H, Keys KL, Lurmann F, Jain D, Abecasis G, Kang HM, Nickerson DA, Germer S, Zody MC, Winterkorn L, Reeves C, Huntsman S, Eng C, Salazar S, Oh SS, Gilliland FD, Chen Z, Kumar R, Martínez FD, Wu AC, Ziv E, Hakonarson H, Himes BE, Williams LK, Seibold MA, **Burchard EG**. Lung Function in African American Children with Asthma Is Associated with Novel Regulatory Variants of the KIT Ligand KITLG/SCF and Gene-By-Air-Pollution Interaction. *Genetics*. 2020 Jul;215(3):869-886. doi: 10.1534/genetics.120.303231. Epub 2020 Apr 23. PMID: 32327564

Cocco MP, White E, Xiao S, Hu D, Mak A, Sleiman P, Yang M, Bobbitt KR, Gui H, Levin AM, Hochstadt S, Whitehouse K, Rynkowski D, Barczak AJ, Abecasis G, Blackwell TW, Kang HM, Nickerson DA, Germer S, Ding J, Lanfear DE, Gilliland F, Gauderman WJ, Kumar R, Erle DJ, Martinez F, Hakonarson H, **Burchard EG**, Williams LK. Asthma and its relationship to mitochondrial copy number: Results from the Asthma Translational Genomics Collaborative (ATGC) of the Trans-Omics for Precision Medicine (TOPMed) program. *PLoS One*. 2020 Nov 25;15(11): e0242364. doi: 10.1371/journal.pone.0242364. eCollection 2020.PMID: 33237978

Hernandez-Pacheco N, Gorenjak M, Jurgec S, Corrales A, Jorgensen A, Karimi L, Vijverberg SJ, Berce V, Schieck M, Acosta-Herrera M, Kerick M, Samedy-Bates LA, Tavendale R, Villar J, Mukhopadhyay S, Pirmohamed M, Verhamme KMC, Kabesch M, Hawcutt DB, Turner S, Palmer CN, **Burchard EG**, Maitland-van der Zee AH, Flores C, Potočnik U, Pino-Yanes M; PiCA and SysPharmPedia consortia. Combined analysis of transcriptomic and genetic data for the identification of loci involved in glucocorticosteroid response in asthma. *Allergy*. 2020 Aug 12:10.1111/all.14552. doi: 10.1111/all.14552. Online ahead of print. PMID: 32786158

Ávila-Arcos MC, McManus KF, Sandoval K, Rodríguez-Rodríguez JE, Villa-Islas V, Martin AR, Luisi P, Peñaloza-Espinosa RI, Eng C, Huntsman S, **Burchard EG**, Gignoux CR, Bustamante CD, Moreno-Estrada A. Population History and Gene Divergence in Native Mexicans Inferred from 76 Human Exomes. *Mol Biol Evol*. 2020 Apr 1;37(4):994-1006. doi: 10.1093/molbev/msz282.PMID: 31848607

Thurston GD, Balmes JR, Garcia E, Gilliland FD, Rice MB, Schikowski T, Van Winkle LS, Annesi-Maesano I, **Burchard EG**, Carlsten C, Harkema JR, Khreis H, Kleeberger SR, Kodavanti UP, London SJ, McConnell R, Peden DB, Pinkerton KE, Reibman J, White CW. Outdoor Air Pollution and New-Onset Airway Disease. An Official American Thoracic Society Workshop Report. *Ann Am Thorac Soc.* 2020 Apr;17(4):387-398. doi: 10.1513/Annals ATS.202001-046TH.PMTH: 32233861

Lee EY, Mak ACY, Hu D, Sajuthi S, White MJ, Keys KL, Eckalbar W, Bonser L, Huntsman S, Urbanek C, Eng C, Jain D, Abecasis G, Kang HM, Germer S, Zody MC, Nickerson DA, Erle D, Ziv E, Rodriguez-Santana J, Seibold MA, **Burchard EG**. *Am J Respir Crit Care Med*. 2020 Oct 1;202(7):962-972. doi: 10.1164/rccm.202002-0351OC.PMID: 32459537

\Moecking J, Laohamonthonkul P, Chalker K, White MJ, Harapas CR, Yu CH, Davidson S, Hrovat-Schaale K, Hu D, Eng C, Huntsman S, Calleja DJ, Horvat JC, Hansbro PM, O'Donoghue RJJ, Ting JP, **Burchard EG**, Geyer M, Gerlic M, Masters SL. NLRP1 variant M1184V decreases inflammasome activation in the context of DPP9 inhibition and asthma severity. *J Allergy Clin Immunol*. 2020 Dec 27: S0091-6749(20)32426-X. doi: 10.1016/j.jaci.2020.12.636. Online ahead of print. PMID: 33378691

Quick C, Anugu P, Musani S, Weiss ST, **Burchard EG**, White MJ, Keys KL, Cucca F, Sidore C, Boehnke M, Fuchsberger C. Sequencing and imputation in GWAS: Cost-effective strategies to increase power and genomic coverage across diverse populations. *Genet Epidemiol*. 2020 Sep;44(6):537-549. doi: 10.1002/gepi.22326. Epub 2020 Jun 9. PMID: 32519380

Ávila-Arcos MC, McManus KF, Sandoval K, Rodríguez-Rodríguez JE, Villa-Islas V, Martin AR, Luisi P, Peñaloza-Espinosa RI, Eng C, Huntsman S, **Burchard EG**, Gignoux CR, Bustamante CD, Moreno-Estrada A. Population history and gene divergence in Native Mexicans inferred from 76 human exomes. *Mol Biol Evol*. 2019 Dec 17. pii: msz282. doi: 10.1093/molbev/msz282. [Epub ahead of print]
PMID: 31848607

Dijk FN, Vijverberg SJ, Hernandez-Pacheco N, Repnik K, Karimi L, Mitratza M, Farzan N, Nawijn MC, **Burchard EG**, Engelkes M, Verhamme KM, Potočnik U, Pino-Yanes M, Postma DS, Maitland-van der Zee AH, Koppelman GH. IL1RL1 gene variations are associated with asthma exacerbations in children and adolescents using inhaled corticosteroids. *Allergy*. 2019 Nov 22. doi: 10.1111/all.14125. [Epub ahead of print] No abstract available. PMID: 31755552

Kumar R, Seibold MA, **Burchard EG**. Atopic dermatitis, race, and genetics. *J Allergy Clin Immunol*. 2020 Jan;145(1):108-110. doi: 10.1016/j.jaci.2019.11.008. Epub 2019 Nov 15. No abstract available. PMID: 31738993

Zeiger AM, McGarry ME, Mak ACY, Medina V, Salazar S, Eng C, Liu AK, Oh SS, Nuckton TJ, Jain D, Blackwell TW, Kang HM, Abecasis G, Oñate LC, Seibold MA, **Burchard EG**, Rodriguez-Santana J. Identification of CFTR variants in Latino patients with systic fibrosis from the Dominican Republic and Puerto Rico. *Pediatr Pulmonol*. 2020 Feb;55(2):533-540. doi: 10.1002/ppul.24549. Epub 2019 Oct 30. PMID: 31665830

Kachroo P, Hecker J, Chawes BL, Ahluwalia TS, Cho MH, Qiao D, Kelly RS, Chu SH, Virkud YV, Huang M, Barnes KC, **Burchard EG**, Eng C, Hu D, Celedón JC, Daya M, Levin AM, Gui H, Williams LK, Forno E, Mak ACY, Avila L, Soto-Quiros ME, Cloutier MM, Acosta-Pérez E, Canino G, Bonnelykke K, Bisgaard H, Raby BA, Lange C, Weiss ST, Lasky-Su JA; National Heart, Lung, and Blood Institute Trans-Omics for Precision Medicine (TOPMed) Consortium. Whole Genome Sequencing Identifies CRISPLD2 as a Lung Function Gene in Children with Asthma. *Chest.* 2019 Dec;156(6):1068-1079. doi: 10.1016/j.chest.2019.08.2202. Epub 2019 Sep 23. PMID: 31557467

Szpiech ZA, Mak ACY, White MJ, Hu D, Eng C, **Burchard EG**, Hernandez RD. Ancestry-Dependent Enrichment of Deleterious Homozygotes in Runs of Homozygosity. *Am J Hum Genet.* 2019 Oct 3;105(4):747-762. doi: 10.1016/j.ajhg.2019.08.011. Epub 2019 Sep 19. PMID: 31543216

Espuela-Ortiz A, Lorenzo-Diaz F, Baez-Ortega A, Eng C, Hernandez-Pacheco N, Oh SS, Lenoir M, **Burchard EG**, Flores C, Pino-Yanes M. Bacterial salivary microbiome associates with asthma among african american children and young adults. *Pediatr Pulmonol*. 2019 Dec;54(12):1948-1956. doi: 10.1002/ppul.24504. Epub 2019 Sep 9. PMID: 31496123

Daya M, Rafaels N, Brunetti TM, Chavan S, Levin AM, Shetty A, Gignoux CR, Boorgula MP, Wojcik G, Campbell M, Vergara C, Torgerson DG, Ortega VE, Doumatey A, Johnston HR, Acevedo N, Araujo MI, Avila PC, Belbin G, Bleecker E, Bustamante C, Caraballo L, Cruz A, Dunston GM, Eng C, Faruque MU, Ferguson TS, Figueiredo C, Ford JG, Gan W, Gourraud PA, Hansel NN, Hernandez RD, Herrera-Paz EF, Jiménez S, Kenny EE, Knight-Madden J, Kumar R, Lange LA, Lange EM, Lizee A, Maul P, Maul T, Mayorga A, Meyers D, Nicolae DL, O'Connor TD, Oliveira RR, Olopade CO, Olopade O, Qin ZS, Rotimi C, Vince N, Watson H, Wilks RJ, Wilson JG, Salzberg S, Ober C, **Burchard EG**, Williams LK, Beaty TH, Taub MA, Ruczinski I, Mathias RA, Barnes KC; CAAPA. Author Correction: Association study in African-admixed populations across the Americas recapitulates asthma risk loci in non-African populations. *Nat Commun.* 2019 Sep 4;10(1):4082. doi: 10.1038/s41467-019-12158-w. PMID: 31484942

Neophytou AM, Oh SS, Hu D, Huntsman S, Eng C, Rodríguez-Santana JR, Kumar R, Balmes JR, Eisen EA, **Burchard EG**. In utero tobacco smoke exposure, DNA methylation, and asthma in Latino children. *Environ Epidemiol*. 2019 Jun 19;3(3): e048. doi: 10.1097/EE9.0000000000000048. eCollection 2019 Jun. PMID: 31342008

Lona-Durazo F, Hernandez-Pacheco N, Fan S, Zhang T, Choi J, Kovacs MA, Loftus SK, Le P, Edwards M, Fortes-Lima CA, Eng C, Huntsman S, Hu D, Gómez-Cabezas EJ, Marín-Padrón LC, Grauholm J, Mors O, **Burchard EG**, Norton HL, Pavan WJ, Brown KM, Tishkoff S, Pino-Yanes M, Beleza S, Marcheco-Teruel B, Parra EJ. Meta-analysis of GWA studies provides new insights on the genetic architecture of skin pigmentation in recently admixed populations. *BMC Genet*. 2019 Jul 17;20(1):59. doi: 10.1186/s12863-019-0765-5. PMID: 31315583

Lee EY, Oh SS, White MJ, Eng CS, Elhawary JR, Borrell LN, Nuckton TJ, Zeiger AM, Keys KL, Mak ACY, Hu D, Huntsman S, Contreras MG, Samedy LA, Goddard PC, Salazar SL, Brigino-Buenaventura EN, Davis A, Meade KE, LeNoir MA, Lurmann FW, **Burchard EG**, Eisen EA, Balmes JR. Ambient air pollution, asthma drug response, and telomere length in African American youth. *J Allergy Clin Immunol*. 2019 Sep;144(3):839-845.e10. doi: 10.1016/j.jaci.2019.06.009. Epub 2019 Jun 24. PMID: 31247265

Samedy-Bates LA, Oh SS, Nuckton TJ, Elhawary JR, White M, Elliot T, Zeiger AM, Eng C, Salazar S, LeNoir MA, Meade K, Farber HJ, Serebrisky D, Brigino-Buenaventura E, Rodriguez-Cintron W, Bibbins-Domingo K, Kumar R, Thyne S, Borrell LN, Rodriguez-Santana JR, Pino-Yanes M, Burchard EG. Racial/Ethnic-Specific Differences in the Effects of Inhaled Corticosteroid Use on Bronchodilator Response in Patients with Asthma. *Clin Pharmacol Ther*. 2019 Nov;106(5):1133-1140. doi: 10.1002/cpt.1555. Epub 2019 Jul 23. PMID: 31209858

Everman JL, Sajuthi S, Saef B, Rios C, Stoner AM, Numata M, Hu D, Eng C, Oh S, Rodriguez-Santana J, Vladar EK, Voelker DR, **Burchard EG**, Seibold MA. Functional genomics of CDHR3 confirms its role in HRV-C infection and childhood asthma exacerbations. *J Allergy Clin Immunol.* 2019 Oct;144(4):962-971. doi: 10.1016/j.jaci.2019.01.052. Epub 2019 Mar 29. PMID: 30930175

Daya M, Rafaels N, Brunetti TM, Chavan S, Levin AM, Shetty A, Gignoux CR, Boorgula MP, Wojcik G, Campbell M, Vergara C, Torgerson DG, Ortega VE, Doumatey A, Johnston HR, Acevedo N, Araujo MI, Avila PC, Belbin G, Bleecker E, Bustamante C, Caraballo L, Cruz A, Dunston GM, Eng C, Faruque MU, Ferguson TS, Figueiredo C, Ford JG, Gan W, Gourraud PA, Hansel NN, Hernandez RD, Herrera-Paz EF, Jiménez S, Kenny EE, Knight-Madden J, Kumar R, Lange LA, Lange EM, Lizee A, Maul P, Maul T, Mayorga A, Meyers D, Nicolae DL, O'Connor TD, Oliveira RR, Olopade CO, Olopade O, Qin ZS, Rotimi C, Vince N, Watson H, Wilks RJ, Wilson JG, Salzberg S, Ober C, **Burchard EG,** Williams LK, Beaty TH, Taub MA, Ruczinski I, Mathias RA, Barnes KC; CAAPA. Association study in African-admixed populations across the Americas recapitulates asthma risk loci in non-African populations. *Nat Commun.* 2019 Feb 20;10(1):880. doi: 10.1038/s41467-019-08469-7. PMID: 30787307

Thakur N, Borrell LN, Ye M, Oh SS, Eng C, Meade K, Avila PC, Farber HJ, Serebrisky D, Brigino-Buenaventura E, Rodriguez-Cintron W, Kumar R, Bibbins-Domingo K, Thyne S, Sen S, Rodriguez-Santana JR, **Burchard EG**. Acculturation is associated with asthma burden and pulmonary function in Latino youth: The GALA II study. *J Allergy Clin Immunol.* 2019 Jan 22. pii: S0091-6749(19)30083-1. doi: 10.1016/j.jaci.2018.12.1015. [Epub ahead of print]. PMID: 30682453

Sherman RM, Forman J, Antonescu V, Puiu D, Daya M, Rafaels N, Boorgula MP, Chavan S, Vergara C, Ortega VE, Levin AM, Eng C, Yazdanbakhsh M, Wilson JG, Marrugo J, Lange LA, Williams LK, Watson H, Ware LB, Olopade CO, Olopade O, Oliveira RR, Ober C, Nicolae DL, Meyers DA, Mayorga A, Knight-Madden J, Hartert T, Hansel NN, Foreman MG, Ford JG, Faruque MU, Dunston GM, Caraballo L, **Burchard EG**, Bleecker ER, Araujo MI, Herrera-Paz EF, Campbell M, Foster C, Taub MA, Beaty TH, Ruczinski I, Mathias RA, Barnes KC, Salzberg SL. Author Correction: Assembly of a pan-genome from deep sequencing of 910 humans of African descent. *Nat Genet*. 2019 Feb;51(2):364. doi: 10.1038/s41588-018-0335-1. PMID: 30647471

Hoffman J, Fejerman L, Hu D, Huntsman S, Li M, John EM, Torres-Mejia G, Kushi L, Ding YC, Weitzel J, Neuhausen SL, Lott P; COLUMBUS Consortium, Echeverry M, Carvajal-Carmona L, **Burchard E**, Eng C, Long J, Zheng W, Olopade O, Huo D, Haiman C, Ziv E. Identification of novel common breast cancer risk variants at the 6q25 locus among Latinas. *Breast Cancer Res*. 2019 Jan 14;21(1):3. doi: 10.1186/s13058-018-1085-9. PMID: 30642363

Almoguera B, Vazquez L, Mentch F, March ME, Connolly JJ, Peissig PL, Linneman JG, Plaza-Serón MDC, Pino-Yanes M, **Burchard EG**, Brilliant M, Sleiman P, Hakonarson H. Novel locus for atopic dermatitis in African Americans and replication in European Americans. *J Allergy Clin Immunol.* 2019 Mar;143(3):1229-1231. doi: 10.1016/j.jaci.2018.10.038. Epub 2018 Nov 9. No abstract available. PMID: 30414857
Yao TC, Chung RH, Lin CY, Tsai PC, Chang WC, Yeh KW, Tsai MH, Liao SL, Hua MC, Lai SH, Chen LC, Chang SW, Yu YW, Hsu JY, Chang SC, Cheng WC, Hu D, Hong X, **Burchard EG**, Wang X, Tzeng JY, Tsai HJ, Huang JL. Genetic loci determining total immunoglobulin E levels from birth through adulthood. *Allergy*. 2019 Mar;74(3):621-625. doi: 10.1111/all.13654. Epub 2018 Nov 28. No abstract available. PMID: 30378687
Gignoux CR, Torgerson DG, Pino-Yanes M, Uricchio LH, Galanter J, Roth LA, Eng C, Hu D, Nguyen EA, Huntsman S, Mathias RA, Kumar R, Rodriguez-Santana J, Thakur N, Oh SS, McGarry M, Moreno-Estrada A, Sandoval K, Winkler CA, Seibold MA, Padhukasahasram B, Conti DV, Farber HJ, Avila P, Brigino-Buenaventura E, Lenoir M, Meade K, Serebrisky D, Borrell LN, Rodriguez-Cintron W, Thyne S, Joubert BR, Romieu I, Levin AM, Sienra-Monge JJ, Del Rio-Navarro BE, Gan W, Raby BA, Weiss ST, Bleecker E, Meyers DA, Martinez FJ, Gauderman WJ, Gilliland F, London SJ, Bustamante CD, Nicolae DL, Ober C, Sen S, Barnes K, Williams LK, Hernandez RD, **Burchard EG**. An admixture mapping meta-analysis implicates genetic variation at 18q21 with asthma susceptibility in Latinos. *J Allergy Clin Immunol*. 2019 Mar;143(3):957-969. doi: 10.1016/j.jaci.2016.08.057. Epub 2018 Sep 7. PMID: 30201514
Reese SE, Xu CJ, den Dekker HT, Lee MK, Sikdar S, Ruiz-Arenas C, Merid SK, Rezwan FI, Page CM, Ullemar V, Melton PE, Oh SS, Yang IV, Burrows K, Söderhäll C, Jima DD, Gao L, Arathimos R, Küpers LK, Wielscher M, Rzehak P, Lahti J, Laprise C, Madore AM, Ward J, Bennett BD, Wang T, Bell DA; BIOS consortium, Vonk JM, Håberg SE, Zhao S, Karlsson R, Hollams E, Hu D, Richards AJ, Bergström A, Sharp GC, Felix JF, Bustamante M, Gruzieva O, Maguire RL, Gilliland F, Baïz N, Nohr EA, Corpeleijn E, Sebert S, Karmaus W, Grote V, Kajantie E, Magnus MC, Örtqvist AK, Eng C, Liu AH, Kull I, Jaddoe VWV, Sunyer J, Kere J, Hoyo C, Annesi-Maesano I, Arshad SH, Koletzko B, Brunekreef B, Binder EB, Räikkönen K, Reischl E, Holloway JW, Jarvelin MR, Snieder H, Kazmi N, Breton CV, Murphy SK, Pershagen G, Anto JM, Relton CL, Schwartz DA, **Burchard EG**, Huang RC, Nystad W, Almqvist C, Henderson AJ, Melén E, Duijts L, Koppelman GH, London SJ. Epigenome-wide meta-analysis of DNA methylation and childhood asthma. *J Allergy Clin Immunol*. 2019 Jun;143(6):2062-2074. doi: 10.1016/j.jaci.2018.11.043. Epub 2018 Dec 21. PMID: 30579849
Szpiech ZA, Mak ACY, White MJ, Hu D, Eng C, **Burchard EG**, Hernandez RD. Ancestry-Dependent Enrichment of Deleterious Homozygotes in Runs of Homozygosity. *Am J Hum Genet.* 2019 Oct 3;105(4):747-762. doi: 10.1016/j.ajhg.2019.08.011. Epub 2019 Sep 19. PMID: 31543216
Hernandez-Pacheco N, Farzan N, Francis B, Karimi L, Repnik K, Vijverberg SJ, Soares P, Schieck M, Gorenjak M, Forno E, Eng C, Oh SS, Pérez-Méndez L, Berce V, Tavendale R, Samedy LA, Hunstman S, Hu D, Meade K, Farber HJ, Avila PC, Serebrisky D, Thyne SM, Brigino-Buenaventura E, Rodriguez-Cintron W, Sen S, Kumar R, Lenoir M, Rodriguez-Santana JR, Celedón JC, Mukhopadhyay S, Potočnik U, Pirmohamed M, Verhamme KM, Kabesch M, Palmer CNA, Hawcutt DB, Flores C, Maitland-van der Zee AH, **Burchard EG**, Pino-Yanes M. Genome-wide association study of inhaled corticosteroid response in

admixed children with asthma. *Clin Exp Allergy*. 2019 Jun;49(6):789-798. doi: 10.1111/cea.13354. Epub 2019 Feb 15. PMID: 30697902

Lee EY, Oh SS, White MJ, Eng CS, Elhawary JR, Borrell LN, Nuckton TJ, Zeiger AM, Keys KL, Mak ACY, Hu D, Huntsman S, Contreras MG, Samedy LA, Goddard PC, Salazar SL, Brigino-Buenaventura EN, Davis A, Meade KE, LeNoir MA, Lurmann FW, **Burchard EG**, Eisen EA, Balmes JR. Ambient air pollution, asthma drug response, and telomere length in African American youth. *J Allergy Clin Immunol*. 2019 Sep;144(3):839-845.e10. doi: 10.1016/j.jaci.2019.06.009. Epub 2019 Jun 24. PMID: 31247265

Daya M, Rafaels N, Brunetti TM, Chavan S, Levin AM, Shetty A, Gignoux CR, Boorgula MP, Wojcik G, Campbell M, Vergara C, Torgerson DG, Ortega VE, Doumatey A, Johnston HR, Acevedo N, Araujo MI, Avila PC, Belbin G, Bleecker E, Bustamante C, Caraballo L, Cruz A, Dunston GM, Eng C, Faruque MU, Ferguson TS, Figueiredo C, Ford JG, Gan W, Gourraud PA, Hansel NN, Hernandez RD, Herrera-Paz EF, Jiménez S, Kenny EE, Knight-Madden J, Kumar R, Lange LA, Lange EM, Lizee A, Maul P, Maul T, Mayorga A, Meyers D, Nicolae DL, O'Connor TD, Oliveira RR, Olopade CO, Olopade O, Qin ZS, Rotimi C, Vince N, Watson H, Wilks RJ, Wilson JG, Salzberg S, Ober C, **Burchard EG**, Williams LK, Beaty TH, Taub MA, Ruczinski I, Mathias RA, Barnes KC; CAAPA. Association study in African-admixed populations across the Americas recapitulates asthma risk loci in non-African populations. *Nat Commun*. 2019 Feb 20;10(1):880. doi: 10.1038/s41467-019-08469-7.PMID: 30787307

Everman JL, Sajuthi S, Saef B, Rios C, Stoner AM, Numata M, Hu D, Eng C, Oh S, Rodriguez-Santana J, Vladar EK, Voelker DR, **Burchard EG**, Seibold MA. Functional genomics of CDHR3 confirms its role in HRV-C infection and childhood asthma exacerbations. *J Allergy Clin Immunol.* 2019 Oct;144(4):962-971. doi: 10.1016/j.jaci.2019.01.052. Epub 2019 Mar 29. PMID: 30930175

Hoffman J, Fejerman L, Hu D, Huntsman S, Li M, John EM, Torres-Mejia G, Kushi L, Ding YC, Weitzel J, Neuhausen SL, Lott P; COLUMBUS Consortium, Echeverry M, Carvajal-Carmona L, **Burchard E**, Eng C, Long J, Zheng W, Olopade O, Huo D, Haiman C, Ziv E. Identification of novel common breast cancer risk variants at the 6q25 locus among Latinas. *Breast Cancer Res*. 2019 Jan 14;21(1):3. doi: 10.1186/s13058-018-1085-9.PMID: 30642363

Samedy-Bates LA, Oh SS, Nuckton TJ, Elhawary JR, White M, Elliot T, Zeiger AM, Eng C, Salazar S, LeNoir MA, Meade K, Farber HJ, Serebrisky D, Brigino-Buenaventura E, Rodriguez-Cintron W, Bibbins-Domingo K, Kumar R, Thyne S, Borrell LN, Rodriguez-Santana JR, Pino-Yanes M, **Burchard EG**. Racial/Ethnic-Specific Differences in the Effects of Inhaled Corticosteroid Use on Bronchodilator Response in Patients with Asthma. *Clin Pharmacol Ther*. 2019 Nov;106(5):1133-1140. doi: 10.1002/cpt.1555. Epub 2019 Jul 23. PMID: 31209858

Thakur N, Borrell LN, Ye M, Oh SS, Eng C, Meade K, Avila PC, Farber HJ, Serebrisky D, Brigino-Buenaventura E, Rodriguez-Cintron W, Kumar R, Bibbins-Domingo K, Thyne S, Sen S, Rodriguez-Santana JR, **Burchard EG**. Acculturation is associated with asthma burden and pulmonary function in Latino youth: The GALA II study. *J Allergy Clin Immunol*. 2019 May;143(5):1914-1922. doi: 10.1016/j.jaci.2018.12.1015. Epub 2019 Jan 22. PMID: 30682453

Zeiger AM, McGarry ME, Mak ACY, Medina V, Salazar S, Eng C, Liu AK, Oh SS, Nuckton TJ, Jain D, Blackwell TW, Kang HM, Abecasis G, Oñate LC, Seibold MA, **Burchard EG**, Rodriguez-Santana Identification of CFTR variants in Latino patients with cystic fibrosis

from the Dominican Republic and Puerto Rico. *J. Pediatr Pulmonol*. 2020 Feb;55(2):533-540. doi: 10.1002/ppul.24549. Epub 2019 Oct 30. PMID: 31665830

Sherman RM, Forman J, Antonescu V, Puiu D, Daya M, Rafaels N, Boorgula MP, Chavan S, Vergara C, Ortega VE, Levin AM, Eng C, Yazdanbakhsh M, Wilson JG, Marrugo J, Lange LA, Williams LK, Watson H, Ware LB, Olopade CO, Olopade O, Oliveira RR, Ober C, Nicolae DL, Meyers DA, Mayorga A, Knight-Madden J, Hartert T, Hansel NN, Foreman MG, Ford JG, Faruque MU, Dunston GM, Caraballo L, **Burchard EG**, Bleecker ER, Araujo MI, Herrera-Paz EF, Campbell M, Foster C, Taub MA, Beaty TH, Ruczinski I, Mathias RA, Barnes KC, Salzberg SL. Author Correction: Assembly of a pan-genome from deep sequencing of 910 humans of African descent. *Nat Genet*. 2019 Feb;51(2):364. doi: 10.1038/s41588-018-0335-1.PMID: 30647471

Almoguera B, Vazquez L, Mentch F, March ME, Connolly JJ, Peissig PL, Linneman JG, Plaza-Serón MDC, Pino-Yanes M, **Burchard EG**, Brilliant M, Sleiman P, Hakonarson H. Novel locus for atopic dermatitis in African Americans and replication in European Americans. *J Allergy Clin Immunol*. 2019 Mar;143(3):1229-1231. doi: 10.1016/j.jaci.2018.10.038. Epub 2018 Nov 9. PMID: 30414857

Gignoux CR, Torgerson DG, Pino-Yanes M, Uricchio LH, Galanter J, Roth LA, Eng C, Hu D, Nguyen EA, Huntsman S, Mathias RA, Kumar R, Rodriguez-Santana J, Thakur N, Oh SS, McGarry M, Moreno-Estrada A, Sandoval K, Winkler CA, Seibold MA, Padhukasahasram B, Conti DV, Farber HJ, Avila P, Brigino-Buenaventura E, Lenoir M, Meade K, Serebrisky D, Borrell LN, Rodriguez-Cintron W, Thyne S, Joubert BR, Romieu I, Levin AM, Sienra-Monge JJ, Del Rio-Navarro BE, Gan W, Raby BA, Weiss ST, Bleecker E, Meyers DA, Martinez FJ, Gauderman WJ, Gilliland F, London SJ, Bustamante CD, Nicolae DL, Ober C, Sen S, Barnes K, Williams LK, Hernandez RD, **Burchard EG**. An admixture mapping meta-analysis implicates genetic variation at 18q21 with asthma susceptibility in Latinos. *J Allergy Clin Immunol*. 2019 Mar;143(3):957-969. doi: 10.1016/j.jaci.2016.08.057. Epub 2018 Sep 7. PMID: 30201514

Zekavat SM, Ruotsalainen S, Handsaker RE, Alver M, Bloom J, Poterba T, Seed C, Ernst J, Chaffin M, Engreitz J, Peloso GM, Manichaikul A, Yang C, Ryan KA, Fu M, Johnson WC, Tsai M, Budoff M, Vasan RS, Cupples LA, Rotter JI, Rich SS, Post W, Mitchell BD, Correa A, Metspalu A, Wilson JG, Salomaa V, Kellis M, Daly MJ, Neale BM, McCarroll S, Surakka I, Esko T, Ganna A, Ripatti S, Kathiresan S, Natarajan P; NHLBI TOPMed Lipids Working Group. Publisher Correction: Deep coverage whole genome sequences and plasma lipoprotein(a) in individuals of European and African ancestries. *Nat Commun*. 2020 Apr 1;11(1):1715. doi: 10.1038/s41467-020-15236-6.PMID: 32238811

Spear ML, Hu D, Pino-Yanes M, Huntsman S, Eng C, Levin AM, Ortega VE, White MJ, McGarry ME, Thakur N, Galanter J, Mak ACY, Oh SS, Ampleford E, Peters SP, Davis A, Kumar R, Farber HJ, Meade K, Avila PC, Serebrisky D, Lenoir MA, Brigino-Buenaventura E, Cintron WR, Thyne SM, Rodriguez-Santana JR, Ford JG, Chapela R, Estrada AM, Sandoval K, Seibold MA, Winkler CA, Bleecker ER, Myers DA, Williams LK, Hernandez RD, Torgerson DG, **Burchard EG**. A genome-wide association and admixture mapping study of bronchodilator drug response in African Americans with asthma. *Pharmacogenomics J*. 2019 Jun;19(3):249-259. doi: 10.1038/s41397-018-0042-4. Epub 2018 Sep 12. PMID: 30206298

Harold Chapman, M.D.

Wei Y, Dong W, Jackson J, Ho TC, Le Saux CJ, Brumwell A, Li X, Klesney-Tait J, Cohen ML, Wolters PJ, **Chapman HA**. Blocking LOXL2 and TGFβ1 signalling induces collagen I turnover in precision-cut lung slices derived from patients with idiopathic pulmonary fibrosis. *Thorax*. 2021 Jan 20: thoraxjnl-2020-215745. doi: 10.1136/thoraxjnl-2020-215745. Online ahead of print. PMID: 33472968

Chapman HA, Wei Y, Montas G, Leong D, Golden JA, Trinh BN, Wolters PJ, Le Saux CJ, Jones KD, Hills NK, Foster E, Oldham JM, Linderholm AL, Kotak P, Decaris M, Turner S, Song JW. Reversal of TGFβ1-Driven Profibrotic State in Patients with Pulmonary Fibrosis. *N Engl J Med*. 2020 Mar 12;382(11):1068-1070. doi: 10.1056/NEJMc1915189. PMID: 32160670

Peng DH, Rodriguez BL, Diao L, Chen L, Wang J, Byers LA, Wei Y, **Chapman HA,** Yamauchi M, Behrens C, Raso G, Soto LMS, Cuentes ERP, Wistuba II, Kurie JM, Gibbons DL. Collagen promotes anti-PD-1/PD-L1 resistance in cancer through LAIR1-dependent CD8+ T cell exhaustion. *Nat Commun.* 2020 Sep 9;11(1):4520. doi: 10.1038/s41467-020-18298-8. PMID: 32908154

Strunz M, Simon LM, Ansari M, Kathiriya JJ, Angelidis I, Mayr CH, Tsidiridis G, Lange M, Mattner LF, Yee M, Ogar P, Sengupta A, Kukhtevich I, Schneider R, Zhao Z, Voss C, Stoeger T, Neumann JHL, Hilgendorff A, Behr J, O'Reilly M, Lehmann M, Burgstaller G, Königshoff M, **Chapman HA**, Theis FJ, Schiller HB. Alveolar regeneration through a Krt8+ transitional stem cell state that persists in human lung fibrosis. *Nat Commun*. 2020 Jul 16;11(1):3559. doi: 10.1038/s41467-020-17358-3. PMID: 32678092

Kathiriya JJ, **Chapman HA**. VEGF Drives the Car toward Better Gas Exchange. *Dev Cell.* 2020 Mar 9;52(5):546-547. doi: 10.1016/j.devcel.2020.02.009. PMID: 32155436

Racine JJ, **Chapman HD**, Doty R, Cairns BM, Hines TJ, Tadenev ALD, Anderson LC, Green T, Dyer ME, Wotton JM, Bichler Z, White JK, Ettinger R, Burgess RW, Serreze DV. T Cells from NOD-PerIg Mice Target Both Pancreatic and Neuronal Tissue. *J Immunol*. 2020 Oct 15;205(8):2026-2038. doi: 10.4049/jimmunol.2000114. Epub 2020 Sep 16. PMID: 32938729

Kathiriya JJ, Brumwell AN, Jackson JR, Tang X, **Chapman HA**. Distinct Airway Epithelial Stem Cells Hide among Club Cells but Mobilize to Promote Alveolar Regeneration. *Cell Stem Cell*. 2020 Jan 23. pii: S1934-5909(19)30572-7. doi: 10.1016/j.stem.2019.12.014. [Epub ahead of print]. PMID: 31978363

Wiley CD, Brumwell AN, Davis SS, Jackson JR, Valdovinos A, Calhoun C, Alimirah F, Castellanos CA, Ruan R, Wei Y, **Chapman HA**, Ramanathan A, Campisi J, Jourdan Le Saux C. Secretion of leukotrienes by senescent lung fibroblasts promotes pulmonary fibrosis. *JCI Insight.* 2019 Dec 19;4(24). pii: 130056. doi: 10.1172/jci.insight.130056. PMID: 31687975

Egia-Mendikute L, Arpa B, Rosell-Mases E, Corral-Pujol M, Carrascal J, Carrillo J, Mora C, **Chapman H**, Panosa A, Vives-Pi M, Stratmann T, Serreze D, Verdaguer J. B-Lymphocyte Phenotype Determines T-Lymphocyte Subset Differentiation in Autoimmune Diabetes. *Front Immunol*. 2019 Jul 25; 10:1732. doi: 10.3389/fimmu.2019.01732. eCollection 2019. PMID: 31428087

LaCanna R, Liccardo D, Zhang P, Tragesser L, Wang Y, Cao T, **Chapman HA**, Morrisey EE, Shen H, Koch WJ, Kosmider B, Wolfson MR, Tian Y. Yap/Taz regulate alveolar

regeneration and resolution of lung inflammation. *J Clin Invest*. 2019 Apr 15;129(5):2107-2122. doi: 10.1172/JCI125014. eCollection 2019 Apr 15. PMID: 30985294
Thamsen M, Ghosh R, Auyeung VC, Brumwell A, **Chapman HA**, Backes BJ, Perara G, Maly DJ, Sheppard D, Papa FR. Small molecule inhibition of IRE1α kinase/RNase has anti-fibrotic effects in the lung. *PLoS One*. 2019 Jan 9;14(1): e0209824. doi: 10.1371/journal.pone.0209824. eCollection 2019. PMID: 30625178

Anthony DeFranco, Ph.D.
Almeida SO, Honoris L, **Defranco A**, Port S, Li D, Nasir K, Kronmal R, Barr RG, Budoff M. Reliability of CAC Scoring on Nongated Compared with Gated Cardiac CT Scans From MESA. *JACC Cardiovasc Imaging*. 2020 Jan;13(1 Pt 1):177-178. doi: 10.1016/j.jcmg.2019.08.007. Epub 2019 Sep 18. PMID: 31542523
Roback J, Ammar Z, Shah S, **DeFranco A**, Jahangir A, Jan MF, Allaqaband SQ, Bajwa T, Ammar KA. Insights from Modern Imaging and Catheter Wire Measurements in Patients Undergoing Transcatheter Aortic Valve Replacement. *J Invasive Cardiol*. 2020 Jul;32(7):262-268. PMID: 32610267
Chandrasekhar J, Baber U, Sartori S, Aquino M, Moalem K, Kini AS, Rao SV, Weintraub W, Henry TD, Vogel B, Ge Z, Muhlestein JB, Weiss S, Strauss C, Toma C, **DeFranco A**, Claessen BE, Keller S, Baker BA, Effron MB, Pocock S, Dangas G, Kapadia S, Mehran R. Prasugrel use and clinical outcomes by age among patients undergoing PCI for acute coronary syndrome: from the PROMETHEUS study. *Clin Res Cardiol*. 2020 Jun;109(6):725-734. doi: 10.1007/s00392-019-01561-4. Epub 2020 Jan 8. PMID: 31915997
Chandiramani R, Chen H, Aoi S, Giustino G, Claessen B, Sartori S, Aquino M, Sorrentino S, Cao D, Goel R, Kini A, Rao S, Weintraub W, Henry TD, Kapadia S, **DeFranco A**, Muhlestein JB, Toma C, Effron MB, Keller S, Baker BA, Pocock S, Baber U, Mehran R. Incidence, predictors and impact of stroke on mortality among patients with acute coronary syndromes following percutaneous coronary intervention-Results from the PROMETHEUS registry. *Catheter Cardiovasc Interv.* 2020 Apr 1;95(5):885-892. doi: 10.1002/ccd.28369. Epub 2019 Jun 14. PMID: 31197962
Chandrasekhar J, Baber U, Sartori S, Aquino M, Moalem K, Kini AS, Rao SV, Weintraub W, Henry TD, Vogel B, Ge Z, Muhlestein JB, Weiss S, Strauss C, Toma C, **DeFranco A**, Claessen BE, Keller S, Baker BA, Effron MB, Pocock S, Dangas G, Kapadia S, Mehran R. Prasugrel use and clinical outcomes by age among patients undergoing PCI for acute coronary syndrome: from the PROMETHEUS study. *Clin Res Cardiol.* 2020 Jan 8. doi: 10.1007/s00392-019-01561-4. [Epub ahead of print]. PMID: 31915997
Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, Tardif JC, Baum SJ, Steinhagen-Thiessen E, Shapiro MD, Stroes ES, Moriarty PM, Nordestgaard BG, Xia S, Guerriero J, Viney NJ, O'Dea L, Witztum JL; AKCEA-APO(a)-LRx Study Investigators. Lipoprotein(a) Reduction in Persons with Cardiovascular Disease. *N Engl J Med*. 2020 Jan 16;382(3):244-255. doi: 10.1056/NEJMoa1905239. Epub 2020 Jan 1. PMID: 31893580
Almeida SO, Honoris L, **Defranco A**, Port S, Li D, Nasir K, Kronmal R, Barr RG, Budoff M. Reliability of CAC Scoring on Nongated Compared with Gated Cardiac CT Scans From MESA. *JACC Cardiovasc Imaging*. 2020 Jan;13(1 Pt 1):177-178. doi: 10.1016/j.jcmg.2019.08.007. Epub 2019 Sep 18. No abstract available. PMID: 31542523

Wigton EJ, **DeFranco AL,** Ansel KM. *Immunohorizons*. 2019 Aug 19;3(8):389-401. doiAntigen Complexed with a TLR9 Agonist Bolsters c-Myc and mTORC1 Activity in Germinal Center B Lymphocytes. : 10.4049/immunohorizons.1900030. PMID: 31427364
Chandiramani R, Chen H, Aoi S, Giustino G, Claessen B, Sartori S, Aquino M, Sorrentino S, Cao D, Goel R, Kini A, Rao S, Weintraub W, Henry TD, Kapadia S, **DeFranco A,** Muhlestein JB, Toma C, Effron MB, Keller S, Baker BA, Pocock S, Baber U, Mehran R. Incidence, predictors and impact of stroke on mortality among patients with acute coronary syndromes following percutaneous coronary intervention-Results from the PROMETHEUS registry. *Catheter Cardiovasc Interv.* 2019 Jun 14. doi: 10.1002/ccd.28369. [Epub ahead of print]. PMID: 31197962
Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, Bajwa T, Heiser JC, Merhi W, Kleiman NS, Askew J, Sorajja P, Rovin J, Chetcuti SJ, Adams DH, Teirstein PS, Zorn GL 3rd, Forrest JK, Tchétché D, Resar J, Walton A, Piazza N, Ramlawi B, Robinson N, Petrossian G, Gleason TG, Oh JK, Boulware MJ, Qiao H, Mugglin AS, Reardon MJ; Evolut Low Risk Trial Investigators. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. *N Engl J Med*. 2019 May 2;380(18):1706-1715. doi: 10.1056/NEJMoa1816885. Epub 2019 Mar 16. PMID: 30883053
Ge Z, Baber U, Claessen BE, Chandrasekhar J, Chandiramani R, Li SX, Sartori S, Kini AS, Rao SV, Weiss S, Henry TD, Kapadia S, Muhlestein B, Strauss C, Toma C, **DeFranco A,** Effron MB, Keller S, Baker BA, Pocock S, Dangas G, Mehran R. Associations between use of prasugrel vs clopidogrel and outcomes by type of acute coronary syndrome: an analysis from the PROMETHEUS registry. *J Thromb Thrombolysis*. 2019 Mar 28. doi: 10.1007/s11239-019-01842-9. [Epub ahead of print]. PMID: 30924052
Faggioni M, Baber U, Chandrasekhar J, Sartori S, Weintraub W, Rao SV, Vogel B, Claessen B, Kini A, Effron M, Ge Z, Keller S, Strauss C, Snyder C, Toma C, Weiss S, Aquino M, Baker B, **Defranco A**, Bansilal S, Muhlestein B, Kapadia S, Pocock S, Poddar KL, Henry TD, Mehran R. Use of prasugrel and clinical outcomes in African-American patients treated with percutaneous coronary intervention for acute coronary syndromes. *Catheter Cardiovasc Interv*. 2019 Jan 17. doi: 10.1002/ccd.28033. [Epub ahead of print]. PMID: 30656812
Faggioni M, Baber U, Chandrasekhar J, Sartori S, Claessen BE, Rao SV, Vogel B, Effron MB, Poddar K, Farhan S, Kini A, Weintraub W, Toma C, Sorrentino S, Weiss S, Snyder C, Muhlestein JB, Kapadia S, Keller S, Strauss C, Aquino M, Baker B, **Defranco A,** Pocock S, Henry T, Mehran R. Use of prasugrel vs clopidogrel and outcomes in patients with and without diabetes mellitus presenting with acute coronary syndrome undergoing percutaneous coronary intervention. *Int J Cardiol.* 2019 Jan 15; 275:31-35. doi: 10.1016/j.ijcard.2018.10.071. Epub 2018 Oct 25. PMID: 30391067
Ge Z, Baber U, Claessen BE, Farhan S, Chandrasekhar J, Li SX, Sartori S, Kini AS, Rao SV, Weiss S, Henry TD, Vogel B, Sorrentino S, Faggioni M, Kapadia S, Muhlestein B, Strauss C, Toma C, **DeFranco A**, Effron MB, Keller S, Baker BA, Pocock S, Dangas G, Mehran R. The prevalence, predictors and outcomes of guideline-directed medical therapy in patients with acute myocardial infarction undergoing PCI, an analysis from the PROMETHEUS registry. *Catheter Cardiovasc Interv*. 2019 Feb 15;93(3): E112-E119. doi: 10.1002/ccd.27860. Epub 2018 Oct 23. PMID: 30351514

William F. DeGrado

Mann SI, Nayak A, Gassner GT, Therien MJ, **DeGrado WF.** *De Novo* Design, Solution Characterization, and Crystallographic Structure of an Abiological Mn-Porphyrin-Binding Protein Capable of Stabilizing a Mn(V) Species. *J Am Chem Soc*. 2021 Jan 13;143(1):252-259. doi: 10.1021/jacs.0c10136. Epub 2020 Dec 29. PMID: 33373215

Newberry RW, Leong JT, Chow ED, Kampmann M, **DeGrado WF.** Deep mutational scanning reveals the structural basis for α-synuclein activity. *Nat Chem Biol*. 2020 Jun;16(6):653-659. doi: 10.1038/s41589-020-0480-6. Epub 2020 Mar 9. PMID: 32152544

Korendovych IV, **DeGrado WF.** *De novo* protein design, a retrospective. *Q Rev Biophys*. 2020 Feb 11;53: e3. doi: 10.1017/S0033583519000131. PMID: 32041676

Condello C, **DeGrado WF**, Prusiner SB. Prion biology: implications for Alzheimer's disease therapeutics. *Lancet Neurol*. 2020 Oct;19(10):802-803. doi: 10.1016/S1474-4422(20)30274-X. Epub 2020 Sep 16. PMID: 32949533

Sundaram A, Chen C, Isik Reed N, Liu S, Ki Yeon S, McIntosh J, Tang YZ, Yang H, Adler M, Beresis R, Seiple IB, Sheppard D, **DeGrado WF**, Jo H. Dual antagonists of α5β1/αvβ1 integrin for airway hyperresponsiveness. *Bioorg Med Chem Lett.* 2020 Nov 15;30(22):127578. doi: 10.1016/j.bmcl.2020.127578. Epub 2020 Sep 29. PMID: 33007395

Boyce JH, Dang B, Ary B, Edmondson Q, Craik CS, **DeGrado WF**, Seiple IB. Platform to Discover Protease-Activated Antibiotics and Application to Siderophore-Antibiotic Conjugates. *J Am Chem Soc*. 2020 Dec 23;142(51):21310-21321. doi: 10.1021/jacs.0c06987. Epub 2020 Dec 10. PMID: 33301681

Pirro F, Schmidt N, Lincoff J, Widel ZX, Polizzi NF, Liu L, Therien MJ, Grabe M, Chino M, Lombardi A, **DeGrado WF.** Allosteric cooperation in a de novo-designed two-domain protein. *Proc Natl Acad Sci U S A*. 2020 Dec 29;117(52):33246-33253. doi: 10.1073/pnas.2017062117. Epub 2020 Dec 14. PMID: 33318174 Free

Polizzi NF, **DeGrado WF.** A defined structural unit enables de novo design of small-molecule-binding proteins. *Science.* 2020 Sep 4;369(6508):1227-1233. doi: 10.1126/science.abb8330. PMID: 32883865

Newberry RW, Arhar T, Costello J, Hartoularos GC, Maxwell AM, Naing ZZC, Pittman M, Reddy NR, Schwarz DMC, Wassarman DR, Wu TS, Barrero D, Caggiano C, Catching A, Cavazos TB, Estes LS, Faust B, Fink EA, Goldman MA, Gomez YK, Gordon MG, Gunsalus LM, Hoppe N, Jaime-Garza M, Johnson MC, Jones MG, Kung AF, Lopez KE, Lumpe J, Martyn C, McCarthy EE, Miller-Vedam LE, Navarro EJ, Palar A, Pellegrino J, Saylor W, Stephens CA, Strickland J, Torosyan H, Wankowicz SA, Wong DR, Wong G, Redding S, Chow ED, **DeGrado WF**, Kampmann M. Robust Sequence Determinants of α-Synuclein Toxicity in Yeast Implicate Membrane Binding. *ACS Chem Biol*. 2020 Aug 21;15(8):2137-2153. doi: 10.1021/acschembio.0c00339. Epub 2020 Aug 12. PMID: 32786289

Watkins LC, **DeGrado WF**, Voth GA. Influenza A M2 Inhibitor Binding Understood through Mechanisms of Excess Proton Stabilization and Channel Dynamics. *J Am Chem Soc*. 2020 Oct 14;142(41):17425-17433. doi: 10.1021/jacs.0c06419. Epub 2020 Sep 29. PMID: 32933245

Thomaston JL, Konstantinidi A, Liu L, Lambrinidis G, Tan J, Caffrey M, Wang J, **Degrado WF**, Kolocouris A. X-ray Crystal Structures of the Influenza M2 Proton Channel Drug-Resistant V27A Mutant Bound to a Spiro-Adamantyl Amine Inhibitor Reveal the Mechanism

of Adamantane Resistance. *Biochemistry*. 2020 Feb 4;59(4):627-634. doi: 10.1021/acs.biochem.9b00971. Epub 2020 Jan 13. PMID: 31894969

Park J, Selvaraj B, McShan AC, Boyken SE, Wei KY, Oberdorfer G, **DeGrado W**, Sgourakis NG, Cuneo MJ, Myles DA, Baker D. De novo design of a homo-trimeric amantadine-binding protein. *Elife*. 2019 Dec 19;8. pii: e47839. doi: 10.7554/eLife.47839. PMID: 31854299

Del Cid JS, Reed NI, Molnar K, Liu S, Dang B, Jensen SA, **DeGrado W**, Handford PA, Sheppard D, Sundaram AB. A disease-associated mutation in fibrillin-1 differentially regulates integrin-mediated cell adhesion. *J Biol Chem*. 2019 Nov 29;294(48):1823 2-18243. doi: 10.1074/jbc.RA119.011109. Epub 2019 Oct 22. PMID: 31640988

Dregni AJ, Mandala VS, Wu H, Elkins MR, Wang HK, Hung I, **DeGrado WF**, Hong M. In vitro 0N4R tau fibrils contain a monomorphic β-sheet core enclosed by dynamically heterogeneous fuzzy coat segments. *Proc Natl Acad Sci U S A*. 2019 Aug 13;116(33):16357-16366. doi: 10.1073/pnas.1906839116. Epub 2019 Jul 29. PMID: 31358628

Tan SK, Fong KP, Polizzi NF, Sternisha A, Slusky JSG, Yoon K, **DeGrado WF,** Bennett JS. Modulating Integrin αIIbβ3 Activity through Mutagenesis of Allosterically Regulated Intersubunit Contacts. *Biochemistry*. 2019 Jul 30;58(30):3251-3259. doi: 10.1021/acs.biochem.9b00430. Epub 2019 Jul 12. PMID: 31264850

Watkins LC, Liang R, Swanson JMJ, **DeGrado WF**, Voth GA. Proton-Induced Conformational and Hydration Dynamics in the Influenza A M2 Channel. *J Am Chem Soc*. 2019 Jul 24;141(29):11667-11676. doi: 10.1021/jacs.9b05136. Epub 2019 Jul 12. PMID: 31264413

Thomaston JL, Wu Y, Polizzi N, Liu L, Wang J, **DeGrado WF**. X-ray Crystal Structure of the Influenza a M2 Proton Channel S31N Mutant in Two Conformational States: An Open and Shut Case. *J Am Chem Soc*. 2019 Jul 24;141(29):11481-11488. doi: 10.1021/jacs.9b02196. Epub 2019 Jul 11. PMID: 31184871

Litvinov RI, Mravic M, Zhu H, Weisel JW, **DeGrado WF**, Bennett JS. Unique transmembrane domain interactions differentially modulate integrin αvβ3 and αIIbβ3 function. *Proc Natl Acad Sci U S A*. 2019 Jun 18;116(25):12295-12300. doi: 10.1073/pnas.1904867116. Epub 2019 Jun 3. Erratum in: *Proc Natl Acad Sci U S A*. 2019 Jun 24;. PMID: 31160446

Aoyagi A, Condello C, Stöhr J, Yue W, Rivera BM, Lee JC, Woerman AL, Halliday G, van Duinen S, Ingelsson M, Lannfelt L, Graff C, Bird TD, Keene CD, Seeley WW, **DeGrado WF,** Prusiner SB. Aβ and tau prion-like activities decline with longevity in the Alzheimer's disease human brain. *Sci Transl Med.* 2019 May 1;11(490). pii: eaat8462. doi: 10.1126/scitranslmed. aat8462. PMID: 31043574

Yang B, Wang N, Schnier PD, Zheng F, Zhu H, Polizzi NF, Ittuveetil A, Saikam V, **DeGrado WF**, Wang Q, Wang PG, Wang L. Genetically Introducing Biochemically Reactive Amino Acids Dehydroalanine and Dehydrobutyrine in Proteins. *J Am Chem Soc*. 2019 May 15;141(19):7698-7703. doi: 10.1021/jacs.9b02611. Epub 2019 May 3. PMID: 31038942

Wu H, Saltzberg DJ, Kratochvil HT, Jo H, Sali A, **DeGrado WF**. Glutamine Side Chain 13C═18O as a Nonperturbative IR Probe of Amyloid Fibril Hydration and Assembly. *J Am Chem Soc*. 2019 May 8;141(18):7320-7326. doi: 10.1021/jacs.9b00577. Epub 2019 Apr 24. PMID: 30998340

Lombardi A, Pirro F, Maglio O, Chino M, **DeGrado WF**. De Novo Design of Four-Helix Bundle Metalloproteins: One Scaffold, Diverse Reactivities. *Acc Chem Res*. 2019 May 21;52(5):1148-1159. doi: 10.1021/acs.accounts.8b00674. Epub 2019 Apr 11. PMID: 30973707

Zhang K, Ahmed IA, Kratochvil HT, **DeGrado WF**, Gai F, Jo H. Synthesis and application of the blue, fluorescent amino acid l-4-cyanotryptophan to assess peptide-membrane interactions. *Chem Commun* (Camb). 2019 Apr 8. doi: 10.1039/c9cc01152h. [Epub ahead of print]. PMID: 30957824

Dang B, Mravic M, Hu H, Schmidt N, Mensa B, **DeGrado WF**. SNAC-tag for sequence-specific chemical protein cleavage. *Nat Methods*. 2019 Apr;16(4):319-322. doi: 10.1038/s41592-019-0357-3. Epub 2019 Mar 25. PMID: 30923372

Mravic M, Thomaston JL, Tucker M, Solomon PE, Liu L, **DeGrado WF**. Packing of apolar side chains enables accurate design of highly stable membrane proteins. *Science*. 2019 Mar 29;363(6434):1418-1423. doi: 10.1126/science. aav7541. PMID: 30923216

Ahmed IA, Acharyya A, Eng CM, Rodgers JM, **DeGrado WF**, Jo H, Gai F. 4-Cyanoindole-2'-deoxyribonucleoside as a Dual Fluorescence and Infrared Probe of DNA Structure and Dynamics. *Molecules*. 2019 Feb 8;24(3). pii: E602. doi: 10.3390/molecules24030602. PMID: 30744004

Acharyya A, Ge Y, Wu H, **DeGrado WF**, Voelz VA, Gai F. Exposing the Nucleation Site in α-Helix Folding: A Joint Experimental and Simulation Study. *J Phys Chem B*. 2019 Feb 28;123(8):1797-1807. doi: 10.1021/acs.jpcb.8b12220. Epub 2019 Feb 14. PMID: 30694671

David Erle, M.D.

Bonser LR, Koh KD, Johansson K, Choksi SP, Cheng D, Liu L, Sun DI, Zlock LT, Eckalbar WL, Finkbeiner WE, **Erle DJ.** Flow-Cytometric Analysis and Purification of Airway Epithelial-Cell Subsets. *Am J Respir Cell Mol Biol*. 2021 Mar;64(3):308-317. doi: 10.1165/rcmb.2020-0149MA. PMID: 33196316

Gui H, Levin AM, Hu D, Sleiman P, Xiao S, Mak ACY, Yang M, Barczak AJ, Huntsman S, Eng C, Hochstadt S, Zhang E, Whitehouse K, Simons S, Cabral W, Takriti S, Abecasis G, Blackwell TW, Kang HM, Nickerson DA, Germer S, Lanfear DE, Gilliland F, Gauderman WJ, Kumar R, **Erle DJ**, Martinez FD, Hakonarson H, Burchard EG, Williams LK. Mapping the 17q12-21.1 Locus for Variants Associated with Early-Onset Asthma in African Americans. *Am J Respir Crit Care Med.* 2021 Feb 15;203(4):424-436. doi: 10.1164/rccm.202006-2623OC. PMID: 32966749

Sarma A, Christenson S, Mick E, Deiss T, DeVoe C, Pisco A, Ghale R, Jauregui A, Byrne A, Moazed F, Spottiswoode N, Sinha P, Zha B, Neff N, Tan M, Serpa PH, Ansel KM, Wilson J, Leligdowicz A, Seigel E, Sirota M, DeRisi J, Matthay M, Consortium C, Hendrickson C, Kangelaris K, Krummel M, Woodruff P, **Erle D**, Calfee C, Langelier C. COVID-19 ARDS is characterized by a dysregulated host response that differs from cytokine storm and is modified by dexamethasone. *Res Sq.* 2021 Jan 14: rs.3.rs-141578. doi: 10.21203/rs.3.rs-141578/v1. Preprint. PMID: 33469573

Siddiqui S, Johansson K, Joo A, Bonser LR, Koh KD, Le Tonqueze O, Bolourchi S, Bautista RA, Zlock L, Roth TL, Marson A, Bhakta NR, Ansel KM, Finkbeiner WE, **Erle DJ**, Woodruff PG. Epithelial miR-141 regulates IL-13-induced airway mucus production. *JCI Insight*. 2021 Mar 8;6(5):139019. doi: 10.1172/jci.insight.139019. PMID: 33682796

Bonser LR, Eckalbar WL, Rodriguez L, Shen J, Koh KD, Zlock LT, Christenson S, Woodruff PG, Finkbeiner WE, **Erle DJ.** The type 2 asthma mediator IL-13 inhibits SARS-CoV-2 infection of bronchial epithelium. *bioRxiv*. 2021 Feb 25:2021.02.25.432762. doi: 10.1101/2021.02.25.432762. Preprint. PMID: 33655249

Combes AJ, Courau T, Kuhn NF, Hu KH, Ray A, Chen WS, Chew NW, Cleary SJ, Kushnoor D, Reeder GC, Shen A, Tsui J, Hiam-Galvez KJ, Muñoz-Sandoval P, Zhu WS, Lee DS, Sun Y, You R, Magnen M, Rodriguez L, Im KW, Serwas NK, Leligdowicz A, Zamecnik CR, Loudermilk RP, Wilson MR, Ye CJ, Fragiadakis GK, Looney MR, Chan V, Ward A, Carrillo S; UCSF COMET Consortium, Matthay M, **Erle DJ**, Woodruff PG, Langelier C, Kangelaris K, Hendrickson CM, Calfee C, Rao AA, Krummel MF. Global absence and targeting of protective immune states in severe COVID-19. *Nature.* 2021 Mar;591(7848):124-130. doi: 10.1038/s41586-021-03234-7. Epub 2021 Jan 25. PMID: 33494096

Samuel RM, Majd H, Richter MN, Ghazizadeh Z, Zekavat SM, Navickas A, Ramirez JT, Asgharian H, Simoneau CR, Bonser LR, Koh KD, Garcia-Knight M, Tassetto M, Sunshine S, Farahvashi S, Kalantari A, Liu W, Andino R, Zhao H, Natarajan P, **Erle DJ**, Ott M, Goodarzi H, Fattahi F. Androgen Signaling Regulates SARS-CoV-2 Receptor Levels and Is Associated with Severe COVID-19 Symptoms in Men. *Cell Stem Cell.* 2020 Dec 3;27(6):876-889.e12. doi: 10.1016/j.stem.2020.11.009. Epub 2020 Nov 17. PMID: 33232663

Koh KD, **Erle DJ.** Steps toward Cell Therapy for Cystic Fibrosis. *Am J Respir Cell Mol Biol*. 2020 Sep;63(3):275-276. doi: 10.1165/rcmb.2020-0235ED. PMID: 32648785

Koh KD, Siddiqui S, Cheng D, Bonser LR, Sun DI, Zlock LT, Finkbeiner WE, Woodruff PG, **Erle DJ.** Efficient RNP-directed Human Gene Targeting Reveals SPDEF Is Required for IL-13-induced Mucostasis. *Am J Respir Cell Mol Biol*. 2020 Mar;62(3):373-381. doi: 10.1165/rcmb.2019-0266OC. PMID: 31596609

Lee EY, Mak ACY, Hu D, Sajuthi S, White MJ, Keys KL, Eckalbar W, Bonser L, Huntsman S, Urbanek C, Eng C, Jain D, Abecasis G, Kang HM, Germer S, Zody MC, Nickerson DA, **Erle D**, Ziv E, Rodriguez-Santana J, Seibold MA, Burchard EG. Whole-Genome Sequencing Identifies Novel Functional Loci Associated with Lung Function in Puerto Rican Youth. *Am J Respir Crit Care Med*. 2020 Oct 1;202(7):962-972. doi: 10.1164/rccm.202002-0351OC. PMID: 32459537

Cocco MP, White E, Xiao S, Hu D, Mak A, Sleiman P, Yang M, Bobbitt KR, Gui H, Levin AM, Hochstadt S, Whitehouse K, Rynkowski D, Barczak AJ, Abecasis G, Blackwell TW, Kang HM, Nickerson DA, Germer S, Ding J, Lanfear DE, Gilliland F, Gauderman WJ, Kumar R, **Erle DJ**, Martinez F, Hakonarson H, Burchard EG, Williams LK. Asthma and its relationship to mitochondrial copy number: Results from the Asthma Translational Genomics Collaborative (ATGC) of the Trans-Omics for Precision Medicine (TOPMed) program. *PLoS One*. 2020 Nov 25;15(11): e0242364. doi: 10.1371/journal.pone.0242364. eCollection 2020. PMID: 33237978 Free PMC article.

Godoy PM, Barczak AJ, DeHoff P, Srinivasan S, Etheridge A, Galas D, Das S, **Erle DJ**, Laurent LC. Comparison of Reproducibility, Accuracy, Sensitivity, and Specificity of miRNA Quantification Platforms. *Cell Rep*. 2019 Dec 17;29(12):4212-4222.e5. doi: 10.1016/j.celrep.2019.11.078. PMID: 31851944

Koh KD, Siddiqui S, Cheng D, Bonser LR, Sun DI, Zlock LT, Finkbeiner WE, Woodruff PG, **Erle DJ**. Efficient RNP-Directed Human Gene Targeting Reveals SPDEF is Required

for IL-13-Induced Mucostasis. *Am J Respir Cell Mol Biol.* 2019 Oct 9. doi: 10.1165/rcmb.2019-0266OC. [Epub ahead of print]. PMID: 31596609
Bonser LR, **Erle DJ**. The airway epithelium in asthma. *Adv Immunol*. 2019; 142:1-34. doi: 10.1016/bs.ai.2019.05.001. Epub 2019 Jul 1. PMID: 31296301
Sin JH, Zuckerman C, Cortez JT, Eckalbar WL, **Erle DJ**, Anderson MS, Waterfield MR. The epigenetic regulator ATF7ip inhibits Il2 expression, regulating Th17 responses. *J Exp Med*. 2019 Sep 2;216(9):2024-2037. doi: 10.1084/jem.20182316. Epub 2019 Jun 19. PMID: 31217192
Litterman AJ, Kageyama R, Le Tonqueze O, Zhao W, Gagnon JD, Goodarzi H, **Erle DJ**, Ansel KM. A massively parallel 3' UTR reporter assay reveals relationships between nucleotide content, sequence conservation, and mRNA destabilization. *Genome Res*. 2019 Jun;29(6):896-906. doi: 10.1101/gr.242552.118. Epub 2019 May 31. PMID: 31152051
Eckalbar WL, **Erle DJ**. Singling out Th2 cells in eosinophilic esophagitis. *J Clin Invest*. 2019 Apr 8;130. pii: 128479. doi: 10.1172/JCI128479. eCollection 2019 Apr 8. PMID:30958801
Christenson SA, van den Berge M, Faiz A, Inkamp K, Bhakta N, Bonser LR, Zlock LT, Barjaktarevic IZ, Barr RG, Bleecker ER, Boucher RC, Bowler RP, Comellas AP, Curtis JL, Han MK, Hansel NN, Hiemstra PS, Kaner RJ, Krishnanm JA, Martinez FJ, O'Neal WK, Paine R 3rd, Timens W, Wells JM, Spira A, **Erle DJ**, Woodruff PG. An airway epithelial IL-17A response signature identifies a steroid-unresponsive COPD patient subgroup. *J Clin Invest*. 2019 Jan 2;129(1):169-181. doi: 10.1172/JCI121087. Epub 2018 Nov 26. PMID:30383540
Bonser LR, **Erle DJ**. Putting Mucins on the Map. *Am J Respir Crit Care Med*. 2019 Mar 15;199(6):681-682. doi: 10.1164/rccm.201809-1818ED. No abstract available. PMID:30376352

John Fahy, M.D.
Maun HR, Jackman JK, Choy DF, Loyet KM, Staton TL, Jia G, Dressen A, Hackney JA, Bremer M, Walters BT, Vij R, Chen X, Trivedi NN, Morando A, Lipari MT, Franke Y, Wu X, Zhang J, Liu J, Wu P, Chang D, Orozco LD, Christensen E, Wong M, Corpuz R, Hang JQ, Lutman J, Sukumaran S, Wu Y, Ubhayakar S, Liang X, Schwartz LB, Babina M, Woodruff PG, **Fahy JV**, Ahuja R, Caughey GH, Kusi A, Dennis MS, Eigenbrot C, Kirchhofer D, Austin CD, Wu LC, Koerber JT, Lee WP, Yaspan BL, Alatsis KR, Arron JR, Lazarus RA, Yi T. An Allosteric Anti-tryptase Antibody for the Treatment of Mast Cell-Mediated Severe Asthma. *Cell.* 2020 Jan 23;180(2):406. doi: 10.1016/j.cell.2020.01.003. No abstract available. PMID: 31978350
Zein J, Gaston B, Bazeley P, DeBoer MD, Igo RP Jr, Bleecker ER, Meyers D, Comhair S, Marozkina NV, Cotton C, Patel M, Alyamani M, Xu W, Busse WW, Calhoun WJ, Ortega V, Hawkins GA, Castro M, Chung KF, **Fahy JV**, Fitzpatrick AM, Israel E, Jarjour NN, Levy B, Mauger DT, Moore WC, Noel P, Peters SP, Teague WG, Wenzel SE, Erzurum SC, Sharifi N. HSD3B1 genotype identifies glucocorticoid responsiveness in severe asthma. *Proc Natl Acad Sci U S A*. 2020 Jan 28;117(4):2187-2193. doi: 10.1073/pnas.1918819117. Epub 2020 Jan 13. PMID: 31932420
Ross KR, Gupta R, DeBoer MD, Zein J, Phillips BR, Mauger DT, Li C, Myers RE, Phipatanakul W, Fitzpatrick AM, Ly NP, Bacharier LB, Jackson DJ, Celedón JC, Larkin A, Israel E, Levy B, **Fahy JV**, Castro M, Bleecker ER, Meyers D, Moore WC, Wenzel SE,

Jarjour NN, Erzurum SC, Teague WG, Gaston B. Severe asthma during childhood and adolescence: A longitudinal study. *J Allergy Clin Immunol*. 2020 Jan;145(1):140-146.e9. doi: 10.1016/j.jaci.2019.09.030. Epub 2019 Oct 14. PMID: 31622688

Fitzpatrick AM, Szefler SJ, Mauger DT, Phillips BR, Denlinger LC, Moore WC, Sorkness RL, Wenzel SE, Gergen PJ, Bleecker ER, Castro M, Erzurum SC, **Fahy JV**, Gaston BM, Israel E, Levy BD, Meyers DA, Teague WG, Bacharier LB, Ly NP, Phipatanakul W, Ross KR, Zein J, Jarjour NN. Development and initial validation of the Asthma Severity Scoring System (ASSESS). *J Allergy Clin Immunol*. 2020 Jan;145(1):127-139. doi: 10.1016/j.jaci.2019.09.018. Epub 2019 Oct 8. PMID: 31604088

Li X, Hastie AT, Peters MC, Hawkins GA, Phipatanakul W, Li H, Moore WC, Busse WW, Castro M, Erzurum SC, Gaston B, Israel E, Jarjour NN, Levy BD, Wenzel SE, Meyers DA, **Fahy JV**, Bleecker ER; National Heart, Lung, and Blood Institute's Severe Asthma Research Program (SARP) Networks. Investigation of the relationship between IL-6 and type 2 biomarkers in patients with severe asthma. *J Allergy Clin Immunol*. 2020 Jan;145(1):430-433. doi: 10.1016/j.jaci.2019.08.031. Epub 2019 Sep 9. No abstract available. PMID: 31513878

Maun HR, Jackman JK, Choy DF, Loyet KM, Staton TL, Jia G, Dressen A, Hackney JA, Bremer M, Walters BT, Vij R, Chen X, Trivedi NN, Morando A, Lipari MT, Franke Y, Wu X, Zhang J, Liu J, Wu P, Chang D, Orozco LD, Christensen E, Wong M, Corpuz R, Hang JQ, Lutman J, Sukumaran S, Wu Y, Ubhayakar S, Liang X, Schwartz LB, Babina M, Woodruff PG, **Fahy JV**, Ahuja R, Caughey GH, Kusi A, Dennis MS, Eigenbrot C, Kirchhofer D, Austin CD, Wu LC, Koerber JT, Lee WP, Yaspan BL, Alatsis KR, Arron JR, Lazarus RA, Yi T . An Allosteric Anti-tryptase Antibody for the Treatment of Mast Cell-Mediated Severe Asthma. *Cell.* 2019 Oct 3;179(2):417-431.e19. doi: 10.1016/j.cell.2019.09.009. Erratum in: Cell. 2020 Jan 23;180(2):406. PMID: 31585081

Mah PT, O'Connell P, Focaroli S, Lundy R, O'Mahony TF, Hastedt JE, Gitlin I, Oscarson S, **Fahy JV**, Healy AM. The use of hydrophobic amino acids in protecting spray dried trehalose formulations against moisture-induced changes. *Eur J Pharm Biopharm*. 2019 Nov; 144:139-153. doi: 10.1016/j.ejpb.2019.09.014. Epub 2019 Sep 16. PMID: 31536784

Ash SY, Sanchez-Ferrero GV, Schiebler ML, Rahaghi FN, Rai A, Come CE, Ross JC, Colon AG, Cardet JC, Bleecker ER, Castro M, **Fahy JV**, Fain SB, Gaston BM, Hoffman EA, Jarjour NN, Lempel JK, Mauger DT, Tattersall MC, Wenzel SE, Levy BD, Washko GR, Israel E, San Jose Estepar R; SARP Investigators. Estimated Ventricular Size, Asthma Severity, and Exacerbations: The Severe Asthma Research Program III Cohort. *Chest*. 2020 Feb;157(2):258-267. doi: 10.1016/j.chest.2019.08.2185. Epub 2019 Sep 12. PMID: 31521672

Fahy JV, Locksley RM. Making Asthma Crystal Clear. *N Engl J Med*. 2019 Aug 29;381(9):882-884. doi: 10.1056/NEJMcibr1908064. No abstract available. PMID: 31461600

Coverstone AM, Bacharier LB, Wilson BS, Fitzpatrick AM, Teague WG, Phipatanakul W, Wenzel SE, Gaston BM, Bleecker ER, Moore WC, Ramratnam S, Jarjour NN, Ly NP, **Fahy JV**, Mauger DT, Schechtman KB, Yin-DeClue H, Boomer JS, Castro M. Clinical significance of the bronchodilator response in children with severe asthma. *Pediatr Pulmonol.* 2019 Nov;54(11):1694-1703. doi: 10.1002/ppul.24473. Epub 2019 Aug 19. PMID: 31424170

Lazarus SC, Krishnan JA, King TS, Lang JE, Blake KV, Covar R, Lugogo N, Wenzel S, Chinchilli VM, Mauger DT, Dyer AM, Boushey HA, **Fahy JV**, Woodruff PG, Bacharier LB, Cabana MD, Cardet JC, Castro M, Chmiel J, Denlinger L, DiMango E, Fitzpatrick AM, Gentile D, Hastie A, Holguin F, Israel E, Jackson D, Kraft M, LaForce C, Lemanske RF Jr, Martinez FD, Moore W, Morgan WJ, Moy JN, Myers R, Peters SP, Phipatanakul W, Pongracic JA, Que L, Ross K, Smith L, Szefler SJ, Wechsler ME, Sorkness CA; National Heart, Lung, and Blood Institute AsthmaNet. Mometasone or Tiotropium in Mild Asthma with a Low Sputum Eosinophil Level. *N Engl J Med*. 2019 May 23;380(21):2009-2019. doi: 10.1056/NEJMoa1814917. Epub 2019 May 19. PMID: 31112384

Schaefer N, Li X, Seibold MA, Jarjour NN, Denlinger LC, Castro M, Coverstone AM, Teague WG, Boomer J, Bleecker ER, Meyers DA, Moore WC, Hawkins GA, **Fahy J,** Phillips BR, Mauger DT, Dakhama A, Gellatly S, Pavelka N, Berman R, Di YP, Wenzel SE, Chu HW. The effect of BPIFA1/SPLUNC1 genetic variation on its expression and function in asthmatic airway epithelium. *JCI Insight.* 2019 Apr 18;4(8). pii: 127237. doi: 10.1172/jci.insight.127237. eCollection 2019 Apr 18. PMID: 30996135

Lambrecht BN, Hammad H, **Fahy JV**. The Cytokines of Asthma. *Immunity.* 2019 Apr 16;50(4):975-991. doi: 10.1016/j.immuni.2019.03.018. Review. PMID: 30995510

Lachowicz-Scroggins ME, Dunican EM, Charbit AR, Raymond W, Looney MR, Peters MC, Gordon ED, Woodruff PG, Lefrançais E, Phillips BR, Mauger DT, Comhair SA, Erzurum SC, Johansson MW, Jarjour NN, Coverstone AM, Castro M, Hastie AT, Bleecker ER, Fajt ML, Wenzel SE, Israel E, D Levy B, **Fahy JV**; National Heart, Lung, and Blood Institute Severe Asthma Research Program-3 Investigators. Extracellular DNA, Neutrophil Extracellular Traps, and Inflammasome Activation in Severe Asthma. *Am J Respir Crit Care Med.* 2019 Mar 19. doi: 10.1164/rccm.201810-1869OC. [Epub ahead of print]. PMID: 30888839

Wu W, Bang S, Bleecker ER, Castro M, Denlinger L, Erzurum SC, **Fahy JV,** Fitzpatrick AM, Gaston BM, Hastie AT, Israel E, Jarjour NN, Levy BD, Mauger DT, Meyers DA, Moore WC, Peters M, Phillips BR, Phipatanakul W, Sorkness RL, Wenzel SE. Multiview Cluster Analysis Identifies Variable Corticosteroid Response Phenotypes in Severe Asthma. *Am J Respir Crit Care Med*. 2019 Jan 25. doi: 10.1164/rccm.201808-1543OC. [Epub ahead of print]. PMID:30682261

Fitzpatrick AM, Gillespie SE, Mauger DT, Phillips BR, Bleecker ER, Israel E, Meyers DA, Moore WC, Sorkness RL, Wenzel SE, Bacharier LB, Castro M, Denlinger LC, Erzurum SC, **Fahy JV**, Gaston BM, Jarjour NN, Larkin A, Levy BD, Ly NP, Ortega VE, Peters SP, Phipatanakul W, Ramratnam S, Teague WG. Racial disparities in asthma-related health care use in the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol.* 2019 Jan 8. pii: S0091-6749(18)31732-9. doi: 10.1016/j.jaci.2018.11.022. [Epub ahead of print]. PMID:30635198

Peters MC, Ringel L, Dyjack N, Herrin R, Woodruff PG, Rios C, O'Connor B, **Fahy JV,** Seibold MA. A Transcriptomic Method to Determine Airway Immune Dysfunction in T2-High and T2-Low Asthma. *Am J Respir Crit Care Med*. 2019 Feb 15;199(4):465-477. doi: 10.1164/rccm.201807-1291OC. PMID:30371106

James S. Fraser, Ph.D.

Rotow JK, Gui P, Wu W, Raymond VM, Lanman RB, Kaye FJ, Peled N, Fece de la Cruz F, Nadres B, Corcoran RB, Yeh I, Bastian BC, Starostik P, Newsom K, Olivas VR, Wolff AM, **Fraser JS**, Collisson EA, McCoach CE, Camidge DR, Pacheco J, Bazhenova L, Li T, Bivona TG, Blakely CM. Co-occurring Alterations in the RAS-MAPK Pathway Limit Response to MET Inhibitor Treatment in MET Exon 14 Skipping Mutation-Positive Lung Cancer. *Clin Cancer Res*. 2020 Jan 15;26(2):439-449. doi: 10.1158/1078-0432.CCR-19-1667. Epub 2019 Sep 23. PMID: 31548343

Stojković V, Myasnikov AG, Young ID, Frost A, **Fraser JS**, Fujimori DG. Assessment of the nucleotide modifications in the high-resolution cryo-electron microscopy structure of the Escherichia coli 50S subunit. *Nucleic Acids Res*. 2020 Jan 28. pii: gkaa037. doi: 10.1093/nar/gkaa037. [Epub ahead of print]. PMID: 31989172

Barad BA, Liu L, Diaz RE, Basilio R, Van Dyken SJ, Locksley RM, **Fraser JS**. Differences in the chitinolytic activity of mammalian chitinases on soluble and insoluble substrates. *Protein Sci*. 2020 Jan 12. doi: 10.1002/pro.3822. [Epub ahead of print]. PMID: 31930591

Wych DC, **Fraser JS**, Mobley DL, Wall ME. Liquid-like and rigid-body motions in molecular-dynamics simulations of a crystalline protein. *Struct Dyn*. 2019 Dec 18;6(6):064704. doi: 10.1063/1.5132692. eCollection 2019 Nov. PMID: 31867408

Dasgupta M, Budday D, de Oliveira SHP, Madzelan P, Marchany-Rivera D, Seravalli J, Hayes B, Sierra RG, Boutet S, Hunter MS, Alonso-Mori R, Batyuk A, Wierman J, Lyubimov A, Brewster AS, Sauter NK, Applegate GA, Tiwari VK, Berkowitz DB, Thompson MC, Cohen AE, **Fraser JS**, Wall ME, van den Bedem H, Wilson MA. Mix-and-inject XFEL crystallography reveals gated conformational dynamics during enzyme catalysis. *Proc Natl Acad Sci U S A*. 2019 Dec 17;116(51):25634-25640. doi: 10.1073/pnas.1901864116. Epub 2019 Dec 4. PMID: 31801874

Glasgow AA, Huang YM, Mandell DJ, Thompson M, Ritterson R, Loshbaugh AL, Pellegrino J, Krivacic C, Pache RA, Barlow KA, Ollikainen N, Jeon D, Kelly MJS, **Fraser JS**, Kortemme T. Computational design of a modular protein sense-response system. *Science*. 2019 Nov 22;366(6468):1024-1028. doi: 10.1126/science. aax8780. PMID: 31754004

Thompson MC, Barad BA, Wolff AM, Sun Cho H, Schotte F, Schwarz DMC, Anfinrud P, **Fraser JS.** Temperature-jump solution X-ray scattering reveals distinct motions in a dynamic enzyme. *Nat Chem*. 2019 Nov;11(11):1058-1066. doi: 10.1038/s41557-019-0329-3. Epub 2019 Sep 16. PMID: 31527847

Chatterjee N, Pazarentzos E, Mayekar MK, Gui P, Allegakoen DV, Hrustanovic G, Olivas V, Lin L, Verschueren E, Johnson JR, Hofree M, Yan JJ, Newton BW, Dollen JV, Earnshaw CH, Flanagan J, Chan E, Asthana S, Ideker T, Wu W, Suzuki J, Barad BA, Kirichok Y, **Fraser JS**, Weiss WA, Krogan NJ, Tulpule A, Sabnis AJ, Bivona TG. Synthetic Essentiality of Metabolic Regulator PDHK1 in PTEN-Deficient Cells and Cancers. *Cell Rep*. 2019 Aug 27;28(9):2317-2330.e8. doi: 10.1016/j.celrep.2019.07.063. PMID: 31461649

PLUMED consortium. Promoting transparency and reproducibility in enhanced molecular simulations. *Nat Methods*. 2019 Aug;16(8):670-673. doi: 10.1038/s41592-019-0506-8. No abstract available. PMID: 31363226

Young ID, **Fraser JS**. Biomaterials in non-integer dimensions. *Nat Chem*. 2019 Jul;11(7):599-600. doi: 10.1038/s41557-019-0286-x. No abstract available.

PMID: 31209301
Eshun-Wilson L, Zhang R, Portran D, Nachury MV, Toso DB, Löhr T, Vendruscolo M, Bonomi M, **Fraser JS**, Nogales E. Effects of α-tubulin acetylation on microtubule structure and stability. *Proc Natl Acad Sci U S A*. 2019 May 21;116(21):10366-10371. doi: 10.1073/pnas.1900441116. Epub 2019 May 9. PMID: 31072936
Hu S, Offenbacher AR, Thompson EM, Gee CL, Wilcoxen J, Carr CAM, Prigozhin DM, Yang V, Alber T, Britt RD, **Fraser JS**, Klinman JP. Biophysical Characterization of a Disabled Double Mutant of Soybean Lipoxygenase: The "Undoing" of Precise Substrate Positioning Relative to Metal Cofactor and an Identified Dynamical Network. *J Am Chem Soc*. 2019 Jan 30;141(4):1555-1567. doi: 10.1021/jacs.8b10992. Epub 2019 Jan 15. PMID: 30645119
Herzik MA Jr, **Fraser JS,** Lander GC. A Multi-model Approach to Assessing Local and Global Cryo-EM Map Quality. *Structure*. 2019 Feb 5;27(2):344-358.e3. doi: 10.1016/j.str.2018.10.003. Epub 2018 Nov 15. PMID: 30449687

Andrew N. Goldberg, M.D., M.S.
Cai Y, Zheng YJ, Gulati A, Butrymowicz A, Krauter R, Pletcher SD, Sharon JD, **Goldberg AN**, Chang JL. Patient Use of Low-Cost Digital Videoscopes and Smartphones for Remote Ear and Oropharyngeal Examinations. *JAMA Otolaryngol Head Neck Surg*. 2021 Jan 21: e205223. doi: 10.1001/jamaoto.2020.5223. Online ahead of print. PMID: 33475683
Bendall S, Halliwell P, **Goldberg A**, Robinson A. Ankle Arthritis Networking: Getting the right treatment to the right patient first time. *Foot Ankle Surg*. 2021 Mar 18: S1268-7731(21)00043-6. doi: 10.1016/j.fas.2021.03.006. Online ahead of print. PMID: 33757730
Cai Y, Juszczak HM, Cope EK, **Goldberg AN.** The Microbiome in Obstructive Sleep Apnea. *Sleep*. 2021 Mar 11: zsab061. doi: 10.1093/sleep/zsab061. Online ahead of print. PMID: 33705556
Najefi AA, Ghani Y, **Goldberg AJ.** Bone Cysts and Osteolysis in Ankle Replacement. *Foot Ankle Int*. 2021 Jan;42(1):55-61. doi: 10.1177/1071100720955155. Epub 2020 Sep 16. PMID: 32935609
Calhoun AW, Pian-Smith M, Shah A, Levine A, Gaba D, DeMaria S, **Goldberg A**, Meyer EC. Guidelines for the Responsible Use of Deception in Simulation: Ethical and Educational Considerations. *Simul Healthc*. 2020 Aug;15(4):282-288. doi: 10.1097/SIH.0000000000000440. PMID: 32776776
Wengler K, **Goldberg AT**, Chahine G, Horga G. Distinct hierarchical alterations of intrinsic neural timescales account for different manifestations of psychosis. *Elife*. 2020 Oct 27;9: e56151. doi: 10.7554/eLife.56151. PMID: 33107431
Sechrest ER, Murphy J, Senapati S, **Goldberg AFX**, Park PS, Kolandaivelu S. Loss of PRCD alters number and packaging density of rhodopsin in rod photoreceptor disc membranes. *Sci Rep*. 2020 Oct 21;10(1):17885. doi: 10.1038/s41598-020-74628-2. PMID: 33087780
Gray VL, **Goldberg AP**, Rogers MW, Anthony L, Terrin ML, Guralnik JM, Blackwelder WC, Lam DFH, Sikdar S, Lal BK. Asymptomatic carotid stenosis is associated with mobility and cognitive dysfunction and heightens falls in older adults. *J Vasc Surg*. 2020 Jun;71(6):1930-1937. doi: 10.1016/j.jvs.2019.09.020. Epub 2019 Nov 4. PMID: 31699511
28

Miller M, Ryan A, Reed RM, Goggins C, Sorkin J, **Goldberg AP.** Effect of Icosapent Ethyl on Gynoid Fat and Bone Mineral Health in the Metabolic Syndrome: A Preliminary Report. *Clin Ther*. 2020 Nov;42(11):2226-2230. doi: 10.1016/j.clinthera.2020.09.005. Epub 2020 Sep 20. PMID: 32967775

Bernasconi A, Najefi AA, **Goldberg AJ.** Comparison of Mechanical Axis of the Limb Versus Anatomical Axis of the Tibia for Assessment of Tibiotalar Alignment in End-Stage Ankle Arthritis. *Foot Ankle Int*. 2020 Nov 20:1071100720972664. doi: 10.1177/1071100720972664. Online ahead of print. PMID: 33218259

Muller P, Skene SS, Chowdhury K, Cro S, **Goldberg AJ**, Doré CJ; TARVA Study Group. A randomised, multi-centre trial of total ankle replacement versus ankle arthrodesis in the treatment of patients with end stage ankle osteoarthritis (TARVA): statistical analysis plan. *Trials*. 2020 Feb 18;21(1):197. doi: 10.1186/s13063-019-3973-4. PMID: 32070409

Wang N, Xu MJ, House AE, Strohl MP, **Goldberg AN**, Murr AH. Communication Chaos from Discrepancies in Personal Protective Equipment and Preoperative Guidelines. *Laryngoscope*. 2021 Mar;131(3): E746-E754. doi: 10.1002/lary.29257. Epub 2020 Nov 11. PMID: 33128391

Milstein ML, Cavanaugh BL, Roussey NM, Volland S, Williams DS, **Goldberg AFX.** Multistep peripherin-2/rds self-assembly drives membrane curvature for outer segment disk architecture and photoreceptor viability. *Proc Natl Acad Sci U S A*. 2020 Feb 25;117(8):4400-4410. doi: 10.1073/pnas.1912513117. Epub 2020 Feb 10. PMID: 32041874

Mummaneni PV, Burke JF, Chan AK, Sosa JA, Lobo EP, Mummaneni VP, Antrum S, Berven SH, Conte MS, Doernberg SB, **Goldberg AN**, Hess CP, Hetts SW, Josephson SA, Kohi MP, Ma CB, Mahadevan VS, Molinaro AM, Murr AH, Narayana S, Roberts JP, Stoller ML, Theodosopoulos PV, Vail TP, Wienholz S, Gropper MA, Green A, Berger MS. Consensus-based perioperative protocols during the COVID-19 pandemic. *J Neurosurg Spine*. 2020 Oct 2:1-9. doi: 10.3171/2020.6. SPINE20777. Online ahead of print. PMID: 33007752

Cai Y, **Goldberg AN**, Chang JL. The Nose and Nasal Breathing in Sleep Apnea. *Otolaryngol Clin North Am*. 2020 Jun;53(3):385-395. doi: 10.1016/j.otc.2020.02.002. Epub 2020 Mar 17. PMID: 32192710

Gray VL, **Goldberg AP**, Rogers MW, Anthony L, Terrin ML, Guralnik JM, Blackwelder WC, Lam DFH, Sikdar S, Lal BK. Asymptomatic carotid stenosis is associated with mobility and cognitive dysfunction and heightens falls in older adults. *J Vasc Surg*. 2019 Nov 4. pii: S0741-5214(19)32320-1. doi: 10.1016/j.jvs.2019.09.020. [Epub ahead of print] PMID: 31699511

Katz D, Blasius K, Isaak R, Lipps J, Kushelev M, **Goldberg A**, Fastman J, Marsh B, DeMaria S. Exposure to incivility hinders clinical performance in a simulated operative crisis. *BMJ Qual Saf*. 2019 Sep;28(9):750-757. doi: 10.1136/bmjqs-2019-009598. Epub 2019 May 31. PMID: 31152113

Burnett G, **Goldberg A**, DeMaria S Jr, Levine A, Katz D. Knowledge retention after simulated crisis: importance of independent practice and simulated mortality. *Br J Anaesth*. 2019 Jul;123(1):81-87. doi: 10.1016/j.bja.2019.02.030. Epub 2019 Apr 24. PMID: 31027912

Kim H, Williams D, Qiu Y, Song Z, Yang Z, Kimler V, **Goldberg A**, Zhang R, Yang Z, Chen X, Wang L, Fang D, Lin JD, Zhang K. Regulation of hepatic autophagy by stress-

sensing transcription factor CREBH. *FASEB J*. 2019 Jul;33(7):7896-7914. doi: 10.1096/fj.201802528R. Epub 2019 Mar 26. PMID: 30912978
Grenell A, Wang Y, Yam M, Swarup A, Dilan TL, Hauer A, Linton JD, Philp NJ, Gregor E, Zhu S, Shi Q, Murphy J, Guan T, Lohner D, Kolandaivelu S, Ramamurthy V, **Goldberg AFX**, Hurley JB, Du J. Loss of MPC1 reprograms retinal metabolism to impair visual function. *Proc Natl Acad Sci U S A.* 2019 Feb 26;116(9):3530-3535. doi: 10.1073/pnas.1812941116. Epub 2019 Feb 11. PMID: 30808746
Hurley B, **Goldberg AP**, Hagberg JM. John O. Holloszy: An Enduring Legacy in Exercise Physiology, Aging, and Muscle Research. *J Gerontol A Biol Sci Med Sci.* 2019 Mar 14;74(4):588-589. doi: 10.1093/gerona/glz043. No abstract available. PMID: 30753307
Tietjens JR, Claman D, Kezirian EJ, De Marco T, Mirzayan A, Sadroonri B, **Goldberg AN**, Long C, Gerstenfeld EP, Yeghiazarians Y. Obstructive Sleep Apnea in Cardiovascular Disease: A Review of the Literature and Proposed Multidisciplinary Clinical Management Strategy. *J Am Heart Assoc*. 2019 Jan 8;8(1): e010440. doi: 10.1161/JAHA.118.010440. No abstract available. PMID: 30590966

Erin Gordon, M.D.
Dugger DT, Fung M, Zlock L, Caldera S, Sharp L, Hays SR, Singer JP, Leard LE, Golden JA, Shah RJ, Kukreja J, **Gordon E**, Finkbeiner W, Kleinhenz ME, Langelier C, Greenland JR. Cystic Fibrosis Lung Transplant Recipients Have Suppressed Airway Interferon Responses during *Pseudomonas* Infection. *Cell Rep Med*. 2020 Jul 21;1(4):100055. doi: 10.1016/j.xcrm.2020.100055. PMID: 32754722
Gordon EE, Jaquiss RDB. *J Thorac Cardiovasc Surg*. 2019 Jun;157(6): e398-e399. doi: 10.1016/j.jtcvs.2019.02.087. Epub 2019 Apr 10. No abstract available. PMID: 30981521
Lachowicz-Scroggins ME, Dunican EM, Charbit AR, Raymond W, Looney MR, Peters MC, **Gordon ED**, Woodruff PG, Lefrançais E, Phillips BR, Mauger DT, Comhair SA, Erzurum SC, Johansson MW, Jarjour NN, Coverstone AM, Castro M, Hastie AT, Bleecker ER, Fajt ML, Wenzel SE, Israel E, D Levy B, Fahy JV; National Heart, Lung, and Blood Institute Severe Asthma Research Program-3 Investigators. Extracellular DNA, Neutrophil Extracellular Traps, and Inflammasome Activation in Severe Asthma. *Am J Respir Crit Care Med*. 2019 Mar 19. doi: 10.1164/rccm.201810-1869OC. [Epub ahead of print]. PMID: 30888839.

Matthew Krummel, Ph.D.
Hahn WC, Bader JS, Braun TP, Califano A, Clemons PA, Druker BJ, Ewald AJ, Fu H, Jagu S, Kemp CJ, Kim W, Kuo CJ, McManus M, B Mills G, Mo X, Sahni N, Schreiber SL, Talamas JA, Tamayo P, Tyner JW, Wagner BK, Weiss WA, Gerhard DS; Cancer Target Discovery and Development Network. An expanded universe of cancer targets. *Cell*. 2021 Mar 4;184(5):1142-1155. doi: 10.1016/j.cell.2021.02.020. PMID: 3366736
Chan V, Gherardini PF, **Krummel MF**, Fragiadakis GK. A "data sharing trust" model for rapid, collaborative science. *Cell.* 2021 Feb 4;184(3):566-570. doi: 10.1016/j.cell.2021.01.006. PMID: 33545032
Sarma A, Christenson S, Mick E, Deiss T, DeVoe C, Pisco A, Ghale R, Jauregui A, Byrne A, Moazed F, Spottiswoode N, Sinha P, Zha B, Neff N, Tan M, Serpa PH, Ansel KM, Wilson J, Leligdowicz A, Seigel E, Sirota M, DeRisi J, Matthay M, Consortium C, Hendrickson C, Kangelaris K, **Krummel M**, Woodruff P, Erle D, Calfee C, Langelier C. COVID-19 ARDS

is characterized by a dysregulated host response that differs from cytokine storm and is modified by dexamethasone. *Res Sq*. 2021 Jan 14: rs.3.rs-141578. doi: 10.21203/rs.3.rs-141578/v1. Preprint. PMID: 33469573

Combes AJ, Courau T, Kuhn NF, Hu KH, Ray A, Chen WS, Chew NW, Cleary SJ, Kushnoor D, Reeder GC, Shen A, Tsui J, Hiam-Galvez KJ, Muñoz-Sandoval P, Zhu WS, Lee DS, Sun Y, You R, Magnen M, Rodriguez L, Im KW, Serwas NK, Leligdowicz A, Zamecnik CR, Loudermilk RP, Wilson MR, Ye CJ, Fragiadakis GK, Looney MR, Chan V, Ward A, Carrillo S; UCSF COMET Consortium, Matthay M, Erle DJ, Woodruff PG, Langelier C, Kangelaris K, Hendrickson CM, Calfee C, Rao AA, **Krummel MF.** Global absence and targeting of protective immune states in severe COVID-19. *Nature*. 2021 Mar;591(7848):124-130. doi: 10.1038/s41586-021-03234-7. Epub 2021 Jan 25. PMID: 33494096

Bald T, **Krummel MF**, Smyth MJ, Barry KC. The NK cell-cancer cycle: advances and new challenges in NK cell-based immunotherapies. *Nat Immunol*. 2020 Aug;21(8):835-847. doi: 10.1038/s41590-020-0728-z. Epub 2020 Jul 20. PMID: 32690952

Ruhland MK, Roberts EW, Cai E, Mujal AM, Marchuk K, Beppler C, Nam D, Serwas NK, Binnewies M, **Krummel MF.** Visualizing Synaptic Transfer of Tumor Antigens among Dendritic Cells. *Cancer Cell*. 2020 Jun 8;37(6):786-799.e5. doi: 10.1016/j.ccell.2020.05.002. PMID: 32516589

Crotty S, Blish C, Cadwell K, Chi H, Goldrath A, Green D, Kaech SM, **Krummel M**, Pepper M, Rothlin CV, Wherry EJ; Once-a-Year Pledge Supporters. Reinvigorating NIH Grant Peer Review. *Immunity*. 2020 Jan 14;52(1):1-3. doi: 10.1016/j.immuni.2019.12.016. PMID: 31940266

Tang S, Cannon J, Yang K, **Krummel MF**, Baker JR Jr, Choi SK. Spacer-Mediated Control of Coumarin Uncaging for Photocaged Thymidine. *J Org Chem*. 2020 Mar 6;85(5):2945-2955. doi: 10.1021/acs.joc.9b02617. Epub 2020 Feb 5. PMID: 32020803

Levine LS, Mahuron KM, Tsai KK, Wu C, Mattis DM, Pauli ML, Oglesby A, Lee JC, Spitzer MH, **Krummel MF**, Algazi AP, Rosenblum MD, Alvarado M, Daud AI. Tumor Immune Profiling-Based Neoadjuvant Immunotherapy for Locally Advanced Melanoma. *Ann Surg Oncol.* 2020 Oct;27(11):4122-4130. doi: 10.1245/s10434-020-08648-7. Epub 2020 Jun 2. PMID: 32488521

Argüello RJ, Combes AJ, Char R, Gigan JP, Baaziz AI, Bousiquot E, Camosseto V, Samad B, Tsui J, Yan P, Boissonneau S, Figarella-Branger D, Gatti E, Tabouret E, **Krummel MF**, Pierre P. SCENITH: A Flow Cytometry-Based Method to Functionally Profile Energy Metabolism with Single-Cell Resolution. *Cell Metab*. 2020 Dec 1;32(6):1063-1075.e7. doi: 10.1016/j.cmet.2020.11.007. PMID: 33264598

Krummel M, Hu K, de Vries EGE, Goetz JG, Passaro D, Subramaniam S, Misteli T, Skala M, Bravo-Cordero JJ, Sutcliffe JL. Visualizing Cancer. *Cancer Cell*. 2020 Dec 14;38(6):753-756. doi: 10.1016/j.ccell.2020.11.014. PMID: 33321083

Freedman TS, Headley MB, Serwas N, Ruhland M, Castellanos CA, Combes AJ, **Krummel MF.** Lessons of COVID-19: A roadmap for post-pandemic science.
J Exp Med. 2020 Sep 7;217(9): e20201276. doi: 10.1084/jem.20201276. PMID: 32735669

Combes AJ, Courau T, Kuhn NF, Hu KH, Ray A, Chen WS, Cleary SJ, Chew NW, Kushnoor D, Reeder GC, Shen A, Tsui J, Hiam-Galvez KJ, Muñoz-Sandoval P, Zhu WS, Lee DS, Sun Y, You R, Magnen M, Rodriguez L, Leligdowicz A, Zamecnik CR, Loudermilk RP, Wilson MR, Ye CJ, Fragiadakis GK, Looney MR, Chan V, Ward A, Carrillo S; UCSF

COMET Consortium, Matthay M, Erle DJ, Woodruff PG, Langelier C, Kangelaris K, Hendrickson CM, Calfee C, Rao AA, **Krummel MF.** Global Absence and Targeting of Protective Immune States in Severe COVID-19. *Res Sq*. 2020 Oct 28: rs.3.rs-97042. doi: 10.21203/rs.3.rs-97042/v1. Preprint. PMID: 33140041

Combes AJ, Courau T, Kuhn NF, Hu KH, Ray A, Chen WS, Cleary SJ, Chew NW, Kushnoor D, Reeder GC, Shen A, Tsui J, Hiam-Galvez KJ, Muñoz-Sandoval P, Zhu WS, Lee DS, Sun Y, You R, Magnen M, Rodriguez L, Leligdowicz A, Zamecnik CR, Loudermilk RP, Wilson MR, Ye CJ, Fragiadakis GK, Looney MR, Chan V, Ward A, Carrillo S, Matthay M, Erle DJ, Woodruff PG, Langelier C, Kangelaris K, Hendrickson CM, Calfee C, Rao AA, **Krummel MF.** Global Absence and Targeting of Protective Immune States in Severe COVID-19. *bioRxiv*. 2020 Oct 29:2020.10.28.359935. doi: 10.1101/2020.10.28.359935. Preprint. PMID: 33140050

Hung LY, Sen D, Oniskey TK, Katzen J, Cohen NA, Vaughan AE, Nieves W, Urisman A, Beers MF, **Krummel MF**, Herbert DR. Macrophages promote epithelial proliferation following infectious and non-infectious lung injury through a Trefoil factor 2-dependent mechanism. *Mucosal Immunol.* 2019 Jan;12(1):64-76. doi: 10.1038/s41385-018-0096-2. Epub 2018 Oct 18. PMID: 30337651

Tang S, Cannon J, Yang K, **Krummel MF**, Baker JR Jr, Choi SK. Spacer-Mediated Control of Coumarin Uncaging for Photocaged Thymidine. *J Org Chem*. 2020 Feb 5. doi: 10.1021/acs.joc.9b02617. [Epub ahead of print]. PMID: 32020803

Crotty S, Blish C, Cadwell K, Chi H, Goldrath A, Green D, Kaech SM, **Krummel M**, Pepper M, Rothlin CV, Wherry EJ; Once-a-Year Pledge Supporters. Reinvigorating NIH Grant Peer Review. *Immunity*. 2020 Jan 14;52(1):1-3. doi: 10.1016/j.immuni.2019.12.016. No abstract available. PMID: 31940266

Hu KH, Eichorst JP, McGinnis CS, Patterson DM, Chow ED, Kersten K, Jameson SC, Gartner ZJ, Rao AA, **Krummel MF.** ZipSeq: barcoding for real-time mapping of single cell transcriptomes. *Nat Methods*. 2020 Aug;17(8):833-843. doi: 10.1038/s41592-020-0880-2. Epub 2020 Jul 6. PMID: 32632238

Lowe MM, Boothby I, Clancy S, Ahn RS, Liao W, Nguyen DN, Schumann K, Marson A, Mahuron KM, Kingsbury GA, Liu Z, Munoz Sandoval P, Rodriguez RS, Pauli ML, Taravati K, Arron ST, Neuhaus IM, Harris HW, Kim EA, Shin US, **Krummel MF**, Daud A, Scharschmidt TC, Rosenblum MD Regulatory T cells use arginase 2 to enhance their metabolic fitness in tissues. *JCI Insight*. 2019 Dec 19;4(24). pii: 129756. doi: 10.1172/jci.insight.129756. PMID: 31852848

Krummel M, Blish C, Kuhns M, Cadwell K, Oberst A, Goldrath A, Ansel KM, Chi H, O'Connell R, Wherry EJ, Pepper M; Future Immunology Consortium. Universal Principled Review: A Community-Driven Method to Improve Peer Review. *Cell*. 2019 Dec 12;179(7):1441-1445. doi: 10.1016/j.cell.2019.11.029. PMID: 31835023

Wculek SK, Cueto FJ, Mujal AM, Melero I, **Krummel MF**, Sancho D. Dendritic cells in cancer immunology and immunotherapy. *Nat Rev Immunol.* 2020 Jan;20(1):7-24. doi: 10.1038/s41577-019-0210-z. Epub 2019 Aug 29. Review. PMID: 31467405

Jahchan NS, Mujal AM, Pollack JL, Binnewies M, Sriram V, Reyno L, **Krummel MF**. Tuning the Tumor Myeloid Microenvironment to Fight Cancer. *Front Immunol*. 2019 Jul 25; 10:1611. doi: 10.3389/fimmu.2019.01611. eCollection 2019. Review. PMID: 31402908

Puttur F, Denney L, Gregory LG, Vuononvirta J, Oliver R, Entwistle LJ, Walker SA, Headley MB, McGhee EJ, Pease JE, **Krummel MF**, Carlin LM, Lloyd CM. Pulmonary environmental cues drive group 2 innate lymphoid cell dynamics in mice and humans. *Sci Immunol.* 2019 Jun 7;4(36). pii: eaav7638. doi: 10.1126/sciimmunol. aav7638. PMID: 31175176

Binnewies M, Mujal AM, Pollack JL, Combes AJ, Hardison EA, Barry KC, Tsui J, Ruhland MK, Kersten K, Abushawish MA, Spasic M, Giurintano JP, Chan V, Daud AI, Ha P, Ye CJ, Roberts EW, **Krummel MF**. Unleashing Type-2 Dendritic Cells to Drive Protective Antitumor CD4+ T Cell Immunity. *Cell*. 2019 Mar 12. pii: S0092-8674(19)30154-0. doi: 10.1016/j.cell.2019.02.005. [Epub ahead of print]. PMID: 30955881

Mujal AM, **Krummel MF**. Immunity as a continuum of archetypes. *Science*. 2019 Apr 5;364(6435):28-29. doi: 10.1126/science. aau8694. No abstract available. PMID: 30948539

Dahlgren MW, Jones SW, Cautivo KM, Dubinin A, Ortiz-Carpena JF, Farhat S, Yu KS, Lee K, Wang C, Molofsky AV, Tward AD, **Krummel MF**, Peng T, Molofsky AB. Adventitial Stromal Cells Define Group 2 Innate Lymphoid Cell Tissue Niches. *Immunity*. 2019 Mar 19;50(3):707-722.e6. doi: 10.1016/j.immuni.2019.02.002. Epub 2019 Feb 26. PMID: 30824323

Dahlgren MW, Jones SW, Cautivo KM, Dubinin A, Ortiz-Carpena JF, Farhat S, Yu KS, Lee K, Wang C, Molofsky AV, Tward AD, **Krummel MF**, Peng T, Molofsky AB. Adventitial Stromal Cells Define Group 2 Innate Lymphoid Cell Tissue Niches. *Immunity.* 2019 Mar 19;50(3):707-722.e6. doi: 10.1016/j.immuni.2019.02.002. Epub 2019 Feb 26. PMID: 30824323

Lowe MM, Boothby I, Clancy S, Ahn RS, Liao W, Nguyen DN, Schumann K, Marson A, Mahuron KM, Kingsbury GA, Liu Z, Munoz Sandoval P, Rodriguez RS, Pauli ML, Taravati K, Arron ST, Neuhaus IM, Harris HW, Kim EA, Shin US, **Krummel MF**, Daud A, Scharschmidt TC, Rosenblum MD. Regulatory T cells use arginase 2 to enhance their metabolic fitness in tissues. *JCI Insight*. 2019 Dec 19;4(24): e129756. doi: 10.1172/jci.insight.129756. PMID: 31852848

Puttur F, Denney L, Gregory LG, Vuononvirta J, Oliver R, Entwistle LJ, Walker SA, Headley MB, McGhee EJ, Pease JE, **Krummel MF**, Carlin LM, Lloyd CM. Pulmonary environmental cues drive group 2 innate lymphoid cell dynamics in mice and humans. *Sci Immunol.* 2019 Jun 7;4(36): eaav7638. doi: 10.1126/sciimmunol. aav7638. PMID: 31175176

Mujal AM, **Krummel MF.** Immunity as a continuum of archetypes. *Science*. 2019 Apr 5;364(6435):28-29. doi: 10.1126/science. aau8694. PMID: 30948539

Jahchan NS, Mujal AM, Pollack JL, Binnewies M, Sriram V, Reyno L, **Krummel MF.** Tuning the Tumor Myeloid Microenvironment to Fight Cancer. *Front Immunol*. 2019 Jul 25; 10:1611. doi: 10.3389/fimmu.2019.01611. eCollection 2019. PMID: 31402908

Krummel M, Blish C, Kuhns M, Cadwell K, Oberst A, Goldrath A, Ansel KM, Chi H, O'Connell R, Wherry EJ, Pepper M; Future Immunology Consortium. Universal Principled Review: A Community-Driven Method to Improve Peer Review. *Cell*. 2019 Dec 12;179(7):1441-1445. doi: 10.1016/j.cell.2019.11.029. PMID: 31835023

Richard M. Locksley, M.D.

Bielecki P, Riesenfeld SJ, Hütter JC, Torlai Triglia E, Kowalczyk MS, Ricardo-Gonzalez RR, Lian M, Amezcua Vesely MC, Kroehling L, Xu H, Slyper M, Muus C, Ludwig LS, Christian E, Tao L, Kedaigle AJ, Steach HR, York AG, Skadow MH, Yaghoubi P, Dionne D, Jarret A, McGee HM, Porter CBM, Licona-Limón P, Bailis W, Jackson R, Gagliani N, Gasteiger G, **Locksley RM**, Regev A, Flavell RA. Skin-resident innate lymphoid cells converge on a pathogenic effector state. *Nature*. 2021 Feb 3. doi: 10.1038/s41586-021-03188-w. Online ahead of print. PMID: 33536623

Ricardo-Gonzalez RR, Schneider C, Liao C, Lee J, Liang HE, **Locksley RM.** Tissue-specific pathways extrude activated ILC2s to disseminate type 2 immunity. *J Exp Med*. 2020 Apr 6;217(4). pii: e20191172. doi: 10.1084/jem.20191172. PMID: 32031571

Barad BA, Liu L, Diaz RE, Basilio R, Van Dyken SJ, **Locksley RM**, Fraser JS. Differences in the chitinolytic activity of mammalian chitinases on soluble and insoluble substrates. *Protein Sci*. 2020 Jan 12. doi: 10.1002/pro.3822. [Epub ahead of print]. PMID: 31930591

Molofsky AB, **Locksley RM**. Tissue immunity broadcasts near and far. *Nat Rev Immunol.* 2020 Feb;20(2):93-94. doi: 10.1038/s41577-019-0250-4. No abstract available. PMID: 31748703

Molofsky AB, **Locksley RM.** Tissue immunity broadcasts near and far. *Nat Rev Immunol*. 2020 Feb;20(2):93-94. doi: 10.1038/s41577-019-0250-4. PMID: 31748703

Zeis P, Lian M, Fan X, Herman JS, Hernandez DC, Gentek R, Elias S, Symowski C, Knöpper K, Peltokangas N, Friedrich C, Doucet-Ladeveze R, Kabat AM, **Locksley RM**, Voehringer D, Bajenoff M, Rudensky AY, Romagnani C, Grün D, Gasteiger G. In Situ Maturation and Tissue Adaptation of Type 2 Innate Lymphoid Cell Progenitors. *Immunity*. 2020 Oct 13;53(4):775-792.e9. doi: 10.1016/j.immuni.2020.09.002. Epub 2020 Sep 30. PMID: 33002412

Barad BA, Liu L, Diaz RE, Basilio R, Van Dyken SJ, **Locksley RM**, Fraser JS. Differences in the chitinolytic activity of mammalian chitinases on soluble and insoluble substrates. *Protein Sci*. 2020 Apr;29(4):966-977. doi: 10.1002/pro.3822. Epub 2020 Jan 21. PMID: 31930591

Ricardo-Gonzalez RR, Schneider C, Liao C, Lee J, Liang HE, **Locksley RM.** Tissue-specific pathways extrude activated ILC2s to disseminate type 2 immunity. *J Exp Med*. 2020 Apr 6;217(4): e20191172. doi: 10.1084/jem.20191172. PMID: 32031571.

Barad BA, Liu L, Diaz RE, Basilio R, Van Dyken SJ, **Locksley RM**, Fraser JS. Tissue-specific pathways extrude activated ILC2s to disseminate type 2 immunity. *Protein Sci.* 2020 Apr;29(4):966-977. doi: 10.1002/pro.3822. Epub 2020 Jan 21. PMID: 31930591

Howe M, Bauer J, Schulze A, Kropp S, **Locksley RM**, Alferink J, Weighardt H, Scheu S. Production of IFNβ by Conventional Dendritic Cells after Stimulation with Viral Compounds and IFNβ-Independent IFNAR1-Signaling Pathways are Associated with Aggravation of Polymicrobial Sepsis. *Int J Mol Sci.* 2019 Sep 7;20(18). pii: E4410. doi: 10.3390/ijms20184410. PMID: 31500303

Fahy JV, **Locksley RM**. Making Asthma Crystal Clear. *N Engl J Med*. 2019 Aug 29;381(9):882-884. doi: 10.1056/NEJMcibr1908064. No abstract available. PMID: 31461600

Ricardo-Gonzalez RR, **Locksley RM**. ILC2s chew the fat. *J Exp Med.* 2019 Sept. 2;216(9):1972-1973. doi: 10.1084/jem.20191098. Epub 2019 Aug 12. PMID: 31405894

Schneider C, Lee J, Koga S, Ricardo-Gonzalez RR, Nussbaum JC, Smith LK, Villeda SA, Liang HE, **Locksley RM**. Tissue-Resident Group 2 Innate Lymphoid Cells Differentiate by Layered Ontogeny and In Situ Perinatal Priming. *Immunity*. 2019 Jun 18;50(6):1425-1438.e5. doi: 10.1016/j.immuni.2019.04.019. Epub 2019 May 22. PMID: 31128962
Schneider C, O'Leary CE, **Locksley RM**. Regulation of immune responses by tuft cells. *Nat Rev Immunol*. 2019 Sep;19(9):584-593. doi: 10.1038/s41577-019-0176-x. Review. PMID: 31114038
Tan C, Mueller JL, Noviski M, Huizar J, Lau D, Dubinin A, **Molofsky A**, Wilson PC, Zikherman J. Nur77 Links Chronic Antigen Stimulation to B Cell Tolerance by Restricting the Survival of Self-Reactive B Cells in the Periphery. *J Immunol*. 2019 May 15;202(10):2907-2923. doi: 10.4049/jimmunol.1801565. Epub 2019 Apr 8. PMID: 30962292

Ari Molofsky
Nguyen PT, Dorman LC, Pan S, Vainchtein ID, Han RT, Nakao-Inoue H, Taloma SE, Barron JJ, **Molofsky AB**, Kheirbek MA, Molofsky AV. Microglial Remodeling of the Extracellular Matrix Promotes Synapse Plasticity. *Cell*. 2020 Jul 23;182(2):388-403.e15. doi: 10.1016/j.cell.2020.05.050. Epub 2020 Jul 1. PMID: 32615087
Cassandras M, Wang C, Kathiriya J, Tsukui T, Matatia P, Matthay M, Wolters P, **Molofsky A**, Sheppard D, Chapman H, Peng T. Gli1^{+} mesenchymal stromal cells form a pathological niche to promote airway progenitor metaplasia in the fibrotic lung.
Nat Cell Biol. 2020 Nov;22(11):1295-1306. doi: 10.1038/s41556-020-00591-9. Epub 2020 Oct 12. PMID: 33046884
Cautivo KM, Steer CA, **Molofsky AB.** Immune outposts in the adventitia: One foot in sea and one on shore. *Curr Opin Immunol*. 2020 Apr 24; 64:34-41. doi: 10.1016/j.coi.2020.03.005. Online ahead of print. PMID: 32339862
Krummel M, Blish C, Kuhns M, Cadwell K, Oberst A, Goldrath A, Ansel KM, Chi H, O'Connell R, Wherry EJ, Pepper M; Future Immunology Consortium. Universal Principled Review: A Community-Driven Method to Improve Peer Review. *Cell*. 2019 Dec 12;179(7):1441-1445. doi: 10.1016/j.cell.2019.11.029. PMID: 31835023
Molofsky AB, Locksley RM. Tissue immunity broadcasts near and far. *Nat Rev Immunol.* 2020 Feb;20(2):93-94. doi: 10.1038/s41577-019-0250-4. No abstract available. PMID: 31748703
Dahlgren MW, **Molofsky AB**. Adventitial Cuffs: Regional Hubs for Tissue Immunity. *Trends Immunol*. 2019 Oct;40(10):877-887. doi: 10.1016/j.it.2019.08.002. Epub 2019 Sep 13. Review. PMID: 31522963
Cameron GJM, Cautivo KM, Loering S, Jiang SH, Deshpande AV, Foster PS, McKenzie ANJ, **Molofsky AB**, Hansbro PM, Starkey MR. Group 2 Innate Lymphoid Cells Are Redundant in Experimental Renal Ischemia-Reperfusion Injury. *Front Immunol.* 2019 Apr 16; 10:826. doi: 10.3389/fimmu.2019.00826. eCollection 2019. PMID: 31057549
Tan C, Mueller JL, Noviski M, Huizar J, Lau D, Dubinin A, **Molofsky A**, Wilson PC, Zikherman J. Nur77 Links Chronic Antigen Stimulation to B Cell Tolerance by Restricting the Survival of Self-Reactive B Cells in the Periphery. *J Immunol*. 2019 Apr 8. pii: ji1801565. doi: 10.4049/jimmunol.1801565. [Epub ahead of print]. PMID: 30962292
Dahlgren MW, Jones SW, Cautivo KM, Dubinin A, Ortiz-Carpena JF, Farhat S, Yu KS, Lee K, Wang C, Molofsky AV, Tward AD, Krummel MF, Peng T, **Molofsky AB**. Adventitial Stromal Cells Define Group 2 Innate Lymphoid Cell Tissue Niches. *Immunity*. 2019 Mar

19;50(3):707-722.e6. doi: 10.1016/j.immuni.2019.02.002. Epub 2019 Feb 26. PMID: 30824323

Steven D. Pletcher, M.D.

Cai Y, Zheng YJ, Gulati A, Butrymowicz A, Krauter R, **Pletcher SD**, Sharon JD, Goldberg AN, Chang JL. Patient Use of Low-Cost Digital Videoscopes and Smartphones for Remote Ear and Oropharyngeal Examinations. *JAMA Otolaryngol Head Neck Surg.* 2021 Jan 21: e205223. doi: 10.1001/jamaoto.2020.5223. Online ahead of print. PMID: 33475683

Chang CWD, **Pletcher SD**, Thorne MC, Malekzadeh S. Preference Signaling for the Otolaryngology Interview Market. *Laryngoscope.* 2021 Mar;131(3): E744-E745. doi: 10.1002/lary.29151. Epub 2020 Oct 6. PMID: 33022091

Park JS, El-Sayed IH, Young VN, **Pletcher SD.** Development of clinical care guidelines for faculty and residents in the era of COVID-19. *Head Neck*. 2020 Jul;42(7):1403-1408. doi: 10.1002/hed.26225. Epub 2020 May 6. PMID: 32348581

Cai Y, Gulati A, Jiam NT, Wai KC, Shuman EA, **Pletcher SD**, Durr ML, Chang JL. Evolving Otolaryngology Resident Roles and Concerns at the Peak of the US COVID-19 Pandemic. *Head Neck*. 2020 Dec;42(12):3712-3719. doi: 10.1002/hed.26438. Epub 2020 Sep 14. PMID: 32926482

Chou DW, **Pletcher SD**, Bruss D, Sung CK, Diaz RC, Liang J, Durr ML. Otolaryngology Residency Interviews in a Socially Distanced World: Strategies to Recruit and Assess Applicants. *Otolaryngol Head Neck Surg.* 2020 Sep 1:194599820957961. doi: 10.1177/0194599820957961. Online ahead of print. PMID: 32870721

Dean Sheppard, M.D.

Auyeung VC, **Sheppard D.** Stuck in a Moment: Does Abnormal Persistence of Epithelial Progenitors Drive Pulmonary Fibrosis? *Am J Respir Crit Care Med*. 2021 Mar 15;203(6):667-669. doi: 10.1164/rccm.202010-3898ED. PMID: 33226835

Nishimichi N, Tsujino K, Kanno K, Sentani K, Kobayashi T, Chayama K, **Sheppard D**, Yokosaki Y. Induced hepatic stellate cell integrin, α8β1, enhances cellular contractility and TGFβ activity in liver fibrosis. *J Pathol*. 2021 Jan 12. doi: 10.1002/path.5618. Online ahead of print. PMID: 33433924

Cassandras M, Wang C, Kathiriya J, Tsukui T, Matatia P, Matthay M, Wolters P, Molofsky A, **Sheppard D**, Chapman H, Peng T. $Gli1^+$ mesenchymal stromal cells form a pathological niche to promote airway progenitor metaplasia in the fibrotic lung. *Nat Cell Biol*. 2020 Nov;22(11):1295-1306. doi: 10.1038/s41556-020-00591-9. Epub 2020 Oct 12. PMID: 33046884

Santander N, Lizama CO, Meky E, McKinsey GL, Jung B, **Sheppard D**, Betsholtz C, Arnold TD. Lack of Flvcr2 impairs brain angiogenesis without affecting the blood-brain barrier. *J Clin Invest.* 2020 Aug 3;130(8):4055-4068. doi: 10.1172/JCI136578. PMID: 32369453

Zhang Z, Bai M, Barbosa GO, Chen A, Wei Y, Luo S, Wang X, Wang B, Tsukui T, Li H, **Sheppard D**, Kornberg TB, Ma DK. Broadly conserved roles of TMEM131 family proteins in intracellular collagen assembly and secretory cargo trafficking. *Sci Adv*. 2020 Feb 12;6(7): eaay7667. doi: 10.1126/sciadv. aay7667. eCollection 2020 Feb. PMID: 32095531

Sundaram A, Chen C, Isik Reed N, Liu S, Ki Yeon S, McIntosh J, Tang YZ, Yang H, Adler M, Beresis R, Seiple IB, **Sheppard D**, DeGrado WF, Jo H. Dual antagonists of α5β1/αvβ1

integrin for airway hyperresponsiveness. *Bioorg Med Chem Lett*. 2020 Nov 15;30(22):127578. doi: 10.1016/j.bmcl.2020.127578. Epub 2020 Sep 29. PMID: 33007395
Wong JC, Perez-Mancera PA, Huang TQ, Kim J, Grego-Bessa J, Del Pilar Alzamora M, Kogan SC, Sharir A, Keefe SH, Morales CE, Schanze D, Castel P, Hirose K, Huang GN, Zenker M, **Sheppard D**, Klein OD, Tuveson DA, Braun BS, Shannon K. KrasP34R and KrasT58I mutations induce distinct RASopathy phenotypes in mice. *JCI Insight*. 2020 Nov 5;5(21): e140495. doi: 10.1172/jci.insight.140495. PMID: 32990679
Tsukui T, Sun KH, Wetter JB, Wilson-Kanamori JR, Hazelwood LA, Henderson NC, Adams TS, Schupp JC, Poli SD, Rosas IO, Kaminski N, Matthay MA, Wolters PJ, **Sheppard D.** Collagen-producing lung cell atlas identifies multiple subsets with distinct localization and relevance to fibrosis. *Nat Commun*. 2020 Apr 21;11(1):1920. doi: 10.1038/s41467-020-15647-5. PMID: 32317643
Alsamman S, Christenson SA, Yu A, Ayad NME, Mooring MS, Segal JM, Hu JK, Schaub JR, Ho SS, Rao V, Marlow MM, Turner SM, Sedki M, Pantano L, Ghoshal S, Ferreira DDS, Ma HY, Duwaerts CC, Espanol-Suner R, Wei L, Newcomb B, Mileva I, Canals D, Hannun YA, Chung RT, Mattis AN, Fuchs BC, Tager AM, Yimlamai D, Weaver VM, Mullen AC, **Sheppard D**, Chen JY. Targeting acid ceramidase inhibits YAP/TAZ signaling to reduce fibrosis in mice. *Sci Transl Med*. 2020 Aug 19;12(557): eaay8798. doi: 10.1126/scitranslmed. aay8798. PMID: 32817366
Del Cid JS, Reed NI, Molnar K, Liu S, Dang B, Jensen SA, DeGrado W, Handford PA, **Sheppard D**, Sundaram AB. A disease-associated mutation in fibrillin-1 differentially regulates integrin-mediated cell adhesion. *J Biol Chem*. 2019 Nov 29;294(48):18232-18243. doi: 10.1074/jbc.RA119.011109. Epub 2019 Oct 22. PMID: 31640988
Arnold TD, Lizama CO, Cautivo KM, Santander N, Lin L, Qiu H, Huang EJ, Liu C, Mukouyama YS, Reichardt LF, Zovein AC, **Sheppard D**. Impaired αVβ8 and TGFβ signaling lead to microglial dysmaturation and neuromotor dysfunction. *J Exp Med.* 2019 Apr 1;216(4):900-915. doi: 10.1084/jem.20181290. Epub 2019 Mar 7. PMID: 30846482
Bulek K, Chen X, Parron V, Sundaram A, Herjan T, Ouyang S, Liu C, Majors A, Zepp J, Gao J, Dongre A, Bodaszewska-Lubas M, Echard A, Aronica M, Carman J, Garantziotis S, **Sheppard D**, Li X. IL-17A Recruits Rab35 to IL-17R to Mediate PKCα-Dependent Stress Fiber Formation and Airway Smooth Muscle Contractility. *J Immunol*. 2019 Mar 1;202(5):1540-1548. doi: 10.4049./jimmunol.1801025. Epub 2019 Jan 25. PMID: 30683702
Bengs S, Becker E, Busenhart P, Spalinger MR, Raselli T, Kasper S, Lang S, Atrott K, Mamie C, Vavricka SR, von Boehmer L, Knuth A, Tuomisto A, Mäkinen MJ, Hruz P, Turina M, Rickenbacher A, Petrowsky H, Weber A, Frei P, Halama M, Jenkins G, **Sheppard D**, Croner RS, Christoph J, Britzen-Laurent N, Naschberger E, Schellerer V, Stürzl M, Fried M, Rogler G, Scharl M. β6 -integrin serves as a novel serum tumor marker for colorectal carcinoma. *Int J Cancer.* 2019 Jan 17. doi: 10.1002/ijc.32137. [Epub ahead of print] PMID: 30653264
Thamsen M, Ghosh R, Auyeung VC, Brumwell A, Chapman HA, Backes BJ, Perara G, Maly DJ, **Sheppard D**, Papa FR. Small molecule inhibition of IRE1α kinase/RNase has anti-fibrotic effects in the lung. *PLoS One*. 2019 Jan 9;14(1): e0209824. doi: 10.1371/journal.pone.0209824. eCollection 2019. PMID: 30625178
Greenhalgh SN, Matchett KP, Taylor RS, Huang K, Li JT, Saeteurn K, Donnelly MC, Simpson EEM, Pollack JL, Atakilit A, Simpson KJ, Maher JJ, Iredale JP, **Sheppard D**, Henderson NC. Loss of Integrin αvβ8 in Murine Hepatocytes Accelerates Liver

Regeneration. *Am J Pathol*. 2019 Feb;189(2):258-271. doi: 10.1016/j.ajpath.2018.10.007. Epub 2018 Nov 16. PMID: 30448409

Jeoung-Sook Shin

Deng Z, Law CS, Ho FO, Wang KM, Jones KD, **Shin JS**, Shum AK. A Defect in Thymic Tolerance Causes T Cell-Mediated Autoimmunity in a Murine Model of COPA Syndrome. *J Immunol*. 2020 May 1;204(9):2360-2373. doi: 10.4049/jimmunol.2000028. Epub 2020 Mar 20. PMID: 32198142

Shin JS. Unexpected role of dendritic cells in pulmonary fibrosis. *Thorax*. 2019 Oct;74(10):925-926. doi: 10.1136/thoraxjnl-2019-213510. Epub 2019 Jul 30. No abstract available. PMID: 31363019

Aparna Sundaram, M.D.

Lazar AM, Irannejad R, Baldwin TA, **Sundaram AB**, Gutkind JS, Inoue A, Dessauer CW, Von Zastrow M. *Elife.* 2020 Jun 9;9: e58039. doi: 10.7554/eLife.58039. PMID: 32515353

Sundaram A, Chen C, Isik Reed N, Liu S, Ki Yeon S, McIntosh J, Tang YZ, Yang H, Adler M, Beresis R, Seiple IB, Sheppard D, DeGrado WF, Jo H. Dual antagonists of α5β1/αvβ1 integrin for airway hyperresponsiveness. G protein-regulated endocytic trafficking of adenylyl cyclase type 9. *Bioorg Med Chem Lett*. 2020 Nov 15;30(22):127578. doi: 10.1016/j.bmcl.2020.127578. Epub 2020 Sep 29. PMID: 33007395

Shekhar C, **Sundaram A**, Alagarajan M, Pradhan MR, Sahoo H. Providing quality abortion care: Findings from a study of six states in India. *Sex Reprod Healthc*. 2020 Jun; 24:100497. doi: 10.1016/j.srhc.2020.100497. Epub 2020 Jan 30. PMID: 32036281

Singh S, **Sundaram A**, Hossain A, Puri MC, Sathar Z, Shekhar C, Crowell M, Moore AM. Abortion service provision in South Asia: A comparative study of four countries. *Contraception*. 2020 Sep;102(3):210-219. doi: 10.1016/j.contraception.2020.05.015. Epub 2020 May 29. PMID: 32479764

Shekhar C, **Sundaram A**, Alagarajan M, Pradhan MR, Sahoo H. Providing quality abortion care: Findings from a study of six states in India. *Sex Reprod Healthc.* 2020 Jan 30; 24:100497. doi: 10.1016/j.srhc.2020.100497. [Epub ahead of print]. PMID: 32036281

Del Cid JS, Reed NI, Molnar K, Liu S, Dang B, Jensen SA, DeGrado W, Handford PA, Sheppard D, **Sundaram AB**. A disease-associated mutation in fibrillin-1 differentially regulates integrin-mediated cell adhesion. *J Biol Chem.* 2019 Nov 29;294(48):18232-18243. doi: 10.1074/jbc.RA119.011109. Epub 2019 Oct 22. PMID: 31640988

Bulek K, Chen X, Parron V, **Sundaram A**, Herjan T, Ouyang S, Liu C, Majors A, Zepp J, Gao J, Dongre A, Bodaszewska-Lubas M, Echard A, Aronica M, Carman J, Garantziotis S, Sheppard D, Li X. IL-17A Recruits Rab35 to IL-17R to Mediate PKCa-Dependent Stress Fiber Formation and Airway Smooth Muscle Contractility. *J Immunol*. 2019 Jan. (PMID 30683702).

Arthur Weiss, M.D., Ph.D.

Shen L, Matloubian M, Kadlecek TA, **Weiss A.** A disease-associated mutation that weakens ZAP70 autoinhibition enhances responses to weak and self-ligands. *Sci Signal*. 2021 Feb 2;14(668): eabc4479. doi: 10.1126/scisignal.abc4479. PMID: 33531381

Ganti RS, Lo WL, McAffee DB, Groves JT, **Weiss A**, Chakraborty AK. How the T cell signaling network processes information to discriminate between self and agonist ligands.

Proc Natl Acad Sci U S A. 2020 Oct 20;117(42):26020-26030. doi: 0.1073/pnas.2008303117. Epub 2020 Oct 5. PMID: 33020303
Courtney AH, Shvets AA, Lu W, Griffante G, Mollenauer M, Horkova V, Lo WL, Yu S, Stepanek O, Chakraborty AK, **Weiss A**. CD45 functions as a signaling gatekeeper in T cells. *Sci Signal*. 2019 Oct 22;12(604). pii: eaaw8151. doi: 10.1126/scisignal. aaw8151. PMID: 31641081
Wang Y, Huynh W, Skokan TD, Lu W, **Weiss A**, Vale RD. CRACR2a is a calcium-activated dynein adaptor protein that regulates endocytic traffic. *J Cell Biol*. 2019 Feb 27. pii: jcb.201806097. doi: 10.1083/jcb.201806097. [Epub ahead of print]. PMID: 30814157
Lo WL, Shah NH, Rubin SA, Zhang W, Horkova V, Fallahee IR, Stepanek O, Zon LI, Kuriyan J, **Weiss A**. Slow phosphorylation of a tyrosine residue in LAT optimizes T cell ligand discrimination. *Nat Immunol*. 2019 Nov;20(11):1481-1493. doi: 10.1038/s41590-019-0502-2. Epub 2019 Oct 14. PMID: 31611699
Ashouri JF, Hsu LY, Yu S, Rychkov D, Chen Y, Cheng DA, Sirota M, Hansen E, Lattanza L, Zikherman J, **Weiss A**. Reporters of TCR signaling identify arthritogenic T cells in murine and human autoimmune arthritis. *Proc Natl Acad Sci U S A*. 2019 Sep 10;116(37):18517-18527. doi: 10.1073/pnas.1904271116. Epub 2019 Aug 27. PMID: 31455730
Zinzow-Kramer WM, **Weiss A**, Au-Yeung BB. Adaptation by naïve CD4+ T cells to self antigen dependent TCR signaling induces functional heterogeneity and tolerance. *Proc Natl Acad Sci U S A*. 2019 Jul 23;116(30):15160-15169. doi: 10.1073/pnas.1904096116. Epub 2019 Jul 8. PMID: 31285342
Chung JK, Nocka LM, Decker A, Wang Q, Kadlecek TA, **Weiss A**, Kuriyan J, Groves JT. Switch-like activation of Bruton's tyrosine kinase by membrane-mediated dimerization. *Proc Natl Acad Sci U S A*. 2019 May 28;116(22):10798-10803. doi: 10.1073/pnas.1819309116. Epub 2019 May 10. PMID: 31076553

Jonathan Weissman, Ph.D.
Yan X, Stuurman N, Ribeiro SA, Tanenbaum ME, Horlbeck MA, Liem CR, Jost M, **Weissman JS**, Vale RD. High-content imaging-based pooled CRISPR screens in mammalian cells. *J Cell Biol*. 2021 Feb 1;220(2): e202008158. doi: 10.1083/jcb.202008158. PMID: 33465779
Liu SJ, Horlbeck MA, **Weissman JS**, Lim DA. Genome-Scale Perturbation of Long Noncoding RNA Expression Using CRISPR Interference. *Methods Mol Biol*. 2021; 2254:323-338. doi: 10.1007/978-1-0716-1158-6_20. PMID: 33326085
Liu K, Santos DA, Hussmann JA, Wang Y, Sutter BM, **Weissman JS**, Tu BP. Regulation of translation by methylation multiplicity of 18S rRNA. *Cell Rep*. 2021 Mar 9;34(10):108825. doi: 10.1016/j.celrep.2021.108825. PMID: 33691096
Tian R, Samelson AJ, Rezelj VV, Chen M, Ramadoss GN, Guo X, Kain AM, Tran QD, Lim SA, Lui I, Nunez J, Rockwood SJ, Liu N, Carlson-Stevermer J, Oki J, Maures T, Holden K, **Weissman JS**, Wells JA, Conklin B, Vignuzzi M, Kampmann M. BRD2 inhibition blocks SARS-CoV-2 infection in vitro by reducing transcription of the host cell receptor ACE2. *bioRxiv*. 2021 Jan 19:2021.01.19.427194. doi: 10.1101/2021.01.19.427194. Preprint. PMID: 33501440
Lo YH, Kolahi KS, Du Y, Chang CY, Krokhotin A, Nair A, Sobba WD, Karlsson K, Jones SJ, Longacre TA, Mah AT, Tercan B, Sockell A, Xu H, Seoane JA, Chen J, Shmulevich I,

Weissman JS, Curtis C, Califano A, Fu H, Crabtree GR, Kuo CJ. A CRISPR/Cas9-engineered ARID1A-deficient human gastric cancer organoid model reveals essential and non-essential modes of oncogenic transformation. *Cancer Discov*. 2021 Jan 15: candisc.1109.2020. doi: 10.1158/2159-8290.CD-20-1109. Online ahead of print. PMID: 33451982

Quinn JJ, Jones MG, Okimoto RA, Nanjo S, Chan MM, Yosef N, Bivona TG, **Weissman JS.** Single-cell lineages reveal the rates, routes, and drivers of metastasis in cancer xenografts. *Science*. 2021 Feb 26;371(6532): eabc1944. doi: 10.1126/science.abc1944. Epub 2021 Jan 21. PMID: 33479121

Jones MG, Khodaverdian A, Quinn JJ, Chan MM, Hussmann JA, Wang R, Xu C, **Weissman JS**, Yosef N. Inference of single-cell phylogenies from lineage tracing data using Cassiopeia. *Genome Biol*. 2020 Apr 14;21(1):92. doi: 10.1186/s13059-020-02000-8. PMID: 32290857

Jiménez-Rojo N, Leonetti MD, Zoni V, Colom A, Feng S, Iyengar NR, Matile S, Roux A, Vanni S, **Weissman JS**, Riezman H. Conserved Functions of Ether Lipids and Sphingolipids in the Early Secretory Pathway. *Curr Biol*. 2020 Oct 5;30(19):3775-3787.e7. doi: 10.1016/j.cub.2020.07.059. Epub 2020 Aug 27. PMID: 32857977

Hawkins JS, Silvis MR, Koo BM, Peters JM, Osadnik H, Jost M, Hearne CC, **Weissman JS**, Todor H, Gross CA. Mismatch-CRISPRi Reveals the Co-varying Expression-Fitness Relationships of Essential Genes in Escherichia coli and Bacillus subtilis. *Cell Syst*. 2020 Nov 18;11(5):523-535.e9. doi: 10.1016/j.cels.2020.09.009. Epub 2020 Oct 19. PMID: 33080209

Vargas EJM, Matamoros AJ, Qiu J, Jan CH, Wang Q, Gorczyca D, Han TW, **Weissman JS**, Jan YN, Banerjee S, Song Y. The microtubule regulator *ringer* functions downstream from the RNA repair/splicing pathway to promote axon regeneration. *Genes Dev*. 2020 Feb 1;34(3-4):194-208. doi: 10.1101/gad.331330.119. Epub 2020 Jan 9. PMID: 31919191

O'Loughlin S, Capece MC, Klimova M, Wills NM, Coakley A, Samatova E, O'Connor PBF, Loughran G, **Weissman JS**, Baranov PV, Rodnina MV, Puglisi JD, Atkins JF. Polysomes Bypass a 50-Nucleotide Coding Gap Less Efficiently Than Monosomes Due to Attenuation of a 5' mRNA Stem-Loop and Enhanced Drop-off. *J Mol Biol.* 2020 Jul 24;432(16):4369-4387. doi: 10.1016/j.jmb.2020.05.010. Epub 2020 May 23. PMID: 32454154

Miller-Vedam LE, Bräuning B, Popova KD, Schirle Oakdale NT, Bonnar JL, Prabu JR, Boydston EA, Sevillano N, Shurtleff MJ, Stroud RM, Craik CS, Schulman BA, Frost A, **Weissman JS.** Structural and mechanistic basis of the EMC-dependent biogenesis of distinct transmembrane clients. *Elife*. 2020 Nov 25;9: e62611. doi: 10.7554/eLife.62611. PMID: 33236988

Qi LS, Larson MH, Gilbert LA, Doudna JA, **Weissman JS**, Arkin AP, Lim WA. Repurposing CRISPR as an RNA-guided platform for sequence-specific control of gene expression. *Cell*. 2021 Feb 4;184(3):844. doi: 10.1016/j.cell.2021.01.019. PMID: 33545038

Jost M, Santos DA, Saunders RA, Horlbeck MA, Hawkins JS, Scaria SM, Norman TM, Hussmann JA, Liem CR, Gross CA, **Weissman JS.** Titrating gene expression using libraries of systematically attenuated CRISPR guide RNAs. *Nat Biotechnol*. 2020 Mar;38(3):355-364. doi: 10.1038/s41587-019-0387-5. Epub 2020 Jan 13. PMID: 31932729

Hickey KL, Dickson K, Cogan JZ, Replogle JM, Schoof M, D'Orazio KN, Sinha NK, Hussmann JA, Jost M, Frost A, Green R, **Weissman JS**, Kostova KK. Mol GIGYF2 and 4EHP Inhibit Translation Initiation of Defective Messenger RNAs to Assist Ribosome-

Associated Quality Control. *Cell*. 2020 Sep 17;79(6):950-962.e6. doi: 10.1016/j.molcel.2020.07.007. Epub 2020 Jul 28. PMID: 32726578

Liu SJ, Malatesta M, Lien BV, Saha P, Thombare SS, Hong SJ, Pedraza L, Koontz M, Seo K, Horlbeck MA, He D, Birk HS, Jain M, Olsen HE, Akeson M, **Weissman JS**, Monje M, Gupta N, Raleigh DR, Ullian EM, Lim DA. CRISPRi-based radiation modifier screen identifies long non-coding RNA therapeutic targets in glioma. *Genome Biol.* 2020 Mar 31;21(1):83. doi: 10.1186/s13059-020-01995-4. PMID: 32234056

Zou K, Rouskin S, Dervishi K, McCormick MA, Sasikumar A, Deng C, Chen Z, Kaeberlein M, Brem RB, Polymenis M, Kennedy BK, **Weissman JS**, Zheng J, Ouyang Q, Li H. Life span extension by glucose restriction is abrogated by methionine supplementation: Crosstalk between glucose and methionine and implication of methionine as a key regulator of life span. *Sci Adv*. 2020 Aug 5;6(32): eaba1306. doi: 10.1126/sciadv. aba1306. eCollection 2020 Aug. PMID: 32821821

Maynard A, McCoach CE, Rotow JK, Harris L, Haderk F, Kerr DL, Yu EA, Schenk EL, Tan W, Zee A, Tan M, Gui P, Lea T, Wu W, Urisman A, Jones K, Sit R, Kolli PK, Seeley E, Gesthalter Y, Le DD, Yamauchi KA, Naeger DM, Bandyopadhyay S, Shah K, Cech L, Thomas NJ, Gupta A, Gonzalez M, Do H, Tan L, Bacaltos B, Gomez-Sjoberg R, Gubens M, Jahan T, Kratz JR, Jablons D, Neff N, Doebele RC, **Weissman J**, Blakely CM, Darmanis S, Bivona TG. Therapy-Induced Evolution of Human Lung Cancer Revealed by Single-Cell RNA Sequencing. *Cell*. 2020 Sep 3;182(5):1232-1251.e22. doi: 10.1016/j.cell.2020.07.017. Epub 2020 Aug 20. PMID: 32822576

Chen J, Brunner AD, Cogan JZ, Nuñez JK, Fields AP, Adamson B, Itzhak DN, Li JY, Mann M, Leonetti MD, **Weissman JS.** Pervasive functional translation of noncanonical human open reading frames. *Science*. 2020 Mar 6;367(6482):1140-1146. doi: 10.1126/science. aay0262. PMID: 32139545

Replogle JM, Norman TM, Xu A, Hussmann JA, Chen J, Cogan JZ, Meer EJ, Terry JM, Riordan DP, Srinivas N, Fiddes IT, Arthur JG, Alvarado LJ, Pfeiffer KA, Mikkelsen TS, **Weissman JS**, Adamson B. Combinatorial single-cell CRISPR screens by direct guide RNA capture and targeted sequencing. *Nat Biotechnol.* 2020 Aug;38(8):954-961. doi: 10.1038/s41587-020-0470-y. Epub 2020 Mar 30. PMID: 32231336

Jost M, Chen Y, Gilbert LA, Horlbeck MA, Krenning L, Menchon G, Rai A, Cho MY, Stern JJ, Prota AE, Kampmann M, Akhmanova A, Steinmetz MO, Tanenbaum ME, **Weissman JS.** Pharmaceutical-Grade Rigosertib Is a Microtubule-Destabilizing Agent. *Mol Cell*. 2020 Jul 2;79(1):191-198.e3. doi: 10.1016/j.molcel.2020.06.008. PMID: 32619469

Horlbeck MA, Liu SJ, Chang HY, Lim DA, **Weissman JS.** Fitness effects of CRISPR/Cas9-targeting of long noncoding RNA genes. *Nat Biotechnol*. 2020 May;38(5):573-576. doi: 10.1038/s41587-020-0428-0. Epub 2020 Feb 24. PMID: 32094656

Jost M, Santos DA, Saunders RA, Horlbeck MA, Hawkins JS, Scaria SM, Norman TM, Hussmann JA, Liem CR, Gross CA, **Weissman JS**. Titrating gene expression using libraries of systematically attenuated CRISPR guide RNAs. *Nat Biotechnol.* 2020 Jan 13. doi: 10.1038/s41587-019-0387-5. [Epub ahead of print] PMID: 31932729

Vargas EJM, Matamoros AJ, Qiu J, Jan CH, Wang Q, Gorczyca D, Han TW, **Weissman JS**, Jan YN, Banerjee S, Song Y. The microtubule regulator ringer functions downstream from the RNA repair/splicing pathway to promote axon regeneration. *Genes Dev.* 2020 Feb 1;34(3-4):194-208. doi: 10.1101/gad.331330.119. Epub 2020 Jan 9. PMID: 31919191

Ngo AM, Shurtleff MJ, Popova KD, Kulsuptrakul J, **Weissman JS**, Puschnik AS. The ER membrane protein complex is required to ensure correct topology and stable expression of flavivirus polyproteins. *Elife*. 2019 Sep 13;8. pii: e48469. doi: 10.7554/eLife.48469. PMID: 31516121

Bassaganyas L, Popa SJ, Horlbeck M, Puri C, Stewart SE, Campelo F, Ashok A, Butnaru CM, Brouwers N, Heydari K, Ripoche J, **Weissman J**, Rubinsztein DC, Schekman R, Malhotra V, Moreau K, Villeneuve J. New factors for protein transport identified by a genome wide CRISPRi screen in mammalian cells. *J Cell Biol.* 2019 Nov 4;218(11):3861-3879. doi: 10.1083/jcb.201902028. Epub 2019 Sep 5. PMID: 31488582

Norman TM, Horlbeck MA, Replogle JM, Ge AY, Xu A, Jost M, Gilbert LA, **Weissman JS.** Exploring genetic interaction manifolds constructed from rich single-cell phenotypes. *Science.* 2019 Aug 23;365(6455):786-793. doi: 10.1126/science. aax4438. Epub 2019 Aug 8. PMID: 31395745

McGinnis CS, Patterson DM, Winkler J, Conrad DN, Hein MY, Srivastava V, Hu JL, Murrow LM, **Weissman JS**, Werb Z, Chow ED, Gartner ZJ. MULTI-seq: sample multiplexing for single-cell RNA sequencing using lipid-tagged indices. *Nat Methods.* 2019 Jul;16(7):619-626. doi: 10.1038/s41592-019-0433-8. Epub 2019 Jun 17. PMID: 31209384

Torres SE, Gallagher CM, Plate L, Gupta M, Liem CR, Guo X, Tian R, Stroud RM, Kampmann M, **Weissman JS,** Walter P. Ceapins block the unfolded protein response sensor ATF6α by inducing a neomorphic inter-organelle tether. *Elife.* 2019 May 31;8. pii: e46595. doi: 10.7554/eLife.46595. PMID: 31149896

Igbaria A, Merksamer PI, Trusina A, Tilahun F, Johnson JR, Brandman O, Krogan NJ, **Weissman JS**, Papa FR. Chaperone-mediated reflux of secretory proteins to the cytosol during endoplasmic reticulum stress. *Proc Natl Acad Sci U S A*. 2019 Jun 4;116(23):11291-11298. doi: 10.1073/pnas.1904516116. Epub 2019 May 17. PMID: 31101715

Chan MM, Smith ZD, Grosswendt S, Kretzmer H, Norman TM, Adamson B, Jost M, Quinn JJ, Yang D, Jones MG, Khodaverdian A, Yosef N, Meissner A, **Weissman JS.** Molecular recording of mammalian embryogenesis. *Nature*. 2019 Jun;570(7759):77-82. doi:

Santos DA, Shi L, Tu BP, **Weissman JS.** Cycloheximide can distort measurements of mRNA levels and translation efficiency. *Nucleic Acids Res*. 2019 Mar 27. pii: gkz205. doi: 10.1093/nar/gkz205. [Epub ahead of print]. PMID: 30916348
Liaud N, Horlbeck MA, Gilbert LA, Gjoni K, **Weissman JS**, Cate JHD. Cellular response to small molecules that selectively stall protein synthesis by the ribosome. *PLoS Genet*. 2019 Mar 15;15(3): e1008057. doi: 10.1371/journal.pgen.1008057. eCollection 2019 Mar. PMID: 30875366
Piccolis M, Bond LM, Kampmann M, Pulimeno P, Chitraju C, Jayson CBK, Vaites LP, Boland S, Lai ZW, Gabriel KR, Elliott SD, Paulo JA, Harper JW, **Weissman JS,** Walther TC, Farese RV Jr. Probing the Global Cellular Responses to Lipotoxicity Caused by Saturated Fatty Acids. *Mol Cell*. 2019 Apr 4;74(1):32-44. e8. doi: 10.1016/j.molcel.2019.01.036. Epub 2019 Mar 4. PMID: 30846318

Prescott Woodruff
Li X, Christenson SA, Modena B, Li H, Busse WW, Castro M, Denlinger LC, Erzurum SC, Fahy JV, Gaston B, Hastie AT, Israel E, Jarjour NN, Levy BD, Moore WC, **Woodruff PG**, Kaminski N, Wenzel SE, Bleecker ER, Meyers DA; NHLBI Severe Asthma Research Program (SARP). Genetic analyses identify GSDMB associated with asthma severity, exacerbations, and antiviral pathways. *J Allergy Clin Immunol.* 2021 Mar;147(3):894-909. doi: 10.1016/j.jaci.2020.07.030. Epub 2020 Aug 11. PMID: 32795586
Sarma A, Christenson S, Mick E, Deiss T, DeVoe C, Pisco A, Ghale R, Jauregui A, Byrne A, Moazed F, Spottiswoode N, Sinha P, Zha B, Neff N, Tan M, Serpa PH, Ansel KM, Wilson J, Leligdowicz A, Seigel E, Sirota M, DeRisi J, Matthay M, Consortium C, Hendrickson C, Kangelaris K, Krummel M, **Woodruff P**, Erle D, Calfee C, Langelier C. COVID-19 ARDS is characterized by a dysregulated host response that differs from cytokine storm and is modified by dexamethasone. *Res Sq*. 2021 Jan 14: rs.3.rs-141578. doi: 10.21203/rs.3.rs-141578/v1. Preprint. PMID: 33469573
Siddiqui S, Johansson K, Joo A, Bonser LR, Koh KD, Le Tonqueze O, Bolourchi S, Bautista RA, Zlock L, Roth TL, Marson A, Bhakta NR, Ansel KM, Finkbeiner WE, Erle DJ, **Woodruff PG.** Epithelial miR-141 regulates IL-13-induced airway mucus production. *JCI Insight*. 2021 Mar 8;6(5):139019. doi: 10.1172/jci.insight.139019. PMID: 33682796
Oh AL, Mularski RA, Barjaktarevic I, Barr RG, Bowler RP, Comellas AP, Cooper CB, Criner GJ, Han MK, Hansel NN, Hoffman EA, Kanner RE, Krishnan JA, Paine R 3rd, Parekh TM, Peters SP, Christenson SA, **Woodruff PG**; SPIROMICS Investigators. Defining Resilience to Smoking Related Lung Disease: A Modified Delphi Approach from SPIROMICS. *Ann Am Thorac Soc*. 2021 Feb 25. doi: 10.1513/AnnalsATS.202006-757OC. Online ahead of print. PMID: 33631079
Bonser LR, Eckalbar WL, Rodriguez L, Shen J, Koh KD, Zlock LT, Christenson S, **Woodruff PG**, Finkbeiner WE, Erle DJ. The type 2 asthma mediator IL-13 inhibits SARS-CoV-2 infection of bronchial epithelium. *bioRxiv*. 2021 Feb 25:2021.02.25.432762. doi: 10.1101/2021.02.25.432762. Preprint. PMID: 33655249
Fortis S, Comellas A, Bhatt SP, Hoffman EA, Han MK, Bhakta NR, Paine R 3rd, Ronish B, Kanner RE, Dransfield M, Hoesterey D, Buhr RG, Barr RG, Dolezal B, Ortega VE, Drummond MB, Arjomandi M, Kaner RJ, Kim V, Curtis JL, Bowler RP, Martinez F, Labaki WW, Cooper CB, O'Neal WK, Criner G, Hansel NN, Krishnan JA, **Woodruff P**, Couper D, Tashkin D, Barjaktarevic I. Ratio of Forced Expiratory Volume in 1 second /Slow Vital

Capacity (FEV_1/SVC) <0.7 is associated with clinical, functional, and radiologic features of obstructive lung disease in smokers with preserved lung function. *Chest*. 2021 Feb 1: S0012-3692(21)00229-4. doi: 10.1016/j.chest.2021.01.067. Online ahead of print. PMID: 33539837

Combes AJ, Courau T, Kuhn NF, Hu KH, Ray A, Chen WS, Chew NW, Cleary SJ, Kushnoor D, Reeder GC, Shen A, Tsui J, Hiam-Galvez KJ, Muñoz-Sandoval P, Zhu WS, Lee DS, Sun Y, You R, Magnen M, Rodriguez L, Im KW, Serwas NK, Leligdowicz A, Zamecnik CR, Loudermilk RP, Wilson MR, Ye CJ, Fragiadakis GK, Looney MR, Chan V, Ward A, Carrillo S; UCSF COMET Consortium, Matthay M, Erle DJ, **Woodruff PG**, Langelier C, Kangelaris K, Hendrickson CM, Calfee C, Rao AA, Krummel MF. Global absence and targeting of protective immune states in severe COVID-19. *Nature*. 2021 Mar;591(7848):124-130. doi: 10.1038/s41586-021-03234-7. Epub 2021 Jan 25. PMID: 33494096

Li F, Choi J, Zou C, Newell JD Jr, Comellas AP, Lee CH, Ko H, Barr RG, Bleecker ER, Cooper CB, Abtin F, Barjaktarevic I, Couper D, Han M, Hansel NN, Kanner RE, Paine R 3rd, Kazerooni EA, Martinez FJ, O'Neal W, Rennard SI, Smith BM, **Woodruff PG**, Hoffman EA, Lin CL. Latent traits of lung tissue patterns in former smokers derived by dual channel deep learning in computed tomography images. *Sci Rep*. 2021 Mar 1;11(1):4916. doi: 10.1038/s41598-021-84547-5. PMID: 33649381

Opron K, Begley LA, Erb-Downward JR, Freeman C, Madapoosi S, Alexis NE, Barjaktarevic I, Graham Barr R, Bleecker ER, Bowler RP, Christenson SA, Comellas AP, Cooper CB, Couper DJ, Doerschuk CM, Dransfield MT, Han MK, Hansel NN, Hastie AT, Hoffman EA, Kaner RJ, Krishnan J, O'Neal WK, Ortega VE, Paine R 3rd, Peters SP, Michael Wells J, **Woodruff PG**, Martinez FJ, Curtis JL, Huffnagle GB, Huang YJ. Lung microbiota associations with clinical features of COPD in the SPIROMICS cohort. *NPJ Biofilms Microbiomes*. 2021 Feb 5;7(1):14. doi: 10.1038/s41522-021-00185-9. PMID: 33547327

Woodruff PG, Lazarus SC. Long-term Sequelae of Nonobstructive Chronic Bronchitis-Is Airflow Obstruction Important? *JAMA Intern Med.* 2020 Mar 2. doi: 10.1001/jamainternmed.2019.7280. [Epub ahead of print] No abstract available. PMID: 32119027

Fitzpatrick AM, Chipps BE, Holguin F, **Woodruff PG**. T2-"Low" Asthma: Overview and Management Strategies. *J Allergy Clin Immunol Pract.* 2020 Feb;8(2):452-463. doi: 10.1016/j.jaip.2019.11.006. PMID: 32037109

Maun HR, Jackman JK, Choy DF, Loyet KM, Staton TL, Jia G, Dressen A, Hackney JA, Bremer M, Walters BT, Vij R, Chen X, Trivedi NN, Morando A, Lipari MT, Franke Y, Wu X, Zhang J, Liu J, Wu P, Chang D, Orozco LD, Christensen E, Wong M, Corpuz R, Hang JQ, Lutman J, Sukumaran S, Wu Y, Ubhayakar S, Liang X, Schwartz LB, Babina M, **Woodruff PG**, Fahy JV, Ahuja R, Caughey GH, Kusi A, Dennis MS, Eigenbrot C, Kirchhofer D, Austin CD, Wu LC, Koerber JT, Lee WP, Yaspan BL, Alatsis KR, Arron JR, Lazarus RA, Yi T. An Allosteric Anti-tryptase Antibody for the Treatment of Mast Cell-Mediated Severe Asthma. *Cell*. 2020 Jan 23;180(2):406. doi: 10.1016/j.cell.2020.01.003. No abstract available. PMID: 31978350

Burkes RM, Ceppe AS, Doerschuk CM, Couper D, Hoffman EA, Comellas AP, Barr RG, Krishnan JA, Cooper C, Labaki WW, Ortega VE, Wells JM, Criner GJ, **Woodruff PG**, Bowler RP, Pirozzi CS, Hansel NN, Wise RA, Brown TT, Drummond MB; SPIROMICS

Investigators. Associations Among 25-Hydroxyvitamin D Levels, Lung Function, and Exacerbation Outcomes in COPD: An Analysis of the SPIROMICS Cohort. *Chest*. 2020 Jan 17. pii: S0012-3692(20)30030-1. doi: 10.1016/j.chest.2019.11.047. [Epub ahead of print]. PMID: 31958447

Cho HB, Chae KJ, Jin GY, Choi J, Lin CL, Hoffman EA, Wenzel SE, Castro M, Fain SB, Jarjour NN, Schiebler ML, Barr RG, Hansel N, Cooper CB, Kleerup EC, Han MK, **Woodruff PG,** Kanner RE, Bleecker ER, Peters SP, Moore WC, Lee CH, Choi S; National Heart, Lung and Blood Institute's SubPopulations and InteRmediate Outcome Measures in COPD Study (SPIROMICS) and Severe Asthma Research Program (SARP). Erratum: Structural and Functional Features on Quantitative Chest Computed Tomography in the Korean Asian versus the White American Healthy Non-Smokers. *Korean J Radiol*. 2020 Jan;21(1):117. doi: 10.3348/kjr.2019.0912. PMID: 31920035

Zhang WZ, Rice MC, Hoffman KL, Oromendia C, Barjaktarevic IZ, Wells JM, Hastie AT, Labaki WW, Cooper CB, Comellas AP, Criner GJ, Krishnan JA, Paine R 3rd, Hansel NN, Bowler RP, Barr RG, Peters SP, **Woodruff PG**, Curtis JL, Han MK, Ballman KV, Martinez FJ, Choi AM, Nakahira K, Cloonan SM, Choi ME; SPIROMICS Investigators. Association of urine mitochondrial DNA with clinical measures of COPD in the SPIROMICS cohort. *JCI Insight.* 2020 Feb 13;5(3). pii: 133984. doi: 10.1172/jci.insight.133984. PMID: 31895696

Keene JD, Jacobson S, Kechris K, Kinney GL, Foreman MG, Doerschuk CM, Make BJ, Curtis JL, Rennard SI, Barr RG, Bleecker ER, Kanner RE, Kleerup EC, Hansel NN, **Woodruff PG**, Han MK, Paine R 3rd, Martinez FJ, Bowler RP, O'Neal WK; COPDGene and SPIROMICS Investigators. Biomarkers Predictive of Exacerbations in the SPIROMICS and COPDGene Cohorts. *Am J Respir Crit Care Med*. 2020 Jan 1;201(1):473-481. doi: 10.1164/rccm.201607-1330OC.201.1.test. PMID: 31891318

Arger NK, Ho ME, Allen IE, Benn BS, **Woodruff PG**, Koth LL. CXCL9 and CXCL10 are differentially associated with systemic organ involvement and pulmonary disease severity in sarcoidosis. *Respir Med*. 2020 Jan; 161:105822. doi: 10.1016/j.rmed.2019.105822. Epub 2019 Nov 20. PMID: 31783271

Wells JM, Xing D, Viera L, Burkes RM, Wu Y, Bhatt SP, Dransfield MT, Couper DJ, O'Neal W, Hoffman EA, Gaggar A, Barjaktarevic I, Curtis JL, Labaki WW, Han MLK, Freeman CM, Putcha N, Schlange T, Blalock JE; SPIROMICS Investigators. The matrikine acetyl-proline-glycine-proline and clinical features of COPD: findings from SPIROMICS. *Respir Res*. 2019 Nov 12;20(1):254. doi: 10.1186/s12931-019-1230-8. PMID: 31718676

Ortega VE, Li X, O'Neal WK, Lackey L, Ampleford E, Hawkins GA, Grayeski PJ, Laederach A, Barjaktarevic I, Barr RG, Cooper C, Couper D, Han MK, Kanner RE, Kleerup EC, Martinez FJ, Paine R 3rd, Peters SP, Pirozzi C, Rennard SI, **Woodruff PG**, Hoffman EA, Meyers DA, Bleecker ER; NHLBI Subpopulations and Intermediate Outcomes Measures in COPD Study (SPIROMICS). The Effects of Rare SERPINA1 Variants on Lung Function and Emphysema in SPIROMICS. *Am J Respir Crit Care Med*. 2020 Mar 1;201(5):540-554. doi: 10.1164/rccm.201904-0769OC. PMID: 31661293

Koh KD, Siddiqui S, Cheng D, Bonser LR, Sun DI, Zlock LT, Finkbeiner WE, **Woodruff PG**, Erle DJ. Efficient RNP-directed Human Gene Targeting Reveals SPDEF Is Required for IL-13-induced Mucostasis. *Am J Respir Cell Mol Biol.* 2020 Mar;62(3):373-381. doi: 10.1165/rcmb.2019-0266OC. PMID: 31596609

Peters MC, Sajuthi S, Deford P, Christenson S, Rios CL, Montgomery MT, **Woodruff PG**, Mauger DT, Erzurum SC, Johansson MW, Denlinger LC, Jarjour NN, Castro M, Hastie AT, Moore W, Ortega VE, Bleecker ER, Wenzel SE, Israel E, Levy BD, Seibold MA, Fahy JV. COVID-19-related Genes in Sputum Cells in Asthma. Relationship to Demographic Features and Corticosteroids. *Am J Respir Crit Care Med*. 2020 Jul 1;202(1):83-90. doi: 10.1164/rccm.202003-0821OC. PMID: 32348692

Smith BM, Kirby M, Hoffman EA, Kronmal RA, Aaron SD, Allen NB, Bertoni A, Coxson HO, Cooper C, Couper DJ, Criner G, Dransfield MT, Han MK, Hansel NN, Jacobs DR Jr, Kaufman JD, Lin CL, Manichaikul A, Martinez FJ, Michos ED, Oelsner EC, Paine R 3rd, Watson KE, Benedetti A, Tan WC, Bourbeau J, **Woodruff PG**, Barr RG; MESA Lung, CanCOLD, and SPIROMICS Investigators. Association of Dysanapsis With Chronic Obstructive Pulmonary Disease Among Older Adults. *JAMA*. 2020 Jun 9;323(22):2268-2280. doi: 10.1001/jama.2020.6918. PMID: 32515814

Ortega VE, Li X, O'Neal WK, Lackey L, Ampleford E, Hawkins GA, Grayeski PJ, Laederach A, Barjaktarevic I, Barr RG, Cooper C, Couper D, Han MK, Kanner RE, Kleerup EC, Martinez FJ, Paine R 3rd, Peters SP, Pirozzi C, Rennard SI, **Woodruff PG**, Hoffman EA, Meyers DA, Bleecker ER; NHLBI Subpopulations and Intermediate Outcomes Measures in COPD Study (SPIROMICS). The Effects of Rare *SERPINA1* Variants on Lung Function and Emphysema in SPIROMICS. *Am J Respir Crit Care Med*. 2020 Mar 1;201(5):540-554. doi: 10.1164/rccm.201904-0769OC. PMID: 31661293

Burkes RM, Ceppe AS, Doerschuk CM, Couper D, Hoffman EA, Comellas AP, Barr RG, Krishnan JA, Cooper C, Labaki WW, Ortega VE, Wells JM, Criner GJ, **Woodruff PG**, Bowler RP, Pirozzi CS, Hansel NN, Wise RA, Brown TT, Drummond MB; SPIROMICS Investigators. Associations Among 25-Hydroxyvitamin D Levels, Lung Function, and Exacerbation Outcomes in COPD: An Analysis of the SPIROMICS Cohort. *Chest*. 2020 Apr;157(4):856-865. doi: 10.1016/j.chest.2019.11.047. Epub 2020 Jan 17. PMID: 31958447

Putcha N, Fawzy A, Matsui EC, Liu MC, Bowler RP, **Woodruff PG**, O'Neal WK, Comellas AP, Han MK, Dransfield MT, Wells JM, Lugogo N, Gao L, Talbot CC Jr, Hoffman EA, Cooper CB, Paulin LM, Kanner RE, Criner G, Ortega VE, Barr RG, Krishnan JA, Martinez FJ, Drummond MB, Wise RA, Diette GB, Hersh CP, Hansel NN. Clinical Phenotypes of Atopy and Asthma in COPD: A Meta-analysis of SPIROMICS and COPDGene. *Chest*. 2020 Dec;158(6):2333-2345. doi: 10.1016/j.chest.2020.04.069. Epub 2020 May 23. PMID: 32450244

Han MK, Ye W, Kim DY, **Woodruff P**; Pulmonary Trials Cooperative Investigators. Design of the Redefining Therapy in Early COPD Study. *Chronic Obstr Pulm Dis*. 2020 Oct;7(4):382-389. doi: 10.15326/jcopdf.7.4.2020.0157. PMID: 32989941

Leitao Filho FS, Mattman A, Schellenberg R, Criner GJ, **Woodruff P**, Lazarus SC, Albert RK, Connett J, Han MK, Gay SE, Martinez FJ, Fuhlbrigge AL, Stoller JK, MacIntyre NR, Casaburi R, Diaz P, Panos RJ, Cooper JA Jr, Bailey WC, LaFon DC, Sciurba FC, Kanner RE, Yusen RD, Au DH, Pike KC, Fan VS, Leung JM, Man SP, Aaron SD, Reed RM, Sin DD. Serum IgG Levels and Risk of COPD Hospitalization: A Pooled Meta-analysis. *Chest*. 2020 Oct;158(4):1420-1430. doi: 10.1016/j.chest.2020.04.058. Epub 2020 May 19. PMID: 32439504

Combes AJ, Courau T, Kuhn NF, Hu KH, Ray A, Chen WS, Cleary SJ, Chew NW, Kushnoor D, Reeder GC, Shen A, Tsui J, Hiam-Galvez KJ, Muñoz-Sandoval P, Zhu WS,

Lee DS, Sun Y, You R, Magnen M, Rodriguez L, Leligdowicz A, Zamecnik CR, Loudermilk RP, Wilson MR, Ye CJ, Fragiadakis GK, Looney MR, Chan V, Ward A, Carrillo S; UCSF COMET Consortium, Matthay M, Erle DJ, **Woodruff PG**, Langelier C, Kangelaris K, Hendrickson CM, Calfee C, Rao AA, Krummel MF. Global Absence and Targeting of Protective Immune States in Severe COVID-19. *Res Sq*. 2020 Oct 28: rs.3.rs-97042. doi: 10.21203/rs.3.rs-97042/v1. Preprint. PMID: 33140041

Stott-Miller M, Müllerová H, Miller B, Tabberer M, El Baou C, Keeley T, Martinez FJ, Han M, Dransfield M, Hansel NN, Cooper CB, **Woodruff P**, Ortega VE, Comellas AP, Paine Iii R, Kanner RE, Anderson W, Drummond MB, Kim V, Tal-Singer R, Lazaar AL. Defining Chronic Mucus Hypersecretion Using the CAT in the SPIROMICS Cohort. *Int J Chron Obstruct Pulmon Dis*. 2020 Oct 13;15:2467-2476. doi: 10.2147/COPD.S267002. eCollection 2020. PMID: 33116463

Combes AJ, Courau T, Kuhn NF, Hu KH, Ray A, Chen WS, Cleary SJ, Chew NW, Kushnoor D, Reeder GC, Shen A, Tsui J, Hiam-Galvez KJ, Muñoz-Sandoval P, Zhu WS, Lee DS, Sun Y, You R, Magnen M, Rodriguez L, Leligdowicz A, Zamecnik CR, Loudermilk RP, Wilson MR, Ye CJ, Fragiadakis GK, Looney MR, Chan V, Ward A, Carrillo S, Matthay M, Erle DJ, **Woodruff PG**, Langelier C, Kangelaris K, Hendrickson CM, Calfee C, Rao AA, Krummel MF. Global Absence and Targeting of Protective Immune States in Severe COVID-19. *bioRxiv*. 2020 Oct 29:2020.10.28.359935. doi: 10.1101/2020.10.28.359935. Preprint. PMID: 33140050

Dunican EM, Elicker BM, Henry T, Gierada DS, Schiebler ML, Anderson W, Barjaktarevic I, Barr RG, Bleecker ER, Boucher RC, Bowler RP, Christenson SA, Comellas A, Cooper CB, Couper D, Criner GJ, Dransfield M, Doerschuk CM, Drummond MB, Hansel NN, Han MK, Hastie AT, Hoffman EA, Krishnan JA, Lazarus SC, Martinez FJ, McCulloch CE, O'Neal WK, Ortega VE, Paine R 3rd, Peters S, Schroeder JD, **Woodruff PG**, Fahy JV. Mucus Plugs and Emphysema in the Pathophysiology of Airflow Obstruction and Hypoxemia in Smokers. *Am J Respir Crit Care Med*. 2020 Nov 12. doi: 10.1164/rccm.202006-2248OC. Online ahead of print. PMID: 33180550

Arger NK, Machiraju S, Allen IE, **Woodruff PG**, Koth LL. T-bet Expression in Peripheral Th17.0 Cells Is Associated with Pulmonary Function Changes in Sarcoidosis. *Front Immunol*. 2020 Jul 22; 11:1129. doi: 10.3389/fimmu.2020.01129. eCollection 2020. PMID: 32774332

Cooper CB, Paine R, Curtis JL, Kanner RE, Martinez CH, Meldrum CA, Bowler R, O'Neal W, Hoffman EA, Couper D, Quibrera M, Criner G, Dransfield MT, Han MK, Hansel NN, Krishnan JA, Lazarus SC, Peters SP, Barr RG, Martinez FJ, **Woodruff PG**; SPIROMICS investigators. Novel Respiratory Disability Score Predicts COPD Exacerbations and Mortality in the SPIROMICS Cohort. *Int J Chron Obstruct Pulmon Dis*. 2020 Aug 4; 15:1887-1898. doi: 10.2147/COPD.S250191. eCollection 2020. PMID: 32821092

Zhang WZ, Oromendia C, Kikkers SA, Butler JJ, O'Beirne S, Kim K, O'Neal WK, Freeman CM, Christenson SA, Peters SP, Wells JM, Doerschuk C, Putcha N, Barjaktarevic I, **Woodruff PG**, Cooper CB, Bowler RP, Comellas AP, Criner GJ, Paine R 3rd, Hansel NN, Han MK, Crystal RG, Kaner RJ, Ballman KV, Curtis JL, Martinez FJ, Cloonan SM. Increased airway iron parameters and risk for exacerbation in COPD: an analysis from SPIROMICS. *Sci Rep*. 2020 Jun 29;10(1):10562. doi: 10.1038/s41598-020-67047-w. PMID: 32601308

Ash SY, Sanchez-Ferrero GV, Schiebler ML, Rahaghi FN, Rai A, Come CE, Ross JC, Colon AG, Cardet JC, Bleecker ER, Castro M, Fahy JV, Fain SB, Gaston BM, Hoffman EA, Jarjour NN, Lempel JK, Mauger DT, Tattersall MC, Wenzel SE, Levy BD, Washko GR, Israel E, San Jose Estepar R; SARP Investigators. Estimated Ventricular Size, Asthma Severity, and Exacerbations: The Severe Asthma Research Program III Cohort. *Chest*. 2020 Feb;157(2):258-267. doi: 10.1016/j.chest.2019.08.2185. Epub 2019 Sep 12. PMID: 31521672

Denlinger LC, Phillips BR, Sorkness RL, Bleecker ER, Castro M, DeBoer MD, Fitzpatrick AM, Hastie AT, Gaffin JM, Moore WC, Peters MC, Peters SP, Phipatanakul W, Cardet JC, Erzurum SC, Fahy JV, Fajt ML, Gaston B, Levy BD, Meyers DA, Ross K, Teague WG, Wenzel SE, **Woodruff PG**, Zein J, Jarjour NN, Mauger DT, Israel E; National Heart, Lung and Blood Institute's Severe Asthma Research Program-3 Investigators. Responsiveness to Parenteral Corticosteroids and Lung Function Trajectory in Adults with Moderate to Severe Asthma. *Am J Respir Crit Care Med*. 2020 Dec 8. doi: 10.1164/rccm.202002-0454OC. Online ahead of print. PMID: 33290668

Austin CD, Gonzalez Edick M, Ferrando RE, Solon M, Baca M, Mesh K, Bradding P, Gauvreau GM, Sumino K, FitzGerald JM, Israel E, Bjermer L, Bourdin A, Arron JR, Choy DF, Olsson JK, Abreu F, Howard M, Wong K, Cai F, Peng K, Putnam WS, Holweg CTJ, Matthews JG, Kraft M, **Woodruff PG**; CLAVIER Investigators. A randomized, placebo-controlled trial evaluating effects of lebrikizumab on airway eosinophilic inflammation and remodelling in uncontrolled asthma (CLAVIER). *Clin Exp Allergy*. 2020 Dec;50(12):1342-1351. doi: 10.1111/cea.13731. Epub 2020 Oct 4. PMID: 32909660

Kim V, Jeong S, Zhao H, Kesimer M, Boucher RC, Wells JM, Christenson SA, Han MK, Dransfield M, Paine R 3rd, Cooper CB, Barjaktarevic I, Bowler R, Curtis JL, Kaner RJ, O'Beirne SL, O'Neal WK, Rennard SI, Martinez FJ, **Woodruff PG.** Current smoking with or without chronic bronchitis is independently associated with goblet cell hyperplasia in healthy smokers and COPD subjects. *Sci Rep*. 2020 Nov 18;10(1):20133. doi: 10.1038/s41598-020-77229-1. PMID: 33208859

Boudewijn IM, Lan A, Faiz A, Cox CA, Brouwer S, Schokker S, Vroegop SJ, Nawijn MC, **Woodruff PG**, Christenson SA, Hagedoorn P, Frijlink HW, Choy DF, Brouwer U, Wisman M, Postma DS, Fingleton J, Beasley R, van den Berge M, Guryev V. Nasal gene expression changes with inhaled corticosteroid treatment in asthma. *Allergy*. 2020 Jan;75(1):191-194. doi: 10.1111/all.13952. Epub 2019 Jul 15. No abstract available. PMID: 31230369

Arger NK, Ho M, **Woodruff PG**, Koth LL. Serum CXCL11 correlates with pulmonary outcomes and disease burden in sarcoidosis. *Respir Med*. 2019 Jun; 152:89-96. doi: 10.1016/j.rmed.2019.04.005. Epub 2019 Apr 17. PMID: 31128616

Lazarus SC, Krishnan JA, King TS, Lang JE, Blake KV, Covar R, Lugogo N, Wenzel S, Chinchilli VM, Mauger DT, Dyer AM, Boushey HA, Fahy JV, **Woodruff PG**, Bacharier LB, Cabana MD, Cardet JC, Castro M, Chmiel J, Denlinger L, DiMango E, Fitzpatrick AM, Gentile D, Hastie A, Holguin F, Israel E, Jackson D, Kraft M, LaForce C, Lemanske RF Jr, Martinez FD, Moore W, Morgan WJ, Moy JN, Myers R, Peters SP, Phipatanakul W, Pongracic JA, Que L, Ross K, Smith L, Szefler SJ, Wechsler ME, Sorkness CA; National Heart, Lung, and Blood Institute AsthmaNet. Mometasone or Tiotropium in Mild Asthma with a Low Sputum Eosinophil Level. *N Engl J Med*. 2019 May 23;380(21):2009-2019. doi: 10.1056/NEJMoa1814917. Epub 2019 May 19. PMID: 31112384

Shrine N, Guyatt AL, Erzurumluoglu AM, Jackson VE, Hobbs BD, Melbourne CA, Batini C, Fawcett KA, Song K, Sakornsakolpat P, Li X, Boxall R, Reeve NF, Obeidat M, Zhao JH, Wielscher M; Understanding Society Scientific Group, Weiss S, Kentistou KA, Cook JP, Sun BB, Zhou J, Hui J, Karrasch S, Imboden M, Harris SE, Marten J, Enroth S, Kerr SM, Surakka I, Vitart V, Lehtimäki T, Allen RJ, Bakke PS, Beaty TH, Bleecker ER, Bossé Y, Brandsma CA, Chen Z, Crapo JD, Danesh J, DeMeo DL, Dudbridge F, Ewert R, Gieger C, Gulsvik A, Hansell AL, Hao K, Hoffman JD, Hokanson JE, Homuth G, Joshi PK, Joubert P, Langenberg C, Li X, Li L, Lin K, Lind L, Locantore N, Luan J, Mahajan A, Maranville JC, Murray A, Nickle DC, Packer R, Parker MM, Paynton ML, Porteous DJ, Prokopenko D, Qiao D, Rawal R, Runz H, Sayers I, Sin DD, Smith BH, Artigas MS, Sparrow D, Tal-Singer R, Timmers PRHJ, Van den Berge M, Whittaker JC, **Woodruff PG**, Yerges-Armstrong LM, Troyanskaya OG, Raitakari OT, Kähönen M, Polašek O, Gyllensten U, Rudan I, Deary IJ, Probst-Hensch NM, Schulz H, James AL, Wilson JF, Stubbe B, Zeggini E, Jarvelin MR, Wareham N, Silverman EK, Hayward C, Morris AP, Butterworth AS, Scott RA, Walters RG, Meyers DA, Cho MH, Strachan DP, Hall IP, Tobin MD, Wain LV. Author Correction: New genetic signals for lung function highlight pathways and chronic obstructive pulmonary disease associations across multiple ancestries. *Nat Genet*. 2019 Jun;51(6):1067. doi: 10.1038/s41588-019-0438-3. PMID: 31110354

Nakada EM, Bhakta NR, Korwin-Mihavics BR, Kumar A, Chamberlain N, Bruno SR, Chapman DG, Hoffman SM, Daphtary N, Aliyeva M, Irvin CG, Dixon AE, **Woodruff PG**, Amin S, Poynter ME, Desai DH, Anathy V. Conjugated bile acids attenuate allergen-induced airway inflammation and hyperresponsiveness by inhibiting UPR transducers. *JCI Insight*. 2019 May 2;4(9). pii: 98101. doi: 10.1172/jci.insight.98101. eCollection 2019 May 2. PMID: 31045581

Gu BH, Choi JC, Shen YH, Song LZ, Scheurer ME, Luong A, Rodriguez A, **Woodruff P**, Koth L, Corry DB, Kheradmand F, LeMaire SA. Elastin-Specific Autoimmunity in Smokers with Thoracic Aortic Aneurysm and Dissection is Independent of Chronic Obstructive Pulmonary Disease. *J Am Heart Assoc*. 2019 Apr 16;8(8): e011671. doi: 10.1161/JAHA.118.011671. PMID: 30957625

Das S; Extracellular RNA Communication Consortium, Ansel KM, Bitzer M, Breakefield XO, Charest A, Galas DJ, Gerstein MB, Gupta M, Milosavljevic A, McManus MT, Patel T, Raffai RL, Rozowsky J, Roth ME, Saugstad JA, Van Keuren-Jensen K, Weaver AM, Laurent LC. The Extracellular RNA Communication Consortium: Establishing Foundational Knowledge and Technologies for Extracellular RNA Research. *Cell*. 2019 Apr 4;177(2):231-242. doi: 10.1016/j.cell.2019.03.023. Review. PMID: 30951667

Oelsner EC, Ortega VE, Smith BM, Nguyen JN, Manichaikul AW, Hoffman EA, Guo X, Taylor KD, **Woodruff PG**, Couper DJ, Hansel NN, Martinez FJ, Paine Iii R, Han MK, Cooper C, Dransfield MT, Criner G, Krishnan JA, Bowler R, Bleecker ER, Peters S, Rich SS, Meyers DA, Rotter JI, Barr RG. A Genetic Risk Score Associated with COPD Susceptibility and Lung Structure on Computed Tomography. *Am J Respir Crit Care Med*. 2019 Mar 29. doi: 10.1164/rccm.201812-2355OC. [Epub ahead of print]. PMID: 30925230

Lachowicz-Scroggins ME, Dunican EM, Charbit AR, Raymond W, Looney MR, Peters MC, Gordon ED, **Woodruff PG**, Lefrançais E, Phillips BR, Mauger DT, Comhair SA, Erzurum SC, Johansson MW, Jarjour NN, Coverstone AM, Castro M, Hastie AT, Bleecker ER, Fajt ML, Wenzel SE, Israel E, D Levy B, Fahy JV; National Heart, Lung, and Blood Institute Severe Asthma Research Program-3 Investigators. Extracellular DNA, Neutrophil

Extracellular Traps, and Inflammasome Activation in Severe Asthma. *Am J Respir Crit Care Med*. 2019 Mar 19. doi: 10.1164/rccm.201810-1869OC. [Epub ahead of print]. PMID: 30888839

Shrine N, Guyatt AL, Erzurumluoglu AM, Jackson VE, Hobbs BD, Melbourne CA, Batini C, Fawcett KA, Song K, Sakornsakolpat P, Li X, Boxall R, Reeve NF, Obeidat M, Zhao JH, Wielscher M; Understanding Society Scientific Group, Weiss S, Kentistou KA, Cook JP, Sun BB, Zhou J, Hui J, Karrasch S, Imboden M, Harris SE, Marten J, Enroth S, Kerr SM, Surakka I, Vitart V, Lehtimäki T, Allen RJ, Bakke PS, Beaty TH, Bleecker ER, Bossé Y, Brandsma CA, Chen Z, Crapo JD, Danesh J, DeMeo DL, Dudbridge F, Ewert R, Gieger C, Gulsvik A, Hansell AL, Hao K, Hoffman JD, Hokanson JE, Homuth G, Joshi PK, Joubert P, Langenberg C, Li X, Li L, Lin K, Lind L, Locantore N, Luan J, Mahajan A, Maranville JC, Murray A, Nickle DC, Packer R, Parker MM, Paynton ML, Porteous DJ, Prokopenko D, Qiao D, Rawal R, Runz H, Sayers I, Sin DD, Smith BH, Soler Artigas M, Sparrow D, Tal-Singer R, Timmers PRHJ, Van den Berge M, Whittaker JC, **Woodruff PG**, Yerges-Armstrong LM, Troyanskaya OG, Raitakari OT, Kähönen M, Polašek O, Gyllensten U, Rudan I, Deary IJ, Probst-Hensch NM, Schulz H, James AL, Wilson JF, Stubbe B, Zeggini E, Jarvelin MR, Wareham N, Silverman EK, Hayward C, Morris AP, Butterworth AS, Scott RA, Walters RG, Meyers DA, Cho MH, Strachan DP, Hall IP, Tobin MD, Wain LV. New genetic signals for lung function highlight pathways and chronic obstructive pulmonary disease associations across multiple ancestries. *Nat Genet*. 2019 Mar;51(3):481-493. doi: 10.1038/s41588-018-0321-7. Epub 2019 Feb 25. PMID: 30804560

Wells JM, Arenberg DA, Barjaktarevic I, Bhatt SP, Bowler RP, Christenson SA, Couper DJ, Dransfield MT, Han MK, Hoffman EA, Kaner RJ, Kim V, Kleerup E, Martinez FJ, Moore WC, O'Beirne SL, Paine R 3rd, Putcha N, Raman SM, Barr RG, Rennard SI, **Woodruff PG**, Curtis JL. Safety and Tolerability of Comprehensive Research Bronchoscopy in Chronic Obstructive Pulmonary Disease. Results from the SPIROMICS Bronchoscopy Substudy. *Ann Am Thorac Soc*. 2019 Apr;16(4):439-446. doi: 10.1513/AnnalsATS.201807-441OC. PMID: 30653926

Christenson SA, van den Berge M, Faiz A, Inkamp K, Bhakta N, Bonser LR, Zlock LT, Barjaktarevic IZ, Barr RG, Bleecker ER, Boucher RC, Bowler RP, Comellas AP, Curtis JL, Han MK, Hansel NN, Hiemstra PS, Kaner RJ, Krishnanm JA, Martinez FJ, O'Neal WK, Paine R 3rd, Timens W, Wells JM, Spira A, Erle DJ, **Woodruff PG**. An airway epithelial IL-17A response signature identifies a steroid-unresponsive COPD patient subgroup. *J Clin Invest*. 2019 Jan 2;129(1):169-181. doi: 10.1172/JCI121087. Epub 2018 Nov 26. PMID: 30383540

Ghosh S, Anderson WH, Putcha N, Han MK, Curtis JL, Criner GJ, Dransfield MT, Barr RG, Krishnan JA, Lazarus SC, Cooper CB, Paine R 3rd, Peters SP, Hansel NN, Martinez FJ, Drummond MB; Current and former investigators of the SPIROMICS sites and reading centers. Alignment of Inhaled Chronic Obstructive Pulmonary Disease Therapies with Published Strategies. Analysis of the Global Initiative for Chronic Obstructive Lung Disease Recommendations in SPIROMICS. *Ann Am Thorac Soc*. 2019 Feb;16(2):200-208. doi: 10.1513/AnnalsATS.201804-283OC. PMID: 30216731

Barjaktarevic IZ, Buhr RG, Wang X, Hu S, Couper D, Anderson W, Kanner RE, Paine Iii R, Bhatt SP, Bhakta NR, Arjomandi M, Kaner RJ, Pirozzi CS, Curtis JL, O'Neal WK, **Woodruff PG**, Han MK, Martinez FJ, Hansel N, Wells JM, Ortega VE, Hoffman EA, Doerschuk CM, Kim V, Dransfield MT, Drummond MB, Bowler R, Criner G, Christenson

SA, Ronish B, Peters SP, Krishnan JA, Tashkin DP, Cooper CB; NHLBI SubPopulations and InteRmediate Outcome Measures In COPD Study (SPIROMICS). Clinical Significance of Bronchodilator Responsiveness Evaluated by Forced Vital Capacity in COPD: SPIROMICS Cohort Analysis. *Int J Chron Obstruct Pulmon Dis*. 2019 Dec 20; 14:2927-2938. doi: 10.2147/COPD.S220164. eCollection 2019. PMID: 31908441
Wells JM, Arenberg DA, Barjaktarevic I, Bhatt SP, Bowler RP, Christenson SA, Couper DJ, Dransfield MT, Han MK, Hoffman EA, Kaner RJ, Kim V, Kleerup E, Martinez FJ, Moore WC, O'Beirne SL, Paine R 3rd, Putcha N, Raman SM, Barr RG, Rennard SI, **Woodruff PG**, Curtis JL. Safety and Tolerability of Comprehensive Research Bronchoscopy in Chronic Obstructive Pulmonary Disease. Results from the SPIROMICS Bronchoscopy Substudy. *Ann Am Thorac Soc*. 2019 Apr;16(4):439-446. doi: 10.1513/AnnalsATS.201807-441OC. PMID: 30653926
Oelsner EC, Ortega VE, Smith BM, Nguyen JN, Manichaikul AW, Hoffman EA, Guo X, Taylor KD, **Woodruff PG**, Couper DJ, Hansel NN, Martinez FJ, Paine R 3rd, Han MK, Cooper C, Dransfield MT, Criner G, Krishnan JA, Bowler R, Bleecker ER, Peters S, Rich SS, Meyers DA, Rotter JI, Barr RG. A Genetic Risk Score Associated with Chronic Obstructive Pulmonary Disease Susceptibility and Lung Structure on Computed Tomography. *Am J Respir Crit Care Med*. 2019 Sep 15;200(6):721-731. doi: 10.1164/rccm.201812-2355OC. PMID: 30925230
Cho HB, Chae KJ, Jin GY, Choi J, Lin CL, Hoffman EA, Wenzel SE, Castro M, Fain SB, Jarjour NN, Schiebler ML, Barr RG, Hansel N, Cooper CB, Kleerup EC, Han MK, **Woodruff PG**, Kanner RE, Bleecker ER, Peters SP, Moore WC, Lee CH, Choi S; National Heart, Lung and Blood Institute's SubPopulations and InteRmediate Outcome Measures in COPD Study (SPIROMICS) and Severe Asthma Research Program (SARP). Structural and Functional Features on Quantitative Chest Computed Tomography in the Korean Asian versus the White American Healthy Non-Smokers. *Korean J Radiol*. 2019 Jul;20(7):1236-1245. doi: 10.3348/kjr.2019.0083. PMID: 31270987
Garudadri S, **Woodruff PG**, Han MK, Curtis JL, Barr RG, Bleecker ER, Bowler RP, Comellas A, Cooper CB, Criner G, Dransfield MT, Hansel NN, Paine R 3rd, Krishnan JA, Peters SP, Hastie AT, Martinez FJ, O'Neal WK, Couper DJ, Alexis NE, Christenson SA. Systemic Markers of Inflammation in Smokers with Symptoms Despite Preserved Spirometry in SPIROMICS. *Chest*. 2019 May;155(5):908-917. doi: 10.1016/j.chest.2018.12.022. Epub 2019 Jan 23. PMID: 30684474
Haghighi B, Choi S, Choi J, Hoffman EA, Comellas AP, Newell JD Jr, Lee CH, Barr RG, Bleecker E, Cooper CB, Couper D, Han ML, Hansel NN, Kanner RE, Kazerooni EA, Kleerup EAC, Martinez FJ, O'Neal W, Paine R 3rd, Rennard SI, Smith BM, **Woodruff PG**, Lin CL. Imaging-based clusters in former smokers of the COPD cohort associate with clinical characteristics: The SubPopulations and intermediate outcome measures in COPD study (SPIROMICS). *Respir Res*. 2019 Jul 15;20(1):153. doi: 10.1186/s12931-019-1121-z. PMID: 31307479
Maun HR, Jackman JK, Choy DF, Loyet KM, Staton TL, Jia G, Dressen A, Hackney JA, Bremer M, Walters BT, Vij R, Chen X, Trivedi NN, Morando A, Lipari MT, Franke Y, Wu X, Zhang J, Liu J, Wu P, Chang D, Orozco LD, Christensen E, Wong M, Corpuz R, Hang JQ, Lutman J, Sukumaran S, Wu Y, Ubhayakar S, Liang X, Schwartz LB, Babina M, **Woodruff PG**, Fahy JV, Ahuja R, Caughey GH, Kusi A, Dennis MS, Eigenbrot C, Kirchhofer D, Austin CD, Wu LC, Koerber JT, Lee WP, Yaspan BL, Alatsis KR, Arron JR,

Lazarus RA, Yi T. An Allosteric Anti-tryptase Antibody for the Treatment of Mast Cell-Mediated Severe Asthma. *Cell*. 2019 Oct 3;179(2):417-431.e19. doi: 10.1016/j.cell.2019.09.009. Erratum in: *Cell*. 2020 Jan 23;180(2):406. PMID: 31585081

Jeon D, Chang EG, McGing M, Hartman-Filson M, Sommers M, Lewis E, Balmes JR, Moisi D, Lederman MM, Madsen KA, **Woodruff PG**, Hunt PW, Huang L; Inflammation, Aging, Microbes and Obstructive Lung Disease (I AM OLD) Study. Pneumoproteins are associated with pulmonary function in HIV-infected persons. *PLoS One*. 2019 Oct 1;14(10): e0223263. doi: 10.1371/journal.pone.0223263. eCollection 2019. PMID: 31574118

Arjomandi M, Zeng S, Barjaktarevic I, Barr RG, Bleecker ER, Bowler RP, Buhr RG, Criner GJ, Comellas AP, Cooper CB, Couper DJ, Curtis JL, Dransfield MT, Han MK, Hansel NN, Hoffman EA, Kaner RJ, Kanner RE, Krishnan JA, Paine R 3rd, Peters SP, Rennard SI, **Woodruff PG**; SPIROMICS Investigators. Radiographic lung volumes predict progression to COPD in smokers with preserved spirometry in SPIROMICS. *Eur Respir J.* 2019 Oct 31;54(4). pii: 1802214. doi: 10.1183/13993003.02214-2018. Print 2019 Oct. PMID: 31439683

Labaki WW, Gu T, Murray S, Curtis JL, Yeomans L, Bowler RP, Barr RG, Comellas AP, Hansel NN, Cooper CB, Barjaktarevic I, Kanner RE, Paine R 3rd, McDonald MN, Krishnan JA, Peters SP, **Woodruff PG**, O'Neal WK, Diao W, He B, Martinez FJ, Standiford TJ, Stringer KA, Han MK. Serum amino acid concentrations and clinical outcomes in smokers: SPIROMICS metabolomics study. *Sci Rep*. 2019 Aug 6;9(1):11367. doi: 10.1038/s41598-019-47761-w. PMID: 31388056

Halper-Stromberg E, Gillenwater L, Cruickshank-Quinn C, O'Neal WK, Reisdorph N, Petrache I, Zhuang Y, Labaki WW, Curtis JL, Wells J, Rennard S, Pratte KA, **Woodruff P**, Stringer KA, Kechris K, Bowler RP. Bronchoalveolar Lavage Fluid from COPD Patients Reveals More Compounds Associated with Disease than Matched Plasma. *Metabolites.* 2019 Jul 25;9(8). pii: E157. doi: 10.3390/metabo9080157. PMID: 31349744

Haghighi B, Choi S, Choi J, Hoffman EA, Comellas AP, Newell JD Jr, Lee CH, Barr RG, Bleecker E, Cooper CB, Couper D, Han ML, Hansel NN, Kanner RE, Kazerooni EA, Kleerup EAC, Martinez FJ, O'Neal W, Paine R 3rd, Rennard SI, Smith BM, **Woodruff PG**, Lin CL. Imaging-based clusters in former smokers of the COPD cohort associate with clinical characteristics: The SubPopulations and intermediate outcome measures in COPD study (SPIROMICS). *Respir Res*. 2019 Jul 15;20(1):153. doi: 10.1186/s12931-019-1121-z. PMID: 31307479

Cho HB, Chae KJ, Jin GY, Choi J, Lin CL, Hoffman EA, Wenzel SE, Castro M, Fain SB, Jarjour NN, Schiebler ML, Barr RG, Hansel N, Cooper CB, Kleerup EC, Han MK, **Woodruff PG,** Kanner RE, Bleecker ER, Peters SP, Moore WC, Lee CH, Choi S; National Heart, Lung and Blood Institute's SubPopulations and InteRmediate Outcome Measures in COPD Study (SPIROMICS) and Severe Asthma Research Program (SARP). Structural and Functional Features on Quantitative Chest Computed Tomography in the Korean Asian versus the White American Healthy Non-Smokers. *Korean J Radiol*. 2019 Jul;20(7):1236-1245. doi: 10.3348/kjr.2019.0083. Erratum in: *Korean J Radiol*. 2020 Jan;21(1):117. PMID: 31270987

Barjaktarevic IZ, Buhr RG, Wang X, Hu S, Couper D, Anderson W, Kanner RE, Paine Iii R, Bhatt SP, Bhakta NR, Arjomandi M, Kaner RJ, Pirozzi CS, Curtis JL, O'Neal WK, **Woodruff PG**, Han MK, Martinez FJ, Hansel N, Wells JM, Ortega VE, Hoffman EA, Doerschuk CM, Kim V, Dransfield MT, Drummond MB, Bowler R, Criner G, Christenson

SA, Ronish B, Peters SP, Krishnan JA, Tashkin DP, Cooper CB; NHLBI SubPopulations and InteRmediate Outcome Measures in COPD Study (SPIROMICS). Clinical Significance of Bronchodilator Responsiveness Evaluated by Forced Vital Capacity in COPD: SPIROMICS Cohort Analysis. *Int J Chron Obstruct Pulmon Dis*. 2019 Dec 20; 14:2927-2938. doi: 10.2147/COPD.S220164. eCollection 2019. PMID: 31908441

Peters MC, Ringel L, Dyjack N, Herrin R, **Woodruff PG**, Rios C, O'Connor B, Fahy JV, Seibold MA. A Transcriptomic Method to Determine Airway Immune Dysfunction in T2-High and T2-Low Asthma. *Am J Respir Crit Care Med*. 2019 Feb 15;199(4):465-477. doi: 10.1164/rccm.201807-1291OC. PMID: 30371106

Peters MC, Kerr S, Dunican EM, **Woodruff PG**, Fajt ML, Levy BD, Israel E, Phillips BR, Mauger DT, Comhair SA, Erzurum SC, Johansson MW, Jarjour NN, Coverstone AM, Castro M, Hastie AT, Bleecker ER, Wenzel SE, Fahy JV; National Heart, Lung and Blood Institute Severe Asthma Research Program 3. Refractory airway type 2 inflammation in a large subgroup of asthmatic patients treated with inhaled corticosteroids. *J Allergy Clin Immunol*. 2019 Jan;143(1):104-113.e14. doi: 10.1016/j.jaci.2017.12.1009. Epub 2018 Mar 7. PMID: 29524537

Menzies-Gow A, Bafadhel M, Busse WW, Casale TB, Kocks JWH, Pavord ID, Szefler SJ, **Woodruff PG**, de Giorgio-Miller A, Trudo F, Fageras M, Ambrose CS. An expert consensus framework for asthma remission as a treatment goal. *J Allergy Clin Immunol.* 2019 Dec 19. pii: S0091-6749(19)31708-7. doi: 10.1016/j.jaci.2019.12.006. [Epub ahead of print] PMID: 31866436

Dransfield MT, Voelker H, Bhatt SP, Brenner K, Casaburi R, Come CE, Cooper JAD, Criner GJ, Curtis JL, Han MK, Hatipoğlu U, Helgeson ES, Jain VV, Kalhan R, Kaminsky D, Kaner R, Kunisaki KM, Lambert AA, Lammi MR, Lindberg S, Make BJ, Martinez FJ, McEvoy C, Panos RJ, Reed RM, Scanlon PD, Sciurba FC, Smith A, Sriram PS, Stringer WW, Weingarten JA, Wells JM, Westfall E, Lazarus SC, Connett JE, BLOCK COPD Trial Group. Metoprolol for the Prevention of Acute Exacerbations of COPD. *N Engl J Med.* 2019 Dec 12;381(24):2304-2314. doi: 10.1056/NEJMoa1908142. Epub 2019 Oct 20. PMID: 31633896

Krummel M, Blish C, Kuhns M, Cadwell K, Oberst A, Goldrath A, Ansel KM, Chi H, O'Connell R, Wherry EJ, Pepper M; Future Immunology Consortium. Universal Principled Review: A Community-Driven Method to Improve Peer Review. *Cell.* 2019 Dec 12;179(7):1441-1445. doi: 10.1016/j.cell.2019.11.029. PMID: 31835023

Paulin LM, Gassett AJ, Alexis NE, Kirwa K, Kanner RE, Peters S, Krishnan JA, Paine R 3rd, Dransfield M, **Woodruff PG**, Cooper CB, Barr RG, Comellas AP, Pirozzi CS, Han M, Hoffman EA, Martinez FJ, Woo H, Peng RD, Fawzy A, Putcha N, Breysse PN, Kaufman JD, Hansel NN; for SPIROMICS investigators. Association of Long-term Ambient Ozone Exposure with Respiratory Morbidity in Smokers. *JAMA Intern Med*. 2019 Dec 9. doi: 10.1001/jamainternmed.2019.5498. [Epub ahead of print]. PMID: 31816012

Menzies-Gow A, Bafadhel M, Busse WW, Casale TB, Kocks JWH, Pavord ID, Szefler SJ, **Woodruff PG**, de Giorgio-Miller A, Trudo F, Fageras M, Ambrose CS. An expert consensus framework for asthma remission as a treatment goal. *J Allergy Clin Immunol*. 2020 Mar;145(3):757-765. doi: 10.1016/j.jaci.2019.12.006. Epub 2019 Dec 19. PMID: 31866436

Das S; Extracellular RNA Communication Consortium, Ansel KM, Bitzer M, Breakefield XO, Charest A, Galas DJ, Gerstein MB, Gupta M, Milosavljevic A, McManus MT, Patel T, Raffai RL, Rozowsky J, Roth ME, Saugstad JA, Van Keuren-Jensen K, Weaver AM, Laurent

LC. The Extracellular RNA Communication Consortium: Establishing Foundational Knowledge and Technologies for Extracellular RNA Research. *Cell*. 2019 Apr 4;177(2):231-242. doi: 10.1016/j.cell.2019.03.023. PMID: 30951667

Looking to the Future

Richard M. Locksley, M.D.

Despite the difficulties of a pandemic year, the SABRE Center made substantive contributions to our mission to advance basic research discoveries in asthma, including foundational insights into innate lymphoid cell biology, regulation of IgE, roles for microRNAs in driving critical hubs of the asthma pathway, lung epithelial cell biology, and to increasing emphasis on the role of mucus plugs as biomarkers for patients at risk for substantial morbidity. With the flexibility provided by Sandler Foundation support, SABRE investigators were able to pivot quickly within the UCSF COMET consortium to meet the challenge of COVID-19, participating in over 20 manuscripts, many in high-impact journals, identifying risk factors, mechanisms of pathology, and potential for novel therapeutics, including some developed by SABRE investigators. The NIH PRIMERO study has enrolled over 700 parent-newborns for intense clinical and biomarker analytics that will be followed over 10 years to identify predictors for asthma development. Finally, SABRE investigators participate in major leadership positions at UCSF in academic and graduate student programs, in advocating for Diversity, Leadership, and Equity voices on campus, and in leadership positions with NIH in national asthma consortia, including the Severe Asthma Research Program (SARP) and the PrecISE Asthma Trials Networks, to guide use of standard biomarkers and outcomes for academic and industry trials. Punctuated by access to emergency grants for COVID-19-related research, grant dollars continue to increase and to provide support for students, postdocs, and clinical investigator trainees, but also support for new research-enabling technologies.

There are many uncertainties on the horizon, particularly with major renovations of the hospital and the construction of large, new research building at the Parnassus campus. The SABRE Center model played a formative role in shaping the footprint for patient-oriented, disease-focused, basic research at UCSF within 'Discovery Zones' that will, for the first time, re-organize investigative laboratories around distinct themes, each traversing the space from the most basic research to translational aspects of disease, each rooted closely to the study of human health and disease. Initial plans would localized most SABRE investigators within contiguous space with lung biologists and pulmonary scientists, which will enhance the breadth and depth of interactions and create even better access to human tissues and furthering cutting-edge technologic advances. We continue to support a nimble, transformative research platform with the ability to move quickly as needed, and to position SABRE as an important component of the research efforts to achieve the greatest return for cutting-edge investments in basic science as applied to human biology and disease. We continue to believe this is best suited by a SABRE-style organizational network putting basic and clinical scientists side-by-side with access to patients and patient tissues in proximity to rapidly evolving technology hubs.

We look forward to continuing novel and unexpected discoveries made by SABRE Center laboratories that will significantly impact asthma and asthma-related research and alter the course of human disease. Increasingly, we are moving closer to therapeutics, with mucolytics under intensive development by the Fahy lab and collaborators,

chitinases under study as potential interventional support for late fibrotic disease, and close collaborations with Genentech/Roche involving anti-tryptase drugs for mast cell-dependent asthma, a subgroup in part defined by investigators supported by SABRE. Dr. Woodruff is submitting a renewal for COMET consortia support with Genentech/Roche that includes some underwriting costs for the Asthma Clinical Research Center and access to highly characterized patient specimens. Finally, as projects have matured, SABRE investigators are beginning discussions for a second co-project Program Project Grant oriented towards novel scientific discovery as a spin-off from the currently funded NIH Program Project Grant. Assembly of a competitive second large effort will take 2-3 years of preparation, acquisition of preliminary data, and submission and response, but we are confident that the quality of the science and the intensity of investigator interaction will push the success. At the same time, we have consolidated administrative support to maximize SABRE finances towards scientific discovery and investigator support. Here, we emphasize the flexibility and breadth of Sandler Foundation and Jewish Community Federation support of SABRE, which is not possible from NIH or corporate funding, and which enabled rapid development and deployment of cutting edge technology to push innovative science forward. We are most grateful for support from the Foundation that has enabled our continued progress despite the limitations imposed by sheltering, Zoom-ing, and loss of access to lab benches and equipment.

Our goal is to continue the trajectory established over the first decade of the SABRE Center in our mission to understand and ultimately conquer asthma. These challenges we take seriously for the future in order to honor the extraordinary vision of the Sandler family and Sandler Foundation in committing resources to asthma basic research at UCSF. Although the pandemic has necessarily re-directed and slowed some of these efforts, we continue to work hard and resolutely to accomplish our mission. We are most grateful for the opportunity to respond to the challenge and look forward to discoveries that will have a lasting impact on asthma as a major debilitating disease.

BIOGRAPHICAL SKETCHES

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BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Christopher David Caballero Allen, Ph.D.	Associate Professor of Anatomy and Investigator, Cardiovascular Research Institute & Sandler Asthma Basic Research Center

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Massachusetts Institute of Technology	B.S.	06/2001	Biology
University of California, San Francisco	Ph.D.	06/2007	Biomedical Sciences
University of California, San Francisco	Postdoctoral	10/2007	Immunology

Positions

1998-2000	Summer Research Intern, Department of Molecular and Cellular Pharmacology, Isis Pharmaceuticals, Carlsbad, CA
2000	Undergraduate Student Researcher, Laboratory of Herman Eisen, Center for Cancer Research, Massachusetts Institute of Technology
2001-2007	Graduate Student Researcher, Laboratory of Jason Cyster, Biomedical Sciences Graduate Program and Immunology Graduate Program, University of California, San Francisco, CA
2007	Postdoctoral Scholar, Laboratory of Jason Cyster, Department of Microbiology and Immunology, University of California, San Francisco, CA
2007-2012	Sandler-Newmann Foundation UCSF Fellow in Asthma Research, Sandler Asthma Basic Research Center and the Department of Microbiology and Immunology, University of California, San Francisco, CA
2012-2018	Assistant Professor of Anatomy and Investigator, Cardiovascular Research Institute, University of California, San Francisco, CA
2018 -	Associate Professor of Anatomy and Investigator, Cardiovascular Research Institute and Sandler Asthma Basic Research Center, University of California, San Francisco, CA

Other Experience and Professional Memberships

2013 -	Regular Member, American Association of Immunologists (AAI)

Honors

1994	National Science Foundation Young Scholars Program Fellowship
1997	National Hispanic Scholar
1999	Academic Excellence Award, Office of Minority Education, Massachusetts Institute of Technology
2001	Whitehead Prize in Biomedical Research, Whitehead Institute and Massachusetts Institute of Technology
2001	Phi Beta Kappa, Massachusetts Institute of Technology

2001-2002	Regents Fellowship, University of California
2002-2007	Predoctoral Fellowship, Howard Hughes Medical Institute
2010	Top Cited Article 2008-2010, *Seminars in Immunology*
2012	NIH Director's New Innovator Award, National Institutes of Health
2013	Research Award, Weston Havens Foundation
2016	Pew Biomedical Scholar, The Pew Charitable Trusts

Contribution to Science

As a graduate student in the laboratory of Jason Cyster, a major emphasis of my dissertation project was to study the guidance factors responsible for organizing the germinal center. This structure forms in lymphoid organs (such as lymph nodes) during immune responses and plays a key role in the generation of high affinity antibodies and B cell memory that comprise protective humoral immunity. As early as the 1930s it was described that the germinal center is divided into two zones termed dark and light zones, yet the cues responsible for this spatial segregation occurs remained unknown. I found that the chemokine CXCL12 (SDF-1) was expressed in the dark zone and I established that its receptor, CXCR4, was essential for the formation of the dark zone and for the positioning of B cells within this region. Conversely, CXCL13 (BCA-1/BLC) was expressed in the light zone and I showed that its receptor, CXCR5, was essential for the positioning of B cells within the light zone. This work provided the first insights into the mechanism by which the germinal center is organized into two zones. I also contributed experiments and scientific input to a paper showing that CXCL13/CXCR5 recruits follicular helper T cells to the light zone. I further initiated studies of the functional role of CXCR4-mediated dark zone segregation in the germinal center response and I also identified the sphingosine-1-phosphate receptor S1PR2 as another candidate molecule involved in germinal center organization; both of these findings were followed up in stories subsequently published by the Cyster Lab on which I am a coauthor.

a. **Allen CDC,** Ansel KM, Low C, Lesley R, Tamamura H, Fujii N, Cyster JG. Germinal center dark and light zone organization is mediated by CXCR4 and CXCR5. *Nat Immunol*. 2004 Sep; 5(9): 943-52. PubMed PMID: 15300245.
b. Haynes NM, **Allen CDC**, Lesley R, Ansel KM, Killeen N, Cyster JG. Role of CXCR5 and CCR7 in follicular Th cell positioning and appearance of a programmed cell death gene-1high germinal center-associated subpopulation. *J Immunol*. 2007 Oct 15; 179(8): 5099-108. PubMed PMID: 17911595.
c. Green JA, Suzuki K, Cho B, Willison LD, Palmer D, **Allen CDC**, Schmidt TH, Xu Y, Proia RL, Coughlin SR, Cyster JG. The sphingosine 1-phosphate receptor $S1P_2$ maintains the homeostasis of germinal center B cells and promotes niche confinement. *Nat Immunol*. 2011 Jun 5; 12(7): 672-80. PubMed PMID: 21642988; PubMed Central PMCID: PMC3158008.
d. Bannard O, Horton RM, **Allen CDC**, An J, Nagasawa T, Cyster JG. Germinal center centroblasts transition to a centrocyte phenotype according to a timed program and depend on the dark zone for effective selection. *Immunity*. 2013 Nov 14; 39(5): 912-24. PubMed PMID: 24184055; PubMed Central PMCID: PMC3828484.

A second major emphasis of my dissertation project in the laboratory of Jason Cyster was the study of the dynamic behavior of B cells within the germinal center. I established a model system for imaging the germinal center in intact lymph nodes by two-photon microscopy. This approach allowed me to visualize cell migration and interactions during the process of selection of high affinity B cells, for the first time. I analyzed the movements of germinal center B cells between dark and light zones and I

characterized the interactions between B cells and T cells in the light zone. Based on these findings, we proposed a new model for the selection of high affinity B cells within the germinal center. This model was an important paradigm shift for the field and has since been corroborated by other groups. I subsequently collaborated with a theoretical biologist to gain new insights on germinal center B cell migration by an extensive computational analysis of our dataset. This analysis revealed a previously unappreciated net migration of B cells from the dark zone to the light zone.

a. **Allen CDC**, Okada T, Tang HL, Cyster JG. Imaging of germinal center selection events during affinity maturation. *Science*. 2007 Jan 26; 315(5811): 528-31. PubMed PMID: 17185562.
b. **Allen CDC**, Okada T, Cyster JG. Germinal-center organization and cellular dynamics (Review). *Immunity*. 2007 Aug; 27(2): 190-202. PubMed PMID: 17723214; PubMed Central PMCID: PMC2242846.
c. Beltman JB, **Allen CDC**, Cyster JG, de Boer RJ. B cells within germinal centers migrate preferentially from dark to light zone. *Proc Natl Acad Sci U S A*. 2011 May 24; 108(21): 8755-60. PubMed PMID: 21555569; PubMed Central PMCID: PMC3102384.

Basophils are innate immune cells that are activated through IgE, yet their functional role in the immune response has been poorly understood and controversial. I achieved the first dynamic imaging of basophils in the lungs and lymph nodes by two-photon microscopy after infection with helminth parasites or immunization with a protease allergen. Using a reporter mouse generated by Richard Locksley's laboratory, I found that basophils did not interact with T cells during the priming phase of the immune response in lymph nodes, indicating that basophils do not serve as major antigen presenting cells. However, basophils did form repetitive, sustained interactions with T cells during the effector phase of the immune response in the lungs, a site in which T cells were shown to activate basophils to secrete IL-4 that contributed to helminth immunity. I also contributed my imaging expertise to the study of IgE-mediated basophil function in eosinophil recruitment in a mouse model of contact dermatitis. My laboratory also demonstrated that an antibody widely used to deplete mouse basophils, MAR-1, unexpectedly binds to Fcγ receptors on tissue macrophages and monocytes, potentially explaining discrepancies between the results reported by antibody-mediated versus genetic methods of basophil depletion in mice.

a. Sullivan BM, Liang HE, Bando JK, Wu D, Cheng LE, McKerrow JK, **Allen CDC***, Locksley RM*. Genetic analysis of basophil function in vivo. *Nat Immunol*. 2011 Jun; 12(6): 527-35. PubMed PMID: 21552267; PubMed Central PMCID: PMC3271435. *Co-corresponding author
b. Cheng LE, Sullivan BM, Retana LE, **Allen CDC**, Liang HE, Locksley RM. IgE-activated basophils regulate eosinophil tissue entry by modulating endothelial function. *J Exp Med*. 2015 Apr 6; 212(4): 513-24. PubMed PMID: 25779634; PubMed Central PMCID: PMC4387286.
c. Tang XZ, Jung JB, Allen CDC. A case of mistaken identity: The MAR-1 antibody to mouse FcεRIα cross-reacts with FcγRI and FcγRIV. *J Allergy Clin Immunol*. 2019 in press

IgE antibodies play a major role in allergic responses underlying numerous diseases, yet little was known about the cells that produce these antibodies due to technical limitations. In order to overcome these roadblocks, my lab generated a novel fluorescent reporter mouse as well as an improved flow cytometry method to identify and track rare B cells and plasma cells that express IgE. We used these tools to study the genesis and fate of IgE-expressing B cells in primary immune responses to protein antigens and helminth infection. This analysis revealed that IgE-expressing B cells showed an increased propensity to undergo plasma cell differentiation and

only transiently participated in germinal centers, which limited the affinity and duration of the IgE antibody response in healthy mice. We further revealed that these properties of IgE-expressing B cells can be traced to constitutive activity of the IgE B cell receptor. In a collaborative study, we established that IgE responses were severely curtailed by haploinsufficiency of IL-4, suggesting that limited amounts of IL-4 are available in vivo to promote IgE class switch recombination. Conversely, we recently demonstrated that IL-21 is the major extrinsic factor that inhibits IgE class switch recombination in mouse and human B cells, whereas IFN-gamma, IL-10, and IL-6 were dispensable. Overall, our studies have provided critical new insights into understanding the mechanisms regulating IgE antibody responses in vivo. For these studies, I designed experiments, directed research, and helped collect and analyze data. We have also published a review and methods chapter related to these studies.

a. Yang Z, Sullivan BM, **Allen CDC**. Fluorescent in vivo detection reveals that IgE(+) B cells are restrained by an intrinsic cell fate predisposition. *Immunity*. 2012 May 25; 36(5): 857-72. PubMed PMID: 22406270.
b. Yang Z, Robinson MJ, **Allen CDC**. Regulatory constraints in the generation and differentiation of IgE-expressing B cells (Review). *Curr Opin Immunol*. 2014 Jun; 28:64-70. PubMed PMID: 24632082; PubMed Central PMCID: PMC4069329.
c. Robinson MJ, Prout M, Mearns H, Kyle R, Camberis M, Forbes-Blom EE, Paul WE, **Allen CDC**, Le Gros G. IL-4 Haploinsufficiency Specifically Impairs IgE Responses against Allergens in Mice. *J Immunol*. 2017 Jan 23; PubMed PMID: 28115531. NIHMSID: NIHMS840227.
d. Yang Z, Robinson MJ, Chen X, Smith GA, Taunton J, Liu W, **Allen CDC.** Regulation of B cell fate by chronic activity of the IgE B cell receptor. *eLife*. 2016 Dec 9; 5 pii: e21238 PubMed PMID: 27935477; PubMed Central PMCID: PMC5207771.

In the course of our above studies, we have devoted considerable effort to optimizing techniques for the genetic manipulation of B cells. We have developed an efficient protocol for retroviral transduction of primary mouse B cells and B cell lines, using a self-inactivating retrovirus in which gene expression can be directed by a ubiquitous or specific promoter. By inserting the EF1 ubiquitous promoter we achieved far more uniform expression than is normally observed with the gene expression driven by the viral long terminal repeat (LTR). Using CRISR-Cas9 technology, we successfully introduced insertion-deletion mutations and point mutations into genes in cultured primary human B cells, in collaboration with the laboratories of Alex Marson at UCSF and Joan Wither at the University of Toronto. Some highlights of this work include that gene editing could be achieved in B cells that have undergone minimal stimulation, and that we electroporated CRISPR-Cas9 ribonucleoproteins without the use of viruses, facilitating potential therapeutic approaches and high throughput screens. We are currently using a similar CRISPR-Cas9 approach to target genes in mouse B cells.

a. Yang Z, **Allen CDC**. Expression of Exogenous Genes in Murine Primary B Cells and B Cell Lines Using Retroviral Vectors. *Methods Mol Biol*. 2018; 1707:39-49. PubMed PMID: 29388098; PubMed Central PMCID: PMC6675621.
b. Wu CM, Roth TL, Baglaenko Y, Ferri DM, Brauer P, Zuniga-Pflucker JC, Rosbe KW, Wither JE, Marson A, **Allen CDC.** Genetic engineering in primary human B cells with CRISPR-Cas9 ribonucleoproteins. *J Immunol* Methods. 2018 Jun; 457:33-40. PubMed PMID: 29614266; PubMed Central PMCID: PMC6124898.

Complete List of Published Work in MyBibliography: http://usa.gov/1rS9D69

Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

R21 AI 154335 Allen, Christopher David Caballero (PI) 01/21/21–12/31/22
Molecular basis for the regulation of IgE class switch recombination by IL-21 and STAT3
The overall goal of the proposed project is to elucidate the molecular mechanism by which IL-21, acting through the IL-21R and STAT3 in B cells, inhibits IgE germline transcription and thereby negatively regulates IgE class switch recombination.
Role: PI

R01 AI 130470 Allen, Christopher David Caballero (PI) 11/20/17–10/31/22
Regulation of IgE responses by B cell receptor signaling
The overall goal of the proposed project is to elucidate the mechanisms by which B cell receptor signaling regulates IgE germinal center B cell and plasma cell responses in mice and to evaluate whether these findings are applicable to human samples.
Role: PI

New Frontiers Research Grant Award Allen, Christopher David Caballero (PI) 06/01/20 – 11/30/21
UCSF Program for Breakthrough Biomedical Research
Is allergy caused by rogue cells due to somatic mutations? The overall goal of this proposal is to determine whether IgE antibodies to allergens are derived from 'rogue' B cells that acquire specific somatic mutations, allowing them to escape normal regulatory mechanisms.
Role: PI

The Pew Charitable Trusts
Biomedical Scholar Award Allen, Christopher David Caballero (PI) 08/01/16–07/31/21
Unraveling the mysteries of allergen specific IgE production
The major goal of this project is to identify cell types and molecules involved in promoting the production of IgE in allergic responses versus the suppression of IgE in healthy individuals.
Role: PI

Completed Research Support

R21 AI 130495 Allen, Christopher David Caballero (PI) 06/07/17–05/31/19
Function of bronchus-associated macrophages
The overall goal of this proposal was to characterize and determine the function of a population of macrophages proximal to the bronchial airways.
Role: PI

BIOGRAPHICAL SKETCH

NAME **K. Mark Ansel**	POSITION TITLE Professor of Microbiology and Immunology
eRA COMMONS USER NAME anselm	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Virginia Tech, Blacksburg, VA	B.S.	5/1996	Biochemistry
University of California, San Francisco	Ph.D.	9/2001	Biomedical Sciences
Immune Disease Institute, Harvard Medical School		12/2007	Immunology

Positions

2001 - 2005	Postdoctoral Fellow, Immune Disease Institute, Harvard Medical School, Boston, MA
2005 - 2007	Instructor, Department of Pediatrics, Children's Hospital and Immune Disease Institute, Harvard Medical School, Boston, MA
2008 - 2013	Assistant Professor, Department of Microbiology and Immunology and Sandler Asthma Basic Research Center, University of California San Francisco
2013 – 2014	Associate Director, Biomedical Sciences Graduate Program, UCSF
2008	Investigator, Sandler Asthma Basic Research Program, UCSF, San Francisco, CA
2013 -	Associate Professor, Department of Microbiology & Immunology and Sandler Asthma Basic Research Center, University of California San Francisco
2014 -	Director, Biomedical Sciences Graduate Program, University of California San Francisco
2018 -	Professor, Department of Microbiology & Immunology, UCSF

Other Experience and Professional Memberships

1998-	American Association for the Advancement of Science
2006-	American Association of Immunologists
2007-	International Cytokine Society
2011-	Reviewing Editor, Science Signaling
2011-2012	International Predoctoral Fellows Reviewer, Howard Hughes Medical Institute
2012-2014	Ad hoc reviewer, NIH CMIB study section
2012-2015	Associate Editor-in-chief, American Journal of Clinical & Experimental Immunology
2013-2017	Associate Editor, Journal of Immunology
2013	Guest Editor, RNA Regulation of the Immune System issue, Immunological Reviews
2014	Current Opinions in Immunology, Allergy & Hypersensitivity section, Guest Editor
2014-2017	Member, Faculty of 100 Section on Leukocyte Signaling and Gene Expression
2016	Standing member, NIH CMIB study section

2017	Section Editor, Journal of Immunology

Awards and Honors

1997	Predoctoral Fellow, Howard Hughes Medical Institute
2001	Postdoctoral Fellow, Damon Runyon Cancer Research Fund
2005	Special Fellow, Leukemia and Lymphoma Society
2006	Career Award in Biomedical Sciences, Burroughs Wellcome
2007	Outstanding Postdoctoral Fellow, International Cytokine Society
2009	Human Immunology Scholar, Dana Foundation
2012	Scholar, Leukemia & Lymphoma Society
2015	150th Anniversary Alumni Excellence Award, UCSF Alumni Association
2020	UCSF Biomedical Sciences Graduate Program Mentoring Award

Contribution to Science

1. I pioneered the study of microRNA (miRNA) regulation of the immune system during my postdoctoral training, and I have continued this core research in my own laboratory. We reported the first descriptions of miRNA expression programs in purified cell populations, dynamic regulation of miRNAs during immune cell activation, the global requirements for miRNAs in helper T cells, and the impact of a single miRNA on normal mammalian physiology. These early studies established the importance of miRNAs in immune regulation and presented many new avenues for investigation. Recent work has revealed mechanisms that alter miRNA homeostasis during immune responses, including transcriptional and post-transcriptional regulation of cellular miRNA homeostasis, and extracellular release of vesicles containing miRNAs and other small RNAs.

a. Muljo SA*, **Ansel KM***, Kanellopoulou C*, Livingston DM, Rao A, et al. Aberrant T cell differentiation in the absence of Dicer. J Exp Med. 2005 Jul 18;202(2):261-9. PMID: 16009718; PMCID: PMC2212998. *equal contribution
b. Bronevetsky Y, Villarino AV, Eisley CJ, Barbeau R, Barczak AJ, Heinz GA, Kremmer E, Heissmeyer V, McManus MT, Erle DJ, Rao A, **Ansel KM**. T cell activation induces proteasomal degradation of Argonaute and rapid remodeling of the microRNA repertoire. J Exp Med. 2013 Feb 11; 210(2):417-32. PMID: 23382546
c. Chiou NT, Kageyama R, **Ansel KM**. Selective Export into Extracellular Vesicles and Function of tRNA Fragments during T Cell Activation. Cell Rep. 2018 Dec 18;25(12):3356-3370.e4. PMID: 30566862
d. Pua HH, Happ HC, Gray CJ, Mar DJ, Chiou NT, Hesse LE, **Ansel KM**. Increased Hematopoietic Extracellular RNAs and Vesicles in the Lung during Allergic Airway Responses. Cell Rep. 2019 Jan 22;26(4):933-944.e4. PMID: 30673615

2. Helper T cells lacking all miRNAs exhibit defective proliferation and survival, as well as rapid and aberrant differentiation into effector cells with the ability to secrete inflammatory cytokines. This complex phenotype indicates significant contributions from many miRNAs and mapping specific regulatory impacts to individual miRNAs or families of related miRNAs remains one of the central pursuits of my laboratory and one of the major challenges for the field as a whole. We developed and deployed a ‘rescue screening’ technology to determine which miRNAs regulate various aspects of T cell proliferation and differentiation. This led to the discovery that miR-29 potently inhibits Th1 cell differentiation through inhibition of a functionally related set of direct

mRNA targets. We extended this approach to leverage our ability to assign biological functions to miRNAs and identify their direct target mRNAs as a means of directed pathway discovery. For example, we found that miR-24 and miR-27 potently inhibit Th2 responses and used combined empirical and bioinformatic methods to identified a network of functionally relevant target mRNAs, including well-known regulators of Th2 cell differentiation and others that represent novel players in Th2 biology. Biochemical approaches to target discovery further advanced our ability to define miRNA-directed gene expression networks.

a. Steiner DF, Thomas MF, Hu JK, Yang Z, Babiarz JE, et al. MicroRNA-29 regulates T-box transcription factors and interferon-γ production in helper T cells. Immunity. 2011 Aug 26;35(2):169-81. PMID: 21820330; PMCID: PMC3361370.
b. Pua HH, Steiner DF, Patel S, Gonzalez JR, Ortiz-Carpena JF, et al. MicroRNAs 24 and 27 Suppress Allergic Inflammation and Target a Network of Regulators of T Helper 2 Cell-Associated Cytokine Production. Immunity. 2016 Apr 19;44(4):821-32. PMID: 26850657; PMCID: PMC4838571.
c. Simpson LJ, Ansel KM. MicroRNA regulation of lymphocyte tolerance and autoimmunity. J Clin Invest. 2015 Jun;125(6):2242-9. PMID: 26030228; PMCID: PMC4497751.
d. Gagnon JD, Kageyama R, Shehata HM, Fassett MS, Mar DJ, Wigton EJ, Johansson K, Litterman AJ, Odorizzi P, Simeonov D, Laidlaw BJ, Panduro M, Patel S, Jeker LT, Feeney ME, McManus MT, Marson A, Matloubian M, Sanjabi S, Ansel KM. miR-15/16 Restrain Memory T Cell Differentiation, Cell Cycle, and Survival. Cell Rep. 2019 Aug;28(8):2169-2181.e4. PMID: 31433990; PMCID: PMC6715152.

3. We have also used miRNA expression profiling as a complementary strategy to prioritize miRNAs of potential functional relevance in immunity and immune dysfunction. We developed and optimized small RNA deep sequencing as well as a high-throughput 9216-plex microfluidic qPCR platform for measuring miRNAs expression in clinical samples of less than 1000 cells. We then applied this system to RNA samples extracted from FACS-sorted helper T cells from bronchial lavage of healthy and asthmatic subjects. These studies were conducted in collaboration with the UCSF Airway Clinical Research Center and Genentech. One miRNA, miR-19a, stood out as being highly expressed in all asthmatic subjects, but lower and more variable in healthy subjects. Mechanistic experiments in mouse and human T cells revealed that miR-19 is required for robust Th2 cytokine production and allergic inflammation in a mouse model of asthma. We found that at least 3 direct miR-19 target mRNAs are limiting factors for Th2 cytokine production, and each of these encodes an inhibitor of antigen and/or cytokine receptor signaling (PTEN, SOCS, and A20). More recently, we generated the first miRNA expression profiles for type 2 innate lymphocytes and showed that miR-19 also regulated ILC2 homeostasis and cytokine production through an overlapping but non-identical set of target mRNAs. These studies demonstrate how investigating miRNA expression in isolated cells involved in disease pathogenesis can generate hypotheses for mechanistic studies of miRNA function in the relevant underlying biology.

a. Seumois G, Vijayanand P, Eisley CJ, Omran N, Kalinke L, et al. An integrated nano-scale approach to profile miRNAs in limited clinical samples. Am J Clin Exp Immunol. 2012 Nov 30;1(2):70-89. PMID: 23304658; PMCID: PMC3538381.
b. Simpson LJ, Patel S, Bhakta NR, Choy DF, Brightbill HD, et al. A microRNA upregulated in asthma airway T cells promotes TH2 cytokine production. Nat Immunol. 2014 Dec;15(12):1162-70. PMID: 25362490; PMCID: PMC4233009.

c. Singh PB, Pua HH, Happ HC, Schneider C, von Moltke J, Locksley RM, Baumjohann D, Ansel KM. MicroRNA regulation of type 2 innate lymphoid cell homeostasis and function in allergic inflammation. J Exp Med. 2017 Dec;214(12):3627-43. PMID: 29122948; PMCID: PMC5716040.
d. Montoya MM, Maul J, Singh PB, Pua HH, Dahlström F, Wu N, Huang X, Ansel KM*, Baumjohann D*. A Distinct Inhibitory Function for miR-18a in Th17 Cell Differentiation. J Immunol. 2017 Jul 15;199(2):559-569. PMID: 28607111; PubMed Central PMCID: PMC5508756.

4. Recently, we further developed our ability to interrogate post-transcriptional regulation through biochemical analysis of RNA: RBP (RNA binding protiein) interactions. We developed Global CrossLinking Protein Purification (GCLiPP), an RNA interactome capture assay that generates transcriptome-wide maps of RBP occupancy in primary mouse and human T cells (and other cell types). We used these data to generate libraries for a massively parallel reporter assay that measured effects on RNA stability across 26,000 RBP-occupied putative cis-regulatory RNA elements. These experiments revealed strong correlations between nucleotide content, local RNA folding potential, and transcript destabilizing activity. They also uncovered surprising patterns of RNA conservation in vertebrate evolution and opened the door to functional genetics to leverage human variation and cancer genetics for interrogation of biologically important post-transcriptional regulatory elements and RBP-directed gene expression networks.

a. Litterman AJ, Kageyama R, Le Tonqueze O, Zhao W, Gagnon JD, Goodarzi H, Erle DJ, Ansel KM. A massively parallel 3' UTR reporter assay reveals relationships between nucleotide content, sequence conservation, and mRNA destabilization. Genome Res. 2019 Jun;29(6):896-906. doi: 10.1101/gr.242552.118. PubMed PMID: 31152051; PubMedCentral PMCID: PMC6581050.
b. Litterman AJ*, Zhu WS*, Kageyama R, Zhao W, Zaitlen N, Erle DJ, Ansel KM. A global map of RNA binding protein occupancy guides functional dissection of post-transcriptional regulation of the T cell transcriptome. BioRxiv 448654 [Preprint]. Oct 22, 2018. Available from: https://doi.org/10.1101/448654
c. Chatrikhi R, Mallory MJ, Gazzara MR, Agosto LM, Zhu WS, Litterman AJ, Ansel KM, Lynch KW. RNA Binding Protein CELF2 Regulates Signal-Induced Alternative Polyadenylation by Competing with Enhancers of the Polyadenylation Machinery. Cell Rep. 2019 Sep;28(11):2795-2806.e3. doi: 10.1016/j.celrep.2019.08.022. PMID: 31509743; PMCID: PMC6752737
d. Gordon ED, Simpson LJ, Rios CL, Ringel L, Lachowicz-Scroggins ME, et al. Alternative splicing of interleukin-33 and type 2 inflammation in asthma. Proc Natl Acad Sci U S A. 2016 Aug 2;113(31):8765-70. PMID: 27432971; PMCID: PMC4978244.

5. We have also made important contributions to the understanding of antibody responses, interrogating the programming of both B cells and follicular helper T (Tfh) cells. This interest goes back to my first publications as a graduate student in Jason Cyster's laboratory (see complete list of publications, below), and is a growing area of research in my lab. Drawing on knowledge and genetic tools generated during my postdoctoral studies, we illuminated the cis-regulatory control of Tfh expression of IL-4, a key Tfh cytokine that supports B cell growth and induces immunoglobulin class-switching to IgG1 and IgE. We investigated the role that "TLR help" can play in supporting B cell metabolism and participation in antibody responses when antigens are linked with pathogen-associated molecular patterns. We described the early kinetics of BCL6 expression in differentiating Tfh cells and applied our expertise in miRNA biology to demonstrate that the miR-17~92 cluster of miRNAs is essential for robust Tfh cell responses. These miRNAs maintain the fidelity of Tfh cell gene expression by inhibiting the transcription factor ROR-α, which otherwise induces a Th17/Th22-like gene expression program.

a. Wigton EJ, DeFranco AL, Ansel KM. Antigen Complexed with a TLR9 Agonist Bolsters c-Myc and mTORC1 Activity in Germinal Center B Lymphocytes. Immunohorizons. 2019 Aug 19;3(8):389-401. doi: 10.4049/immunohorizons.1900030. PMID: 31427364. PMCID: PMC6738343.

b. Vijayanand P, Seumois G, Simpson LJ, Abdul-Wajid S, Baumjohann D, et al. Interleukin-4 production by follicular helper T cells requires the conserved Il4 enhancer hypersensitivity site V. Immunity. 2012 Feb 24;36(2):175-87. PMID: 22326582; PMCID: PMC3288297.
c. Baumjohann D, Okada T, Ansel KM. Cutting Edge: Distinct waves of BCL6 expression during T follicular helper cell development. J Immunol. 2011 Sep 1;187(5):2089-92. PMID: 21804014.
d. Baumjohann D, Kageyama R, Clingan JM, Morar MM, Patel S, et al. The microRNA cluster miR-17~92 promotes TFH cell differentiation and represses subset-inappropriate gene expression. Nat Immunol. 2013 Aug;14(8):840-8. PMID: 23812098; PMCID: PMC3720769.

Complete list of publications: https://www.ncbi.nlm.nih.gov/pubmed/?term=Ansel+KM

Research Support
Ongoing

2 P01HL107202 Fahy (PI) 4/1/19-7/31/24
Exploring the biology of persistent type 2 airway niches in asthma
This project aims to uncover tissue-immune checkpoints that lead to persistent airway type 2 inflammation and mucus plug formation in asthma. We will use image-guided bronchoscopy, high-dimensional single cell analytics, and other experimental approaches to decode the regulatory networks that sustain severe disease.
Role: Project 2 Leader, Project 3 co-investigator

R01HL109102 Ansel (PI) 8/1/11-3/30/24
MicroRNA directed pathway discovery in allergy and asthma
The major goals of this project are to identify and characterize the in vivo activity and molecular targets of miRNAs that regulate lymphocyte functions relevant to allergy and asthma.
Role: PI

U19 AI077439 Erle (PI) 5/8/20-3/31/22
UCSF COVID-19: Extended Immunophenotyping Studies
We hypothesize that there are patterns in the immune responses seen in COVID-19 patients that define those that are susceptible to developing ARDS. We will apply multiplexed CITE-seq and scRNA-seq to tracheal aspirates and blood, assay for NETS, and measure immune cell activation status in single cells taken from patients.
Role: Co-project Leader, rapid supplement award

FastGrants2020 Ansel, Spitzer (co-PIs) 5/1/20-4/30/21
High Dimensional Analysis of the Inflammatory Cytokine Storm in COVID-19
Discerning immune cell signaling states associated with disease escalation in COVID-19 based on prospective patient samples to identify therapeutic targets to modulate inflammation in COVID-19 patients.
Role: Co-PI

BIOGRAPHICAL SKETCH

NAME **Nirav Rati Bhakta, M.D., Ph.D.**	POSITION TITLE Assistant Professor of Medicine
eRA COMMONS USER NAME (credential, e.g., agency login) BHANIR	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Massachusetts Institute of Technology	SB	06/1998	Electrical Engineering
Stanford University School of Medicine	MD	06/2006	Medicine
Stanford University School of Medicine	PhD	06/2006	Mol. and Cell Physiology
University of California, San Francisco	Internship	06/2007	Internal Medicine
University of California, San Francisco	Residency	06/2008	Internal Medicine
University of California, San Francisco	Fellowship	06/2011	Pulmonary, Critical Care
University of California, San Francisco	Postdoctoral	206/011	Asthma

Positions and Employment

07/2011-06/2013	Instructor, Department of Medicine, Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, University of California, San Francisco.
07/2013 – present	Assistant Professor, Department of Medicine, Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, University of California, San Francisco
08/2016 – present	Director of Education, Adult Pulmonary Function Laboratory
2017 – present	Pulmonary Fellowship Site Director and Coach, UCSF Parnassus Campus
2020 – present	Associate Director, Adult Pulmonary Function Laboratory

Other Experience and Professional Memberships

2007 – Present	American College of Physicians, Associate Member
2008 – Present	American Thoracic Society
2008 – Present	California Medical License
2009	Board Certification in Internal Medicine by the ABIM
2011	Board Certification in Pulmonary Medicine by the ABIM
2011 – 2014	American College of Chest Physicians, Affiliate Member
2011 – Present	Review ~3 articles a year for American Thoracic Society Journals, Clinical and Experimental Allergy, and other journals.
2012	Board Certification in Critical Care Medicine by the ABIM
2016 – 2017	Associate Scientific Advisor for Science Translational Medicine. Over a period of one year, I wrote eight editorial pieces that appeared in the journal.

2018-2018	Grant Reviewer, Asthma UK
2019-present	Member of the Proficiency Standards for Pulmonary Function Laboratories Committee, American Thoracic Society
2020-present	Co-Chair of joint ATS/ERS Task Force to update the Lung Volumes Measurement Technical Standard, American Thoracic Society

Honors

2017	Invited Grand Rounds speaker, Department of Pathology, University of Vermont
2016	Visiting professor to SFGH pulmonary function laboratory November 2, 2016
11/2016	Nina Ireland Program for Lung Health Award
05/2015	American Thoracic Society International Conference, Invitational post-graduate course seminar in genomics
3/2014	The American Academy of Allergy, Asthma, and Immunology Annual Meeting: Invitational lecture on the role of exosomes in asthma
1/2012-12/2012	Ruth L. Kirschstein National Service Award (F32) for Individual Postdoctoral Fellows
2011-2012	Podell Hewett Fellowship in Translational Airway Research,
12/2010	Awarded $500 travel award to present at the Pittsburg International Lung Conference
2005	Invited to speak at the Howard Hughes Medical Institute workshop on Imaging the Immune System, Chevy Chase, MD.
2005	Awarded Keystone Symposia $1000 Scholarship to present at Leukocyte Trafficking meeting
2001	Dept. of Health and Human Services national semi-finalists, Innovation in Health Promotion, South Asian Preventive Health Outreach Program

Contribution to Science

I developed and used a metric to reproducibly quantify type 2 inflammation in human airway epithelial brushings. I conceived and performed all data analyses. As a physician in this study, I also examined study subjects, ensured they met inclusion/exclusion criteria, performed research bronchoscopies, and supervised sputum inductions. Given the importance of type 2 inflammation in predicting response to existing and emerging therapies, this metric has been valuable as a gold standard to assess less invasive biomarkers and understand the relationship of any given clinical or molecular feature of asthma to the level of type 2 inflammation. The last two references listed underscore my track record in serving as a core resource to collaborators by quantifying Th2 inflammation in airway brushings for mechanistic studies of asthma.

a. **Bhakta NR**, Solberg OD, Nguyen CP, Nguyen CN, Arron JR, Fahy JV, Woodruff PG. A qPCR-based metric of Th2 airway inflammation in asthma. *Clin Transl Allergy*. 2013 Jul 17; 3(1): 24, PMC3724712.
b. **Bhakta NR**, Christenson SA, Nerella S, Solberg OD, Nguyen CP, Choy DF, Jung KL, Garudadri S, Bonser LR, Pollack JL, Zlock LT, Erle DJ, Langelier C, Derisi JL, Arron JR, Fahy JV, Woodruff PG. Interferon-stimulated Gene Expression, Type-2

Inflammation and Endoplasmic Reticulum Stress in Asthma. *Am J Respir Crit Care Med* 2018 Feb1;197(3):313-324. PMC5811952.

c. Lachowicz-Scroggins ME, Finkbeiner WE, Gordon ED, Yuan S, Zlock L, **Bhakta NR,** Woodruff PG, Fahy JV, Boushey HA. Corticosteroid and long-acting ß-agonist therapy reduces epithelial goblet cell metaplasia. *Clin Exp Allergy*. 2017 Dec; 47(12):1534-1545.

d. Durack J, Lynch SV, Nariya S, **Bhakta NR**, Beigelman A, Castro M, Dyer AM, Israel E, Kraft M, Martin RJ, Mauger DT, Rosenberg SR, Sharp-King T, White SR, Woodruff PG, Avila PC, Denlinger LC, Holguin F, Lazarus SC, Lugogo N, Moore WC, Peters SP, Que L, Smith LJ, Sorkness CA, Wechsler ME, Wenzel SE, Boushey HA, Huang YJ. Features of the bronchial bacterial microbiome associated with atopy, asthma, and responsiveness to inhaled corticosteroid treatment. *J Allergy Clin Immunol.* 2016 Nov 10. In press (available online at http://dx.doi.org/10.1016/j.jaci.2016.08.055).

I designed, performed and analyzed expression profiling of cellular and extracellular miRNA to study their role as biomarkers and regulators of airway epithelial and T cell function in asthma. These collaborative efforts in mechanistic studies of asthma highlight my success in processing precious human samples and analyzing the resulting datasets to yield meaningful contributions.

a. Solberg OD, Ostrin EJ, Love MI, Peng JC, **Bhakta NR**, Hou L, Nguyen C, Solon M, Nguyen C, Barczak AJ, Zlock LT, Blagev DP, Finkbeiner WE, Ansel KM, Arron JR, Erle DJ, Woodruff PG. Airway Epithelial miRNA Expression is Altered in Asthma. *Am J Respir Crit Care Med* 186(10): 965-74. 2012.

b. Levänen B, **Bhakta NR**, Torregrosa Paredes P, Barbeau R, Hiltbrunner S, Pollack JL, Sköld CM, Svartengren M, Grunewald J, Gabrielsson S, Eklund A, Larsson BM, Woodruff PG, Erle DJ, Wheelock AM. Altered microRNA profiles in bronchoalveolar lavage fluid exosomes in asthmatic patients. *J Allergy Clin Immunol.* 2013 Mar; 131(3): 894-903.e8. PMID: 23333113

c. Simpson LJ, Patel S, **Bhakta NR**, Choy DF, Brightbill HD, Ren X, Wang Y, Pua HH, Baumjohann D, Montoya MM, Panduro M, Remedios KA, Huang X, Fahy JV, Arron JR, Woodruff PG, Ansel KM. A microRNA upregulated in asthma airway T cells promotes TH2 cytokine production. *Nat Immunol*. 2014 Dec; 15(12): 1162-70. *PubMed PMID*: 25362490; PubMed Central PMCID: PMC4233009.

I designed, performed, and analyzed studies involving gene expression profiling to identify disease biomarkers. The first two studies show that I am capable of assisting other groups in the development of biomarkers, assessment of their durability, and determination of their relationship to disease outcomes. In the third publication listed, I primarily performed the data analysis in a collaboration to develop single-cell gene expression signatures.

a. Koth LL, Solberg OD, Peng JC, **Bhakta NR**, Nguyen CP, Woodruff PG. Sarcoidosis blood transcriptome reflects lung inflammation and overlaps with tuberculosis. *Am J Respir Crit Care Med*. 2011. 184: 1154-1163. 2011. PMC3262024.

b. Su R, Li MM, **Bhakta NR**, Solberg OD, Darnell EP, Ramstein J, Garudadri S, Ho M, Woodruff PG, Koth LL. Longitudinal analysis of sarcoidosis blood transcriptomic

signatures and disease outcomes. *Eur Respir J*. 2014 Oct; 44(4):985-93. PMID: 25142485.

c. Lawson DA, **Bhakta NR**, Kessenbrock K, Prummel KD, Yu Y, Takai K, Zhou A, Eyob H, Balakrishnan S, Wang CY, Yaswen P, Goga A, Werb Z. Single-cell analysis reveals a stem-cell program in human metastatic breast cancer cells. *Nature*. 2015 Oct 1; 526(7571):131-5. PMC4648562.

I have examined study subjects, ensured they qualify based on study inclusion/exclusion criteria, participated in bronchoscopies, and performed gene expression analyses in induced sputum samples as part of the UCSF site in the Severe Asthma Research Program (SARP). The three publications listed below are evidence of my experience in human subjects research across a range of asthma severity, and of my participation and contribution to monthly working groups that led to the development of these manuscripts.

a. Phipatanakul W, Mauger DT, Sorkness RL, Gaffin JM, Holguin F, Woodruff PG, Ly NP, Bacharier LB, **Bhakta NR**, Moore WC, Bleecker ER, Hastie AT, Meyers DA, Castro M, Fahy J, Fitzpatrick A, Gaston BM, Jarjour NN, Levy BD, Peters SP, Teague WG, Fajt M, Wenzel SE, Erzurum SC, Israel E. Effects of Age and Disease Severity on Systemic Corticosteroid Responses in Asthma. *Am J Respir Crit Care Med*. 2016 Dec 14. PMID: 27967215.

b. Denlinger LC, Phillips BR, Ramratnam S, Ross K, **Bhakta NR**, Cardet JC, Castro M, Peters SP, Phipatanakul W, Aujla S, Bacharier LB, Bleecker ER, Comhair SA, Coverstone A, DeBoer M, Erzurum SC, Fain SB, Fajt M, Fitzpatrick AM, Gaffin J, Gaston B, Hastie AT, Hawkins GA, Holguin F, Irani AM, Israel E, Levy BD, Ly N, Meyers DA, Moore WC, Myers R, Opina MT, Peters MC, Schiebler ML, Sorkness RL, Teague WG, Wenzel SE, Woodruff PG, Mauger DT, Fahy JV, Jarjour NN. Inflammatory and Comorbid Features of Patients with Severe Asthma and Frequent Exacerbations. *Am J Respir Crit Care Med*. 2017 Feb 1;195(3):302-313. PMID: 27556234.

c. Duvall MG, Barnig C, Cernadas M, Ricklefs I, Krishnamoorthy N, Grossman NL, **Bhakta NR**, Fahy JV, Bleecker ER, Castro M, Erzurum SC, Gaston BM, Jarjour NN, Mauger DT, Noel PJ, Wenzel SE, Comhair SA, Coverstone AM, Fajt ML, Hastie AT, Johansson MW, Peters MC, Phillips BR, Israel E, and Levy B. Natural Killer Cell-Mediated Inflammation Resolution Is Disabled In Severe Asthma. *Sci Immunol.* 2017 Mar 10; 2(9). (available online at https://doi.org/10.1126/sciimmunol.aam5446)

With my PhD thesis advisor, I built a two-photon microscope to study T cell development: the optics and micro-controllers to guide/scan the laser, the alignment of the laser into the microscope, the chamber to keep tissue warm, humidified and oxygenated. I wrote the scripts for image analysis. I bred all of the mice and performed all tissue harvesting, labeling and imaging experiments. The techniques we developed continue to be used by immunologists to study signaling and motility of immune cells in their native environments.

Bhakta NR, Oh DY, Lewis RS. Intracellular calcium oscillations control thymocyte motility during positive selection in the three-dimensional thymic environment. *Nature Immunology* 6: 143-151. 2005.

Bousso P, **Bhakta NR**, Lewis RS, Robey E. Dynamics of thymocyte-stromal cell interactions visualized by two-photon microscopy. *Science* 296: 1876-80. 2002.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/nirav.bhakta.1/bibliography/47340518/public/?sort=date&direction=descending

Research Support

Nina Ireland Program in Lung Health Bhakta (PI). 01/01/17-present
Understanding cellular sources of airway cytokines in interferon-high asthma
Role: PI

U19 AI 077439. Erle (PI) 04/01/18-03/31/23
NIH/NIAID, Understanding Asthma Endotypes
Role: Core Leader

U19 AI070535-15 NIH/NIDAD, Airway inflammation and airway remodeling
09/01/2020-08/31/2021
Role: Co-Investigator

R35 HL145235. Erle (PI) 01/01/19-12/31/26
NIH/NHLBI, Airway epithelial cell gene regulation: new mechanisms and therapeutic strategies
Role: Co-Investigator

P01 HL107202. Fahy (PI) 07/01/19-08/31/24
NIH/NHLBI, Innate and Adaptive Immune Responses in Th2 High Asthma
Role: Co-Investigator

UCSF Catalyst Program Bhakta (PI). 03/1/21-04/1/21
Computer Vision-based spirometry ("Breathily")

Completed Research Support

1F32HL110720-01 01/01/12-12/31/12
NIH
Using signatures of T-helper cell inflammation to phenotype human asthma
Ruth L. Kirschstein National Service Award (F32) for Individual Postdoctoral Fellows.
Role: PI

U19 AI070412. Baseman (PI) 04/01/13-03/31/14
NIH/NIAD
Studies on airway extracellular miRNA in human asthma
Role: Subcontract PI

R01 AI100082. McCune (PI) 08/21/12-07/31/15
NIH
Layering of the human immune system, viral infections, and childhood asthma
Role: Co-Investigator

BIOGRAPHICAL SKETCH

NAME **Mallar Bhattacharya, M.D., M.Sc.**	POSITION TITLE Assistant Professor of Medicine
eRA COMMONS USERNAME (credential, e.g., agency login) BMALLAR	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Harvard University, Cambridge, MA	A.B.	06/1998	Biology & Psychology
Oxford University, Oxford, U.K.	M.Sc.	10/1999	Neuroscience
Harvard University, Cambridge, MA	M.D.	06/2004	Medicine
Johns Hopkins Hospital, Baltimore, MD	Residency	06/2007	Internal Medicine
University of California, San Francisco	Fellowship	06/2010	Pulmonary, Critical Care

Positions and Employment

1998-1999	Honorary Frank Knox Memorial Fellowship (awarded by Harvard University), Oxford U.K.
2002-2003	Ruth L. Kirschstein Medical Student National Research Service Award Fellowship, Fred Hutchison Cancer Research Center, Seattle, WA
2004-2007	Residency in Internal Medicine, Johns Hopkins Hospital, Baltimore, MD
2007-2010	Fellowship, Pulmonary/Critical Care Medicine, UCSF
2010-2012	Instructor, Department of Medicine, Division of Pulmonary and Critical Care Medicine, UCSF
2012-2019	Assistant Professor, Department of Medicine, Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, UCSF
2019-present	Associate Professor, Department of Medicine, Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, UCSF

Other Experience and Professional Memberships

2007 -	American Thoracic Society
2007 -	Board Certification in Internal Medicine by the ABIM
2009 -	Board Certification in Pulmonary Medicine by the ABIM
2010	Board Certification in Critical Care Medicine by the ABIM

Honors

2008-2009	Will Rogers Institute Fellowship
2000	American Neurological Association Summer Fellowship
2000	Pasteur Summer Research Fellowship for Medical Students

1997	Member, Phi Beta Kappa Society, Harvard College Chapter
1994 -1998	New York State Robert C. Byrd Honors Scholarship
1994 – 1998	Dean's List, Harvard College
1995, 97, 98	John Harvard Scholarship
1996	Harvard College Scholarship

Contribution to Science

1) Integrins in cytoskeletal organization during acute lung injury: During my postdoctoral research training, I studied the role of integrins and their ligands in determining responses to injury. These studies utilized *in vivo* models with mice lacking the integrin ligand laminin or alpha-v integrins and defined novel properties of matrix adhesion and intracellular cytoskeletal dynamics, with disease relevance. The studies on sepsis and vascular leak were instrumental in demonstrating the role of integrins in regulating actin cytoskeletal organization of the endothelium, which in turn determined cell-cell junctional integrity and barrier function during acute lung injury and sepsis. I performed a proteomic screen that identified the novel integrin binding partner Iqgap1 and found a role for Iqgap1 in endothelial actin organization during acute lung injury. Specifically, Iqgap1 was necessary for integrin-based regulation of cortical actin, and its deletion impaired cell-cell adhesion as well as vascular barrier function in mice subjected to lung injury with LPS and *E coli* pneumonia.
   a. Su G, Atakilit A, Li JT, Wu N, Luong J, Chen R, **Bhattacharya M**, Sheppard D. Effective treatment of mouse sepsis with an inhibitory antibody targeting integrin αvβ5. (2013) *Crit Care Med* Feb;41(2):546-53. PMID: 23263571.
   b. Su G, Atakilit A, Li JT, Wu N., **Bhattacharya M**, Zhu J, Shieh JE, Li E, Sheppard D. (2012) Absence of integrin αvβ3 enhances vascular leak in mice by inhibiting endothelial cortical actin formation. *Am J Respir Crit Care Med*. 185(1):58-66. PMID: 21980034. PMCID: PMC3262039.
   c. **Bhattacharya M**, Su G, Su X, Oses-Prieto JA, Li JT, Huang X, Hernandez H, Atakilit A, Burlingame AL, Matthay M, Sheppard D. (2012) IQGAP1 is necessary for pulmonary vascular barrier protection in murine acute injury and pneumonia. *Am J Physiol Lung Cell Mol Physiol* 303(1): L12-19. PMID: 22561460. PMCID: PMC3426434.

2) RhoA activation in lung inflammation: Following up on the results of a proteomic screen completed during my fellowship, in my early faculty years I pursued the novel integrin binding partner and cytoskeletal organizing protein Iqgap1. I found that Iqgap1 suppressed activation of the GTPase RhoA, whose role in airway contraction led us to test Iqgap1-/- mice in airway inflammation models. These studies revealed that Iqgap1 inhibits airway smooth muscle RhoA by serving as a scaffold for the negative regulator p190A-RhoGAP. A qPCR screen of RhoGEFs using a riboprofiling approach led to the discovery that Arhgef12 was highly expressed in mouse and human airway smooth muscle. We then found that Arhgef12 was necessary for IL17A-induced RhoA activation and allergic airway hyperresponsiveness in mice. Arhgef12 thus represents a novel therapeutic target in asthma.
   a. **Bhattacharya M**, Sundaram A, Kudo M, Farmer J, Ganesan P, Khalifeh-Soltani A, Arjomandi M, Atabai K, Huang X, Sheppard D. (2014) IQGAP1-dependent scaffold suppresses RhoA and inhibits airway smooth muscle contraction. *The Journal of Clinical Investigation* 124(11): 4895-8. PMID: 25271629. PMCID: PMC4347230.

b. Fong V, Hsu A, Wu E, Looney AP, Ganesan P, Ren X, Sheppard D, Wicher SA, Thompson MA, Britt Jr. RD, Prakash YS, **Bhattacharya M**. (2018) Arhgef12 drives IL17A-induced airway contractility and airway hyperresponsiveness in mice. *JCI Insight*. Nov 2;3(21) PMID: 30385725. PMCID: PMC6238747.

3) Macrophages in lung injury and fibrosis: A major focus of my group now is on the role of macrophages in lung injury and fibrosis. In recent work, I used single cell mRNA sequencing to profile macrophages that localize to sites of fibroblast accumulation after bleomycin-induced lung injury. As part of this project, working with computational collaborators, I developed a tool (SingleR) that annotates cellular identity in single cell RNA-seq by reference to bulk RNA-seq datasets of pure cell types. Now publicly available, this tool is widely used for cell type annotation; in our study, it enabled clustering of cells revealing a transitional state of monocyte-derived macrophages acquiring lung-resident identity within the fibrotic niche. Our cell ablation experiments targeting these Cx3cr1-expressing monocyte-derived macrophages revealed a pro-fibrotic and activating effect of this subset of macrophages on adjacent fibroblasts.
   a. Looney, AP and **Bhattacharya, M**. (2019). Fibroblast Gap-closure Assay: Microscopy-based *in vitro* Assay Measuring the Migration of Murine Fibroblasts. *Bio-protocol* 9(16): e3333. DOI: doi.org/10.21769/BioProtoc.3333. PMID: 31531389. PMCID: PMC6748635.
   b. Aran D, Looney AP, Liu L, Wu E, Fong V, Hsu A, Chak S, Naikawadi RP, Wolters PJ, Abate A, Butte AJ, **Bhattacharya M**. (2019) Reference-based analysis of lung single cell RNA-seq reveals a transitional profibrotic macrophage. *Nature Immunology*. 20(2):163-172. PMID: 30643263. PMCID: PMC6340744.
   c. Alam Z, Devalaraja S, Li M, To TKJ, Folkert IW, Mitchell-Velasquez E, Dang MT, Young P, Wilbur CJ, Silverman MA, Li X, Chen YH, Hernandez PT, Bhattacharyya A, **Bhattacharya M**, Levine MH, Haldar M. (2020) Counter Regulation of Spic by NF-kB and STAT Signaling Controls Inflammation and Iron Metabolism in Macrophages. *Cell Reports.* Jun;31(13):107825. PMID: 32610126. PMCID: Pending.

4) Cellular senescence: Recent work in my lab has addressed cellular senescence in the lung. In collaboration with the Anil Bhushan Lab at UCSF, we have found that invariant NK T cells coordinate clearance of senescent cells after acute lung injury, with resulting improvement in fibrosis and in mortality. My lab performed the murine fibrosis and survival studies for this work, which is currently in review for publication. A second project, cited below, has taken advantage of the UCSF Nina Ireland Biorepository of healthy human donor lungs not used for transplant. In this work, we profiled 86 human lungs across the adult lifespan by RNA-seq and other methods. Our analysis revealed an increasing senescence profile, decreasing telomere length, and an increase in pro-fibrotic pathways in the aging lung.
   a. Lee J, Islam MI, Boostanpour K, Aran D, Christenson S, Matthay MA, Eckalbar W, DePianto DJ, Arron JR, Magee L, Bhattacharya S, Matsumoto R, Kubota M, Farber DL, Bhattacharya, Wolters PJ, **Bhattacharya M.** Molecular programs of fibrotic change in aging human lung. Biorxiv 427195. [Preprint]. January 18, 2021. Available from: https://doi.org/10.1101/2021.01.18.427195.

A complete list of my publications is available at:

https://www.ncbi.nlm.nih.gov/myncbi/1hyab8c8hE3A_/bibliography/public/

Research Support

Ongoing Research Support

1R01HL131560-04 05/01/2016 – 04/30/2021
NHLBI
Title: The Regulation of RhoA Activation in Airway Smooth Muscle
Role: PI
The goal of this award is to study the role of RhoA activators in airway smooth muscle contraction, including identification and functional testing of relevant guanine exchange factors.

Completed Research Support

UCSF Nina Ireland Program for Lung Health
01/01/2019 – 12/31/2020
Title: Defining macrophage pro-fibrotic mechanisms in lung fibrosis.
Role: PI
The goal of this award is to investigate the pro-fibrotic effect of monocyte-derived macrophages in the lung fibrotic niche. Mouse models and human tissues are studied to elucidate the role of paracrine factors.

UCSF Resource Allocation Program 01/01/2019 – 12/31/2019
Title: Macrophage function in lung fibrosis
Role: PI

4K08HL114641-05 09/01/2012 – 06/30/2018
NHLBI
Title: IQGAP1 in vascular barrier regulation during acute lung injury
Role: PI

U54HL119893 01/01/2018 – 06/30/2018
NHLBI
Title: Targeting ArhGEF12 in Asthma
Role: PI for subproject

UCSF Marcus Program for Precision Medicine 04/01/2016 – 12/31/2017
Title: Microfluidic droplet capture for gene expression analysis of airway smooth muscle in asthma
Role: PI

BIOGRAPHICAL SKETCH

NAME **Homer A. Boushey, Jr., M.D.**	POSITION TITLE Professor of Medicine (Emeritus)
eRA COMMONS USER NAME Boushey	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Stanford University, Palo Alto, CA	A.B.	1964	Biology
University of California, San Francisco	M.D.	1968	Medicine
University of California, San Francisco	Residency	1970	Internal Medicine
Beth Israel Hospital, Boston, MA	Residency	1971	Internal Medicine
Oxford University, Oxford, England	Fellowship	1972	Pulmonary Medicine

Positions and Honors

1974-1981	Assistant Professor of Medicine in residence, University of California, San Francisco.
1981-1987	Associate Professor of Medicine in residency, University of California, San Francisco.
1986- Present	Member, senior staff, Cardiovascular Research Institute, University of California, San Francisco
1987-1989	Professor of Medicine in residence, University of California, San Francisco
1989-Present	Professor of Medicine, University of California, San Francisco.
1989-1995	Vice Chair for Clinical Affairs, Department of Medicine, University of California, San Francisco
1996-2009	Chief, Allergy/Immunology Division, Department of Medicine, University of California, San Francisco

Honors and Awards

1964	Phi Beta Kappa
1967	AOA
1964-1968	Regents' Scholar
1968	Gold-Headed Cane Recipient
1977	H. J. Kaiser Award for Excellence in Teaching
1988, ’90, ’95, 99, 2000	Faculty-Student Teaching Award for "An Outstanding Lecture"
1993	Clean Air Award (Education/Research), American Lung Association, San Francisco

1993	California Medal, American Lung Association-California
1996	UCSF Alumnus of the Year Award
1997-2000	Bay Area's Best Physicians, San Francisco Focus Magazine
2000	Medical Student Teaching Award: "An Outstanding Clinical Correlation Lecturer"

Contribution to Science

Throughout my career, I have focused on the responses of the lungs to inhaled materials. I first studied neural mechanisms of response in laboratory animals, and then studied the effects of exposure to air pollutants in healthy people and in people with asthma. These findings figured importantly in the EPA's setting of Ambient Air Quality Standards for the United States of America.

a. **Boushey HA**, Richardson PS, Widdicombe JG. Reflex effects of laryngeal irritation on the pattern of breathing and total lung resistance. *J Physiol* (Lond) 1972; 224:501-513.
b. Holtzman MJ, Cunningham JH, Sheller JR, Irsigler GB, Nadel JA, **Boushey HA**. Effect of ozone on bronchial reactivity in atopic and non-atopic subjects. *Am Rev Respir Dis* 1979; 120:1059-1067.
c. Seltzer J, Bigby BG, Stulbarg M, Holtzman MJ, Nadel JA, Ueki IF, Leikauf GD, Goetzl EJ, **Boushey HA**. O3-induced change in bronchial reactivity to methacholine and airway inflammation in humans. *J Appl Physiol* 1986; 60:1321-1326.
d. Sheppard D, Wong WS, Uehara CF, Nadel JA, **Boushey HA**. Lower threshold and greater bronchomotor responsiveness of asthmatic subjects to sulfur dioxide. *Am Rev Respir Dis* 1980; 122:873-878.

The study of airways responses to inhaled materials led to my interest in asthma, a condition associated with airway inflammation and exaggerated bronchial responsiveness. John Fahy and I demonstrated the validity of sputum induction for assessing airway mucosal inflammation, and applied it to study therapies for asthma (egs., monoclonal anti-IgE antibody, inhaled corticosteroids, long-acting beta-agonists).

a. Fahy JV, Liu J, Wong H, **Boushey HA**. Analysis of cellular and biochemical constituents of induced sputum after allergen challenge: A method for studying allergic airway inflammation. *J Allergy Clin Immunol* 1994; 93:1031-1039.
b. Fahy JV, Kim KW, Liu J, **Boushey HA**. Prominent neutrophilic inflammation in sputum from subjects with asthma exacerbation *J Allergy Clin Immunol* 1995;95(4):843-852.
c. Fahy JV, Wong H, Liu J, **Boushey HA**. Comparison of samples collected by sputum induction and bronchoscopy from asthmatic and healthy subjects. *Am J Respir Crit Care Med* 1995; 152:53-58
d. Fahy JV, Fleming HE, Wong HH, Liu JT, Su JQ, Reimann J, Fick RB, **Boushey HA**. The effect of an anti-IgE monoclonal antibody on the early and late phase responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med* 1997; 155:1828-1834.

These studies led naturally to my involvement in clinical research on treatments for asthma, and led as well to my serving as Principal Investigator for UCSF's participation in the NHLBI's Asthma Clinical Research Network and its successor, AsthmaNet , for over 20 years. The findings of studies conducted by these networks have informed clinical practice through their impact on national and international guidelines for the treatment of asthma. Studies for which I served in a leadership role include the following:

a. Lazarus SC, **Boushey HA**, Fahy JV, Chinchilli VM, Lemanske RF Jr, Sorkness CA, Kraft M, Szefler SJ. Long-Acting beta2-Agonist Monotherapy vs. Continued Therapy With Inhaled Corticosteroids in Patients With Persistent Asthma. *JAMA*. 2001 (20): 2583-2593.
b. **Boushey HA**, Sorkness CA, King TS, Sullivan SD, Fahy JV, Lazarus SC, Daily versus as-needed corticosteroids for mild persistent asthma" *New Eng EJ Med*. 2005; 352(15) 1519-28.
c. Stoloff SW, **Boushey HA**, "Severity, Control, and Responsiveness in Asthma" *J Allergy Clin Immunol* 2006; 117(3): 544-48.
d. Calhoun WJ, Ameredes BT, King TS, Icitovic N, Bleecker ER, Castro M, Cherniack RM, Chinchilli VM, Craig T, Szefler SJ, Wasserman SI, Walter MJ, Wechsler ME, **Boushey HA**; Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT Trial. *JAMA*. 2012 Sep 12; 308(10): 987-9

My interest in bronchial inflammation also led to studies of the mechanisms by which viral respiratory infections cause exacerbations of asthma, CF, and COPD. Collaborative studies with Drs. Avila and Dolgnaov at UCSF and Widdicombe and Wu at UC Davis suggested that the severity of lower respiratory responses to human rhinovirus (HRV) infection is a function of the state of differentiation of the bronchial epithelium and of properties intrinsic to the infecting HRV strain. An outgrowth of this work was collaboration with Drs. Derisi and Ganem in their development of a microarray-based approach to detecting viruses (the ViroChip), and then, with Amy Kistler (postdoctoral fellow), in expanding the array to include sequences for all known serotypes of rhinovirus. Applying this method studies of asthmatic patients showed a high diversity of HRV serotypes circulating concurrently, higher than expected rates of infection with "rare" viral pathogens (HKU and NL063 coronaviruses), and the existence a previously unknown phylogenetic branch of the RV genus, HRV-C. I additionally collaborated with Dr. Kistler in her work on genomic variations among RV serotypes, identifying the regions under greatest selective pressure.

a. Wang D, Coscoy L, Zylberberg M, Avila PC, **Boushey HA**, Ganem D, DeRisi JL.Microarray-bsed detection and genotyping of viral pathogens *Proc Natl Acad Sci USA*. 2002; 99(24): 15687-92.
b. Kistler A, Avila PC, Rouskin S, Wang D, Ward T, Yagi S, Schnurr D, Ganem D, DeRisi J, and **Boushey HA**. "Pan-viral Screening of Respiratory Tract Infections in Adults with and without Asthma Reveals Unexpected Coronavirus and Human Rhinovirus Diversity." *Journal of Infectious Diseases*; 2007; 196(6): 817-825c.
c. Lopez-Souza N, Favoreto S, Wong H, Ward T, Yagi S, Schnurr D, Finkbeiner WE, Dolganov GM, Widdicombe JH, **Boushey HA**, Avila PC. In vitro susceptibility to

rhinovirus infection is greater for bronchial than for nasal airway epithelial cells in human subjects. *J Allergy Clin Immunology*, 2009 Jun; 123(6): 1384-90

d. Lachowicz ME, **Boushey HA**, Widdicombe JH. Interleukin-13 induced mucous metaplasia increases susceptibility of human aireay epithelium to rhinovirus infection. *Amer J. Resp Cell & Molec Biol*, Jan., 2010 doi: 10.1165/rcmb.2009-0244OC

My involvement in studies applying new methods for detecting viruses led to a collaborative partnership with Dr. Susan Lynch (UCSF) in applying a new, culture-independent method, the "16S rRNA PhyloChip" to determine whether distinct bacterial communities are present in the bronchi of people with asthma. This work led to collaborative studies with AsthmaNet (NHLBI), with the Inner City Asthma Consortium (NIAID), and with investigators at Henry Ford Hospital (PPG, NIAID). These studies show differences between the bronchial microbiome of healthy and asthmatic subjects and suggests that exposure to high levels of environmental allergens and diverse bacteria is associated with protection against development of allergic asthma.

a. Huang YJ, Nelson CE, Brodie EL, DeSantis TZ, Baek MS, Liu J, Woyke T, Allaier M, Bristow J, Wiener-Kronish JP, Sutherland ER, King TS, Icitovic N, Martin RJ, Calhoun WJ, Castro M, Denlinger LC, Dimango E, Kraft M, Peters SP, Wasserman SI, Wechsler ME, **Boushey HA**, and Lynch SV. Airway microbiota and bronchial hyperresponsiveness in patients with sub-optimally controlled asthma. *JACI* 2011; 127:372-381
b. Lynch SV, Wood RA, **Boushey HA**, Bacharier LB, Bloomberg GR, Kattan M, O'Connor GT, Sandel MT, Calatroni A, Matsui E, Johnson CC, Lynn H, Visness CM, Jaffee KF, Gergen PJ, Gold DR, Wright RJ, Fujimura K, Rauch M, Busse WW, Gern JE. Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children. *J Allergy Clin Immunol*. 2014; 134(3): 593-601.
c. Huang YJ, Sethi S, Murphy T, Nariya S, **Boushey HA**, Lynch SV. Airway microbiome dynamics in exacerbations of chronic obstructive pulmonary disease. *J Clin Microbiol*. 2014; 52(8): 2813-23.
d. Huang YJ, **Boushey HA**. The microbiome in asthma. *J Allergy Clin Immunol*. 2015; 135(1): 25-30. (PMCID: PMC4287960)

BIOGRAPHICAL SKETCH

NAME **Esteban González Burchard, M.D., M.P.H.**	POSITION TITLE: Harry Wm. and Diana V. Hind Distinguished Professorship in Pharmaceutical Sciences, Schools of Pharmacy and Medicine, Departments of Bioengineering & Therapeutic Sciences and Medicine
eRA COMMONS USER NAME: Eburchard	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
San Francisco State University, San Francisco, CA	B.S.	05/1990	Cellular & Molecular Biology
Stanford University School of Medicine, Stanford, CA	M.D.	06/1995	Medicine
Harvard School of Public Health, Boston, MA	Certificate	08/1997	Program in Clinical Effectiveness
Brigham and Women's Hospital, Boston, MA	Resident	06/1998	Internal Medicine
University of California, San Francisco, SF, CA	Fellow	06/2001	Pulmonary & Critical Care Medicine
Stanford University, Stanford, CA		05/2002	Genetic Epidemiology
University of California, Berkeley	M.P.H.	05/2006	Epidemiology

Positions and Honors

1995 – 1996	Intern in Medicine, Brigham & Women's Hospital, Harvard Medical School, Boston, MA
1996-1998	Junior/Senior Resident in Medicine, Bringham and Women's Hospital, Harvard Medical School, Boston, MA
1998 – 2001	Fellow in Pulmonary and Critical Care Medicine, UCSF
2001 -	Director, UCSF Asthma Collaboratory
2008	Director, UCSF Center on Genes, Environments & Health
2009 -	Director, UCSF Clinical Pharmacology Training Program
2010 - 2014	Vice Chair, UCSF Department of Bioengineering & Therapeutic Sciences
2011 - Lifetime	Hind Distinguished Tenured Professor Schools of Pharmacy & Medicine, UCSF
2015-Present	Board Member, African American Wellness Project
2010-Present	Professor, UCSF Medicine and Bioengineering and Therapeutic Sciences
2017-Present	RWJ Amos Medical Faculty Development Program, National Advisory Committee

Selected Honors

1988, 1989	NCAA Div. II Academic All-American, Wrestling
2005–2010	RWJ Amos Medical Faculty Development Award
2008-2014	NIH Study Section Member, Genetics of Health and Disease (GHD)
2009	American Society of Clinical Investigation (ASCI), elected member
2009	Guest Speaker, Tavis Smiley Show
2010	Guest Speaker, NPR's Science Friday, hosted by Ira Flatow
2011	Athletic Hall of Fame, San Francisco State University

2013	American Museum of Natural History (AMNH) documentary on Esteban Burchard and his research. This documentary was exhibited at the AMNH for two years and distributed to all U.S. public high schools.
2013	Guest Speaker, Smithsonian Institution National Museum of Natural History (NMNH)
2014	UCSF Medal. The UCSF Medal is UCSF's most prestigious award, given to individuals who have made outstanding personal contributions in the areas associated with the University's mission, goals and values.
2015	National Academy of Sciences, Engineering and Medicine, Committee on Incorporating 21st Century Science into Risk-Based Evaluations
2015	President Obama's Precision Medicine Initiative, Advisory Committee to the Director Innovations in Health Equality – Lifetime Achievement Award
2016	Lifetime Achievement Award, American Thoracic Society, Innovations in Health Equality
2017	RWJ Amos Medical Faculty Development Program, National Advisory Committee
2018	Lifetime Achievement Award, National Medical Association (NMA), Allergy and Immunology Section. The NMA is the largest and oldest Black Medical Organization in the nation.
2018	Alumni Hall of Fame, San Francisco State University
2018	Apple Teaching Award
2019	Keynote Speaker, SACNAS (Society for the Advancement of Chicanos and Native Americans in Science).

Contributions to Science

1. I conceived and created the GALA and SAGE studies; I recruited patients alongside with my collaborators, I built the biorespository and database to house the biologic and clinical data, my colleagues and I did the analyses and wrote more than 200 manuscripts from this study. We demonstrated that Puerto Rican children have lower drug response to albuterol than Mexican children.

    a. **Burchard EG**, Avila PC, (23 authors), Silverman EK; Lower Bronchodilator Responsiveness in Puerto Rican than in Mexican Asthmatic Subjects. *AJRCCM.* 2004; 169(3): 386-92. PMID: 14617512

2. We demonstrated ethnic-specific differences in pharmacogenetic associations of bronchodilator drug responsiveness between Puerto Rican and Mexican children with asthma. I conceived the idea to test the beta 2 adrenergic receptor (β_2AR) gene as part of the candidate gene list in the original GALA proposal.

    a. Choudhry S., Ung N, (28 authors**), Burchard EG**. Pharmacogenetic Differences in Response to Bronchodilators between Puerto Rican and Mexican Asthmatics. *AJRCCM.* 2005; 171(6):563-70 PMID: 15557128

3. We identified genetic variants in the asthma candidate gene, human acidic mammalian chitinase, which resulted in a gain of enzymatic function. I conceived the idea and oversaw the graduate student who performed the experiments.

a. Seibold MA, Reese TA (21 authors), **Burchard EG.** Differential enzymatic activity of common haplotypic versions of the human acidic Mammalian chitinase protein. *JBC*. 2009; 284(29): 19650-8 PMCID: PMC2740590

4. We identified a significant inverse relationship between African and Native American ancestry and forced expiratory volume at one second (FEV_1) and forced vital capacity (FVC) in African American and Mexican participants. In predicting lung function, the ancestry-based model improved the diagnostic accuracy of lung disease by as much as 15% when compared to the current clinical standard. In addition, the ancestry-based models reclassified asthma severity (based on percent predicted FEV1) in African American and Mexican children with asthma. Current predictive equations, which rely on self-identified race/ethnicity misclassify (misdiagnose) lung function among admixed individuals. Incorporating genetic ancestry into normative reference equations improves lung function estimates and more accurately categorizes disease diagnosis and disease severity. I conceived the idea to test genetic ancestry and lung function. Students, fellows and staff from my lab, whom I have hired and trained, did the analyses.

   a. Kumar R*, Seibold MA*, Aldrich MCF*, Williams KL*, (23 authors), **Burchard EG**. *Equal contributions. Genetic ancestry in lung-function predictions. *NEJM.* 2010 Jul 22; 363(4): 321-30. PMCID: PMC2922981

   b. Andrés Moreno-Estrada, Christopher R. Gignoux, (35 authors), Irma Silva-Zolezzi, * **Esteban Gonzalez Burchard**, *Carlos D. Bustamante. The genetics of Mexico recapitulates Native American substructure and affects biomedical traits. *Science*. 2014 Jun 13; 344(6189):1280-1285 PMID: 24926019 PMCID: PMC4156478. *Shared senior authors. We independently conceived the idea. My laboratory performed all of the genetic analyses, estimates of local ancestry. My lead graduate student, Chris Gignoux, worked with the co-first author on the population genetics. As a pulmonologist it was easy to expand the population genetics results to clinical applications.

   c. Nishimura KK, Galanter JM, (19 Authors)**, Burchard, E.G** Early Life Air Pollution and Asthma Risk in Minority Children: The GALA II & SAGE II Studies. *AJRCCM* 2013; 188(3): 309-18. PMID: 23750510; PMCID: PMC3778732

   d. Pino-Yanes M, Thakur N, (37 authors), **Burchard EG**. Genetic ancestry influences asthma susceptibility and lung function among Latinos. *JACI*. 2014 Sep 13. PMID: 25301036. PMCID: PMC4289103.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/esteban.burchard.1/bibliography/41458007/public/?sort=date&direction=ascending Note: A more accurate publicly available list is available at UCSF Profiles:http://profiles.ucsf.edu/esteban.burchard#toc-id9

Research Support

Ongoing Research Support

T32GM007546 Burchard (PI)07/01/2008 - 06/30/2025
NIH/NIGMS
UCSF Clinical Pharmacology and Therapeutics Training Grant
Goal: To train physician, pharmacist and Ph.D. scientists in clinical and therapeutic actions of drugs in humans.
Role: Principal Investigator

27IR-0030 Burchard (PI) 04/01/2018 - 03/31/2021
TRDRP
Tobacco Exposure and Asthma Disparity in Minority Children
Goal: To evaluate independent and collective contributions of IUS/SHS tobacco exposure, racial/ethnic differences, and epigenetic mediators predicting ICS responsiveness among African American and Latino children.
Role: Principal Investigator

R01HL141992 Himes (PI) 05/01/2018 - 04/30/2021
NIH/NHLBI
University of Pennsylvania
Integrative Analyses to Uncover Biological Mechanisms Mediating Gene Associations with Asthma Drug Response Among Minority Children.
Goal: To understand the biological basis of differential drug response that leads to observed racial/ethnic asthma disparities. In this proposal, we use two cloud-based apps we developed to identify functional biologic mechanisms of genes that are associated with racial/ethnic variation in asthma therapies.
Role: Subcontract PI

R01HL135156 Seibold (PI) 05/01/2017 - 04/30/2022
NIH/NHLBI
Transcriptomic and Pharmacogenetic Asthma Endotypes in Minority Children
Goal: To understand the genetic basis of racial/ethnic differences in asthma severity and lung function, and to examine data from 4,379 minority children with asthma to determine how asthma endotypes influence response to albuterol and risk for severe asthma.
Role: Co-investigator

U01HL138626-01A1 Burchard (MPI) 09/24/2018 - 07/31/2023
NIH-NHLBI
Natural History of Viral Induced Airway Dysfunction and Asthma in Minority Children
Goal: To determine why early-life viral infections cause severe respiratory illnesses in some infants and identify airway endotypes that high-risk groups exhibit in early childhood, prior to asthma onset by recruiting and longitudinally following 3,000 Puerto Rican infants under 1 year of age with varying risk for asthma. Results from this proposal will inform public health policy and clinical practice and aide in being able to determine incidence of asthma, including persistence of wheeze with viral infections and health care utilization.
Role: Principal Investigator

R01HL141845 (Williams LK) 02/01/2019 - 01/31/2023
NHLBI
Title: Poly-omic Study of Asthma Exacerbations in Diverse Populations
Goal: Asthma attacks are common and potentially life-threatening, yet simple and reliable ways to identify susceptible individuals do not exist. African Americans and Latinos are two groups at highest risk for these serious events. This application represents the first sizable study to investigate genetic risk factors for asthma attacks in these groups. We will integrate data from whole genome sequencing, RNA-seq, and mass spec proteomic analysis to identify these susceptibility markers.
Role: Subcontract PI

2R01HL117004-05 (Burchard) 07/01/2019 - 06/30/2023
NIH/NHLBI (Renewal)

Project title: The Airway Functional Genomics of Bronchodilator Drug Response in Minority Children with Asthma
Goal: To understand the genetic and environmental basis of racial/ethnic differences in asthma and drug response. Results from this proposal will inform public health policy and clinical practice and aid in the understanding of the asthma racial paradox, which may lead to more targeted therapies.
Role: Principal Investigator

GRANT12997630 (Burchard) 09/01/2020 - 08/31/2025
NIH Center for Scientific Review (NIH CSR)
Epigenomics of asthma risk factors and clinical subtypes in minority children
The major goals of this project are to examine the phenotypic and epigenetic expressions of asthma, asthma-related subtypes, and drug response among minority children.

U01 FD005978-04S1 (Kathleen Giacomini) 09/01/2019 - 08/31/2021 NCE
FOOD AND DRUG ADMINISTRATION
UCSF-Stanford Center of Excellence in Regulatory Science
Collaborative Research Project #46: Characterizing Population-Specific Clinical Asthma Profiles
Goal: Characterize clinical asthma profiles and their biologic determinants in three predominant minority populations. Our objective is to produce population-specific profiles of asthma severity, exacerbations, and control for Puerto Rican, African American, and Mexican American patients.

Completed Research Support

R56MD013312 Zaitlen/Burchard (MPI) 09/25/2018 - 09/24/2019
NIH/NIMHD
Project title: Epigenetics of Socio-Environmental Effects on Asthma in Minorities
Goal: (1) Perform whole genome methylation in a multi-ethnic cohort with existing genetics, transcriptomic, and socio-environmental measures; (2) Develop advanced computation methods needed to identify and characterize associations between epigenetic variation and socio-environmental asthma risk factors; (3) Establish approaches to uncover the causal relationships between socio-environmental factors, epigenetic variation, and asthma
Role: Principal Investigator

U01HG009080 (Eimear) 08/15/2019 - 03/31/2020
NIH-NHGRI $117,090 (sub only)
Subcontract from Stanford University
Center for Multi- and Trans-ethnic Mapping of Mendelian and Complex Diseases
Goal: To develop new methods, study designs and computational tools to comprehensively identify risk and protective variants for a variety of phenotypes with different disease architectures in ethnically diverse populations.
Role: Principle Investigator

R01Hl128439 Seibold (PI) 08/15/2015 - 05/30/2020
NIH-Subcontract (#2020100601)
Genetic Control of Airway Epithelium Gene Expression in Childhood Asthmatics
Goal: To participate and advise the design, performance, interpretation of all proposed sequencing and genetic analyses.
Role: Subcontract PI

BIOGRAPHICAL SKETCH

NAME **Harold A. Chapman, M.D.**	POSITION TITLE Professor of Medicine
eRA COMMONS USER NAME Halchapman	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Tulane University		1968	Premedical
University of Alabama School of Medicine	M.D.	1972	Medicine
Residency in Internal Medicine, University of Utah Affiliated Hospitals, Salt Lake City, UT		1975	Medicine
Associate Investigator, V.A. Medical Center, Salt Lake City, UT		1977	Infectious Disease
Pulmonary Fellow, University of Utah Affiliated Hospitals, Salt Lake City, UT		1979	Pulmonary/Critical Care

Positions and Honors

1979-1985	Assistant Professor of Medicine, University of Utah, Department of Medicine, Salt Lake City, UT
1985	Associate Professor of Medicine, University of Utah, Department of Medicine, Salt Lake City UT
1985-1999	Associate Professor of Medicine, Harvard Medical School, Department of Medicine, Boston, MA
1992-1999	Physician, Brigham and Women's Hospital, Boston, MA
1992-1999	Associate Professor of Environmental Health, Harvard School of Public Health, Boston, MA
2000-2008	Chief, Division of Pulmonary and Critical Care Medicine, University of California, San Francisco
2000	Attending Physician, Moffitt-Long Hospital, University of California San Francisco
2000	Professor of Medicine, University of California, San Francisco
2000	Senior Member, Cardiovascular Research Institute, University of California San Francisco

1985-1990 Career Investigator Award, American Lung Association
1987 American Society for Clinical Investigation
1998 American Association of Physicians
2001-2012 MERIT Award, NIH/NHLBI

Ad Hoc member of various NIH study sections, including Chair and Co-Chair of two NIH study sections in the last three years. Permanent member NIH LRRI study section 2017-2023.

Editorial Boards
Journal of Clinical Investigation

Contribution to Science

The nature of the cells and proteases important to human emphysema was uncertain not very long ago, with almost all of the attention directed at neutrophils. However we developed and published data in the early 1980s that lung macrophages could be as or more important in elastin degradation. But believing that we did not know the important macrophage enzymes, we generated a human alveolar macrophage-derived DNA expression library to search for additional proteases. My colleagues and I were able to clone four new cysteine proteases from this library and then the group spent the next several years understanding their biology. We also shared the library with other investigators in the field, e.g. Steve Shapiro's group used the library to clone human macrophage metallo-elastase. We found cysteine proteases with non-redundant functions in antigen presentation, bone collagen turnover, thymic development, and neuronal lysosomal lipufuscin degradation. Cathepsin S, the first enzyme characterized, proved to be a potent elastase and a critical enzyme in MHC class II maturation. Collaborating with geneticists, we were able to link two of the enzymes to human genetic disorders and inhibitors of one of these, cathepsin K, has recently proven effective in a phase III clinical trial for post-menopausal osteoporosis (Merck).

a. Shi GP, Munger JS, Meara JP, Rich DH, **Chapman HA**. Molecular cloning and expression of human alveolar macrophage cathepsin S, an elastinolytic cysteine protease *J Biol Chem* 1992 15; 267:7258-62.
b. Riese R, Wolf P, Bromme D, Natkin L, Villadangos JA, Ploegh H and **HA Chapman.** Essential role for cathepsin S in MHC Class II-associated invariant chain processing and antigen presentation *Immunity* 1996; 4:357-366.
c. Gelb BD, Shi GP, **Chapman HA** Jr, Desnick RJ. Pycnodysostosis, a lysosomal disease caused by cathepsin K deficiency. *Science* 1996; 273:1236-1238.
d. Tang CH, Lee JW, Galvez MG, Robillard L, Mole SE, **Chapman HA**. Murine cathepsin F deficiency causes neuronal lipofuscinosis and late-onset neurological disease. *Mol Cell Biol*. 2006; 26: 2309-16.

The nearly century-long observation that urokinase/plasmin activity is higher in tumors than surrounding normal tissues generated great interest in the nature of urokinase activators and their function in cell migration. In studying urokinase activity in macrophages I discovered and reported for the first time that a cell-bound form of urokinase exists and proposed this focused protease activity to the immediate cell surface, thereby promoting invasion. This

observation led to the subsequent identification of the urokinase receptor (uPAR). Although my group did not clone the receptor initially we did then identify the receptor as also an adhesion receptor for vitronectin, directly linking adhesion and protease activity. The crystal structure of uPAR confirmed the dual nature of the receptor. Subsequently we described the interaction of uPAR with several integrins, further connecting focal protease activation with cell attachment and motility. These studies spawned numerous subsequent studies examining the interplay between uPAR, matrix proteins, and adhesion receptors in cancer biology, establishing an important role for uPAR in tumor invasion.

a. **Chapman HA** Jr, Vavrin Z, Hibbs JB Jr. Macrophage fibrinolytic activity: Two pathways of plasmin formation by intact cells and an inhibitor of plasminogen activator. *Cell* 1982; 28:653-662.
b. Wei Y, Waltz D, Rao N, Drummond R, Rosenberg S, **Chapman HA**. Identification of the urokinase receptor as an adhesion receptor for vitronectin. *J Biol Chem*, 1994; 209:32380-32388.
c. Wei Y, Lukasev M, Simon DI, Bodary SC, Rosenberg S, Doyle MV, **Chapman HA**. Regulation of integrin function by the urokinase receptor. *Science* 1996; 273:1551-1555.
d. Wei Y, Yang X, Quimei Liu, Wilkins JA, and **Chapman HA**. Role for caveolin and urokinase receptors in integrin-mediated adhesion and signaling. *J Cell Biol* 1999; 144:1285-1294.

Although epithelial mesenchymal interactions are well known to influence extracellular matrix remodeling, the role of epithelial plasticity in this biology in the lung had been largely undefined. I asked the question of whether epithelial to mesenchymal transition (EMT) occurs in vivo in the lung in the context of injury and, if so, does this contribute importantly to pulmonary fibrosis. Using lineage labeling in vivo we discovered that epithelial cells express mesenchymal genes during fibrogenesis and activation of this pathway required extracellular matrix-induced TGFβ1 activation. These results inspired a series of studies examining the influence of integrin receptors on TGFβ1 signaling ultimately linking Symbol-catenin-rich cell:cell contacts, integrin α3β1, and Smad signaling. Disruption of this signaling pathway in vivo attenuated epithelial transition and fibrogenesis. The implication that epithelial transition is important to fibrogenesis was subsequently confirmed by Kevin Kim, independent in his own lab, using an epithelial-specific knockout of collagen 1.

a. Kim KK, Kugler MC, Wolters PJ, Robillard L, Galvez MG, Brumwell AN, Sheppard D, **Chapman HA**. Alveolar epithelial cell mesenchymal transition develops *in vivo* during pulmonary fibrosis and is regulated by the extracellular matrix. *Proc Natl Acad Sci* 2006; 103(35): 13180-5. Epub 2006 Aug 21
b. Kim KK, Wei Y, Szekeres C, Kugler MC, Wolters PJ, Hill ML, Frank JA, Brumwell AN, Wheeler SE, Kreidberg JA, **Chapman HA**. Epithelial cell alpha3beta1 integrin links beta-catenin and Smad signaling to promote myofibroblast formation and pulmonary fibrosis. *J Clin Invest*. 2009 Jan; 119(1): 213-24. doi: 10.1172/JCI36940.
c. Kim Y, Kugler MC, Wei Y, Kim KK, Li X, Brumwell AN, **Chapman HA**. Integrin alpha3beta1-dependent beta-catenin phosphorylation links epithelial Smad signaling to cell contacts. *J Cell Biol.* 2009 Jan 26; 184(2): 309-22.

d. Xi Y, Wei Y, Sennino, Ulsamer A, Kwan I, Brumwell AN, Tan K, Aghi MK, McDonald DM, Jablons DM, **Chapman HA**. Identification of pY654-β-catenin as a critical co-factor in hypoxia-inducible factor-1α signaling and tumor responses to hypoxia *Oncogene* 2013, Dec 17. 2(42): 5048-57. PMID: 23246962

I led in vivo investigations of the role of epithelial mesenchymal transition (EMT) in pulmonary fibrosis and in the course of studying epithelial plasticity we discovered a population of lung epithelial progenitors expressing the integrin α6β4 capable of regenerative activity in vitro and in vivo in response to major injury. Follow-up studies led to the discovery that the actual stem/progenitor cells are relatively rare distal airway epithelial subpopulations devoid of mature lineage markers but capable of rapid proliferation and pluripotent differentiation in vivo. Their fates in vivo were recently found to be regulated by local lung hypoxia via its impact on Notch signaling.

a. **Chapman HA**, Li X, Alexander JP, Brumwell A, Lorizio W, Tan K, Sonnenberg A, Wei Y, Vu T. Integrin α6β4 identifies an adult distal lung epithelial population with regenerative potential in mice. *J Clin Invest*. 2011, 121:2855-62.
b. Vaughan AE, Brumwell A, Xi Y, Gotts J, Brownfield DG, Treutlein B, Tan K, Tan V, Liu F, Looney MR, Matthay M, Rock J, **Chapman HA**. Lineage-negative Progenitors Mobilize to Regenerate Lung Epithelium after Major Injury. *Nature* 2015 517(7536):621-5. PMID: 25533958
c. Xi Y,Kim T, Brumwell AN, Driver I, Wei Y, Tan V, Jackson J, Xu J, Lee DK, Gotts J, Matthay M, Shannon JM, **Chapman HA** (corresponding author), and Vaughan AE. Local lung hypoxia determines epithelial fate decisions during alveolar regeneration. *Nature Cell Biology* 2017, Aug;19(8):904-914. PMID: 28737769.

A logical extension of studies directed at elucidating mechanisms of fibrosis is the development of new drug targets to block fibrosis. In 2012, I initiated a small molecule screen through the UCSF Discovery Center for inhibitors of EMT in vitro that did not block Smad signaling directly but blocked fibrosis in vivo. We identified several promising candidates, one of which methacycline has been reported, that proved the screening methodology could be successful. We then used this methodology to screen for other compounds that acted similarly. Ultimately this has led a novel therapeutic approach to attenuate fibrosis and the disease promoting effects of tissue stiffness by specifically targeting T SymbolRI kinase in lysyl oxidase-like 2 (LOXL2)-expressing cells, a fibroblast-specific pathway of TGFβ1 inhibition.

a. Xi Y, Tan K, Brumwell AN, Chen S, Kim YH, Kim TJ, Wei Y, **Chapman HA**. Inhibition of Epithelial to Mesenchymal Transition and Pulmonary Fibrosis by Methacycline. *Am J Respir Cell Mol Biol.* 2014 50(1):51-60. PMCID: PMC3930932
b. Wei Y, Kim TJ, Peng DH, Duan D, Gibbons DL, Yamauchi M, Jackson JR, Le Saux CJ, Derynck R, Backes BJ, **Chapman HA**. Attenuation of lung and tumor fibrosis by fibroblast-specific inhibition of TGFβ1 signaling, *J of Clin Invest.* 2017, Sep 5 [ePUB ahead of print]. PMCID: PMC5617667
Recommended as exceptional (3 stars) by F1000.

Full reference list can be found at:
http://www.ncbi.nlm.nih.gov/sites/myncbi/harold.chapman.1/bibliograpahy/40691690/public/?sort=date&direction=ascending

Research Support

Ongoing Research Support

R01HL128484-01 (Chapman HA PI) Epithelial Stem/Progenitor Cells in Repair of the Injured Lung 7/1/2015-6/30/20

The major goals of this project are to define determinants of alveolar stem/progenitor cell differentiation after lung injury and identify the human equivalent of recently identified undifferentiated epithelial cells in the mouse lung parenchyma.

U01HL134766 (Chapman, HA PI) 9/1/2016-8/31/2023
Epithelial stem/progenitor cells as repair agents in diffuse alveolar damage.
This project describes a new therapeutic approach to lung repair that extends recent results in mice demonstrating that lung stem/progenitor cells can transplant and engraft in damaged lungs. The application is driven by the frustrating current state of pulmonary medicine that offers little more than supportive care in the management of acute respiratory failure and progressive fibrotic lung diseases. A group of investigators have come together to overcome the hurdles of stem/progenitor cell replacement therapy in humans.

RO1 HL142265-01A1 Chapman, HA PI 02/1/2019-1/13/2024
LOXL-2 dependent blockade of TGFβ1 signaling and lung fibrosis. The major objectives of this project are to define the structural basis for inhibition of TβRI/II kinase by a LOXL2-dependent trihydroxyphenolic metabolite(s). Second, to test the hypothesis that the trihydroxyphenolic EGCG limits and reverses fibrosis in both a chronic bleomycin mouse model in vivo and precision cut lung slices (PCLS) of IPF patient explants. And to execute a proof-of-principle pilot study in ILD patients with lung fibrosis, testing the hypothesis that oral EGCG will suppress lung Snail1 and pSmad3 accumulation and block collagen mRNA in vivo.

Recently Completed

U01 HL111054-01 Chapman HA, PI NIH/NHLBI
Epithelial Progenitor Cells in Lung Repair and Regeneration 1/1/2012-12/31/2016
The specific aims of this project are (1) Test the hypothesis that differential expression of adhesion receptors underlies the capacity of epithelial subtypes to self-organize and promote repair. (2) Define the requirement for neuroendocrine cells (PNECS) and alveolar progenitor cells in maintenance and reconstitution of distal airway and alveolar cells following lung injury. (3) Analyze and further develop a novel, single cell in vivo lung organoid assay in kidney capsules in order to optimize the capacity of adult epithelial progenitor cells to generate functional respiratory units de novo.

PO1 HL108794 Sheppard PI, Chapman HA, project leader
Targeting epithelial cells to treat pulmonary fibrosis. 8/1/2012-7/31/2017
The major goal of this project is to deliver one or more novel therapeutics based on recently identified regulators of EMT in lung epithelial cells for further drug development.

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Anthony L. DeFranco, Ph.D.	Professor,
eRA COMMONS USER NAME	Department of Microbiology & Immunology
DeFranco	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Harvard University, Cambridge, MA	A.B.	6/1975	Biochem. Science
University of California, Berkeley, CA	Ph.D.	10/1979	Biochemistry
National Institutes of Health, Bethesda, MD	Postdoctoral	8/1983	Immunology

Positions

1972-1975	Undergraduate research, laboratory of Dr. Jack Strominger. HLA antigens.
1976-1979	Graduate research, laboratory of Dr. Daniel E. Koshland, Jr. Bacterial chemotaxis.
1979-1983	Postdoctoral research, laboratory of Dr. William E. Paul. B cell activation
1983-1988	Assistant Professor, UCSF, Department of Microbiology & Immunology,
1988-1994	Associate Professor, UCSF, Department of Microbiology & Immunology
1989-1990	Sabbatical with David Baltimore, Whitehead Insititute, MIT, Cambridge, MA
1994-present	Professor, UCSF, Department of Microbiology & Immunology
1997-1998	Sabbatical with Suzanne Cory, Walter and Eliza Hall Institute, Melbourne, Australia
1998-2004	Scientific Advisory Board, Abgenix, Inc. Fremont, CA
1999-2009	Chairman, Department of Microbiology & Immunology, UCSF
2012-	Scientific Advisory Board, UCB Celtech, Slough, UK
2015-present	Professor Emeritus of Microbiology & Immunology, UCSF (with continuing research and teaching activities)

Honors

1974	Dreyfuss Foundation Fellow
1975	Phi Beta Kappa, Harvard University
1975-1978	NSF Predoctoral Fellow
1979-1982	Helen Hay Whitney Postdoctoral Fellow
1993	2nd Rose Lieberman Lecturer, NIH
1994	NIAID Merit Award
1997-1998	NIH Fogarty Senior International Award

Contribution to Science

1). Mechanism of signal transduction by the BCR - A longstanding problem is how lymphocytes recognize the presence of the antigen that they recognize. We were the first (along with two other independent groups) to demonstrate that the BCR signals by inducing protein tyrosine phosphorylation (a). We demonstrated a number of features of the BCR signaling pathway, including the rapid tyrosine phosphorylation of Igα and Igβ of engaged receptors, activation of the PI 3-kinase pathway, and phosphorylation of PLC-γ2 as the mechanism of stimulation of PIP2 breakdown, as well as other findings. Some recent contributions are highlighted in the references cited here, including studies demonstrating that BCR signaling results in rapid release of ezrin from linkages to plasma membrane proteins, which facilitates membrane rearrangements that support BCR signaling (b), an analysis of the role of reactive oxygen species in BCR signaling, which disproved a long-standing model in the field (c), and studies in which BCR-induced diacylglycerol signaling to Erk was specifically enhanced by removal of the negative regulator DGKζ, which showed that Erk signaling is an important determinant of expansion of B cell numbers, especially at the plasmablast stage. In addition, the data strongly suggested that BCR affinity for antigen is primarily sensed by the B cell via the magnitude of Erk signaling (d).

a. Gold, M.R., D.A. Law and **A.L. DeFranco**. (1990) Stimulation of protein tyrosine phosphorylation by the B lymphocyte antigen receptor. *Nature* 345: 810-813.
b. Gupta, N., B. Wollscheid, J.D. Watts, B. Scheer, R. Aebersold, and **A.L. DeFranco** (2006). Quantitative proteomic analysis of B cell lipid rafts reveals that ezrin regulates antigen receptor-mediated lipid raft dynamics. *Nature Immunol*. 7: 625-633.
c. Wheeler, M.L., and **A.L. DeFranco** (2012). Prolonged production of reactive oxygen species in response to BCR stimulation promotes B cell activation and proliferation. *J. Immunol*. 189: 4405-4416. PMC3515638.
d. Wheeler ML, Dong MB, Brink R, Zhong X-P, and **DeFranco AL**. (2013). Diacylglycerol kinase zeta limits B cell antigen receptor-induced ERK signaling and the early antibody response. *Sci. Signaling* 6 (297): ra91. PMC4128120.

2). Role of Lyn in inhibitory signaling in B cells - In a long-standing collaboration with Dr. Clifford Lowell (UCSF), we have studied the function of the protein tyrosine kinase Lyn in B cells in vitro and in vivo. Lyn is a member of the Src-family of tyrosine kinases, which at the time were implicated in the initiation of antigen receptor signaling in T cells and B cells. We found that Lyn did indeed participate in the initiation of BCR signaling, but that it was redundant with the other Src family kinases expressed in B cells (primarily Fyn and Blk), a conclusion later confirmed by Tarakhovsky, who made the Lyn-/-Fyn-/-Blk-/- triple KO. Importantly, we found that Lyn is uniquely responsible for enabling the function of the inhibitory receptors CD22 and FcγRIIb, and therefore in its absence BCR signaling was of much greater magnitude after the first few minutes (2a, 2b). We subsequently found that the inhibitory function of the Lyn-CD22-Shp1 pathway is much greater in mature B cells than in immature B cells (2c). This finding is likely relevant to the striking breakdown in B cell tolerance in Lyn-deficient mice, which spontaneously develop a strong lupus-like autoimmunity (see next category). Indeed, selective deletion of Lyn in B cells was shown to be sufficient for lupus-like autoantibody production and lupus nephritis, indicating that B cell tolerance defects contribute importantly to the lupus-like autoimmunity of Lyn-deficient mice (3d).

a. Chan, V.W.F., F. Meng, P. Soriano, **A.L. DeFranco**, and C.A. Lowell (1997). Characterization of the B lymphocyte populations in Lyn-deficient mice and the role of Lyn in signal initiation and downregulation. *Immunity* 7: 69-81.

b. Chan, V.W.F., C.A.Lowell, and **A.L. DeFranco** (1998). Defective negative regulation of antigen receptor signaling in Lyn-deficient B lymphocytes. *Curr. Biol.* 8: 545-553.
c. Gross, A.J., J.R. Lyandres, A.K. Panigrahi, E., T.L. Prak, and **A.L. DeFranco** (2009). Developmental acquisition of the Lyn-CD22-SHP-1 inhibitory pathway promotes B cell tolerance. *J. Immunol*. 182: 5382-92. PMC2840041.
d. Lamagna, C., Y. Hu, **A.L. DeFranco**, and C.A. Lowell (2014). B cell-specific loss of Lyn kinase leads to autoimmunity. *J. Immunol*. 192: 919-928. PMC3900234

3). Analysis of Lyn-deficient mice as a murine model of lupus - Also in collaboration with Dr. Lowell, we have studied the autoimmunity that develops in Lyn-deficient mice. We have found that mice deficient in Lyn and Fyn have stronger lupus nephritis than do Lyn-/- mice, which probably reflects a role for Fyn in the homeostasis of the epithelial foot processes of the glomeruli (a). We showed that DCs contribute importantly to the autoimmune disease of Lyn-deficient mice by producing BAFF and stimulating interferon-γ production from T cells (b) and that DCs require MyD88-dependent signaling to promote inflammatory disease in this model (c). Selective deletion of Lyn in B cells also leads to lupus-like autoantibody production and lupus nephritis, indicating that B cell tolerance defects contribute to the lupus-like autoimmunity of Lyn-deficient mice (d). In studies nearing publication, we have found that combination of Lyn-deficiency with a hypomorphic allele of Aire, which is important for thymic expression of organ-specific autoantigens, results in spontaneous autoimmune uveitis, providing a model for multigenic autoimmune susceptibility. This project is the subject of the current application.

a. Yu, C.C.K., T.S.B. Yen, C.A. Lowell, and **A.L. DeFranco** (2001). Lupus-like kidney disease in mice deficient in Src-family protein tyrosine kinases Lyn and Fyn. *Curr. Biol.* 11:34-38.
b. Scapini, P., Y. Hu, C.L. Chu, T.S. Migone, **A.L. DeFranco**, M.A. Cassatella, and C.A. Lowell (2010). Myeloid cells, BAFF, and IFN-γ establish an inflammatory loop that exacerbates autoimmunity in Lyn-deficient mice. *J. Exp. Med*. 207: 1757-73. PMC2916124
c. Lamagna C, Scapini P, Van Ziffle J, Hou B, **DeFranco AL**, and Lowell CA. (2013). Hyperactivated MyD88 signaling in dendritic cells, through specific deletion of Lyn kinase, causes severe autoimmunity and inflammation. *Proc. Natl. Acad. Sci. USA*. 110: E3311-20. PMC3761623
d. Proekt, I., Miller, C.N., Jeanne, M., Fasano, K., Moon, J.J., Lowell, C.A., Gould, D.B., Anderson, M.S., and **DeFranco, A.L**. (2016). LYN- and AIRE-mediated tolerance checkpoint defects synergize to trigger organ-specific autoimmunity. *J. Clin. Invest*. 126: 3758-3771. doi: 10.1172/JCI84440.

4). Roles of TLR signaling in dendritic cells and macrophages for the innate response to adjuvants and infections - To dissect the roles of TLRs in immune responses in vivo, we created a conditional allele of the TLR signaling component MyD88 with the Cre/loxP system, and verified its utility for deletion of MyD88 selectively in dendritic cells (DCs) (a). These studies showed that DCs are the major producers of inflammatory cytokines in the spleen following i.v. infusion of TLR ligands, and that splenic macrophages are a minor contributor. In collaborative studies with Felix Yarovinsky (UT Southwestern), we used these mice to demonstrate that infection with *Toxoplasma gondii* results in TLR-dependent IL-12 production by peritoneal DCs, which is critical for innate host defense by inducing infiltrating NK cells to make interferon-γ which in turn promotes killing of parasites by inflammatory monocytes (b). This was the first study to clearly demonstrate a critical role for type 1 innate immunity in control of *Toxoplasma* infection as previous studies had been interpreted in light

of effects on the Th1 response, which is also essential to control of *Toxoplasma*. This work was primarily conducted in my lab by the first author, although Dr. Yarovinsky provided important support for these studies. This collaboration lead to two other important papers that were primarily conducted in Dr. Yarovinsky's lab (4c and 5b). In contrast to the critical role of DCs in response to *Toxoplasma gondii* infection, in a murine malaria model, splenic red pulp macrophages were found to be critical for early cytokine production (4d). The conditional allele of *Myd88* was deposited with Jackson Lab soon after initial publication and is available to academic investigators for their studies.

a. Hou, B., B. Reizis, and **A.L. DeFranco** (2008). Toll-like receptors activate innate and adaptive immunity using dendritic cell-dependent and -independent mechanisms. *Immunity* 29: 272-82. PMC2847796.
b. Hou, B., A. Benson, L. Kuzmich, **A.L. DeFranco** and F. Yarovinsky (2011). Critical coordination of innate immune defense against *Toxoplasma gondii* by dendritic cells responding via their Toll-like receptors. *Proc. Natl. Acad. Sci USA* 108: 278-283. PMC3017180**.**
c. Raetz,M, Hwang, S-H, Wilhelm, C, Kirkland, D, Benson, A, Sturge, C, Mirpuri, J, Vaishnava, S, Hou, B, **DeFranco, AL**, Gilpin, CJ, Hooper, LV, Yarovinsky, F. (2013). Parasite-induced Th1 cells promote intestinal dysbiosis via IFN-dependent elimination of Paneth cells. *Nat. Immunol*. 14: 136-142. PMC3552073.
d. Lee, L.M., Ji, M., Sinha, M., Dong, M.B., Ren, X., Wang, Y., Lowell, C.A., Ghosh, S., Locksley, R.M., and **DeFranco, A.L**. (2016). Determinants of divergent adaptive immune responses after airway sensitization with ligands for Toll-like receptor 5 or Toll-like receptor 9. PLoS ONE in press.

5). TLR7/9 in B cells promote germinal center responses Although TLRs are not required for antibody responses, TLR ligands are excellent adjuvants. Previously, it was thought that TLR signaling in B cells promoted extrafollicular antibody responses, but we showed that TLR7 and TLR9 can strongly enhance GC responses to virus particles (5a). Subsequently, other groups showed that mice lacking TLR7 or MyD88 selectively in B cells fail to make a normal neutralizing antibody response against LCMV, Friend virus, or endogenous retroviruses, leading to poor control of these virus infections, thus demonstrating an important biological role of the pathway we first described. We showed that this mechanism is also required for production of anti-nuclear antibodies in the Lyn-deficient mouse model of lupus (5c) and we have recently dissected the cellular mechanisms of this response (5d). In addition, in collaboration with Dr. Yarovinsky we found that MyD88 function in B cells promotes the rapid IgM response to colonic bacteria following damage to colonic epithelium.

a. Hou, B., P. Saudan, G. Ott, M.L. Wheeler, M. Ji, L. Kuzmich, L.M. Lee, R.L. Coffman, M.F. Bachmann, **Anthony L. DeFranco** (2011). Selective utilization of Toll-like receptor and MyD88 signaling in B cells for enhancement of the anti-viral germinal center response. *Immunity* 34: 375-84. PMC3064721
b. Rookhuizen, D.C. and **A.L. DeFranco** (2014). Toll-like receptor 9 signaling acts on multiple elements of the germinal center to enhance antibody responses. *Proc. Natl. Acad. Sci USA* 111: E3224-33. PMC4128120.
c. Tian M, Hua Z, Hong S, Zhang Z, Liu C, Lin L, Chen J, Zhang W, Zhou X, Zhang F, DeFranco AL, Hou B. (2018). B Cell-Intrinsic MyD88 Signaling Promotes Initial Cell Proliferation and Differentiation to Enhance the Germinal Center Response to a Virus-like Particle. J Immunol. 200: 937-948 doi: 10.4049/jimmunol.1701067.
d. Wigton EJ, **DeFranco AL**, and Ansel KM (2019). Antigen complexed with a TLR9 agonist bolsters m-myc and mTORC1 activity in germinal center B lymphocytes. Immunohorizons 3: 389-401. PMCID: PMC6738343.

A complete list of my publications is available at:
http://www.ncbi.nlm.nih.gov/sites/myncbi/anthony.defranco.1/bibliography/41142681/public/?sort=date&direction=ascending

Research Support

Active
"Organ-specific autoimmunity resulting from two genetic defects in tolerance"
Principal Investigator: Anthony DeFranco, 2.4 calendar mo. effort
1R01 AI138479-01
3/1/18-2/28/23.
Agency: NIH/NIAID

Completed (last 3 years)

"B cell TLRs and Germinal Centers"
Principal Investigator: Anthony DeFranco, 1.2 calendar mo. effort
1R21AI117378-01
7/1/15-6/30/17
Agency: NIH/NIAID

BIOGRAPHICAL SKETCH

NAME **William F. DeGrado**	POSITION TITLE Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Kalamazoo College, Kalamazoo, MI	B.S.	02/1978	Chemistry
University of California, San Francisco	Ph.D.	06/1981	Organic Chemistry

Positions

1981-1990	Research Chemist, CR&D, DuPont Company, Wilmington, DE
1990-1992	Research Leader, CR&D, DuPont Company, Wilmington, DE
1992-1994	Research Fellow, R&D, The DuPont Merck Pharmaceutical Company, Wilmington, DE
1994-1996	Senior Director, R&D, The DuPont Merck Pharmaceutical Company, Wilmington, DE
1996-2011	Professor, Dept. of Biochemistry & Biophysics, University of Pennsylvania, Philadelphia, PA
2001-2003	President, The Protein Society
2011-present	Professor, UCSF Department of Pharmaceutical Chemistry

Visiting Positions

1987	Sloan Visiting Lecturer of Chemistry, Dept. of Chemistry, Harvard University
1987-1989	Adjunct Professor, Department of Biophysics, Johns Hopkins Medical School
1991	Adjunct Professor, Departments of Biochemistry & Biophysics, University of Pennsylvania
2010-2011	Visiting professor, UCSF Department of Pharmaceutical Chemistry.

Honors

1988	du Vigneaud Award for Peptide Research
1989	Protein Society Young Investigator Award
1992	Eli Lilly Award in Biological Chemistry
1994	Fellow, American Association for the Advancement of Science
1998	Member, American Academy of Arts and Sciences
1999	Member, National Academy of Sciences (U.S.A.)
2003	Merrifield Award, (presented by the Peptide Society)
2008	Ralph F. Hirschmann Award in Peptide Chemistry (American Chemical Society)
2009	Makineni Award (APS)
2014	Member, National Academy of Inventors (U.S.A.)
2015	Stein & Moore Award (Protein Society)
2016	Max Perutz Memorial Lecture (Weizmann Institute, Israel)
2017	Distinguished Alumnus Award (Kalamazoo College)

2018 Cope Scholar Award (American Chemical Society, Organic Division)
2018 M. Goodman Memorial Prize (American Chemical Society, Biological Division)

Contribution to Science

1) Protein Design. When our group first pioneered de novo protein design, proteins were seen as impossibly complex molecules whose structure could not be predicted or designed. We therefore adopted a minimalist approach to protein design in which we set out to engineer sequences of the minimum complexity required for folding and a given function. Our group was the first to design and convincingly characterize a protein from scratch – a four-helix bundle. De novo protein design proved useful for probing the features required for forming secondary structures (e.g., O'Neil and DeGrado's well-known thermodynamic scale of helix propensity), compact states known as "molten globules" and ultimately well-packed native protein structures. This method was then used to design proteins that bound DNA, transition metals, and redox-active cofactors, including both natural and non-natural porphyrins. For example, our group predicted the DNA-bound structures of the leucine zipper, HLH and related transcription factors before their high-resolution crystallographic structures were known. We designed minimalist versions of these proteins to illustrate the mechanisms by which they folded and recognized DNA in a sequence-specific manner.

In the several years, our work on di-metal proteins has deepened our understanding of how a protein creates an environment to tune the activity of its metal ion cofactors. We have shown how small changes to ligand environment convert a protein from an oxidase to a hydroxylase. We also designed Zn^{2+}-binding peptides that adopt catalytically active cross-beta fibrils, with potential to open new doors for the design of catalytic materials as well as implications concerning the evolution of life[1]. We also designed proteins that bind and coat various materials, including carbon nanotubes[2] and proteins that bind a variety electrical and optical cofactors. We have designed a protein that stabilizes organic radicals for weeks in aqueous solution[3]. Most recently, we solved a long-standing challenge of designing a protein that binds an metalloporphyrin in a unique conformation, and determined that the experimental structure and placement of the cofactor agreed with the design to within less than 1.0 Å r.m.s.d.[4].

[1] Rufo, C. M., Moroz, Y. S., Moroz, O. V., Stohr, J., Smith, T. A., Hu, X., DeGrado, W. F., and Korendovych, I. V. (**2014**) Short peptides self-assemble to produce catalytic amyloids, ***Nature Chemistry*** *6*, 303-309. PMC3996680

[2] Grigoryan, G., Kim, Y. H., Acharya, R., Axelrod, K., Jain, R. M., Willis, L., Drndic, M., Kikkawa, J. M., and DeGrado, W. F. (**2011**) Computational design of virus-like protein assemblies on carbon nanotube surfaces, ***Science*** *332*, 1071-1076. PMC3264056

[3] Ulas G, Lemmin T, Wu Y, Gassner GT and DeGrado WF (**2016**) Designed metalloprotein stabilizes a semiquinone radical. ***Nature Chemistry*** 8:354-9. PMC4857601

[4] Polizzi, N, Wu, Y., Lemmin, T, Maxwell, A, Zhang, SQ, Rawson, J., Beratan, DN, Therien, M.J., DeGrado, WF. (**2017**) De novo design of a hyperstable, non-natural protein-ligand complex with sub-Å accuracy. ***Nature Chemistry*** 9:1157-1164. PMC5859929

2) Membrane protein design. We used minimalist design principles to delineate the features required for assembly and conduction of ion channels, and we then used these principles to design TM, multi-porphyrin helical bundles that catalyze electron transfer through phospholipid membranes. Simultaneous with Engelman's group, we showed the role of polar amino acids in inducing association of transmembrane helices, and their role in membrane protein folding and assembly. Recent work has focused on defining a sequence-specific code for recognition of TM helices in membranes. We developed a computational approach to design peptides that target the TM regions of membrane proteins in much the same way that antibodies are used to block protein-protein interactions in water-soluble proteins[5], and we showed the utility of these peptides to help dissect signal transduction pathways[6]. We also

have designed helical bundles that use a Zn(II) gradient to drive the transport of protons up a concentration gradient (and vice versa)[7]. This work was particularly significant, as it was the first example of a designed membrane protein whose structure was determined at high resolution, and it had the most complex function of a membrane protein designed to date.

[5] Yin, H., Slusky, J. S., Berger, B. W., Walters, R. S., Vilaire, G., Litvinov, R. I., Lear, J. D., Caputo, G. A., Bennett, J. S., and DeGrado, W. F. (**2007**) Computational design of peptides that target transmembrane helices, **Science** *315*, 1817-1822.

[6] Fong KP, Zhu H, Span LM, Moore DT, Yoon K, Tamura R, Yin HH, DeGrado WF and Bennett JS (**2016**) Directly Activating alphaIIbbeta3 Initiates Outside-In Signaling by Causing alphaIIbbeta3 Clustering. ***J Biol Chem***. doi: 10.1074/jbc.M116.716613. PMCID in process.

[7] Joh, N. H., Wang, T., Bhate, M. P., Acharya, R., Wu, Y., Grabe, M., Hong, M., Grigoryan, G., and DeGrado, W. F. (**2014**) De novo design of a transmembrane Zn^{2+}-transporting four-helix bundle, ***Science*** *346*, 1520-1524. PMC4400864

3) Structure/Function of the M2 proton channel from influenza A virus. Our early work with the groups of Robert Lamb and Larry Pinto established the overall fold and mechanism of the M2 proton channel, which is the target of the anti-influenza drugs, amantadine and rimantadine. We first proposed the transporter-like and His-shuttle mechanisms, which are now widely accepted. A decade later our group's crystallographic and solution NMR structures[9] provided direct support for these mechanisms. These structures defined the drug-binding site and explained how mutations led to amantadine-resistance[10,11]. We have solved extremely high-resolution (1.05 Å) crystal structures of M2's pore, which rank among the highest resolution crystal structures of any membrane protein[12]. These structures showed well-defined water-wires for conduction of protons through the length of the pore, leading to the critical His37 proton-shuttling residue. Beyond the medical importance of M2, these studies provide important insight into the structure of water in confined spaces and its contribution to proton conduction throughout biology.

[9] Stouffer, A. L., Acharya, R., Salom, D., Levine, A. S., Di Costanzo, L., Soto, C. S., Tereshko, V., Nanda, V., Stayrook, S., and DeGrado, W. F. (**2008**) Structural basis for the function and inhibition of an influenza virus proton channel, ***Nature*** *451*, 596-599. PMC3889492

[10] Wang, J., Wu, Y., Ma, C., Fiorin, G., Wang, J., Pinto, L. H., Lamb, R. A., Klein, M. L., and DeGrado, W. F. (**2013**) Structure and inhibition of the drug-resistant S31N mutant of the M2 ion channel of influenza A virus, ***PNAS*** *110*, 1315-1320. PMC3557100

[11] Thomaston JL and DeGrado WF (**2016**) Crystal structure of the drug-resistant S31N influenza M2 proton channel. ***Protein Sci***. doi: 10.1002/pro.2937. PMCID in process.

[12] Thomaston JL, Alfonso-Prieto M, Woldeyes RA, Fraser JS, Klein ML, Fiorin G and DeGrado WF (**2015**) High-resolution structures of the M2 channel from influenza A virus reveal dynamic pathways for proton stabilization and transduction. ***PNAS*** 112:14260-5. PMC4655559

4) Small molecule inhibitors of M2 proton channel. Currently circulating strains of M2 are largely resistant to amantadine, which has greatly curtailed options for treating influenza virus infections. With Lamb and Pinto, we extensively characterized the electrophysiological properties of many drug-resistant mutants of the channel, and identified those most likely to lead to resistance in the future. My group solved the first structures of drugs bound to the pharmacologically relevant site of the channel in micelles by X-ray crystallography and solution NMR, and in bilayers by SSNMR (collaboration with Mei Hong, MIT)[9,10,13]. Based on our proposed conductance mechanism, we designed novel small molecules that inhibit known clinically problematic mutants[14-16].

[13] Cady SD, Schmidt-Rohr K, Wang J, Soto CS, DeGrado WF and Hong M (**2010**) Structure of the amantadine binding site of influenza M2 proton channels in lipid bilayers. ***Nature*** 463:689-92. PMC4403401.

[14] Wang J, Ma C, Fiorin G, Carnevale V, Wang T, Hu F, Lamb RA, Pinto LH, Hong M, Klein ML and DeGrado WF (**2011**) Molecular dynamics simulation directed rational

design of inhibitors targeting drug-resistant mutants of influenza A virus M2. ***J Am Chem Soc*** 133:12834-41. PMC3354620
[15] Wu Y, Canturk B, Jo H, Ma C, Gianti E, Klein ML, Pinto LH, Lamb RA, Fiorin G, Wang J and DeGrado WF (**2014**) Flipping in the Pore: Discovery of Dual Inhibitors That Bind in Different Orientations to the Wild-Type versus the Amantadine-Resistant S31N Mutant of the Influenza A Virus M2 Proton Channel. ***J Am Chem Soc*** 136:17987-95. PMC4286326
[16] Li F, Ma C, DeGrado WF and Wang J (**2016**) Discovery of Highly Potent Inhibitors Targeting the Predominant Drug-Resistant S31N Mutant of the Influenza A Virus M2 Proton Channel. ***J Med Chem*** 59:1207-16. PMC4829348

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/pubmed/?term=DeGrado%20WF[Author]&cauthor=true&cauthor_uid=7481798

Research Support - Active

R35 GM122603 (DeGrado) 05/01/17—04/30/22
NIH/NIGMS
Deciphering the relationship between structure, dynamics and function in helical bundle proteins
Our lab uses *de novo* protein design to test the principles of protein structure and function – if we *understand* proteins we should be able to *design* them from scratch. We also study the structure and inhibition of M2, a transmembrane proton transporter from influenza A virus, which is the target of amantadine. Finally, we study transmembrane histidine kinases, which are used by bacteria to sense their environment.

P01 HL146373 (Bennett) 05/10/20 – 4/30/25
NIH-NHLBI/UPENN
Studies of Physiologic and Pathologic Platelet Plug Formation
The major goals of this project are to determine the molecular basis for recognition and signaling through integrins. Integrins are proteins on the surface of cells that integrate information about the extracellular milieu with theintracellular processes. We will determine three-dimensional structures of integrins in defined signaling states using cryo-EM
Role: Co-PI

A134555 (DeGrado) 02/15/20—02/15/22
Oxford Nanopore Technologies
De novo Design of Nanopore
With the expertise of the DeGrado lab in optimizing peptides for analyte binding, we will design / redesign Porep (i.e.: CsgF peptides in 1a and 1b) such that they are not only capable of forming stable complexes with PoreP but also have the ability to interact strongly with analytes that are translocating through the protein channel, such as DNA. With aims to disrupt the paradigm of biological analysis by making high performance devices for DNA/RNA sequencing and protein analysis that is accessible and easy to use.

P01 AG002132 (Prusiner) 06/16/14—03/31/25

NIH/NIA
Degenerative and Dementing Diseases of Aging
We plan to study the molecular biology, biophysics and structure of A□ and tau become prions causing neurodegenerative diseases. In Project 2 we will apply multiple techniques to further determine the molecular basis of prion strain differences and better understand the fidelity of their propagation, in addition to studying how mutations in proteins associated with AD impact Aβ sequestration and processing. Project 2 will also provide broad-ranging biophysical and chemical biological approaches to generate structural information for integration.
Role: Co-PI

RF1AG061874 (Condello; DeGrado) 09/1/18—03/31/23
NIH/NIA
Relationships between conformational strains of tau and amyloid-beta,TREM2 and APOE variants, and phenotypic variations of Alzheimer's Disease
Dr. DeGrado will be responsible for the design, execution, analysis, and reporting for all aspects of the study. He will co-supervise the efforts of Greg Merz and Alison Maxwell. As a Co-PI on this proposal, Dr. DeGrado will be responsible for submission of progress reports and communications with the Agency. WFD will also be personally involved in various aspects of the scientific work, including designing assays to quantify the population distributions of amyloidogenic oligomers of Aβ and tau; designing small molecule fluorescent strain-sensitive probes. Choosing conditions for NMR spectroscopy; directing efforts in the purification and sequential extraction of human and mouse brain-purified Aβ aggregates used in all assays.
Role: Co-PI

FA9550-191-0331 (Beratan; DeGrado) 07/01/19--06/30/22
AFOSR/Duke University
De Novo Biomachines
The grant provides salary support and materials and supplies for a postdoctoral fellow to work on the design of the proteins that bind to and modulate the activities of optically active and redox cofactors in
Role: Co-PI

CHE-1413295 (Therien; DeGrado) 08/01/17—07/31/21
NSF/Duke University
Collaborative Research: De novo Protein Constructs for Photosynthetic Energy Transduction
This collaborative proposal aims to understand the essential design principles of photosynthetic energy transduction and storage. An integrated, multi-disciplinary approach is employed toward this goal, and focuses on the computational design of peptide-cofactor complexes that undergo photoinduced charge-transfer reactions, where the protein matrix stabilizes the charge-separated state and guides the efficient separation of electrons and holes. A postdoc in DeGrado's group works on the design of proteins that bind non-biological cofactors for energy transduction.
Role: Co-PI

BIOGRAPHICAL SKETCH

NAME **David J. Erle, M.D.**	POSITION TITLE Professor of Medicine
eRA COMMONS USER NAME DJERLE	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Harvard College, Cambridge, MA	A.B.	5/1980	Biochemistry
University of California, San Francisco, CA	M.D.	5/1984	Medicine
University of California, San Francisco, CA	Resident	6/1987	Internal Medicine
University of California, San Francisco, CA	Fellow	6/1988	Pulmonary Disease
University of California, San Francisco, CA	Postdoc	6/1990	Cell & Molecular Biology

Positions

1984-1987	Resident in Internal Medicine, University of California Hospitals, San Francisco
1987-1988	Clinical Pulmonary Fellow, University of California Hospitals, San Francisco
1988-1990	Research Fellow, Lung Biology Center and Cardiovascular Research Institute, UCSF
1990-1992	Adjunct Assistant Professor of Medicine, UCSF
1990-present	Attending Physician, San Francisco General Hospital
1992-1998	Assistant Professor of Medicine in Residence, UCSF
1996-present	Faculty, UCSF Immunology and Biomedical Sciences Graduate Programs
1997-2001	UCSF/SFGH General Clinical Research Center (GCRC) Advisory Committee
1998-2004	Associate Professor of Medicine, UCSF
1999-present	Investigator, Cardiovascular Research Institute, UCSF
2000-present	Director, Functional Genomics Core Facility, UCSF SABRE Center
2004-present	Professor of Medicine, UCSF
2006-2011	Associate Director, UCSF Clinical and Translational Sciences Institute Bioinformatics Program
2013-present	Founder and Director, UCSF K12 Career Development Program in Omics of Lung Diseases
2017	Associate Chair for Biomedical Research, UCSF Department of Medicine
2017-2019	Lead, Central Research Labs (CoLabs) Planning Committee
2018-	Member, UCSF Institute for Human Genetics
2018-	Member, Immuno X program
2020-	Director, UCSF CoLabs

Other Experience and Professional Memberships

1988-	Member, American Thoracic Society
1996-1999	American Lung Association/American Thoracic Society Scientific Advisory Council
1998-1999	RCMB Assembly Nominating Committee, American Thoracic Society
1999-2002	American Thoracic Society Scientific Advisory Council
2001-2004	RCMB Assembly Program Committee, American Thoracic Society
2005-	NIH Special Emphasis Panels for Member Conflicts
2008-2012	NIH LCMI Study Section, member (chair, 2010-2012)
2010-	Editorial Board, American Journal of Respiratory Cell and Molecular Biology
2014-2015	Chair, RCMB Assembly Nominating Committee, American Thoracic Society

Honors

1977	Detur Prize
1977, 1978	John Harvard Scholarship
1980	Magna cum laude, Harvard College, Cambridge, MA
1984	Alpha Omega Alpha, elected
1990-1993	Edward Livingston Trudeau Award of the American Lung Association
2018	Elected member, Association of American Physicians
2019	NHLBI Outstanding Investigator Award (R35)

Contributions to Science

1. I have led a series of studies investigating how the cytokine interleukin-13 acts on cells in the airway to contribute to pathophysiologic changes that are important in a large subset of individuals with asthma. We used transgenic mouse modeling and human cell culture-based studies to demonstrate how IL-13, acting directly on airway epithelial cells, causes mucus metaplasia and airway hyperreactivity, two characteristic features of asthma. We identified many IL-13-induced genes and dissected out their contributions to disease. We have also collaborated closely with patient-based researchers to demonstrate the relevance of these pathways in humans with asthma. Antibodies against IL-13 are now in clinical trials for treatment of severe asthma.

    a. Kuperman DA, Huang X, Koth LL, Chang GH, Dolganov GM, Zhu Z, Elias JA, Sheppard D, **Erle DJ**. Direct effects of interleukin-13 on epithelial cells cause airway hyperreactivity and mucus overproduction in asthma. *Nat Med.* 2002; 8:885-9. PMID: 12091879.
    b. Zhen G, Park SW, Nguyenvu LT, Rodriguez MW, Barbeau R, Paquet AC, **Erle DJ**. IL-13 and epidermal growth factor receptor have critical but distinct roles in epithelial cell mucin production. *Am J Respir Cell Mol Biol.* 2007; 36:244-53. PMID: 16980555; PMCID: PMC1899314.
    c. Woodruff PG, Boushey HA, Dolganov GM, Barker CS, Yang YH, Donnelly S, Ellwanger A, Sidhu SS, Dao-Pick TP, Pantoja C, **Erle DJ**, Yamamoto KR, Fahy JV. Genome-wide profiling identifies epithelial cell genes associated with asthma and with treatment response to corticosteroids. *Proc Natl Acad Sci USA.* 2007; 104:15858-63. PMID: 17898169; PMCID: PMC2000427.
    d. Bonser LR, Zlock L, Finkbeiner W, **Erle DJ**. A heterogenous mucus gel impairs mucociliary transport in asthma. *J Clin Invest* 2016; 126:2367-71. PMID: 27183390; PMC4887179.

    Since founding the UCSF Sandler Asthma Basic Research Functional Genomics Core Facility in 2000, I have made extensive use of genomics approaches in my own work and in collaborative projects with

many other investigators. Many studies listed elsewhere in this biosketch include genomics work performed in my lab. In addition, recent publications from genomics projects performed by members of my group or as collaborations between our core and other investigators include:

a. Van Dyken SJ, Nussbaum JC, Lee J, Molofsky AB, Liang HE, Pollack JL, Gate RE, Haliburton GE, Ye CJ, Marson A, **Erle DJ**, Locksley RM. A tissue checkpoint regulates type 2 immunity. *Nat Immunol*. 2016; 17:1381-1387. PubMed PMID: 27749840. PMCID: PMC5275767.
b. Van Dyken SJ, Liang HE, Naikawadi RP, Woodruff PG, Wolters PJ, **Erle DJ**, Locksley RM. Spontaneous chitin accumulation in airways and age-related fibrotic lung disease. *Cell*. 2017; 169:497-509. PMID: 28431248. PMCID: PMC5444468
c. Ricardo-Gonzalez RR, Van Dyken SJ, Schneider C, Lee J, Nussbaum JC, Liang HE, Vaka D, Eckalbar WL, Molofsky AB, **Erle DJ**, Locksley RM. Tissue signals imprint ILC2 identity with anticipatory function. *Nat Immunol.* 2018; 19:1093-1099. PMID: 30201992; PMCID: PMC6202223.
d. Miller CN, Proekt I, von Moltke J, Wells KL, Rajpurkar AR, Wang H, Rattay K, Khan IS, Metzger TC, Pollack JL, Fries AC, Lwin WW, Wigton EJ, Parent AV, Kyewski B, **Erle DJ**, Hogquist KA, Steinmetz LM, Locksley RM, Anderson MS. Thymic tuft cells promote an IL4-enriched medulla and shape thymocyte development. *Nature* 2018; 559:627-631. PMID: 30022164; PMCID: PMC6062473.

I have a strong interest in understanding basic mechanisms of post-transcriptional gene regulation in health and disease (especially asthma). We have developed novel massively parallel methods for functional annotation of 3' UTRs and used these to identify novel regulatory elements in human 3' UTRs. In asthma, we have identified changes in miRNA expression in airway epithelial cells in asthma and identified one pathway that contributes to these changes.

a. Solberg OD, Ostrin EJ, Love MI, Peng JC, Bhakta NR, Hou L, Nguyen C, Solon M, Nguyen C, Barczak AJ, Zlock LT, Blagev DP, Finkbeiner WE, Ansel KM, Arron JR, **Erle DJ***, Woodruff PG*. Airway epithelial miRNA expression is altered in asthma. Am J Respir Crit Care Med. 2012; 186:965-74. PMID: 22955319; PMCID: PMC3530212. *, equal contributions.
b. Zhao W, Pollack JL, Blagev DP, Zaitlen N, McManus MT, **Erle DJ.** Massively parallel functional annotation of 3' untranslated regions. Nat Biotechnol. 2014; 32:387-91. PMID: 24633241; PMCID: PMC3981918.
c. Zhao W, **Erle DJ.** Widespread effects of chemokine 3' untranslated regions on mRNA degradation and protein production in human cells. J Immunol. 2018; 201:1053-1061. PMID: 29907706; PMCID: PMC6057839.
d. Litterman AJ, Kageyama R, Le Tonqueze O, Zhao W, Gagnon JD, Goodarzi H, **Erle DJ**, Ansel KM. A massively parallel 3' UTR reporter assay reveals relationships between nucleotide content, sequence conservation, and mRNA destabilization. Genome Res. 2019; 29:896-906. PMID: 31152051; PMCID: PMC6581050.

Mucosal epithelial cell biology is another major interest of the lab. There are 19 members of the protein disulfide isomerase (PDI) family of ER-resident proteins in humans but the roles of most of these remain poorly understood. Our discovery that the PDI family member AGR2 is induced in asthma led us to study the roles of AGR2 and its homolog AGR3. We produced *Agr2*$^{-/-}$ mice and used these to show that AGR2 is essential for mucus production in the intestine and is also important for allergen-induced mucus overproduction in a mouse model of asthma. Surprisingly, we found that the close AGR2 homolog AGR3 has a very different role in airway epithelium: it is expressed in ciliated cells rather than mucus cells and helps regulate ciliary beat frequency.

a. Park SW, Zhen G, Verhaeghe C, Nakagami Y, Nguyenvu LT, Barczak AJ, Killeen N, Erle **DJ**. The protein disulfide isomerase AGR2 is essential for production of intestinal mucus. *Proc Natl Acad Sci USA*. 2009; 106:6950-5. PMID: 19359471; PMCID: PMC2678445.
b. Schroeder BW, Verhaeghe C, Park SW, Nguyenvu LT, Huang X, Zhen G, **Erle DJ**. AGR2 is induced in asthma and promotes allergen-induced mucin overproduction. *Am J Respir Cell Mol Biol.* 2012; 47:178-85. PMID: 22403803; PMCID: PMC3423459.
c. Bonser LR, Schroeder BW, Ostrin LA, Schmid N, Olson JL, Salathe M, **Erle DJ**. The ER resident protein AGR3 is required for regulation of ciliary beat frequency in the airway. *Am J Respir Cell Mol Biol.* 2015; 53(4):536-43. PMID: 25751668; PMCID: PMC4742895.
d. Bonser LR, **Erle DJ**. The airway epithelium in asthma. *Adv Immunol*. 2019; 142:1-34. PubMed PMID:31296301.

My early focus was on the identification and functional characterization of members of the integrin family of cell adhesion molecules. We cloned 3 novel integrin subunits, analyzed their expression on various cell types (especially immune cells), and identified ligands for these integrins. Most of my work focused on integrin **β7** and the integrin **α4β7** heterodimer that directs lymphocyte trafficking to the intestine. Subsequent work by other investigators led to the development of the anti-integrin **α4β7** antibody vedolizumab as an FDA-approved treatment for inflammatory bowel disease.

a. **Erle DJ**, Rüegg C, Sheppard D, Pytela R. Complete amino acid sequence of an integrin β subunit (β7) identified in leukocytes. *J Biol Chem.* 1991; 266:11009-16. PMID: 2040616.
b. Rüegg C, Postigo AA, Sikorski EE, Butcher EC, Pytela R, **Erle DJ**. Role of integrin α4β7/α4βP in lymphocyte adherence to fibronectin and VCAM-1 and in homotypic cell clustering. *J Cell Biol*. 1992; 117:179-89. PMID: 1372909; PMCID: PMC2289398.
c. **Erle DJ**, Briskin MJ, Butcher EC, Garcia-Pardo A, Lazarovits AI, Tidswell M. Expression and function of the MAdCAM-1 receptor, integrin **α4β7**, on human leukocytes. *J Immunol*. 1994; 153:517-28. PMID: 7517418.
d. Pachynski RK, Wu SW, Gunn MD, **Erle DJ**. Secondary lymphoid-tissue chemokine (SLC) stimulates integrin α4β7-mediated adhesion of lymphocytes to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) under flow. *J Immunol.* 1998; 161:952-6. PMID: 9670974.

Complete list of publications in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/david.erle.1/bibliography/40554417/public/?sort=date&direction=descending

Research Support

Ongoing Research Support

R35 HL145235 Erle (PI) 04/15/2019-02/28/2026
Airway Epithelial Cell Gene Regulation: New Mechanisms and Therapeutic Strategies
This project will study how genes are regulated in airway epithelial cells and is designed to provide a scientific basis for designing new approaches to prevent, cure, or treat airway diseases.
Role: PI

U19 AI 077439 Erle (PI) 04/01/2018-03/31/2023
Understanding Asthma Endotypes
Our Center is focused on understanding how airway epithelial cells are involved in causing different forms of asthma. Our studies will uncover new knowledge about mechanisms of asthma and help to pave the way for new treatments for this common disease.
Role: PI, project 1 leader

Cystic Fibrosis Foundation Urnov (PI) 02/01/2020-01/31/2023
URNOV19XX0
Advancing delivery of novel genome editing enzymes to correct orphan CF mutations
We are testing novel methods for delivering CRISPR-based gene editing methods to human airway epithelial cells.
Role: UCSF subcontract PI

U19 AI 077439-13S1 Erle (PI) 05/08/2020-03/31/2022
UCSF COVID-19: Extended Immunophenotyping Studies
UCSF immunophenotyping studies in inpatients with COVID-19
Role: PI

U19 AI 077439-13S2 Erle (PI) 05/08/2020-03/31/2022
UCSF COVID-19 Immunophenotyping Clinical Study and Core Laboratories
Supports the UCSF site for the NIAID IMPACC COVID-19 study
Role: PI

T32 HL007185-41 Sheppard/Huang/Erle (MPI) 07/01/2017-06/30/2022
Multidisciplinary Training Program in Lung Disease
The goal is to support postdoctoral training of MDs and PhDs.
Role: PI

Completed Research Support

R21 AI128047 Ansel (PI) 05/10/2018-04/30/2020
Global Analysis of T Cell Post-Transcriptional Regulatory Elements
Make a genome scale map of regulatory elements that cause T cell RNA gene products to be stable or unstable.
Role: Co-I

R01 HL124285-01 Erle (PI). 07/01/2014-06/30/2019 (with NCE)
Massively Parallel Identification of Causative 3′ UTR Variants in Asthma
The goal is to identify 3' UTR variants that alter gene expression and risk of asthma.
Role: PI

BIOGRAPHICAL SKETCH

NAME **John Vincent Fahy, M.D., M.Sc.**	POSITION TITLE Professor
eRA COMMONS USER NAME johnfahy	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University College Dublin	MB BAO BCH	6/1985	Medicine
Trinity College Dublin	Internal Medicine (Residency)	6/1988	Internal Medicine
University College Dublin	Pulmonary Medicine (Medical Registrar)	6/1989	Pulmonary Medicine
University of California, San Francisco	Postdoctoral Fellowship	6/1993	Pulmonary/Critical Care Medicine
University College Dublin	M.D. (doctorate by thesis)	6/1997	Airway Inflammation
Trinity College Dublin	M.Sc.	2003 6/2003 (Sabbatical)	Molecular Medicine

Positions

1989-1993	Fellow, Division of Pulmonary and Critical Care Medicine, Department of Medicine (DOM) and Cardiovascular Research institute (CVRI), UCSF.
1993-1998	Assistant Professor of Medicine, Division of Pulmonary and Critical Care Medicine, DOM and CVRI, UCSF.
1999-2005	Associate Professor of Medicine, Division of Pulmonary and Critical Care Medicine, DOM and CVRI, UCSF.
2002-2003	Visiting Scholar, Trinity College Dublin and University College Dublin (sabbatical year)
2005-present	Professor of Medicine, Division of Pulmonary and Critical Care Medicine, DOM and CVRI, UCSF.

Other Experience and Professional Memberships

1989-	Member, American Thoracic Society
2014-	Member, European Respiratory Society
2009-	Member, Organizing Committee - Transatlantic Airway Conference (TAC).
2012-2014	NIH Workshop: Primary prevention of lung disease - chair of asthma subcommittee.
2014	NIH Strategic Planning Working Group: Member, disease modification subcommittee.

2015 Ad hoc NIH Peer reviewer, Lung Cellular, Molecular Immunobiology Study Section

Honors

1990 Traveling Studentship in Medicine, National University of Ireland.
2009 Michael S. Stulbarg Endowed Chair in Pulmonary Medicine, UCSF.
2015 Scientific Accomplishment Award, American Thoracic Society, Allergy Immunology and Inflammation Assembly.
2016 Election to Association of American Physicians (AAP)
2017 ATS Recognition Awardees for Scientific Accomplishments.
2019 European Respiratory Society (ERS) Gold Medal in Asthma (the ERS presents this award annually to recognize excellence in the field of asthma research)

Contribution to Science

Molecular Phenotypes of Asthma
Background: Asthma is clinically heterogeneous, and previous concepts held that this heterogeneity could be explained by variability in the levels of type 2 (eosinophilic) inflammation in the airway. This concept has now been replaced by the view that asthma is not mechanistically homogenous and that different molecular mechanisms are responsible for disease expression in different subsets of patients. This realization has emphasized the importance of mechanism-oriented research in human subjects, and my lab has been at the forefront of mechanism-oriented studies that are designed to uncover molecular phenotypes of asthma.
Central findings: My initial work as a fellow and junior faculty member involved developing methods to non invasively study airway inflammation using analysis of induced sputum for cells and mediators of asthma (publication A below). I later extended this sputum-based work to cell and molecular analyses of other airway biospecimens, including epithelial brushings, bronchial mucosal biopsies, and bronchial lavage. By applying and optimizing rigorous analytic methods, including OMIC technologies to the analysis of these biospecimens, my lab had made major contributions to current understanding of disease heterogeneity in asthma. These findings have included the identification of Th2-high and Th2-low endotypes of asthma (publications A-D) as well as the recent identification of IL-6 high asthma (publication E).
Impact: The impact of discovery of Th2-high asthma by my lab in collaboration with Prescott Woodruff's lab (UCSF) and Joe Arron's group (Genentech) has been large. Asthma research now routinely segregates patients into Th2-high and low subgroups and clinical trials of Th2 inhibitors are specifically targeting patients with Th2-high asthma using biomarkers like periostin that I helped discover.
My role: I lead a large research group that is involved in mechanism-oriented research in asthma. My role is that of a senior investigator who manages a clinical research lab, generates funding, manages and mentors personnel, interprets data, writes papers, and sets the course for my group. Key grants for this activity include P01HL107202 and U10HL109146.

a. Woodruff PG, Modrek M, Choy DF, Guiquan J. Abbas AR, Ellwanger A, Koth LL, Arron JR, **Fahy JV.** *TH2-driven inflammation defines major sub-phenotypes of asthma. Am J Respir Crit Care Med*. 2009; 180:388-95.
b. Sukhvinder SS, Yuan S, Innes AL, Kerr S, Woodruff PG, Solon M, Hou L, Muller SL, **Fahy JV.** Epithelial cell-derived periostin: roles in TGFβ activation, collagen production and collagen elasticity in asthma. PNAS 2010; 107:14170-5.
c. Gordon ED, Simpson LJ, Rios CL, Ringel L, Lachowicz-Scroggins ME, Peters MC, Wesolowska-Andersen A, Gonzalez JR, MacLeod HJ, Christian LS, Yuan S, Barry L, Woodruff PG, Ansel KM, Nocka K, Seibold MA, **Fahy JV.** '*Proc Natl Acad Sci U S A*. 2016 Aug 2; 113(31): 8765-70.
d. Peters MC, McGrath KW, Hawkins GA, Hastie AT, Levy BD, Israel E, Phillips BR, Mauger DT, Comhair SA, Erzurum SC, Johansson MW, Jarjour NN, Coverstone AM, Castro M, Holguin F, Wenzel SE, Woodruff PG, Bleecker ER, **Fahy JV.** Plasma IL6 levels, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. *Lancet Respiratory Medicine* 2016:4:574-84

(II) Airway Mucas Pathology

Background: Airway mucus is normally a lightly cross-linked gel that is easily transported out of the lung via the mucociliary escalator. This mucus gel becomes more elastic and harder to clear In lung disease, and mucus stasis then causes airflow obstruction and lung infection. Mucus pathology is a feature of all major lung disease especially asthma, COPD, and cystic fibrosis. The study of mucus in lung disease has been a major focus of my lab and my group has optimized multiple methodologies to apply to quantify mucus cells and mucin proteins in the airway and to quantify mucus plugging using image-based scoring.

Central findings: My lab identified intelectin-1 is a prominent protein constituent of mucus plugs in eosinophilic asthma role (publication A) and proposed oxidative stress as a key driver of pathologic airway mucus gels in cystic fibrosis (publication B). I also led studies that uncovered prominent mucus plug phenotypes in severe forms of asthma and COPD that have been unsuspected based on cough and sputum symptoms (publications C and D).

Impact: There are few treatments targeting mucus pathology in lung disease despite the common occurrence of mucus-associated disease. My lab's focus on mechanisms of mucus gel pathology, on mucus phenotypes that can be identified using imaging, and on novel mucolytic treatment approaches are helping to advance precision-based treatment for mucus plugging in asthma and other lung diseases.

My role: I generate funding for studies of mucus pathology in my lab attract personnel to pursue studies of mucus pathology and guide specific research projects designed to reveal mechanism and test mucus-directed therapies. Key grants for this activity include R01HL080414 and P01HL128191.

A. Kerr SC, Carrington SD, Oscarson S, Gallagher ME, Solon M, Yuan S, Ahn JN, Dougherty RH, Finkbeiner WE, Peters MC, **Fahy JV**. *Intelectin-1 is a prominent protein constituent of pathologic mucus associated with eosinophilic airway inflammation in asthma.* Am J Respir Crit Care Med. 2014 Apr 15;189(8):1005-7. PMID: 24735037. PMCID: PMC4098098
B. Yuan S, Hollinger M, Lachowicz-Scroggins ME, Kerr SC, Daniel BM, Ghosh S, Erzurum SC, Willard B, Hazen SL, Huang X, Carrington SD, Oscarson S, **Fahy JV**. *Oxidation Increases Mucin Polymer Cross-links to Stiffen Airway Mucus Gels*. Science Translational Med. Sci Transl Med. 2015;7(276) 276ra27 PMCID: PMC4403633.

C. Dunican EM, Elicker BM, Gierada DS, Nagle SK, Schiebler ML, Newell JD, Raymond WW, Lachowicz-Scroggins ME, Di Maio S, Hoffman EA, Castro M, Fain SB, Jarjour NN, Israel E, Levy BD, Erzurum SC, Wenzel SE, Meyers DA, Bleecker ER, Phillips BR, Mauger DT, Gordon ED, Woodruff PG, Peters MC, **Fahy JV.** *Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction.* J Clin Invest. 2018;128:997-1009. PMCID: PMC582487.

D. Dunican EM, Elicker BM, Henry T, Gierada DS, Schiebler ML, Anderson W, Barjaktarevic I, Barr RG, Bleecker ER, Boucher RC, Bowler RP, Christenson SA, Comellas A, Cooper CB, Couper D, Criner GJ, Dransfield M, Doerschuk CM, Drummond MB, Hansel NN, Han MK, Hastie AT, Hoffman EA, Krishnan JA, Lazarus SC, Martinez FJ, McCulloch CE, O'Neal WK, Ortega VE, Paine R 3rd, Peters S, Schroeder JD, Woodruff PG, **Fahy JV**. *Mucus Plugs and Emphysema in the Pathophysiology of Airflow Obstruction and Hypoxemia in Smokers*. Am J Respir Crit Care Med. 2020 Nov 12. PMID: 33180550

(III) NOVEL DRUGS FOR AIRWAY DISEASE

Background: Airway diseases such as asthma and COPD affect millions of patients and cause a significant public health care burden. Current treatments are suboptimal and new treatments are needed to alleviate the morbidity and mortality associated with these diseases. As new treatment targets are identified and novel inhibitors are developed, it is necessary to carefully conduct early phase proof of concept studies to determine the safety an efficacy of these new treatments. Choosing the right study design and the right study population for these early phase studies is critically important for the proper assessment of drug potential. I have used my expertise in clinical medicine, airway biology, and clinical research to help company's design and test new drugs for airway disease in early phase studies, including drugs directed against neurokinin (NK) receptors, IgE, selectins, and EGFR. Most recently, I have built an academic drug development program to bring a novel mucolytic to the clinic (see P01HL128191 below).
***Central findings*:** Although inhibition of NK-1, selectins, or EGFR did not have beneficial effects in clinical trials (publications A and B below), blocking IgE with a recombinant humanized monoclonal anti-IgE antibody (Omalizumab) proved effective in reducing early and late phase responses to inhaled allergen in patients with asthma (publication C).
***Impact*:** The Phase 1B study I led was pivotal in the drug development of Omalizumab and paved the way for later phase 2 and 3 trials of Omalizumab. This drug (marked as Xolair now has been in clinical use for 10 years, and it has helped many patients with asthma experience better asthma control.
***My role*:** Early in my career I worked closely on trial design, data analysis, and manuscript preparation with Homer Boushey (my mentor), and I was first author on our publications. Later, I have been the senior investigator contributing to trial design, data analysis and manuscript writing, while supervising and mentoring my junior colleagues. A key grant for this activity is P01HL128191.

A. **Fahy JV**, Wong HH, Geppetti P, Reis JM, Harris SC, Nadel, JA, Boushey HA. *Effect of an NK-1 receptor antagonist (CP-99, 994) on hypertonic saline-induced bronchoconstriction and cough in male asthmatic subjects*. Am J Respir Crit Care Med 1995; 152:879-884. PMID: 7663799 DOI: 10.1164/ajrccm.152.3.7663799

B. Woodruff PG, Wolff M, Hohlfeld JM, Krug N, Dransfield MT, Sutherland ER, Criner GJ, Kim V, Prasse A, Nivens MC, Tetzlaff K, Heilker R, **Fahy JV.** *Safety and efficacy of an inhaled epidermal growth factor receptor inhibitor in chronic obstructive pulmonary disease*. Am J Respir Crit Care Med. 2010; 181:438-45. PMID: 20007923 DOI: 10.1164/rccm.200909-1415OC

C. **Fahy JV**, Fleming HE, Wong HH, Liu JT, Su JQ, Reimann J, Fick RB, Boushey HA. *The effect of an anti-IgE monoclonal antibody-E25 on the early and late phase responses to allergen inhalation in asthmatic subjects*. Am J Respir Crit Care Med 1997; 155:1828-1834. PMID: 9196082.

Complete List of Published Work - UCSF Profiles: **http://profiles.ucsf.edu/john.fahy#toc-id8**;
H Index (Google Scholar): 85

Research Support – Active

R01 HL080414 (Fahy, JV) 07/01/05 - 04/30/21 (NCE)
Mechanism of mucus pathology in asthma exacerbations: The major goals of this project are to investigate how stiff mucus gels form in the airway to cause airway obstruction in acute severe asthma. Role: PI

UG1 HL139106 (Fahy, JV) 9/23/2017 - 6/30/2023
Sequential, Multiple Assignment, Randomized Trial in Severe Asthma Protocol (SMART-SA)
This is the UCSF application to the UG1 PrecISE program to conduct precision medicine clinical trials in severe asthma.

P01 HL107202 (Fahy, JV) 08/1/12 - 6/30/24
Exploring the biology of persistent type 2 airway niches in asthma: This PPG is investigating the molecular underpinnings of persistent type 2 inflammation in asthma
Role: Overall PPG PI (Leader of project 3; Core leader - Administrative Core & the Human Subjects Core).

P01 HL128191 (Fahy, JV) 09/01/2016 - 07/31/2021
Carbohydrate-based Therapy for Lung Disease: This tPPG is advancing a program of research to bring a novel mucolytic treatment to the clinic for the treatment of mucus-associated diseases of the lung.
Role: Overall PPG PI (Project leader for project 3 and Core leader for the Administrative Core).

BIOGRAPHICAL SKETCH

NAME **James Solomon Fraser, Ph.D.**	POSITION TITLE Associate Professor of Bioengineering and Therapeutic Sciences
eRA COMMONS USER NAME (credential, e.g., agency login) FRASERJA	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	MM/YY	FIELD OF STUDY
McGill University, Montreal, QC, Canada	B.Sc.	5/2005	Biology
University of California, Berkeley, CA	Ph.D.	12/2010	Molecular and Cell Biology

Positions

2011-2012	QB3 at UCSF Fellow (Principal Investigator) Department of Cellular and Molecular Pharmacology, UCSF California Institute of Quantitative Biosciences (QB3)
2013-Present	Assistant Professor Department of Bioengineering and Therapeutic Sciences, UCSF California Institute of Quantitative Biosciences (QB3)
2016 -	Consulting Professor Department of Photon Science SLAC National Accelerator Laboratory
2016 -	Associate Professor Department of Bioengineering and Therapeutic Sciences, UCSF California Institute of Quantitative Biosciences (QB3)
2019 -	Faculty Scientist Molecular Biophysics and Integrated Bioimaging Division Lawrence Berkeley National Lab

2007-2012	Author of problems and solutions manual for physical biochemistry textbook “The Molecules of Life” (Garland Science, Authors: John Kuriyan, Boyana Konforti, David Wemmer)
2008-2009	Assistant to Professor Howard Schachman for NIH Ethics Training (MCB 293C)
2013-2015	Advanced Light Source Proposal Review (Structural Biology), Panel Member
2015-2018	Linac Coherent Light Source (XFEL) Proposal Review Panel (BIO-C), Chair
2016-	Beamline 8.3.1. at the Advanced Light Source, Head of Participating Research Team
2016-	ASAPbio (Accelerating Science and Publication in biology) Board of Directors, Treasurer
2016-	Relay Therapeutics, Consultant
2017-	Quantitative Biosciences Institute of UCSF, Associate Director
2017-	ALS-ENABLE P30 Resource, Deputy Director
2017-	Collaboration for Structural Simulations and Scattering, Project Director
2018	Protein Society Annual Symposium, Co-Chair

2018-	PHENIX (Python-based Hierarchical ENvironment for Integrated Xtallography), Advisory Board
2019	UCSF Biophysics Graduate Program, Associate Director

Honors and Awards

2001-2005	Canadian Millennium Excellence Undergraduate Scholarship
2004	NSERC Undergraduate Summer Research Award (Mentor: Alan Davidson)
2006-2007	Natural Sciences and Engineering Research Council (Canada) Postgraduate Fellowship
2007-2010	Natural Sciences and Engineering Research Council (Canada) Doctoral Fellowship
2007-2010	National Science Foundation Graduate Research Fellowship
2010	EMBO Short Term Fellowship (Host: Dan Tawfik, Weizmann Institute, Israel)
2010	Warren DeLano Award, Structural Bioinformatics and Computational B
2011	Nicholas Cozzarelli Prize for Best Dissertation in Molecular and Cell Biology (UCB)
2011	Forbes 30 under 30 Science
2014	Searle Scholar, Kinship Foundation
2014	Pew Scholar, Pew Charitable Trusts
2014	Packard Fellow, The David and Lucille Packard Foundation
2017-2018	UCSF/Berkeley Sabbatical Exchange Fellowship (Host: Eva Nogales)
2020	Byers Award in Basic Science (UCSF)
2020	W.H. and W.L. Bragg Prize (IUCr)

Contribution to Science

1. Identifying hidden alternative conformations of proteins in biophysical data. We study proteins as conformational ensembles. Although X-ray crystallography is an ensemble experiment, the results are typically summarized with a single static structure. As a graduate student, and now in my own lab, we have developed software to discover the structural ensembles present in the crystal. The ensemble nature of proteins highlighted by this work feeds into all of our mechanistic studies that interpret the functional effects of mutations, that characterize designed and artificially evolved proteins, or that seek to modulate protein function with small molecules. We are expanding this direction to include modeling and validating protein structural data generated by cryoelectron microscopy, through EMRinger and collaborations with Gabe Lander's lab on ensemble modeling, and through integrative approaches to discover cryptic sites.

    a. Eshun-Wilcon L, Zhang R, Portran D, Toso D, Lohr T, Vendruscolo M, Bonomi M, **Fraser JS**, Nogales E. Effects of α-tubulin acetylation on microtubule structure and stability. *PNAS*. 2019. PMCID: PMC6535015
    b. van Zundert GCP*, Hudson BM*, Oliveira SHP, Keedy DA, Fonseca R, Heliou A, Suresh P, Borrelli K, Day T, **Fraser JS,** van den Bedem H. qFit-ligand reveals widespread conformational heterogeneity of drug-like molecules in X-ray electron density maps. *J Med Chem.* 2018. PMCID: PMC6820680.

c. Keedy DA*, Hill ZB*, Biel JT, Kang E, Rettenmaier TJ, Brandao-Neto J, Pearce NM, von Delft F, Wells JA, Fraser JS. An expanded allosteric network in PTP1B by multitemperature crystallography, fragment screening, and covalent tethering. eLife. 2018. PMCID: PMC6039181.
d. Fischer M, Coleman RG, Fraser JS, Shoichet BK. Incorporation of protein flexibility and conformational energy penalties in docking screens to improve ligand discovery. Nature Chemistry. 2014. PMCID: PMC4144196.

1. **Determining structures that influence microbial-host interactions**. I have a longstanding interest in microbiology, beginning from my undergraduate work with Alan Davidson (Toronto) on bacteriophage structure prediction that led to the surprising discovery of a class of mobile immunoglobulin domains. I have collaborated with the Zusman lab (UC Berkeley) to determine the structure of FrzS, a key signaling regulator of Myxococcus xanthus, with the Fischbach lab (Stanford) to determine how the gut microbiome produces the neurotransmitter tryptamine, and with the Tawfik lab (Weizmann Institute, Israel) to determine the role of epistasis in restricting antibiotic resistance mutations. We are expanding this interest to include the interaction of human enzymes in degrading chitin molecules that can cause inflammation in the context of allergy and asthma (in collaboration with Richard Locksley and structure-based antibiotic design using cryoEM (in collaboration with Ian Seiple and Danica Fujimori).
    a. Li Q*, Pellegrino J*, Lee DJ, Tran AA, Chaires HC, Wang R, Park JE, Ji K, Chow D, Zhang N, Brilot AF, Biel JT, van Zundert G, Borrelli K, Shinabarger D, Wolfe C, Murray B, Jacobson MP, Mühle E, Chesneau O, **Fraser JS**, Seiple IB. Synthetic group A streptogramin antibiotics that overcome Vat resistance. *Nature*. 2020. PMCID: PMC7546582
    b. Stojković V, Myasnikov AG, Young ID, Frost A, **Fraser JS,** Fujimori DG. High-resolution cryo-electron microscopy structure of the Escherichia coli 50S subunit and validation of nucleotide modifications. *Nucleic Acids Research.* 2020. PMCID: PMC7049716.
    c. Dellus-Gur E, Elias M, Caselli E, Prati F, Salverda ML, de Visser JA, **Fraser JS**, Tawfik DS. Negative epistasis and evolvability in TEM-1 β-lactamase - The thin line between an enzyme's conformational freedom and disorder. J Mol Biol. 2015. PMCID: PMC4718737.
    d. Barad BA, Liu L, Diaz RE, Basillo R, Van Dyken SJ, Locksley RM, **Fraser JS**. Dissecting the chitinolytic activity of mammalian chitinases. Protein Science. 2020. PMCID: PMC7096708

2. **Creating multi-temperature X-ray data collection methods to inform mechanistic studies**. We recognized that the standard practice of cryocooling crystals could distort protein conformations. In both larger surveys and isolated mechanistic studies, we have demonstrated the value of room temperature data collection for revealing the structural basis of protein conformational dynamics, leading to new insights into the enzymes PTP1B, CypA, H-Ras, and DHFR, and increasing connections to dynamics studies from NMR and simulations. Additionally, we have identified how temperature can bias small molecule discovery, leading some fragment sites inaccessible at cryogenic temperatures, and the positioning of crucial water molecules in the flu ion channel M2.

a. **Fraser JS**, van den Bedem H, Samelson AJ, Lang PT, Holton JM, Echols N, Alber T. Accessing protein conformational ensembles by room-temperature X-ray crystallography. *PNAS*. 2011. PMCID: PMC3182744.
b. Otten R*, Liu L*, Kenner LR, Clarkson MW, Mavor D, Tawfik DS, Kern D, **Fraser JS.** Rescue of conformational dynamics in enzyme catalysis by directed evolution. *Nature Communications.* 2018. PMCID: PMC5883053.
c. Keedy DA*, Kenner LR*, Warkentin M*, Woldeyes RA*, et al, van den Bedem H, Thorne RE**, Fraser JS**. Mapping the Conformational Landscape of a Dynamic Enzyme by XFEL and Multitemperature Crystallography. *eLife*. 2015. PMCID: PMC4721965.
d. **Fraser JS**, Clarkson MW, Degnan SC, Erion R, Kern D, Alber T. Hidden alternative structures of proline isomerase essential for catalysis. *Nature*. 2009. PMCID: PMC2805857.

3. **Developing new X-ray diffuse and time-resolved scattering experiments to probe correlated motions in proteins**. A major limitation of most biophysical techniques is the inability to directly reveal correlations in motions between distinct regions of macromolecules. Diffuse scattering has the potential to reveal these motions; however, we currently lack the ability to collect, integrate, and refine diffuse scattering data. We are tackling each of these problems directly with collaborators: Michael Wall, Nicholas Sauter, Tom Terwilliger, and Paul Adams. Our long-term goal is to increase the information content of every X-ray diffraction experiment to reveal atomic level coupling at high resolution and improved models of grouped flexibility at low resolution. We are also taking advantage of the new capabilities of next-generation X-ray free electron laser (X-FEL) light sources to perform radiation damage-free imaging of proteins and to watch how protein ensembles respond when perturbed by rapid temperature jumps using the X-FEL.
    a. Dasgupta M, et al, **Fraser JS**, Wall ME, **van den Bedem H**, Wilson MA. Mix-and-inject XFEL crystallography reveals gated conformational dynamics during enzyme catalysis. *PNAS*. 2019. PMCID: PMC6926069
    b. Van Benschoten AH, Liu L, Gonzalez A, Brewster AS, Sauter NK, **Fraser JS**, Wall ME. Measuring and modeling diffuse scattering in protein X-ray crystallography. *PNAS*. 2016. PMCID: PMC4839442.
    c. Thompson MC, Barad BA, Wolff AM, Cho HS, Schotte F, Schwarz DMC, Anfinrud P, **Fraser JS**. Temperature-Jump Solution X-ray Scattering Reveals Distinct Motions in a Dynamic Enzyme. *Nature Chemistry.* 2019. PMCID: PMC6815256.
    d. Thomaston JL, Woldeyes RA, et al, **Fraser JS**, DeGrado WF. XFEL structures of the influenza M2 proton channel: Room temperature water networks and insights into proton conduction. *PNAS*. 2017. PMCID: PMC5754760

4. **Identifying unifying concepts between systems and structural biology**. With Nevan Krogan, we have articulated the similarities in genetic epistasis and thermodynamic measurements and applied these insights to large-scale studies of point mutants and posttranslational modifications. This framework forms the basis for the UCSF graduate course that I direct, PUBS (Physical Underpinnings of Biological Systems), which uses deep sequencing to determine the context dependence of fitness effects of mutations. The class is taught through project-based learning where incoming students perform all library

preparations, load samples directly on the MiSeq, and write all their own code to process sequencing data.

a. Braberg H, et al, **Fraser JS**, Holstege FC, Hieter P, Guthrie C, Kaplan CD, Krogan NJ. From structure to systems: high-resolution, quantitative genetic analysis of RNA polymerase II. *Cell*. 2013. PMCID: PMC3932829
b. **Fraser JS**, Gross JD, Krogan NJ. From systems to structure: bridging networks and mechanism. *Mol Cell*. 2013. PMCID: PMC3558917
c. Mavor D, et al (including ~30 student authors), **Fraser JS**. Determination of Ubiquitin Fitness Landscapes Under Different Chemical Stresses in a Classroom Setting. *eLife*. 2016. PMCID: PMC4862753
d. Gordon DE, et al (more than 80 collaborators), **Fraser JS**, Gross JD, Sali A, Roth BL, Ruggero D, Taunton J, Kortemme T, Beltrao P, Vignuzzi M, García-Sastre A, Shokat KM, Shoichet BK, Krogan NJ. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* 2020. PMCID: PMC7431030

Complete List of 81 Publications in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/james.fraser.1/bibliography/public/

Research Support

Ongoing Research Support

R01 GM123159 Fraser (PI) 12/01/17 – 11/31/21
NIH/NIGMS
Resolving ensemble averaged conformations by multi-temperature x-ray crystallography
The objective of this research program is to experimentally access and computationally model multi-scale heterogeneity in allosteric protein-ligand complexes.

T29IP0554 Fraser (PI) 09/01/19 – 08/31/21
UC Tobacco-Related Disease Research Pgm
Engineered Proteins to Reverse Chitin Buildup and Fibrotic Lung Disease
The goal of this project is to test and characterize hyper-active chitinases, discovered through directed evolution, by biophysical methods including single molecule TIRF microscopy and cryoelectron microscopy.

Technologies, Methodologies & Cores Award Fraser (PI) 0/01/19 – 06/30/21
UCSF Program for Breakthrough Biomedical Research (PBBR)
Leveraging the Macromolecular Structure Group and Beamline Resources for High-throughput Liganding
The goal of this project (with co-investigators Arkin, Gestwicki, and Irwin) is to set up an infrastructure for UCSF investigators to perform high-throughput soaking experiments.

P30 GM0519206 Adams (PI) 07/01/17 – 06/30/22
NIH/NIGMS
ALS Efficiently Networking Advanced Beam Line Experiments (ALS-ENABLE)
Fraser administers the project as Deputy Director of Macromolecular Crystallography and performs outreach. Fraser is the deputy project director, overseeing the crystallography component of the project.

BIOGRAPHICAL SKETCH

NAME **Andrew N. Goldberg**	POSITION TITLE Research Investigator
eRA COMMONS USER NAME (credential, e.g., agency login) ANGOLDBERG	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	MM/YY	FIELD OF STUDY
Boston University, Boston, MA	BA	1982	Mathematics
Boston University, Boston, MA	MD	1985	Medicine
Los Angeles County-Harbor/UCLA Medical Center, Torrance, CA	Intern	1986	General Medicine
University of Pittsburgh, School of Medicine Eye & Ear Hospital, Pittsburgh, PA	Residency	1990	Otolaryngology, Head and Neck Surgery
National Cancer Institute, Center for Epidemiology and Biostatistics, Philadelphia, PA	Fellow	1996	Clinical Epidemiology of Cancer
University of Pennsylvania, Philadelphia, PA	MS	2003	Clinical Epidemiology

Positions

2007-Present	Professor, Neurological Surgery, University of California, San Francisco
2006-Present	Professor, Otolaryngology - Head and Neck Surgery, University of California, San Francisco
2000-2006	Associate Professor, Otolaryngology, Head and Neck Surgery, University of California, San Francisco
1993 – 2000	Assistant Professor, Otolaryngology, Head and Neck Surgery University of Pennsylvania Medical School, Philadelphia, PA
1992 – 1993	Assistant Professor, Otolaryngology, Head and Neck Surgery, Washington University School of Medicine, St. Louis, MO
1990 – 1992	Instructor, Otolaryngology, Head and Neck Surgery, Washington University School of Medicine, St. Louis, MO

Honors

1989	George C. Schein, MD Research Award University of Pittsburgh, School of Medicine
1993	Resident Appreciation Award Washington University of St. Louis, Department of Otolaryngology, Head and Neck Surgery
2002	Distinction in Teaching Award, Honorable Mention UCSF Academic Senate
2002	Roger Boles Resident Teaching Award UCSF Otolaryngology, Head and Neck Surgery

2003 Best Doctors in San Francisco, San Francisco Magazine
2005 Fellow, American Rhinologic Society
2005 Excellence in Direct Teaching Award
UCSF Haile T. Debas Academy of Medical Educators
2005 Honor Award, American Academy of Otolaryngology,
Head and Neck Surgery
2006 Research Award, 3rd prize, American Society of Ophthalmic
Plastic and Reconstructive Surgery
2007 Clinical Research Award, American Rhinological Society
2010 Francis A. Sooy, MD Resident's Award for Clinical Excellence
UCSF, Otolaryngology, Head and Neck Surgery

Contribution to Science

My principle interest in research involves the application of basic science techniques in determining the causes of and treatment for chronic sinusitis. I have been involved in a number of research efforts that characterize the microbial flora in the sinuses. Initially, culture-based techniques were used and subsequently, non-culture-based techniques. We have assembled a multidisciplinary team and hired Dr. Emily Cope to help develop this area of research. We have created a mouse model of sinusitis and have been able to duplicate the clinical and histologic pattern seen in humans in this model. At this point, we have published a manuscript that outlines our technique and a manuscript has also been published that combines our genetic information on the microbiome with animal and clinical data. In this manuscript, we discuss a new etiology for chronic sinusitis that may lead to interventions for treatment. We presently are submitting a manuscript that proposes categories of sinotypes for sinus infection and begins to delineate pathways for chronicity in sinus infection. The research is unique, and we have been recognized as leaders in the field because of our work.

a. Abreu NA, Nagalingam NA, Song Y, Roediger FC, Pletcher SD, **Goldberg AN**, Lynch SV. Sinus microbiome diversity depletion and Corynebacterium tuberculostearicum enrichment mediates rhinosinusitis. Sci Transl Med. 2012 Sep 12; 4(151):151ra124
b. Cope EK, **Goldberg AN,** Pletcher SD, Lynch SV. A chronic rhinosinusitis-derived isolate of Pseudomonas aeruginosa induces acute and pervasive effects on the murine upper airway microbiome and host immune response. *Int Forum Allergy Rhinol*. 2016 Sep 6.
c. Gelber JT, Cope EK, **Goldberg AN,** Pletcher SD. Evaluation of Malassezia and Common Fungal Pathogens in Subtypes of Chronic Rhinosinusitis. *Int Forum Allergy Rhinol*. 2016 Sep; 6(9): 950-5
d. Cope E, **Goldberg AN**, Pletcher SD, Lynch S. Compositionally and Functionally Distinct Sinus Microbiota in Chronic Rhinosinusitis have Immunological and Clinically Divergent Consequences. *Microbiome.* 2017 May 12; 5(1):53.

When at the University of Pennsylvania, I began a course of study to increase my knowledge and skills in clinical research and outcomes by becoming a fellow in the Clinical Epidemiology of Cancer through the Center for Clinical Epidemiology and Biostatistics and the National Cancer Institute. I continued this study with formal classroom study and earned a Master of Science in

Clinical Epidemiology with my thesis being "A Chemosensory Questionnaire for Patients Treated for Cancer of the Head and Neck." This involved over 200 patients who had been treated for cancer of the head and neck investigating the chemosensory changes that occurred as a result of this disease and its treatment. I have used my advanced training in research methods to teach research methods and have used this training to mentor residents and junior faculty in their research. In a significant number of my publications, my role has been in study design, methodology, and analysis for research initiated by other investigators.

a. **Goldberg AN,** Shea JA, Deems DA, Doty RL. A ChemoSensory questionnaire for patients treated for cancer of the head and neck. *Laryngoscope*. 2005 Dec; 115(12): 2077-86.

Research Support

P01 HL107202 (Fahy) Co-Investigator

07/01/2019 03/31/2024

Exploring the biology of persistent type 2 airway niches in asthma $ 1,615,416 total

This project aims to uncover the key tissue-immune checkpoints that lead to persistent airway type 2 inflammation and mucus plug formation in asthma. We will use novel experimental approaches including image guided bronchoscopy and high-dimensional single cell analytics to decode the regulatory networks that sustain severe disease. NIH/NHLBI

R15 (Cope/Caporaso MPI) Co-Investigator

07/01/2019 06/30/2022

Determining the Role of the Upper and Lower Airway Microbiota as Drivers of Concomitant Inflammatory Responses in patients with Chronic Rhinosinusitis and Asthma. $ 300,000 total

This project focuses on characterizing the airway bacterial microbiome and metabolome CRS patients with asthma. Mechanistic in vitro studies of CRS/asthma associated metabolites will uncover specific microbial mechanisms that exacerbate host inflammatory responses in the upper and lower airways. Role: Co-Investigator. NIH/NIAID

R01 AG062562-01 (Geschwind) Co-Investigator

08/01/2019 07/31/2024

Tracking longitudinal change in presymptomatic genetic prion disease (TLC-Pre-gPrD) $ 600,112 total

The overarching goal of this proposal is to track the PreSx phase of gPrD to identify biomarkers for treatment trials. JIT response relates to this grant. NIH/NIA

BIOGRAPHICAL SKETCH

NAME **Erin Duncan Gordon**	POSITION TITLE Assistant Professor
eRA COMMONS USER NAME egordon1	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of California, Berkeley	B.A.	05/01	Molecular & Cell Biology
University of Southern California	M.D.	05/05	Medicine
University of California, San Diego	Board Cert. in Medicine 2009	07/05-06/07	Internal Medicine
University of California, San Francisco	Board Cert. Pulmonary 2010 Critical Care 2011	07/07-06/10	Pulmonary & Critical Care

Positions

07/05-06/07	Resident Physician, Internal Medicine, University of California, San Diego
07/07-12/08	Clinical Fellow, Pulmonary/Critical Care, University of California, San Francisco
01/09-06/11	Research Fellow, Pulmonary/Critical Care, University of California, San Francisco
07/11-06/12	Clinical Instructor, Pulmonary/Critical Care, University of California, San Francisco
07/12-06/17	Assistant Professor, Pulmonary/Critical Care, University of California, San Francisco
07/17-Present	Assistant Professor, Pulmonary/Critical Care, University of California, San Francisco, Sandler Asthma Basic Research Center

Honors

Ruth L. Kirschstein National Research Service Award, 01/11.
American Medical Association Student Achievement Award – first ranked student, Class of 2005 USC SOM (05/05).
American Medical Women's Association Janet M. Glasgow Memorial Award – first ranked female student, Class of 2005 USC SOM (05/05).
Summa cum Laude, Keck School of Medicine, USC (05/2005).

Merck Manual Award – awarded to the four highest ranking students in the basic sciences at USC SOM (05/05).
Alpha Omega Alpha, Gamma Chapter, Keck School of Medicine, USC – elected as a junior (05/04).
Dean's Scholar – awarded to top 10% of students each year of medical school (May 2002, 2003, 2004, 2005).
Recipient of merit-based full tuition scholarship at Keck School of Medicine, USC (05/01-05/05).
Grace Fimognari Memorial Award – awarded to the highest achieving graduate in Molecular & Cell Biology, Biochemistry, University of California, Berkeley (05/01).
Phi Beta Kappa, University of California, Berkeley (05/01).
Graduate with Honors, University of California, Berkeley – awarded for undergraduate research thesis (05/01).

Professional Societies

American Thoracic Society

Board Certification

American Board of Internal Medicine, September 2008
American Board of Internal Medicine, Pulmonary Medicine, September 2010
American Board of Internal Medicine, Critical Care Medicine, September 2011

Contributions to Science

1. IL-33 is a key upstream driver of type 2 inflammation in mouse models of asthma. The biology surrounding its activity as an extracellular cytokine remains unclear however. Full length IL-33 is a nuclear protein produced by the airway epithelial cell, and the mechanism of release is unknown. It has been postulated that release occurs in the context of epithelial cell death; however, cell death is not a prominent feature in most asthmatics including many mild asthmatics that display evidence of airway type 2 inflammation. I have discovered a novel mechanism of IL-33 release from epithelial cells which involves alternative splicing of IL-33 RNA transcripts. Specifically, a deletion of exons 3 and 4 (Δexon 3,4) is the second most abundant IL-33 transcript in the human airway epithelial cell (following the full length transcript). Its protein product is biologically active and localizes to the cell cytoplasm. Upon overexpression, this transcript produces a protein, which is released from the cell in a calcium dependent fashion, distinct from the biology of full length IL-33. Finally, among a cohort of mild-moderate asthmatics, only this Δexon 3,4 transcript variant is positively associated with airway type 2 inflammation, while the full-length IL-33 transcript is not. These findings are described in a manuscript, which was recently published in the *Proceedings of the National Academy of Science*. I am the first author of this publication; I conceived of the experiments, generated the proteins products of the alternatively spliced transcripts, demonstrated their biological activity in vitro, overexpressed them in primary airway epithelial cells and an airway epithelial cell line, and wrote the manuscript.

a. **Gordon ED**, Simpson LJ, Rios CL, Ringel L, Lachowicz-Scroggins ME, Peters MC, Wesolowska-Andersen A, Gonzalez JR, MacLeod HJ, Christian LS, Yuan S, Barry L, Woodruff PG, Ansel KM, Nocka K, Seibold MA, Fahy JV. Alternative splicing of IL-33 and type 2 inflammation in asthma. *PNAS*, 2016; 113(31):8765-70. PMCID: PMC4978244

b. **Gordon ED**, Locksley RM, Fahy JV. Cross-Talk between Epithelial Cells and Type 2 Immune Signaling. The Role of IL-25. *Am J Respir Crit Care Med.* 2016 May 1;193(9):935-6. PMCID: PMC4872659

2. The ST2/*IL1RL1* gene is among the most replicated asthma genetic associations documented to date; however, it remains unclear how genetic polymorphisms in this gene confer disease risk and how they relate to the major disease endotype, type 2 high asthma. The *IL1RL1* gene produces two gene transcripts from two distinct promoters via alternative splicing. One transcript encodes the membrane bound receptor for IL-33 while the other transcript encodes a soluble receptor, which inhibits IL-33 activity. In mouse models, IL-33 induces airway type 2 inflammation. I discovered two distinct genetic signals in the *IL1RL1* gene that are associated with circulating plasma levels of the soluble ST2 protein. However, in circulating blood cells there is no evidence of genetic control of gene expression at these loci. Instead, there is strong genetic control at one locus, rs1420101, of sST2 protein and gene expression in human airway epithelial cells. Moreover, this and another locus rs11685480 both demonstrate strong control over the gene expression of sST2 in distal lung tissue. I further demonstrated that these two independent genetic effects are consistent with the use of different promoters in different cell types. Airway epithelial cells use only the proximal promoter while lung alveolar epithelial cells equally use both the distal and proximal promoters. I have shown that these two SNP blocks demonstrate an additive effect on circulating soluble ST2 levels among asthmatics further suggesting their independent effects. We are currently performing fine mapping using DNA sequencing to narrow down the causative SNP and using Crispr-Cas9 technology to determine the causative SNP in vitro. Finally, I have demonstrated that these two SNPs are associated with the type 2 high asthma endotype. These results are described in a recently published manuscript in *Journal of Clinical Investigation Insight*. I am the first author of this publication, and I conceived of the study, performed all of the airway epithelial cell culture, sST2 ELISA, sST2 gene expression by Taqman PCR, analyzed the data and wrote the manuscript.

a. **Gordon ED**, Palandra J, Wesolowska-Andersen A, Ringel L, Rios CL, Lachowicz-Scroggins ME, Sharp LZ, Everman JL, MacLeod HJ, Lee JW, Mason RJ, Matthay MA, Sheldon RT, Peters MC, Nocka KH, Fahy JV, Seibold MA. *IL1RL1* Asthma Risk Variants Regulate Airway Type 2 Inflammation. *JCI Insight*. 2016;1(14):287871. PMCID: PMC5033813

b. **Gordon ED**, Locksley RM, Fahy JV. Cross-Talk between Epithelial Cells and Type 2 Immune Signaling. The Role of IL-25. *Am J Respir Crit Care Med*. 2016 May 1;193(9):935-6. PMCID: PMC4872659

3. Asthma is a heterogeneous disease, which is variably heritable within families. While genome wide association studies have been successful in discovering common risk alleles for asthma, only a small portion of the heritability is accounted for by these variants. This has been termed “missing heritability,” and many possible explanations have been proposed to

account for it including rare variants, structural variants such as copy number variation, and genetic risk due to interaction effects. Interaction effects encompass both gene-gene interactions as well as gene-environment interactions and are likely to explain a large majority of this genetic risk; however, they are difficult to capture in traditional epidemiological studies. Because asthma is a heterogeneous disease, with the largest subgroup demonstrating evidence of airway type 2 inflammation, we have explored gene-gene interactions within airway epithelial cells by exposing cells to the type 2 cytokine IL-13. We hypothesize that genetic variants in IL-13 responsive genes account for the variable response of the epithelium to IL-13 stimulation. Specifically, individuals may display varying degrees of tissue remodeling, mucus hyperplasia, airway fibrosis, or eosinophilic or mast cell infiltrates depending on the degree to which the epithelium can orchestrate such responses in the presence of IL-13. In order to examine this type of interaction, I have taken a novel approach by culturing airway epithelial cells from over 140 unique donors at air liquid interface and stimulating these cells with IL-13. I have performed RNA sequencing before and after IL-13 stimulation and DNA SNP arrays on these donors. We find over 2000 significant expression quantitative trait loci (eQTL), many of which are revealed only upon stimulation with IL-13. As proof of the validity of our experimental design, we find strong eQTL for at least nine known asthma genome wide association study loci, including HLA-DQB1, GSDMB, ORMDL3, and TSLP. Moreover, for many of these loci including GSDMB, ORMDL3 and TSLP, no one has demonstrated an eQTL in the airway epithelium, which is the primary site of dysfunction in asthma. We are currently preparing this data for publication this fall.

a. **Gordon ED**, Palandra J, Wesolowska-Andersen A, Ringel L, Rios CL, Lachowicz-Scroggins ME, Sharp LZ, Everman JL, MacLeod HJ, Lee JW, Mason RJ, Matthay MA, Sheldon RT, Peters MC, Nocka KH, Fahy JV, Seibold MA. *IL1RL1* Asthma Risk Variants Regulate Airway Type 2 Inflammation. *JCI Insight*. 2016;1(14):287871. PMCID: PMC5033813

b. **Gordon ED**, Simpson LJ, Rios CL, Ringel L, Lachowicz-Scroggins ME, Peters MC, Wesolowska-Andersen A, Gonzalez JR, MacLeod HJ, Christian LS, Yuan S, Barry L, Woodruff PG, Ansel KM, Nocka K, Seibold MA, Fahy JV. Alternative splicing of IL-33 and type 2 inflammation in asthma. *PNAS*, 2016; 113(31):8765-70. PMCID: PMC4978244

c. Sweerus K*, Lachowicz-Scroggins ME*, **Gordon ED**, LaFemina M, Huang X, Parikh M, Fahy JV, Frank JA. Claudin-18 deficiency is associated with airway epithelial barrier dysfunction and asthma. *J Allergy Clin ImmunoI*, 2016 Apr 20. pii: S0091-6749(16)30089-6. PMCID: PMC5073041

d. **Gordon ED,** Sidhu SS, Wang ZE, Woodruff PG, Yuan S, Solon MC, Conway SJ, Huang X, Locksley RM, Fahy JV. A protective role of periostin and TGF-β in IgE-mediated allergy and airway hyperresponsiveness. *Clinical and Experimental Allergy*, 2012. PMCID: PMC3271792

Research Support

Ongoing Research Support

R01AI136962 Gordon (PI) 01/15/2018-12/31/2022
NIH/NIAID
Understanding the Molecular Genetic Mechanisms of Asthma Risk Loci: IL33, IL1RL1, and GSDMB. The goal of this study is to explore novel genetic mechanisms that influence the development of type 2 inflammation, the most common disease pathology, in asthma.

P01HL107202 Fahy (PI). 09/01/19-05/31/24
NIH/NHLBI
Exploring the biology of persistent type 2 airway niches in asthma.
The goal of this program project grant is to uncover the tissue and immune requirements for persistent type 2 inflammation in human asthma including the role of ILC2, tuft cells, mucus plug formation, and epigenetic reprogramming of immune and epithelial cells.
Role: Co-investigator

Recently Completed Research Support

U19 K08HL114645-04 Gordon (PI) 08/04/13-05/31/18
NIH-NHLBI
The function and regulation of IL-33 in the airway epithelium in asthma
The goal of this study is to understand the role of IL-33 and its receptor ST2 in the induction of type 2 inflammation in human asthma.

Nina Ireland Program Gordon (PI) 01/01/17-12/31/18
Gaining Mechanistic Insight into Severe Asthma Through the Study of Extreme Phenotypes: Nasal Polyposis
The goal of this study is to explore the whole transcriptome epithelial response to IL-13 in sinus epithelium of patients with nasal polyposis compared to healthy subjects.

AI077439 Opportunity Fund Gordon (PI) 09/01/16-08/31/17
NIH-NIAID
Role of Notch Signaling in Mucus Metaplasia in Asthma
The goal of this study is to explore the role of notch signaling in mucus metaplasia in type 2 low asthma.

PFIZER Seibold/Fahy/Gordon (Co-PI) 07/01/13-11/30/16
QB3-UCSF Pfizer Collaboration
A Precision Medicine Approach to IL-33 Inhibition in Asthma
The goal of this project is to identify a subgroup of asthma patients with evidence of active IL-33 activity and identify possible genetic, protein, or gene expression biomarkers to identify this population.

BIOGRAPHICAL SKETCH

NAME **Matthew Frederick Krummel, Ph.D**	POSITION TITLE Professor
eRA COMMONS USER NAME Krummel	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of California at Berkeley	Ph.D.	05/1995	Immunology
University of Illinois at Champaign-Urbana	B.S.	05/1989	Biology and Chemistry
University College, London England	Exchange Student	06/1988	Dept of Chemistry

Positions

2018-Present	Co-founder and Inaugural Chair, UCSF ImmunoX Initiative, UCSF
2012-Present	Professor, Department of Pathology, University of California at San Francisco
2006-present	Faculty Director, Biological Imaging Development Center, University of California at San Francisco
2006-2011	Associate Professor, Department of Pathology, University of California at San Francisco
2001-2006	Assistant Professor, Department of Pathology, University of California at San Francisco
1997-2001	Postdoctoral Fellow, HHMI, Beckman Institute, Stanford University. Advisor: Dr. Mark M. Davis
1996-1997	Postdoctoral Fellow, Dendritic Cell Biology, Walter and Eliza Hall Institute, Melbourne Australia. Advisors: Dr. Bill Heath and Dr. Ken Shortman
1995-1996	Postdoctoral Fellow, MCB, UC Berkeley. Advisor: Dr. James P. Allison
1989-1995	Graduate Research Assistant, MCB, UC Berkeley. Advisor: Dr. James Allison
1988-1988	Stagiare (Technician), UGM, UGM, Institut Pasteur. Advisors: Dr. Julian Davies and Dr. Tom Holt
1987-1987	HHMI Summer Fellow, Neurobiology, UTHSC Dallas. Advisor: Dr. Flora Katz

Other Experience and Professional Memberships

2002-present	Ad hoc member of study sections, NIH: CMIA (formerly Aly), TTT
2003-present	Ad hoc reviewer, Wellcome Trust
2004-present	Ad hoc reviewer, US-Israeli Binational Science Foundation

2008-2009	Member: Board of Scientific Counselors, NIAID
2008-present	Referee, European Research Council

Honors

2016	Robert E. Smith Endowed Chair in Experimental Pathology
2013	Pediatrics FLAG Mentorship Award, University of California, San Francisco
2009	Fellow of the American Asthma Foundation
2005	Leukemia and Lymphoma Foundation, Career Award
2004	Cancer Research Institute, Investigator Award
1998	Patent: J.P.Allison, D.R.Leach, and M.F. Krummel. Blockade of T lymphocyte down-regulation associated with CTLA-4 signaling
1997	NRSA Postdoctoral Fellowship, National Institutes of Health
1996	Postdoctoral Fellowship, Juvenile Diabetes Foundation International
1989	Luce scholars competition finalist, Henry Luce Foundation
1986	James scholar, University of Illinois
1985	Illinois State Scholar, National Merit scholar, Westinghouse Science Award

Contribution to Science

1. Direct Imaging of Immune Subversion in Solid Tumors and Identification of Immune Stimulatory Pathways and Antigen-presenting cells. My laboratory has developed mouse models through which to study the T cell-APC dynamics within spontaneous tumors in living animals. This has allowed us to track antigen-presentation pathways and to identify sites and APC subsets involved in immune subversion. Recently, we used this combined with 11-color flow cytometry to isolate a rare antigen-presenting cell that is required for T cell mediated tumor rejection and which is present in most tumors at very low levels.

    a. Broz M, Binnewies M, Boldajipour B, Nelson A, Pollock J, Erle DJ, Barczak A, Rosenblum M, Daud A, Barber DL, Amigorena S, van't Veer LJ, Sperling A, Wolf DM, **Krummel MF**: Dissecting the Tumor Myeloid Compartment Reveals A Rare Antigen Presenting Critical for T cell Immunity. *Cancer Cell*, 2014 26(5):638-52. PMC4254577
    b. Roberts, E.W., Broz, M.L., Binnewies, M., Headley, M.B., Nelson, A.E., Wolf, D.M., Kaisho, T., Bogunovic, D., Bhardwaj, N., and **Krummel, M.F**. 2016. Critical Role for CD103+/CD141+ Dendritic Cells bearing CCR7 for Tumor Antigen Trafficking and Priming of T cell Immunity in Melanoma. *Cancer Cell*. PMC in progress.
    c. Barry KC, Hsu J, Broz ML, Cueto FJ, Binnewies M, Combes AJ, Nelson AE, Loo K, Kumar R, Rosenblum MD, Alvarado MD, Wolf DM, Bogunovic D, Bhardwaj N, Daud AI, Ha PK, Ryan WR, Pollack JL, Samad B, Asthana S, Chan V, **Krummel MF**. A natural killer-dendritic cell axis defines checkpoint therapy-responsive tumor microenvironments. **Nat Med.** 2018 Aug;24(8):1178-1191. doi: 10.1038/s41591-018-0085-8. Epub 2018 Jun 25. PMID: 29942093
    d. Binnewies M, Mujal AM, Pollack JL, Combes AJ, Hardison EA, Barry KC, Tsui J, Ruhland MK, Kersten K, Abushawish MA, Spasic M, Giurintano JP, Chan V, Daud AI, Ha P, Ye CJ, Roberts EW, **Krummel MF**. Unleashing Type-2 Dendritic Cells to Drive Protective Antitumor CD4+ T Cell Immunity. **Cell.** 2019 Apr 18; 177(3):556-571.e16. PMID: 30955881

2. Vital and Intravital Imaging of Immune Responses in the Lung. My laboratory has developed intravital imaging methods for assessment of immune responses directly in

tissues. Using combinations of custom-built multiphoton microscopes and matched stabilization methods, we have been able to understand immune responses directly in fully ventilated lungs. This has permitted us to understand normal neutrophil surveillance and the early stages of lung injury. Additionally, it has permitted a direct study of dendritic cell functions in the lungs. This demonstrated direct antigen uptake, across the epithelium, by alveolar but not airway DC. Further, it allowed us to demonstrate that these DC cluster near the reactive airway and re-stimulate T cells there. We've applied this method to track myeloid cell differentiation in allergy and recently adapted this to track mast cell probing of vessels in the trachea. We've also applied this method to understand nematode interactions with the immune system in the lung.

a. Engelhardt JJ, Boldajipour B, Beemiller P, Pandurangi P, Sorensen C, Werb Z, Egeblad M, **Krummel, MF**. 2012. Marginating Dendritic Cells of the Tumor Microenvironment Cross-Present Tumor Antigens and Stably Engage Tumor-Specific T Cells. Cancer Cell 21, March 20; 402-417. PMC3311997.
b. Thornton EE, Looney MR, Bose O, Sen D, Sheppard D, Locksley R, Huang X, **Krummel, MF**. 2012. Spatiotemporally Separated Antigen Uptake by Alveolar Dendritic Cells and Airway Presentation to T Cells in the Lung. J Exp Med., 209(6):1183-99. PMC3371730
c. Looney MR, Thornton EE, Sen D, Lamm WJ, Glenny RW, **Krummel MF**. 2010. Stabilized imaging of immune surveillance in the mouse lung. Nat Methods. 8(1):91-6. PMC3076005
d. Patnode,M.L., Bando, J.K., Krummel, M.F., Locksley, R.M., Rosen, S.D. Leukotriene B4 Amplifies Eosinophil Accumulation in Response to Nematodes. J. Exp.Med. 2014 Jun 30;211(7):1281-8. PMC4076593
e. Headley MR, Bins A, Nip A, Roberts EW, Looney M, Gerard A, **Krummel MF**. Visualization of Immediate Immune Responses to Pioneer Metastatic Cells in the Lung. Nature. March 24, 2016.

3. Dynamic Imaging of Immune Synapse Assembly in vitro and in vivo. My laboratory and I have defined the dynamics of immune synapse assembly, starting with the relationship of TCR and CD4 clustering and centralization to the onset of calcium signaling. We pioneered imaging of the TCR complex visualized in T cells within T cell-zones of vital lymph nodes by multiphoton microscopy. We defined how TCRs could signal while T cells are still moving across the APC surface. And,we've defined synaptic assembly between neighboring activating T cells, for the sharing of cytokine signals.

a) Cai, E., Marchuk, K., Beemiller, P., Beppler, C., Rubashkin, M.G., Weaver, V.M., Chen,B-C., Betzig,E., Bartumeus, F., **Krummel, M.F**.,Visualizing Dynamic Microvillar Search and Stabilization during Ligand Detection by T cells. *Science* 2017. In press.
b) Friedman, R.S., Beemiller, P., Sorensen, C.M., Jacobelli, J., **Krummel, M.F**. 2010 Nov 1. Real-time analysis of T cell receptors in naive cells in vitro and in vivo reveals flexibility in synapse and signaling dynamics. *J Exp Med*. 11(10): 953-61. PMC2989766.
c) Beemiller, P., Jacobelli, J., **Krummel, M.F**., 2012. Integration of Signaling Microclusters Movement with Cellular Motility in Immunological Synapses. *Nat Immunol.* Jul 1. doi: 10.1038/ni.2364. PMC3902181.

d) Gérard, A., Khan, O., Beemiller, P., Oswald, E., Hu, J., Matloubian, M., **Krummel, M.F**. 2013. Secondary T cell-T cell synaptic interactions drive the differentiation of protective CD8+ T cells. *Nat Immunol*. 2013 14(4): 356-63. PMC3962671

4. Identification of Key Cytoskeletal Regulators of T cell motility and arrest. My laboratory defined the key roles for Myosin IIA in facilitating optimal migration in T cells as well as its phosphorylation as part of the T cell 'stop' signal. We also identified the unconventional septin cytoskeleton as a key player in T cell shape and motility. Most recently, we demonstrated that the unconventional Myosin Myo1c is necessary for random turning and thereby provides optimal surveillance strategy for antigen-detection.

   a) Jacobelli, J. Chmura, S.A., Buxton,D.B., Davis , M.M. and **Krummel, M. F**. 2004. Class II Myosin Heavy Chain 2A/MyH9 Is Involved in the T Cell Stop Signal but is not Required for Synapse Formation. *Nature Immunology.*5 (5): 531-8.
   b) Jacobelli, J., Friedman, R.S., Conti, M.A., Lennon-Dumenil, A. -M., Piel, M., Sorensen, C.M., Adelstein, R.S., **Krummel, M.F**. 2010. Confinement-optimized three-dimensional T cell amoeboid motility is modulated via myosin IIA-regulated adhesions. *Nat Immunol.* 11, 953-961. PMC2943564
   c) Gilden, J.K., Peck, S., Chen, Y.C.M., **Krummel, M.F**. 2012. The septin cytoskeleton facilitates membrane retraction during motility and blebbing. *J Cell Biol.* Jan 9; 196(1): 103-14. PMC3255977
   d) Gérard, A., Patino-Lopez, G., Beemiller, P., Nambiar, R., Ben-Aissa, K., Liu, Y., Totah, F.J., Tyska, M.J., Shaw, S., **Krummel, M.F.** Detection of Rare Antigen-Presenting Cells through T Cell-Intrinsic Meandering Motility, Mediated by Myo1g. *Cell.* 2014 Jul 31; 158(3): 492-505 PMC4119593

5. Identification of CTLA-4 as an Inhibitor of T cell Responses and Modulation to Regulate Immunity In vivo. My work as a graduate student demonstrated that both CD4 and CD8 T cells express a homolog of the costimulatory molecule CD28, CTLA-4, after activation. I generated mouse antibodies to these and demonstrated that engagement of CTLA-4 by antibodies or by its ligand resulted in dampening of T cell responses. I subsequently injected this antibody into mice and demonstrated that this could be used to block this pathway and thus up regulate T cell responses in vivo. This served as a generalized method that we applied across multiple mouse models including augmenting anti-tumor immunity. This work was led to a patent for CTLA-4 blockade in cancer and immunization and has now become 'Checkpoint Blockade' Therapy. The FDA approved anti-CTLA-4, also known as Yervoy or ipilulumab, the first FDA approved immunotherapeutic in cancer, in 2011.

   a) **Krummel, M.F**. and Allison, J.P. 1995. CD28 and CTLA-4 deliver opposing signals, which regulate the response of T cells to stimulation. *Journal of Experimental Medicine.* 182, 459-465.
   b) Allison, J.P. and **Krummel, M.F**. 1995. The yin and yang of T cell costimulation. *Science.* 270,932-933.
   c) Leach, D.R., **Krummel, M.F**. and Allison, J.P. 1996. Enhancement of antitumor immunity by CTLA-4 blockade. *Science.* 271, 1734-1736.
   d) **Krummel, M.F.** and Allison, J.P. 1996. CTLA-4 engagement inhibits IL-2 accumulation and cell cycle progression upon activation of resting T cells. *Journal of Experimental Medicine.* 183, 2533-2540. PMC2192613.

Complete List of PubMed-indexed Published Work:
http://www.ncbi.nlm.nih.gov/pubmed/?term=krummel+mf

Research support

R01 AI52116 Krummel (PI). 01/01/18-12/31/22
NIH, Spatiotemporal Control of T Cell Synapse Stabilization and Signaling
The major goals of this project are to analyze MyoIIA regulation during T cell motility and synapse formation. This includes mutational analyses as well as generation and analyses of knockout animals.
Role: PI

R01 AI052116 Krummel (PI) 05/27/20-12/31/21
NIH/NIAID, COVID19 Admin Supplement to Rapidly Translate Immunobiology for Patient Belief
This project will utilize a deep knowledge of T cell-myeloid biology to identify and rank immunotherapeutics that will be clinically useful to modulate the severity of catastrophic lung damage int he context of SARS-CoV-2.
Role: PI

1R01CA197363 Krummel (PI) 03/15/17-02/28/22
NIH/NCI, Anti-Tumor Mechanisms of Intratumoral Stimulatory Dendritic Cells
The goal of this project is to study the generation and function of rare stimulatory dendritic cell populations in mouse and human tumors, with emphasis on determining the flow of antigens from tumors towards pathways that stimulate T cells.
Role: PI

U01CA217864 Balmain, Krummel, Weiss (PI) 8/17/17-07/31/22
NIH/NCI, Integrating targeted and immunotherapy to treat genetically heterogeneous cancers.
The goal of this project is to perform crispr screens in monocytes and T cells to identify genes associated with tumor entry and function in two distinct tumor types. Will use genetic or pharmacological perturbation of newly generated candidate genes involved in metabolic stress and ros-induced DNA damage to increase mutation load and antigen abundance in a tumor-specific manner, leading to improved responses to IMT. Will also exploit gene expression networks to identify druggable targets and pathways that augment immune responses.
Role: co PI

Consortia of Pharma Companies Krummel (PI) 01/1/2020 - 12/31/2022
UCSF Immunoprofiler. (immunoprofiler.org)
This is funding of consortia of laboratories, initiated by Krummel Lab, for a project designed to profile the immune composition, localization, and gene-expression of hundreds of human tumors from multiple cancer indications. Funds largely drive a UCSF campus-wide clinical project designed to generate a common database of immune profiles.
Role: PI

3U19AI077439-13S1 Erle, Krummel (PI). 05/08/22-03/31/22
NIH-NIAID, UCSF COVID-19 extended immunophenotyping studies
The major goal of this emergency COVID-19 supplement is to apply key and cutting-edge immunophenotyping assays to patient samples derived from the Immunophenotyping

assessment in a COVID-19 Cohort (IMPACC) study to understand the critical features that characterize hospitalized patients with COVID-19, a pandemic disease characterized by immune exacerbations of lung injury.
Role: Co-PI

3U19AI0774309-13S2 Erle, Krummel (PI) 05/07/20-03/31/20
NIH-NIAID, UCSF COVID-19 Immunophenotyping Clinical Study and Core Laboratories
The major goal of this emergency COVID-19 supplement is to develop and particiate IMPACC multi-center longitudinal clincial study of hospitalized patients with COVID-19 and to immunophenotype participants using shared immunological methods that will be designed and carried out by core laboratories at UCSF and at other participating institution.
Role: Co-PI

Completed Research Support

American Asthma Foundation Krummel (PI) 07/01/09-06/30/12
Directing Antigens to Specific APC and T cell Subsets in the Lung
The major goals of this project are to screen for conditions that bias antigens towards particular antigen presenting cell populations and then to read out, through imaging and functional assays, the resulting T cell responses with the aim of optimizing regulatory interaction pathways.
1S10RR029266-01 Krummel (PI) 06/05/11-06/04/13
NIH/NCRR
Multiphoton Instrumentation for Translational Assays from Human Tissue Biopsies
This equipment grant is to purchase a state-of-the art multiphoton microscope specifically configured and situated to accommodate a portfolio of translational imaging approaches and further dedicated to extension of two-photon technology to human biopsy tissues.
Role: PI

1R21CA167601 Krummel (PI) 04/01/12-03/31/14
NIH/NCI
Defining the First Hours of Lung metastasis using Intravital Live-Imaging
This proposal will apply novel intravital imaging of the lung to define the first hours following the arrival of metastatic cells into the mouse lung. As we know very little about why metastatic tumor cells survive in this environment, this represents a major undertaking in determining how to decrease their success.
Role: PI

BIOGRAPHICAL SKETCH

NAME **Richard Michael Locksley, M.D.**	POSITION TITLE Sandler Distinguished Professor, Department of Medicine, University of California, San Francisco
eRA COMMONS USER NAME Locksley	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Harvard College, Cambridge, MA	B.A.	1970	Biochemistry
University of Rochester, Rochester, NY	M.D.	1976	Medicine
University of California, San Francisco, CA		1976-80	Resident, Chief Resident
University of Washington, Seattle, WA		1980-83	Infectious Diseases Fellow

Positions

1986-2003	Chief, Division of Infectious Diseases, UCSF Medical Center, San Francisco, CA
1988-93	Member and Chair (1991-93), Tropical Medicine and Parasitology Study Section, NIH
1991-94	Co-Director, Immunology Section, Biology of Parasitism Course, Woods Hole, MA
1994-99	Chair, Parasitology Pathogenesis Committee, WHO, Geneva
1995-05	Council, Chair (1998), Midwinter Conference of Immunologists, Asilomar
1995-01	Faculty, Association of American Immunology Annual Course, Advanced Immunology
1997-	Investigator, Howard Hughes Medical Institute, UCSF
1998-01	Member, Chair (2000-01), US-Japan Immunology Board, NIH
2002-05	Council, NIAID, National Institutes of Health
2003 -	Director, Strategic Asthma Basic Research Center, UCSF
2016 -	Member, Albert Lasker Basic Medical Research Awards Jury
2017 -	Member, National Advisory Committee, Pew Scholars Program in Biomedical Sciences
Editorial Boards	Immunity, Journal Clinical Investigation, Immunology & Cell Biology, Annual Review Immunology

Honors

American Society for Clinical Investigation, 1991; Burroughs Wellcome Fund Scholar in Molecular Parasitology, 1992-97; Fellow, Infectious Diseases Society of American, 1992; Association of American Physicians, 1994; Bailey K Ashford Medal, American Society Tropical Medicine and Hygiene, 1994; Ellison Medical Foundation Senior Scholar in Global Infectious Diseases, 2001-05; Distinguished Service Award, American Association of Immunologists, 2003; Inspirational Teacher Award, UCSF class of 2006; Sandler Distinguished Professorship, 2003; American Academy of Arts & Sciences, 2005; R37 MERIT Award, NIAID/NIH, 2006; Thomson Reuters 'Top 1% highly cited researchers in immunology', 2014; Inaugural William Paul Award for Cytokine Research, International Cytokine & Interferon Society, 2017; Fellow, American Academy of Microbiology, 2017; National Academy of Sciences, 2017; AAI Distinguished Fellow (inaugural class), 2019; Univ of Rochester School of Medicine, Distinguished Alumnus, 2019.

Contribution to Science

1. My early work contributed to the discovery of T helper subsets, initially using the model of cutaneous leishmaniasis mediated by L. major in susceptible and resistant mice. Th subsets were discovered in studies of mouse T cell clones by Mosmann and Coffman in 1986, and my studies in 1987 were the first to report that infectious outcomes in vivo were mediated by disparate types of Th responses. My laboratory discovered that interventions aimed at discrete cytokines, such as IL-4 and IFN-γ, at early time points following infectious challenges, could profoundly affect disease outcome by altering Th subset differentiation. These studies were extrapolated to multiple infectious and inflammatory diseases, and served to coalesce studies targeting cytokines to alter disease outcomes. I was the PI for these studies.

a. **Locksley RM**, FP Heinzel, MD Sadick, BJ Holaday, KD Gardner. 1987. Murine cutaneous leishmaniasis. Susceptibility correlates with differential expansion of helper T-cell subsets. *Ann Inst Pasteur/Immunol* 138:744-49.
b. Heinzel FP, MD Sadick, BJ Holaday, RL Coffman, **RM Locksley**. 1989. Reciprocal expression of gamma-interferon or interleukin-4 during the resolution or progression of murine leishmaniasis. Evidence for expansion of distinct helper T-cell subsets. *J Exp Med* 169:59-72.
c. Sadick MD, FP Heinzel, BJ Holaday, RT Pu, RS Dawkins, **RM Locksley**. 1990. Cure of murine leishmaniasis with anti-IL-4 monoclonal antibody. Evidence for a T cell-dependent, IFN-g- independent mechanism. *J Exp Med* 171:115-27.
d. Reiner SL, ZE Wang, F Hatam, P Scott, **RM Locksley**. 1993. Th1 and Th2 cell antigen receptors in experimental leishmaniasis. *Science* 259:1457-60.

2. Having established critical roles for cytokines in mediating the business of immunity, my laboratory turned to studies of cytokine expression, reasoning that such study might reveal key pathways by which cytokine expression is turned on, off and regulated. We collaborated with the Rubin laboratory at UC Berkeley to further understanding of CNSs, or conserved noncoding sequences, which could be identified by sequence comparisons among many species, and which are now known to identify major enhancer, promoter and boundary elements that regulate cell-specific gene expression. These studies have been extrapolated to understanding major organizational aspects of gene expression in many cell types. I was

the PI for all of these studies except for the collaboration with the Rubin laboratory, where I coordinated the immunologic aspects of that study to complement the genetics expertise of the Rubin lab.

a. Bix M, **RM Locksley.** 1998. Independent and epigenetic regulation of the interleukin-4 alleles in CD4+ T cells. *Science* 281:1352-54.
b. Loots GG, **RM Locksley,** CM Blankespoor, Z-E Wang, W Miller, EM Rubin, KA Frazer. 2000. Identification of a coordinate regulator of interleukins 4, 13 and 5 by cross-species sequence comparisons. *Science* 288:136-40.
c. Grogan JL, M Mohrs, B Harmon, DA Lacy, JW Sedat, **RM Locksley.** 2001. Early transcriptions and silencing of cytokine genes underlie polarization of T helper cell subsets. *Immunity* 14:205-15.
d. Mohrs M, CM Blankespoor, ZE Wang, GG Loots, V Afzal, H Hadeiba, K Shinkai, EM Rubin, **RM Locksley.** 2001. Deletion of a coordinate regulator of type 2-cytokine expression in mice. *Nat Immunol* 2:842-47.

3. The regulation of cytokine expression was clearly a key determinant of the immune response, but the field lacked tools to study cytokine expression in situ. To this end, we developed reporter mice that faithfully mimicked cytokine expression in vivo while leaving the endogenous cytokines intact through use of viral IRES elements. These reagents have revolutionized the capacity to study the immune system, which previously relied on isolating cells and re-stimulating in vitro. Key discoveries directly attributable to various strains of these mice include the discrete regulation of the duplicated genes, IL-4 and IL-13, in different types of lymphoid cells, including the production of IL-4 by follicular helper T cells; characterization of a tissue checkpoint mediated by epithelial cytokines important in the regulation of allergic immunity; and the identification of innate lymphoid cells that produce these cytokines (see area 4, below). Mouse strains generated in my laboratory are distributed to Jackson Laboratories for use by the scientific community, where they have been utilized in many publications. The strategy we introduced is now widely used in the scientific community. I was PI for all of these contributions.

a. Mohrs M, K Shinkai, K Mohrs, **RM Locksley**. 2001. Analysis of type 2 immunity in vivo with a biscistronic IL-4 reporter. *Immunity* 15:303-11.
b. Reinhardt RL, H-E Liang, **RM Locksley**. 2009. Cytokine-secreting follicular T cells shape the antibody repertoire. *Nat Immunol* 10:385-93. PMCID: PMC2714053
c. Liang H-E, RL Reinhardt, JK Bando, BM Sullivan, I-C Ho, **RM Locksley**. 2011. Divergent expression patterns of IL-4 and IL-13 define unique functions in allergic immunity. *Nat Immunol* 13:58-66. PMCID: PMC3242938
d. Van Dyken SJ, JC Nussbaum, J Lee, AB Molofsky, H-E Liang, JL Pollack, RE Gate, GE Haliburton, CJ Ye, A Marson, DJ Erle, **RM Locksley**. 2016. A tissue checkpoint regulates type 2 immunity. *Nat Immunol* 17:1381-1387. PMCID: PMC5275767

4. The ability to identify cytokine-producing cells in vivo allowed us to identify Group 2 innate lymphoid cells, or ILC2s, as innate lymphocytes that are located in tissues, where they contribute to early cytokine responses. We were one of three laboratories to call attention to the key role for these cells during biologic responses in vivo in 2010, and uncovered roles for these cells in migratory helminth infection and allergic challenge. My laboratory has investigated the development of these cells during embryogenesis, and their tissue-specific transcriptomic signatures using single-cell RNA sequencing. This continues to be a rapidly advancing field with implications for the understanding of tissue homeostasis and allergic

immunopathology, including in human disease. I was the PI for all of the primary studies and took part in the nomenclature meetings chaired by Dr. Spits for the scientific community.

a. Price AE, H-E Liang, BM Sullivan, RL Reinhardt, CJ Eisley, DJ Erle, **RM Locksley**. 2010. Systemically dispersed innate IL-13-expressing cells in type 2 immunity. *Proc Natl Acad Sci USA*. 107:11489-94. PMCID: PMC2895098
b. Nussbaum JC, SJ Van Dyken, J von Moltke, LE Cheng, A Mohapatra, AB Molofsky, EE Thornton, MF Krummel, A Chawla, H-E Liang, **RM Locksley**. 2013. Type 2 innate lymphoid cells control eosinophil homeostasis. *Nature* 502:245-248. PMCID: PMC3795960
c. Ricardo-Gonzalez RR, SJ Van Dyken, C Schneider, J Lee, JC Nussbaum, HE Liang, D Vaka, WL Eckalbar, AB Molofsky, DJ Erle, **RM Locksley**. 2018. Tissue signals imprint ILC2 identity with anticipatory function. *Nature Immunol* 19:1093-9. PMCID: PMC6202223
d. Schneider C, J Lee, S Koga, R Ricardo-Gonzalez, JC Nussbaum, LK Smith, SA Villeda, H-E Liang, RM Locksley. 2019. Tissue-resident group 2 innate lymphoid cells differentiate by layered ontogeny and in situ perinatal priming. Immunity 50:1425-1438. PMCID: PMC6770674

5. The discovery of ILC2s that expressed type 2 cytokines in situ generated questions regarding upstream activation signals and downstream targets of effector output from these cells. These approaches have revealed unsuspected circuits by which ILC2s communicate with epithelial cells in different organs to sustain homeostasis. In lung, ILC2 output elevates chitinase production by a subset of epithelial club cells to enhance degradation of non-soluble chitin fragments from the environment; mice without epithelial chitinase develop spontaneous accumulation of chitin fragments and, over time, lung fibrosis. In small intestine, we discovered that epithelial tuft cells are the source of IL-25, which is released in response to luminal succinate generated by protozoan protist fermentation. IL-25 activates ILC2s to alter crypt stem cell outputs to increase secretory cells, including goblet cells and tuft cells, thus explaining the intestinal remodeling induced by these organisms. I was PI for each of these studies.

a. Reese TA, H-E Liang, AM Tager, AD Luster, N van Rooijen, D Voehringer, **RM Locksley**. 2007. Chitin induces accumulation in tissue of innate immune cells associated with allergy. *Nature* 447:92-96. PMCID: PMC2527589
b. Van Dyken SJ, H-E Liang, RP Naikawadi, PG Woodruff, PJ Wolters, DJ Erle, **RM Locksley**. 2017. Spontaneous chitin accumulation in airways and age-related fibrotic lung disease. *Cell* 169:497-509. PMCID: PMC5444468
c. von Moltke J, M Ji, H-E Liang, **RM Locksley**. 2016. Tuft cell-derived IL-25 regulates an intestinal ILC2- epithelial response circuit. *Nature* 529:221-225. PMCID: PMC4830391
d. Schneider C, CE O'Leary, J von Moltke, HE Liang, Q Yan Ang, PJ Turnbaugh, S Radhakrishnan, M Pellizzon, A Ma, **RM Locksley**. 2018. A metabolite-triggered tuft cell-ILC2 circuit drives small intestinal remodeling. *Cell* 174:271-284. PMCID: PMC6046262

PubMed:
http://www.ncbi.nlm.nih.gov/pubmed (search 'locksley rm')

My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/richard.locksley.1/bibliograpahy/40681139/public/?sort=date&direction=descending

Research Support - Active

Investigator Award (Locksley) 9/1/1997 – 8/31/2025 (budgeted annually)
Howard Hughes Medical Institute
Activation of Immunity
The major goals of this project are to uncover new strategies to optimize host defense and tissue preservation in response to immunopathologic responses to infectious, allergic and inflammatory challenges. HHMI support is critical in generating and maintaining mouse strains necessary for these studies.
Support from HHMI pays Dr. Locksley's salary.

P01 HL107202 (Fahy) 8/15/2012 – 7/31/2024
NIH/NHLBI
Exploring the biology of persistent type 2 airway niches in asthma
ILC2 and epithelial cell heterogeneity and self-sustaining type 2 airway niches in asthma (Project 1)
The major goals of this project are to define the factors that drive remodeled airway niches in asthma and serve to underlie persistence and recurrent attacks that initiate from the same altered foci. My role as PI of subproject 1 is to investigate the role of ILC2s and epithelial tuft cells in these pathways.

R01 AI026918-30 (Locksley) 7/1/1988 – 4/30/2023
NIH/NIAID
Parasite immunity orchestrated by Th2 cells
The major goals of this project are to explore the mechanisms driving the tuft cell – ILC2 circuit in the intestinal tract in response to luminal parasitic infection, with emphasis on metabolic and dietary effects on microbiota.

T29IP0554 (Fraser) 9/1/2019 – 8/31/2021
UC Tobacco-Related Disease Research Program
Engineered Proteins to Reverse Chitin Buildup and Fibrotic Lung Disease
The major goals of this project are to optimize chitinolytic activity of mouse AMCase and use structural and biophysical approaches to assess mechanisms for improved degradation of native chitin substrates.

BIOGRAPHICAL SKETCH

NAME **Ari Benjamin Molofsky, M.D., Ph.D.**	POSITION TITLE Assistant Professor, Department of Laboratory Medicine, University of California, San Francisco
eRA COMMONS USER NAME ARIBMOLOSKY	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of Texas, Austin	B.S.	05/1999	Molecular Biology
University of Michigan, Ann Arbor	M.D./Ph.D.	05/2007	Medicine/ Microbiology Immunology
University of California, San Francisco	Resident/ Chief Resident	2007-2011	Laboratory Medicine
University of California, San Francisco	Clinical Fellow	2009-2010	Hematopathology,
University of California, San Francisco	Postdoctoral Fellow	2011-2015	Immunology

Positions and Employment

1997-1999	Undergrad Research Fellow, Lab of Janice Fischer, PhD, Developmental Genetics, University of Texas
1999-2007	Medical Scientist Training Program (MSTP), director Ron Koenig MD PhD, University of Michigan
2001-2005	Graduate Student, Lab of Michele S. Swanson, PhD, University of Michigan Micro/Immunology
2007-2009	Laboratory Medicine Resident/Chief Resident, Dept. Chair Clifford Lowell MD PhD, UCSF
2009-2010	Clinical Fellow, Hematopathology, program director Joan Etzell, MD, UCSF
2010-2011	Laboratory Medicine Resident, 3rd year, Dept. Chair Clifford Lowell MD PhD, UCSF
2011-2015	Research Fellow (80% time), Lab of Richard M. Locksley, MD, HHMI, UCSF
2011-2013	Clinical Instructor (20% time), Hematology Section, Dept. of Laboratory Medicine, UCSF
2013-2015	Assistant Adjunct Professor (20% time), Hematology Section, Dept. of Lab Medicine, UCSF
2015-	Assistant Professor in Residence, Department of Laboratory Medicine, UCSF
2015-	Affiliate Professor, Diabetes Center, UCSF
2019-	Associate Professor in line, Dept of Laboratory Medicine

Honors/Awards

1995-1999	National Merit Finalist Scholarship, U. of Texas
1997	Fellowship, Howard Hughes Molecular Biology Summer Research, U. of Texas
1998-1999	Undergraduate Research Fellowship Award, U. of Texas
1999	The Dean's Honored Graduate in Molecular Biology, U. of Texas
2002-2004	Predoctoral Fellowship, Genetics Training Grant, U. of Michigan
2004-2005	Frederick G. Novy Fellowship, Microbiology & Immunology, U. of Michigan
2006	Rackham Distinguished Dissertation Award Nominee, U. of Michigan
2006	Ward J. MacNeal Distinguished Dissertation Award, Microbiology/Immunology
2006	Alpha Omega Alpha (AOA) Medical Honors Society, U. of Michigan
2007	MD, *graduate with research distinction*, U. of Michigan
2009-2012	Molecular Medicine Research Fellowship, UCSF
2014	Mentored Clinical Scientist Research Career Development Award (K08)
2016-2019	Larry L. Hillblom Foundation Junior Investigator Award
2017	American Association of Immunology, Travel Award
2017	New Frontiers Research Awardee, UCSF Program for Breakthrough Biomedical Research
2017	Milstein Young Investigator, International Cytokine & Interferon Society
2019	Nina Ireland Progra for Lung Health Award

Professional Societies

2001-2003	MSTP Program Activities Committee, Recruiting Coordinator, U of Michigan
2007-	College of American Pathologists, Member
2008-	American Society of Hematology (ASH), Member
2009-	Board licensed physician and surgeon, Medical Board of California
2011-	American Association of Immunologists (AAI), Member
2012-	International Clinical Cytometry Society, Member
2016-	International Cytokine and Interferon Society, Member

Contribution to Science

1. We aim to understand the control and function of tissue-resident lymphocytes in multiple systems, including models of normal tissue development and (re)modeling, infection, pathology, and aging. Our group's work has focused on the positive and negative regulation of ILC2s and Th2 lymphocytes, critical cells that organize type 2 'allergic' immune responses. Our studies include work defining the regulation and sources of the cytokines IL-33 and IFN□, and the relationship of tissue ILC2s with regulatory T cells (Treg). We have also defined a novel stromal mesenchymal cell niche for type 2 lymphocytes in multiple tissues that is required for their maintenance and activation, and our ongoing work focuses on understanding the cells and signals that control tissue lymphocytic niches.

a. Dahlgren MW, Jones SW, Cautivo KM, Dubinin A, Ortiz-Carpena JF, Farhat S, Yu KS, Lee K, Wang C, Molofsky AV, Tward AD, Krummel MF, Peng T, **Molofsky AB**. Adventitial stromal cells define group 2 innate lymphoid cell tissue niches. *Immunity*, 2019. PMCID: PMC6553479

b. Wu, D., **Molofsky, A. B**., Liang, H.-E., Ricardo-Gonzalez, R. R., Jouihan, H. A., Bando, J. K., Chawla, A., Locksley, R.M. (2011). Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. *Science*, *332*(6026), 243–247. PMCID: PMC3144160
c. **Molofsky, A. B**., Nussbaum, J. C., Liang, H.-E., Van Dyken, S. J., Cheng, L. E., Mohapatra, A., Chawla, A., Locksley R.M. (2013). Innate lymphoid type 2 cells sustain visceral adipose tissue eosinophils and alternatively activated macrophages. *Journal of Experimental Medicine*, *210*(3), 535–549. PMCID: PMC3600903
d. **Molofsky, A.B.**, Van Gool, F., Liang, H.-E., Van Dyken, S.J., Nussbaum, J.C., Lee, J., Bluestone, J.A., and Locksley, R.M. (2015). Interleukin-33 and Interferon-γ Counter-Regulate Group 2 Innate Lymphoid Cell Activation during Immune Perturbation. *Immunity* 43, 1-14. PMCID: PMC4512852

2. We aim to understand how immune cells and cytokines control normal central nervous system (CNS) development and go awry in neuropsychiatric disease. In collaboration with the Anna Molofsky lab, we have uncovered IL-33 as a novel cytokine that regulates microglial function, defining how astrocyte-derived IL-33 promotes microglial activation and neuronal synapse engulfment during CNS development. We have also helped define a hippocampal pathway by which neuronal-derived IL-33 regulates microglial function and extracellular matrix composition, ultimately regulating activity-dependent synapse remodeling. Our ongoing work aims to define how meningeal-resident lymphocytes, including type 2 innate lymphoid cells (ILC2s), impact CNS glia and neural circuit formation during brain development and how meningeal- and brain-resident lymphocytes regulate CNS damage.

a. Vainchtein, I.D., Chin, G., Cho, F.S., Kelley, K.W., Miller, J.G., Chien, E.C., Liddelow, S.A., Nguyen, P.T., Nakao-Inoue, H., Dorman, L.C., Akil, O., Joshita, S., Barres, B.A., Paz, J.T., **Molofsky, A.B**.[#], Molofsky, A.V.[#], 2018. Astrocyte-derived interleukin-33 promotes microglial synapse engulfment and neural circuit development. *Science* 359: 1269-1273, PMCID pending. *# co-corresponding*
b. Nguyen, P.T., Dorman, L.C., Pan, S., Vainchtein, I.D., Han, R.T., Nakao-Inoue, H., Taloma, S.E., Barron, J.J., **Molofsky, A.B**., Kheirbek, M.A., Molofsky, A.V. (2020). Microglial Remodeling of the Extracellular Matrix Promotes Synapse Plasticity. Cell *182*, 1–16.

3. We have engaged in a range of collaborative projects aim to understand the function and diversity of stromal 'niche' cells that regulate resident-lymphocytes in adipose tissue, lung, liver, and brain. We helped characterize the non-redundant roles of the epithelial cytokines IL-33, IL-25, and TSLP in activating lung ILC2s, as well as the contribution of type 2 allergic immunity to adipose tissue metabolic health and disease. We helped define the heterogeneity of tissue ILC2s from multiple organs. Using 3D imaging, we worked to delineate stromal cell heterogeneity and function in lung damage and fibrosis. Together, this collaborative work has advanced our knowledge of the regulation and function of tissue-immune niche interactions.

a. Cassandras, M., Wang, C., Kathiriya, J., Tsukui, T., Matatia, P., Matthay, M., Wolters, P., **Molofsky, AB,** Sheppard, D., Chapman, H., et al. (2019). Gli1+ mesenchymal stromal cells modulate epithelial metaplasia in lung fibrosis. BioRxiv 841957.

b. Reyes de Mochel, N., Cheong, K.N., Cassandras, M., Wang, C., Krasilnikov, M., Matatia, P., **Molofsky, AB**, Campisi, J., and Peng, T. (2020). Sentinel p16-INK4a+ cells in the basement membrane form a reparative niche in the lung. BioRxiv 2020.06.10.142893.
c. Nussbaum JC, Van Dyken SJ, von Moltke J, Cheng LE, Mohapatra A, **Molofsky AB**, Thornton EE, Krummel MF, Chawla A, Liang HE, Locksley RM. (2013) Type 2 innate lymphoid cells control eosinophil homeostasis. *Nature* 502**,** 245–248. PMCID: PMC3795960
d. Ricardo-Gonzalez, R.R., Van Dyken, S.J., Schneider, C., Lee, J., Nussbaum, J.C., Liang, H.-E.E., Vaka, D., Eckalbar, W.L., **Molofsky, A.B.,** Erle, D.J., et al. (2018). Tissue signals imprint ILC2 identity with anticipatory function. *Nat Immunol 19*, 1093–1099. PMCID: PMC6202223

4. *L. pneumophila* is a model intracellular bacterium that alternates between an intracellular replicating phase and a transmissible 'virulent' phase and is causative agent of Legionnaire's disease. My graduate work in the laboratory of Michele S. Swanson focused on the molecular mechanisms regulating *Legionella pneumophila* replication and virulence. I discovered that flagellin, the major protein that comprises the flagellum, is the key cytoplasmic pathogen associated molecular pattern (PAMP) that macrophages recognize to restrict *L. pneumophila* replication. My work on macrophage innate recognition of flagellin was a seminal early work that helped launch the field of inflammasome biology and the study of pyroptotic cell death.

a. **Molofsky, A.B.,** & Swanson, M.S. (2003). Legionella pneumophila CsrA is a pivotal repressor of transmission traits and activator of replication. *Mol Microbiol*, *50*(2), 445–461.
b. **Molofsky, A.B.,** Shetron-Rama, L.M., & Swanson, M.S. (2005). Components of the Legionella pneumophila flagellar regulon contribute to multiple virulence traits, including lysosome avoidance and macrophage death. *Infection and immunity*, *73*(9), 5720–5734. PMCID: PMC1231111
c. **Molofsky, A. B.,** Byrne, B. G., Whitfield, N. N., Madigan, C. A., Fuse, E. T., Tateda, K., & Swanson, M. S. (2006). Cytosolic recognition of flagellin by mouse macrophages restricts Legionella pneumophila infection. *The Journal of experimental medicine*, *203*(4), 1093–1104. PMCID: PMC1584282

5. As a Clinical Pathologist and Hematopathologist, my clinical work focuses on diagnosing benign and neoplastic disorders of blood and immune cells. In the clinical arena, I have a limited but active role in teaching and clinical research, publishing several case reports and reviews. I have a particular interest in the use of flow cytometry in benign and neoplastic hematology.

a. **Molofsky A.B.** and Lu C.M. (2009). Anaplastic Large Cell Lymphoma, Anaplastic Lymphoma Kinase-Positive (ALCL, ALK+). Check Sample, Hematology, American Society of Clinical Pathology.
b. Rollins, M.D., **Molofsky, A.B**., Nambiar, A., Pandey, S., Weiskopf, R.B., & Toy, P. (2012). Two septic transfusion reactions presenting as transfusion-related acute lung injury from a split plateletpheresis unit. *Critical care medicine*, *40*(8), 2488–2491. PMCID: PMC3733455
c. Dawson, A.L., LeBoit, P.E., **Molofsky, A.B**., Ai, W.Z., Pincus, L.B. (2014) Peripheral T-Cell Lymphoma, Not Otherwise Specified Presenting as Erythroderma. *Pathology Case Reviews*, 19(4) 221-226.
d. Li Y, Gupa G, **Molofsky AB**, Xie Y, Shihabi N, McCormick J, Jaffe ES (2018) B

lymphoblastic leukemia/lymphoma with Burkitt-like morphology and Igh/Myc rearrangement. *Am J Surg Pathol,* 42; 269-276.

A full list of my publications is available at: My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/14AY37wr6bCAj/bibliography/43618536/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

R01 NIH/NHLBI (Molofsky, PI) 9/1/2019 – 8/31/2023
Defining group 2 innate lymphoid cell lung niches.
The major goal of this five-year R01 is to define the micro-anatomic niches of mouse lung ILC2, including their development, regulation, and response to infections.

Tobacco Related Disease Research Program (Molofsky, PI) 11/1/2019 – 10/31/2022
Regulation of lung type 2 immunity in tobacco smoke-related allergic asthma
The major goal of this grant is to define the impact of tobacco smoke on lung type 2 immune niches in mouse models of allergic asthma.

R01 NIH/NHLBI (Erlebacher/Molofsky, Co-PI) 9/1/2019 – 8/31/2024
The IL-33/ST2 axis in parturition
The major goal of this five-year R01 is to is to delineate how IL-33 activity in the prepartum mouse uterus stimulates parturition onset.

Completed Research Support

Nina Ireland Program for Lung Health (Molofsky, PI) 1/2019 – 12/2020
Defining lung lymphocyte niches
The major goal of this pilot grant is to develop 3D imaging techniques for normal human lungs and begin to define human lung lymphocyte and stromal cell niches.

Liver Center Pilot Grant (Molofsky, PI) 3/2019-3/2020
Defining liver type 2 lymphocyte niches with 3D imaging
The major goal of this pilot grant is to define the localization and stromal interactions of liver group 2 innate lymphoid cells.

R56HL142701-01 NIH/NHLBI (Molofsky, PI) 9/1/2018 – 8/31/2019
Defining group 2 innate lymphoid cell lung niches.
The major goal of this one-year ‘bridge’ grant is to continue to generate preliminary and supporting data testing our hypothesis that lung ILC2 engage in a cross talk with adventitial stromal cells that regulate their development and function.

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Dean Sheppard	Professor of Medicine
eRA COMMONS USER NAME sheppard	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Harvard College, Cambridge, MA	AB	6/72	
SUNY at Stony Brook, Stony Brook, NY	MD	6/75	Medicine
University of Washington, Seattle, WA	Resident	7/75-6/78	Internal Medicine
University of California, San Francisco, San	Fellow	7/78-6/81	Pulmonary

Positions

2009-Present	Chief, Pulmonary, Critical Care, Allergy and Sleep Division, UCSF
1986-Present	Director, Lung Biology Center, University of California, San Francisco
1999-2004	Acting Director, Sandler Basic Asthma Research Center, UCSF
1981-1987	Assistant Professor of Medicine, University of California, San Francisco
1987-1992	Associate Professor of Medicine, University of California, San Francisco
1992-Present	Professor of Medicine, University of California, San Francisco
1997-2009	Associate Chair for Biomedical Research, Department of Medicine, UCSF

Other Experience

Member, NHLBI Program Project Review Committee, 1998-2002, Chair 2000-2002
Member, Lung Injury and Repair Study Section, 2004-2008, Chair 2006-2008
Scientific Advisory Board, Parker B. Francis Foundation 2006-2009
Editorial Board, Journal of Clinical Investigation 2003-present
Editorial Board, Clinical and Translational Science 2008-present
Associate Editor, American Journal of Respiratory Cell and Molecular Biology 1995-2002
Editorial Board, American Journal of Physiology; Lung Cell and Molecular Biology 1996-2007
Chair, OSMB, NHLBI Lung Tissue Consortium, 2004-present

Honors and Awards

Elected member, American Society for Clinical Investigation, 1992
Elected member, Association of American Physicians, 1995
Clean Air Award, American Lung Association of California, 1995

Parker B. Francis Lecturer, Aspen Lung Conference, 1996
Lifetime Scientific Achievement Award, American Thoracic Society, 1998
Jerome I. Flance Visiting Professor, Washington University, 2000
Roger Mitchell Lecturer, Aspen Lung Conference, 2001
NIH Merit Award, 2004-2014
Robert Johnston Lecturer, Drexel University, 2005
McClement Lecturer, New York University, 2006
Kass Medal, University of Nebraska, 2007
Amberson Lecturer, American Thoracic Society, 2010
McClennan Lecturer, University of Iowa, 2012
Frank Austen Visiting Professor, Brigham and Woman's Hospital, 2013
Listed as one of top 20 translational scientists in the world by Nature Biotechnology, 2013
Harold and Marilyn Menkes Memorial Lectureship, Johns Hopkins University, 2014
UCSF Faculty Lecture, Translational Science, 2016
Elected Member, American Academy of Arts and Sciences, 2017
Christopher Spilios Memorial Lecture, Brigham, and Women's Hospital, 2019
Jerome Brody Memorial Lecture, Dartmouth Medical School, 2020

Contribution to Science

1. Early in my career I focused on the effects of common air pollutants and occupational exposures on airway function in susceptible people, especially people with asthma. My work identified the potent effects of even short-term exposure of patients with mild asthma to low concentrations of the air pollutant sulfur dioxide. This work played an important role in re-evaluating National and California air pollution standards. I also developed a small animal model of occupational asthma induced by toluene diisocyanate and identified the important role of afferent airway C fibers in regulating responses to this important industrial pollutant.

a) **Sheppard D**, Wong SC, Uehara CF, Nadel JA, Boushey HA. Lower threshold and greater bronchomotor responsiveness of asthmatic subjects to sulfur dioxide. *Am Rev Respir Dis* 1980; 122:873-878. PMID: 7458061

b) **Sheppard D,** Saisho A, Nadel JA, Boushey HA. Exercise increases sulfur dioxide-induced bronchoconstriction in asthmatic subjects. *Am Rev Respir Dis* 1981; 123:486-491. PMID: 7235370

c) **Sheppard D**, Thompson JE, Scypinski L, Dusser D, Nadel JA, Borson DB. Toluene diisocyanate increases airway responsiveness to substance P and decreases airway neutral endopeptidase. *J Clin Invest* 1988; 81:1111-1115. PMCID: PMC329638

d) **Sheppard D,** Scypinski L. A tachykinin receptor antagonist inhibits, and an inhibitor of tachykinin metabolism potentiates toluene diisocyanate induced airway hyperresponsiveness. *Am Rev Respir Dis* 1988, 138:547-551. PMID: 2462379

2. When I was appointed to build a center at UCSF focused on applying cell and molecular approaches to the study of lung diseases, I spent a sabbatical year with Robert Pytela, one of the faculty members I recruited to this center. During this sabbatical Robert, David Erle and I developed a method (homology-based PCR) to identify sequences encoding new members of the integrin family, a family of heterodimeric transmembrane receptors know at that time as

receptors for components of the extracellular matrix. I used this method to identify several new integrins subunits expressed on cells obtained from the lungs, screened expression libraries to complete the full length sequences of these subunits and used biochemical approaches to identify heterodimer partners for each and to begin to identify relevant ligands for these new integrins These studies helped to substantially expand the known scope of the integrin family and stimulated my lab and a number of other labs around the world to pursue studies to understand the relevance of each to cell behavior and in vivo biology.

a) **Sheppard D**, Rozzo C, Starr L, Quaranta V, Erle DJ, Pytela R. Complete amino acid sequence of a novel integrin β subunit (β_6) identified from epithelial cells using the polymerase chain reaction. *J Biol Chem* 1990; 265:11502-11507. PMID: 2365683
b) Busk M, Pytela R, **Sheppard D**. Characterization of the integrin αvβ6 as a fibronectin-binding protein. *J Biol Chem* 1992; 267:5790-96. PMID: 1532572
c) Palmer EL, Rüegg C, Ferrando R, Pytela R, **Sheppard D**. Sequence and tissue distribution of the integrin α9 subunit, a novel partner of β1 that is widely distributed in epithelia and muscle. *J Cell Biol* 1993; 123(5):1289-97. PMCID: PMC2119880
d) Yokosaki Y, Palmer EL, Prieto AL, Crossin KL, Bourdon MA, Pytela R, **Sheppard D**. The integrin α9β1 mediates cell attachment to a non-RGD site in the third fibronectin type III repeat of tenascin. *J Biol Chem* 1994; 269:26691-26696. PMID: 7523411

3. To better understand the in vivo relevance of members of the integrin family we had identified, my lab generated integrin subunit knockout mice and used the phenotypes we identified in those mice to identify novel integrin ligands and molecular pathways upstream and downstream of these integrins that contribute to development and disease. Through these studies we identified a completely unexpected role for integrins in activating latent TGFβ and showed that this pathway is important, though distinct effects on different responding cells, in experimental models of pulmonary fibrosis, emphysema, acute lung injury, allergic asthma and in modulating immune responses to tumors. These studies have stimulated substantial interest in potential anti-integrin therapeutics, including one humanized monoclonal antibody generated based on work in my lab that is now in phase 2 clinical trials for potential treatment of idiopathic pulmonary fibrosis and antibodies and small molecule inhibitors we have developed targeting the αvβ8, αϖβ5, αvβ1 and α5β1 integrins that are in various stages of clinical development for treatment of severe asthma, fibrotic diseases, acute lung injury and for tumor immunotherapy

a. Munger JS, Huang XZ, Kawakatsu H, Griffiths MJD, Dalton SL, Wu JF, Pittet JF, Kaminiski N, Garat C, Matthay MA, Rifkin DB, **Sheppard D**. The integrin αvβ6 binds and activates latent TGFβ1: a mechanism for regulating pulmonary inflammation and fibrosis. *Cell* 1999; 96:319-328. PMID: 10025398
b. Morris DG, Huang X, Kaminski N, Wang Y, Shapiro SD, Dolganov G, Glick, A, **Sheppard D**. Loss of integrin αvβ6-mediated TGFβ activation causes Mmp12-dependent emphysema. *Nature* 2003 422:169-173. PMID: 12634787
c. Travis MA, Reizis B, Melton AC Masteller E, Tang Q, Proctor J, Wang Y, Bernstein X, Huang X, Riechardt L, Bluestone J, **Sheppard D.** Loss of integrin αvβ8 on dendritic cells causes autoimmunity and colitis in mice. *Nature* 2007 449:361-365. PMCID: 2670239

d. Sundaram A, Chen C, Khalifeh-Soltani A, Atakilit A, Qiu W, Jo H, DeGrado W, Huang X, **Sheppard D**. Integrin alpha5beta1 as a novel target for airway hyperresponsiveness in asthma *J. Clin Invest* 2017 127:365-374 PMID: 27918306

Having identified an integrin (αvβ6) that played an important role in activating TGFβ only in close proximity to contracting epithelial cells, we sought to determine whether there were other integrins that could also activate this growth factor in other contexts. We found that the αvβ8 integrin is an important activator of TGFβ in the context of antigen presentation by dendritic cells and that this process is essential for the generation of Th17 cells. Using mice, we generated specifically lacking this integrin in dendritic cells we identified important roles for this process in models of multiple sclerosis and allergic asthma. We have subsequently found that there is another αv integrin on activated fibroblasts (αvβ1) that is critical to pathologic fibrosis in the lungs, liver, and kidney. This work has led us to appreciation of the importance of multiple αv-containing integrins as potential therapeutic targets in a variety of immune-mediated and fibrotic diseases. This work also led us to further explore the mechanisms underlying fibrosis by using scRNAseq to identify novel populations of fibroblasts that play important roles in lung homeostasis and pathologic fibrosis.

a. Henderson NC, Arnold TD, Katamura Y, Giacomini MM, Rodriguez JD, McCarty JH, Ruminski PG, Griggs DW, Maher JJ, Iredale JP, Lacy-Hulbert A, Adams RH, **Sheppard D**. Selective αv integrin deletion identifies a core, targetable molecular pathway that regulates fibrosis across solid organs. Nature Medicine 2013 19:1617-1624 NIHMS495176, PMCID:3855865.
b. Reed NI, Jo H, Chen C, Tsujino K, Arnold TD, DeGrado WF, **Sheppard D**. The αvβ1 integrin plays a critical in vivo role in tissue fibrosis. Science Translational Medicine 2015 7:288-294. PMCID: 4461057
c. Arnold T, Lizama CO, Cautivo KM, Lin L, Qui H, Huang E, Lui C, Mukouyama Y, Reichardt L, Zovein AC, **Sheppard D**. Microglial dysmaturation and developmental neuromotor dysfunction result from impaired alphavbeta8-TGFbeta signaling J. Exp Med. 2019 216:900-915 PMCID: 6446869
d. Tsukui T, Sun K-H, Wetter JB, Wilson-Kanamori JR, Hazelwood LA, Henderson NC, Adams TS, Schupp JC, Poli SD, Rosas IO, Kaminski N, Matthay MA, Wolters PJ, **Sheppard D**. Collagen-producing lung cell atlas identifies multiple subsets with distinct localization and relevance to fibrosis Nature Communications, 2020:11:1920. PMCID: 7174390

A full listing of my publications is available at:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/41543684/?sort=date&direction=descending
http://profiles.ucsf.edu/dean.sheppard

Research Support

RO1 HL142568 (Sheppard) 04/01/2020-03/31/2024
NIH/NHLBI
Fibroblast heterogeneity in pulmonary fibrosis

Role: PI
Overall project goal – Functionally characterize the multiple fibroblast subsets we identified from scRNAseq in mouse and human lungs and determine their spatial distribution and fate in models of acute and persistent pulmonary fibrosis

RO1 HL145037 (Sheppard) 01/15/2019-12/31/2022
NIH/NHLBI
Interventional Targeting of the IRE1alpha-TGFbeta signaling loop in pulmonary fibrosis
Role: Co-PI, Contact PI
Overall project goal – Determining the mechanisms of cross talk between the unfolded protein response and
TGFbeta activation and signaling that drives pulmonary fibrosis

Sponsored Research Agreement (Sheppard) 08/15/2014- 02/1/2021
AbbVie
Characterizing molecular diversity of renal and hepatic fibroblasts in the setting of tissue fibrosis
Role: PI
Overall project goal: Discovery of novel biomarkers and therapeutic targets for hepatic fibrosis from single cell RNAseq

T32 HL007185 (Sheppard). 07/01/2012–06/30/2022
NIH/NHLBI
Multidisciplinary training program in lung disease
Role: Program Co-PI
Overall project goal: This is a training grant to train future leaders in basic, clinical and translational pulmonary science. There are 13 annual training slots on this grant.

UCSF Pfizer CTI Program (Sheppard) 12/07/2012-11/30/2020
Pfizer, Inc
Targeting the □v□8 integrin for tumor immunotherapy
Role: PI
Overall project goal: The goal of this proposal is to develop humanized monoclonal antibodies to the αvβ8 integrin for immunotherapy of human tumors. This project with Pfizer is focused on developing clinical candidates and advancing them into the clinic. The first clinical candidate is currently in Phase 1 clinical trials.

BIOGRAPHICAL SKETCH

NAME **Jeoung-Sook Shin, Ph.D.**	POSITION TITLE Associate Professor
eRA COMMONS USER NAME SHINJS	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Duke University, Durham, NC	Ph.D.	5/2002	Pathology
Duke University, Durham, NC	Postdoctoral	8/2003	Pathology
Yale University, New Haven, CT	Postdoctoral	1/2008	Cell Biology

Professional Positions

1996	Research Associate, Cheong-Am Biotech, Seoul, Korea
2008-2014	Assistant Professor, University of California San Francisco, Dept. of Microbiology, Immunology & Sandler Asthma Basic Research Center
2014-present	Associate Professor, University of California San Francisco, Dept. of Microbiology, Immunology & Sandler Asthma Basic Research Center

Professional Memberships

2008-2009	American Thoracic Society, member
2010-Present	American Association of Immunologists, member
2008-Present	Adhoc reviewer for Journal of Cell Biology, Journal of Experimental Medicine, PNAS, European Journal of Immunology, ACS Chemical Biology, The Wellcome Trust Research Training Fellowship Program, and KSEA Young Investigator Award
2017	NIH study section ZRG1 IMM-T90
2017-2019	Treasurer, Association of Korean Immunologists in America
2018	NIH study section ZRG1 F70-U20
2019	NIH study section ZRG1 IMM-T57
2020	NIH study section ZRG1 IMM-T57

Honors and Awards

1999	The Best Research Student Award in the Department of Pathology, 9th Graduate Student Symposium, Duke University
2004	The Jane Coffin Childs Memorial Fund Research Fellowship Award

2009	Sandler Innovative Award in Asthma Research, Sandler Asthma Basic Research Center
2009	Cancer Research Institute Investigator Award
2010	American Heart Association Scientist Development Award
2016	AAI laboratory travel award
2018	AAI Careers in Immunology Fellowship Award

Contribution to Science

1. **Role of MARCH1 in dendritic cell and B cell function**

Although MARCH1 mediates ubiquitination and endocytosis of MHCII and CD86 in antigen presenting cells, its functional role was unclear. We found that this ubiquitin ligase plays an important role in dendritic cell selection of regulatory T cells. The mechanism involved MARCH1-dependent ubiquitination of MHCII, which was required for thymic dendritic cells to preserve functional integrity of the plasma membrane microdomain that facilitates activation of engaged thymocytes. We also found that MARCH1-dependent MHCII ubiquitination is required for germinal center B cells to effectively exchange MHCII-loaded peptide and mature into high-affinity antibody producing cells. I served as the primary investigator, co-investigator, or principle investigator in these studies.

a. Oh. J, Perry, JSA, Pua, H, Irgens-Moller, N, Ishido, S, Hsieh, CS, and **Shin, JS.** MARCH1 protects the lipid raft and tetraspanin web from MHCII proteotoxicity in dendritic cells. *J Cell Biol*, 217:1395-1410, 2018. PubMed PMID: 29371232; PubMed Central PMCID: PMC5881489
b. Oh, J, Wu, N, Barczak, AJ, Barbeau, R, Erle, DJ, and **Shin, JS.** CD40 mediates maturation of thymic dendritic cells driven by self-reactive CD4+ thymocytes and supports development of natural regulatory T cells. *J Immunology*, 200:1399, 2018. PubMed PMID: 29321275; PubMed Central PMCID: PMC5809249
c. Bannard O, McGowan SJ, Ersching J, Ishido S, Victora GD, **Shin JS**, and Cyster JG. Ubiquitin-mediated fluctuations in MHCII class II facilitate efficient germinal center B cell responses. *J Exp Med.* 213:993, 2016. PubMed PMID: 27162138; PubMed Central PMCID: PMC4886361
d. Oh J, Wu N, Baravalle G, Cohn B, Ma J, Lo B, Mellman I, Ishido S, Anderson M, **Shin JS.** MARCH1-mediated MHCII ubiquitination promotes dendritic cell selection of natural regulatory T cells. *J Exp Med*. 2013 Jun 3;210(6):1069-77. PubMed PMID: 23712430; PubMed Central PMCID: PMC3674695.

2. Ubiquitination of MHCII and CD86

It is well known that dendritic cells regulate the surface expression of MHCII during maturation, however its molecular mechanism has been elusive. My colleagues and I found that MHCII is ubiquitinated in dendritic cells, this ubiquitination mediates MHCII endocytosis and lysosomal degradation controlling the surface level of MHCII, and the ubiquitination is down-regulated during maturation of dendritic cells resulting in the accumulation of MHCII at cell surface. More recently, we found that MHCII

ubiquitination plays a significant role for dendritic cells to mediate regulatory T cell development in the thymus. This finding results in a significantly improved understanding of the functional role of MHCII ubiquitination. It also reveals a significant contribution of dendritic cells to regulatory T cell development and the underlying mechanism. I served as the primary investigator, co-investigator, or principle investigator in all these studies.

a. Oh, J and **Shin, JS**. Molecular mechanism and cellular function of MHCII ubiquitination, *Immunological Reviews,* 266:134, 2015. PubMed PMID: 26085212; PubMed Central PMCID: PMC4677682
b. Ma, JK, Platt MY, Eastham-Anderson, J, **Shin, JS*,** and Mellman, I*. MHC class II distribution in dendritic cells and B cells is determined by ubiquitin chain length, *PNAS.* 109:8820, 2012. Pubmed PMID: 22566640; PubMed Central PMCID: PMC3384207 ***Shin, JS** and Mellman, I contributed equally to this work
c. Baravalle, G, Park, H, McSweeney, M, Ohmura-Hoshino, M, Matsuki, Y, **Shin, JS.** Ubiquitination of CD86 is a key mechanism in regulating antigen presentation by dendritic cells, *J Immunology*. 187:2966, 2011. PubMed PMID: 21849678; PubMed Central PMCID: PMC4472313
d. **Shin JS**, Ebersold M, Pypaert M, Delamarre L, Hartley A, Mellman I. Surface expression of MHC class II in dendritic cells is controlled by regulated ubiquitination. *Nature*. 2006 Nov 2;444(7115):115-8. PubMed PMID: 17051151.

3. Endocytosis of FcεRI in dendritic cells

The expression of the high affinity IgE receptor in human dendritic cells has been known for more than two decades, but its functional role is not clearly understood. My colleagues and I found that this receptor mediates cellular entry and degradation of circulating IgE, thus promoting serum IgE clearance. We also found that this pathway of IgE entry results in dendritic cell presentation of IgE-bound antigens to naïve T cells and that this presentation results in development of antigen-specific T cell tolerance. These findings reveal the functional role of the IgE receptor expressed in DCs and also suggest that this receptor could be therapeutically targeted to develop tolerance to disease-causing allergens or auto-antigens. I served as the principle investigator in these studies.

a. **Shin, JS** and Greer, AM. The role of FcεRI expressed in dendritic cells and monocytes, *Cellular and Molecular Life Science*, 72:2349, 2015. PubMed PMID: 25715742; PubMed Central PMCID: PMC4479177
b. Greer AM, Wu N, Putnam AL, Woodruff PG, Wolters P, Kinet JP, **Shin JS**. Serum IgE clearance is facilitated by human FcεRI internalization. *J Clin Invest.* 124(3):1187-98, 2014. PubMed PMID: 24569373; PubMed Central PMCID: PMC3938266.
c. Baravalle G, Greer AM, LaFlam TN, **Shin JS.** Antigen-conjugated human IgE induces antigen-specific T cell tolerance in a humanized mouse model. *J Immunol.* 192(7):3280-8, 2014. PubMed PMID: 24610015; PubMed Central PMCID: PMC4472313
d. Greer, AM, Matthay, MA, Kukreja, J, Bhakta, NR, Nguyen, CP, Wolters, PJ, Woodruff, PG, Fahy, JV, and **Shin, JS**. Accumulation of BDCA1+ dendritic cells in interstitial fibrotic lung

diseases and Th2-high asthma. *PLoS ONE*, Jun 10;9(6): e99084, 2014. PubMed PMID: 24915147; PubMed Central PMCID: PMC4051692

4. Endocytosis mediated by caveolae and lipid raft

Caveolae and lipid raft have been known as the endocytic membrane domain that mammalian cells utilize to take up nutrients from outside. However, whether this domain could be exploited by microbes for host invasion had not been known. My colleagues and I found that the fimbriated uropathogenic *E. coli* exploits this membrane domain to enter mouse mast cells and epithelial cells and reside in a compartment protected from proteolytic degradation. These findings prompted other investigators in the field, resulting in a series of findings that caveolae and lipid raft are utilized by a broad array of microbes including virus and parasite to invade various types of host cells. I served as the primary investigator or co-investigator in this study as shown below.

a. **Shin, JS,** Shelburne, CP, Jin, C, LeFurgey, EA, Abraham, SN. Harboring of particulate allergens within secretory compartments by mast cells following IgE/FceRI-lipid raft mediated phagocytosis, *J Immunol.* 177:5791-5800, 2006. PubMed PMID: 17056503
b. Duncan MJ, Li G, **Shin JS**, Carson JL, Abraham SN. Bacterial penetration of bladder epithelium through lipid rafts. *J Biol Chem*. 279(18):18944-51, 2004. PubMed PMID: 14976212.
c. **Shin JS,** Abraham SN. Cell biology. Caveolae--not just craters in the cellular landscape. *Science*. 293:1447-8, 2001. PubMed PMID: 11520975
d. **Shin JS**, Gao Z, Abraham SN. Involvement of cellular caveolae in bacterial entry into mast cells. *Science*. 289(5480):785-8, 2000. PubMed PMID: 10926542.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/1zW5inwS0Ljkk/bibliography/46542569/public/?sort=date&direction=ascending

Research Support

Ongoing Research Support

R35GM131702, National Institute of Health. 06/01/2019 - 03/31/2024
Shin, Jeoung-Sook (PI)
Mechanism and function of membrane trafficking in dendritic cells
The goal of this project is to define the molecular mechanism underlying MARCH1 ubiquitin ligase activity and identify new substrates of MARCH1.

Completed Research Support During Last Three Years

R01GM105800, National Institute of Health. 09/05/2013 - 05/31/2019
Shin, Jeoung-Sook (PI)
Role of MARCH1 E3 ubiquitin ligase in thymic dendritic cell function
The major goal of this project is to identify the specific molecular mechanisms by which dendritic cells mediate clonal deletion and regulatory T cell differentiation in the thymus.

W81XWH1810110, Department of Defense. 06/01/2018 – 11/30/2019
Shin, Jeoung-Sook (PI)

Assessing the candidacy of MARCH1 as a therapeutic target for treatment of asthma
The goals of this project are to determine the role of MARCH1 in the effectuation phase of allergic asthma and identify the specific motif of mouse CD83 transmembrane domain that binds to MARCH1.

NIH/NCATS UL1TR001872-A127552, National Institute of Health. 02/01/2017 – 05/31/2018
Shin, Jeoung-Sook (PI)
Development of a small molecule inhibitor of MARCH1 for treatment of asthma
The goal of this project is to develop tool compounds to be used for the validation of the hypothesis that asthma is improved by inhibiting MARCH1.

BIOGRAPHICAL SKETCH

NAME **Aparna Bala Sundaram**	POSITION TITLE Assistant Professor of Medicine Division of Pulmonary & Critical Care Medicine Department of Medicine
eRA COMMONS USER NAME ASUNDARAM	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	MM/YY	FIELD OF STUDY
Northwestern University, Evanston IL	BS	06/03	Biomedical Engineering, Honors Program in Medical Education
Northwestern University, Chicago IL	MD	06/06	Medicine
Northwestern University, Chicago IL	n/a	06/09	Internal Medicine
University of California, San Francisco CA	n/a	06/12	Pulmonary & Critical Care Medicine

Positions and Employment

2006-2007 Intern, Internal Medicine, Northwestern University
2007-2009 Resident, Internal Medicine, Northwestern University
2009-2012 Fellow, Pulmonary and Critical Care Medicine, UCSF
2012-2014 Clinical Instructor, Division of Pulmonary and Critical Care Medicine, UCSF
2014-present Assistant Professor of Medicine, Division of Pulmonary and Critical Care Medicine, UCSF
2020-present Associate Program Director, Molecular Medicine Pathway, Internal Medicine Residency, UCSF

Other Experience

2016-present Scientific Reviewer, Resource Allocation Program Technology Committee UCSF
2016-present Member, Chancellor's Committee on the Status of Women, UCSF

Honors

1999-2006 Honors Program in Medical Education, Northwestern University
2006-2009 Resident Teaching Award, Northwestern University
2009-present American Board of Internal Medicine for Internal Medicine Certification
2011-present American Board of Internal Medicine for Pulmonary Diseases Certification
2012-present American Board of Internal Medicine for Critical Care Medicine Certification
2013 Respiratory Disease Young Investigators' Forum Finalist, ARC

2014 Respiratory Structure and Function Abstract Scholarship, American Thoracic Society
2014-2015 Early Stage Investigator Award, NIH/NIAID AADCRC

Professional Societies

2007-present Member of American Thoracic Society, Respiratory Cell & Molecular Biology Assembly Member

Contributions to Science

I began my research training studying the effect of integrin β_6 subunit knockout mice on experimental models of allergic asthma. Integrin β_6 plays an important role in activating latent TGFβ, and mice lacking integrin β_6 are protected from airway hyperresponsiveness. I determined that this protective effect is due in part to TGFβ mediated alteration in expression of mouse mast cell proteases 1 and 4, which have opposing effects on airway contraction. The closest human orthologue of mouse mast cell protease 4 is mast cell chymase, which I found also has a protective effect on airway contraction.

> Sugimoto K, Kudo M, **Sundaram AB**, Ren X, Huang K, Bernstein X, Wang Y, Raymond WW, Erle DJ, Abrink M, Caughey GH, Huang X, Sheppard D. The αvβ6 integrin modulates airway hyperresponsiveness in mice by regulating intraepithelial mast cells. *J Clin Invest.* 2012 Feb 1. (PMC 3366785)

Having gained mastery over a variety of techniques to dissect smooth muscle physiology and interrogate associated signaling pathways, I began to work on identifying novel pathways that contribute to airway narrowing using mouse models of asthma. I determined that the scaffold protein IQGAP1 regulates airway contraction by facilitating the interaction of RhoA and its regulator proteins. I also used the expertise I have developed in *in vitro, ex vivo, and in vivo* smooth muscle analysis to collaborate with a diverse group of researchers within UCSF to study novel regulators of airway smooth muscle physiology.

> Katsumoto TR, Kudo M, Chen C, **Sundaram A**, Callahan EC, Zhu JW, Lin J, Rosen CE, Manz BN, Lee JW, Matthay MA, Huang X, Sheppard D, Weiss A. The phosphatase CD148 promotes airway hyperresponsiveness through SRC family kinases. *J Clin Invest.* 2013 Apr 1. (PMC3635736)

> **Sundaram A***, Bhattacharya M*, Kudo M, Farmer J, Ganesan P, Khalifeh-Soltani A, Arjomandi M, Atabai K, Huang X, Sheppard D. IQGAP1-dependent scaffold suppresses RhoA and inhibits airway smooth muscle contraction. *J Clin Invest.* 2014 Oct 1. (PMC 4347230) (*shared first author)

> Bulek K, Chen X, Parron V, **Sundaram A**, Herjan T, Ouyang S, Liu C, Majors A, Zepp J, Gao J, Dongre A, Bodaszewska-Lubas M, Echard A, Aronica M, Carman J, Garantziotis S, Sheppard D, Li X. IL-17A recruits Rab35 to IL-17R to mediate

PKCα-dependent stress fiber formation and airway smooth muscle contractility. J Immunol. 2019 Mar. (PMC6379809)

Lazar AM, Irannejad R, Baldwin TA, **Sundaram AB**, Gutkind JS, Inoue A, Dessauer CW, Von Zastrow M. G protein-regulated endocytic trafficking of adenylyl cyclase type 9. Elife. 2020 Jun. (PMC7332294)

For the last several years, the main focus of my laboratory has been on the role of transmembrane proteins in transmitting force generated by smooth muscle. I discovered that human mast cell chymase exerts its protective effect on airway contraction primarily by modulating smooth muscle adhesion to fibronectin, and that these effects are reproducible by directly blocking integrin α5β1. My laboratory has extended these findings to other integrins interacting with other ligands. The current proposal explores the mechanism by which inter-cellular tethering proteins such as cadherin-11 are capable of transmitting force. These avenues of investigation have also allowed for fruitful collaborations with investigators in the Department of Pharmaceutical Chemistry to design novel small molecule inhibitors of proteins we identify.

Sundaram A, Chen C, Khalifeh-Soltani A, Atakilit A, Ren X, Qiu W, Jo H, DeGrado W, Huang X, Sheppard D. Targeting integrin $\alpha_5\beta_1$ ameliorates severe airway hyperresponsiveness in experimental asthma. J Clin Invest. 2017 Jan. (PMC5199700)

Sundaram A, Chen C, Isik Reed N, Liu S, Ki Yeon S, McIntosh J, Tang YZ, Yang H, Adler M, Beresis R, Seiple IB, Sheppard D, DeGrado WF, Jo H. Dual antagonists of α5β1/ αvβ1 integrin for airway hyperresponsiveness. Bioorg Med Chem Lett. 2020 Sep. PMID: 33007395.

A full list of my publications can be found at:
https://www.ncbi.nlm.nih.gov/myncbi/1pkI5O8fJQW5K/bibliography/public/

Research Support

InVent Fund (co-PI)
2020 – 2022
UCSF
Profile the specificity, ADME and PK of lead compound inhibitors of integrin α5β1 and conduct the ex vivo and in vivo testing in mouse models of asthma. I am responsible for the supervision of the in vitro, ex vivo, and in vivo biological assays.

Recently Completed

T32 HL 007185 2009 – 2012
NIH/NHLBI
Training grant provided to the University of California, San Francisco during the fellowship training period in the Division of Pulmonary and Critical Care Medicine.

F32 HL112588 (PI)

2012 – 2014

NIH/NHLBI

Regulation of Allergic Asthma by TGF-β-induced Modulation of mMCP-1 and mMCP-4

Determine whether mMCP-1 and mMCP-4 modulate airway hyperreactivity 1) through effects on the adjacent epithelium or through direct effects on smooth muscle cells and 2) whether their effect is upstream or downstream of changes in intracellular calcium concentration.

5U19 AI070412 ESI (PI)

2014 – 2015

NIH/NIAID

Role of Human Chymase in Smooth Muscle Contraction

Early-stage investigator award to study the convergence of pathways between chymase and integrin ligation in smooth muscle modulation of airway contraction and allergen challenge.

Resource Allocation Program (RAP) Shared Instrument Award (PI). 2016 – 2017

UCSF

Grant to supplement purchase of new muscle bath system to serve as a core for measurement of contractility with capacity for higher throughput screening.

Nina Ireland Program for Lung Health, Innovative Grant Program (PI) 2017 – 2019

UCSF

Investigating mechanisms of smooth muscle tension transmission via cell-matrix and cell-cell connections.

UCSF Resource Allocation Program (RAP) Catalyst Award (co-PI) 2018 – 2020

UCSF/ShangPharma

Design and screening of more potent and specific small molecule inhibitors of integrin α2β1.

UC-CAI (co-I) 2018 – 2020

UCSF/NIH-NHLBI

Synthesis and screening of potent inhibitors of integrin α5β1 for inhaled or oral delivery using novel scaffolds and structure-based-synthesis approach.

K08 HL124049 (PI) 2015 – 2020

NIH/NHLBI

Role of Human Chymase in Smooth Muscle Contraction in Asthma

Explore the effect of chymase on organization of the extracellular matrix and integrins, the interplay between cytokines and integrins, and the effect of integrin ligation on airway contraction and allergen challenge. I am responsible for the execution and analysis of all of the proposed studies.

BIOGRAPHICAL SKETCH

NAME **Zhi-En Wang, M.D., M.S.**	POSITION TITLE Research Specialist
eRA COMMONS USER NAME	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Xian Medical University, Xian, China	M.D.	12/82	Medicine
Xian Medical University, Xian, China	M.S.	12/85	Immunology

Positions and Honors

1986-1987	Research and Teaching Associate, Department of Microbiology and Immunology, Xian University, Xian, China
1987-1989	Assistant Researcher and Lecturer, Xian University, Xian China
1989-1990	Cheng Scholar and Visiting Scientist, University of California, San Francisco, CA
1990-1991	Research Fellow, Temple University School of Medicine, Philadelphia, PA
1991-1994	Research Fellow, University of California, San Francisco Department of Medicine
1994-1997	Senior Research Associate, Cell Genesys Inc., Foster City, CA
1997 to Present	Research Specialist II, Howard Hughes Medical Institute (HHMI) San Francisco, CA

Selected Peer-reviewed Publications

1. Sadick, M.D., Holaday, B.J., Heinzel, F.P., **Wang, Z**. and Locksley, R.M.: Leishmania major-specific CD4+ T cells transferred protective immunity to severe-combine immunodeficient (scid) mice." *The Journal of FASEB*, 1990 4(7):1953.
2. Holaday, B.J., Saidck, M.D. Henizel, F.P., **Wang, Z**. and Locksley, R.M.: Establishment of Th1 and Th2-like cell lines from mice infected with Leishmania major. *The Journal of FASEB*, 1990 4(7): 3046.
3. Holaday, B.J., Saidck, M.D. Henizel, F.P., **Wang, Z**. and Locksley, R.M.: Reconstitution of Leishmania major scid mice using Th1 and Th2 cell lines. *Journal of Immunology*, 1991 147(5): 1653.

4. Locksley, R.M., Reiner, S.J., Sadick, M.D., **Wang, Z**., Heinzel, H.P. and Holaday, B.J.: Evidence for restricted V-D-Jß T cell receptor usage in the Th2 response to Leishmania major. 1991 *FASEB J*. 5:A1369.
5. Reiner SL, S Zheng, **Z Wang**, L Stowring, RM Locksley. 1994. Leishmania promastigotes evade IL-12 induction by macrophages and stimulate a broad range of cytokines from CD4 cells during initiation of infection. *J Exp Med* 179:447-56.
6. Loh, E., Wang, M., **Wang, Z**., Hyjek, E., and Kozbor, D.: Expression functional g/d□T cell receptor recognize tetanus toxin. *J of Cellular Biochemistry*. 1992 165(D): 67.
7. Kozbor, D., Hyjek, E., Wiaderkiewicz, R., **Wang, Z**., Wang, M. and Loh, E.: Competitor mRNA fragments for quantitation of cytokine specific transcripts in cell lysates. *Molecular Immunology*, 1993. 30(1): 1.
8. Reiner SL**, Z Wang**, F Hatam, P Scott, RM Locksley. 1993. Th1 and Th2 cell antigen receptors in experimental leishmaniasis. *Science* 259:1457-60.
9. **Wang Z,** SL Reiner, F Hatam, FP Heinzel, J Bouvier, CW Turck, RM Locksley. 1993. Targeted activation of CD8 cells and infection of □2-microglobulin-deficient mice fail to confirm a primary protective role for CD8 cells in experimental leishmaniasis . *J Immunol* 151:2077-86.
10. Reiner SL, S Zheng, **Z Wang**, L Stowring, RM Locksley. 1994. Leishmania promastigotes evade IL-12 induction by macrophages and stimulate a broad range of cytokines from CD4 cells during initiation of infection. *J Exp Med* 179:447-56.
11. Mougneau E, F Altare, AE Wakil, S Zheng, T Coppola, **ZE Wang**, R Waldmann, RM Locksley, N Glaichenhaus, N. 1995. Expression cloning of a protective *Leishmania* antigen. *Science* 268:563-6.
12. Wakil AE, **ZE Wang**, RM Locksley. 1996. Leishmania major: targeting IL-4 in successful immunomodulation of murine infection. *Exp Parasitol* 84:214-22.
13. Pingel S, **ZE Wang**, RM Locksley. 1998. Distribution of protein kinase C isoforms after infection of macrophages with Leishmania major. *Infect Immun* 66:1795-9.
14. Wakil AE, **ZE Wang**, JC Ryan, DJ Fowell, RM Locksley. 1998. Interferon gamma derived from CD4 (+) T cells is sufficient to mediate helper cell type 1 development. *J Exp Med* 188:1651-6.
15. Bix, M, **ZE Wang**, B Thiel, NJ Schork, RM Locksley. 1998. Genetic regulation of commitment to interleukin 4 production by a CD4 (+) T cell-intrinsic mechanism. *J Exp Med* 188:2289-99.
16. Symula DJ, KA Frazer, Y Ueda, P Denefle, ME Stevens, **ZE Wang**, RM Locksley, EM Rubin. 1999. Functional screening of asthma QTL in YAC transgenic mice. *Nat Genet* 23:241-4.
17. Cretu G, RM Locksley, **ZE Wang**, EM Rubin, KA Frazer. 2000. Functional analysis of CNS-1 in YAC transgenic mice. *Science* 288:136-9.
18. Lacy DA, **ZE Wang**, DJ Symola, C McArthur, EM Rubin, KA Frazer, RM Locksley. 2000. Faithful expression of the human 5q31 cytokine cluster in transgenic mice. *J Immunol* 164:4569-75.

19. Loots GG, RM Locksley, CM Blankespoor, **ZE Wang**, W Miller, [EM] Rubin, KA Frazer. 2000. Identification of a coordinate regulator of interleukins 4, 13, and 5 by cross-species sequence comparisons. *Science* 288:136-140.
20. Mohrs M, CM Blankespoor, **Z Wang**, GG Loots, V Afzal, H Hadeiba, K Shinkai, EM Rubin, RM Locksley. 2001. Deletion of a coordinate regulator of type 2 cytokine expression in mice. *Nat Immunol* 2, 842-7.
21. Grogan JL, **ZE Wang**, S Stanley, B Harmon, GG Loots, EM Rubin, RM Locksley. 2003. Basal chromatin modification at the IL-4 gene in helper T cells. *J Immunol* 171:6672-9.
22. Xu M, **ZE Wang**, RM Locksley. 2004. Innate immune responses in peptidoglycan recognition protein L-deficient mice. *Mol Cell Biol* 24:7949-57.
23. Reinhardt RL, S Hong, SJ Kang**, ZE Wang**, RM Locksley. 2006. Visualization of IL-12/23p40 in vivo reveals immunostimulatory dendritic cell migrants that promote Th1 differentiation. *J Immunol* 177:1618-27.
24. Cheng LE**, ZE Wang**, RM Locksley. 2010. Murine B cells regulate serum IgE levels in a CD23-dependent manner. *J Immunol* 185:5040-7.
25. Yang Z, **ZE Wang**, PT Doulias, W Wei, H Ischiropoulos, RM Locksley, L Liu. 2010. Lymphocyte development requires S-nitrosoglutathione reductase. *J Immunol* 185:6664-9.
26. Gordon E, S Sidhu, **Z-E Wang**, P Woodruff, S Yuan, M Solonm S Conway, X Huang, RM Locksley, J Fahy. 2012. A protective role for periostin and TGF-β in IgE-mediated allergy and airway hyperresponsiveness. *Clin Exp Allergy* 42: 144-155. PMC3271792

BIOGRAPHICAL SKETCH

NAME **Arthur Weiss, M.D., Ph.D.**	POSITION TITLE Professor of Medicine and of Microbiology and Immunology
eRA COMMONS USER NAME weissa	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
John Hopkins University, Baltimore	B.A.	05/1973	Biology
University of Chicago	Ph.D.	05/1978	Immunology
University of Chicago	M.D.	05/1979	Medicine

Positions and Employment

1979-1980	Postdoctoral Fellow, Swiss Institute for Experimental Cancer Research, Lausanne, Switzerland
1980-1982	Resident, Department of Medicine, University of California, San Francisco (UCSF)
1982-1984	Fellow in Rheumatology/Clinical Immunology, UCSF
1982-1985	Associate, Howard Hughes Medical Institute, UCSF
1984-1985	Instructor, Department of Medicine, Division of Rheumatology/Clinical Immunology, UCSF
1985-1989	Assistant Investigator, Howard Hughes Medical Institute, UCSF
1985-1989	Assistant Professor of Medicine, Microbiology and Immunology, UCSF
1987-	Chief, Division of Rheumatology/Clinical Immunology, Department of Medicine, University of California, San Francisco
1989-1993	Associate Professor or Medicine, Microbiology and Immunology, UCSF
1989-1994	Associate Investigator, Howard Hughes Medical Institute, UCSF
1991-	Ephraim P. Engleman Distinguished Professor of Rheumatology, UCSF
1992-	Professor of Medicine, Microbiology and Immunology, UCSF
1993-	Investigator, Howard Hughes Medical Institute, UCSF
1998-2005	Associate Director, The Rosalind Russell Medical Research Center for Arthritis, UCSF
2002-2006	Director, Medical Scientist Training Program (MSTP), UCSF
2007-2010	Co-Director, Institute for Molecular Medicine, UCSF

Other Experience and Professional Memberships

1986-1991	Councilor, American Federation for Clinical Research
1991	President, Western Region of the American College of Rheumatology
1998-2002	Member, Allergy and Immunology Study Section (NIH)
1999-2011	Chair, Scientific Advisory Board, American Asthma Foundation
2000-2002	Chair, Allergy and Immunology Study Section (NIH)
2003-2010	Council, American Association of Immunologists

2008-2009	President, American Association of Immunologists
2005-2012	Advisory Council, RIKEN Research Center for Allergy & Immunology Yokohama, Japan
2012-present.	Co-founder and Consultant of Nurix Therapeutics
2013-2016	Chair, Section 43 (Immunology and Inflammation), National Academy of Sciences

Honors

1990	Young Investigator Award, Western Society for Clinical Investigation
1990	Henry Kunkel Young Investigator Award, American College of Rheumatology
1993	Junior Investigator Award, American Association of Immunologists
1997	Lee C. Howley Prize, Arthritis Foundation
1998	Forty-First Faculty Research Lecturer, University of California, San Francisco
2001	American Association of Immunologist-Huang Foundation Meritorious Career Award
2003	Fellow, American Academy of Arts and Sciences
2004	Member, National Academy of Sciences
2004	Fellow, American Academy of Microbiology
2004	Member, Institute of Medicine
2004	Distinguished Investigator Award, American College of Rheumatology
2004	Walter Bauer Visiting Professor in Rheumatology, Massachusetts General Hospital
2004	Bridget Ogilvie Lecture, University of Dundee, Scotland
2004	Sue Kim Hansen Lecture, Boston University School of Medicine
2005	Dan H. Campbell Memorial Lecture, Midwinter Conference of Immunologists, Asilomar, CA
2005	Visiting Professor, Harvard Medical School Rheumatology Division
2005	Beirne B. Carter Lecture in Immunology, University of Virginia
2005	Dan H. Campbell Memorial Lecture, Midwinter Conference of Immunologists, Asilomar, CA
2006	Keynote Speaker, American Association of Immunologists, Advanced Immunology Course
2009	Ishizaka Lecture, La Jolla Institute for Allergy and Immunology
2009	46th Charles A. Stuart Memorial Lecture, Brown University
2010	Dorothy Baugh Harmon Endowed Lectureship, Oklahoma Medical Research Foundation
2012	Lifetime Achievement Award, American Association of Immunologists
2012	UCSF Lifetime Achievement in Mentoring Award
2014	Nathan Zwaifler Lecturer, UCSD
2016	Frank and Shirley Fitch Lecture, University of Chicago
2016	Merit Award, NIAID, NIH
2016	Ephraim P. Engleman Memorial Lecture, American College of Rheumatology
2017	Associate Member, European Molecular Biology Organization
2018	Howard and Martha Holley Research Prize in Rheumatology
2019	AAI Distinguished Fellow, American Association of Immunologists
2019	William B. Coley Award for Distinguished Research in Basic Immunology, Cancer Research Inst.
2019	Establishment of the Arthur Weiss Lectureship in Rheumatology and Immunology, UCSF

Contribution to Science

1. The Oligomeric TCR Complex. The T cell antigen receptor (TCR) was identified by others during my postdoctoral studies. As a postdoctoral fellow and junior faculty member I focused on the oligomeric complexity of the TCR. Taking advantage of the Jurkat T cell leukemic line as an experimental model, I used somatic cell genetics to show, in collaborative studies with Tak Mak's group, that the TCR αβ heterodimer had a requisite association with the CD3 complex for cell surface expression. My group first showed the transmembrane domains as the basis for the interaction of the αβ heterodimer with CD3. This led us to show that the zeta chain cytoplasmic domain, when transferred to another heterologous receptor (CD8), could confer upon that receptor the signaling capability of the TCR. The latter experiment was the inspiration for chimeric antigen receptors that are currently used in cell-based tumor immunotherapy.

a. **Weiss A**, Stobo J. Requirement for the coexpression of T3 and the T cell antigen receptor on a malignant human T cell. *J. Exp. Med*. 1984 160:1284-1299.
b. Ohashi P, Mak T, Van den Elsen P, Yanagi Y, Yasunobu Y, Calman A, Terhorst C, Stobo J, **Weiss A**. Reconstitution of an active surface T3/T-cell antigen receptor by DNA transfer. *Nature* 1985 316:606-609.
c. Tan L, Turner J, **Weiss A**. Regions of the T cell antigen receptor α and β chains that are responsible for interactions with CD3. *J. Exp. Med.* 1991 173:1247-1256.
d. Irving BA. **Weiss A**. The cytoplasmic domain of the T cell receptor ζ chain is sufficient to couple to receptor-associated signal transduction pathways. *Cell* 1991. 64:891-901.

2. The Two Signals Required for T cell Activation. In the early 1980's little was known about the signaling events that were required for T cells to become activated. Using the Jurkat leukemic T cell line, while a postdoc in the Stobo lab, I showed that two signals were required for IL-2 transcription. One signal was provided by the TCR and the other by a second signal which could be mimicked by phorbol esters, which at that time were known to activate PKC. Using a calcium sensitive dye, John Imboden and I showed that stimulation of the TCR/CD3 complex in Jurkat could induce calcium increases and calcium ionophores and phorbol esters could mimic the two signals required for IL-2 transcription. This led us to search for physiologic stimuli that could provide the second signal required for IL-2 production. We found that mAbs against Tp44, later named CD28, as a molecule that could provide the second signal for Jurkat or for normal human T cell activation. We identified a region in the IL-2 upstream regulatory region that was responsive to CD28 signals, distinguishing it from typical NFAT sites that were responsive to TCR signals. This CD28 response element proved to be a composite binding site for c-Rel and AP-1.

a. **Weiss A**, Wiskocil R, Stobo JD. The role of T3 surface molecules in the activation of human T cells: A two-stimulus requirement for IL-2 production reflects events occurring at a pre-translational level. *J. Immunol*. 1984 133:123-128.
b. **Weiss A**, Imboden J, Shoback D, Stobo J. Role of T3 surface molecules in human T cell activation: T3 dependent activation results in a rise in cytoplasmic free calcium. *Proc. Natl. Acad. Sci. USA* 1984 81:4169-4173.
c. **Weiss A**, Manger B, Imboden J. Synergy between the T3/antigen receptor complex and Tp44 in the activation of human T cells. *J. Immunol.* 1986 137:819-825.
d. Fraser JD, Irving BA, Crabtree GR, **Weiss A**. Regulation of interleukin-2 gene enhancer activity by the T cell accessory molecule CD28. *Science* 1991 251:313-316.

3. The Tyrosine Kinases that Initiate TCR Signaling. The mechanism by which the TCR signaled to increase calcium was unknown. Some speculated that G-proteins were involved and some that tyrosine phosphorylation was involved. We took a somatic cell genetic approach and isolated TCR signaling mutants from the Jurkat T cell leukemic line. The first of these, J. CaM1 proved to be deficient in the Src family kinase Lck. At the same time, we attempted to understand how the TCR zeta chain mediated a signal via a conserved motif ultimately called the immunoreceptor tyrosine-based activation motif (ITAM). We found that stimulated zeta interacted with a 70 kDa tyrosine phosphoprotein, which we purified and cloned as ZAP-70. The importance of ZAP-70 has been substantiated by the severe combined

immunodeficiency that results from inactivating mutations. This led us to develop a model for TCR signaling whereby Lck and ZAP-70 interacted with ITAMs in a sequential and ordered manner. This model has withstood more than 20 years of subsequent investigation.

a. Straus DB, **Weiss A**. Genetic evidence for the involvement of the lck tyrosine kinase in signal transduction through the T cell antigen receptor. *Cell* 1992 70:585-593.
b. Chan AC, Iwashima M, Turck CW, **Weiss A**. ZAP-70: A 70kD protein tyrosine kinase that associates with the TCR zeta chain. *Cell* 1992 71:649-662.
c. Chan AC, Kadlecek T, Elder ME, Filipovich AH, Kuo W-L, Iwashima M, Parslow TG, **Weiss A**. ZAP-70 deficiency in an autosomal recessive form of severe combined immunodeficiency. *Science* 1994 264:1599-1601.
d. Iwashima M, Irving BA, van Oers NSC, Chan AC, **Weiss A**. Sequential interactions of the TCR with two distinct cytoplasmic tyrosine kinases. *Science* 1994. 263:1136-1139.

4. TCR Signaling Mechanisms. The consequences of TCR signaling by the proximal kinases demanded the identification of key substrates and the pathways they activated. We were among the first to show that TCR stimulation led to phosphorylation of phospholipase C gamma1 (PLCγ1), providing a mechanism for TCR-induced calcium increases and PKC activation. Subsequently, using two of our somatic cell Jurkat mutants, we demonstrated that the adaptors LAT and SLP-76, substrates of ZAP-70 were critically important for TCR signaling leading to PLCγ1 activation and most other downstream pathways, i.e., calcium increases, PKC activation, and Ras/MAPK pathways. The critical importance of ZAP-70 in activating these pathways and most T cell responses was further validated using a chemical genetic approach towards small molecule inhibition of a catalytic mutant of ZAP-70.

a. **Weiss A**, Koretzky G, Kadlecek, T. Stimulation of the T cell antigen receptor induces tyrosine phosphorylation of phospholipase Cγ1. *Proc. Natl. Acad. Sci. USA* 1991 88:5484-5488.
b. Yablonski D, Kuhne MR, Kadlecek. T, **Weiss A**. Uncoupling of non-receptor tyrosine kinases from PLC-γ1 in a SLP-76-deficient T cell. *Science* 1998 281:413-416.
c. Finco TS, Kadlecek T, Zhang W, Samelson LE, **Weiss A**. LAT is required for TCR-mediated activation of PLCγ1 and the Ras pathway. *Immunity* 1998 9:617-626.
d. Au-Yeung BB, Levin SE, Zhang C, Hsu L-Y, Cheng D, Killeen N, Shokat KM, **Weiss A**. A genetically selective ZAP-70 kinase inhibitor reveals requirements for catalytic function in Treg cells. *Nature Immunol*. 2010 11:1085-1093. PMCID: PMC3711183

5. The Regulation of Src Family Kinases. Src family kinases (SFKs), such as Lck and Fyn in TCR signaling, are the most proximal kinase required for signaling by ITAM-coupled receptors in the hematopoietic lineage. Their proper regulation is also critical. We established the positive regulatory function of CD45 in TCR proximal signaling events by isolating CD45 deficient T cell lines from Jurkat and HPB-ALL. We showed their signaling defects were the result of CD45's ability to dephosphorylate the negative regulatory tyrosine phosphorylation sites in Lck and Fyn. We have subsequently used an allelic series of mice, expressing different levels of CD45, to show that CD45 quantitatively regulates the phosphorylation status of the negative regulatory sites of SFKs in T cells, controls the magnitude of TCR signaling abilities, and influences T cell development. Similar findings were made with this allelic series in B cells. However, we found that in B cells and in macrophages another transmembrane phosphatase, CD148, plays a partially redundant role with CD45 to control the negative regulatory site of SFKs. In a recent series of studies, we have established that the Csk cytoplasmic tyrosine kinase that phosphorylates the negative regulatory tyrosine phosphorylation site in SFKs is the principle negative regulator of signaling in the basal state by TCRs, BCRs and macrophage FcRs. Our studies suggest that the opposing actions of Csk and CD45 control basal signaling in T cells, B cells and macrophages as well as establishing a threshold for antigen receptor signaling.

a. Koretzky GA, Picus, J, Thomas ML, **Weiss, A**.: Tyrosine phosphatase CD45 is essential for coupling of the T cell antigen receptor to the phosphatidylinositol second messenger pathway. *Nature* 1990 346:66-68.

b. Zikherman J, Jenne C, Watson S, Doan K, Raschke W, Goodnow CC, **Weiss A**. CD45-Csk phosphatase-kinase titration uncouples basal and inducible T cell receptor signaling during thymic development. *Immunity*. 2010 32:342-54. PMCID: PMC2865198.
c. Zhu JW, Brdicka T, Katsumoto TR, Lin J, **Weiss A**. Structurally distinct phosphatases CD45 and CD148 both regulate B cell and macrophage immunoreceptor signaling. *Immunity*. 2008 28:183-96. PMCID: PMC2265106.
d. Tan Y-X, Manz BN, Freedman TS, Zhang C, Shokat KM, **Weiss A**. Inhibition of the kinase Csk in thymocytes reveals a requirement for actin remodeling in the initiation of full TCR signaling. *Nature Immunol*. 2014 15:186-94 PMC3946925.

Complete List of Published Work in My Bibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/arthur.weiss.1/collections/48006977/public/

Research Support

Ongoing Research Support

Howard Hughes Medical Institute, Weiss (PI) 07/01/85-08/31/22
Cell surface molecules and molecular events involved in human T cell activation.
The goal is to study cell surface molecules and molecular events involved in T cell activation. HHMI personnel (1 student, 1 postdoc and 4 technicians) focus on structure of the TCR and the ZAP-70 protein tyrosine kinase.
Role: Principal Investigator

2P01AI091580-06
NIH/NIAID (Program Leader A. Weiss) 07/01/2016-06/30/2021
Defining the Unique Properties of the Distinct Signaling Machinery Used by the TCR
The goals of this project are to understand the unique properties that define the tyrosine phosphorylation signaling and Ras pathways immediately downstream of the TCR.
Role: Principal Investigator (Project #1)

1R37AI114575
NIH/NIAID Weiss (PI) 12/08/15-11/30/2020
The cell and molecular mechanisms underlying CD28 costimulation
The goals of this project are to understand the molecular signaling machinery that mediates CD28 costimulation in T cells.
Role: Principal Investigator

1R01AI13841-01A1 07/01/18-06/30/23
NIH/NIAID (Sub-PI, A. Weiss)
Novel Roles for the DNA Damage Response Kinase CHK1 in TCR/ITAM Signaling
The goals of this project are to understand how CHK1 inhibitors influence proximal TCR signaling mechanism, with an emphasis on the activities of the proximal kinases, Lck and Zap70.

2017195 10/01/18-09/30/19
United States – Israel (Co-PI, A. Weiss)
Binational Science Foundation
Molecular Gating of T Cell Responsiveness by the Gads Adaptor Protein
The goal of this project is to understand how dimerization of the Gads adaptor protein may regulate LAT-dependent TCR signaling.

BIOGRAPHICAL SKETCH

NAME **Jonathan S. Weissman, Ph.D.**	POSITION TITLE Professor, University of California San Francisco Investigator, Howard Hughes Medical Institute
eRA COMMONS USER NAME WEISSMAN	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Harvard University	A.B.	06/1988	Physics
Massachusetts Institute of Technology	Ph.D.	05/1993	Physics

Positions and Honors

1993 - 1996	Postdoctoral Fellow, Yale University, Structural and Biochemical Studies of GroEL
1996 - 2000	Assistant Professor, University of California San Francisco, Departments of Cellular & Molecular Pharmacology, and Biochemistry & Biophysics
2000 - 2005	Assistant Investigator, Howard Hughes Medical Institute
2000 - 2003	Associate Professor, University of California San Francisco, Departments of Cellular & Molecular Pharmacology, and Biochemistry & Biophysics
2003 - Present	Professor, University of California San Francisco, Departments of Cellular & Molecular Pharmacology, and Biochemistry & Biophysics
2010-present	Vice-chair of Department of Cellular and Molecular Pharmacology, UCSF
2016-present	Presidents Advisory Committee of the Chan-Zuckerberg Biohub

Other Experience and Professional Memberships

Permanent Member, NIH Molecular Biology and Protein Processing Study Section (2004-2008); Reviewer, CDF-2 NIH study section (2001-2003, ad hoc); Member, NIH College of CSR Reviewers (2010).
Juror, New York Academy of Sciences Blavatnik Awards for Young Scientists (2014-present). External Reviewer, Lawrence Berkeley National Lab, Physical Biosciences Division (2005); Member, Harvard Medical School Review Committee (2015). Head of the program committee for the 2016 annual meeting of the American Society of Cell Biology. Co-founder KSQ therapeutics.

Editorial Boards: Molecular Cell (2001-present); BMC Cell Biology (2003-present); PLoS Biology (2003-present); Molecular Biology of the Cell (2005-2008); Journal of Molecular Biology (2006-present); Cell (2008-present); Current Opinion in Cell Biology (2009-present); Journal of Biology (2009-present); Board of Reviewing Editors, Science (2007-present).

Scientific Advisory Board: NIH, Amyloid Diseases (2005-2007); Proteostasis Therapeutics (2009-2013); Merck Research Labs (2010-2013), Helen Hay Whitney Foundation (2013-present); Stowers Institute for Medical Research (2016-present) Amgen (2016-present), Princeton Department of Molecular Biology (2015-present), KSQ Therapeutics, (2015-present), Stowers Institute for Medical

Research, Chair (2016-present, Chair since 2017), Tenaya Therapeutics (2018-present), Maze Therapeutics (2018-present), Venture Partner, 5AM Ventures (2018-present).

Honors and Awards

1988	Summa Cum Laude in Physics, Harvard University
1988	National Science Foundation Pre-doctoral Fellowship
1996	David and Lucile Packard Fellowship
1997	Searle Scholars Program Fellowship
2004	Irving Sigal Young Investigator Award, Protein Society
2008	Raymond & Beverly Sackler International Prize in Biophysics
2009	Alexander M. Cruikshank Lecturer, Gordon Research Conference on Stress
2009	Elected to the National Academy of Sciences
2010	David Perlman Award Lecturer of the ACS Division of Biochemical Technology (BIOT)
2010	Fellow, American Academy of Microbiology
2011	Don Summers Memorial Lecturer, University of Utah Bioscience Symposium
2012	Richard A. Scott, M.D. Lecturer, Center for Genetic Medicine, Northwestern University
2013	Marshall Nirenberg Lecturer, National Institutes of Health (NIH)
2013	Bashour Distinguished Lecturer, University of Texas Southwestern Medical Center
2013	Max Planck Distinguished Seminar, Max Planck Institute (MPI) for Developmental Biology
2014	Cedars-Sinai Medical Center Research Day 2014 Lecturer, Cedars-Sinai Medical Center
2014	Academic Senate Faculty Research Lecturer in Basic Science, University of California San Francisco (UCSF)
2015	12th Annual Albert L. Lehninger Lecturer, Johns Hopkins University
2016	Frank H. Westheimer Prize Lecture, Harvard University
2017	Frederic M. Richards Lecture, Yale University
2017	Election to EMBO Membership (European Molecular Biology Organization), Theodor Bucher Medal Lecture at the 2017 FEBS meeting, Jerusalem
2019	T.Y. Shen Lecturer, MIT
2020	Ira Herskowitz Award from the Genetic Society of America

Contribution to Science

Development of CRISPRi/CRISPRa. While the catalog of mammalian transcripts and their expression levels in different cell types and disease states is rapidly expanding, our understanding of their function lags behind. We present a robust technology enabling systematic investigation of the cellular consequences of repressing or inducing individual transcripts. We identify rules for specific targeting of transcriptional repressors (CRISPRi), typically achieving 90-99% knockdown with minimal off-target effects, and activators (CRISPRa) to endogenous genes via endonuclease-deficient Cas9. Together they enable modulation of gene expression over a ~1000-fold range. Using these rules, we construct and validate genome-scale CRISPRi and CRISPRa libraries that enable systematic analysis of gene function including both essential and nonessential as well as long noncoding RNAs. Our results establish CRISPRi and CRISPRa as powerful tools that provide rich and complementary information for mapping complex pathways. We have now adapted this approach to allow the large-scale analysis of double knockdowns. This enables the systematic search for synthetic lethal interactions that will inform the rational design of combination drug therapies. We are broadly applying the CRISPRi/a approach to understanding disease mechanisms, defining drug targets, and

even potentially treating disease by reversibly regulating gene expression without permanently altering patients' DNA.

a. Adamson B, Norman TM, Jost M, Cho MY, Nuñez JK, Chen Y, Villalta JE, Gilbert LA, Horlbeck MA, Hein MY, Pak RA, Gray AN, Gross CA, Dixit A, Parnas O, Regev A, **Weissman JS** (2016) A Multiplexed Single-Cell CRISPR Screening Platform Enables Systematic Dissection of the Unfolded Protein Response. *Cell*. 167(7): 1867-1882.
b. Liu SJ, Horlbeck MA, Cho SW, Birk HS, Malatesta M, He D, Attenello FJ, Villalta JE, Cho MY, Chen Y, Mandegar MA, Olvera MP, Gilbert LA, Conklin BR, Chang HY, **Weissman JS**, Lim DA. (2016) CRISPRi-based genome-scale identification of functional long noncoding RNA loci in human cells. *Science*. Dec 15. pii: aah7111. [Epub ahead of print]
c. Gilbert LA, Horlbeck MA, Adamson B, Villalta JE, Chen Y, Whitehead EH, Guimaraes C, Panning B, Ploegh HL, Bassik MC, Qi LS, Kampmann M, **Weissman JS**. (2014) Genome-Scale CRISPR-Mediated Control of Gene Repression and Activation. *Cell*, 159: 647-61. PMC4253859
d. Horlbeck MA, Gilbert LA, Villalta JE, Adamson B, Pak RA, Chen Y, Fields AP, Park CY, Corn JE, Kampmann M, **Weissman JS**. (2016) Compact and highly active next-generation libraries for CRISPR-mediated gene repression and activation. *Elife*. Sep 23; 5. pii: e19760.

Development of Ribosome Profiling: We developed a ribosome profiling approach based on deep-sequencing of ribosome-protected fragments that makes it possible to determine the rate of translation with a depth, speed and accuracy that rivals or exceeds existing approaches for following mRNA levels. We have applied these techniques to address a number of fundamental questions including: (1) Development of ribosome profiling protocols for a wide variety of eukaryotic and prokaryotic organisms. (2) Uses of ribosome profiling to globally monitor when chaperones, targeting factors or processing enzymes engage nascent chains. (3) Development of a strategy for monitoring subcellular translation. (4) Position-specific ribosome profiling to decipher the driving force and biological consequences underlying the choice of synonymous codons. (5) Use of ribosome profiling to define the protein coding potential of complex genomes.

a. Ingolia NT, Ghaemmaghami S, Newman JRS, **Weissman JS**. (2009) Genome-wide analysis in vivo of translation with nucleotide resolution using ribosome profiling. *Science*, 324(5924) 218-23. PMC2746483
b. Ingolia NT, Lareau LF, **Weissman JS.** (2011) Ribosome profiling of mouse embryonic stem cells reveals the complexity and dynamics of Mammalian proteomes. *Cell,* 147: 789-802. PMC3225288
c. Li GW, Oh E, **Weissman JS**. (2012) The anti-Shine-Dalgamo sequence drives translational pausing and codon choice in bacteria. *Nature*, 484: 538-41. PMC3338875
d. Jan CH, Williams CC, **Weissman JS**. (2014) Principles of ER cotranslational translocation revealed by proximity-specific ribosome profiling. *Science*, 346: 1257521. PMC4285348

Systematic analysis of the Endoplamic reticulum (ER). As a rule, proteins that enter the secretory pathway fold within the ER. The ER establishes and maintains a highly specialized environment optimized for folding. Understanding how this is accomplished is a major focus of our research. Major recent findings include the following: Identification of Yos9 as a sugar sensor of misfolded proteins. Discovery of a novel branch of the metazoan UPR, termed RIDD, involving targeted mRNA destruction. Identification of the GET pathway: a conserved system responsible for the biogenesis of tail-anchored membrane proteins. Discovery of a molecular caliper mechanism for determining the

length of very long-chain fatty acids. Identification of the Orm family of proteins as critical mediators of sphingolipid homeostasis.

a. Hollien J, **Weissman JS**. (2006) Decay of endoplasmic reticulum-localized mRNAs during the unfolded protein response. *Science*, 313:104-7. PMID 16825573
b. Denic V, **Weissman JS**. (2007) A molecular caliper mechanism for determining the length of very long-chain fatty acids. *Cell*, 130:663-67. PMID 17719544
c. Schuldiner M, Metz J, Schmid V, Denic V, Schmitt HD, Schwappach B, **Weissman JS**. (2008) The GET complex mediates the intersection of tail-anchored proteins into the ER membrane. *Cell*, 134:634-45. PMC2572727
d. Breslow DK, Collins SR, Bodenmiller B, Aebersold R, Simons K, Shevchenko A, Ejsing CS, **Weissman JS**. (2010) ORM family proteins mediate sphingolipid homeostasis. *Nature*, 463:1048-53. PMC2877384

Mechanism of prion propagation: My lab has used the yeast [PSI+] prion to elucidate the principles of prion-based inheritance. Most notably, we developed an approach for producing distinct infectious (prion) conformation of the yeast Sup35 prion protein. We showed that when introduced into yeast, these distinct infectious conformations led to distinct strains of the [PSI+] prion. This work provided the first and still the most direct demonstration of the protein only hypothesis of prion propagation and established that prion strains results from distinct self-propagating infectious conformations.

a. DePace AH, Santoso A, Hillner P, **Weissman JS**. (1998) A critical role for amino-terminal glutamine/asparagine repeats in the formation and propagation of a yeast prion. *Cell*, 93:1241-52. PMID 9657156
b. Tanaka M, Chien P, Naber N, Cooke R, **Weissman JS**. (2004) Conformational variations in an infectious protein determine prion strain differences. *Nature,* 428:323-8. PMID 15029196
c. Toyama B, Kelly MOS, Gross JD, **Weissman JS**. (2007) The structural basis of yeast prion strain variants. *Nature,* 449:233-7. PMID 17767153

Full List of Published Work:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/45844241/?sort=date&direction=ascending

Research Support

Howard Hughes Medical Institute (Weissman) 10/01/00 - 08/31/24
Prion-Based Inheritance, Protein Folding, and Analysis of Cellular Systems
This grant supports our studies of how cells insure that proteins fold into their correct shape, as well as the role of protein misfolding in disease and normal physiology.

HR0011-19-2-0007 (Weissman) 04/01/2019 – 03/31/2023
DOD Defense Advanced Res Projects Agency (DOD DARPA)
An IND-Enabling Platform for CBRN Threat Protection via Transient, RNA-guided, Targeted Epigenome Editing In Vivo
This grant proposes to build a vertically integrated, target-agnostic, and IND-enabling platform for clinic-ready, transient, RNA-guided, targeted epigenome editing in vivo. We will deploy this platform to develop an experimental therapeutic for prophylactic or post-exposure protection of hematopoiesis and the gastrointestinal (GI) tract from high-dose radiation exposure.

HR0011-17-2-0043 (Doudna) 04/01/17–03/31/2021
DARPA
Next-Generation CRISPR and anti-CRISPR Tools and Delivery Systems for Safely Engineering the

Genome and Epigenome
This grant proposes to develop next generation CRISPR tools for editing the genome, epigenome and transcriptome with application as advanced anti-viral therapeutics. This grant also proposes to identify, characterize, refine and implement natural and engineered anti-CRISPR agents as a means of controlling the activity of dual use gene editing platforms.

1U01 CA217882-01 (MPI: McManus, Bandyopadhyay, Bivona, Weissman) 07/01/2017-06/30/2022
NIH/NCI
The Cancer Target Discovery and Development Network at UCSF
The goal of this proposal is directly to bridge the gap between the enormous volumes of data generated by the comprehensive molecular characterization of a number of cancer types– and the ability to use these data for the development of human cancer therapeutics.

1RM1 HG009490-01 (PI: Doudna; Co-Investigator: Weissman) 08/08/2017 – 05/31/2022
NIH/NHGRI
Center for Genome Editing and Recording
The major goals of this project are to create technologies to enable robust, comprehensive exploration of genes and genetic pathways responsible for human disease.

1U54 CA224081-01 (PI: Bivona; Co-investigator: Weissman) 9/1/2017-8/31/2022
NIH/NCI
Bay Area Team Against Resistance
The Bay Area Team Against Resistance U54 Project (BATAR-UP) is an interdisciplinary effort of investigators to apply their knowledge and expertise to dissect the molecular and cellular basis of incomplete response and resistance to current treatments and to identify new treatment strategies to better neutralize or eliminate residual disease and prevent resistance.

2019-203762 (Weissman) 8/01/2019-3/31/2020
Chan Zuckerberg Initiative
Lineage Tracer Supplement #2
This work will develop methods for permanently recording cell state changes in DNA in a compact manner that can be read out in single cell format using droplet-based single cell RNA-seq.

1 R01 NS113429-01 (Wang) 2/1/2020-1/31/2025
NIH/NINDS
Molecular Pathogenesis of Hereditary Hemorrhagic Telangiectasia
The main objective is to establish a novel HHT2-AVM mouse model, with which to identify molecular regulators crucial for AVM pathogenesis, using both a targeted approach and unbiased genome-wide expression profiling.

BIOGRAPHICAL SKETCH

NAME **Prescott Gurney Woodruff, M.D., M.P.H.**	POSITION TITLE Associate Professor of Medicine in Residence
eRA COMMONS USER NAME woodruffp	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Wesleyan University, Middletown, CT	B.A.	5/1989	Letters
Columbia College of Physicians & Surgeons, NY	M.D.	5/1993	Medicine
Massachusetts General Hospital	Residency	7/93-1996	Internal Medicine
Harvard School of Public Health	M.P.H.	06/98	Epidemiology
Brigham and Women's Hospital	Fellow	07/97-98	Respiratory Epidemiology
University of California, San Francisco	Fellow	07/98-02	Pulmonary/Critical Care

Positions and Honors

1998-2002	Clinical and Research Fellow, Pulmonary/Critical Care Medicine & Cardiovascular Research Institute, Department of Medicine, University of California San Francisco, San Francisco, CA
2002-2005	Assistant Adjunct Professor; University of California San Francisco
2005- 2010	Assistant Professor in Residence, Pulmonary/Critical Care Medicine, Department of Medicine and CVRI, University of California San Francisco
2010-2014	Associate Professor in Residence, Division of Pulmonary and Critical Care Medicine, Department of Medicine and CVRI, University of California San Francisco
2014-present	Professor in Residence, Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of California San Francisco
2018 -	Vice Chief for Research, Division of Pulmonary and Critical Care Medicine, Department of Medicine
Honors	
1993	Alpha Omega Alpha, Columbia College of Physicians and Surgeons, NY, NY
2012	Elected to Membership, American Society for Clinical Investigation
2020	Faculty Mentoring award, UCSF Division of Pulmonary, Critical Care, Sleep and Allergy

Contribution to Science

C. Contribution to Science

1. Molecular phenotyping of asthma and COPD. My work in this area has contributed to endotyping of asthma and COPD based on patterns of type-2, interferon and IL-17 driven inflammation and has influenced the direction of biological therapy development in these diseases. It has led directly

to my study of airway epithelial ER stress as a feature related to these endotypes in asthma. Mentees have been very actively involved in these studies over the past 5 years.

a. **Woodruff PG**, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, Koth LL, Arron JR, and Fahy JV. Th2-driven inflammation defines major sub-phenotypes of asthma. Am J Respir Crit Care Med 2009 Sep 1;180(5):388-95. PMCID: PMC2742757
b. **Woodruff PG**, Boushey HA, Dolganov GM, Barker CS, Yang YH, Donnelly S, Ellwanger A, Sidhu SS, Dao-Pick TP, Pantoja C, Erle DJ, Yamamoto KR, Fahy JV. Genome-Wide Profiling Identifies Epithelial Cell Genes Associated with Asthma and with Treatment Response to Corticosteroids. Proc Natl Acad Sci U S A. 2007 Oct 2;104(40):15858-63. PMCID: PMC2000427
c. Christenson SA, Steiling K, van den Berge M, Hijazi K, Hiemstra PS, Postma DS, Lenberg ME, Spira A, **Woodruff PG**. Asthma-COPD Overlap: Clinical Relevance of Genomic Signatures of Type 2 Inflammation in COPD. Am J Respir Crit Care Med. 2015 Jan 22. PMCID: PMC4407484.
d. Bhakta NR, Christenson SA, Nerella S, Solberg OD, Nguyen CP, Choy DF, Jung KL, Garudadri S, Bonser LR, Pollack JL, Zlock LT, Erle DJ, Langelier C, Derisi JL, Arron JR, Fahy JV, **Woodruff PG**. IFN-stimulated Gene Expression, Type 2 Inflammation, and Endoplasmic Reticulum Stress in Asthma. Am J Respir Crit Care Med. 2018 Feb 1;197(3):313-324. doi: 10.1164/rccm.201706-1070OC. PMCID: PMC5811952.
e. Christenson SA, van den Berge M, Faiz A, Inkamp K, Bhakta N, Bonser LR, Zlock LT, Barjaktarevic IZ, Barr RG, Bleecker ER, Boucher RC, Bowler RP, Comellas AP, Curtis JL, Han MK, Hansel NN, Hiemstra PS, Kaner RJ, Krishnanm JA, Martinez FJ, O'Neal WK, Paine R 3rd, Timens W, Wells JM, Spira A, Erle DJ, **Woodruff PG**. An airway epithelial IL-17A response signature identifies a steroid-unresponsive COPD patient subgroup. J Clin Invest. 2019 Jan 2;129(1):169-181. PMID: 30383540. PMCID: PMC6307967

2. Studies of airway epithelial mucus production in asthma and COPD. This work has included studies of human airway epithelial cells and sputum samples from well characterized subjects with asthma and COPD, and cell culture and mouse models of airway epithelial cell mucus production. These studies have shown that asthma and T2 inflammation generally are associated with an increase in MUC5AC as compared to MUC5B, that MUC5AC tracks with disease severity in COPD as well as asthma, and that miR-141 regulates MUC5AC production (and can be targeted using RNA interfering strategies)
   a. **Woodruff PG**, Boushey HA, Dolganov GM, Barker CS, Yang YH, Donnelly S, Ellwanger A, Sidhu SS, Dao-Pick TP, Pantoja C, Erle DJ, Yamamoto KR, Fahy JV. Genome-Wide Profiling Identifies Epithelial Cell Genes Associated with Asthma and with Treatment Response to Corticosteroids. Proc Natl Acad Sci U S A. 2007 Oct 2;104(40):15858-63. PMCID: PMC2000427
   b. Siddiqui S*, Johansson K*, Joo A, Bonser LR, Koh KD, Le Tonqueze O, Bolourchi S, Bautista RA, Zlock L, Roth TL, Marson A, Bhakta NR, Ansel KM, Finkbeiner WE, Erle DJ, **Woodruff PG**. Epithelial miR-141 regulates IL-13-induced airway mucus production. JCI Insight. [In Press]
   c. Innes AL*, **Woodruff PG***, Ferrando RE, Donnelly S, Dolganov GM, Lazarus SC, Fahy JV. Epithelial mucin stores are increased in the large airways of smokers with airflow obstruction. Chest. 2006 Oct;130(4):1102-8. *denotes authors contributed equally
   d. Roy MG, Livraghi-Butrico A, Fletcher AA, McElwee MM, Evans SE, Boerner RM, Alexander SN, Bellinghausen LK, Song AS, Petrova YM, Tuvim MJ, Adachi R, Romo I, Bordt AS, Bowden MG, Sisson JH, **Woodruff PG**, Thornton DJ, Rousseau K, De la Garza MM, Moghaddam SJ, Karmouty-Quintana H, Blackburn MR, Drouin SM, Davis CW, Terrell KA, Grubb BR, O'Neal WK, Flores SC, Cota-Gomez A, Lozupone CA, Donnelly JM, Watson AM, Hennessy CE, Keith RC, Yang IV, Barthel L, Henson PM, Janssen WJ,

Schwartz DA, Boucher RC, Dickey BF, Evans CM. Muc5b is required for airway defence. Nature. 2014 Jan 16;505(7483):412-6. PMCID: PMC4001806

e. Kesimer M, Ford AA, Ceppe A, Radicioni G, Cao R, Davis CW, Doerschuk CM, Alexis NE, Anderson WH, Henderson AG, Barr RG, Bleecker ER, Christenson SA, Cooper CB, Han MK, Hansel NN, Hastie AT, Hoffman EA, Kanner RE, Martinez F, Paine R 3rd, **Woodruff PG**, O'Neal WK, Boucher RC. Airway Mucin Concentration as a Marker of Chronic Bronchitis. N Engl J Med. 2017 Sep 7;377(10):911-922. PMCID: PMC5706541.

3. Studies of early COPD and mechanisms of resilience to smoking. One of my major contributions to clinical subphenotyping in COPD has been in the description of "Smokers with symptoms despite preserved spirometry". These studies have now expanded into the study mechanisms of resilience to the lung effects of smoking.
   a. **Woodruff PG**, Barr RG, Bleecker E, Christenson SA, Couper D, Curtis JL, Gouskova NA, Hansel NN, Hoffman EA, Kanner RE, Kleerup E, Lazarus SC, Martinez FJ, Paine R, Rennard S, Tashkin DP, Han MK. Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function. N Engl J Med. 2016 May 12; 374(19):1811-21. PMCID: PMC4968204
   b. Kesimer M, Ford AA, Ceppe A, Radicioni G, Cao R, Davis CW, Doerschuk CM, Alexis NE, Anderson WH, Henderson AG, Barr RG, Bleecker ER, Christenson SA, Cooper CB, Han MK, Hansel NN, Hastie AT, Hoffman EA, Kanner RE, Martinez F, Paine R 3rd, **Woodruff PG**, O'Neal WK, Boucher RC. Airway Mucin Concentration as a Marker of Chronic Bronchitis. N Engl J Med. 2017 Sep 7;377(10):911-922. doi: 10.1056/NEJMoa1701632. PMID: 28877023; PMCID: PMC5706541.
   c. Garudadri S, **Woodruff PG**, Han MK, Curtis JL, Barr RG, Bleecker ER, Bowler RP, Comellas A, Cooper CB, Criner G, Dransfield MT, Hansel NN, Paine R 3rd, Krishnan JA, Peters SP, Hastie AT, Martinez FJ, O'Neal WK, Couper DJ, Alexis NE, Christenson SA. Systemic Markers of Inflammation in Smokers With Symptoms Despite Preserved Spirometry in SPIROMICS. Chest. 2019 May;155(5):908-917. doi: 10.1016/j.chest.2018.12.022. Epub 2019 Jan 23. PMID: 30684474; PMCID: PMC6533449.
   d. Arjomandi M, Zeng S, Barjaktarevic I, Barr RG, Bleecker ER, Bowler RP, Buhr RG, Criner GJ, Comellas AP, Cooper CB, Couper DJ, Curtis JL, Dransfield MT, Han MK, Hansel NN, Hoffman EA, Kaner RJ, Kanner RE, Krishnan JA, Paine R 3rd, Peters SP, Rennard SI, **Woodruff PG**; SPIROMICS Investigators. Radiographic lung volumes predict progression to COPD in smokers with preserved spirometry in SPIROMICS. Eur Respir J. 2019 Oct 31;54(4):1802214. doi: 10.1183/13993003.02214-2018. PMID: 31439683; PMCID: PMC7089627.

4. Clinical Trials of novel therapeutic approaches in asthma and COPD. These studies include large multi-center trials novel therapeutic approaches in asthma and COPD and an ongoing study of the potential role of bronchodilators in smokers with symptoms despite preserved spirometry, the Redefining Therapy in Early COPD (RETHINC) Study.
   a. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JAD, Criner GJ, Curtis JL, Dransfield MT, Han MK, Lazarus SC, Make B, Marchetti N, Martinez FJ, Madinger NA, McEvoyC, Niewoehner DE, Porsasz J, Price, CS, Reilly J, Scanlon PD, Sciurba FC, Scharf SM, Washko GR, **Woodruff PG**, and Anthonisen NR. for the COPD Clinical Research Network. Azithromycin for Prevention of Exacerbations of COPD. N Engl J Med 2011; 365:689-698. PMCID: PMC3220999
   b. Criner GJ, Connett JE, Aaron SD, Albert RK, Bailey WC, Casaburi R, Cooper JA Jr, Curtis JL, Dransfield MT, Han MK, Make B, Marchetti N, Martinez FJ, Niewoehner DE, Scanlon PD, Sciurba FC, Scharf SM, Sin DD, Voelker H, Washko GR, **Woodruff PG**, Lazarus SC; the COPD Clinical Research Network and the Canadian Institutes of Health Research.

Simvastatin for the Prevention of Exacerbations in Moderate-to-Severe COPD. N Engl J Med. 2014 Jun 5;370(23):2201-10. PMCID: PMC4375247

c. **Woodruff PG**, Albert RK, Bailey WC, Casaburi R, Connett JE, Cooper JAD, Criner GJ, Curtis JL, Dransfield MT, Han MK, Harnden SM, Kim V, Marchetti N, Martinez FJ, McEvoy CE, Niewoehner DE, Reilly JJ, Rice K, Scanlon PD, Scharf SM, Sciurba FC, Washko GR, Lazarus SC for the COPD Clinical Research Network. Randomized Trial of Zileuton for Treatment of COPD Exacerbations Requiring Hospitalization. COPD. 2011 Feb;8(1):21-9. PMCID: PMC3775706

d. Lazarus SC, Krishnan JA, King TS, Lang JE, Blake KV, Covar R, Lugogo N, Wenzel S, Chinchilli VM, Mauger DT, Dyer AM, Boushey HA, Fahy JV, **Woodruff PG**, Bacharier LB, Cabana MD, Cardet JC, Castro M, Chmiel J, Denlinger L, DiMango E, Fitzpatrick AM, Gentile D, Hastie A, Holguin F, Israel E, Jackson D, Kraft M, LaForce C, Lemanske RF Jr, Martinez FD, Moore W, Morgan WJ, Moy JN, Myers R, Peters SP, Phipatanakul W, Pongracic JA, Que L, Ross K, Smith L, Szefler SJ, Wechsler ME, Sorkness CA; National Heart, Lung, and Blood Institute AsthmaNet. Mometasone or Tiotropium in Mild Asthma with a Low Sputum Eosinophil Level. N Engl J Med. 2019 May 23;380(21):2009-2019. doi: 10.1056/NEJMoa1814917. Epub 2019 May 19. PMID: 31112384; PMCID: PMC6711475.

e. Han MK, Ye W, Kim DY, **Woodruff P**; Pulmonary Trials Cooperative Investigators. Design of the Redefining Therapy in Early COPD (RETHINC) Study. Chronic Obstr Pulm Dis. 2020 Sep 28;7(4). doi: 10.15326/jcopdf.7.4.2020.0157. Epub ahead of print. PMID:32989941. PMCID In process

5. Deep immunophenotyping studies of COVID-19. Since early in the pandemic, I initiated and have participated in several COVID-19 cohort studies in both the inpatient and outpatient settings. These studies are designed to leverage my existing expertise in immunophenotyping in airway disease to characterize risk factors and mechanisms of disease in severe COVID-19 and include 2 inpatient cohorts (IMPACC [funded by the NIAID] and COMET+ [funded by Genentech]) and one large outpatient cohort ("C4R" Collaborative Cohort of Cohorts for COVID-19 [funded by the NHLBI].

   a. Combes AJ, Courau T, Kuhn NF, Hu KH, Ray A, Chen WS, Chew NW, Cleary SJ, Kushnoor D, Reeder GC, Shen A, Tsui J, Hiam-Galvez KJ, Muñoz-Sandoval P, Zhu WS, Lee DS, Sun Y, You R, Magnen M, Rodriguez L, Im KW, Serwas NK, Leligdowicz A, Zamecnik CR, Loudermilk RP, Wilson MR, Ye CJ, Fragiadakis GK, Looney MR, Chan V, Ward A, Carrillo S; UCSF COMET Consortium, Matthay M, Erle DJ, **Woodruff PG**, Langelier C, Kangelaris K, Hendrickson CM, Calfee C, Rao AA, Krummel MF. Global absence and targeting of protective immune states in severe COVID-19. Nature. 2021 Mar;591(7848):124-130.

   b. Peters MC, Sajuthi S, Deford P, Christenson S, Rios CL, Montgomery MT, **Woodruff PG**, Mauger DT, Erzurum SC, Johansson MW, Denlinger LC, Jarjour NN, Castro M, Hastie AT, Moore W, Ortega VE, Bleecker ER, Wenzel SE, Israel E, Levy BD, Seibold MA, Fahy JV. COVID-19-related Genes in Sputum Cells in Asthma. Relationship to Demographic Features and Corticosteroids. Am J Respir Crit Care Med. 2020 Jul 1;202(1):83-90.

   c. Sarma A, Christenson S, Mick E, Deiss T, DeVoe C, Pisco A, Ghale R, Jauregui A, Byrne A, Moazed F, Spottiswoode N, Sinha P, Zha B, Neff N, Tan M, Serpa PH, Ansel KM, Wilson J, Leligdowicz A, Seigel E, Sirota M, DeRisi J, Matthay M, Consortium C, Hendrickson C, Kangelaris K, Krummel M, **Woodruff P**, Erle D, Calfee C, Langelier C. COVID-19 ARDS is characterized by a dysregulated host response that differs from cytokine storm and is modified by dexamethasone. Res Sq [Preprint]. 2021 Jan 14: rs.3.rs-141578. PMCID: PMC7814832.

   d. Bonser LR, Eckalbar WL, Rodriguez L, Shen J, Koh KD, Zlock LT, Christenson S, **Woodruff PG**, Finkbeiner WE, Erle DJ. The type 2 asthma mediator IL-13 inhibits SARS-

CoV-2 infection of bronchial epithelium. bioRxiv [Preprint]. 2021 Feb 25:2021.02.25.432762. PMCID: PMC7924269.

Complete List of Published Work in MyBibliography (209 Publications):
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40802581/?sort=date&direction=descending

Ongoing Research Support

K24 HL137013 (PI Woodruff) 04/28/17-3/31/22
Mentoring Research in Precision Medicine for Lung Disease
To mentor students, fellows, and junior faculty in patient-oriented precision medicine related research in respiratory disease.

U01 HL137880 (PI Woodruff) 09/15/17-5/31/22
NHLBI SPIROMICS II: Biological underpinnings of COPD heterogeneity and progression.
To establish the biological underpinnings of COPD heterogeneity, progression and exacerbations using the SPIROMICS cohort.

R01 HL146002 (PI Woodruff, MPI mechanism, Levy B Contact PI) NIH/NHLBI 9/23/2019-6/30/24
Severe Asthma Research Program 4: Immunometabolic phenotypes in adult severe asthma and disease progression. This is a national, multicenter collaborative study with a mechanistic translational approach with 4 specific aims to investigate the molecular and cellular origin of SA immunometabolic phenotypes rigorously and comprehensively and their relationship to disease progression.

P01 HL107202 (Core director and Project 2 Co-I: Woodruff, Overall PI: Fahy) 9/01/19-07/31/24
Exploring the Biology of Persistent Type 2 Airway Niches in Asthma
To identify mechanisms of persistence of T2 inflammation in airway niches relevant to asthma.

U19 AI077439 (Project leader: Woodruff, PI: Erle) 04/01/18-3/31/23
Understanding Asthma Endotypes
To study the roles of interferon driven inflammation and airway epithelial ER stress in asthma.

U19 AI077439 supplement (Co-I: Woodruff, overall PI: Erle). 5/8/2020-3/31/22
UCSF COVID-19 Immunophenotyping Clinical Study and Core laboratories
Our goal is to establish relationship between viral load, host immunological responses, and poor clinical outcomes in COVID-19.

R35 HL145235 (Erle DJ, Woodruff Co-I) 02/15/19-12/31/26
Airway Epithelial Cell Gene Regulation: New Mechanisms and Therapeutic Strategies
Our overall goals are to identify genomic elements that are important in airway epithelial cell differentiation in asthma and to develop approaches for targeting these elements.

UG1HL139106 (Co-I Woodruff, Fahy PI) 09/23/17-06/30/23
Sequential, Multiple Assignment, Randomized Trial in Severe Asthma Protocol (SMART-SA)
The goal of this project is to advance precision medicine for patients with more severe forms of asthma. It is otherwise known as the PRECISE study.

R01 HL143998 (PI Woodruff, MPI mechanism, Huang L Contact PI). 09/15/19-07/31/23
Integrated Analysis of Microbial and Genomic data in Obstructive Lung Disease (I AM GOLD) Study
This study investigates mechanisms underlying the increased risk of COPD with HIV infection in an ongoing international longitudinal multi-center study of HIV-associated COPD in Uganda and San Francisco.