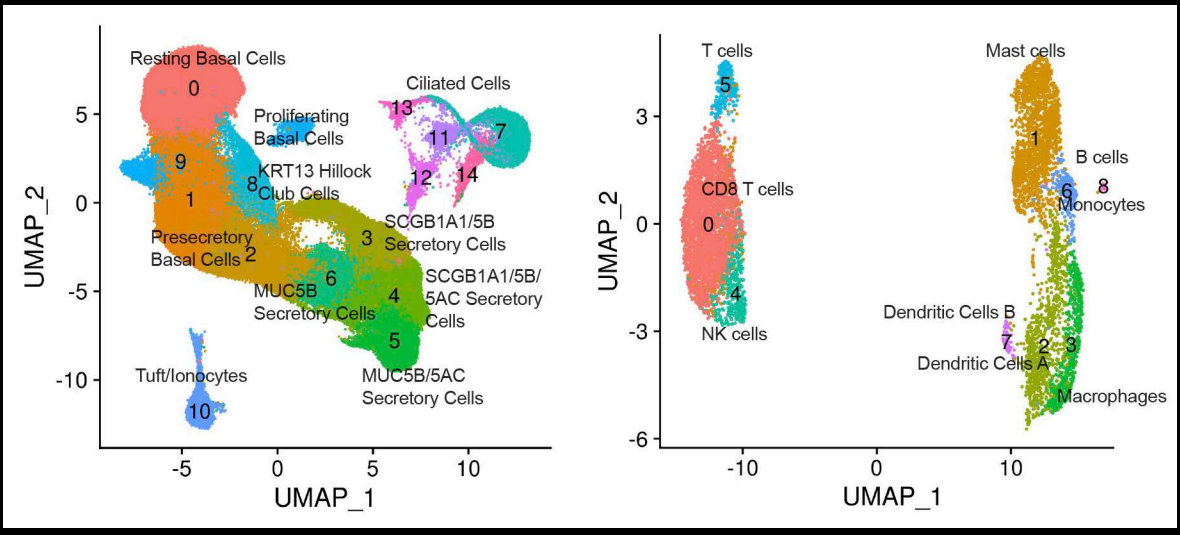
Sandler Asthma Basic REsearch Center
University of California San Francisco



Progress
Report Year 21
July 2020

Figure Legend: *Single cell RNA Sequencing of sinus epithelial brushes from 4 healthy controls and 5 nasal polyp patients reveals an expansion of MUC5AC+ secretory cells and mast cells. Rare cell types such as tuft cells (0.2-0.5% of the epithelium) are identified here and reveal and novel inflammatory gene signature in patients with nasal polyps.*

In Memorium

We wish to acknowledge with condolences the passing of Executive Advisory Board member, Zena Werb (3/24/45-6/17/20), whose vision, leadership, inspiration and encouragement helped establish and sustain the SABRE Center at UCSF to make the world better for persons with asthma. We remain committed to her ideals.

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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 larger 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

This year witnessed the SARV-CoV2 pandemic with its unprecedented impact on academic life, research and the health care system. SABRE labs were shuttered in March and only partially reopened in late May, and currently remains at a 25% limit in persons allowed in the lab at a given time. 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 continued to make contributions to the understanding of asthma and allergic disease, while also 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) Esteban Burchard was awarded a $10 million grant from the NIH, designated PRIMERO, to study 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. Despite the pandemic, over 100 births have been enrolled and the study has already spawned additional NIH submissions to expand on this rich data set.
(2) John Fahy used the NIH Severe Asthma Research Program repository to rapidly assess the expression of viral SARS-CoV-2 receptors on sputum cells of asthma patients as compared to controls, revealing a potential protective role for corticosteroids.
(3) Mark Ansel, John Fahy, Prescott Woodruff and David Erle were among the UCSF consortium of immunologists and basic scientists uniting to form COMET as an NIH-partnered institutional commitment to apply next-gen sequencing, proteomics and cell analysis to better understanding of effects of COVID-19 on lung functions, including their impact on allergic lung diseases.
(4) Among basic research contributions, the Allen lab discovered the role of IL-21 in inhibiting IgE class switch recombination in mouse and human B cells (JEM, 2020). The Locksley lab continued to elucidate mechanisms driving ILC2 biology, including extrusion from tissues in response to perturbation to mediate systemic effects (JEM, 2020). The Shin lab continued to explore the role of MARCH1 regulation in dendritic cells and effects on T cell differentiation (Nat Comm, 2018).

Overview – 2020
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, 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 activities suspended at UCSF in March. 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 laboratories at UCSF cautiously expanding to 25% capacity in late May, we have slowly increased research across SABRE while adhering to the realities of the pandemic. SABRE members remain integrated across the leadership areas of UCSF in order to work quickly and supportively in this new environment while bringing projects back online to further our Mission. Scientific leadership on national and international scales included participation and organization of 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 organization of the 4th International Conference on Innate Lymphoid Cells to be held in San Francisco. Both activities had to be postponed and will hopefully be held in 2021.

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. 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 this past year 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. We briefly review the individual 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 has been obtained to support these activities.

K. Mark Ansel, Ph.D., is working to understand the gene expression networks that mediate immune cell differentiation and effector functions in allergy and asthma. His studies focus on microRNAs and RNA binding proteins as critical executioners of these pathways. His lab has developed novel techniques to discover and interrogate the genomic sequences through which these executioners act and gain specificity. In addition, he developed a related research program to improve and expand characterization of inflammatory cells that infiltrate airways in asthma. Dr. Ansel avidly pursues studies using materials collected from patients in the Airway Clinical Research Center. He has worked with Dr. Woodruff, Dr. Fahy, Dr. Gordon, Dr. Koth and Dr. Boushey to improve and apply high-dimensional flow cytometry and mass cytometry (CyTOF) analysis of human airway biospecimens. He works closely with Dr. Woodruff and Dr. Erle to push the boundaries of genomic analyses of RNA regulation, and collaborates actively with Dr. Locksley, Dr. Allen and other investigators in the SABRE Center and throughout UCSF.

As the COVID-19 pandemic swept across the world, pulmonologists, infectious disease experts, and immunologists at UCSF united to form COMET, a consortium capable of deploying established expertise to interrogate the immune phenotypes associated with COVID-19 disease pathology in a team science effort to accelerate discovery of biomarkers and therapies to ameliorate the disease and its impact on patients and society. Dr. Ansel's role in COMET is to investigate the cellular heterogeneity and signaling status of immune and epithelial cells recovered from the airways of COVID-19 patients. In addition to leveraging the experience gained in Dr. Ansel's prior studies of asthma, this work also directly benefits his ongoing asthma research, as it has provided access to airway biospecimens, closer collaboration with CyTOF expert Dr. Matt Spitzer, and urgency to rapidly develop and empirically test the technical and computational analysis pipelines to investigate airway diseases using this powerful technology.

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. Postdoctoral fellow Kristina Johansson is supported by the Swedish Heart Lung Foundation and the Sweden-America Foundation; Marlys Fassett received a K08 Career Development Award this year; graduate student Didi Zhu was awarded a Hooper Foundation Fellowship; and Priscila Muñoz-Sandoval was awarded the 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 director of the UCSF Biomedical Sciences (BMS) graduate program and the principal investigator of its newly 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 has worked with the 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 Doctor of Pharmacy program at UCSF.

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 mechanism 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 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 has also found that the endocytic pathway of the IgE receptor could be exploited to establish immune tolerance against the IgE-bound antigens. More recently, Dr. Shin has investigated the role of the ubiquitin ligase MARCH1 in dendritic cell function in allergic asthma. She and others had previously 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. During this study, she generated a few genetically manipulated mouse strains and established mouse models of acute and chronic asthma sensitive to house dust mite allergens. These experimental tools

have been disseminated to wide scientific community including NIH and Canada to accelerate new discovery. More recently, she has launched into examination of the heterogeneity of lung dendritic cells involved in allergic asthma. This new project reveals that respiratory allergens are captured by three distinct dendritic cell subsets in the lungs. One of them is localized close to airway and highly endocytic and migratory while the others are not readily accessed from the airway and less endocytic and lung-resident. This finding implicates versatile roles of dendritic cells in allergic asthma and functional specialization of these subsets.

Dr. Shin contributed 5 peer-reviewed publications in 2018-2020. A new manuscript reporting the role of MARCH1 in allergic asthma has been recently submitted for consideration of publication. Dr. Shin was awarded a R35 Outstanding Investigator Award from NIGMS in 2019. She was also awarded the Careers in Immunology Fellowship Award from the American Association of Immunologists. Dr. Shin has been invited to give an oral presentation from the 2020 Keystone Symposia on Asthma and also invited to write an editorial from the journal Thorax.

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 awarded the Trainee Abstract Award from the American Association of Immunologists, and the other has received the best poster prize from the Annual Biomedical Research Conference for Minority Students. In addition, Dr. Shin has recently received a supplement fund from the NIGMS to promote diversity in health-related research. Dr. Shin's first graduate student was recently appointed to be a tenure-track assistant professor at the University of Colorado Boulder. One of her postdoctoral trainees was recruited by Amgen and appointed to be a Scientist in the Department of Oncology. Dr. Shin serves an organizer of the UCSF ImmunoX faculty seminar and serves an organizer of the SABRE monthly asthma conference. She also serves a grant reviewer for NIH HAMI (Hypersensitivity, allergy, and mucosal immunology) study section.

Chris Allen, Ph.D., joined the SABRE center twelve 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. Dr. Allen recently

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 about to submit 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 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 has also developed methodology to characterize human IgE+ B cells. To facilitate mechanistic studies of human B cells, Dr. Allen has 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 he completed an 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 was recruited to the Cardiovascular Research Institute (CVRI) at UCSF in 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. He remains committed to investigations into the basic pathogenesis of asthma. Dr. Allen remains an active member of SABRE and participates in monthly and quarterly meetings with SABRE investigators on the Parnassus site. Dr. Allen continues to collaborate with SABRE members on research projects and as collaborators on recently submitted NIH grant proposals, including Dr. Ansel, Dr. Bhattacharya, and Dr. Sundaram. Dr. Allen recently contributed his expertise on IgE B cells to a study on microRNA regulation of B cell class switch recombination in Dr. Ansel's lab, under review at the *Journal of Experimental Medicine*.

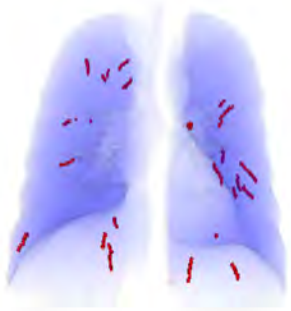
Dr. Allen is currently mentoring three PhD students and a new postdoc in his lab. This postdoc is following up on the project of a previous PhD student in the lab, focused on a population of macrophages in the lung that capture inhaled allergen and present it to T cells, which may trigger inflammation contributing to asthma. Dr. Allen's newest PhD student is following up on work from a previous postdoc regarding the generation of IgE B cells in mouse models of asthma, and another PhD student is working on the molecular pathways that control the genesis of IgE B cells. Dr. Allen has also mentored a medical student who worked for five years in his laboratory in various stints 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.

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 10 peer-reviewed publications, 5 reviews and 3 commentaries in 2018-2020, with 3 additional manuscripts in various stages of revision after 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. Deep integration of these and additional studies with findings from other University laboratories are in various stages of revision. 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 Mary and Albert 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 and an American Dermatology Research Fellowship. 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 has been delayed at least one year due to the pandemic.

John Fahy, M.D. is a longstanding participant in SABRE research and a formal faculty member in the SABRE Center for the past 7 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), a translational PO1 program in academic drug discovery that aims to advance mucolytics 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).



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 mucus plug treatments.

In response to the COVID19 emergency,

Dr Fahy and colleagues rapidly published a manuscript in April 2019 detailing the expression of COVID19-related genes in sputum cells from asthma patients (PMID: 32348692). This paper drew attention to patient subgroups with potential for higher risk of morbidity from COVID19. In addition he was awarded funding via the UCSF COVID19 Related Rapid Research Pilot Initiative for his proposal titled "Thiol-based drugs to inhibit SARS-CoV2". This proposal will study the possibility that the novel thiol-based drug his lab is developing as a mucolytic for asthma might have efficacy as a direct antiviral treatment for COVID19.

Dr. Fahy is a frequent advisor to the National Heart, Lung and Blood Center regarding research needs in asthma. Recent honors include election to the American Association of Physicians in 2016 and a Recognition Award for Scientific Accomplishments from the American Thoracic Society in 2017. In addition, Dr. Fahy was recognized by the European Respiratory Society (ERS) in 2019 with the ERS Gold Medal in Asthma and by the American Academy of Allergy, Asthma, and Immunology (AAAAI) with the inaugural K. Frank Austen Bench to Bedside Plenary Lectureship.

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 6 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 1) non-type 2 mechanisms of disease that may drive severe asthma, 2) type 2 and non-type 2 inflammatory mechanisms in allied diseases such as COPD and chronic bronchitis, and 3) immunophenotyping in critically ill patients with COVID-19 (through the new NIAID IMPACC Study). Dr. Woodruff's research program also includes studies of microRNA regulation of airway epithelial mucin production. 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) a NHLBI U01 grant designed to develop reference profiles for exRNAs across 12 different human body fluids, 4) the NHLBI RETHINC clinical trial in COPD, and 5) a NHLBI study of obstructive lung disease in patients living with HIV (the NIH "I AM GOLD") Study and 6) 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 is co-Chair the Keystone Symposium on Asthma in 2020 (delayed due to the pandemic) which was organized by the former American Foundation for Asthma and has been supported by the Sandler Foundation. Dr. Woodruff's honors include election to membership in the American Society for Clinical Investigation.

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. Puerto Ricans have the highest asthma prevalence and mortality in the world and experience a disproportionate amount of early-life respiratory illnesses.(Wohlford et al. *PLoS One* 2020) 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 relations hip 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 into PRIMERO. We 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, and blood at birth, during respiratory illness, and at yearly clinical evaluations. PRIMERO offers the opportunity to study how socio-environmental factors such as race, genetic ancestry, family structure, and socioeconomic status (SES) affect the immunological profiles of mothers and their 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 establishing the birth cohort and are a testament to the substantial investment in political capital that Drs. Burchard and Rodriguez-Santana have made. Despite Puerto Rico's Shelter in Place mandate, recruitment and specimen collection has continued during the COVID-19 pandemic and to date, the PRIMERO team have successfully recruited over 120 mother-infant dyads. Given the scale and complexity of the study (e.g., coordinating recruitment visits, study visits, and the unique procedures associated with each visit), the team developed an electronic record keeping software de novo to track these tasks for all 3,000 participants as they progress through each stage of the study. In addition, in 2019, the team established a state-of-the-art cell biology and sample processing laboratory at the recruitment hospital in Puerto Rico for the PRIMERO study. The laboratory, directed by co-Principal Investigator Dr. Rodriquez-Santana and co-supervised by Celeste Eng, manager of the UCSF *Asthma Collaboratory* for the last 16 years, is outfitted with BSL-2 biosafety cabinets, cell culture incubators, centrifuges, refrigerator, freezer, liquid nitrogen storage, and other laboratory equipment. In line with Dr. Burchard's goal to make PRIMERO a university-wide resource, the *Asthma Collaboratory* has expanded PRIMERO to study SARS-CoV-2 and microbiome with other investigators within UCSF (Rutherford, Lynch, Chan, Ziv, and Halkias).

Outside of PRIMERO, the *Asthma Collaboratory* has recently led efforts to identify genetic variants associated with lung function in Puerto Rican and African American children with asthma. We demonstrated that 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.(Lee et al. *Am J Respir Crit Care Med* 2020; Mak et al. *Genetics* 2020) These findings grow on a body of previous research in the area of genetic ancestry and lung function (*NEJM* 2010, *Science* 2014). Importantly, since exposure to these risk factors is so varied across minority populations, such variance may help us untangle why some children develop asthma while others do not.

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 have 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 to the Microscopy Core, under the guidance of Dr. Krummel, and have moved into novel areas of technology to facilitate their use both in SABRE labs and across the campus. The Microscopy Core continues to lead applications in 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. We have also moved to support deep-sequencing efforts, including single-cell RNAseq and epigenetic analyses, such as ATACseq methods, were accelerated by providing funds for sequencing and bioinformatics. 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.

The Genetics Asthma Collaboratory has become the largest collection of annotated genomes among defined ethnic groups ever assembled for asthma, 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 in order to define genetic contributions to disposition, severity and treatment response. Dr. Burchard's work to date has focused the potential for illuminating genetic/environmental aspects underlying asthma on Puerto Rico, where the prevalence of asthma is near 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 for 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 already begun enrollment and collection of data while instituting rigorous methods for sample collection, storage and both on-site in Puerto Rico and UCSF analytical studies, for which SABRE has provided some funding in order to obtain pre-submission materials for a grant 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 has also 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. 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 realize 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. Dr. Battacharya investigates lung injury, and has pivoted rapidly to address mechanisms by which COVID-19 mediates such devastating lung destruction. 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. Each of their CVs has been included.

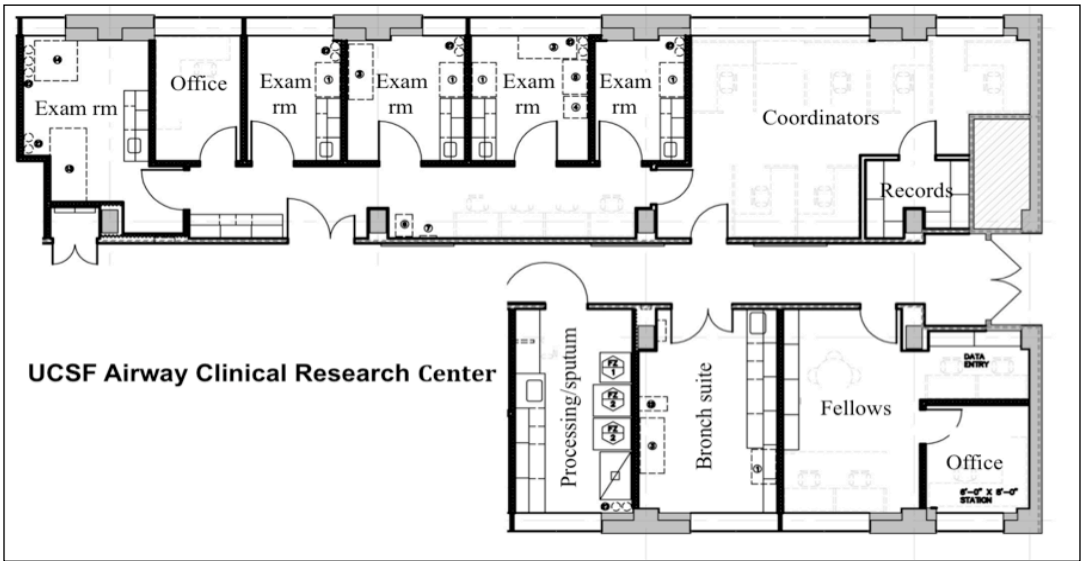
SABRE RNA-seq Initiative

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/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 are beginning to accrue 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. All of these data are established in the public science space with proper masking of human data. This initiative will be repeated in the coming academic year as appropriate to proceed with timely follow-up of these promising discoveries, some of which are noted in manuscripts highlighted below.

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.

The ACRC enables approximately 800 subject visits per year. The ACRC supports multiple NIH research programs that involve human-based study of airway disease

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.

Current Active 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. 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.

4. 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.

5. 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.

6. 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.

7. U10 HL109146 (07/01/2011 – 07/01/24): **:** *Clinical and Molecular Phenotypes of Severe Asthma*. 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 4 patients with severe asthma

8. U01 HL128952 (09/09/15-7/31/19 in no cost extension): *Redefining Therapy In Early COPD*: RETHINC (Woodruff). The goal of this grant is to determine whether current and former smokers with preserved spirometry and respiratory symptoms will respond to inhaled bronchodilator therapy with improvement of their symptoms in a randomized controlled trial.

9. R01 HL121774 (01/01/17-08/31/20) *Functional Analysis of the Pulmonary Microbiome during COPD* (Woodruff Co-I). This study investigates a pathway that links inflammation, Gram negative bacterial overgrowth, mucus production and chronic bacterial colonization in COPD.

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. 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.

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. The goal of this study is to define the heart failure phenotypes associated with COPD using 4D MRI and exercise echo by leveraging the SPIROMICS study.

15. U01 HL126493 (8/01/14-4/30/19 in no cost estension): *Defining a Comprehensive Reference Profile of Circulating Human Extracellular RNA* (Woodruff, Erle). The goal of this study is to use RNA sequencing to establish the reference range of exRNAs as biomarkers in 12 different body fluids.

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 Parnassus. Richard Locksley organizes the basic immunology research seminars and is a Co-PI on the Gnotobiotic Initiative.

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 had to be postponed at least a year due to the SARVS-CoV-2 pandemic.

Human Upper Respiratory Tract Analysis

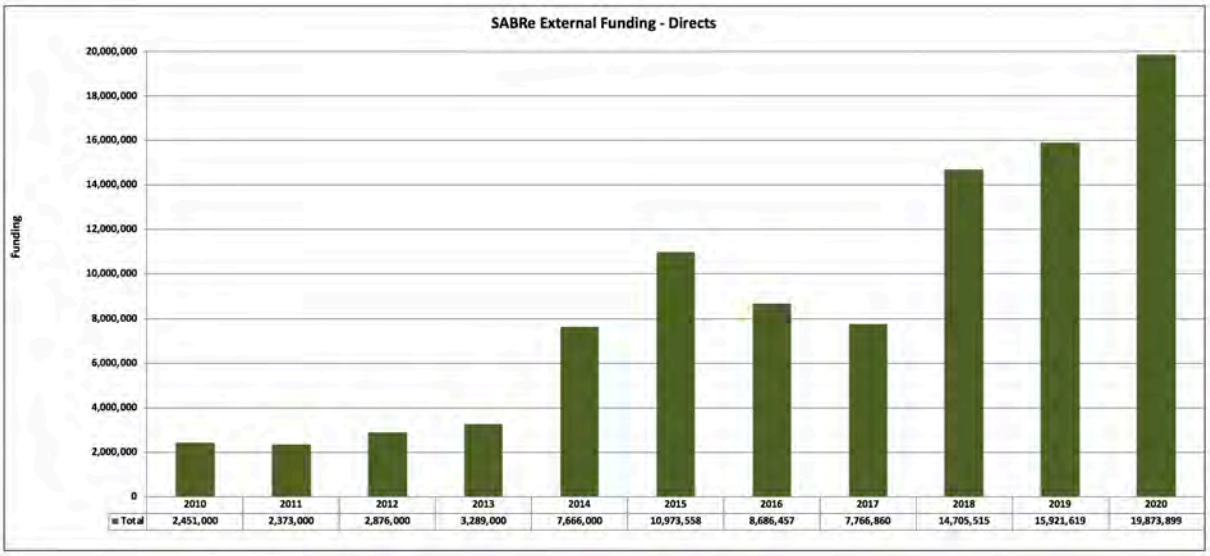
The SABRE Center is working with a UCSF surgical practice located at Mt. Zion campus with experience taking care of large number of patients with allergic nasal polyposis. These investigators, Drs. Andrew Goldberg and Steven Pletcher, faculty in the Department of Otolaryngology and Head and Neck Surgery 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, which remains enthusiastic and receptive to our overtures. 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 also

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 will be 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 total extramural funding procured by core investigators was highlighted by the Burchard lab's $10 million dollar grant over 5+ years to prospectively study the prevalence of asthma in 1,000 Puerto Rican newborn children.

Activities related to the SABRE Center resulted in publication of numerous manuscripts and contributions to many successfully awarded grants and fellowships of various types to investigators at UCSF. Despite our successes in competing for extramural resources, the flexibility of SABRE support is not matched by these types of grant monies.

Highlighted SABRE Center-supported manuscripts impacting asthma-related research in 2019-20

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.

Pua HH, HC Happ, CH Gray, DJ Mar, NT Chiou, LE Hesse, KM Ansel. 2019. Increased hematopoietic extracellular RNAs and vesicles in the lung during allergic airway responses. *Cell Reports* 26:933-44.

High-throughput RNA-sequencing has provided an unprecedented exploration of gene expression in tissues, but exploration of extracellular RNAs in body fluids and exosomes,

and assessment of their biologic significance, is just beginning. Here, the Ansel lab established an epithelial origin for most extracellular RNAs in resting bronchoalveolar fluids, but these increase dramatically and are joined by RNAs originating from infiltrating immune cells, including microRNAs with known functions in regulating inflammatory genes. These studies done in mice pave the way for functional studies and analysis of humans with asthma to determine the role for extracellular RNAs in allergic lung disease.

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.

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 immune cells differentiate by layered ontogeny and *in situ* perinatal priming. *Immunity* 50:1425-38.

Using a novel fate-mapping system, this study revealed the development and differentiation of group 2 innate lymphoid cells, or ILC2s, that have been implicated in allergic diseases. ILC2s in the mouse develop during fetal hematopoiesis, when cells are first deposited into tissues. Upon birth, ILC2s undergo proliferation in situ, and acquire

transcriptomes that are specific to the tissues in which they reside. As established by parabiosis and fate-mapping, ILC2s are largely tissue resident cells that appear to respond locally to local perturbations in ways matched to the metabolic and functional needs of each tissue. Over time, adult-derived cells slowly replace fetally derived ILC2s, and the functional capacity of these cells will require further study to assess their role in tissue health and disease.

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 our 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.

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

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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. Lechner AJ, IH Driver, J Lee, CM Conroy, A Nagle, **RM Locksley**, JR Rock. 2017. Recruited monocytes and type 2 immunity promote lung regeneration following pneumonectomy. *Cell Stem Cell* 21:120-134.
8. 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.
9. 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..
10. 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.
11. 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.
12. Kotas ME, **RM Locksley**. 2018. Why Innate Lymphoid Cells? *Immunity* 48:1081-1090.
13. 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.
14. 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.
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. PMC6645687.

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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.
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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.
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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.
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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

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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
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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 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 260 publications with more than 80 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 poor 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. White MJ, Risse-Adams O, Goddard P, Contreras MG, Adams J, Hu D, Eng C, Oh SS, Davis A, Meade K, Brigino-Buenaventura E, LeNoir MA, Bibbins-Domingo K, Pino-Yanes M, **Burchard EG**. Novel genetic risk factors for asthma in African American children: Precision Medicine and the SAGE II Study. *Immunogenetics*. 2016 May 3. PubMed PMID: 27142222.
2. Oh SS, Galanter J, Thakur N, Pino-Yanes M, Barcelo NE, White MJ, de Bruin DM, Greenblatt RM, Bibbins-Domingo K, Wu AH, Borrell LN, Gunter C, Powe NR, **Burchard EG**. Diversity in Clinical and Biomedical Research: A Promise Yet to Be Fulfilled. *PLoS Med*. 2015 Dec 15; 12(12): e1001918. PubMed PMID: 26671224; PubMed Central PMCID: PMC4679830
3. Brehm JM, Man Tse S, Croteau-Chonka DC, Forno E, Litonjua AA, Raby BA, Chen W, Yan Q, Boutaoui N, Acosta-Pérez E, Avila L, Weiss ST, Soto-Quiros M, Cloutier MM, Hu D, Pino-Yanes M, Wenzel SE, Spear ML, Kolls JK, **Burchard EG**, Canino G, Celedón JC, A Genome-Wide Association Study of Post-bronchodilator Lung Function in Children with Asthma. *AJRCCM*, Vol. 192, No. 5, September 1, 2015: 634-7 PMID: 26325155
4. Pino-Yanes M, Gignoux CR, Galanter JM, Levin AM, Campbell CD, Eng C, Huntsman S, Nishimura KK, Gourraud PA, Mohajeri K, O'Roak BJ, Hu D, Mathias RA, Nguyen EA,Roth LA, Padhukasahasram B, Moreno-Estrada A, Sandoval K, Winkler CA, Lurmann F, Davis A, Farber HJ, Meade K, Avila PC, Serebrisky D, Chapela R, Ford JG, LenoirMA, Thyne SM, Brigino-Buenaventura E, Borrell LN, Rodriguez-Cintron W, Sen S,Kumar R, Rodriguez-Santana JR, Bustamante CD, Martinez FD, Raby BA, Weiss ST,Nicolae DL, Ober C, Meyers DA, Bleecker ER, Mack SJ, Hernandez RD, Eichler EE,Barnes KC, Williams LK, Torgerson DG, **Burchard EG**. Genome-wide association study and admixture mapping reveal new loci associated with total IgE levels in Latinos. *J Allergy Clin Immunol*. 2015 Jun;135(6):1502-10 PMID: 25488688; PMCID: PMC4458233
5. McGarry ME, Castellanos E, Thakur N, Oh SS, Eng C, Davis A, Meade K, LeNoir MA, Avila PC, Farber HJ, Serebrisky D, Brigino-Buenaventura E, Rodriguez-Cintron W, Kumar R, Bibbins-Domingo K, Thyne SM, Sen S, Rodriguez-Santana JR, Borrell LN, **Burchard EG**. Obesity and Bronchodilator Response in African American and Hispanic Children and Adolescents with Asthma. *Chest.* 2015 Mar 5. PMID: 25742612

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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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Jeoung-Sook Shin is an Associate Professor in the Department of Microbiology & Immunology. She completed her B.S. and M.S. in Chemistry at Seoul National University, Korea. She received her Ph.D. from Duke University and her postdoctoral training at Yale University as a Jane Coffin Childs Memorial Fund Postdoctoral Fellow.

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
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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
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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
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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
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12. Greer, AM and **Shin, JS**. The Role of FceRI expressed by dendritic cells and monocytes. *Cellular and Molecular Life Sciences.* 72:2349, 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. 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.
2. 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.
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5. 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.
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SABRE CENTER ASSOCIATES

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Mallar Bhattacharya is an Assistant Professor in the Department of Medicine, Division of Pulmonary and Critical Care. He completed his A.B. and M.D. at Harvard University and his M.Sc. at University of Oxford. He completed internal medicine residency at Johns Hopkins Hospital followed by clinical and postdoctoral research training at University of California, San Francisco.

The Bhattacharya laboratory is interested in understanding the molecular mechanisms by which lung macrophages signal to other lineages under acute inflammatory conditions. The current research is focused on interactions between **monocyte-derived macrophages and fibroblasts**. We seek to determine the functional role of macrophage contacts with fibroblasts in airway and lung interstitial inflammation. The inflammatory "micro-niches" of the lung, whether the interstitial fibrotic niche that develops after lung injury or the bronchovascular cuff where inflammatory cells accumulate after allergen challenge, are rife with cell-cell interactions whose significance is unknown. In our lab, we are using mouse lung slice imaging to unpack this complexity with a focus on pathways regulated by monocyte-derived macrophages. These cells establish contacts with fibroblasts in the first few days after lung injury or with airway allergen challenge. Current projects focus on macrophage-derived signals, including both growth factors and metabolites, that regulate fibroblastic activation with reciprocal effects on lung repair and immunity.

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.
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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.

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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.
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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.

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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.

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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

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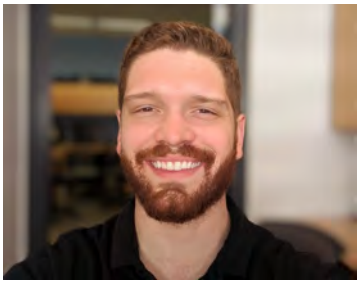
d. Sweerus K*, Lachowicz-Scroggins ME*, **Gordon ED**, LaFemina M, Huang X, Parikh M, Fahy JV, Frank JA. Claudin-18 deficiency is associated with airway epithelial barrier dysfunction and asthma. J Allergy Clin ImmunoI, 2016 Apr 20. pii: S0091-6749(16)30089-6. PMCID: PMC5073041

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 Bio Informatics 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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Aparna Sundaram is an Assistant Professor in the Division of Pulmonary and Critical Care Medicine in the Department of Medicine. She completed both her B.S. in Biomedical Engineering and M.D. at Northwestern University. After completing her internship and residency in Internal Medicine at Northwestern, she pursued fellowship training in Pulmonary and Critical Care Medicine at the University of California, San Francisco. She then completed a postdoctoral research fellowship in the laboratory of Dr. Dean Sheppard in the Lung Biology Center and Cardiovascular Research Institute at the University of California, San Francisco.

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. 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
2. 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.
3. 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.
4. 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.

5. 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.
6. 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.
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8. 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.

Strategic Goals

The efforts of this center are being directed toward improving imaging technologies for the normal and allergic lung. In 2020, 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 automate a novel microscopy platform in collaboration with the Krummel Lab that enables spatial tagging of cells for downstream single cell RNA sequencing analysis.
4. To incorporate the newly released Micro-Manager (open-source and UCSF based) Python extension Pycro-Manager, into our homebuilt 2-photon, light-sheet, spinning disk, and widefield microscopy systems.
5. To integrate additional open-source machine learning pixel-classification software such as Ilastik, DeepCell, StarDist, YaPiC, LabKit, and PyImageQualityRanking into the Multiplexed Ion Beam Imaging (MIBI) and other data analysis pipelines.
6. To extend the BIDC's 3D cell surface morphology analysis program to include multi-channel comparison and correlation studies.
7. 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.

8. To upgrade and extend the capabilities of the selective-plane imaging microscope (SPIM) to include more simultaneous fluorophore imaging capabilities while simultaneously increasing the overall speed of the microscope.
9. To continue to develop in collaboration with the Molofsky lab 8+ color panels for tissue staining.

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

Currently there are 187 unique users of the BIDC. Many users are trained on multiple instruments. These users represent 79 principal investigators or labs. These labs are drawn from 22 departments or organizational units.

In 2019, 139 new user trainings were completed. 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. We do not charge for our time through recharges, thus encouraging 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	Kajimura	Reiter
Anderson	Klein	Roose
Ashworth	Knox	Rosenblum
Bhattacharya	Koliwad	Roybal
Bhushan	Krummel	Santana
Brack	Ku	Sarwal
Bush	Laird	Scharschmidt
Chan	L'Etoile	Schneider

Chang	Looney	Schrepfer
Chapman	Lowell	Schurman
Conti	Ma	Shum
Cyster	Marcucio	Sneddon
Defranco	Marshall	Tlsty
Den	Marson	Tward
Dumont	Matthay	Vaisse
Fahy	McCune	Vasquez
Gartner	McManus	Verkman
Goga	Molofsky	Wang
Gould	Navaratna	Waterfield
Hebrok	Nystul	Weaver
Hervey-Jumper	Okimoto	Werb
Hinrichs	Panter	Wolters
Ho	Paredes	Xu
Hsieh	Peng	Yu
Huang	Piraner	Zhang
Huang	Pollen	
Ibrahim	Rajkovic	

Recent Accomplishments

In 2019, scientifically:

1. John Eichorst (BIDC, Bioinformatics Programmer) in collaboration with the Krummel Lab built a novel microscopy platform that enables spatial tagging of cells for downstream single cell RNA sequencing analysis. This microscope combines standard imaging modalities with the capability to illuminate samples with spatially defined patterns of light for photo-uncaging using a digital micromirror device.
2. John Eichorst (BIDC, Bioinformatics Programmer) in collaboration with the Krummel Lab developed user-friendly software to correlate geometric features in 3D images of t-cells to areas on the exterior of the t-cells containing locally high fluorescence intensities (puncta). The work this past year involved calculating curvature along the cell's exterior, locate and characterize protrusions based on curvature calculation and an optimization of a feature extraction method to locate puncta. The curvature program was generalized to an Imaris Extension.
3. Austin Edwards (BIDC, Bioinformatics Programmer), Katya Maidji and Joshua Vasquez (Vasquez Lab) developed analysis pipelines for granulomas infected with tuberculosis. Austin trained a machine learning classifier to segment bacteria in the tissue and also developed software to draw custom ROI overlays on the tissue and filter the segmentation results based on the ROIs.
4. Austin Edwards (BIDC, Bioinformatics Programmer), Jillian Jespersen and Jody Baron (Baron Lab) trained a machine learning classifier using Ilastik to segment the cells and classify them based on marker and have also developed a tool for spatially clustering cells and measuring the distance of these clusters to the nearest vessels innervating the tissue.

5. 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 in-depth assessments of state-of-the-art technologies for image segmentation and cell detection, such as DeepCell (deep learning) and Ilastik (multi-tool machine learning platform) have opened them up as tools within the BIDC.
6. Jordan Briscoe (BIDC, SRA and Ran Yu (Krummel Lab) successfully imaged the real-time infiltration of bispecific antibodies into live tumors through "leaky" blood vessels.
7. Kyle Marchuk (BIDC, Director) and Madelene Dahlgren (Molofsky Lab) have been refining an 8-color lung tissue staining panel for imaging on the Leica Sp8. The white light laser, user defined emission filters using an AOBS, and spectral unmixing software has made available high-dimensional imaging to the average user.
8. 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.

Introduction of new people and equipment

Over the past year two members of the BIDC, Taylor Shagam and Jordan Briscoe, left to pursue career opportunities outside of UCSF. Microscopy Specialist Tory Harwin has been hired to ensure the BIDC will maintain services. Tory's role will include microscope training and maintenance, book keeping and supply ordering, as well as contributing to the general health of the BIDC. Alongside Bioinformatics Programmer John Eichorst, Tory will become point-person for intravital-imaging services within the BIDC.

The ImmunoX Initiative at Parnassus Heights generously sponsored an equipment RFA to upgrade and improve imaging and analysis capabilities within the BIDC. With additional generous contributions from departments on campus, as well as SABRe, four major upgrades were funded and installed. The Nikon A1r Multi-Photon and Laser Scanning Confocal Microscope received an upgrade to a 1k resonant scanner system alongside adding more modern and sensitive PMTs. This upgrade allows for video rate intravital (including lung) acquisitions with 1024x1024 image resolution compared to 512x512 prior to the upgrade. The BIDC added a Leica Sp8 Laser Scanning Confocal Microscope with a White-Light Laser to our inventory. This microscope was designed for high-dimensional imaging of large cleared tissue sections and has significantly alleviated the reservation burden for the Nikon A1r resulting in the Nikon A1r being more available for intravital (including lung) imaging experiments. Two of the BIDC's Analysis Station workhorses were upgraded to new machines featuring 128 GB RAM, large m.2 SSD hard drives, and CUDA enabled NVIDIA GPUs to increase image analysis processing power. These machines are well suited to take advantage of recently released Imaris 9.6, which includes inline machine learning pipelines. The personal workstations of the BIDC personnel also received much needed replacements, which further makes available the Analysis Suite to our members. Additionally, the BIDC applied for and received a University award to purchase a modern compresstome from Precisionary. The new tissue slicing technology reduces shear and chattering, which allows for thinner slices and increased tissue viability.

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.

Recent publications

A number of recent and forthcoming publications, both methodological and research-orientated, have been produced with help of the facility during the past year. Some of these include:

1. Cleary, Simon J. and Hobbs, Carl and Amison, Richard T. and Arnold, Stephanie and O'Shaughnessy, Blaze G. and Lefrançais, Emma and Mallavia, Beñat and Looney, Mark R. and Page, Clive P. and Pitchford, Simon C. "LPS-induced Lung Platelet Recruitment Occurs Independently from Neutrophils, PSGL-1, and P-Selectin" American Journal of Respiratory Cell and Molecular Biology. 61(2). 232-243. **2019**. [DOI: 10.1165/rcmb.2018-0182OC].
2. Dahlgren MW, Jones SW, Cautivo KM, et al. "Adventitial Stromal Cells Define Group 2 Innate Lymphoid Cell Tissue Niches." *Immunity*. **2019**;50(3):707-722.e6. [doi:10.1016/j.immuni.2019.02.002].
3. Hagerling, C., H. Gonzalez, K. Salari, C.-Y. Wang, C. Lin, I. Robles, M. van Gogh, A. Dejmek, K. Jirström & Z. Werb (**2019**). Immune effector monocyte - neutrophil cooperation induced by the primary tumor prevents metastatic progression of breast cancer. Proc. Natl. Acad. Sci. USA. 116(43):21704-21714. [Epub ahead of print 10/7/19]. PMID:31591235; PMCID:[PMC6815161].
4. Jason Wong, Sara L. Sampson, Hildegarde Bell-Briones, Ann Ouyang, Ann A. Lazar, Jeffrey C. Lotz, Aaron J. Fields. "Nutrient supply and nucleus pulposus cell function: effects of the transport properties of the cartilage endplate and potential implications for intradiscal biologic therapy" *Osteoarthritis Cartilage*. **2019** Jun; 27(6): 956–964. Published online 2019 Feb 2. [doi: 10.1016/j.joca.2019.01.013].
5. Jones KB, Furukawa S, Marangoni P, et al. Quantitative Clonal Analysis and Single-Cell Transcriptomics Reveal Division Kinetics, Hierarchy, and Fate of Oral Epithelial Progenitor Cells. *Cell Stem Cell*. **2019**;24(1):183-192.e8. [doi:10.1016/j.stem.2018.10.015].
6. Owyong, M., J. Chou, R. J. E. van den Bijgaart, N. Kong, G. Efe, C. Maynard, D. Talmi-Frank, I. Solomonov, C. Koopman, E. Hadler-Olsen, M. Headley, C. Lin, C.-Y. Wang, I. Sagi, Z. Werb* & V. Plaks* (**2019**). MMP9 modulates the metastatic cascade and immune landscape for breast cancer anti-metastatic therapy. Life Sci Alliance. 2(6): pii: e201800226; [doi.org/10.26508/lsa.201800226].

7. Sharir, A., Marangoni, P., Zilionis, R. et al. A large pool of actively cycling progenitors orchestrates self-renewal and injury repair of an ectodermal appendage. *Nat Cell Biol* 21, 1102–1112 (**2019**). [https://doi.org/10.1038/s41556-019-0378-2].

Plans for the Coming Year

1. The BIDC will continue to work with the Krummel lab to automate and expand their novel microscopy platform that enables spatial tagging of cells for downstream single cell RNA sequencing analysis. Automation with a user-friendly interface will allow for increased spatial location resolution and allow the technology to span to other microscopes within and outside the BIDC.
2. 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) 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.
3. The Multiplexed Ion Beam Imaging (MIBI) system is now online and producing high-dimensional images. The BIDC will work alongside our collaborators in developing and evaluating analysis pipelines. This includes the learning and understanding of recently published open-source software designed for cell segmentation and identification. Such packages include DeepCell, StarDist, YaPiC, LabKit, and PyImageQualityRanking. Understanding these packages helps make them available as tools for the rest of the BIDC community.
4. John Eichorst (BIDC, Bioinformatic Programmer) has developed a user-friendly interface for his software that evaluates the morphology of cell surfaces in the 3D. This software will be extended to evaluate features between channels including colocalization of puncta and other structures.
5. Kyle Marchuk (BIDC, Director), Ophir Klein (UCSF) and Jeremy Green (King's College, London, UK) are working in collaboration on an automated pipeline for the 3D segmentation and morphological evaluation of epithelial cells undergoing tissue invagination during tissue development.
6. 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.
7. The BIDC will continue to work in collaboration with the Molofsky lab to develop 8+ color panels for cleared tissue imaging. Increasing the fluorophores per sample increases the information gathered per experiment thus increasing the efficiency of experiments. Analysis pipelines and software will be developed as needed.

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. BIDC microcopy specialist Tory Harwin will lead the lung imaging pilots with a focus on improving intravital methods and instrumentation.

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. *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

The ImmunoX Initiative

Principal Investigator, Vincent Chan, Ph.D., ImmunoX Chief Strategist and Assistant Professor

- For the past 2 years, SABRE has supported and participated in the Bakar ImmunoX Program (http://ImmunoX.ucsf.edu/), an initiative on the Parnassus campus, which is jumpstarting a bevy of new collaborative projects that will benefit our scientific community. These projects, called "CoProjects", are designed to integrate our community through common pipelines and data curation, with the aim to build immune profiles for untapped streams of human diseases at UCSF. So far, ImmunoX has had two calls for proposals (2019 and 2020), 8 CoProjects (up to $1m each) and 18 Pilots (up to $100k each).
- The Bakar ImmunoX Program is also expanding its initial five CoLabs (http://colabs.ucsf.edu/) to facilitate the development of new Junior CoLabs to enhance ImmunoX's collaborative-projects model. These Junior CoLabs receive more modest support and have smaller overall goals than the CoLabs do but still make use of the shared ecosystem of research facilities that help maximize researchers' work in biology, flow cytometry, biological imaging development, genomics, and data sciences. Five new Junior CoLabs include:
- BSL3 Junior CoLab
- Microbiome Junior CoLab (with BCMM co-investment)
- Gnotobiotic Junior CoLab
- Mouse Transplant Junior CoLab
- Metabolomic Junior CoLab (with BCMM co-investment)
- A sixth Junior CoLab, the Center for Clinical-Translation Research Management (CenTRe), is under proposal to manage clinical-translational resources, pipelines, and infrastructure, including IRB applications.
- ImmunoX also manages the Immunology Seminar Series, Journal Clubs, Faculty Wine and Cheese Series, and contributes to the Parnassus Research-in-Progress Seminars. It organizes the UCSF ImmunoX/UCB Immunology Annual Retreat and ImmunoSkamania Summit, and funds a slot for the Summer Research Training Program. Recently, it launched a Computational Immunology Emphasis as part of the BMS Immunology Track, which incorporates new Computational Immunology Fellowships for recruitment and an annual Hackathon.

ImmunoX strives to build a thriving and connected community. It has launched a successful seed grant called the ImmunoX Community Initiative (ICI) to enrich and encourage individuals and groups to take on a more active and visible role within the community. Events include:

- Improve with Improv
- Movie Nights at Cole Hall

- Professor and a Pint
- DEI Networking Event
- Breaking Down Biology Blog

It has launched pioneering programs to benefit the community, including:

- ImmunoX Maternity Support Program (*up to $30k for technician assistance*)
- ImmunoXX^{+} Women in Immunology Group (*including an annual WII symposium*)
- ImmunoDiverse URM Group (*with a proposal to increase diversity and awareness across our entire program through newly-allocated resources and required trainings*)
- Sabbatical Assistance Grant (*up to $20k for incoming and outgoing sabbatical studies*)

SABRE RNAseq Consortia

Allen Lab

Accomplishments during prior funding period

My laboratory is investigating the immunological mechanisms that trigger inflammation in the lung in the context of allergic asthma. We are particularly interested in how adaptive immune responses to inhaled allergen are generated. We proposed to use RNAseq technology to elucidate the molecular regulation of IgE production as well as to characterize the distinct functions of antigen presenting cells in the lung that capture inhaled allergens. In the past year, we made major progress in two major areas with the funds awarded to us. First, we used RNAseq to identify genes differentially expressed in B cells undergoing class switch recombination to IgE, a prerequisite step in IgE production. We are now testing the functional role of these candidate genes by CRISPR-mediated mutagenesis in primary B cells to help elucidate the molecular regulation of IgE class switch recombination. Second, we used single-cell RNAseq to profile allergen-capturing myeloid cells in the lung that may serve as antigen-presenting cells. We did this analysis in the context of an inflammatory model induced by house dust mite versus in the absence of inflammation (**Figure 1**), together with a marker to identify infiltrating cells versus resident cells. We are still extensively mining this dataset, but have already developed substantial new insights into the allergen-capturing cells recruited into the lung versus the changes in resident cells in the context of inflammation. This data is generating new hypotheses regarding the functions of these cell types and how adaptive immune responses to inhaled allergens are initiated. For these projects, we have been aided by the technical and analysis expertise of the Lung Biology Center / SABRE Genomics Core, as well as the Institute for Human Genetics Core.

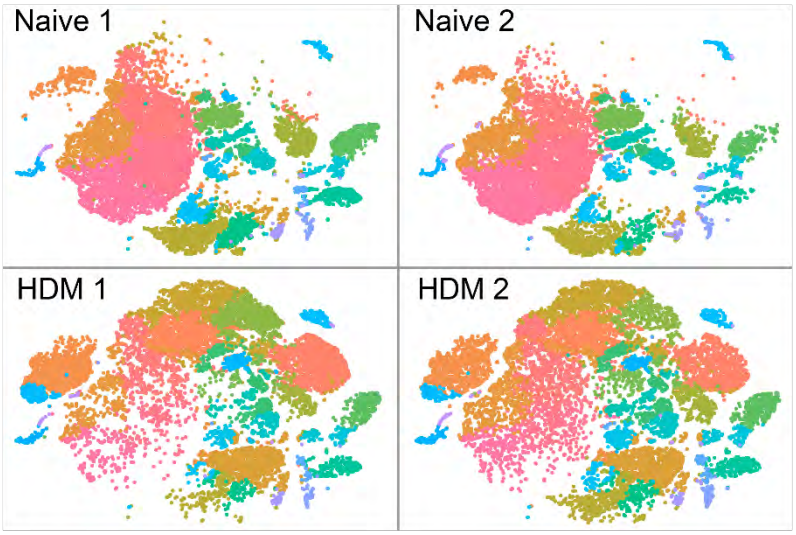

Figure 1. t-SNE plots representing single cell RNAseq analysis (10x platform) of antigen-presenting cells in the lung following exposure to house dust mite (HDM) versus in the naïve state. Two samples of each type were processed, which displayed remarkable similarity.

Request for second year of support

In the next year, we have two major objectives to further elucidate the initiation of allergic immune responses in asthma.

1) We plan to expand our studies of the B cells that produce IgE, focusing this year on using RNAseq technology to gain insight into the mechanisms controlling the fate of IgE-expressing B cells. In particular, we will elucidate the gene expression profile of B cells that have already switched to IgE, whereas last year we focused on the gene expression profile of B cells that were undergoing class switch recombination to IgE. We have previously shown that IgE-switched B cells undergo enhanced plasma cell differentiation and poorly compete within germinal centers, where the generation of high affinity antibodies takes place (Yang et al. Immunity 2012). We have traced these distinct properties of IgE-switched B cells to the IgE B cell receptor (BCR), which has unique signaling properties even in the absence of ligand (Yang et al. eLife 2016). However, the molecular basis by which the IgE BCR controls the fate of these B cells is unknown. We will do RNAseq analysis in which we modulate BCR signaling with genetic mutants and/or pharmacological inhibitors and we will compare B cells expressing the IgE BCR to other BCRs (such as IgG1) in order to elucidate the genes affected by IgE BCR signaling. As an ancillary goal, we will continue to characterize the repertoire of variable regions of the B cell receptors expressed by IgE-expressing B cells induced in response to allergen exposure in the lung.
2) We and other groups have found that basophils, one of the two main types of IgE effector cells, accumulate in the lung in and in lymph nodes in response to some allergens. Studies in human patients have confirmed that basophils accumulate in the lungs of asthmatics with allergic inflammation. However, remarkably the true functions of basophils in these tissues remain poorly defined. Based originally on collaborative studies with Dr. Richard Locksley's laboratory, which made genetic tools to visualize and manipulate basophils, we have been able to image basophils by two-photon microscopy and test the consequences of their elimination under various conditions. In doing so we have defined a lymph node model in which numerous basophils accumulate and orchestrate alternative activation of macrophages and recruitment of other cell types to inflammatory foci. We postulate that a similar role for basophils may occur in the lung in asthma. Of particular interest to our group is the activation of basophils by IgE/allergen in the lung and lymph nodes, as the impact of IgE-mediated activation in vivo is poorly defined and has not been characterized in gene expression studies thus far. We plan to use RNAseq to study the gene expression profile of basophils in these contexts to gain insights into their physiological roles. Co-isolation of other tissue cells (such as resident macrophages and stromal cells) and analysis in single-cell sequencing may also reveal gene expression changes following IgE-mediated activation of basophils, thus proving further insights into basophil function.

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). Among all patients with chronic rhinosinusitis (CRS) the presence of NP 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.

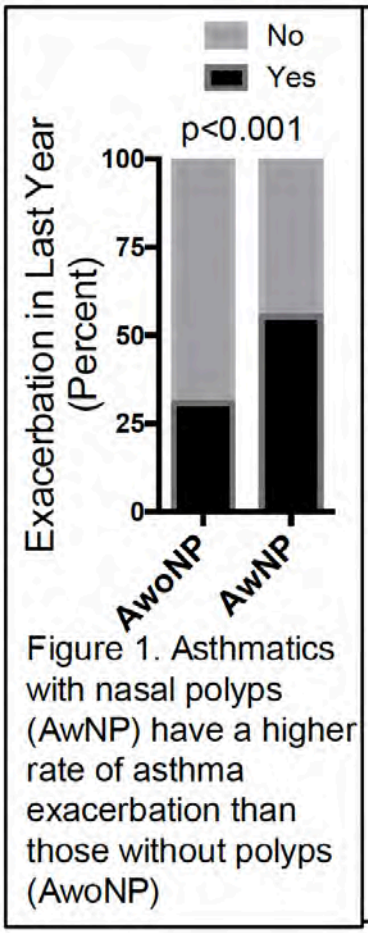

Figure 1. Asthmatics with nasal polyps (AwNP) have a higher rate of asthma exacerbation than those without polyps (AwoNP)

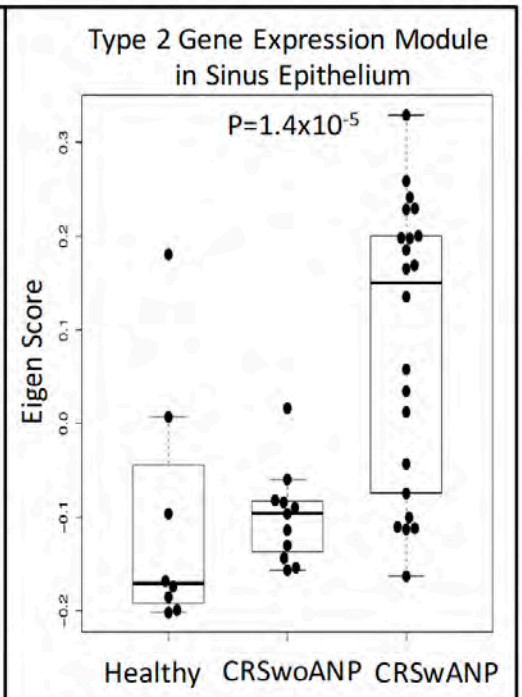

Figure 2. Type 2 Gene Signature is increased in the sinus epithelium of CRS with asthma and nasal polyps (CRSwANP) compared to health and CRS without asthma and polyps (CRSwoANP).

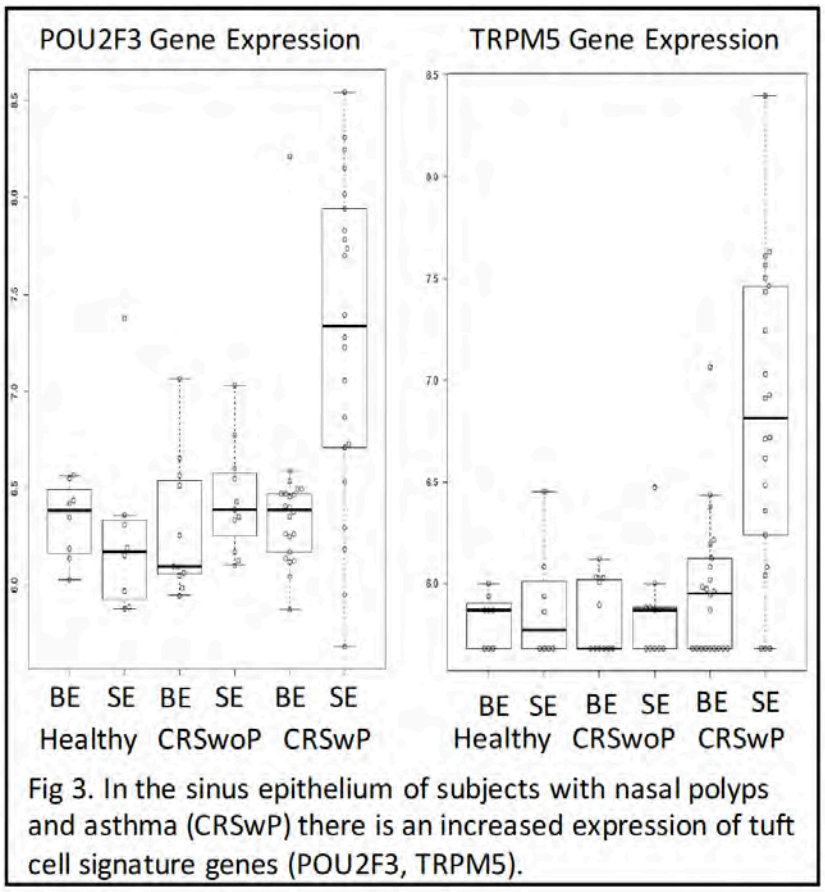

Fig 3. In the sinus epithelium of subjects with nasal polyps and asthma (CRSwP) there is an increased expression of tuft cell signature genes (POU2F3, TRPM5).

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 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. In preliminary data, we find a robust gene expression signature of tuft cells (POU2F3, TRPM5) in the type 2 gene expression module. 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), or suggest a dissociation between the roles 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 nasal polyposis 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). The cell type percentages in each of these clusters was surprisingly similar between polyp and health with the exception of an increase in goblet cells. We were able to identify a population of rare cells in cluster 10 which contained markers of tuft cells and ionocytes. These cells were subclustered using hierarchical clustering and we identified a population of tuft cells with markers that included LRMP, KIT, AVIL, POU2F3, TRPM5. These cells were increased in number 2.5 fold in the polyp epithelium compared to healthy epithelium. We were even more surprised to identify a population of tuft cells within the polyps but not in the healthy controls which were strongly expressing BMX, GNG13, IL17RB. These tuft cells which we called “inflammatory tuft cells” appear also in the nasal epithelium of mice stimulated with IL-13. Given the importance of tuft cells as the producer of IL-25 as well as acetylcholine, prostaglandins, and leukotrienes, further investigations will focus on the function of this novel tuft cell subset.

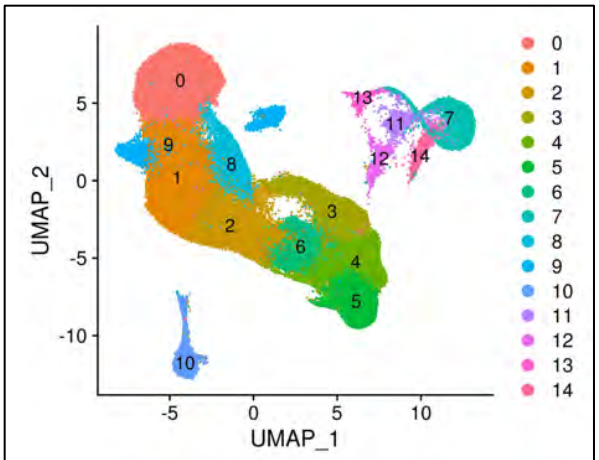

Figure 4: Single cell RNA sequencing reveals 15 clusters of epithelial cells in the sinus epithelium in healthy and nasal polyposis.

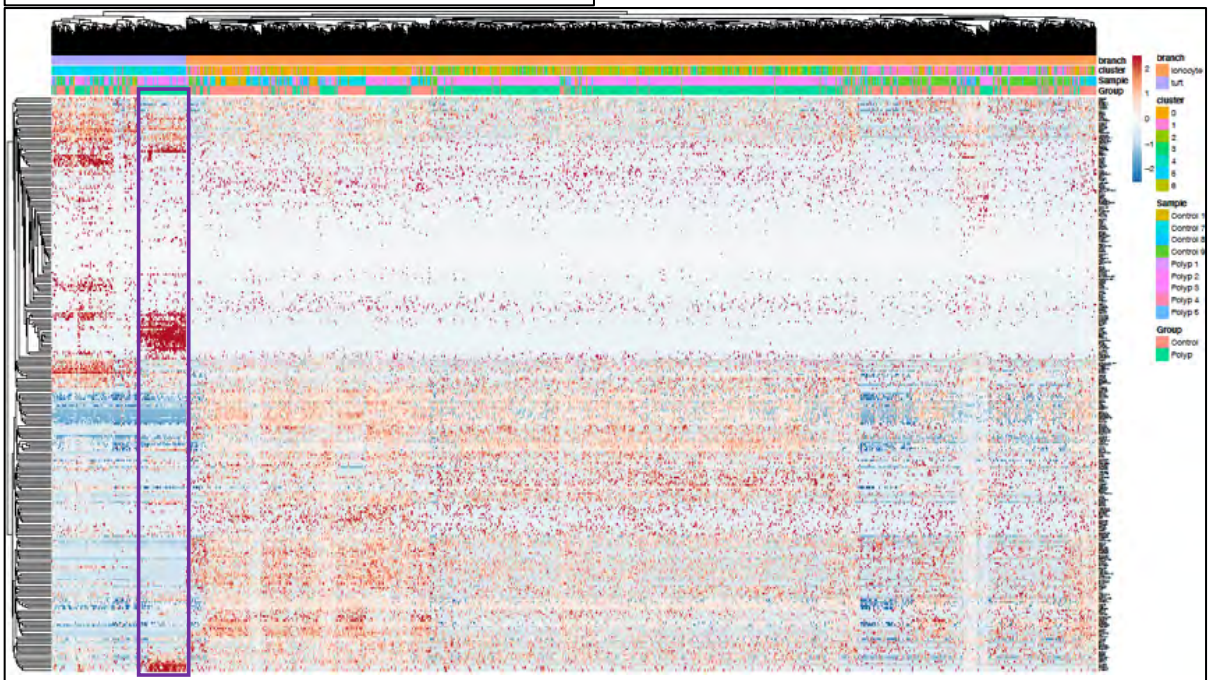

Figure 5. Hierarchical clustering reveals tuft cells in nasal polyps have a distinct inflammatory phenotype.

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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 2019-2020 Schedule
Mondays, 9 am - Room: N-225

Date	Speaker	Host
September 6	Chris Goodnow, *Garvan Institute of Medical Research*	Jason Cyster
September 9	Wayne M. Yokoyama, *Washington University School of Medicine*	Lewis Lanier
September 16	Larry Fong, *UCSF*	
September 23	John T. Harty, *University of Iowa*	Nadia Roan
September 30	Jimmie Ye, *UCSF*	Lindsey Criswell
October 7	Dan R. Littman, *NYU*	David Wofsy
October 14	Maxim N. Artyomov, *Washington University School of Medicine*	Matthew Spitzer
October 21	Bali Pulendran, *Stanford University*	Jody Baron
October 28	Marion Pepper, *University of Washington*	Margaret Feeney
November 4	Francisco Quintana, *Harvard Medical School*	Minnie Sarwal
November 21	Karen E. de Visser, *Netherlands Cancer Institute*	Kelly Kersten
December 2	Marc K. Jenkins, *University of Minnesota*	Mark Andersen
December 9	Ram Savan, *University of Washington*	Mark Ansel
January 6	Richard Flavell, *Yale School of Medicine*	Zena Werb
January 13	Jean-Laurent Casanova, *Rockefeller University*	Joel Ernst
February 3	Nir Hocohen, *Harvard Medical School/MGH*	Melissa Reeves
February 10	Jenny Ting, *University of North Carolina*	Averil Ma
February 24	Paula M. Oliver, *University of Pennsylvania*	Art Weiss
March 2	Vijay Kuchroo, *Harvard Medical School*	ImmunoX Grad Students
March 9	Denise Monack, *Stanford University*	Anthony DeFranco
March 16	Donna Farber, *Columbia University*	Qizhi Tang
March 23	Andrew Oberst, *University of Washington*	Adrian Erlebacher
March 30	Ken Murphy, *Washington University School of Medicine*	Ari Molofsky
April 6	Jennifer Gommerman, *University of Toronto*	Sergio Baranzini
April 13	Galit Alter, *Harvard Medical School*	Satish Pillai
April 20	Dan Mucida, *Rockefeller University*	Mary Helen Barcellos-Hoff
April 27	Manuela Rafffatellu, *U.C. San Diego*	Tiffany Scharschmidt
May 4	Rahul Satija, *NYU*	Jimmie Ye
May 11	K. Christopher Garcia, *Stanford University*	ImmunoX Post Docs
May 18	Filip Swirski, *Harvard Medical School/MGH*	Judith Hellman

UCSF PULMONARY RESEARCH CONFERENCE 2019-2020
Mondays, 4:00 pm - Parnassus

Date	Talk 1 (Clinical)	Talk 2 (Basic)
01/06/20	***Fellows Feedback Session 1***	
01/13/20	Nirav Bhakta	
01/20/20	***MLK Holiday***	
01/27/20	Franklin Heng	Luke Bonser
02/03/20	Shoshana Zha	Mike Podolsky
02/10/20	Zimu Deng	John Greenland
02/17/20	***President's Day Holiday***	
02/24/20	Visiting Professor - Melanie Koenigshoff	
03/02/20	Visiting Professor - Lorraine Ware (Vanderbilt)	
03/09/20	Ram Naikawadi	Chris Berger
03/16/20	Daniah Beleford	Melia Magnen
03/23/20	***Faculty Feedback and appreciation***	
03/30/20	Erica Farrand	Danny Calabrese
04/06/20	Walter Eckalbar	Nadia Herrera
04/13/20	Sam Oh	Aartik Srma
04/20/20	Paola Torre	Elias Cornejo-Taylor
04/27/20	Pratik Sinha	Eunie Lee
05/04/20	Michelle Yu	Christina Yoon
05/11/20	Vaibhav Upadhyay	Michael Peters
05/18/20	***ATS - (no conference)***	
05/25/20	***Memorial Day holiday (no conference)***	
06/01/20	Bhavika Kaul	KD Koh
06/08/20	Olivier Bernard	Elizabeth Yu
06/15/20	***Fellows Feedback Session 2***	

SABRE Asthma Research Conference Schedule 2020

Location: 513 Parnassus Avenue, HSE-402		
Time: 9:00- 10:00AM		
Day: 4th Wednesday of each month (**except Wednesdays that fall on a UCSF holiday*)		
Date	Presenter	Title
2/26/20	K. Mark Ansel, Ph.D.	*RNA regulation of effector and regulatory T cells*
3/25/20	Dean Sheppard	*Cancelled due to COVID-19*
4/22/20	Jeoung-Sook Shin	*Cancelled do to COVID-19*
5/27/20	John Fahy, M.D.	*Update on mucus plugs in airway disease – clinical features, computer vision and mucolytics*
6/24/20	Ari Molofsky, M.D.	*Rescheduled for November 25, 2020*
		Summer Break
9/23/20	Esteban Burchard, M.D.	
10/28/20	Mallar Bhattacharya, M.D.	
11/25/20	Ari Molofsky, M.D.	

UCSF
University of California
San Francisco

BAKAR
IMMUNO

Harnessing Immunology
To Improve Human Health

ImmunoX Inaugural ECO Seminar

A component of the ImmunoX Seminar Series
Monday 2/3, 9 AM, PARNASSUS, N-225

"Predictive rules and altered cell states in the human immune system"

Nir Hacohen, PhD

Professor, Harvard Medical School
Director, Center for Cancer Immunotherapy, MGH

RECENT AND NEW PUBLICATIONS SUPPORTED BY THE SANDLER ASTHMA BASIC RESEARCH CENTER (2018-2020)

Christopher D.C. Allen, Ph.D.

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

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Looking to the Future
Richard M. Locksley, M.D.

The SABRE Center has become an integral component of the research community at UCSF. Challenges have emerged in maintaining interactions among established members at both Parnassus and Mission Bay campuses, but opportunities have also become clear in the increased capacities for genomics, genetics, tissue engineering and precision medicine. We continue to participate in major multi-institutional and multi-investigator initiatives supported by the National Institutes of Health, including the Severe Asthma Research Program (SARP) and the PrecISE Asthma Trials Network, and have successfully renewed the NIH Program Project Grant oriented around patients recruited to the UCSF Airways Clinical Research Center. Dr. Burchard has become a national leader in deconvoluting genomes from minority populations that suffer disproportionally from asthma and will lead a major 10 year prospective study on asthma prevalence in Puerto Rico. SABRE Center members continue to push innovative areas in allergy basic research involving new cells, including innate lymphoid cells and tuft cells, and new pathways in old cells, including IgE-producing B cells, IgE receptor-bearing dendritic cells, regulatory microRNA networks and extracellular RNAs. Core members of the SABRE Center continue to be successful in publishing high impact manuscripts and in accumulating extramural support from the NIH and other granting agencies, and individual members have been recognized by national honor organizations and granting societies. Thus, by a number of metrics, research and leadership contributions from the SABRE Center are increasingly at the forefront in shaping research agendas relevant to asthma.

The COVID-19 pandemic has created major obstacles to research-as-usual, and the flexibility and breadth of Sandler Foundation support of SABRE as enabled rapid movements towards opportunities to leverage our scientists' strengths and resources into help in understanding the virus and its impact on patients, including those with asthma. We emphasize that NIH funding does not provide such flexibility, and SABRE funds have proven most valuable in rapid development and deployment of cutting edge technologies to problems at hand to enable leveraging to assist big projects in going forward. To this end, we have supported efforts related to asthma in massive parallel sequencing, bioinformatics, genetics and the microbiota that spill out across the USCF campus to enable forward progress that includes efforts in understanding SARS-CoV-2 and its pathogenesis. These are trying times, and we are so 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.

We believe that the SABRE Center has played a formative role in shaping the footprint for patient-oriented, disease-focused, basic research at UCSF. As such, this footprint has played out to assist an accelerated community scientific response to COVID-19 in the UCSF community. 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 at all of the UCSF campuses to achieve the greatest return for cutting-edge investments in basic science as applied to human

biology and disease. We look forward to continuing novel and unexpected discoveries made by laboratories at UCSF that will signicantly impact asthma and asthma-related research and alter the course of human disease.

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

BIOGRAPHICAL SKETCHES

Christopher Allen, Ph.D.
K. Mark Ansel, Ph.D.
Nirav Rati Bhakta, M.D., Ph.D.
Mallar Bhattacharya, M.D., MSc.
Homer Boushey, M.D.
Esteban Burchard, M.D., M.P.H.
Harold Chapman, M.D.
Anthony DeFranco, Ph.D.
William DeGrado, Ph.D.
David Erle, M.D.
John Fahy, M.D., M.Sc.
James S. Fraser Ph.D.
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Erin Gordon, M.D.
Matthew Krummel, Ph.D.
Richard Locksley, M.D
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William Seaman, M.D.
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Aparna Sundaram, M.D.
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Jonathan Weissman, PhD.
Zena Werb, PhD.
Prescott Woodruff, M.D., M.P.H.

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Christopher David Caballero Allen, Ph.D.	Assistant 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 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

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

The Pew Charitable Trusts Biomedical Scholar Award
Allen, Christopher David Caballero (PI) 08/01/16–07/31/20
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

DP2 HL117752. Allen, Christopher David Caballero (PI) 09/30/12–06/30/17
Cellular interactions in asthma
This project was focused on the dynamic communication among inflammatory cells in asthmatic lungs. The major goals of this project were to develop technical approaches to simultaneously visualize multiple different types of inflammatory cells in the lung, followed by characterization of relevant cellular interactions in a combinatorial fashion, and then definition of the stromal microenvironments in which these interactions occur.
Role: PI

R01 AI103146 Allen, Christopher David Caballero (PI) 12/01/12–11/30/17
Analysis of basophil function in secondary immune responses
The major goal of this project was to determine the functional role of basophils that have captured antigen via IgE antibodies in secondary immune responses. Specifically, this project sought to evaluate whether basophils contribute to antigen transport, to the enhancement of adaptive immunity, and to tissue damage and repair.
Role: PI

R21 AI130495 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 Associate 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

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 identify 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

R21AI1280471 Ansel (PI) 5/10/18-4/30/20
Global analysis of T cell post-transcriptional regulatory elements
The major goal of the proposed project is to create a map of protein-bound cis-regulatory elements in the transcriptome of resting and activated T cells, and to determine their regulatory functions in gene expression.
Role: PI

R01HL109102 Ansel (PI) 8/1/11-3/31/20
MicroRNA directed pathway discovery in helper T cell driven airway inflammation
The major goals of this project are to identify and characterize the in vivo activity and molecular targets of miRNAs that regulate helper T cell functions relevant to asthma.
Role: PI

P01HL107202 Fahy (PI) 8/1/19-7/31/2024
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

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

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.

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

K23 HL116657 Bhakta (PI) 05/01/14-04/31/19 (NCE through 4/31/2020)
Translational research on the role of IL-17 cytokines in severe asthma
The major goals of this project are to: 1) determine the relationship of this inflammation to the already established concept of Th2-inflammation, 2) explore mechanisms of persistent eosinophilia, and 3) determine the association of IL-17-driven inflammation with two cardinal features of asthma: AHR and airway remodeling (mucous metaplasia).

U19 AI 077439 (PI: David J. Erle) 04/01/2018-03/31/2023
NIH/NIAID
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: Core Leader

R01 HL138424 (PI: David J. Erle) 08/01/2017-06/30/2021
NIH/NHLBI
Airway Epithelial Reprogramming in Asthma
Our overall goals are to identify enhancers that are important in airway epithelial cell differentiation, to determine how enhancer activity changes in asthma, and to develop approaches for targeting the activity of these enhancers.
Role: Co-I

R35 HL145235 (PI: David J. Erle) 01/01/2019-12/31/2026
NIH/NHLBI
Airway epithelial cell gene regulation: new mechanisms and therapeutic strategies
Epithelial cells line the airways and are important for maintaining lung health. Airway epithelial cell dysfunction is a key feature of asthma and other common airway diseases. 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: Co-Investigator

P01 HL107202 Renewal (PI: John V. Fahy) 07/01/2019 - 08/31/2024
NIH/NHLBI
Innate and Adaptive Immune Responses in Th2 High Asthma
This program project grant brings together clinical scientists and immunologists to tackle the problem of persistent airway type 2 inflammation which drives disease in the majority of asthmatics.
Role: Co-Investigator

BIOGRAPHICAL SKETCH

NAME **Mallar Bhattacharya, M.D., M.Sc.**	POSITION TITLE Assistant Professor of Medicine
eRA COMMONS USER NAME (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-Present	Assistant 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) Immune Determinants of Acute Lung Injury and Fibrosis: I have had a longstanding interest in the acute and chronic effects of lung injury. My earlier work focused on the role of alpha-v integrins in vascular leak during the acute phase of lung injury. Using mass spectrometry to identify novel integrin binding partners, I discovered the actin organizer and scaffold IQGAP1 as an effector of the endothelial barrier protective effects of beta-3 integrin. In recent work focusing on the fibrotic period of the wound healing response, I have used single cell mRNA sequencing to identify a subset of murine macrophages that localize to sites of fibroblast accumulation after lung injury and exert a pro-fibrotic effect. 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. This tool enabled clustering of cells revealing a transitional cell state of monocyte-derived macrophages acquiring lung resident identity within sites of fibroblast accumulation, ie the fibrotic niche. Our subsequent studies included cell ablation experiments that indicated the pro-fibrotic and activating effect of these macrophages on adjacent fibroblasts.

   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.

   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.

   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.

   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.

   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.

2) RhoA GTPase in Airway Hyperresponsiveness: The small GTPase RhoA has pro-contractile effects in airway smooth muscle and is therefore a potential therapeutic target in asthma. My interest in this pathway began with the discovery that the intracellular scaffold Iqgap1 suppresses RhoA activation in airway smooth muscle, leading to decreased contraction both at baseline and in murine allergic airway hyperresponsiveness. Mechanistically, we found

that Iqgap1 serves as a protein scaffold, supporting the function of the RhoGAP p190ARhoGAP to inhibit RhoA activation. My current R01 grant is focused on further studies in the RhoA pathway. In recent work, we performed a riboprofiling screen of airway smooth muscle genes that activate RhoA, known as RhoGEFs, with the rationale that they could be targeted for inhibition of bronchospasm. This screen led to the discovery of Arhgef12, which was also highly expressed in human airway smooth muscle. We then found that Arhgef12 is necessary for IL17A-induced airway contractility and allergic airway hyperresponsiveness in vivo. Arhgef12 thus represents a novel therapeutic target in severe asthma patients, a subset of whom have an IL17A-centric airway inflammatory signature.

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

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.

A complete list of my publications is available at:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/48006051/?sort=date&direction=descending

Research Support

Ongoing Research Support

1R01HL131560-03. Role: PI. 04/01/2016 – 03/31/2021
NHLBI
Title: The Regulation of RhoA Activation in Airway Smooth Muscle
UCSF Nina Ireland Program for Lung Health Role: PI. 01/01/2019 – 12/31/2020
Title: Defining macrophage pro-fibrotic mechanisms in lung fibrosis.
UCSF Resource Allocation Program Role: PI. 01/01/2019 – 12/31/2020
Title: Macrophage function in lung fibrosis

Completed Research Support

4K08HL114641-05 Role: PI 09/01/2012 – 06/30/2018
NHLBI
Title: IQGAP1 in vascular barrier regulation during acute lung injury
U54HL119893 Role: PI. 01/01/2018 – 06/30/2018
NHLBI
Title: Targeting ArhGEF12 in Asthma
UCSF Marcus Program for Precision Medicine Role: PI 04/01/2016 – 12/31/2017
Title: Microfluidic droplet capture for gene expression analysis of airway smooth muscle in asthma

UCSF Resource Allocation Program Role: PI. 02/01/2015 – 12/31/2016
Title: Integrin alpha-v beta-5 disrupts endothelial barrier function in acute lung injury
15BGIA22780001 Role: PI. 01/01/2015 – 12/31/2016
American Heart Association
Title: Integrin alpha-v beta-5 is necessary for stress fiber formation and vascular leak during acute lung injury and sepsis
UCSF Nina Ireland Program for Lung Health Role: PI. 01/05/2015 – 12/31/2016
Title: Integrin alpha-v beta-5 drives pulmonary vascular leak from ischemia-reperfusion in lung transplantation

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 -	Vice Chair, UCSF Department of Bioengineering & Therapeutic Sciences
2011 -	Hind Distinguished Tenured Professor Schools of Pharmacy & Medicine, UCSF

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

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 (PI: Burchard) 07/01/08 - 06/30/20
NIH/NIGMS
Role: Co-PI
Project title: 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.

24RT-0025 Burchard (PI). 7/01/2015 - 03/31/2018
TRDRP
Air Pollution, Tobacco Smoke, and Asthma in Minority Children
Goal: To identify genetic variation that contributes to differences in bronchodilator drug response using whole genome sequencing of extreme traits.

Role: Principal Investigator

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

UM1 HG008901 (Darnell) 01/14/2016-11/30/2019
NIH/NHGRI $12,216 (sub only)
Subcontract from New York Genome Center (Burchard)
New York Center for Collaborative Research in Common Disease Genomics
Goal: Dr. Burchard will advise the NYGC on genetic ancestry and risk of disease and asthma in particular. He will also advise on whole genome sequencing and application to disease risk and drug response.
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

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
c. **Chapman HA**, Wei Y, et al. Reversal of TGF□1-driven Profibrotic State in Pulmonary Fibrosis Patients. *New England Journal Medicine*. 2020, 382:1068-1070.

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

U01HL134766 Chapman, HA PI 09/01/2016-8/31/2023
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.

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	POSITION TITLE
William F. DeGrado	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)

Contribution to Science

1) Protein Design. In the 80's our group began a new approach to probe protein conformation and function through the *de novo* design of proteins. At that time, proteins were seen as impossibly complex molecules whose structure could not be predicted or designed. We therefore adopted minimalist approach to protein design in which we set out to engineer sequences of the minimal 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 to be a useful method for probing the features required for forming secondary structures (e.g., O'Neil and DeGrado's well-known thermodynamic scale of helix propensity), forming compact states known as "molten globules" and ultimately for forming 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, and we designed minimalist versions of the protein to illustrate the mechanisms by which they folded and recognized DNA in a sequence-specific manner. Also, our work on diiron proteins has resulted in proteins that catalyze a variety of two-electron processes[2]. We also designed proteins that bind and coat various materials including carbon nanotubes [3], and proteins that bind a variety electrical and optical cofactors. Most recently, we demonstrated the design of catalytically active Zn^{2+}-binding peptides that adopt catalytically active cross-beta fibrils. This work has the potential to open new doors for the design of catalytic materials as well as implications concerning the evolution of life[4].

1. Bryson, J.W., Betz, S.F., Lu, H.S., Suich, D.J., Zhou, H.X., O'Neil, K.T., and **DeGrado, W.F.** (1995) Protein design: a hierarchic approach, *Science* 270, 935-941.
2. Reig, A. J., Pires, M. M., Snyder, R. A., Wu, Y., Jo, H., Kulp, D.W., Butch, S.E., Calhoun, J. R., Szyperski, T.G., Solomon, E.I., and **DeGrado, W.F.** (2012) Alteration of the oxygen-dependent reactivity of de novo Due Ferri proteins, *Nature Chemistry* 4, 900-906. PMCID: PMC3568993
3. 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. PMCID: PMC3264056
4. 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. PMCID: PMC3996680

2) Membrane protein design We also used minimalist design principles to delineate the features required for assembly and conduction of ion channels and also designed transmembrane, multi-porphyrin helical bundles that catalyze electron transfer through phospholipid membranes. Simultaneous with Engelman's group, we also showed the role of polar amino acids in inducing association of transmembrane helices, and its role in a variety

of single-span membrane proteins[5, 6]. We also developed a computational approach to design peptides that target the transmembrane regions of membrane proteins in much the same way that antibodies are used to block protein-protein interactions in water-soluble proteins[7]. In our most recent work[8], 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). This work was particularly significant, as it was the first example of a designed membrane protein whose structure was determined at high resolution, as well as the complexity of the function achieved.

a. Choma, C., Gratkowski, H., Lear, J.D., and **DeGrado, W.F.** (2000) Asparagine-mediated self-association of a model transmembrane helix, *Nature Struct. Biol.* 7, 161-166.
b. Gratkowski, H., Lear, J.D., and **DeGrado, W.F**. (2001) Polar sidechains drive the association of model, transmembrane peptides., *Proc. Natl. Acad. Sci. U.S.A.* 98, 880-885. PMCID: PMC14678
c. 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.
d. 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. PMCID: PMC4400864

3) **Structure-based design of small molecule therapeutics.**

Integrins. Our group has long been involved in the design of cyclic peptides small molecules as inhibitors of integrins to allow the interrogation of their roles in various biological processes. Early work on the integrins αIIbβ3 led to compounds that reached clinical trials. More recently, we explored the role of other integrins involved in platelet adhesion including αvβ3 and α2β1 (a non-RGD collagen receptor). Since moving to UCSF, we have focused on the problem of fibrotic diseases including idiotypic pulmonary fibrosis (IPF). In collaboration with Dean Sheppard we have developed very potent integrin antagonists that inhibit activation of TGF-β1, and work in a variety of animal models of IPF and other fibrotic disorders[9]. We also have had a long-standing collaboration with Joel Bennett on the activation of αIIbβ, particularly the role of its transmembrane helices [7] and engagement of cytoplasmic proteins [10].

The M2 proton channel from Influenza A virus. Our early work with the groups of Robert Lamb and Larry Pinto established the overall structural and mechanism of the M2 proton channel, which is the target of the anti-influenza drugs, amantadine and rimantadine. A decade later our crystallographic[11] and NMR structures defined the fine details of the binding site for these drugs and explained the mechanism of the growing problem of amantadine-resistance. With Robert Lamb and Larry Pinto, we extensively characterized the physiological properties of many drug-resistant mutants of the channel, identified those most likely to lead to resistance. Most recently, we designed and synthesized new drugs to address the problem of drug-resistant forms of influenza A virus[12].

a. Reed, N.I., Jo, H., Chen, C., Tsujino, K., Arnold, T.D., **DeGrado, W.F**., and Sheppard, D. (2015) The αvβ1 integrin plays a critical in vivo role in tissue fibrosis, *Sci Transl Med* 7, 288ra279.
b. Moore, D.T., Nygren, P., Jo, H., Boesze-Battaglia, K., Bennett, J.S., and **DeGrado, W.F.** (2012) Affinity of talin-1 for the beta3-integrin cytosolic domain is modulated by its phospholipid bilayer environment, *Proc Natl Acad Sci U S A* 109, 793-798. PMCID: PMC3271903
c. 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. PMCID: PMC3889492
d. 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, *Proc Natl Acad Sci USA* 110, 1315-1320. PMCID: PMC3557100

4) *Peptide-membrane interactions and development of mimics of host defense peptides*
Viral membrane fusion. Our lab was the first to characterize the conformations and membrane-interactive properties of fusogenic peptides, found at the N-terminus of a number of viral membrane proteins, such as influenza virus hemagglutinin and HIV gp41[13]. More recently, we have derived atomistic models for the mechanism of viral membrane fusion[14].
Small molecule mimics of antimicrobial peptides, and transmembrane signaling in bacteria. Antimicrobial peptides are an essential component of innate immunity in all higher organisms. In early work we used minimalist peptide design to engineer idealized versions of antimicrobial peptides, thereby showing that a basic amphiphilic helix was necessary and sufficient for their activities. Many years later, we returned to this topic through the design of antimicrobial foldamers, which idealized the basic amiphiphilic helices of antimicrobial peptides[15]. Ultimately, we designed polymers and small molecules that were more potent and less toxic to animals than the parent antimicrobial peptides. One such compound, licensed to the company Cellceutix, successfully completed phase IIb clinical trials (in humans) for highly drug-resistant *Staphylococcal aureus* infections, and is moving into phase III studies. Our current work in this area focuses on the mechanisms by which bacteria respond to antimicrobial peptides, as part of their own defense against the innate response of the host. We are defining bacterial histidine kinases and their corresponding response regulators that orchestrate the response to antimicrobial agents and defining the structural mechanisms by which they signal.

a. Lear, J.D., and **DeGrado, W.F.** (1987) Membrane binding and conformational properties of peptides representing the NH2 terminus of influenza HA-2, *J Biol Chem* 262, 6500-6505.
b. Donald, J.E., Zhang, Y., Fiorin, G., Carnevale, V., Slochower, D.R., Gai, F., Klein, ML., and **DeGrado, W.F.** (2011) Transmembrane orientation and possible role of the fusogenic peptide from parainfluenza virus 5 (PIV5) in promoting fusion, *Proc Natl Acad Sci USA* 108, 3958-3963. PMCID: PMC3054033
c. Hamuro, Y., Schneider, J. P., and **DeGrado, W.F**. (1999) De novo design of antibacterial beta-peptides., *J. Amer. Chem. Soc*. 121, 12200-12201. PMCID: PMC3057395

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

R35 GM122603 05/01/17—04/30/22 6.0 Calendar
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.

R01 GM117593 (Zhou/Grabe) 08/01/15—04/30/20 *Effort subsumed*
NIH/NIGMS by R35GM122603
"A Multiscale Model of Protein Mediated Changes in membrane Morphology"
Dr. DeGrado's lab is collaborating with Dr. Zhou and Dr. Grabe on computational modeling for membrane protein stability, and his lab helps determine membrane protein structure and orientation in the membrane for this project. Dr. DeGrado's effort has been subsumed into the R35.

UH2 HL123423-01 (Sheppard/DeGrado) 07/01/16—06/30/19 0.5 Calendar
NIH/NHLBI
"Treatment of pulmonary fibrosis with inhibitors of integrin alphavbeta1"
This project focuses on small-molecule inhibitors of αvβ1, which mediates TGFβ activation on the surface of fibroblasts. The grant provides support for Hyunil Jo, an adjunct assistant professor, to synthesize small molecules that target this integrin, as well as contract ADME/Tox and in vitro and in vivo testing in animal models in the Sheppard Group. My role is to coordinate the activities.

CHE-1709506 (Therien) 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 focuses on peptide-synthetic 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-Investigator

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
2018-	Member, UCSF Institute for Human Genetics
2018-	Member, Immuno X program

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:

R35 HL150767 Chapman, HA PI 02/1/2020-1/31/2027
Program to promote lung regeneration and block fibrosis
The goal of this research program is to understand the interactions between lung epithelial and mesenchymal cells in sufficient detail to deliver new therapeutic interventions in pulmonary fibrosis, a process without disease modifying therapies. This program is focused on further elucidation of mechanisms of a fibroblast-specific trihydroxyphenolic inhibitor of LOXL2 and TGFR1 with potent in vivo anti-fibrotic effects. We will test one of these, EGCG, in a proof of principle clinical trial. Data in press show reversal of a core set of pro-fibrotic tissue biomarkers in IPF patients given EGCG two weeks prior to diagnostic lung biopsy. The R35 mechanism allows us to integrate our capacity to attenuate fibrosis with the broader issue of defective epithelial regeneration in IPF, a competing process with fibrogenesis. This grant replaces two RO1s: R01HL128484-01 and HL142265-01A1.

Recently Completed

Sponsored Research Agreement Chapman HA, PI 01/01/2014-12/31/2016
Biogen Idec.
Elucidation of human lung cellular diversity and epithelial-mesencyhmal interactions

P01 HL108794 Sheppard PI, Chapman HA, project leader
Targeting epithelial cells to treat pulmonary fibrosis. 08/01/2012-07/31/2017
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.

U01 HL111054-01 Chapman HA, PI
NIH/NHLBI
Epithelial Progenitor Cells in Lung Repair and Regeneration 01/01/2012-12/31/2016
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.

R01 HL44712 Chapman HA, PI
NIH/NHLBI
Regulation of Integrin Function 01/01/1991 – 12/31/2014
The major goals of this project are to understand the molecular basis and importance of integrin function in promoting TGFβ1 signaling and pulmonary fibrosis. The hypothesis that epithelial to mesenchymal transition is an important component of pulmonary fibrosis, and regulated by integrins, is the main idea tested in this grant.

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

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
e. 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 Sep 8; 1(14): e87871.

(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. In lung disease this mucus gel becomes more elastic and harder to clear and mucus stasis then causes airflow obstruction and lung infection. Mucus pathology is a feature of all major lung disease especially COPD, asthma 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. I am regarded as a world expert in mucus pathology in the lung (publication A).

Central findings: My lab has described the mucus cell and mucin gene abnormalities that occur in asthma COPD, and in CF (example in publication B) and revealed pathologic mechanisms by which mucus plugs form (publication C) and physiologic mechanisms by which mucins contribute to host defense (publication 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 studies in human lung disease using sputum samples in ex vivo experiments has been impactful in drawing attention to research approaches to answer mechanistic questions and to point to treatment strategies that might be easily applied.

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. 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:PMC5824874.

B. Innes AL. Carrington SD, David J. Thornton DJ, Kirkham S, Dougherty RH, Raymond WW, Caughey GH, Muller SJ, **Fahy JV**. *Ex vivo sputum analysis reveals impairment of protease-dependent mucus degradation by plasma proteins in acute asthma*. *Am J Respir Crit Care Med.* 2009; 180:203-10. PMCID: PMC2724713.
C. Kerr SC, Fischer GJ, Sinha M, McCabe O, Palmer JM, Choera T, Lim FY, Wimmerova M, Carrington SD, Yuan S, Lowell CA, Oscarson S, Keller NP, **Fahy JV**. FleA Expression in Aspergillus fumigatus Is Recognized by Fucosylated Structures on Mucins and Macrophages to Prevent Lung Infection.
PLoS Pathog. 2016 Apr 8;12(4): e1005555.

(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-C 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 D). By revealing oxidation as a key mechanism of mucin cross-linking and mucus gel stiffness and the potential for thiol-based saccharide compounds to have therapeutic advantages over existing mucolytics, I have set the stage for a novel strategy for mucolysis in lung disease (publication E).

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.
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.

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.
D. 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. *Sci Transl Med*. 2015;7(276) 276ra27

Complete List of Published Work - UCSF Profiles: **http://profiles.ucsf.edu/john.fahy#toc-id8**;
H Index (Google Scholar): 71

Research Support – Active

5 R01 HL080414 (Fahy, JV) 07/01/05 - 04/30/20
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

UG1HL139106 (Fahy, JV) 9/23/2017 - 6/30/2023
Sequential, Multiple Assignment, Randomized Trial in Severe Asthma Protocol (SMART-SA) This is the UCSF/UC Davis application to the UG1 PrecISE program to conduct precision medicine clinical trials in severe asthma. Role: PI

1P01HL107202 (Fahy, JV) 08/1/12 - 6/30/18 (NCE)
Innate and Adaptive Immune Responses in Th2-high Asthma: This PPG is investigating the molecular underpinnings of the Th2-high molecular subtype of asthma
Role: Overall PPG PI (Leader of project 3; Core leader - Administrative Core & the Human Subjects Core).

1 P01HL128191 (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	Raymond and Beverly Sackler UCSF/Berkeley Sabbatical Exchange (Host: Eva Nogales)

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. Barad BA, Echols N, Wang RY, Cheng Y, DiMaio F, Adams PD, **Fraser JS.** EMRinger: Side-chain-directed model and map validation for 3D Cryomicroscopy. Nature Methods. 2015. PMCID: PMC4589481.
    d. **Fraser JS**, Clarkson MW, Degnan SC, Erion R, Kern D, Alber T. Hidden alternative structures of proline isomerase essential for catalysis. *Nature*. 2009; 462(7273):669-73. PMCID: PMC2805857.

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. *Proceedings of the National Academy of Sciences.* 2011. PMCID: PMC3182744.
b. 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.
c. Keedy DA*, Kenner LR*, Warkentin M*, Woldeyes RA*, Thompson MC, Brewster AS, Van Benschoten AH, Baxter EL, Hopkins JB, Uervirojnangkoorn M, McPhillips SE, Song J, Alonso-Mori R, Holton JM, Weis WI, Brunger AT, Soltis SM, Lemke H, Gonzalez A, Sauter NK, Cohen AE, 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. Biel JT, Thompson MC, Cunningham CN, Corn JE, **Fraser JS**. Flexibility and design: conformational heterogeneity along the evolutionary trajectory of a redesigned ubiquitin. *Structure.* 2017. PMCID: PMC5415430.

3. Developing new X-ray diffuse scattering and X-FEL 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. Our long term goal is to watch how protein conformational ensembles respond when perturbed by rapid temperature jumps using the X-FEL.

a. 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.
b. Van Benschoten AH, Afonine PV, Terwilliger TC, Wall ME, Jackson CJ, Sauter NK, Adams PD, Urzhumtsev A, **Fraser JS**[#]. Predicting X-ray Diffuse Scattering from Translation Libration Screw Structural Ensembles. *Acta Crystallographica D*. 2015.
c. Wall ME, Van Benschoten AH, Sauter NK, Adams PD, **Fraser JS**, Terwilliger TC. Conformational dynamics of a crystalline protein from microsecond-scale molecular dynamics simulations and diffuse X-ray scattering. *Proceedings of the National Academy of Sciences*. 2014. PMCID: PMC4273327.
d. Thomaston JL, Woldeyes RA, Nakane T, Yamashita A, Tanaka T, Koiwai K, Brewster AS, Barad BA, Chen Y, Lemmin T, Uervirojnangkoorn M, Arima T, Kobayashi J, Masuda T, Suzuki M, Sugahara M, Sauter NK, Tanaka R, Nureki O, Tono K, Joti Y, Nango E, Iwata S, Yumoto F, **Fraser JS**, DeGrado WF. XFEL structures of the influenza M2 proton channel: Room temperature water networks and insights into proton conduction. *Proceedings of the National Academy of Sciences*. 2017. PMCID: in progress

4. **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 lead 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, the hijacking of the proline isomerase CypA in lentiviral evolution, and structure-based antibiotic design using cryoEM.
    a. **Fraser JS**, Yu Z, Maxwell KL, Davidson AR. Ig-like domains on bacteriophages: a tale of promiscuity and deceit. J Mol Biol. 2006. PMID: 16631788.
    b. Williams BB, Van Benschoten AH, Cimermancic P, Donia MS, Zimmermann M, Taketani M, Ishihara A, Kashyap PC, **Fraser JS**, Fischbach MA. Discovery and characterization of gut microbiota decarboxylases that can produce the neurotransmitter tryptamine. Cell Host Microbe. 2014. PMCID: PMC4260654
    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: In process.

5. 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. Beltrao P, Albanèse V, Kenner LR, Swaney DL, Burlingame A, Villén J, Lim WA, **Fraser JS**, Frydman J, Krogan NJ. Systematic functional prioritization of protein posttranslational modifications. *Cell*. 2012. PMCID: PMC3404735
    b. Braberg H, Jin H, Moehle EA, Chan YA, Wang S, Shales M, Benschop JJ, Morris JH, Qiu C, Hu F, Tang LK, **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
    c. **Fraser JS**[#], Gross JD, Krogan NJ. From systems to structure: bridging networks and mechanism. *Mol Cell*. 2013. PMCID: PMC3558917
    d. Mavor D, Barlow KA, Thompson S, Barad BA, Bonny AR, Cario CL, Gaskins G, Liu Z, Deming L, Axen SD, Caceres E, Chen W, Cuesta A, Gate R, Green EM, Hulce KR, Ji W, Kenner LR, Mensa B, Morinishi LS, Moss SM, Mravic M, Muir RK, Niekamp S, Nnadi CI, Palovcak E, Poss EM, Ross TD, Salcedo E, See S, Subramaniam M, Wong AW, Li J, Thorn KS, Conchúir SÓ, Roscoe BP, Chow ED, DeRisi JL, Kortemme T, Bolon DN, **Fraser JS**[#]. Determination of Ubiquitin Fitness Landscapes Under Different Chemical Stresses in a Classroom Setting. *eLife*. 2016. PMCID: PMC4862753

Complete List of 46 Publications in MyBibliography:

http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40891283/?sort=date&direction=descending

Research Support

Technologies, Methodologies & Cores Award Fraser (PI) 10/01/19 – 09/30/20
UCSF Program for Breakthrough Biomedical Research (PBBR)
Leveraging the Macromolecular Structure Group and Beamline Resources for High-throughput Liganding of Challenging Targets
The goal of this project is to set up an infrastructure for UCSF investigators to perform high-throughput soaking experiments.

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.

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.

NSF 11-522 Snell (PI) 09/01/13 – 09/01/23
NSF - OIA - SCI & TECH CTRS
Biology with X-ray Lasers
The major goal of this center is to encourage the development of methods for biophysics using the newly developed x-ray free electron lasers (X-FEL). We participate by generating samples for X-FEL diffraction and comparing the resulting data to room temperature synchrotron datasets.

MCB 1714915 Herschlag (PI) 08/01/17 – 07/31/21
NSF
Collaborative Research: Systematic Investigation of the Structure, Dynamics, and Energetics of Hydrogen Bonds and the Protein Interior Using Ketosteroid Isomerase and Model Systems
The goal of this project is to determine the biophysical and mechanistic basis for enzyme catalysis.

R01 GM0517315 Holton (PI) 07/01/17 – 06/30/22
NIH/NIGMS
Eliminating Critical Systematic Errors in Structural Biology with Next-Generation Simulation
The goal of the project is to use simulations to explore systematic errors to enable improved modeling.

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 Illinois at Champaign-Urbana	B.S.	05/1989	Biology and Chemistry
University of California at Berkeley	Ph.D.	05/1995	Immunology
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. Boldajipour B, Nelson A, **Krummel MF**. Tumor-infiltrating lymphocytes are dynamically desensitized to antigen but are maintained by homeostatic cytokine. JCI Insight. 2016 Dec 8;1(20): e89289. PMCID: PMC5135268.
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

Ongoing 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

1R01AI114787-01A1 Krummel (PI) 07/01/15-06/30/20
NIH/NIAID, Manipulating Ccollectivity and Niches for Developing CD8 Immunity
The goal of this project is to use advanced imaging methods to discover how we could take advantage of co-vaccination regimen to generate strong CD8 T cell immunity, systemically and in target tissue. This will have significant implications for protective immunizations to viruses.
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) 01/1/2015 - 12/31/2019
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

BIOGRAPHICAL SKETCH

NAME **Richard M. 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 and Honors

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; 1st 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; University of Rochester School of Medicine, Distinguished Alumnus, 2019.

Contribution to Science

1. My early contributions 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 disease outcomes in vivo were mediated by disparate types of Th responses. My laboratory also discovered that interventions aimed at discrete cytokines, such as IL-4 and IFN-g, at early time points following infectious challenges, could profoundly affect disease outcome through alterations in Th subset differentiation in situ. 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 all of these contributions.

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 what are now called 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 genetic expression in a variety of cell types, as well as in cancer. 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. *Nature 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, through the use of viral IRES elements, leaving the endogenous cytokines themselves intact. These reagents have revolutionized the capacity to study the immune system, which previously relied on isolating cells and re-stimulating in vivo in order to reveal their effector capacity. 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. *Nature 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 RNAseq. 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. 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 all 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

Howard Hughes Medical Institute 09/01/97-08/31/25 (budgeted annually)
Activation of Immunity
The 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.
Role: PI

R01 AI026918 Locksley (PI) 05/01/18-04/30/23
Parasite immunity orchestrated by type 2 immune cells
The goals of this grant 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.

P01 HL107202 Fahy (PI) 09/19-08/24
Exploiting crosstalk between tuft cells and group 2 ILC2s for tissue homeostasis and disease
Role: PI, Project 1; Innate type 2 cells and tuft cells in allergic lung disease
The goals of this grant are to define characteristics of epigenetically altered sites where allergic pathologies recur in patients and animal models of allergic upper airways disease.
T291P0554 Fraser (PI); Locksley – collaborator 09/19-08/21
University of California Tobacco-Related Disease Research Program/High Impact Pilot Program
Engineered proteins to reverse chitin buildup and fibrotic lung disease
The goals of this project are to optimize chitinolytic activity of AMCase in order to accelerate the capacity for chitin breakdown in lung tissue.

APP1143020 Buchert (PI); Locksley (PI, Project 3) 07/15-12/20
NHMRC Australia
The goals of this project as to assess the ILC2 – tuft cell axis in models of gastric cancer.

Completed Research Support

R01 AI030663 Locksley (PI) 06/01/12-05/31/18
Initiation of allergic immunity by parasites
The major goals of this grant were to understand the innate and adaptive mechanisms for initiation and control of mucosal inflammation by helminths.

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
2018-	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. Our group's research is focused on defining the control and function of tissue-resident immune responses in multiple systems, including models of normal tissue development and (re)modeling, infection, pathology, and aging. I characterized the protective metabolic role of eosinophils in visceral adipose tissue and described group 2 innate lymphoid cells (ILC2) as upstream regulators of adipose tissue eosinophils and alternatively activated macrophages. I found that human IL-2 therapy used to promote regulatory T cell (Treg) during autoimmune disease and graft-versus-host disease activates ILC2 IL-5 production, increasing eosinophils in mice and human. Our group's independent work has focused on the positive and negative regulation of ILC2s, including the regulation and sources of IL-33 and IFN□, and the relationship of tissue ILC2 with regulatory T cells (Treg). Our most recent findings have established a novel stromal niche for type 2 innate lymphocytes in the lung that is required for their maintenance and activation.

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 innate 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 defined a novel circuit where astrocyte-derived IL-33 promotes microglial activation and neuronal synapse engulfment during CNS development. Our ongoing work aims to define how meningeal-resident lymphocytes, including group 2 innate lymphoid cells, impact CNS glia and neural circuit formation during brain development.

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*

3. We have been involved in collaborative work to understand the function and diversity of group 2 innate lymphoid cells in adipose tissue, lung, and elsewhere. We demonstrated the role of ILC2 IL-13 production in the induction of beige fat, a type of adipose tissue that produces heat in response to cold. We helped characterize the non-redundant roles of the epithelial cytokines IL-33, IL-25, and TSLP in activating lung ILC2, as well as the contribution of type 2 allergic immunity to adipose tissue metabolic health and disease. We defined the heterogeneity of tissue ILC2s from multiple organs. Together, this work has advanced our knowledge of the regulation and function of ILC2 in diverse homeostatic, therapeutic, and pathologic settings.

a. Lee, M.-W., Odegaard, J.I., Mukundan, L., Qiu, Y., **Molofsky, A.B**., Nussbaum, J.C., Yun, K., Locksley, R.M., and Chawla, A. (2015). Activated type 2 innate lymphoid cells regulate beige fat biogenesis. Cell *160*, 74–87. PMCID: PMC4297518
b. 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
c. **Molofsky, A.B.,** Savage, A.K., and Locksley, R.M. (2015). Interleukin-33 in Tissue

Homeostasis, Injury, and Inflammation. *Immunity 42*, 1005–1019. PMCID: PMC4471869

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.

UCSF RAP Pilot for Junior Investigators (Molofsky, Co-PI). 1/1/2019 – 12/31/2019
Innate lymphocytes at the developing brain-immune interface.
The major goal of this pilot grant is to continue to develop preliminary data on the composition and function of brain meningeal-resident lymphocytes during normal and pathologic mouse development.

Nina Ireland Program for Lung Health (Molofsky, PI) 1/2019 – 12/2020
Defining lung lymphocyte niches in humans.
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) 3/2019-2/2020
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 at rest and during models of NASH and fibrosis.

Completed Research Support

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 **Steven D. Pletcher**	POSITION TITLE Associate Professor: Otolaryngology – Head and Neck Surgery
eRA COMMONS USER NAME (credential, e.g., agency login)	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	MM/YY	FIELD OF STUDY
Massachusetts Eye and Ear Infirmary, Boston	Fellow	06/06	Rhinology
University of California, San Francisco	Resident	06/05	Otolaryngology-Head and Neck Surgery
University of California, San Francisco	Intern	06/01	General Surgery
University of California, Los Angeles School of Medicine	MD	06/00	AOA
Yale University, New Haven CT	BS	06/95	Cum Laude, Molecular Biochemistry and Physics

Positions and Honors

2012-present Associate Professor, Otolaryngology - Head and Neck Surgery, University of California, San Francisco
2006-2012 Assistant Professor, Otolaryngology - Head and Neck Surgery, University of California, San Francisco
2013-Present Residency Program Director, Otolaryngology - Head and Neck Surgery University of California, San Francisco

Other Experience and Professional Memberships

2009-2011 American Rhinologic Society; Bylaws committee member
2011-present American Academy of Otolaryngology - Head and Neck Surgery; Member, Panamerican Committee
2012-present Society University Otolaryngologists; Member
2013-present American Board of Otolaryngology; Member, New Materials Task Force
2013-present American Rhinologic Society; Awards Committee Member
2013-present American Rhinologic Society; Program Committee
2013-present Otolaryngology Program Directors Organization
2014-present American Academy of Otolaryngology - Head and Neck Surgery; Member, Rhinology and Allergy Education Committee

Honors

2015 Member, Haile T. Debas Academy of Medical Educators
University of California, San Francisco
2015 Francis A. Sooy Resident Award, University of California, San Francisco
2009 Roger Boles MD Teaching Award, University of California, San Francisco
2000 AOA, UCLA School of Medicine
1999 NIH National Research Service Award, National Institutes of Health

Contribution to Science

1. The majority of my current research effort focuses on the role of the sinus microbiome in chronic rhinosinusitis. Our research group produced one of the first major papers in this area with a variety of critical findings:
   1) Diverse microbial communities are present in the sinuses of healthy patients,
   2) CRS is associated with a loss of microbial diversity, but not an increased microbial burden
   3) A newly identified microbial pathogen (C. tuberculostearicum) produces inflammation consistent with sinusitis when introduced into the murine nasal cavity
   4) Development of murine sinonasal inflammation is accelerated when the native microbiome is perturbed through antibiotic treatment
   5) Co-instillation of a commensal microbe (L sakeii) prevents C. tuberculostearicum induced inflammatory changes
   Since publication of this 2012 paper, we have investigated the biogeography of microbial communities, fungal contributions to the sinus microbiome, dominant pathogenic species within the sinus microbiome of CRS patients, and continued to develop our mouse model for evaluation of microbial communities in sinusitis. These investigations have resulted in 2 publications currently under review and are multiple manuscripts in preparation.
   Prior to and concomitant with this line of research I have led studies related to rheologic properties of sinonasal mucus and novel steroid deposition methods for treatment of CRS with nasal polyposis.
   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. PMID: 22972842
   b. Roediger FC, Slusher NA, Allgaier S, Cox ML, **Pletcher SD**, Goldberg AN, Lynch SV. Nucleic acid extraction efficiency and bacterial recovery from maxillary sinus mucosal samples obtained by brushing or biopsy. *Am J Rhinol Allergy*. 2010 Jul-Aug; 24(4): 263-5.
   c. **Pletcher SD**, Goldberg AN. Treatment of recurrent sinonasal polyposis with steroid infused carboxymethylcellulose foam. *Am J Rhinol Allergy* 2010 Nov-Dec; 24(6): 451-3
   d. Saito D, Innes A, **Pletcher SD**. Rheologic properties of sinonasal mucus in patients with chronic sinusitis. *Am J Rhinol Allergy*. 2010 Jan-Feb;24(1):1-5.

Research Support

On-going Research Support

338441 07/01/15-07/01/2017
Cystic Fibrosis Foundation Characterization of upper respiratory microbial communities in CF
Role: Co-PI

Completed Research Support

HRI Grant 01/01/2012-01/01/2013
Culture independent analysis of the impact of antibiotic irrigation on sinonasal microbial communities
Awarded for culture independent analysis of the effects of antibiotic irrigation on bacterial communities in patients with chronic sinusitis.

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

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. Sugimoto K, Kudo M, Sundaram A, Ren X, Huang K, Bernstein X, Wang Y, Raymond WW, Erle D, Abrink M, Caughey GH, Huang X, **Sheppard D**. The αvβ6 integrin modulates airway hyperresponsiveness by regulating intra-epithelial mast cells. *J Clin Invest* 2012 122:748-758, PMCID: PMC3266785
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 integirn 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.

a. 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: PMC2670239
b. Kudo M, Melton AC, Chen C, Engler M, Huang KE, Ren X, Wang Y, Bernstein X, Li J, Atabai K, Huang X, **Sheppard D.** IL-17A produced by αβ T cells drives airway smooth muscle contraction. *Nature Medicine* 2012 18:547-554. PMCID: PMC3321096
c. 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: PMC3855865.
d. 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: PMC4461057

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 HL145037 (Sheppard) 1/15/2019-12/31/2022
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) 08/01/2014- 07/31/2020
AbbVie
Characterizing molecular diversity of renal and hepatic fibroblasts in the setting of tissue fibrosis
Overall project goal: Discovery of novel biomarkers and therapeutic targets for hepatic fibrosis from single cell RNAseq

UCSF Pfizer CTI Program (Sheppard). 12/07/2012-11/30/2019

Pfizer, Inc
Targeting the αvβ8 integrin for tumor immunotherapy
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 a clinical candidate and not on the basic biology underlying the effects ofαvβ8 in tumors, which is the focus of the current proposal

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.

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-Present	Treasurer, Association of Korean Immunologists in America
2019	NIH study section ZRG1 F70-U20
2019	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

1999-2003 National Merit Scholarship
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
2018	Invited lecturer, Use of Mouse Models to Develop Therapies for Human Lung Diseases, UCSF

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. (PMID 22232213)

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. (PMID 23543053)

> **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. (PMID 25271629)
> (*shared first author)

Tsvetanova N, Trester-Zedlitz M, Newton B, Riordan D, **Sundaram A**, Johnson J, Krogan N, von Zastrow M. GPCR endocytosis confers uniformity in responses to chemically distinct ligands. (*Mol Pharmacol.* 2016 Nov. (PMID 27879340).

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).

The main focus of my laboratory is on the role of transmembrane proteins in transmitting tension 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 $\alpha_5\beta_1$. This novel therapeutic approach to reduce airway contraction by inhibiting cellular tethering to the matrix enhances the effect of currently available bronchodilators, and has led to the filing of two patents and further collaborations with investigators in the chemistry department to continue pre-clinical studies for integrin $\alpha_5\beta_1$ as well as other integrins and cadherins that I have identified with therapeutic potential.

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. (PMID 27918306)

A full list of my publications can be found at:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1xeawdbmls-QQ/bibliography/51726728/public/?sort=date&direction=ascending.

Research Support

Ongoing

K08 HL124049-01 (PI). 2015 – 2020
NIH/NHLBI
Role of Human Chymase in Smooth Muscle Contraction in Asthma
The major goals of this project are to explore the effect of chymase on organization of the extracellular matrix and integrin expression, the interplay between cytokines and integrin expression, and the effect of integrin ligation on airway contraction and allergen challenge.

UCSF Resource Allocation Program (RAP) Catalyst Award (co-PI). 2018 – 2020
UCSF/ShangPharma
The major goal of this project is to design and screen more potent and specific small molecule inhibitors of integrin alpha 2 beta 1.

Recently Completed

T32 HL 7185-34 2009 – 2012
NIH/NHLBI
This is a 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 HL112588-01 (PI) 2012 – 2014
NIH/NHLBI
Regulation of Allergic Asthma by TGF-β-induced Modulation of mMCP-1 and mMCP-4
The major goals of this project are: To 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 AI070412-09 ESI (PI) 2014-2015
NIH/NIAID
Role of Human Chymase in Smooth Muscle Contraction
This early stage investigator award is dedicated to studying 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
Funding to purchase 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 the mechanisms of smooth muscle tension transmission via cell-matrix and cell-cell connections.

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
2013-	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 **Zena Werb, Ph.D.**	POSITION TITLE Professor of Anatomy
eRA COMMONS USER NAME werbzena	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of Toronto, Toronto, Canada	B.Sc.	06/1966	Biochemistry
Rockefeller University, New York	Ph.D.	06/1971	Cell Biology
Strangeways Research Laboratory, Cambridge, UK	Postdoc.	06/1973	Protein Chemistry

Positions

1973-1975	Research Scientist, Strangeways Res. Lab., Cambridge, United Kingdom
1975-1976	Visiting Assistant Professor of Medicine, Dartmouth Medical School, Hanover, NH
1976-1980	Assistant Professor Radiobiology, Radiology University of California, San Francisco
1979-1980	Assistant Professor Anatomy, University of California San Francisco
1980-1983	Associate Professor of Anatomy and Radiology University of California, San Francisco
1983-Present	Professor Anatomy, UCSF
1985-1986	Visiting Professor, Sir William Dunn School of Pathology University of Oxford, United Kingdom
1998	Visiting Professor, Institut Curie, Paris
1999-Present	Vice-chair, Dept. of Anatomy, University of California, San Francisco
2006-2008	Visiting Professor, Max-Planck Institute for Biochemistry Martinsried, Germany
2011-present	Co-leader, Cancer, Immunity and Microenvironment Program, UCSF Helen Diller Family Comprehensive Cancer Center
2016-present	Associate Director for Basic Science, Helen Diller Family Comprehensive Cancer Center, UCSF

Editorial Board Memberships

1983-1985	Journal of Cell Biology
1982-1987	American Journal of Physiology
1985-2004	Journal of Experimental Medicine
1990-2001	Science
1999-Present	Matrix Biolog
1999-Present	Neoplasia
2000-2009	Cell
2001-Present	Developmental Cell
2001-Present	Cancer Cell
2002-2006	Molecular Biology of the Cell
2007-2009	Genes & Development
2009-Present	Current Opinion in Cell Biology

2010-Present	Guest Editor, Proc. National Academy Science, USA
2010-Present	Member, Editorial Board, Disease Models and Mechanisms

Professional Memberships

1976-present	American Society for Cell Biology
1979-present	American Society for Biochemistry and Molecular Biology
1967-71 & 1979-present	American Association for the Advancement of Science
1988-present	Society for Developmental Biology
2001-present	American Association for Cancer Research
2001-present	American Society for Matrix Biology
2004-present	International Society for Differentiation

Scientific Leadership *(selected)*

1990-1992	Member, Cell and Molecular Biology Panel, National Cancer Institute of Canada
1991-1995	Member, Board of Scientific Counselors, NIAMS
1992-1995	Council Member, American Society for Cell Biology
1993-1995	Council Delegate, Am. Assoc. for the Advancement of Science
1994-2001	Member, Scientific Advisory Board, Keystone Symposia
2001-2003	Council Member, American Society for Matrix Biology
2001	NIH Oncological SS Boundaries Team
2002	NIH Biochem SS, ad hoc
2003-2005	Council Member, International Society for Matrix Biology
2003-2006	Board of Directors, AACR
2005	President, American Society for Cell Biology
2007-2009	Nominating Committee, AACR
2007	Member, NIH ZRG1 ICI–D01
2008	Reviewer, NIH Pioneer Awards
2008	Chair, NIH ZRG1 MOSS-A (02)
2008-2010	Chair, NIH ICI Study Section
2009-2012	Chair, American Academy of Arts and Sciences, Membership Selection Committee Class II, section
2010	Co-organizer, CNIO Cancer Symposium on Frontiers in Invasion and Metastasis, Madrid
2011-Present	Member, Steering Committee, AACR Council of Scientific Advisors
2011-2016	Member, Scientific Advisory Board, Max Planck Institute for Biology of Ageing, Cologne, Germany

Honors

1996	FASEB Excellence in Science Award
1998	Rotschild/Mayent Fellowship, Institut Curie
2002	Elected Member, Institute of Medicine
2003	Elected Fellow, American Academy of Arts and Sciences
2003	Doctor of Medicine (honoris causa), University of Copenhagen
2006-2007	Alexander von Humboldt Foundation (Germany) Research Award
2007	E.B. Wilson Medal, American Society for Cell Biology
2009	Colin Thomson Memorial Medal, AICR
2010	Elected Member, National Academy of Sciences
2010	American Society for Cell Biology, Women in Cell Biology Senior Award
2011	Zero Breast Cancer 2011 Community Breast Cancer Research Award state of breast tumors.
2011	John H. Blaffer Lecture, M.D. Anderson Cancer Center, Research Award

2011 McAllister Lecture, Pathology Grand Rounds, Yale Medical School, New Haven CT
2012 Keynote Lecture, International Assoc. for Breast Cancer Research Conference
2014 Detlev Bronk Alumni Lecture, Rockefeller University, New York
2014 Billingham Lecture, University of Texas Southwestern, Dallas, TX
2014 Curie-Servier Lecture, Paris, France
2015 UCSF Lifetime Achievement in Mentoring Award, San Francisco, CA
2015 University College, University of Toronto, Alumni of Influence Award, Toronto, Canada
2016 Keynote speaker, American Association of Anatomists Annual Meeting, San Diego CA
2016 Keynote speaker, Gordon Research Conference Plasminogen Activation, Extracellular Proteolysis
2016 Doctor of Medical Science (honoris causa), National Cheng Kung University, Tainan, Taiwan
2016 Inaugural Fellow, American Society for Cell Biology
2018 Distinguished Role Model Award, Northwestern University, Evanston
2018 AACR Distinguished Lectureship in Breast Cancer Research Award, San Antonio Breast Cancer Symposium, San Antonio, TX
2019 International Conference on Tumor Microenvironment and Cellular Stress: Signaling, Metabolism, Imaging and Therapeutic Targets. Crete, Greece. Keynote speaker (pending).
2020 Suffrage Science Award, Life Sciences category, MRC London Institute of Medical Sciences

Contribution to Science

1. I created the groundwork for the field of cell biology of extracellular proteolysis. This includes the first reports of a cellular source for MMPs, that endogenous inhibitors regulate MMPs, the existence of multiple TIMPs, and discovery and cloning of MMPs. We discovered a mechanism for a proteolytic cascade involved in tissue remodeling. We used MMP mutant mice to probe development and neoplasia. We laid out the conceptual framework for the extracellular microenvironment as a stabilizer of cell behavior and of MMPs as provocateurs in altered behavior during invasive processes, both normal and in tumor progression. We put forward the concept that MMPs are the key effectors of signaling in the pericellular environment. With collaborators, we discovered that MMPs are critical regulators of migration and repopulation of hematopoietic, endothelial and mesenchymal stem cells. We also elucidated important nonproteolytic functions of MMPs.

a. **Werb, Z**., C.L. Mainardi, C.A. Vater & E.D. Harris, Jr. (1977). Endogenous activation of latent collagenase by rheumatoid synovial cells. Evidence for a role for plasminogen activator. *New Engl. J. Med.* 296: 1017-1023. PMID: 66627.
b. Vu, T. H., J. M. Shipley, G. Bergers, J. E. Berger, J. A. Helms, D. Hanahan, S.D. Shapiro, R.M. Senior & **Z. Werb** (1998). MMP-9/gelatinase B is a key regulator of growth plate angiogenesis and apoptosis of hypertrophic chondrocytes. *Cell*. 93:411-422. PMCID: PMC2839071.
c. Coussens, L. M., C. L. Tinkle, D. Hanahan & **Z. Werb** (2000). MMP-9 supplied by bone marrow-derived cells regulates skin carcinogenesis. *Cell*. 103:481-490. PMCID: PMC2843102.
d. Kessenbrock, K., G.J.P. Dijkgraaf, D. A. Lawson, L. E. Littlepage, P. Shahi, U. Pieper & **Z. Werb** (2013). A role for matrix metalloproteinases in regulating mammary stem cell function via the Wnt signaling pathway. *Cell Stem Cell.* 13:300-313. PMCID: PMC3769456.

2. I was the first to propose that cell shape and cytoskeleton regulate cell signaling and gene expression. The subsequent series of studies lead to my demonstration for the first time that integrins were involved in signaling cascades, that several distinct signaling pathways were downstream of the same integrin, depending on cellular context and the concept that regulation of cell adhesion and cytoskeleton altered signaling cascades, gene transcription and apoptosis. These papers show that extracellular proteases are key and substantial targets of integrin and actin cytoskeletal based signaling cascades, and were the first to link Rho GTPases to integrin signaling and point out that the mitochondrion is a key signaling center

downstream of this pathway. These pathways are fundamentally involved in the tumor microenvironment and tumor cell behavior.

a. **Werb, Z.**, P.M. Tremble, O. Behrendtsen, E. Crowley & C.H. Damsky (1989). Signal transduction through the fibronectin receptor induces metalloproteinase gene expression. *J. Cell Biol.* 109: 877-889. PMCID: PMC2115739.
b. Kheradmand, F., E. Werner, P. Tremble, M. Symons & **Z. Werb** (1998). Role of Rac1 and oxygen radicals in collagenase-1 gene expression induced by cell shape change. *Science*. 280: 898-902. PMID: 9572733.
c. Ewald, A.J., A. Brenot, M. Duong, B.S. Chan & **Z. Werb** (2008). Collective epithelial migration and cell rearrangements drive mammary branching morphogenesis. *Dev. Cell*. 14:570-581. PMCID: PMC2773823.
d. Cheung, K.J., E. Gabrielson, **Z. Werb** & A. J. Ewald (2013). Collective invasion in breast cancer requires a conserved basal epithelial program. Cell. 155: 1639-1651. PMCID: PMC3941206.

3. Our studies on the developmentally controlled stromal microenvironment and invasive behavior in the mammary gland laid the groundwork for thinking about mechanisms controlling invasion during tumor progression. We developed mutant mouse models to study the role of MMPs in development and showed that disruption of ECM leads to loss of differentiation, apoptosis, and cancer.

a. Sternlicht, M. D., A. Lochter, C. J. Sympson, B. Huey, J. P. Rougier, J. W. Gray, D. Pinkel, M. J. Bissell & **Z. Werb** (1999). The stromal proteinase MMP-3/stromelysin-1 promotes mammary carcinogenesis. *Cell*. 98 : 137-146. PMCID : PMC2853255.
b. Casbon, A.J., D. Reynaud, C. Park, E. Khuc, D. D. Gan, K. Schepers, E. Passegué & **Z. Werb** (2015). Tumors reprogram early myeloid differentiation in the bone marrow to generate immunosuppressive neutrophils. *Proc. Natl. Acad. Sci. U.S.A*. 112 : E566-E575. [Epub Jan. 26]. PMID : 25624500 ; PMCID : PMC4330753.
c. Takai, K., A. Drain, D. A. Lawson, L. E. Littlepage, M. Karpuj, K. Kessenbrock, A. Le, K. Inoue, V. M. Weaver & **Z. Werb** (2018). Discoidin domain receptor 1 (DDR1) ablation promotes tissue fibrosis and hypoxia to induce aggressive, basal-like breast cancers. *Genes Dev*. 32 :244-257. PMCID : PMC5859966.
d. Owyong, M., J. Chou, R. J. E. van den Bijgaart, N. Kong, G. Efe, C. Maynard, D. Talmi-Frank, I. Solomonov, C. Koopman, E. Hadler-Olsen, M. Headley, C. Lin, C.-Y. Wang, I. Sagi, Z. **Werb*** & V. Plaks* (2019). MMP9 modulates the metastatic cascade and immune landscape for breast cancer anti-metastatic therapy. Life Sci Alliance. 2:pii: e201800226; doi.org/10.26508/lsa.201800226.; PMCID:PMC6856766.

4. We defined the stromal microenvironment in mammary tumor progression and metastasis. These studies in particular put forward then validated the hypothesis that proteases are the effectors of the cellular microenvironment and that altering the microenvironmental niche fosters tumor development and progression.

a. Nakasone, E., H. A. Askautrud, T. Kees, V. Plaks, A. J. Ewald, M. G. Rasch, Y. X. Tan, J. Qin, M. Fein, J. Park, P. Sinha, M. J. Bissell, E. Frengen, **Z. Werb** & M. Egeblad (2012). Imaging tumor-stroma interactions during chemotherapy reveals microenvironmental contributions to chemoresistance. *Cancer Cell*. 21 :488-503. PMCID : PMC3332002.
b. Kouros-Mehr, H., S. K. Bechis, E.M. Slorach, L. E. Littlepage, M. Egeblad, A. J. Ewald, S.-Y. Pai, I-C. Ho & **Z. Werb** (2008). GATA-3 links tumor differentiation and dissemination in a luminal breast cancer model. *Cancer Cell*. 13 :141-152. PMCID : PMC2262951.
c. Devignes, C.-S., Y. Aslan, A. Brenot, A. Devillers, K. Schepers, S. Fabre, J. Chou, A.-J. Casbon, **Z. Werb*** & S. Provot* (2018). HIF signalling in osteoprogenitor cells promotes breast cancer growth and metastasis. *Proc. Natl. Acad. Sci. USA*. 115 : E992-E1001. PMCID : PMC5798374.

d. 14 (2019). Immune effector monocyte - neutrophil cooperation induced by the primary tumor prevents metastatic progression of breast cancer. Proc. Natl. Acad. Sci. USA. 116:21704-21714. PMCID:PMC6815161.

5. Our studies on mammary development and mammary stem cells led to new insights into mechanisms and the windows of susceptibility underlying breast cancer progression and metastasis.

a. Chou, J., J.H. Lin, A. Brenot, J.-w. Kim, S. Provot & **Z. Werb** (2013). GATA3 suppresses metastasis and modulates the tumor microenvironment by regulating miR-29 expression. *Nat. Cell Biol.* 15: 201-213. PMCID: PMC3660859.
b. Lawson, D. A., N. Bhakta, K. Kessenbrock, K. Prummel, Y. Yu, K. Takai, A. Zhou, H. Eyob, S. Balakrishnan, C.-Y. Wang, P. Yaswen, A. Goga & **Z. Werb** (2015). Single-cell analysis reveals a distinct stem cell program in human metastatic breast cancer cells. *Nature*. 526, 131–135. PMCID: PMC4648562.
c. Nguyen, Q.H., N. Pervolarakis, K. Blake, D. Ma, R. T. Davis, N. James, A. T. Phung, E. Willey, R. Kumar, E. Jabart, I. Driver, J. Rock, A. Goga, S, Khan, D. A. Lawson, **Z. Werb*** & K. Kessenbrock* (2018). Profiling human breast epithelial cells using single cell RNA sequencing identifies cell diversity. *Nat. Commun*. 9(1):2028. doi: 10.1038/s41467-018-04334-1. PMCID: PMC5966421
d. McGinnis, C.S., D. Patterson, J. Winkler, D.N. Conrad, M.Y. Hein, V. Srivastava, J.L. Hu, L. M. Murrow, J.S. Weissman**, Z. Werb**, E.D. Chow & Z. J. Gartner (2019). MULTI-seq: sample multiplexing for single-cell RNA sequencing using lipid-tagged indices. Nat. Meth. 16: 619-626. doi: 10.1038/s41592-019-0433-8. PMCID: PMC6837808.

Complete List of My Published Work in PubMed:
http://www.ncbi.nlm.nih.gov/pubmed/?term=werb+z

Research Support

NIH/NCI U01 CA199315 Werb (PI). 06/01/16-05/31/21
Integrative Approach to Heterogeneity in Breast Cancer Metastasis
Using single cell multi-parametric, analytic techniques to probe heterogeneity during metastasis of breast cancer.

NIH/NCI R01 CA190851 Werb (PI). 07/01/15-06/30/20
Role of GATA3 in Transcriptional Pathways Suppressing Breast Cancer Metastasis
This proposal determines how GATA3 regulates metastasis.

NIH/NCI P30 CA082103-20 **(**Ashworth, PI) 05/08/99 - 05/31/23

(Werb, Assoc. Director for Basic Science)
Cancer Center Support Grant – Senior Leadership
The Cancer Center Support Grant provides support for administration and infrastructure for the UCSF Helen Diller Family Comprehensive Cancer Center.

METAvivor (Werb, PI) 01/01/20-12/31/22
Identification of Novel Cell Targets for Metastatic Breast Cancer Therapy
This proposal aims to determine the function of heterogenous breast cancer cells.

NIH/NCI T32 CA108462-15 (NCE) (Werb, Program Director) 09/01/04 - 08/31/20
Cellular and Molecular Mechanisms of Cancer
This is a National Cancer Institute Institutional National Research Service Award supporting 8 postdoctoral fellows. (Renewal submitted)

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

Honors

1993	Alpha Omega Alpha, Columbia College of Physicians and Surgeons, NY, NY
2012	Elected to Membership, American Society for Clinical Investigation

Contribution to Science

1. Molecular phenotyping of asthma (and COPD) using genomics. This work, which is based on gene expression studies of airway epithelial cell (as proposed in this grant application), allowed endotyping of asthma and COPD based on patterns of type-2 inflammation, has been shown in clinical trials to identify patients who will respond to inhaled glucocorticosteroids or to novel biologics which target type 2-cytokines and led to the development of a blood biomarker that can be used to personalize asthma treatment.

a. 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.
b. 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. (PubMed PMID: 25611785)
c. **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)
d. **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 Oct 2;104(40):15858-63. (PMCID: PMC2000427)

2. Subphenotyping COPD in the SPIROMICS study. My signature contribution to clinical subphenotyping in COPD thus far has been in the description of a new clinical entity, "Smokers with symptoms despite preserved spirometry" in the SPIROMICS I Study. In addition, I have been subphenotyping on a molecular and cellular basis through the SPIROMICS bronchoscopy and induced sputum studies.

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. Couper D, Lavange LM, Han M, Barr RG, Bleecker E, Hoffman EA, Kanner R, Kleerup E, Martinez FJ, **Woodruff PG**, Rennard S; for the SPIROMICS Research Group. Design of the Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS). *Thorax*. 2013 Sep 12. doi: 10.1136/thoraxjnl-2013 203897. PMCID: PMC5595208
c. O'Neal WK, Anderson W, Basta PV, Carretta EE, Doerschuk CM, Barr RG, Bleecker ER, Christenson SA, Curtis JL, Han MK, Hansel NN, Kanner RE, Kleerup EC, Martinez FJ, Miller BE, Peters SP, Rennard SI, Scholand MB, Tal-Singer R, **Woodruff PG**, Couper DJ, Davis SM; reporting for SPIROMICS Investigators. Comparison of serum, EDTA plasma and P100 plasma for luminex-based biomarker multiplex assays in patients with chronic obstructive pulmonary disease in the SPIROMICS study. *J Transl Med*. 2014 Jan 8;12(1):9. PubMed Central PMCID: PMC3928911.
d. Freeman CM, Crudgington S, Stolberg VR, Brown JP, Sonstein J, Alexis NE, Doerschuk CM, Basta PV, Carretta EE, Couper DJ, Hastie AT, Kaner RJ, O Neal WK, Paine Iii R, Rennard SI, Shimbo D, **Woodruff PG**, Zeidler M, Curtis JL. Design of a multi-center immunophenotyping analysis of peripheral blood, sputum and

bronchoalveolar lavage fluid in the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS). *J Transl Med*. 2015 Jan 27;13(1):19. PubMed Central PMCID: PMC4314767.

3. Studies of airway epithelial mucin stores, mucin gene expression and mechanisms of mucus production in airway disease. In this work I established design-based stereological methods for the measurement of airway epithelial mucin stores and epithelial MUC5AC and MUC5B, showed that airway epithelial mucin stores are increased in smokers and patients with COPD and studied the EGFR pathway as a contributor to airway mucin stores in a randomized trial. In addition, I have studied the relative contributions of MUC5AC and MUC5B to asthma and COPD.

a. 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. PMID: 17035444 *denotes authors contributed equally
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. **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
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 defense. *Nature*. 2014 Jan 16;505(7483):412-6. PMCID: PMC4001806

4. Clinical Trials of novel therapeutic approaches in asthma and COPD. These studies include a large multi-center trial which established the efficacy of a novel therapeutic approach in COPD (azithromycin).

a. 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

b. 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
c. **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 (BIBW 2948 BS) in COPD. *Am J Respir Crit Care Med*. 2010 Mar 1;181(5):438-45. PMID: 20007923
d. **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

Complete List of Published Work in MyBibliography (137 Publications):
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40802581/?sort=date&direction=descending

Research Support

U01 HL137880 (PI Woodruff) 09/15/17-5/30/22
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.

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.

R01 HL146002 MPI (Contact PI Levy, PI Woodruff). 10/1/2019-7/2024
Severe Asthma Research Program 4
To study immunometabolic phenotypes in adult severe asthma and disease

U19 AI077439 (Project leader: Woodruff, overall 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.

R01 HL143998 MPI (Contact PI Huang, PI Woodruff) 09/15/2019-07/31/202
Integrated Analysis of Microbial and Genomic data in Obstructive Lung Disease (I AM GOLD) Study
To study the 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.

R01 HL121774 (PI Huffnagle G, Woodruff Co-I) 01/01/17-08/31/20
Functional Analysis of the Pulmonary Microbiome during COPD
This study investigates a pathway that links inflammation, Gram negative bacterial overgrowth, mucus production and chronic bacterial colonization in COPD.

R35 HL138424 (Erle DJ, Woodruff Co-I) 08/01/17-06/30/21
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.

P01 HL107202 (Core director: Woodruff, Overall PI: Fahy) 09/01/19-07/31/24
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.

R01 HL143998 (Co-PI Woodruff, Contact PI Huang) 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.

R01 HL146002 (Co I Woodruff, PI Barr) 07/01/19-06/30/24
SPIROMICS II Heart Failure
The goal of this study is to define the heart failure phenotypes associated with COPD using 4D MRI and exercise echo by leveraging the SPIROMICS study.

U01 HL126493 (Contact PI: Woodruff, Co-PI: Erle DJ). 08/01/14-4/30/19
NIH/Common Fund (in no cost extension)
Defining a Comprehensive Reference Profile of Circulating Human Extracellular RNA
The goal of this study is to use RNA sequencing to establish the reference range of exRNAs as biomarkers in 12 different body fluids.

U01 HL128952-01 (Co-PI Woodruff, Contact PI: Han) 09/09/15-7/31/19
Redefining Therapy in Early COPD: RETHINC (in no cost extension)
To determine whether current and former smokers with preserved spirometry and respiratory symptoms will respond to inhaled bronchodilator therapy with improvement of their symptoms in a randomized controlled trial.

Completed Research Support

Seeding Bold Ideas Award (PI Christenson, Co-I Langelier and Woodruff) 05/01/17-4/31/19
Marcus Program in Precision Medicine Innovation
Host/Pathogen Metagenomic Deep Sequencing for Precision Diagnosis of Acute Exacerbations of COPD