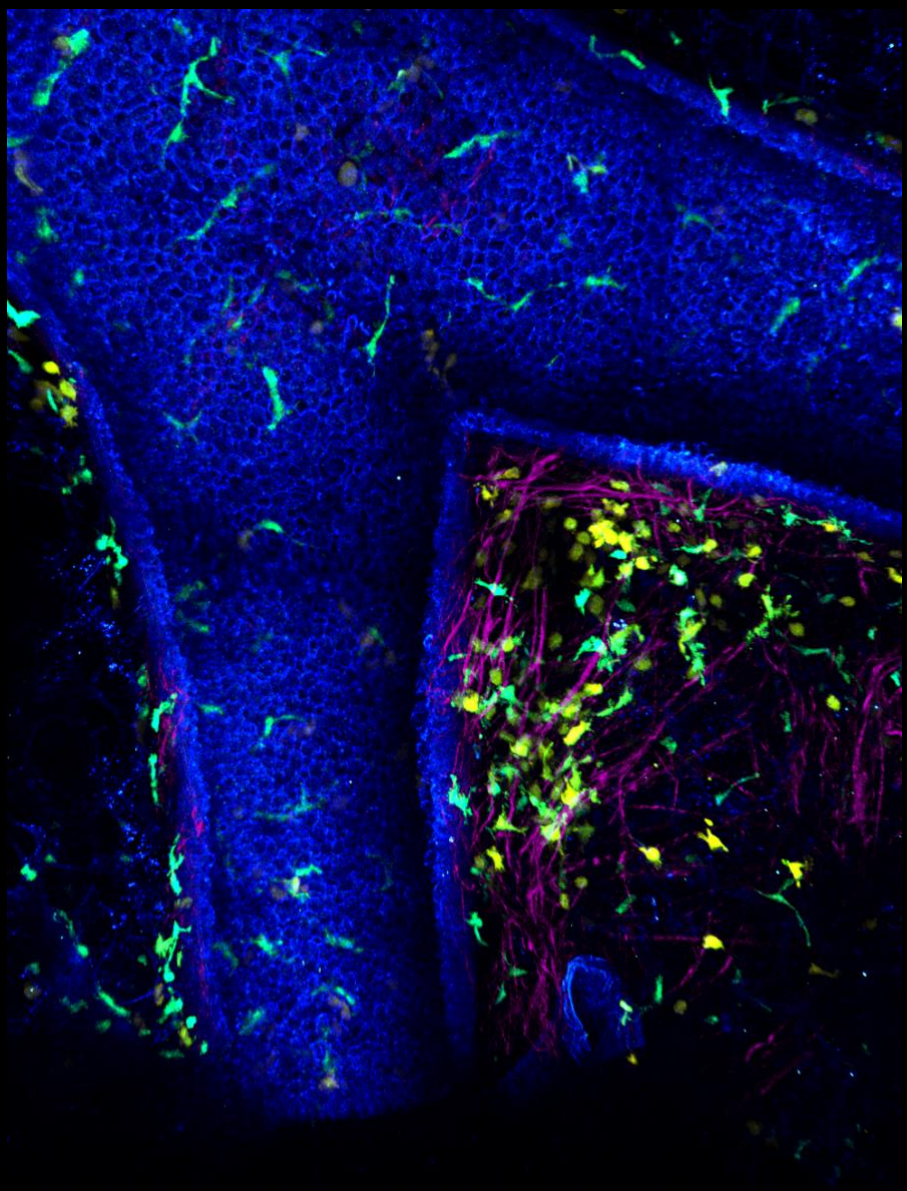
Sandler Asthma Basic REsearch Center

University of California, San Francisco



Progress Report

Year 23

2022

Figure Legend: Two-photon microscopy of the bronchial airways reveals the positioning of sentinel cells that capture inhaled allergens and initiate lung inflammation. Bronchus-associated macrophages (green) are visible underneath the airway epithelium (blue) and are enriched at the branch point of the airway, where collagen (magenta) is abundant. Dendritic cells (yellow) are also enriched at this branch point. Image provided by Emily (Xin-Zi) Tang and Christopher Allen. The Allen Lab in the SABRE center applies sophisticated imaging techniques in studies of asthma. A paper on this research is in press at eLife (Tang, X. et al), entitled: Bronchus-associated macrophages efficiently capture and present soluble inhaled antigens and are capable of local Th2 cell activation.

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Mission Statement

The Sandler Asthma Basic Research Center (SABRE Center) is an investigative unit dedicated to basic research discovery in asthma. Founded in 1999, the SABRE Center is nucleated by basic scientists supported by advanced technology cores and linked with the greater scientific community through Center Grants and Program Projects around asthma research. In 2014, the SABRE Center aligned with the Airway Clinical Research Center (ACRC) at UCSF to enable 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

Despite cautious attempts to open, the omicron and variant SARS-CoV-2 viruses surging in the Bay Area over the past 5 months continue to adversely impact the supply chain and personnel. Animal breeding, sequencing studies, core activities, in-person conferences and seminars remain only partially engaged with most activities remaining in hybrid mode, although the rapid shift to COVID-19-related research generated opportunities that could be met by the flexibility made possible by SABRE funding. SABRE Center investigators continue to make contributions to the understanding of asthma and allergic disease, while also pivoting to address the impact of COVID-19 on lung function among patients with asthma.

Notable accomplishments from SABRE Center members during the 2021-22 period:

(1) The COMET consortium organized by Prescott Woodruff, David Erle, Mark Ansel, John Fahy and others on the Leadership team to coordinate study of COVID patients continues to identify mechanisms driving disease. Key findings included dysregulated anti-viral interferon pathways mediated by aberrant autoantibodies that interfere with immune control and overly active neutrophils that foment tissue damage, but also blood-derived biomarkers predicting immune recovery. Progress was also made in identifying mechanisms driving the relative protection of patients with asthma from severe SARS-CoV-2.
(2) Esteban Burchard continues to enroll mother-infant pairs in the NIH-awarded PRIMERO study to follow asthma development in a prospective cohort of 3000 mother-newborn pairs in Puerto Rico.
(3) Studies from Erin Gordon and the Locksley lab identified a tuft cell-associated prostaglandin gene signature in epithelial cells from patients with nasal polyposis and severe asthma that may be part of a physiologic response to increase mucus transport by enhancing fluid secretion mediated by the cystic fibrosis transmembrane regulator.
(4) Chris Allen contributed a comprehensive review of IgE production by B cells pointing out gaps in information that will be necessary to unravel to fully understand the role of this key effector of allergic pathology.

Overview – 2022

Richard M. Locksley, M.D.

The SABRE Center continues its discovery-oriented mission towards deeper understanding of asthma that will guide innovative therapeutics. Currently comprised of three basic scientists, a population geneticist, two pulmonary basic/translational scientists, a bioinformatics specialist, and three junior 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 began an unprecedented disruption of American society, including research, that continues despite efforts to open up due to the ongoing variant-driven epidemic driving supply chain issues and personnel shortages. An international pivot to COVID-19-related activities coupled with the flexibility of SABRE support allowed many labs to move quickly to research addressing virus-lung interactions, including among patients with asthma. These activities were unified at UCSF to create COMET, an integration of scientists across disciplines to connect with clinicians to bring cutting-edge technologies to bear on understanding this new infectious disease. Boosted by 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. Scientific conferences, including the 2020 Keystone Symposium on Asthma Immunobiology by the former American Asthma Foundation Scientific Board in Utah and the 4th International Conference on Innate Lymphoid Cells in San Francisco were postponed, with the latter scheduled to be held in September 2022 in Hawaii.

Investigators

The pandemic impacted SABRE personnel with particular effects on those from foreign countries. Dr. Jeoung-Sook Shin left UCSF to return to Seoul, South Korea, to join an academic department to continue her science in proximity to her and her husband's families. Several foreign-born postdoctoral trainees returned home due to family hardships driven by COVID-related illness and deaths among family members. The SABRE Center currently consists of the Director, Dr. Locksley; core scientists Drs. Allen, Ansel, Fahy and Woodruff, and Dr. Burchard, who directs the Asthma Collaboratory Genetics Consortium at the Mission Bay campus. Dr. Fahy and Woodruff direct the Airway Clinical Research Center (ACRC) at Parnassus, where Dr. Woodruff assumed his new position as Head of the Division of Pulmonary, Allergy, Critical Care and Sleep Medicine at UCSF. 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. We added a Bioinformatics Specialist, Andrew Schroeder, MPH, to help with large datasets and in developing novel analytic tools generated by next-gen sequencing efforts. Their CVs are included in this report.

The SABRE Center is integrated with the Airway Clinical Research Center (ACRC) under the leadership of Drs. Fahy and Woodruff. SABRE investigators share quarterly lab and research meetings and attend monthly research conferences that also include outside guest investigators. The fruits of this collaborative effort resulted in an NIH Program Project Grant awarded to SABRE investigators in 2012, with a major focus centered on human patients and tissues as organized through the ACRC. The competitive renewal was renewed in 2019 for an additional 5 years, one of the few Program Projects approved for continued funding by the National Heart, Lung and Blood Institutes of the NIH. The SABRE Center remains an active research unit on the UCSF campus with a role in generating new basic understanding while opening new potential therapeutic approaches to asthma. We briefly review the Core Principal Investigators and their progress, followed by an overview of the components of the Center, a brief discussion of achievements and a listing of extramural grants and other resources that has been obtained to support these activities.

Chris Allen, Ph.D., joined the SABRE center fourteen years ago as a former UCSF Sandler Fellows Program (http://fellows.ucsf.edu/) studying asthma. His research focuses on understanding 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 limit somatic hypermutation and thus antibody 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 have driven new hypotheses regarding mechanisms by which some allergic individuals develop high-affinity IgE, and these continue to be a major effort of his laboratory. More recently, Dr. Allen published a paper in the *Journal of Experimental Medicine* regarding cytokine regulation of IgE responses, showing that IL-21 is a major factor limiting the generation of IgE B cells. Dr. Allen is revising a manuscript revealing a mechanism for the elimination of IgE plasma cells by B cell receptor signaling. Dr. Allen has another manuscript under review on how antigen is captured and presented to T cells in the lung by macrophages proximal to the bronchial airway epithelium and is finalizing two manuscripts on the activation and function of basophils, which are IgE effector cells. Dr. Allen's generation of an IgE reporter mouse that enables tracking IgE-switched B cells constitutes an important technical advance for the field and has been shared with numerous investigators. Dr. Allen has published detailed protocols on how to use this reporter mouse to study IgE in the *Methods in Molecular Biology* book series. Dr. Allen also developed methodology to characterize human IgE+ B cells. To facilitate mechanistic studies of human B cells, Dr. Allen optimized approaches to genetically manipulate primary human B cells with CRISPR-Cas9 technology, which was published in the *Journal of Immunological Methods*. Dr. Allen also published a letter in *The Journal of Allergy and Clinical Immunology* showing how an antibody to the IgE receptor, Fc-epsilon-RI, unexpectedly 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 published two reviews on advances in IgE biology for *Current Opinion in Immunology,* a review on the role of B cells in allergy for a special issue of the *Journal of Immunology* highlighting the diversity of scientists, 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 UCSF investigators.

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

Dr. Allen moved his laboratory to the Smith Cardiovascular Research Building on the Mission Bay campus in 2013 in proximity to other researchers working on the lung and using advanced optical imaging techniques. He is an active member of SABRE and participates in monthly and quarterly meetings with SABRE investigators on the Parnassus site. Dr. Allen has contributed his imaging expertise and advanced microscopy capabilities to Dr. Sundaram's research on airway smooth muscle tethering and bronchoconstriction in asthma in a paper published in the *Journal of Clinical Investigation*. Dr. Allen has contributed significantly to Dr. Bhattacharya's imaging studies of macrophage-fibroblast crosstalk in lung injury, with a paper published in *Frontiers in Immunology*. In addition, Dr. Allen contributed his expertise on IgE B cells to a study on microRNA regulation of B cell class switch recombination with Dr. Ansel's lab, which was published in the *Journal of Experimental Medicine*. Dr. Allen has also joined the team led by Dr. Burchard in the longitudinal study of asthma, starting at birth, in the Puerto Rican Infant Metagenomic and Epidemiologic study of Respiratory Outcomes (PRIMERO), for which Dr. Allen will contribute RNAseq and functional studies on lymphocytes from blood samples.

Dr. Allen is currently mentoring a PhD student and a postdoc in his lab and has recruited two undergraduates from UC Berkeley to work on summer projects. The PhD student is following up on work from a previous postdoc regarding the generation of IgE B cells in mouse models of asthma, and the postdoc is working on the IgE-mediated functions of basophils in allergic inflammation. Dr. Allen has 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 was recognized with a 2016-17 HHMI Medical Research Fellows award for a full year of research, followed by extended study through the Pathways program. In recognition of his significant contributions, his maintenance of extramural funding, and his service to UCSF, Dr. Allen was promoted to Associate Professor in 2018.

K. Mark Ansel, Ph.D., is an RNA immunologist working to understand the molecular and cellular underpinnings of the chronic tissue inflammation and dysfunction that manifest in allergic diseases, with a focus on asthma. RNA is a messenger molecule, tasked with carrying information about the state of a cell and its genome so that internal and external cues can be translated into action. The BioNTech/Pfizer and Moderna SARS-CoV-2 RNA vaccines are a

powerful demonstration of the potential of harnessing RNA for the prevention and treatment of human diseases. The Ansel lab has developed novel biochemical and computational techniques to discover the regulatory information encoded in RNA molecules. They use human and mouse genetics to interrogate the function of novel RNA modules in the programming of cell fate and function, with a focus on the lymphocytes and epithelial cells that are central to the pathogenesis of asthma. Since it is now clear that RNA can be delivered safely and effectively to cells, engineering these modules for cell reprogramming is a viable and exciting new path for development of therapeutics and customized cell therapies.

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

Dr. Ansel is an established leader in his field. He contributed to 8 published manuscripts this year, and guest edited and assembled an issue of Immunologic Reviews entitled RNA Regulation in Immunity. He has ongoing funding from R01 and P01 grants from NHLBI, and NIAID supplemental funding for his COVID-19 research. The Ansel laboratory team includes four graduate students, one junior faculty member, two technicians including a post-bac scholar in the UCSF PROPEL program, and one undergraduate researcher. Marlys Fassett is supported by a K08 Career Development Award, graduate student Benjamin Wheeler was awarded a Hooper Foundation Fellowship, and Priscila Muñoz-Sandoval is supported by a prestigious Howard Hughes Medical Institute Gilliam Fellowship. Dr. Ansel's departed trainees have moved successfully into the next phases of their careers as postdoctoral fellows, scientists at biotechnology companies, MD/PhD residents, fellows in research career tracks, and in four cases, as principal investigators of independent laboratories in the US and Germany where they have continued their work on cell programming in asthma.

Dr. Ansel is active in university service and leadership. He co-founded ImmunoX and is the incoming director and chair of the leadership committee. He recently co-founded UCSF PROPEL, a post-baccalaureate research program that has attracted over 80 budding researchers from minoritized and/or disadvantaged backgrounds into junior specialist and research associate positions at UCSF and supports them with community events and a career and scientific development curriculum. This year, he stepped down from his seven-year tenure as faculty director of the UCSF Biomedical Sciences (BMS) graduate program, though he remains the principal investigator of its NIH T32 training grant. He has championed and spearheaded initiatives to enhance diversity, equity and inclusion in the UCSF research community. He successfully organized faculty efforts to advocate for university investment in a new research building on the Parnassus campus and continues to work with university leadership and campus stakeholders to ensure that these investments move forward with maximum benefit. He teaches

medical, dental and graduate students, and designed the immunology curriculum for the UCSF Doctor of Pharmacy program.

Esteban G. Burchard, M.D., M.P.H., directs the UCSF *Asthma Collaboratory*, a large, annotated gene biorepository of minority children with asthma. Data from the biorepository have been shared with over 80 collaborators and have contributed to over 300 publications. The lab has led the way into understanding racial/ethnic differences in asthma and drug response among minority children in the U.S.

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

The PRIMERO team have successfully recruited close to 700 mother-infant dyads and maintained a participant retention rate of 99.7%. Biological samples have been collected from most participants while operating under COVID-19 constraints, and include cord blood (90%), maternal blood (99%), and nasal swabs (99%). Additional NIH funds in late 2020 were awarded to expand PRIMERO to examine the epigenetic inheritance of maternal exposures during pregnancy and how they may impact the child's risk for respiratory disease, which has included examination of the impact of SARS-CoV-2 infection as part of a UCSF-wide effort to contribute to understanding this pandemic and its repercussions.

The *Asthma Collaboratory* has led efforts to identify genetic variants associated with lung function in Puerto Rican and African American children with asthma. By this analysis, 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). Research from the Burchard team has moved to the forefront of the debate on the use of race/ethnicity in clinical decisions while advocating for the epidemiological importance of race/ethnicity in medicine (*Borrell, Elhawary et al. NEJM, 2021*).

John Fahy, M.D. is a longstanding participant in SABRE research and a faculty member in the SABRE Center for the past 9 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 the Airway Clinical Research Center at UCSF, which is a key resource for clinical studies and clinical trials in asthma, COPD, and cystic fibrosis. His mechanism-oriented clinical research program in asthma 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 to humans that advance understanding for how pathologic mucus gels form in asthma. These methods range from analysis of cells and proteins in induced sputum to studies of lung images acquired from patients using computed tomography.

Dr. Fahy has multiple active NIH supported research programs in asthma:

- he leads a PO1/PPG program in type 2 airway inflammation in asthma (with Drs. Locksley, Ansel. Gordon, and Woodruff) and inclusive of Max Seibold, Ph.D. at National Jewish Health.
- he leads a UGI program (which includes investigators at UC Davis) and is the funding mechanism for PrecISE, the Precision Interventions for Severe and/or Exacerbation-Prone Asthma Network. PrecISE is a national network that is studying biomarker informed clinical trials in severe asthma, and Dr Fahy is the network wide PI for the clazakizumab trial which is studying whether IL6 inhibition improves asthma control in "IL-16-high" asthma (an endotype discovered by Dr Fahy's lab).
- he leads an R01 program of research on mechanisms of mucus gel pathology in asthma (Dr. Fahy successfully renewed this longstanding R01 in the past year)
- he leads a newly awarded R01 program focused on uncovering mechanisms of "metabolic asthma", or asthma that is characterized by severity linked to obesity and metabolic dysfunction.
- he is the clinical investigator lead for the UCSF sites in the Severe Asthma Research program (Prescott Woodruff is site PI).

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

Richard Locksley, M.D., is Director of the SABRE Center, an immunologist and infectious diseases-trained physician who pursues basic studies of allergic immunity and asthma. His laboratory focuses on deeper understanding of the role for allergic cytokines in basal homeostasis, with a particular emphasis on group 2 innate lymphoid cells, or ILC2s, that have

become of increasing interest in understanding the origins and dysfunction underlying allergy and 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 13 peer-reviewed publications, 4 open repository contributions, and 4 invited reviews and commentaries during 2020-2022.

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 three to identify an important role for tuft cells, rare epithelial cells in the nose, lung and gut, in allergic immunity. Despite their description for over 60 years, tuft cell function was unknown until these pioneering studies that implicate these cells as the source of IL-25 and leukotrienes that mediate crosstalk between epithelia and ILC2s associated with allergic immunity. Ongoing studies are examining the role of these cells in the nasal epithelium, including in humans, where allergic nasal polyposis is highly associated with severe asthma in adults. His laboratory contributed to some of the initial single-cell RNAseq studies of ILC2s to define their tissue-specific transcriptomic signatures as these cells first enter tissues during fetal development. He is a Professor in the Departments of Medicine and Microbiology & Immunology, and an Investigator in the Howard Hughes Medical Institute. Dr. Locksley is a member of the Lasker Foundation Jury and the National Advisory Committee for the Pew Scholars Program in Biomedical Sciences. He moderated the 2019 NIH Workshop on the role of ILC2s in allergy and asthma. He is a member of the American Academy of Arts & Sciences and the National Academy of Sciences. He received the first annual William Paul Award for contributions to cytokine research from the International Cytokine & Interferon Society in 2016 and was recognized as a Distinguished Fellow of the American Association of Immunologists Inaugural Class. His laboratory is supported by HHMI and by grants from the NIH, and he directs Subproject 1 for the SABRE Center Program Grant, 'Exploring the biology of persistent type 2 airway niches in asthma'. Recent postdoctoral trainees in his laboratory include recipients of Cancer Research Institute Fellowships, a Fulbright Fellowship, a Giannini Fellowship, an American Dermatology Research Fellowship, a Burroughs Wellcome Career Award for Medical Scientists and an NIH F32. Recent postdoctoral graduates have moved into academic faculty positions at UCSF, University of Washington, Washington University St. Louis, University of Wisconsin 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 originally scheduled in San Francisco in October 2020, although this has been delayed due to the pandemic and is currently scheduled to be held in Hawaii in 2022.

Jeoung-Sook Shin, Ph.D., seeks to understand the molecular mechanisms by which dendritic cells contribute to immune homeostasis and diseases. Her laboratory published an important study in *Science Immunology* at the end of 2021 outlining the role of the ubiquitin ligase MARCH1 in a specialized dendritic cell population necessary for the induction of Th2 T cell

responses, a core component of the asthma response. Representing a collaboration among several SABRE and non-SABRE labs at UCSF, this key study concludes Dr. Shin's role in SABRE at UCSF as she relocates back to South Korea in response to family issues compounded by the pandemic. We will miss her scientific intellect, her teaching and mentoring expertise, and her collaborative nature, and wish her success in her new academic environment.

Prescott Woodruff, M.D., is Associate Director of the Airway Clinical Research Center and has been an integral member of the SABRE Center for the past 8 years as a longstanding collaborator with other SABRE investigators. He is a physician-scientist with a primary appointment in the Department of Medicine where he is Chief of the Division of Pulmonary, Critical Care, Allergy and Sleep Medicine (as of July 1, 2022). His research interests include asthma pathogenesis, genomics and translational studies, particularly in the field of precision medicine. His discoveries were among the earliest to identify biomarkers that permit segregation of asthma patients into categories likely to benefit from specific types of therapies that target type 2 inflammation mediated by the IL-4/IL-13 pathway. More recently, he has focused on non-type 2 inflammation in severe asthma and mechanisms of pathological mucus production in asthma. In particular, he has identified a micro-RNA (miR-141) that regulates airway epithelial mucus and which can be therapeutically targeted using an inhaled synthetic oligonucleotide (Siddiqui, *JCI Insight* 2021). Dr. Woodruff also has an active research program in chronic obstructive pulmonary disease (COPD). he is PI or multiple-PI of (1) the NHLBI Severe Asthma Research Program (4th iteration which started in 2019), (2) the NHLBI SPIROMICS study of COPD, (3) the NHLBI RETHINC clinical trial in COPD and (4) a NHLBI K24 award which supports his mentoring of junior faculty and trainees. He is a co-investigator and/or project leader on two NIH-funded asthma grants, 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 Childhood Asthma in Urban Settings (CAUSE) Study. Woodruff's honors include election to the American Society for Clinical Investigation and the Association of American Physicians.

Core Activities and Technology Development

An important 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 direct leveraged support to the Microscopy Core, under the guidance of Dr. Krummel. The Microscopy Core develops applications for *in situ* microscopy of the lung and more powerful approaches for visualizing chemistry in single cells using lattice-sheet microscopy, Clarity, and other cutting-edge technologies. Their updated report is included. We made major efforts to support next-generation deep-sequencing efforts, including single-cell RNAseq and epigenetic analyses, such as ATACseq and CITEseq methods,

which were accelerated by providing funds for sequencing and bioinformatics. To this end, SABRE hired Dr. Andrew Schroeder in 2021 to coordinate bioinformatics needs across SABRE labs and to integrate databases more completely with public and in-house databases from BioHub and ImmunoX. Creation of this infrastructure was essential in enabling the pivot to the crisis of the COVID pandemic, to which these advanced technical and analytical tools were rapidly embraced in confronting the need for human-based study at previously unprecedented scale.

The Genetics Asthma Collaboratory under Dr. Burchard remains among 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 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 approaches 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. Dr. Burchard obtained a $10 million grant from National Heart, Lung and Blood Institute at the NIH in 2019, named PRIMERO, to prospectively study 3,000 newborn/parental family units with cutting-edge repeated evaluations over time to define asthma risk in relationship to genome. This has spawned several leveraged NIH applications from UCSF to monitor the mother-child microbiota and collect environmental data that will be integrated with deep sequencing and cell analysis to provide an unprecedented resource evaluating the evolution of asthma in humans as it develops. Despite the COVID-19 pandemic and its havoc on Puerto Rico and travel, the team has enrolled over 700 infant-mother pairs while instituting rigorous methods for sample collection, storage and analysis both on-site in Puerto Rico and at UCSF for more technical studies, for which SABRE has provided funding to obtain pre-submission materials to facilitate collaborative grants from SABRE investigators.

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. Instruments supported by SABRE matching funds, including CyTOF, liquid mass spectrophotometers and flow cytometry analyzers remain in widespread use among labs at UCSF. We contributed to an Aurora CyTECK multi-laser spectroscopy unit with the capacity to rapidly fill the space between flow cytometry and single-cell sequencing at substantial cost saving once antibody profiles are optimized. The dedication of a Microbiota Center under the leadership of Dr. Susan Lynch has created need for expansion of the gnotobiotic core supporting maintenance of germfree mice under the direction of Dr. Peter Turnbaugh. SABRE investigators, including Drs. Locksley, Allen and Ansel have all used the gnotobiotic core as a resource for controlling and isolating microbiota that have profound effects on metabolism and organ function. With this in mind, SABRE 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 was also involved with contributions towards an additional 10X Genomics sequencer to facilitate single-cell genomic analysis. Negotiations are ongoing to help replace a 15 year-old flow cytometry in the SABRE core lab space with a new instrument by leveraging matching funds from Departmental and School sources.

SABRE Associate Support

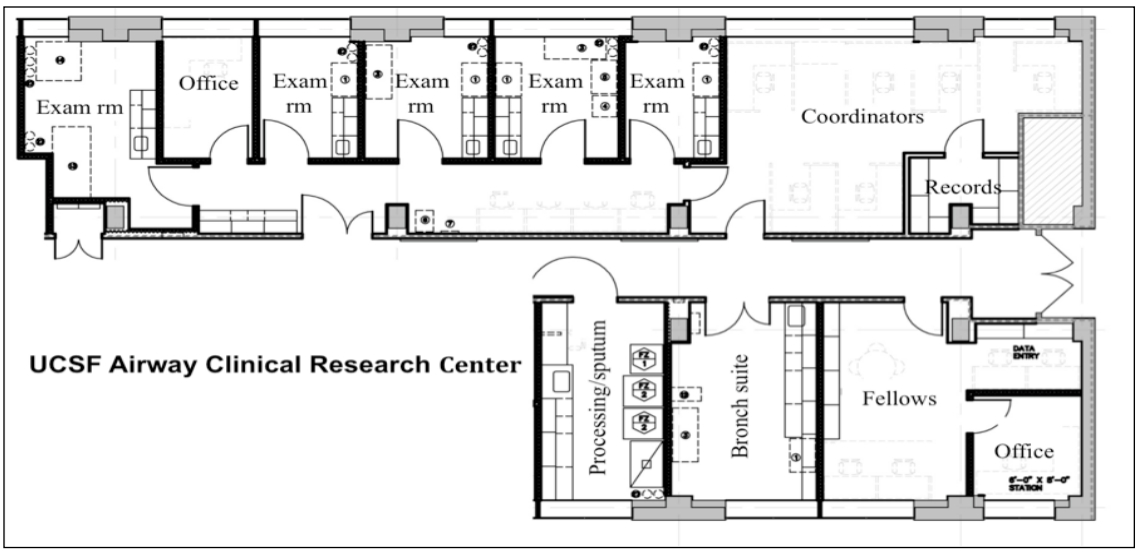
We will support collaborative interactions between SABRE Associates – Drs. Gordon, Bhattacharya and Sundaram – and Investigators to create opportunities in asthma research. These three young scientists have already procured independent grants and interact while contributing to the SABRE Mission. Dr. Gordon, who is on a grant with Drs. Locksley and Fahy, obtained her own grants to further her interests in epithelial responses in asthma. She works closely with Dr. Locksley and surgical colleagues in understanding the mechanisms driving allergic nasal polyposis that emerge among patients with severe poorly controlled asthma. Dr. Bhattacharya investigates lung injury, pivoted rapidly to address mechanisms by which COVID-10 mediates lung destruction, and received an NIH R01 to study pathways resulting in lung fibrosis. 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 continuing to support to allow these new Associates to continue their outstanding trajectories. Their CVs are included.

SABRE RNA-seq Initiative

Since 2019 we have designated commitments to core labs for use in bulk and single-cell RNA-sequencing of airway tissue cells to create a tissue bank for core use and dissemination among labs across UCSF and wider after publication. Studies of mouse nasal and lung ILC2s and epithelial tuft cells (Locksley lab), human airway brushes (Fahy lab), human airway epithelial monolayers under various conditions (Woodruff lab), human nasal polyp tissues from patients with allergic polyposis (Gordon/Locksley 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) have spearheaded these findings. These data have yielded valuable information for comparisons between the mouse and human as well as biologic insights that continue to drive hypothesis-driven studies. These data are established in the public science space with proper masking of human data. Based on the success of these studies, SABRE hired a 50% bioinformatics specialist, Andrew Schroeder, and supported acquisition of an additional 10X single-cell sequencing platform to speed access to this technology, which remains a continued priority.

Airway Clinical Research Center

The Airway Clinical Research Center (ACRC) is a customized space of 3500 sq ft. located on the 13th floor of the UCSF Medical Center. The ACRC comprises 5 separate testing rooms for history and physical examination, phlebotomy, allergen skin tests, spirometry and methacholine challenge (Figure). This center has a research bronchoscopy suite, a sample processing lab, and administrative space for twelve research coordinators and six research fellows. The space is dedicated to clinical research in airway disease; there is no clinical patient care activity in this space. The ACRC has fully equipped exam rooms for conducting pulmonary function testing, research bronchoscopy, participant interviews and specimen collection and processing.



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

ACRC Faculty: John Fahy, Prescott Woodruff, Erin Gordon, Monica Tang, 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. Gordon, Christenson, and Bhakta. Current trainees include Anita Oh, M.D., Aartik Sarma, M.D., Brendan Huang, M.D., William McKleroy, M.D., Aaron Baugh, M.D. Jonathan Witonsky, M.D., and Clarus Leung, M.D.

ACRC Research: The ACRC supports research programs that involve human-centered study of asthma and other airway diseases. Most of this research is funded by NIH grants (below), but ACRC investigators have a strong track record of successful engagement in research alliances with biotech and pharmaceutical companies. Examples include collaborations that Drs Fahy and Woodruff have had with Genentech (GNE) to assist GNE with its therapeutic antibody programs in asthma that target IgE, IL4R, IL33R (ST2) and tryptase. In addition, Dr Fahy has secured funding from NIH for a drug development program that is advancing thiol-modified carbohydrates as novel inhaled mucolytic drugs. This mucolytic program is augmented by biomarker discovery research that has developed and validated an image (CT lung)-based score as a predictive and monitoring biomarker for airway mucus plugs in asthma and COPD. Dr. Woodruff has been pursuing another novel therapeutic approach to reducing pathological mucus production, the inhaled delivery of oligonucleotides which target epithelial miRNAs. This work

is based on his recent demonstration that the miR-141/200 family of micro-RNAs (small regulatory RNAs) regulates airway epithelial mucin production in human and murine airway epithelial cells and that inhaled delivery of a synthetic oligonucleotide that antagonizes miR-141 reduces airway mucus production and resistance in a murine asthma model. UCSF has submitted a patent application based on this work. In other very recent work, Dr. Woodruff has leveraged the existing asthma U19 grant (Understanding Asthma Endotypes) to fund the COMET Study which is performing deep immunophenotyping of patients with severe COVID-19 at UCSF and has demonstrated that severe COVID-19 is associated with antibody-mediated defects in interferon driven anti-viral host responses (Combes A, Nature 2021). This study has led to a Genentech collaboration that Dr. Woodruff directs to match COVID-19 immunophenotypes to existing biological therapies that may be repurposed. Finally, Dr. Fahy has been exploring mechanisms of asthma that do not involve type 2 inflammation pathways and he has been focusing on the "IL-6-high" subtype of asthma that led him to propose IL-6 inhibition as a novel strategy to treat "IL-6-high" asthma. The steering committee for the NHLBI Precise Network (severe asthma clinical trials network) has selected clazakizumab (anti IL-6 ligand) as one of the drugs to be tested in the Precise platform trial. Dr. Fahy now leads the clazakizumab trial for asthma in Precise. The activities of ACRC illustrate how the human centered and mechanism-oriented research of the Center are being translated into treatment programs that have potential to address the unmet needs of patients.

Current NIH Funding

1. P01 HL107202 (8/15/2012-7/31/2024) *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 (SMART-SA).* 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.

3. U19 AI077439 (4/1/2018-3/31/2023) *Understanding Asthma Endotype*. 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. U19 AI077439-13S2 (5/8/2020-3/31/2022) *UCSF COVID-19 Immunophenotyping clinical study and core laboratories.* Dr. David Erle is PI and Dr. Woodruff is co-I and Executive Committee Member. The goal of this project is to identify causes of severe COVID-19 through detailed immunophenotyping in a multi-center longitudinal clinical study (The UCSF COMET Study).

5. Genentech TSK-020586 (12/15/2020-12/15/2023) *COVID-19 Multi-phenotyping for Effective Therapies (COMET) Plus.* Dr. Woodruff is PI. The goal of this study is to identify biological pathways associated with severe COVID-19 using deep immunophenotyping.

6. R01 AI136962 (1/15/2018-12/31/2022) *Understanding the Molecular Genetic Mechanisms of Asthma Risk Loci: IL33, IL1RL1, and GSDMB*. Dr. Gordon has submitted a competitive renewal of her R01 in the past year and is awaiting evaluation.

7. R01 HL164787 (8/1/2022-7/31/2026) *Evaluating the Impact of Metabolic Dysfunction on Asthma Pathology and Physiology*. Dr. Fahy is PI on this new R01 that is exploring obesity related airway dysfunction in asthma.

8. R01 HL080414 (07/01/2022 - 06/31/2027) *Phenotypic and biological features of mucus plugs in asthma*. Dr. Fahy successfully renewed his longstanding R01 that is exploring mechanism of mucus pathology in asthma.

9. U01 HL137880 (9/15/2017-5/30/2022) *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.

10. R01 HL143998 (9/15/2019-7/31/2023) *Integrated Analysis of Microbial and Genomic data in Obstructive Lung Disease (I AM GOLD) Study.* MPI Christenson, Contact PI Huang, co-I Woodruff. 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.

11. U01 HL146002 (9/23/2019-6/30/2024) *Immunometabolic phenotypes in adult severe asthma and disease progression. Severe Asthma Research Program 4.* Dr. Woodruff is PI, Contact PI is BD Levy. This multicenter grant is exploring molecular subtypes of asthma in a cohort of patients with severe asthma.

12. R01 HL128156 (5/1/2020-4/30/2025) *Inflammation, Aging, Microbes, Obstructive Lung Disease, and Diffusion Abnormalities (I AM OLD-DA) Study.* Dr. Huang is PI and Dr. Woodruff is co-I. This grant tests the hypothesis that asymptomatic CMV co-infection and chronic inflammation are associated with lung function abnormalities in patients with HIV/AIDS.

13. R01 HL144718 (5/1/2020-4/30/2023) *Understanding the Origins of Early COPD*. Dr. Woodruff is co-I, PI is Fernando J. Martinez. This grant will establish a longitudinal cohort of patients with "early COPD" and identify the pathophysiologic changes in the lung that predispose smokers to develop *bona fide* COPD that is associated with overt airflow obstruction.

14. OT2 HL156812 (10/1/2020-9/13/2022) *Collaborative Cohort of Cohorts for COVID-19 Research (C4R).* Dr. Woodruff is co-I, PI Barr and Oeslner. The major goals of this project are to leverage longitudinal data and deep phenotyping in fourteen US prospective cohort studies to ascertain all cases of COVID-19 infection, to evaluate risk factors for infection (including the presence of asthma and asthma endotypes), and to track the prognosis of both those with and those without infection.

15. F32 HL158222 (7/1/2021-6/30/2023) *Contribution of nerves and neuropeptides to inflammation in asthma.* Dr. McKleroy is PI, Mentor is Woodruff. This training grant explores the contribution of pulmonary sensory nerves, pulmonary neuroendocrine cells, and their secreted peptides on development and maintenance of TH2-high and -low endotypes in asthma.

Communications, Training and Leadership Initiatives

SABRE is represented on the ImmunoX leadership council at Parnassus by Mark Ansel, a member of the council. John Fahy continues to lead research and clinical planning on Parnassus. Richard Locksley organizes the basic immunology research seminars and is a Co-PI on the Gnotobiotic Initiative. Prescott Woodruff helped organize the COMET NIH-Genentech-UCSF Consortia for rapid acquisition and study of COVID patients, and has re-organized the second-generation request recently submitted, which includes SABRE support for airway specimen collection and patient study. He was recently appointed as the Head of the Division of Pulmonary, Critical Care, Allergy & Sleep Medicine at UCSF.

SABRE Center core scientists meet quarterly to further communication, planning and collaborative investigations of human asthma patients. Each of the core scientists is involved in ongoing or planned investigations based on patient samples from either the ACRC or the Sinus and Upper Airway Clinic at Mt. Zion. We hold monthly research conferences for SABRE/ACRC investigators at the Parnassus site to promote interactions and collaborations.

National and International Meetings

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

Human Upper Respiratory Tract Analysis

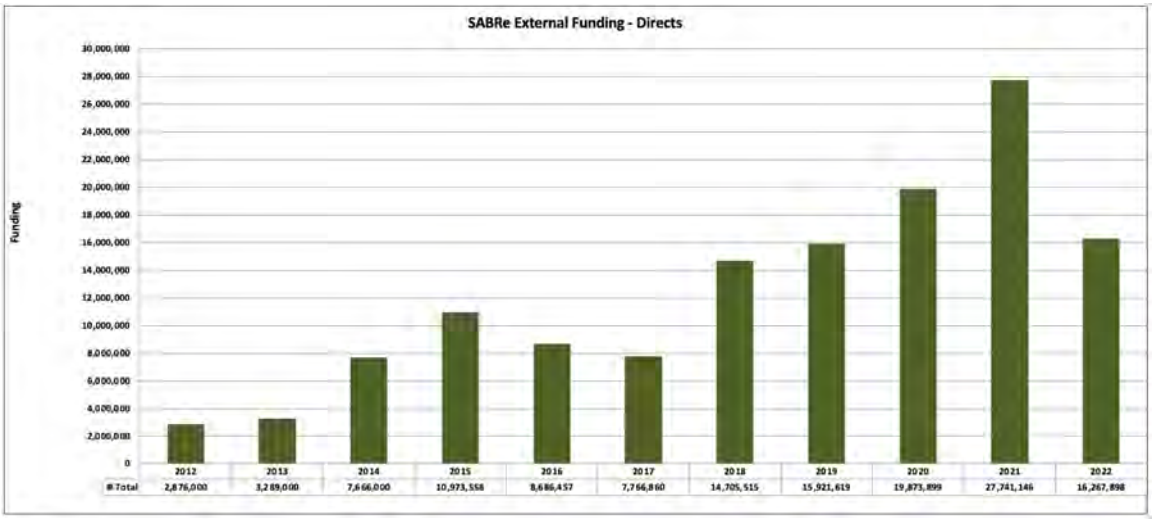
The SABRE Center is working with a UCSF surgical practice located at Mt. Zion campus with experience taking care of large number of patients with allergic nasal polyposis. These investigators, Drs. Andrew Goldberg and Steven Pletcher, faculty in the Department of Otolaryngology and Head and Neck Surgery 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. 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 now involved in these studies while working as an Associate Investigator in the SABRE Center. The first of these studies culminated in studies of human tuft cell involvement in the nasal polyposis syndrome accompanying severe asthma. The biosketches of Dr. Goldberg, Pletcher and Gordon are appended.

Successful competition for extramural support

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

We have maintained substantial procurement of external funds by the core SABRE investigators in support of their research efforts. Although diminished by ~$11 million, this was largely driven by expiration of a large NIH Center Grant to Dr. Woodruff. Support for SABRE members was maintained 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 our funding momentum and research portfolio.



Growth in accumulated extramural funds by SABRE investigators – Drs. Cheng, Fahy and Woodruff joined in 2014; Drs. Liu and Cheng were recruited elsewhere in 2015; Dr. Shin was recruited elsewhere in 2021; Assoc Investigators joined in 2019.

SABRE Center activities resulted in publication of numerous manuscripts and contributed to many successful grants and fellowships of various types to investigators at UCSF. Despite our

successes in competing for extramural resources, the flexibility of SABRE support is not matched by these types of grant monies.

Highlighted SABRE Center-supported manuscripts impacting asthma-related and lung COVID research in 2021-22

Allen CDC. 2022. Features of B cell responses relevant to allergic disease. *J Immunol* 208:257-66.

A concise, thorough analysis of mechanisms driving high-affinity IgE antibodies from the perspective of normal B cell differentiation and maturation that sets out the areas that require experimental clarification to fully understand this foundational cornerstone of the dysregulated allergic state.

Bonser LR, WL Eckalbar, L Rodriguez, J Shen, KD Koh, K Ghia, LT Zlock, S Christensen, Woodruff PG, Finkbeiner WE, Erle DJ. 2022. The type 2 asthma mediator IL-13 inhibits severe acute respiratory syndrome coronavirus 2 infection of bronchial epithelium. *Am J Respir Cell Mol Biol* 66:391-401.

Epidemiologic evidence suggesting protection of asthma patients from severe COVID-19 was supported by these data demonstrating direct effects of IL-13, a key type 2 cytokine associated with asthma, in reducing production of SARS CoV-2 genes and infection on isolated human bronchial epithelial through effects largely independent of mucus production. Although ACE2 reduction was apparent, reduction of many cell targets by IL-13 suggests strategies for new understanding of mechanisms controlling coronavirus replication in human airway epithelia.

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

This widely read discourse on the underpinnings of genetic ancestry and the overt effects of race identity in clinical medicine, distributed via the broad readership of then influential New England Journal of Medicine, has rapidly become a resource for anchoring scientific and societal issues during these tumultuous periods of social justice reckoning.

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

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

Kotas ME, CM Moore, JG Gurrola II, SD Pletcher, AN Goldberg, R Alvarez, S Yamato, PE Bratcher, CA Shaughnessy, PL Zeitlin, IH Zhang, Y Li, MT Montgomery, K Lee, EK Cope, RM Locksley, MA Seibold, ED Gordon. 2022. IL-13-programmed airway tuft cells produce PGE2, which promotes CFTR-dependent mucociliary function. *JCI Insight* 7:e159832.

Patients with chronic rhinosinusitis with nasal polyps are not uncommon among patients with severe asthma, which is more often associated with a high-type 2 phenotype. Kotas et al. studied 5 patients and controls using single-cell RNA sequencing of the polyp epithelia to reveal an IL-13- and polyp-associated tuft cell signature indicative of prostaglandin production and a prostaglandin-driven gene signature as revealed by studies in human epithelial cell lines and mouse models. Prostaglandins drove cystic fibrosis transmembrane receptor ion and fluid fluxes that facilitated mucociliary transport, revealing the physiologic response to the enhanced mucus production driven by the type 2-high response. These findings suggest a homeostatic role for epithelial tuft cells in upper airway clearance that becomes highly activated during polyp formation.

Van der Wijst MGP, SE Vazquez, GC Hartoularos, *et al*. 2021. Longitudinal single-cell epitope and RNA-sequencing reveals the immunological impact of type 1 interferon autoantibodies in critical COVID-19. *Science Transl Med* 13:eabh2624.

Combes AJ, T Courau, NF Kuhn, *et al*. 2021. Global absence and targeting of protective immune states in severe COVID-19. *Nature* 591:124-130.

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

Wigton EJ, Y Mikami, RJ McMonigle, CA Castellans, AK Wade-Vallance, SK Zhou, R Kageyama, A Litterman, S Roy, D Kitamura, EC Dykhuizen, CDC Allen, H Hu, JJ O'Shea, KM Ansel. 2021. MicroRNA-directed pathway discovery elucidates a miR-221/222-mediated regulatory circuit in class switch recombination. *J Exp Med* 218:e2021422.

Using a genetic rescue strategy in microRNA-depleted B cells, the authors identify a role for miR-221/222 in class switch recombination necessary for efficient production of IgE and IgG1 through induction of Foxp1 and Arid1a, thus establishing a hub that might be amenable to therapeutic intervention in control of IgE production.

Organization of the body of this Annual Report

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

We thank the Sandler family for their vision and support in creating and sustaining the SABRE Center. Support for high-risk, open-ended, basic science is difficult to procure in the current funding and fiscal climate. As noted as examples here, the ability of SABRE labs to pivot quickly and decisively has allowed our investigators to add to the understanding of

COVID-19 and its impact on patients with asthma, and these studies continue while the world responds to this unprecedented pandemic. We are most grateful for the continued support of the Sandler Foundation.

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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Department of Medicine

Hal Chapman, M.D., Professor
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Dean Sheppard, M.D., Professor
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Art Weiss, M.D., Ph.D., Professor
Departments of Medicine and Microbiology/Immunology

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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.

Selected Publications

1. Kotas ME, CM Moore, JG Gurrola II, SD Pletcher, AN Goldberg, R Alvarez, S Yamato, PE Bratcher, CA Shaughnessy, PL Zeitlin, I Zhang, Y Li, MT Montgomery, K Lee, EK Cope,

RM Locksley, MA Siebold, ED Gordon. 2022. Il-13-programmed airway tuft cells produce PGE2, which promotes CFTR-dependent mucociliary function. *JCI Insight* 7:e159832.
2. 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.
3. O'Leary CE, C Schneider, **RM Locksley**. 2019. Tuft cells – systemically dispersed sensory epithelia integrating immune and neural circuitry. *Annu Rev Immunol* 37:47-72.
4. 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.
5. 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.
6. Kotas ME, **RM Locksley**. 2018. Why Innate Lymphoid Cells? *Immunity* 48:1081-1090.
7. 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.
8. 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.
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. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. **Locksley RM**. 2010. Asthma and allergic inflammation. *Cell* 140:777-83.

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Dr. Allen is an Investigator of the Cardiovascular Research Institute and the SABRE Center, and an Associate 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**. (2022) Features of B Cell Responses Relevant to Allergic Disease (Review). *The Journal of Immunology*, 208(2):257-66. PMID: 35017215
2. Wade-Vallance A.K., **Allen C.D.C**. (2021) Intrinsic and extrinsic regulation of IgE B cell responses (Review). *Current Opinion in Immunology*, 72:221-9. PMID: 34216934
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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. 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 sustained type 2 airway inflammation in asthma.

Selected Publications

1. Pua H, **Ansel KM**. RNA regulation in immunity. *Immunol Rev*. 2021 Nov;304(1):5-9.
2. Johansson K, Woodruff PG, **Ansel KM**. Regulation of airway immunity by epithelial miRNAs. *Immunol Rev*. 2021 Nov;304(1):141-153.
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4. 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
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6. Gagnon JD, **Ansel KM**. MicroRNA regulation of CD8(+) T cell responses. *Noncoding RNA Investig*. 2019 Aug;3. pii: 24
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Esteban González Burchard, M.D., M.P.H., is a physician-scientist with formal training and expertise in pulmonary medicine, epidemiology, molecular genetics, genetic and clinical research. He has led a large research program focusing on minority children and gene-environment interactions since 2001. Dr. Burchard served as an advisor to the National Academy of Sciences of the U.S. Congress on gene-environment interactions. Dr. Burchard has expertise in the field of precision medicine and served on the Expert Panel for President Obama's Precision Medicine Initiative. He initiated and now directs four independent asthma studies in minority children. He has assembled a collaborative team of co-investigators on several projects with specific expertise in genetics, social and environmental epidemiology. Dr. Burchard is the lead PI of the NIH/NHLBI funded **PRIMERO**, the *Puerto Rican Infant Metagenomic and Epidemiologic study of Respiratory Outcomes* birth cohort study (U01HL138626), which is designed to study early-life respiratory viral infections.

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

Dr. Burchard's team is taking a comprehensive approach to studying asthma and related phenotypes in minority children by focusing on genetic, social and environmental risk factors with the goal of creating innovative therapies and identifying targets for public health inventions.

Dr. Burchard's team was the first to leverage genetic ancestry to identify novel genetic and environmental risk factors for disease and drug response. Dr. Burchard's laboratory recently completed the largest genome-wide association studies (GWAS) and admixture-mapping scans of asthma in minority children and total IgE in the United States. Dr. Burchard and his team published the largest air pollution and genome-wide study of asthma in minority children. His research has been seminal in elucidating the pathogenesis of asthma and asthma related traits in minority populations.

Lab Objectives

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

Selected Publications

1. Borrell LN*, Elhawary JR*, Fuentes-Afflick E, Witonsky J, Bhakta N, Wu AB, Bibbins-Domingo K, Rodriguez-Santana JR, Gavin J, Kittles R, Zaitlen NA, Wilkes DS, Powe N, Ziv E, **Burchard EG***. Race and Genetic Ancestry -- A time for reckoning with racism. *N Engl J Med*. 2021 Feb 4;384(5):474-480. PMID: 33406325. * authors contributed equally.
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3. Mak ACY, Sajuthi S, Joo J, Xiao S, Sleiman PM, White MJ, Lee EY, Saef B, Hu D, Gui H, Keys KL, Lurmann F, Jain D, Abecasis G, Kang HM, Nickerson DA, Germer S, Zody MC, Winterkorn L, Reeves C, Huntsman S, Eng C, Salazar S, Oh SS, Gilliland FD, Chen Z, Kumar R, Martínez FD, Wu AC, Ziv E, Hakonarson H, Himes BE, Williams LK, Seibold MA and **Burchard EG**. Lung Function in African American Children with Asthma Is Associated with Novel Regulatory Variants of the KIT Ligand KITLG/SCF and Gene-By-Air-Pollution Interaction. *Genetics*. 2020 Jul; 215(3):869-886. PMID: 32327564.
4. Neophytou AM, Oh SS, Hu D, Huntsman S, Eng C, Rodríguez-Santana JR, Kumar R, Balmes JR, Eisen EA and **Burchard EG**. In utero tobacco smoke exposure, DNA methylation, and asthma in Latino children. *Environ Epidemiol*. 2019 Jun; 3(3):e048. PMID: 31342008.
5. Thakur N, Borrell LN, Ye M, Oh SS, Eng C, Meade K, Avila PC, Farber HJ, Serebrisky D, Brigino-Buenaventura E, Rodriguez-Cintron W, Kumar R, Bibbins-Domingo K, Thyne S, Sen S, Rodriguez-Santana JR and **Burchard EG**. Acculturation is associated with asthma burden and pulmonary function in Latino youth: The GALA II study. *J Allergy Clin Immunol*. 2019 May; 143(5):1914-1922. PMID: 30682453.

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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. Most recently we have publi9shed several pares on mucus plugs in asthma and COPD that can be identified using CT images of the lungs of patients. We are planning additional publications to further described the mucus plug phenotypes that occur in asthma and how their shear features may influence airflow and treatment responses to muco-active drugs.

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 NIH/NHLBI networks in North America including the Severe Asthma Research Program (SARP) and the Precision Interventions for Severe Asthma (Precise) network.

Lab Objectives

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

Selected Publications

1. Dunican EM, Elicker BM, Henry T, Gierada DS, Schiebler ML, Anderson W, Barjaktarevic I, Barr RG, Bleecker ER, Boucher RC, Bowler R, Christenson SA, Comellas A, Cooper CB, Couper D, Criner GJ, Dransfield M, Doerschuk CM, Drummond MB, Hansel NN, Han MK, Hastie AT, Hoffman EA, Krishnan JA, Lazarus SC, Martinez FJ, McCulloch CE, O'Neal WK, Ortega VE, Paine R, Peters S, Schroeder JD, Woodruff PG, **Fahy JV.** Mucus Plugs and Emphysema in the Pathophysiology of Airflow Obstruction and Hypoxemia in Smokers. *Am J Respir Crit Care Med*. 2021 04 15; 203(8):957-968.
2. Kerr SC, Gonzalez JR, Schanin J, Peters MC, Lambrecht BN, Brock EC, Charbit A, Ansel KM, Youngblood BA, **Fahy JV**. An anti-siglec-8 antibody depletes sputum eosinophils from asthmatic subjects and inhibits lung mast cells. *Clin Exp Allergy*. 2020 08; 50(8):904-914.

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

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

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

Lab Objectives:

These studies fall into three specific categories:

1. The identification of distinct molecular sub-phenotypes of asthma, chronic obstructive pulmonary disease (COPD), and granulomatous lung diseases (e.g. sarcoidosis and hypersensitivity pneumonitis),
2. The elucidation of disease-relevant mechanisms of airway inflammation and remodeling in the lung in these diseases and
3. Clinical trials of novel therapeutic approaches.

Selected Publications

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

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The Bhattacharya laboratory studies lung macrophage function under acute inflammatory conditions. The current research employs mouse and human cellular models to determine how monocyte-derived macrophages activate adjacent fibroblasts. Recent work has focused on IL10 signaling in pro-fibrotic polarization of macrophages. A second focus is cellular senescence: specifically, its role in human lung aging and how it is regulated by immune lineages during lung injury and infection.

Selected Publications

1. Bhattacharyya A, Boostanpour K, Bouzidi M, Magee L, Chen TY, Wolters R, Torre P, Pillai SK, **Bhattacharya M**. (2022). IL10 trains macrophage profibrotic function after lung injury. *Am J Physiol Lung Cell Mol Physiol*. 322(3):L495-L502. PMID: 35107021.
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Erin Gordon is an Associate Professor in the Division of Pulmonary and Critical Care Medicine in the Department of Medicine. She completed both her B.S. in Biochemisty at the University of California, Berkeley and M.D. at the University of Southern California. After completing her internship and residency in Internal Medicine at the University of California, San Diego, 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. John Fahy in the Airway Clinical Research Center and Cardiovascular Research Institute at the University of California, San Francisco.

The Gordon laboratory is a translational research lab focused on understanding how genetics influence disease heterogeneity in asthma. Our laboratory is 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

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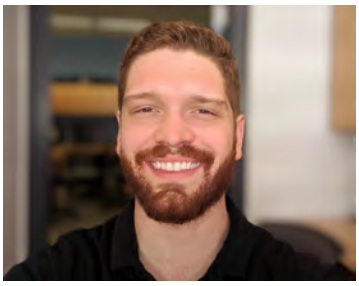

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Andrew Schroeder is a Bioinformatics Scientist in the UCSF Genomics CoLab & Dept. of Pulmonology where he builds computational pipelines for next-generation sequencing analysis (e.g. RNA-seq and scRNA-seq). He is responsible for transcript quality,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

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

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

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

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

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

Selected Publications

1. Liu S, Ngo U, Tang XZ, Ren X, Qiu W, Huang X, DeGrado W, Allen CD, Jo H, Sheppard D, **Sundaram AB**. Integrin α2β1 regulates collagen I tethering to modulate hyperresponsiveness in reactive airway disease models. *J Clin Invest*. 2021 Jun 15;131(12):e138140. PMID: 33956668.
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8. Bhattacharya M, **Sundaram A**, 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 Nov; 124(11):4895-8. PMID: 25271629.
9. 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 May; 123(5):2037-48. PMID: 23543053.
10. 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. The avß6 integrin modulates airway hyperresponsiveness in mice by regulating intraepithelial mast cells. *J Clin Invest*. 2012 Feb; 122(2):748-58. PMID: 22232213.

CORE REPORTS

Microscopy Core

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

Objective/Mandate

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

COVID-19 restrictions and staff turnover resulted in some delays in project timelines, but 2021 still held many scientific successes.

Strategic Goals

The efforts of this center are being directed toward improving imaging technologies for the normal and allergic lung. In 2022, 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 expand the capabilities of the recently completed homebuilt ZipSeq spatialtransciptomics microscope to include protocols for more tissue types, including lung.
4. To develop 6-color IF multiplex panel for the Leica Sp8 confocal microscope equipped with a white light laser and AOBS tunable emission filters.
5. To develop spatial analysis algorithm for the assessment of tumor microenvironment in patient samples stained with 8-plex immunohistochemistry panel.
6. To release a low-level data analysis pipeline and continuously add and develop high-level analysis routines for Multiplexed Ion Beam Imaging (MIBI) microscope.
7. To continue to develop in collaboration with Ophir Klein (UCSF) and Jeremy Green (King's College, London) an automated epithelial cell identification and morphological characterization pipeline for cells undergoing the invagination process during organ development.

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

Organization

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

Current Usage

In 2021, there were 198 unique users of the BIDC. Many users are trained on multiple instruments. These users represent 84 principal investigators or labs. These labs are drawn from departments or organizational units primarily located at Parnassus Heights campus, but span multiple campuses of UCSF.

The BIDC performed 172 new user trainings in 2021. All users received comprehensive training on CoLab instruments or image processing stations. Training is done on an individual basis and reflects the differences in each user's experience, aptitude, and project needs. After initial training, BIDC staff continues to consult and assist with projects on an individual basis. The BIDC does not charge assisted time through recharges, and thus encourages users to ask questions and request assistance as needed. Many projects evolve into collaborations. Within the past year we have specifically worked with users from the following labs.

Alliston, Tamara	Kattah, Michael	Roose, Jeroen
Anderson, Mark	Klein, Ophir	Rosenblum, Michael
Atabai, Kamran	Koliwad, Suneil	Rowitch, David
BARBER, DIANE	Krummel, Matthew	Sarwal, Minnie
Baskin, Laurence	Ku, Gregory	Scharschmidt, Tiffany
Bhattacharya, Mallar	Kutys, Matthew	Schneider, Rich
Bhushan, Anil	L'Etoile, Noelle	Schrepfer, Sonja
Chang, Tammy	Locksley, Richard	Shin, Jeoung-Sook
Chapman, Claude	Looney, Mark	Smith, Alex J
Chapman, Hal	Ma, Averil	Sneddon, Julie
Combes, Alexis	Maltepe, Emin	Tang, Qizhi

Cyster, Jason	Marcucio, Ralph	Tlsty, Thea
DenBesten, Pamela	Marson, Alexander	Tugizov, Sharof
Dubal, Dena	McManus, Michael	Tward, Aaron
Dumont, Sophie	Molofsky, Ari	Vaisse, Christian
Erle, David	Nijagal, Amar	Valdearcos Contreras, Martin
Fahy, John	NSFCCC Marshall Lab	Vasquez, Joshua
Fattahi, Seyedeh Faranak	Nystul, Todd	Vexler, Zena
Gardner, James (UCSF) Lab	Okada, Hideho	Waterfield, Michael
Gartner, Zev	Paredes, Mercedes	Weaver, Valerie
Goga, Andrei	Parent, Audrey	Weiner, Orion
Goodwin, Alice	Pati, Shibani	Weiss, Arthur
Gordon, Erin	Peng, Tien	Wittmann, Torsten
Hebrok, Matthias	Perera, Rushika	Wolters, Paul
Hervey-Jumper, Shawn	Pollen, Alex	Xu, Allison
Ho, Sunita	Rajkovic, Aleksandar	Ye, Chun
Hsiao, Ed	Reeves, Melissa	Yu, Michelle
Huang, Eric	Reiter, Jeremy	Zhang, Yan

Recent Accomplishments

In 2021, scientifically:

1. John Eichorst, PhD (BIDC, Bioinformatics Programmer) increased the functionality, usability, and accessibility of the ZipSeq spatialtranscriptomics microscope (previously built and developed in collaboration with the Krummel lab) to the point that it is now open to the microscopy community.
2. Mohammad Naser, PhD (BIDC, Microscopy Specialist) in collaboration with the Histology and Biomarker Core as well as the Immunoprofiler Initiative (IPI) has developed an 8-plex biomarker panel to detect immune cell populations in tumor samples.
3. Austin Edwards (BIDC, Bioinformatics Programmer) in collaboration with IPI built an analysis pipeline to segment 8-plex images of human tumor, identify cell type, and find spatial correlations between cell types. He also built a graphical user interface (GUI) to view, annotate, and threshold images for this project.
4. Austin Edwards in collaboration with Stefani Spranger's lab at MIT created an image analysis pipeline using Imaris and custom scripts to interrogate the influence of CD8 T-cell clusters on the spatial relationship between Dendritic Cells and Regulatory T-cells in Lung and subcutaneous lymph nodes in mice
5. Austin Edwards in collaboration with Sunita Ho's lab used confocal imaging and image analysis to perform a novel characterization of the distribution of calcium-binding of proteins on human kidney stones.
6. The Scienion sciFLEXARRAYER S3 is now up and running within BIDC space in collaboration with the Genomics Colab. Funded through a UCSF PBBR grant, the instrument is a key component in bringing XYZseq to the CoLabs. The instrument is available to a major user consortium.

7. Kyle Marchuk, PhD (BIDC Director) continued the collaboration with the labs of Ophir Klein (UCSF) and Jeremy Green (King's College, London). The analysis pipeline has been nicknamed Multi-use Application for Reporting General and Region-specific Integral Tissue Attributes with LimeSeg or *Margarita with Lime* and relates individual cell shape analysis with tissue morphologies.
8. John Eichorst, PhD in collaboration with Stephanie Gaw's lab and Joshua Robinson's lab adapted an imaging methodology and data analysis pipeline to identify carbon particles in human tissues. Originally aimed at identifying these particles in placental tissue, the method also works for lung tissue.
9. We continue 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 Tory Harwin left UCSF to start her pursuit of a medical degree, and John Eichorst, PhD left UCSF to move back to the Midwest to be closer to his aging parents. Microscopy Specialist Mohammad Naser, PhD has joined the BIDC from BIOS/Histology Core at Mt. Zion campus. He is an expert in high-dimensional multi-plex panel design and is primarily working in collaboration with the Flow CoLab on MIBI panels as well as working on 8-plex immunohistochemistry panels. Additionally, the BIDC is looking to hire and has two open job postings.

In collaboration with Torsten Wittmann, the BIDC has added a new Nikon spinning disk microscope to its catalog through NIH S10 and UCSF RAP funding mechanisms. The microscope includes the CSU-W1 unit with larger field-of-view and ~2x super-resolution option, an environmental chamber for temperature and CO_2 control, dual-camera Hamamatsu ORCA-FusionBT setup for simultaneous dual-wavelength imaging, and the Polygon 1000 DMD for optogenetics experiments.

The homebuilt ZipSeq microscope that was previous developed by John Eichorst, PhD in collaboration with the Krummel lab has been advanced to the point that is now available through the BIDC to the microscope community. Mohammad Naser, PhD has become the primary point person for this instrument.

Additionally, the BIDC is now housing a Scienion sciFLEXARRAYER S3. The instrument is an automated piezo driven, non-contact dispensing system of ultra-low (pico-liter) volumes with micrometer precision. It is a key component in bringing XYZseq to the CoLabs. Currently, access is limited to the major user base and collaborators. Open access will begin when the supply shortage of deposition tips ends.

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 seven other sites throughout campus including behind the animal barrier.

Plans for the Coming Year

1. The homebuilt ZipSeq spatialtranscriptomics microscope is now available through the BIDC. During the initial phases of opening up the microscope, many more features have been requested. The BIDC will continue to implement the upgrades and increase the functionality and usability.
2. The Scienion sciFLEXARRAYER S3 is a key component in bringing XYZseq to the CoLabs. The system is currently installed in BIDC space and is maintained in collaboration with the Genomics CoLab. Over the next year the BIDC and Genomics CoLab will work in collaboration with a major user group to refine protocols to bring XYZseq online.
3. The Leica Sp8 with white light laser (WLL) and tunable acousto-optical beamsplitter (AOBS) emission filters is an ideal microscope to develop 6-color IF multiplex panels. The BIDC plans to develop a "skeleton" of markers that user's can built upon to expand their panels. Mohammad Naser will lead this project.
4. Austin Edwards will continue to advance the automated data analysis pipeline for the Multiplexed Ion Beam Imaging (MIBI) microscope. This includes writing scripts to automatically pull and segment images from the MIBI database as well as implementing previously developed and new analysis techniques for spatial analysis.
5. The 4th generation of the BIDC's homebuilt multi-photon microscope was originally built utilizing still working components of the decommissioned generation 1 and 2 versions of the microscope. This significantly reduced the price of the microscope while allowing for feature advances. Many of those components are now obsolete and no longer manufactured. The BIDC plans to replace those components with modern technology while increase the functionality of the microscope.
6. Kyle Marchuk (BIDC, Director), Ophir Klein (UCSF) and Jeremy Green (King's College, London, UK) will continue working in collaboration on an automated pipeline for the 3D segmentation and morphological evaluation of epithelial cells undergoing tissue invagination during tissue development. The next steps include improving the segmentation process currently performed in the FIJI plugin LimeSeg, as well as registering tissue morphologies to a common orientation.
7. As part of the ImmunoX equipment RFA, money was allocated to improve the functionality and performance of the selective-plane imaging microscope (SPIM). This microscope will gain additional excitation and emission options for increasing the number of simultaneous fluorophores imaged while increasing the acquisition speed per channel. Custom software and acquisition modes will be written in Pycro-Manager.

Training and Integration with Sandler Program

As noted in previous updates, the BIDC's mission is to provide technical imaging expertise, support, and instrumentation to the UCSF asthma community. We continue to train and collaborate with researchers; this close relationship has allowed us to stay in tune with the current specific needs of a large number of users. Our goal is to continually improve and adapt

both existing and emerging technologies to further the study of asthma. We have hosted hands-on analysis workshops that focus on a particular aspect of analysis, such as creating FIJI macros for automation, allowing users to follow along and build their own skills.

Current Equipment

Permanent Equipment:

1. *Gen3 custom built 2-photon: 6 color/2 lasers
2. *Gen4 custom built 2-photon: 6 color/2 lasers
3. * Nikon C1si spectral laser scanning confocal microscope
4. Nikon spinning-disk confocal with TIRF and photo-ablation (Wittman)
5. Nikon spinning-disk confocal with inline super-resolution and optogenetics
6. Nikon A1R Multiphoton and laser scanning confocal microscope
7. Nikon AZ100 MacroConfocal microscope
8. Zeiss TIRF microscope with IRM
9. Zeiss Cell Observer with Apotome (Nystul)
10. Zeiss AxioImager2 with Apotome
11. Zeiss AxioImagerA1 brightfield microscope
12. Leica SP5 laser scanning confocal microscope
13. Leica SP8 laser scanning confocal microscope with white light laser
14. IVIS Spectrum live animal imager (animal colony)
15. Selective-plane imaging microscope (SPIM) custom built: 3 lasers
16. Lattice Light-Sheet Microscope
17. *FormLabs 3D printer
18. Alveole PRIMO Micropatterning System
19. Scienion SCIFLEXARRAYER s3
20. *Precisionary Compresstome VF 310-02 Vibrating Microtome
21. Leica VT1000S Vibratome
22. *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 9.9, 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:

- Bitplane ‘Imaris’ bestowing a ‘developer’ license.

CONTRIBUTIONS TO RELEVANT SCIENTIFIC ACTIVITIES

ImmunoX Seminar Series (2021-2022)

Time: 9:00 a.m.

Location: N-225 or Zoom

Date	Speaker	Institution
9/6/21	*Labor Day*	
9/13/21	Sebastian Lourido	MIT
9/20/21	Kari Nadeau	Stanford (in Switzerland)
9/27/21	Elizabeth Wayne	Carnegie Mellon University
10/4/21	Carolyn Bertozzi	Stanford
10/11/21	Justin Eyquem	UCSF
10/18/21	Benjamin R. tenOever	NYU
10/25/21	Crystal L. Mackall	Stanford
11/1/21	Carrie Lucas	Yale
11/8/21	Gregory F. Sonnenberg	Weill Cornell
11/15/21	Greg M. Delgoffe	University of Pittsburgh
11/22/21	Alexis Combes	UCSF
11/29/21	*Thanksgiving*	
12/6/21	Jason Sello	UCSF
12/13/21	Christine Brown	City of Hope
12/20/21	*Christmas*	
12/27/21	*Christmas*	
1/3/22	*New Years*	
1/10/22	Shruti Naik	NYU
1/17/22	*MLK Day*	
1/24/22	*Midwinter Conference of Immunologists*	
1/31/22	Suzanne Devkota	Cedars Sinai
2/7/22	Noah Palm	Yale
2/14/22	João Pereira	Yale
2/21/22	*Presidents Day*	
2/28/22	Carla Rothlin	Yale
3/7/22	Michael Patnode	UC, Santa Cruz
3/14/22	~~Jun R. Huh~~	~~Harvard~~
3/21/22	Peng Wu	Scripps Research Institute
3/28/22	Ming Li	MSKCC
4/11/22	Bana Jabri	University of Chicago
4/18/22	Anjana Rao	La Jolla Institute for Immunology
4/25/22	Gabriel D. Victora	The Rockefeller University
5/2/22	Raul Torres	University of Colorado
5/9/22	Olga Rojas	University of Toronto
5/16/22	Bryan Bryson	MIT
5/23/22	Alexander Rudensky	MSKCC
5/30/22	*Memorial Day*	

2021-22 Pulmonary Conference Schedule

Clinical Conference 3:10-4pm, Research Conference 4:10-5pm

Date	Research	Research	Moderator	Location
9/6/21	**HOLIDAY - LABOR DAY**			
9/13/21	Claude Le Saux	Monica Tang	Prescott Woodruff	
9/20/21	Hal Chapman	Chris Berger	Claude Le Saux	
9/27/21	Brian Graham	Aparna Sundaram	Prescott Woodruff	
10/4/21	Carolyn Calfee	Vincent Auyeung	Claude Le Saux	
10/11/21	**HOLIDAY - INDIGENOUS PEOPLES DAY**			
10/18/21	John Greenland	Ernesto Casillas	Prescott Woodruff	
10/25/21	Maya Kotas	William Mckleroy	Mehrdad Arjomandi	
11/1/21	**PULMONARY RESEARCH RETREAT**			
11/8/21	Stephanie Christenson	Priya Shete	John Greenland	
11/15/21	pecial Program with Antonio Gomez, The State of		Prescott Woodruff	
11/22/21	Paul Wolters	Jaymin Kathiriya	Claude Le Saux	
11/29/21	Mehrdad Arjomandi	Nancy Allen	Mallar Bhattacharya	
12/6/21	Patrick Phillips	Dean Sheppard	John Greenland	
12/13/21	**DIVISION HOLIDAY PARTY**			
12/20/21	**F1 FELLOW FEEDBACK SESSION #1**			
12/27/21	**HOLIDAY - WINTER BREAK**			
1/3/22	Michael Peters	Jonathan Budzik	Prescott Woodruff	
1/10/22	**F2/F3 FELLOW FEEDBACK SESSION #1**			
1/17/22	**HOLIDAY - MLK JR. DAY**			
1/24/22	**Visiting Professor: Deepika Mohan (virtual)**		Carolyn Calfee/Lucy Kornblith	
1/31/22	Aaron Baugh	Brendan Huang	Mehrdad Arjomandi	
2/7/22	Feroz Papa	Vaibhav Upadhyay	Claude Le Saux	
2/14/22	David Erle	Max Cohen	John Greenland	
2/21/22	**HOLIDAY - PRESIDENT'S DAY**			
2/28/22	**ACGME Survey Session**			
3/7/22	Mark Ansel	Aida Venado	Claude Le Saux	
3/14/22	**Visiting Professor: Kathleen Barnes**		Erin Gordon	
3/21/22	Danny Calabrese	Katherine Wick	Mallar Bhattacharya	
3/28/22	Tatsuya Tsukui	Lucile Neyton	Prescott Woodruff	
4/4/22	John Fahy	Walter Eckalbar	John Greenland	
4/11/22	**Visiting Professor: Pandurangan Vijayanand**		Mark Ansel	
4/18/22	Jon Singer	Mohamed Seedahmed	Mehrdad Arjomandi	
4/25/22	Michael Matthay	Beth Zha	Claude Le Saux	
5/2/22	**Visiting Professor: Christine Garcia**		Mallar Bhattacharya	
5/9/22	**F2/F3 FELLOW FEEDBACK SESSION #2**			
5/16/22	**ATS**			
5/23/22	**F1 FELLOW FEEDBACK SESSION #2**			
5/30/22	**HOLIDAY - MEMORIAL DAY**			
6/6/22	**FACULTY FEEDBACK & APPRECATION**			
6/13/22	**Visiting Professor: Maria Basil**		Tien Peng	
6/20/22	**HOLIDAY - JUNETEENTH**			
6/27/22	**GRADUATION**			

SABRE Asthma Research Conference Schedule 2021-2022

Location: all conferences held on Zoom		
Time: 9:00 - 10:00AM		
Day: 4th Wednesday of each month (**except Wednesdays that fall on a UCSF holiday*)		
Date	Presenter	Title
9/22/21	Roberto Ricardo-Gonzalez (Locksley Lab)	Skin ILC2s restrict Demodex colonization of the hair follicle
10/27/21	Erin Gordon (Gordon Lab)	Allergic tuft cell PGE2 alters epithelial homeostasis in type 2 inflammation
11/24/21	Aritra Bhattacharyya (Bhattacharya Lab)	Role of macrophage derived factors during lung fibrosis
12/22/21	*No conference*	*Winter Break*
1/26/22	Chris Allen & Adam Wade-Vallace (Allen Lab)	Cognate antigen exposure suppresses specific IgE production
2/23/22	Mark Ansel (Ansel Lab)	MicroRNA directed pathway discovery in B cells reveals regulators of IgE class switch recombination
3/23/22	John Fahy (Fahy Lab)	Update on therapeutic protein treatments for asthma
4/27/22	*No conference*	*Cancelled*
5/25/22	Maya Kotas (Locksley Lab)	IL-13-programmed airway tuft cells produce PGE2, which promotes CFTR-dependent mucociliary function
6/22/22	*No conference*	*Summer Break*
7/27/22	Benjamin Wheeler Woodruff Lab	High dimensional profiling of allergen specific responses reveals systemic antigen specific Th2 cells
8/24/22	Sundaram Lab	Cytokine-mediated Activation of β1 Integrin Enhances Force Transmission in Airway Smooth Muscle

UCSF
University of California
San Francisco

BAKAR IMMUNO
Harnessing Immunology To Improve Human Health

IN PERSON SEMINAR
Everyone will have the option to attend in person in N-225 or attend virtually via Zoom.

ImmunoX Seminars are UC/Gladstone-internal only events open only to trainees or employees of those organizations.

Seminar will start at 9:05am sharp.

Monday 2/28

BAKAR IMMUNO

ImmunoX Seminar Series
9:00AM N-225 /Zoom Link

In-Person Speaker

"Principles of resolving and non-resolving inflammation"

Carla Rothlin, PhD
Yale University

Reminder, as a component of REUNITE Week *this event is followed by an* ImmunoX Tea Hour *in Saunder's Court from 10-11AM. Refreshments will be served, though this event is first come, first serve and maxed at 100 attendees.*

RECENT AND NEW PUBLICATIONS SUPPORTED BY THE SANDLER ASTHMA BASIC RESEARCH CENTER (2020-2022)

Christopher D.C. Allen, Ph.D.

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Woodruff PG, Lazarus SC. Long-term Sequelae of Nonobstructive Chronic Bronchitis-Is Airflow Obstruction Important?. *JAMA Intern Med*. 2020 May 1;180(5):686-687. doi: 10.1001/jamainternmed.2019.7280. PMID: 32119027.

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Koh KD, Siddiqui S, Cheng D, Bonser LR, Sun DI, Zlock LT, Finkbeiner WE, **Woodruff PG**, Erle DJ. Efficient RNP-directed Human Gene Targeting Reveals SPDEF Is Required for IL-13-induced Mucostasis. *Am J Respir Cell Mol Biol*. 2020 Mar;62(3):373-381. doi: 10.1165/rcmb.2019-0266OC. PMID: 31596609; PMCID: PMC7055692.

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Paulin LM, Gassett AJ, Alexis NE, Kirwa K, Kanner RE, Peters S, Krishnan JA, Paine R 3rd, Dransfield M, **Woodruff PG**, Cooper CB, Barr RG, Comellas AP, Pirozzi CS, Han M, Hoffman EA, Martinez FJ, Woo H, Peng RD, Fawzy A, Putcha N, Breysse PN, Kaufman JD, Hansel NN. Association of Long-term Ambient Ozone Exposure With Respiratory Morbidity in Smokers. *JAMA Intern Med*. 2020 Jan 1;180(1):106-115. doi: 10.1001/jamainternmed.2019.5498. PMID: 31816012; PMCID: PMC6902160.

Looking to the Future

Richard M. Locksley, M.D.

Despite the pandemic, the SABRE Center continues to contribute productively to our mission to advance basic research discoveries in asthma, including foundational insights into innate lymphoid cell biology, regulation of IgE, roles for microRNAs in critical hubs driving asthma pathway, lung and nasal sinus epithelial cell biology, and to the role of mucus plugs as biomarkers – and potentially in causal roles - for patients at increased risk for asthma morbidity and mortality.

SABRE investigators participated meaningfully in the UCSF COMET consortium to confront the challenge of COVID-19, and participated in over 20 manuscripts, many in high-impact journals, identifying risk factors, mechanisms of pathology, and potential for novel therapeutics, including some developed by SABRE investigators. The NIH PRIMERO study continues to enroll parent-newborns for intense clinical and biomarker analytics from Puerto Rico that will be followed over the next 10 years to identify predictors for asthma development. Finally, SABRE investigators continued in major leadership positions at UCSF in academic and graduate student programs, in advocating for Diversity, Leadership, and Equity voices on campus, and in leadership positions with NIH in national asthma consortia, including the Severe Asthma Research Program (SARP) and the PrecISE Asthma Trials Networks, to guide use of standard biomarkers and outcomes for academic and industry trials. Punctuated by access to emergency grants for COVID-19-related research, grant dollars have remained robust and continue to provide support for students, postdocs, and clinical investigator trainees, but also support for new research-enabling technologies.

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

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

Genentech/Roche involving anti-tryptase drugs for mast cell-dependent asthma, a subgroup in part defined by investigators supported by SABRE. As projects have matured, SABRE investigators are beginning discussions for a second co-project Program Project Grant oriented towards novel scientific discovery as a spin-off from the currently funded NIH Program Project Grant. Assembly of a competitive second large effort will take 2-3 years of preparation, acquisition of preliminary data, and submission and response, but we are confident that the quality of the science and the intensity of investigator interaction will push the success. At the same time, we have consolidated administrative support to a single position to maximize finances available for scientific discovery and investigator support. Here, we emphasize the flexibility and breadth of Sandler Foundation and Jewish Community Federation support of SABRE, which is not possible from NIH or corporate funding, and which enables rapid development and deployment of cutting-edge technology to push innovative science.

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 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 re-directed and slowed some of these efforts, we continue to work hard and resolutely to accomplish our mission. We are 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

Christopher Allen, Ph.D.

K. Mark Ansel, Ph.D.

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

Mallar Bhattacharya, M.D., MSc.

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.

Andrew N. Goldberg, M.D., M.S.

Erin Gordon, M.D.

Maya Kotas, M.D., Ph.D.

Matthew Krummel, Ph.D.

Richard Locksley, M.D

Ari B. Molofsky, M.D., Ph.D.

Dean Sheppard, M.D.

Aparna Sundaram, M.D.

Zhi-En Wang, M.D., M.S.

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

Prescott Woodruff, M.D., M.P.H.

BIOGRAPHICAL SKETCH

NAME: Allen, Christopher David Caballero

eRA COMMONS USER NAME (credential, e.g., agency login): chrisa

POSITION TITLE: Associate Professor of Anatomy and Investigator, Cardiovascular Research Institute and Sandler Asthma Basic Research Center

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Massachusetts Institute of Technology, Cambridge, MA	BS	06/2001	Biology
University of California, San Francisco, CA	PHD	06/2007	Biomedical Sciences
University of California, San Francisco, CA	Postdoctoral	10/2007	Immunology

Ongoing and recently completed projects:

R21 AI154335
Allen (PI)
01/21/21–12/31/22
Molecular basis for the regulation of IgE class switch recombination by IL-21 and STAT3

R01 AI130470
Allen (PI)
11/20/17–10/31/22
Regulation of IgE responses by B cell receptor signaling

R21 AI130495
Allen (PI)
06/07/17–05/31/19
Function of bronchus-associated macrophages

The Pew Charitable Trusts Biomedical Scholar Award
Allen (PI)
08/01/16–07/31/21
Unraveling the mysteries of allergen-specific IgE production

Highlighted Citations:

1. Tang XZ, Kreuk LSM, Cho C, Metzger RJ, **Allen CDC**. Bronchus-associated macrophages are positioned for soluble antigen capture from the airway lumen and for local Th2 cell activation. BioRxiv 247742 [Preprint]. 2020 Sep 19. Available from: https://doi.org/10.1101/2020.09.18.247742

2. Yang Z, Wu CM, Targ S, **Allen CDC**. IL-21 is a broad negative regulator of IgE class switch recombination in mouse and human B cells. J Exp Med., 2020 Mar 4;217(5):e20190472. PMCID: PMC7201927.
3. 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:e21238. PMCID: PMC5207771.
4. 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. PMID: 22406270.

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2020–Present	Assistant Director for Diversity, Equity, and Inclusion for the Cardiovascular Research Institute, University of California, San Francisco, CA
2020–Present	Scientific Advisory Board Member, Walking Fish Therapeutics
2018–Present	Associate Professor of Anatomy and Investigator, Cardiovascular Research Institute and Sandler Asthma Basic Research Center, University of California, San Francisco, CA
2013–Present	Regular Member, American Association of Immunologists (AAI)
2012–2018	Assistant Professor of Anatomy and Investigator, Cardiovascular Research Institute and Sandler Asthma Basic Research Center, University of California, San Francisco, CA
2007–2012	Sandler-Newman Foundation UCSF Fellow in Asthma Research, Sandler Asthma Basic Research Center and the Department of Microbiology and Immunology, University of California, San Francisco, CA
2007–2007	Postdoctoral Scholar, Laboratory of Jason Cyster, Department of Microbiology and Immunology, University of California, San Francisco, CA (brief appointment following PhD)
2002–2007	Graduate Student Researcher, Laboratory of Jason Cyster, Biomedical Sciences Graduate Program and Immunology Graduate Program, University of California, San Francisco, CA
2000–2000	Undergraduate Student Researcher, Laboratory of Herman Eisen, Center for Cancer Research, Massachusetts Institute of Technology, Cambridge, MA
1998–2000	Summer Research Intern, Department of Molecular and Cellular Pharmacology, Isis Pharmaceuticals, Carlsbad, CA

Selected Honors

2016	Pew Biomedical Scholar, The Pew Charitable Trusts
2013	Research Award, Weston Havens Foundation
2012	NIH Director's New Innovator Award, National Institutes of Health
2010	Top Cited Article 2008-2010, Seminars in Immunology
2002	Predoctoral Fellowship, Howard Hughes Medical Institute
2001	Regents Fellowship, University of California
2001	Phi Beta Kappa, Massachusetts Institute of Technology
2001	Whitehead Prize in Biomedical Research, Whitehead Institute and Massachusetts Institute of Technology
1999, 2000	Academic Excellence Award, Office of Minority Education, Massachusetts Institute of Technology
1997	National Hispanic Scholar, College Board
1994	NSF Young Scholars Program Fellowship, National Science Foundation

Contributions to Science

1. As a graduate student in the laboratory of Jason Cyster, a major emphasis of my dissertation project was to study the guidance factors responsible for organizing the germinal center. This structure forms

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

a. **Allen CDC**, Ansel KM, Low C, Lesley R, Tamamura H, Fujii N, Cyster JG. Germinal center dark and light zone organization is mediated by CXCR4 and CXCR5. Nat Immunol. 2004 Sep;5(9):943-52. PubMed PMID: 15300245.

b. Haynes NM, **Allen CDC**, Lesley R, Ansel KM, Killeen N, Cyster JG. Role of CXCR5 and CCR7 in follicular Th cell positioning and appearance of a programmed cell death gene-1high germinal center-associated subpopulation. J Immunol. 2007 Oct 15;179(8):5099-108. PubMed PMID: 17911595.

c. Green JA, Suzuki K, Cho B, Willison LD, Palmer D, **Allen CDC**, Schmidt TH, Xu Y, Proia RL, Coughlin SR, Cyster JG. The sphingosine 1-phosphate receptor $S1P_2$ maintains the homeostasis of germinal center B cells and promotes niche confinement. Nat Immunol. 2011 Jun 5;12(7):672-80. PubMed PMID: 21642988; PubMed Central PMCID: PMC3158008.

d. Bannard O, Horton RM, **Allen CDC**, An J, Nagasawa T, Cyster JG. Germinal center centroblasts transition to a centrocyte phenotype according to a timed program and depend on the dark zone for effective selection. Immunity. 2013 Nov 14;39(5):912-24. PubMed PMID: 24184055; PubMed Central PMCID: PMC3828484.

2. 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. *corresponding authors

   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.

3. 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 has recently 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. *corresponding authors

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 Apr;143(4):1643-1646.e6 PubMed PMID: 30639345*;* PubMed Central PMCID: PMC6746400.

4. 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, 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:e21238 PubMed PMID: 27935477; PubMed Central PMCID: PMC5207771.

   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;198(5):1815-1822. PubMed PMID: 28115531. PMCID: PMC5886363

   d. Yang Z, Wu CM, Targ S, **Allen CDC**. IL-21 is a broad negative regulator of IgE class switch recombination in mouse and human B cells. J Exp Med., 2020 Mar 4;217(5):e20190472 PubMed PMID: 32130409. PubMed Central PMCID: PMC7201927.

5. 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 My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/christopher.allen.1/bibliography/public/

BIOGRAPHICAL SKETCH

NAME: Ansel, K. Mark

eRA COMMONS USER NAME (credential, e.g., agency login): anselm

POSITION TITLE: Professor of Microbiology & Immunology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
Virginia Tech, Blacksburg, VA	BS	09/1992	05/1996	Biochemistry
University of California San Francisco, San Francisco, CA	PhD	08/1996	09/2001	Biomedical Sciences
Immune Disease Institute, Harvard Medical School	Postdoctoral	10/2001	12/2007	Immunology

Ongoing and recently completed projects:

P01 HL107202
Fahy (PI); Role: Project 2 Leader, Project 3 co-investigator
04/01/19-07/31/24
Exploring the biology of persistent type 2 airway niches in asthma

R01 HL109102
Ansel (PI)
08/01/11-03/30/24
MicroRNA directed pathway discovery in allergy and asthma

U19 AI077439
Erle (PI); Role: Co-project Leader, rapid supplement award
05/08/20-03/31/22
UCSF COVID-19: Extended Immunophenotyping Studies
patients.

FastGrants2020
Ansel, Spitzer (Co-PIs)
05/01/20-04/30/21 (NCE)
High Dimensional Analysis of the Inflammatory Cytokine Storm in COVID-19

Positions, Scientific Appointments, and Honors

Positions and Employment

2018 - Professor, Department of Microbiology & Immunology, UCSF
2008 - Investigator, Sandler Asthma Basic Research Program
2014 - 2021 Director, Biomedical Sciences Graduate Program, UCSF
2013 - 2018 Associate Professor, Department of Microbiology & Immunology, UCSF
2013 - 2014 Associate Director, Biomedical Sciences Graduate Program, UCSF

2008 - 2013	Assistant Professor, Department of Microbiology & Immunology, UCSF
2005 - 2007	Instructor, Department of Pediatrics, Children's Hospital and Immune Disease Institute, Harvard Medical School, Boston, MA
2001 - 2005	Postdoctoral Fellow, Immune Disease Institute (p.k.a. Center for Blood Research), Harvard Medical School, Boston, MA

Other Experience and Professional Memberships

2021	Guest Editor, RNA Regulation of Immunity issue, Immunological Reviews
2017 - 2019	Section Editor, Journal of Immunology
2016 - 2020	Standing member, NIH CMIB study section
2014 - 2017	Member, Faculty of 1000 Section on Leukocyte Signaling and Gene Expression
2014	Current Opinions in Immunology, Allergy & Hypersensitivity section, Guest Editor
2013	Guest Editor, RNA Regulation of the Immune System issue, Immunological Reviews
2013 - 2017	Associate Editor, Journal of Immunology
2012 - 2015	Associate Editor in Chief, American Journal of Clinical & Experimental Immunology
2012 - 2014	Ad hoc reviewer, NIH CMIB study section
2011 - 2012	International Predoctoral Fellows Reviewer, Howard Hughes Medical Institute
2011 -	Reviewing Editor, Science Signaling
2007 -	Member, International Cytokine Society
2006 -	Member, American Association of Immunologists
1998 -	Member, American Association for the Advancement of Science

Selected Honors

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

Contributions 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.
    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. PMCID: PMC3570096
    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;25:3356-3370.e4. PMCID: PMC6392044

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. PMCID: PMC6365014

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 behavior, and we combined biochemical, transcriptomic, and bioinformatic approaches to rigorously map their target networks. We leverage our ability to assign biological functions to miRNAs and to identify their direct target mRNAs as a means of miRNA-directed pathway discovery. For example, we found that miR-24 and miR-27 potently inhibit Th2 responses, and identified a network of novel functionally relevant target mRNAs, including well-known regulators of Th2 cell differentiation and others that represent novel players in Th2 biology. Recently, we adapted our experimental systems to conduct miRNA-directed pathway discovery in B cells as well, and discovered novel regulators of immunoglobulin class switch recombination to the allergic antibody isotype, IgE.
    a. Wigton EJ, Mikami Y, McMonigle RJ, Castellanos CA, Wade-Vallance AK, et al. MicroRNA-directed pathway discovery elucidates an miR-221/222-mediated regulatory circuit in class switch recombination. J Exp Med. 2021 Nov 1;218(11):e20201422. PMID: 34586363
    b. 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;28:2169-2181.e4. PMID: 31433990; PMCID: PMC6715152
    c. 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
    d. 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

3. We have also used miRNA expression profiling in airway-infiltrating lymphocytes and bronchial epithelial cells as a complementary strategy to prioritize miRNAs of potential functional relevance in asthma pathology. We developed and optimized small RNA deep sequencing and high-throughput microfluidic qPCR miRNA detection platforms for clinical samples of less than 1000 cells. In FACS-sorted helper T cells from bronchial lavage, miR-19a stood out as 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). We also generated the first miRNA expression profiles for type 2 innate lymphocytes, and showed that miR-19 also regulates ILC2 homeostasis and cytokine production through an overlapping but non-identical set of target mRNAs. In collaboration with SABRe investigator Prescott Woodruff, we found that miR-141, a member of the highly expressed miR-141/200 family, regulates human epithelial cell mucus cell production. An inhaled miR-141 inhibitor reduced mucus metaplasia and airway hyper-responsiveness in a mouse model of asthma.
    a. Johansson K, Woodruff PG, Ansel KM. Regulation of airway immunity by epithelial miRNAs. Immunol Rev. 2021 Nov;304(1):141-153. PMID: 34549450
    b. Siddiqui S, Johansson K, Joo A, Bonser LR, Koh KD, et al. Epithelial miR-141 regulates IL-13-induced airway mucus production. JCI Insight. 2021 Mar 8;6(5):e139019. doi: 10.1172/jci.insight.139019. PMID: 33682796
    c. 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

d. 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

4. 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 Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/pubmed/?term=Ansel+KM

BIOGRAPHICAL SKETCH

NAME: Bhakta, Nirav Rati

eRA COMMONS USER NAME (credential, e.g., agency login): BHANIR

POSITION TITLE: Associate Professor of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	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	06/2011	Asthma

Ongoing and recently completed projects:

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

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

Highlighted Citations:

1. Siddiqui S, Johansson K, Joo A, Bonser LR, Koh KD, Le Tonqueze O, Bolourchi S, Bautista RA, Zlock L, Roth TL, Marson A, **Bhakta NR**, Ansel KM, Finkbeiner WE, Erle DJ, Woodruff PG. Epithelial miR-141 regulates IL-13-induced airway mucus production. JCI Insight. 2021 Mar 8;6(5). doi: 10.1172/jci.insight.139019. PMC8021117.
2. Bunis DG, Bronevetsky Y, Krow-Lucal E, **Bhakta NR**, Kim CC, Nerella S, Jones N, Mendoza VF, Bryson YJ, Gern JE, Rutishauser RL, Ye CJ, Sirota M, McCune JM, Burt TD. Single-Cell Mapping of Progressive Fetal-to-Adult Transition in Human Naive T Cells. Cell Rep. 2021 Jan 5;34(1):108573.
3. Narla V, **Bhakta N**, Freedman JE, Tanriverdi K, Maka K, Deeks SG, Ganz P, Hsue P. Unique Circulating MicroRNA Profiles in HIV Infection. J Acquir Immune Defic Syndr. 2018 Dec 15;79(5):644-650.

Positions, Scientific Appointments, and Honors

Positions and Employment

2011 - 2013	Instructor, Department of Medicine, Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, University of California, San Francisco.
2013 – 2018	Assistant Professor, Department of Medicine, Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, University of California, San Francisco.
2016 – Present	Director of Education, Adult Pulmonary Function Laboratory
2017 – Present	Pulmonary Fellowship Site Director and Coach, UCSF Parnassus Campus
2020 – Present	Associate Director, Adult Pulmonary Function Laboratory

Other Experience and Professional Memberships

2007 – Present	American College of Physicians, Associate Member
2008 – Present	American Thoracic Society
2008 – Present	California Medical License
2009	Board Certification in Internal Medicine by the ABIM
2011	Board Certification in Pulmonary Medicine by the ABIM
2011 – 2014	American College of Chest Physicians, Affiliate Member
2011 – Present	Review ~3 articles a year for American Thoracic Society Journals, Clinical and Experimental Allergy, and other journals.
2012	Board Certification in Critical Care Medicine by the ABIM
2016 – 2017	Associate Scientific Advisor for *Science Translational Medicine*. Over a period of one year, I wrote eight editorial pieces that appeared in the journal.
2018-2018	Grant Reviewer, Asthma UK
2019-present	Member of the Proficiency Standards for Pulmonary Function Laboratories Committee, American Thoracic Society
2020-present	Co-Chair of joint ATS/ERS Task Force to update the Lung Volumes Measurement Technical Standard, American Thoracic Society
2021-present	Co-Chair of ATS Workshop on the use of Race/Ethnicity in Pulmonary Function Interpretation

Selected Honors

2001	Dept. of Health and Human Services national semi-finalist, Innovation in Health Promotion, South Asian Preventive Health Outreach Program.
2005	Invited speaker, Howard Hughes Medical Institute Workshop on Imaging the Immune System. Chevy Chase, MD.
2005	Keystone Symposia Scholarship (Leukocyte Trafficking meeting).
2010	Travel award, Pittsburgh International Lung Conference
2011 - 2012	Podell Hewett Fellowship in Translational Airway Research
2012	Ruth L. Kirschstein National Service Award (F32)
2014	Invited lecture on the role of exosomes in asthma, American Academy of Allergy, Asthma, and Immunology annual meeting
2015 & 2017	Invited seminar in genomics post-graduate course, American Thoracic Society International Conference
2016	Recipient of Nina Ireland Program for Lung Health Award
2016	Visiting professor to SFGH pulmonary function laboratory November 2 2016
2017	Invited Grand Rounds speaker, Department of Pathology, University of Vermont

Contributions to Science

1. 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. For the second reference I analyzed RNA Seq data. 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.

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, Christian LS, Nariya S, Gonzalez J, **Bhakta NR**, Ansel KM, Beigelman A, Castro M, Dyer AM, Israel E, Kraft M, Martin RJ, Mauger DT, Peters SP, Rosenberg SR, Sorkness CA, Wechsler ME, Wenzel SE, White SR, Lynch SV, Boushey HA, Huang YJ. Distinct associations of sputum and oral microbiota with atopic, immunologic, and clinical features in mild asthma. *J Allergy Clin Immunol*. 2020 Nov;146(5):1016-1026. PMC7406302.

2. 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* 2012. 186(10):965-74. PMC3530212.
   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. PMC4233009.

3. 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.

4. Traditional metrics extracted from pulmonary function test data are limited in their ability to detect lung pathology. Therefore, I have applied my skills in human subjects research, pulmonary physiology,

pulmonary medicine, and programming to develop and test novel metrics. Through an ongoing study I have led at UCSF and that is ready for submission (in lung transplantation), I started collaborations outside of UCSF to apply these techniques to COPD. This work has resulted in multiple publications that form an evidence base to support the incorporation of these metrics into clinical algorithms.

a. Bodduluri S, Nakhmani A, Reinhardt JM, Wilson CG, McDonald ML, Rudraraju R, Jaeger BC, **Bhakta NR**, Castaldi PJ, Sciurba FC, Zhang C, Bangalore PV, Bhatt SP. Deep neural network analyses of spirometry for structural phenotyping of chronic obstructive pulmonary disease. JCI Insight. 2020 Jul 9;5(13):e132781. PMID: 32554922; PMCID: PMC7406302.
b. Vempilly JJ, Abejie BA, Rashidian A, Jain VV, **Bhakta NR.** Air Trapping Correlates With Increased Frequency of Albuterol Use and Severity of Wheeze in Persistent Asthma. Respir Care. 2020 Jul;65(7):994-1000. Epub 2020 Feb 4. PMID: 32019852.
c. Bhatt SP, Bodduluri S, Raghav V, **Bhakta NR**, Wilson CG, Kim YI, Eberlein M, Sciurba FC, Han MK, Dransfield MT, Nakhmani A. The Peak Index: Spirometry Metric for Airflow Obstruction Severity and Heterogeneity. Ann Am Thorac Soc. 2019 Aug;16(8):982-989. PMID: 30865842; PMCID: PMC6774744.
d. Bhatt SP, **Bhakta NR**, Wilson CG, Cooper CB, Barjaktarevic I, Bodduluri S, Kim YI, Eberlein M, Woodruff PG, Sciurba FC, Castaldi PJ, Han MK, Dransfield MT, Nakhmani A. New Spirometry Indices for Detecting Mild Airflow Obstruction. Sci Rep. 2018 Nov 30;8(1):17484. PMID: 30504791; PMCID: PMC6269456.

5. 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.
   a. **Bhakta NR**, Oh DY, Lewis RS. Intracellular calcium oscillations control thymocyte motility during positive selection in the three-dimensional thymic environment. *Nature Immunol*. 6: 143-151. 2005.
   b. 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:
https://www.ncbi.nlm.nih.gov/myncbi/nirav.bhakta.1/bibliography/public/

BIOGRAPHICAL SKETCH

NAME: Bhattacharya, Mallar

eRA COMMONS USER NAME (credential, e.g., agency login): BMALLAR

POSITION TITLE: Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Harvard University, Cambridge, MA	A.B.	06/1998	Biology and Psychology
Oxford University, Oxford, UK	M.Sc.	10/1999	Neuroscience
Harvard University, Boston, MA	M.D.	06/2004	Medicine
Johns Hopkins Hospital, Baltimore, MD	Residency	06/2007	Internal Medicine
University of California, San Francisco, CA	Fellowship	06/2010	Pulmonary and Critical Care

Ongoing and recently completed projects:

DOD PR200067
Bhattacharya (PI)
07/01/21-06/30/25
Targeting ATP receptor P2rx4 for pulmonary fibrosis.

R01 HL131560-04
Bhattacharya (PI)
05/01/16-04/30/21
The Regulation of RhoA Activation in Airway Smooth Muscle

Positions, Scientific Appointments, and Honors

Positions and Scientiic Appointments

1998-1999: Honorary Frank Knox Memorial Fellowship (awarded by Harvard University), Oxford, UK
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- Member, American Thoracic Society
2007-2017 Certified, Internal Medicine, American Board of Internal Medicine
2007-2010: Fellowship, Pulmonary/Critical Care Medicine, UCSF
2009- Certified, Pulmonary Medicine, American Board of Internal Medicine
2010- Certified, Critical Care Medicine, American Board of Internal Medicine
2010-2012: Instructor, Department of Medicine, Division of Pulmonary and Critical Care Medicine, UCSF
2012-2019: Assistant Professor, Department of Medicine, Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, UCSF
2019- Associate Professor, Department of Medicine, Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, UCSF

2021- Investigator, UCSF Bakar Aging Research Institute

Honors

1996 Harvard College Scholarship
1995, 97, 98 John Harvard Scholarship
1994-1998 Dean's List, Harvard College
1994-1998 New York State Robert C. Byrd Honors Scholarship
1997 Member, Phi Beta Kappa Society, Harvard College Chapter
2000 Pasteur Summer Research Fellowship for Medical Students
2000 American Neurological Association Summer Fellowship
2008-2009 Will Rogers Institute Fellowship

Contributions to Science

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

2. RhoA activation in lung inflammation: Following up on the results of a proteomic screen completed during my fellowship, in my early faculty years I pursued the novel integrin binding partner and cytoskeletal organizing protein Iqgap1. I found that Iqgap1 suppressed activation of the GTPase RhoA, whose role in airway contraction led us to test Iqgap1-/- mice in airway inflammation models. These studies revealed that Iqgap1 inhibits airway smooth muscle RhoA by serving as a scaffold for the negative regulator p190A-RhoGAP. A qPCR screen of RhoGEFs using a riboprofiling approach led to the discovery that Arhgef12 was highly expressed in mouse and human airway smooth muscle. We then found that Arhgef12 was necessary for IL17A-induced RhoA activation and allergic airway hyperresponsiveness in mice. Arhgef12 thus represents a novel therapeutic target in asthma.
   a. **Bhattacharya M**, Sundaram A, Kudo M, Farmer J, Ganesan P, Khalifeh-Soltani A, Arjomandi M, Atabai K, Huang X, Sheppard D. (2014) IQGAP1-dependent scaffold suppresses RhoA and inhibits airway smooth muscle contraction. *The Journal of Clinical Investigation* 124(11): 4895-8. PMID: 25271629. PMCID: PMC4347230.
   b. Fong V, Hsu A, Wu E, Looney AP, Ganesan P, Ren X, Sheppard D, Wicher SA, Thompson MA, Britt Jr. RD, Prakash YS, **Bhattacharya M**. (2018) Arhgef12 drives IL17A-induced airway contractility and airway hyperresponsiveness in mice. *JCI Insight*. Nov 2;3(21) PMID: 30385725. PMCID: PMC6238747.

3. Macrophages in lung injury and fibrosis: A major focus of my group now is on the role of macrophages in lung injury and fibrosis. In recent work, I used single cell mRNA sequencing to profile macrophages that localize to sites of fibroblast accumulation after bleomycin-induced lung injury. As part of this project, working with computational collaborators, I developed a tool (SingleR) that annotates cellular identity in single cell RNA-seq by reference to bulk RNA-seq datasets of pure cell types. Now publicly available, this tool is widely used for cell type annotation; in our study, it enabled clustering of cells revealing a transitional state of monocyte-derived macrophages acquiring lung-resident identity within the fibrotic niche. Our cell ablation experiments targeting these Cx3cr1-expressing monocyte-derived macrophages revealed a pro-fibrotic and activating effect of this subset of macrophages on adjacent fibroblasts. Recent work has defined an IL10-dependent pro-fibrotic polarization of lung macrophages in fibrosis.
    a. Looney, AP and **Bhattacharya, M**. (2019). Fibroblast Gap-closure Assay: Microscopy-based *in vitro* Assay Measuring the Migration of Murine Fibroblasts. *Bio-protocol* 9(16): e3333. DOI: doi.org/10.21769/BioProtoc.3333. PMID: 31531389. PMCID: PMC6748635.
    b. Aran D, Looney AP, Liu L, Wu E, Fong V, Hsu A, Chak S, Naikawadi RP, Wolters PJ, Abate A, Butte AJ, **Bhattacharya M**. (2019) Reference-based analysis of lung single cell RNA-seq reveals a transitional profibrotic macrophage. *Nature Immunology*. 20(2):163-172. PMID: 30643263. PMCID: PMC6340744.
    c. Alam Z, Devalaraja S, Li M, To TKJ, Folkert IW, Mitchell-Velasquez E, Dang MT, Young P, Wilbur CJ, Silverman MA, Li X, Chen YH, Hernandez PT, Bhattacharyya A, **Bhattacharya M**, Levine MH, Haldar M. (2020) Counter Regulation of Spic by NF-kB and STAT Signaling Controls Inflammation and Iron Metabolism in Macrophages. *Cell Reports.* Jun;31(13):107825. PMID: 32610126. PMCID: N/A.
    d. Bhattacharyya A, Boostanpour K, Bouzidi M, Magee L, Chen T, Wolters R, Torre P, Pillai SK, Bhattacharya M. (2022) IL10 trains macrophage pro-fibrotic function after lung injury. *American Journal of Physiology: Lung Cell and Molecular Physiology*. In press.

4. Cellular senescence: Recent work in my lab has addressed cellular senescence in the lung. In collaboration with the Anil Bhushan Lab at UCSF, we have found that invariant NK T cells coordinate clearance of senescent cells after acute lung injury, with resulting improvement in fibrosis and in mortality. My lab performed the murine fibrosis and survival studies for this work, which is currently in review for publication. A second project, cited below, has taken advantage of the UCSF Nina Ireland Biorepository of healthy human donor lungs not used for transplant. In this work, we profiled 86 human lungs across the adult lifespan by RNA-seq and other methods. Our analysis revealed an increasing senescence profile, decreasing telomere length, and an increase in pro-fibrotic pathways in the aging lung.
    a. Arora S, Thompson PJ, Wang Y, Bhattacharyya A, Apostolopoulou H, Hatano R, Naikawadi R, Shah A, Wolters PJ, Koliwad S, **Bhattacharya M**, Bhushan A. Invariant Natural Killer T cells coordinate removal of senescent cells. (2021) Invariant natural killer T cells coordinate removal of senescent cells. *Med (NY)* Aug 13;2(8):938-950. PMID: 34617070. PMCID: PMC8491998.
    b. Lee J, Islam MI, Boostanpour K, Aran D, Christenson S, Matthay MA, Eckalbar W, DePianto DJ, Arron JR, Magee L, Bhattacharya S, Matsumoto R, Kubota M, Farber DL, Bhattacharya J, Wolters PJ, **Bhattacharya M.** (2021) Molecular programs of fibrotic change in aging human lung. *Nat Commun* **12,** 6309. PMID: 34728633.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1hyab8c8hE3A_/bibliography/public/

BIOGRAPHICAL SKETCH

NAME: Esteban González Burchard, M.D., M.P.H.

eRA COMMONS USER NAME (credential, e.g., agency login): EBURCHARD

POSITION TITLE: Professor of Medicine and Pharmacy. Harry Wm. and Diana V. Hind Distinguished Professorship in Pharmaceutical Sciences.

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
San Francisco State Univ., San Francisco, CA	B.S.	05/1990	Cellular & Molecular Biology
Stanford Univ. 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

Ongoing and recently completed projects:

T32 GM007546
Burchard (PI)
07/01/08-06/30/25
UCSF Clinical Pharmacology and Therapeutics Training Grant

U01 HL138626
Burchard (PI)
9/24/18-07/31/23
Natural History of Viral Induced Airway Dysfunction and Asthma in Minority Children

R01 HL117004
Burchard (PI)
07/01/19-06/30/23
The Airway Functional Genomics of Bronchodilator Drug Response in Minority Children with Asthma

R0 1HL155024
Burchard (PI)
01/01/21-11/30/24
Epigenomics of asthma risk factors and clinical subtypes in minority children

27IR-0030
Burchard (PI)
04/01/18-03/31/22
Tobacco Exposure and Asthma Disparity in Minority Children

R01 MD010443
Burchard (Co-PI)
04/22/16-12/31/22
Genes, Air Pollution, and Asthma severity in minority children

Highlighted Citations:

1. Lee EY, Mak ACY, Hu D, Sajuthi S, (17 authors), **Burchard E.G**. Whole Genome Sequencing Identifies Novel Functional Loci Associated with Lung Function in Puerto Rican Youth. *Am J Respir Crit Care Med*. 2020 May 27. Epub ahead of print. PMID: 32459537.
2. Mak ACY, Sajuthi S, Joo J, Xiao S, (30 authors), **Burchard E.G**. Novel KITLG/SCF Regulatory Variants Are Associated with Lung Function in African American Children with Asthma. *Genetics*. 2020 Apr 23: genetics.303231.2020. Epub ahead of print. PMID: 32327564.
3. Moreno-Estrada A, Gignoux CR, (35 authors), Silva-Zolezzi I*, **Burchard E.G.***, Bustamante CD*. 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.
4. Kumar R*, Seibold MA*, Aldrich MCF*, Williams KL*, (23 authors), **Burchard E.G**. Genetic ancestry in lung-function predictions. *NEJM.* 2010 Jul 22; 363(4):321-30. PMID: 20647190. *Equal contributions.

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021-Present	President, UCSF Medical Alumni Association
2017-Present	RWJ Amos Medical Faculty Development Program, National Advisory Committee
2011-Lifetime	Hind Distinguished Tenured Professor, Schools of Pharmacy and Medicine, UCSF
2016-Present	New England Journal of Medicine, Advisor
2015-Present	Board Member, African American Wellness Project
2010-Present	Professor, UCSF Medicine and Bioengineering and Therapeutic Sciences
2010-Present	Co-Director, UCSF Career Development Program in Omics of Lung Diseases (K12)
2009-Present	Director, UCSF Clinical Pharmacology T32 Training Program
2008-Present	Director, UCSF Center on Genes, Environments & Health
2001-Present	Director, UCSF Asthma *Collaboratory*
1998-2001	Fellow, Pulmonary and Critical Care Medicine, UCSF
1996-1998	Junior/Senior Resident in Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA
1995-1996	Intern in Medicine, Brigham & Women's Hospital, Harvard Medical School, Boston, MA

Honors

2021	2021-2022 UCSF Faculty Research Lecture Award in Clinical Science
2021	Grants and Media Chair, African American Wellness Project (AAWP) Board
2019	Keynote Speaker, SACNAS (Society for the Advancement of Chicanos and Native Americans in Science)
2018	Lifetime Achievement Award, National Medical Association (NMA), Allergy and Immunology Section
2018	Alumni Hall of Fame, San Francisco State University
2018	Apple Teaching Award
2016-2021	National Advisory Committee, Robert Wood Johnson Amos Medical Faculty Development Program

2016	Lifetime Achievement Award, American Thoracic Society, Innovations in Health Equality
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, Advisor to the Director
2015	UCSF 150th Anniversary Alumni Excellence Award -- 150 alumni of UCSF's four professional schools were chosen based on their excellence and distinction in the major components of UCSF's mission: education, patient care, research, and service—as well as business and industry.
2013	American Museum of Natural History (AMNH) documentary on Esteban Burchard
2013	Harry Wm. and Diana V. Hind Distinguished Professor in Pharmaceutical Sciences II
2013	Guest Speaker, Smithsonian Institution National Museum of Natural History (NMNH)
2011	Athletic Hall of Fame, San Francisco State University
2010	Guest Speaker, NPR's Science Friday, hosted by Ira Flatow
2009	American Society of Clinical Investigation (ASCI), elected member
2009	Guest Speaker, Tavis Smiley Show
2008-2014	NIH Study Section Member, Genetics of Health and Disease (GHD)
2005-2010	RWJ Amos Medical Faculty Development Award
1988,1989	NCAA Division II Academic All-American, Wrestling
1987	Finalist, California State Espoir Freestyle Wrestling State Finals

Contributions to Science

1. Genetics of asthma in African Americans and Latinos. I started and now direct the UCSF Asthma *Collaboratory*. I assembled the largest and most comprehensive gene-environment study of asthma in minority children in the world (n=13,000). I conceived and created the GALA and SAGE studies. My collaborators and I created two parallel studies in Hispanic/Latino children: 1) Genetics of Asthma in Latino Americans (GALA I) Study and the Genes-environments & Admixture in Latino Americans (GALA II). In addition, we created two parallel studies in African American children: Study of African Americans, Asthma, Genes & Environments (SAGE I & II). The GALA and SAGE studies are ongoing multicenter international collaborative efforts, designed to identify and directly compare clinical and genetic risk factors associated with asthma and asthma severity among Latino and African American children. I recruited patients alongside with my collaborators, I built the biorepository and database to house the biologic and clinical data. My colleagues and I did the analyses and wrote more than 300 manuscripts from this effort. We demonstrated striking racial/ethnic clinical and genetic differences in asthma.
    a. **Burchard E.G.**, 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
    b. Choudhry S, Ung N, (28 authors**), Burchard E.G**. Pharmacogenetic Differences in Response to Bronchodilators between Puerto Rican and Mexican Asthmatics. *AJRCCM.* 2005; 171(6):563-70 PMID: 15557128
    c. Naqvi M, Choudhry S, Tsai HJ, Thyne S, Navarro D, Nazario S, Rodriguez-Santana JR, Casal J, Torres A, Chapela R, Watson HG, Meade K, Rodriguez-Cintron W, Lenoir M, Avila PC, **Burchard EG**. Association between IgE levels and asthma severity among African American, Mexican, and Puerto Rican patients with asthma. J *Allergy Clin Immunol*. 2007 Jul;120(1):137-43. PMID: 17498790.
    d. 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

2. Race/ethnicity and genetic ancestry in clinical and biomedical research. The initial sequencing for the Human Genome Project (HGP) was completed in 2000. During the announcement of the completion of the HGP, U.S. President Bill Clinton, Britain's Prime Minister Blair and NIH Director, Francis Collins declared that all humans were 99.9% identical and therefore we should eliminate the idea of

race/ethnicity. Consequently, many social epidemiologists used this pronouncement as an opportunity to declare that race/ethnicity were irrelevant in science and medicine. In a pro/con debate published in the *NEJM*, my colleagues and I used empiric evidence to demonstrate that there are clinically significant genetic differences within and between racial/ethnic groups.

a. **Burchard EG**, Ziv E, Coyle N, Lin-Gomez S, Tang H, Karter AJ, Mountain J, Perez-Stable EJ, Sheppard D, Risch N. The Importance of Race and Ethnic Background in Biomedical Research and Clinical Practice. *NEJM*. 2003; 348(12):1077-1192. PMID: 12646676
b. Borrell LN*, Elhawary JR, Fuentes-Afflick E, Witonsky J, Bhakta N, Wu AHB, Bibbins-Domingo K, Rodríguez-Santana JR, Lenoir MA, Gavin III JR, Kittles RA, Zaitlen NA, Wilkes DS, Powe NR, Ziv E, **Burchard EG***. *Shared senior authors. Race and Genetic Ancestry in Medicine — A Time for Reckoning with Racism. *NEJM* 2021. PMID: 33406325
c. Sequencing of 53,831 diverse genomes from the NHLBI TOPMed Program. Nature 2021. PMID: 33568819 PMCID: PMC7875770

3. Latinos and genetic ancestry in clinical and biomedical research. The U.S. Government and many organizations considered all Hispanic/Latinos the same and categorized Latinos as a monolithic group. We used empiric sociodemographic and genetic evidence to show that Latino ethnic groups are distinct from each other. We also demonstrated the tremendous power that can be leveraged for identifying social, environmental, and genetic determinants of health and disease when we use race/ethnicity in Latino ethnic subgroups.
    a. **Burchard, EG,** Borrell, LN, Choudhry, S, Naqvi, M, Tsai, HJ, Rodriguez-Santana, JR, Chapela, R, Rogers, SD, Mei, R, Rodriguez-Cintron, W, Arena, JF, Kittles, R, Perez-Stable, EJ, Ziv, E and Risch N. Latino Populations: A unique opportunity for the study of Race, Genetics and Social Environment in Epidemiologic Research. *American J Public Health* 2005; 95(12):2161-8. PMID: 16257940. PMCID: PMC1449501

4. Genetic ancestry and lung function. Pulmonary function testing is one of the few applications in clinical medicine in which self-identified race/ethnicity is used to predict normative values that are used to distinguish respiratory health from disease. Lung function varies by age, sex, height, and self-identified race/ethnicity. A healthy African American man has lung function measures that, on average, are 15% less than a healthy White man of the same age and height. A major question is whether self-identified race/ethnicity, which is associated with both genetic determinants of lung function and the cumulative impact of socioeconomic influences on lung function, should be used in these normative equations. This question is of critical importance because lung function measurements are compared to “normal” reference values calculated using a patient’s age, sex, height, and race/ethnicity. My colleagues and I were the first in the world to demonstrate that genetic ancestry was associated with lung function. We demonstrated that incorporating genetic ancestry into lung function prediction equations improves their predictive accuracy even after accounting for social determinants of health such as early life exposures, air pollution, and socioeconomic status. In addition, we demonstrated that sub-continental Native American ancestry also influences current clinical standards for pulmonary reference equations among Latino populations by as much as 10%. This work represents analysis of data from the largest study of Native Americans ever published. In doing so, we were able to illuminate the rich demographic history among indigenous populations in the Americas. Incorporating genetic ancestry into normative pulmonary predicative equations improves lung function estimates and more accurately categorize disease severity in Latino populations. Our results have allowed us to advance precision medicine for populations that are traditionally understudied.
        a. 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, Lenoir MA, 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.

b. Salari K, Choudhry S, Tang H, Naqvi M, Lind D, Avila PC, Coyle NE, Ung N, Nazario S, Casal J, Torres-Palacios A, Clark S, Phong A, Gomez I, Matallana H, Pérez-Stable EJ, Shriver MD, Kwok PY, Sheppard D, Rodriguez-Cintron W, Risch NJ, **Burchard EG*** and Ziv E*. *Shared senior authors. Genetic admixture and asthma-related phenotypes in Mexican American and Puerto Rican asthmatics. *Genet Epidemiol*. 2005 Jul; 29(1):76-86. PMID: 15918156.

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

BIOGRAPHICAL SKETCH

NAME: Harold A. Chapman

eRA COMMONS USER NAME (credential, e.g., agency login): HALCHAPMAN

POSITION TITLE: Professor of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Tulane University		1968	Premedical
University of Alabama School of Medicine	MD	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

Ongoing and recently completed projects:

U01 HL134766
Chapman (PI)
09/01/16-08/31/23
Epithelial stem/progenitor cells as repair agents in diffuse alveolar damage.

R35 HL150767
Chapman (PI)
02/01/20-01/31/27
Program to promote lung regeneration and block fibrosis
This grant replaces two R01s: HL128484 and HL142265

Highlighted Citations:

1. Vaughan AE, Brumwell A, Xi Y, Gotts J, Brownfield DG, Treutlein B, Tan K, Tan V, Liu F, Looney MR, Matthay M, Rock J, **Chapman HA**. (2015). Lineage-negative Progenitors Mobilize to Regenerate Lung Epithelium after Major Injury. Nature, 517(7536):621-5. PMCID: PMC4312207
2. Xi Y, Kim T, Brumwell AN, Driver I, Wei Y, Tan V, Jackson J, Xu J, Lee DK, Gotts J, Matthay M, Shannon JM, **Chapman HA** (corresponding author), Vaughan AE. (2017). Local lung hypoxia determines epithelial fate decisions during alveolar regeneration. Nature Cell Biology, 19(8):904-914. PMCID: PMC5600325
3. Kathiriya J, Brumwell, AN, Jackson JR, Tang X, **Chapman HA**. (2020). Distinct airway epithelial stem cells hide among club cells but mobilize to promote alveolar regeneration. Cell Stem Cell**,** 26:346-358.
4. Kathiriya J, Chaoqun Wang C, Zhou M, Brumwell A, Cassandras M, Le Saux C, Cohen M, Alysandratos K-D, Wang B, Wolters P, Matthay M, Kotton DN, **Chapman HA** (corresponding author),

Peng T. (2021). Human alveolar Type 2 epithelium transdifferentiates into metaplastic KRT5+ basal cells. Nature Cell Biology, DOI: 10.1038/s41556-021-00809-4, online Dec 30, 2021.

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

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, Pulmonary and Critical Care Medicine Division, 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

Honors

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
2021 R35 Award, 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

Contributions to Science

1. The nature of the cells and proteases important to human emphysema was not very long ago uncertain, 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 my 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. PMID: 1373132
    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. PMID: 8612130

c. Gelb BD, Shi GP, **Chapman HA** Jr, Desnick RJ. Pycnodysostosis, a lysosomal disease caused by cathepsin K deficiency. *Science* 1996; 273:1236-1238. PMID: 8703060
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. PMCID: PMC1430281

2. 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. PMID: 6210439
   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. PMID: 7528215
   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. PMID: 8703217
   d. Wei Y, Yang X, Quimei Liu, Wilkins JA, **Chapman HA**. Role for caveolin and urokinase receptors in integrin-mediated adhesion and signaling. *J Cell Biol* 1999;144:1285-1294. PMCID: PMC2150580

3. 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 β-catenin-rich cell:cell contacts, integrin $\alpha 3\beta 1$, 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 PMCID: PMC1551904
   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. PMCID: PMC2613463
   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. PMCID: PMC2654298
   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. PMCID: PMC3871884

4. 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 TGFRI kinase in lysyl oxidase-like 2 (LOXL2)-expressing cells, a fibroblast-specific pathway of TGFβ1 inhibition. Successful completion of the study reported in the *NEJM* encourages us to pursue more extensive safety and efficacy studies in IPF patients.
    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, 121:2855-62. PMCID: PMC5617667 Recommended as exceptional (3 stars) by F1000.
    c. **Chapman HA**, Wei Y, et al. Reversal of TGFβ1-driven Profibrotic State in Pulmonary Fibrosis Patients. *New England Journal Medicine.* 2020, 382:1068-1070
    d. Wei Y, Wenting Dong, Jackson J,Tsung-Che Ho Tsung-Che, Jourdan Le Saux C, Brumwell A, Li X, Klesney-tait J, Cohen ML, Wolters PJ, and **Chapman HA**. Blocking LOXL2 and TGFβ1 signaling induces collagen I turnover in precision-cut lung slices derived from Idiopathic Pulmonary Fibrosis patients. *Thorax.* 2021, 76: 729-732

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/harold.chapman.1/bibliograpahy/40691690/public/?sort=date&direction=ascending

BIOGRAPHICAL SKETCH

NAME: Anthony L. DeFranco

eRA COMMONS USER NAME (credential, e.g., agency login): DeFranco

POSITION TITLE: Professor of Microbiology and Immunology, UCSF

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Harvard University, Cambridge, MA	AB	06/1975	Biochem. Sci.
Univ. California, Berkeley, CA	PhD	10/1979	Biochemistry
National Institutes of Health, Bethesda, MD	Postdoctoral	08/1983	Immunology

Ongoing and recently completed projects:

R01 AI138479
DeFranco (PI)
03/01/18-02/28/23
Organ-specific autoimmunity resulting from two genetic defects in tolerance

Highlighted Citations:

1. 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.
2. 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. Hua, Z., A.J. Gross, C. Lamagna, N. Ramos-Hernandez, P. Scapini, M. Ji, H. Shao, C.A. Lowell, B. Hou and **A.L. DeFranco**. (2014). Requirement for MyD88 signaling in B cells and dendritic cells for germinal center anti-nuclear antibody production in Lyn-deficient mice. J. Immunol. 192: 875-885. PMC4101002.
4. 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. PMCID: PMC5087700.

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

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
1990- 2017	Program Director, UCSF Immunology T32 training program
1994 - 2015	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 attendee, UCB CellTech, Slough, UK
2015-present	Professor Emeritus of Microbiology & Immunology, UCSF (with continuing research and teaching activities)

Selected Honors

1974	Dreyfuss Foundation Fellow
1975	Phi Beta Kappa, Harvard University
1975-78	NSF Predoctoral Fellow
1979-82	Helen Hay Whitney Postdoctoral Fellow
1993	2nd Rose Lieberman Lecturer, NIH
1994	NIAID Merit Award
1997-98	NIH Fogarty Senior International Award

Professional Service (selected list)

Grant Review Committees: Member NIH CMI-A Study Section (2014-2020); Chair (2019-2020); NIH ad hoc grant reviewer (average 2+ reviews per year, 2005-2013; 2021); European Research Council, Immunity and Infection review panel for grants for new PIs in Europe (2012, 2014, 2016), Advanced Grants (2016-17), and Synergy Grants (2018); Leukemia and Lymphoma Society of America, Career Development Program Grant Review Subcommittee (1999-2005; and hoc 2011, 2013, 2014) Member Exptl. Immunol. Study Section (1993-97), Chair (1995-1997)
Journal Editorial Boards: J. Immunol. Associate Editor (1986-90), Section Editor (1990-1994), Deputy Editor (1999-2001); Annual Review of Immunology, Editorial Committee for Volumes 9,13, 15, 17 (1991, '95, '97, '99); Current Biology, Editorial Board (1993-99). Faculty of 1000 contributor 2001-2018 (www.facultyof1000.com/start.asp)
Conference Organizer; AAI educational activities: Lecturer, American Assoc. of Immunologists, Advanced Course 1995-97; Co-organizer: "B cell Immunobiology and Disease", a Keystone symposium, 2001

Contributions 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 (1a). 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 (1b), an analysis of the role of reactive oxygen species in BCR signaling, which disproved a long-standing model in the field (1c), 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 (1d).
   1a. 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.

1b. 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.

1c. 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.

1d. 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).

2a. 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.

2b. 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.

2c. 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.

2d. 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 a 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 (3a). 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 (3b) and that DCs require MyD88-dependent signaling to promote inflammatory disease in this model (3c). 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 powerful new model for multigenic autoimmune susceptibility. These mice are used in the proposed project.

3a. 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.

3b. 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.

3c. Lamagna C., Scapini P., Van Ziffle J., Hou B., **DeFranco A.L**, 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.

3d. 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. PMCID: PMC5087700.

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) (4a). 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 (4b). 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). We also have used studied the induction of Th2 or Th1 immune responses to aerosolized antigen accompanied by TLR ligands as a mouse model of asthma. This work has indicated that lung epithelial cells play a critical role in promoting a Th2 response when flagellin is the adjuvant (4d), which may be relevant to human asthma as house dust frequently contains flagellin. The conditional allele of *Myd88* was deposited with Jackson Lab soon after initial publication and is available to academic investigators for their studies.

4a. 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.

4b. Hou, B., A. Benson, L. Kuzmich, **A.L. DeFranco**, 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.

4c. Raetz, M., Hwang, S-H., Wilhelm, C., Kirkland, D., Benson, A., Sturge, C., Mirpuri, J., Vaishnava, S., Hou, B., **DeFranco, A.L.**, Gilpin, C.J., Hooper, L.V., Yarovinsky, F. (2013). Parasite-induced Th1 cells promote intestinal dysbiosis via IFN-γ-dependent elimination of Paneth cells. Nat. Immunol.,14: 136-142. PMC3552073.

4d. 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, 11(12):e0167693. PMC5157987.

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, 5c). 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 defined the cellular nature of this effect (5b) and showed that signaling pathways enhanced within germinal center B cells increased c-Myc transcriptional activity and increased mTORC1 (5d).

5a. Hou, B., P. Saudan, G. Ott, M.L. Wheeler, M. Ji, L. Kuzmich, L.M. Lee, R.L. Coffman, M.F. Bachmann, **A.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. PMC306472.

5b. 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.

5c. 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.

5d. Wigton EJ, **DeFranco AL**, and Ansel KM. (2019). Antigen complexed with a TLR9 agonist bolsters c-myc and mTORC1 activity in germinal center B lymphocytes. Immunohorizons, 3: 389-401. PMCID: PMC6738343.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/anthony.defranco.1/bibliography/41142681/public/?sort=date&direction=ascending

BIOGRAPHICAL SKETCH

NAME: William F. DeGrado

eRA COMMONS USER NAME (credential, e.g., agency login): DEGRADOW

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Kalamazoo College, Kalamazoo, MI	BS	05/1977	Chemistry
University of Chicago, Chicago, IL	PhD	1981	Organic Chemistry

Ongoing and recently completed projects:

P01 AG002132
Prusiner (PI)
06/16/20-03/31/25
Degenerative and Dementing Diseases of Aging

RF1AG061874
Condello (PI)
09/01/18-03/31/23
Relationships between conformational strains of tau and amyloid-beta, TREM2 and APOE variants, and phenotypic variations of Alzheimer's Disease

R35 GM122603
DeGrado (PI)
05/01/17-04/30/22
Deciphering the relationship between structure, dynamics and function in helical bundle proteins

Positions, Scientific Appointments, and Honors

Professional Experience

2011-present Professor, Department of Pharmaceutical Chemistry, University of California, San Francisco
2001-2003 President, The Protein Society
1996-2011 Professor, Dept. of Biochemistry & Biophysics, University of Pennsylvania, Philadelphia, PA
1994-1996 Senior Director for small molecule and peptide drug discovery, The DuPont Merck Pharmaceutical Company, Wilmington, DE
1992-1994 Research Fellow, R&D, The DuPont Merck Pharmaceutical Company, Wilmington, DE
1990-1992 Research Leader, CR&D, DuPont Company, Wilmington, DE
1981-1990 Research Chemist, CR&D, DuPont Company, Wilmington, DE

Visiting Positions

2010-2011 Visiting professor, UCSF Department of Pharmaceutical Chemistry
1991 Adjunct Professor, Departments of Biochemistry & Biophysics, University of Pennsylvania

1987-1989 Adjunct Professor, Department of Biophysics, Johns Hopkins Medical School
1987 Sloan Visiting Lecturer of Chemistry, Department of Chemistry, Harvard University

Selected Honors

2021 Spiers Memorial Award, Royal Society of Chemistry (Great Britain)
2021 John Scott Award
2018 Goodman Award (ACS Biological Division)
2017 Cope Scholar Award (ACS)
2015 Stein & Moore Award (Protein Society)
2014 Member, National Academy of Inventors (U.S.A.)
2009 Makineni Award (American Peptide Society)
2008 Ralph F. Hirschmann Award in Peptide Chemistry (American Chemical Society)
2003 Merrifield Award (American Peptide Society)
1999 Member, National Academy of Sciences (U.S.A.)
1998 Member, American Academy of Arts and Sciences
1994 Fellow, American Association for the Advancement of Science
1993 DuPont Merck Summit Award
1992 Eli Lilly Award in Biological Chemistry
1989 Protein Society Young Investigator Award
1988 du Vigneaud Award for Peptide Research

Contributions to Science

1. ***Design and synthesis of small molecule inhibitors of M2 proton channel***. Currently circulating strains of M2 are largely resistant to amantadine, which has greatly curtailed options for treating influenza virus infections. With Lamb and Pinto, we extensively characterized the electrophysiological properties of many drug-resistant mutants of the channel, and identified those most likely to lead to resistance in the future. My group solved the first structures of drugs bound to the pharmacologically relevant site of the channel in micelles by X-ray crystallography and solution NMR, and in bilayers by SSNMR (collaboration with Mei Hong, MIT)[1,5-7]. Based on our proposed conductance mechanism, we designed novel small molecules that inhibit known clinically problematic mutants[2-4].
   a. Stouffer, A. L., Acharya, R., Salom, D., Levine, A. S., Di Costanzo, L., Soto, C. S., Tereshko, V., Nanda, V., Stayrook, S., and **DeGrado, W. F**. (2008) Structural basis for the function and inhibition of an influenza virus proton channel, *Nature 451*, 596-599. PMC3889492 PubMed PMID 18235504
   b. Wang J, Ma C, Fiorin G, Carnevale V, Wang T, Hu F, Lamb RA, Pinto LH, Hong M, Klein ML and DeGrado WF (2011) Molecular dynamics simulation directed rational design of inhibitors targeting drug-resistant mutants of influenza A virus M2. *J Am Chem Soc* 133:12834-41. PMC3354620 PubMed PMID 21744829
   c. Wu Y, Canturk B, Jo H, Ma C, Gianti E, Klein ML, Pinto LH, Lamb RA, Fiorin G, Wang J and **DeGrado WF** (2014) Flipping in the Pore: Discovery of Dual Inhibitors That Bind in Different Orientations to the Wild-Type versus the Amantadine-Resistant S31N Mutant of the Influenza A Virus M2 Proton Channel. *J Am Chem Soc* 136:17987-95. PMC4286326 PubMed PMID 25470189
   d. Hu Y, Musharrafieh R, Ma C, Zhang J, Smee DF, **DeGrado WF** and Wang J. An M2-V27A channel blocker demonstrates potent in vitro and in vivo antiviral activities against amantadine-sensitive and -resistant influenza A viruses. *Antiviral Res.* 2017;140:45-54. PMCID: PMC5326599. PubMed PMID 28087313

2. ***Structure/Function of the M2 proton channel from influenza A virus.*** Our early work with the groups of Robert Lamb and Larry Pinto established the overall fold and mechanism of the M2 proton channel, which is the target of the anti-influenza drugs, amantadine and rimantadine. We first proposed the transporter-like and His-shuttle mechanisms, which are now widely accepted. A decade later our group's crystallographic and solution NMR structures[1,3], and in bilayers by SSNMR (collaboration with Mei Hong, MIT)[5]. provided direct support for these mechanisms. These structures also defined the drug-binding site and explained how mutations led to amantadine-resistance[10,11]. We have solved

extremely high-resolution (1.05 Å) crystal structures of M2's pore, which rank among the highest resolution crystal structures of any membrane protein[12]. These structures showed well-defined water-wires for conduction of protons through the length of the pore, leading to the critical His37 proton-shuttling residue.

a. Cady SD, Schmidt-Rohr K, Wang J, Soto CS, **DeGrado WF** and Hong M (2010) Structure of the amantadine binding site of influenza M2 proton channels in lipid bilayers. *Nature* 463:689-92. PMC4403401. PubMed PMID 20130653
b. Wang, J., Wu, Y., Ma, C., Fiorin, G., Wang, J., Pinto, L. H., Lamb, R. A., Klein, M. L., and **DeGrado, W.F**. (2013) Structure and inhibition of the drug-resistant S31N mutant of the M2 ion channel of influenza A virus, *PNAS 110*, 1315-1320. PMC3557100 PubMed PMID 23302696
c. Thomaston JL, Wu Y, Polizzi N, Liu L, Wang J and **DeGrado WF**. X-ray Crystal Structure of the Influenza A M2 Proton Channel S31N Mutant in Two Conformational States: An Open and Shut Case. J Am Chem Soc. 2019;141(29):11481-11488. Epub 2019/06/12. doi: 10.1021/jacs.9b02196. PubMed PMID: 31184871; PMCID: PMC31184871
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 and **DeGrado WF**. XFEL structures of the influenza M2 proton channel: Room temperature water networks and insights into proton conduction. Proc Natl Acad Sci U S A. 2017;114(51):13357-13362. PMCID: PMC5754760. PubMed PMID 28835537

3. ***Structure-based design of small molecule integrin inhibitors as therapeutics*.**
Integrins. Our group has long been involved in the design of 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)[9]. 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 they have shown efficacy in a variety of animal models of IPF and other fibrotic disorders[10]. Most recently, my group has developed small molecule inhibitors of integrins as potential treatments for asthma[11].
Mimics of antimicrobial peptides. Our lab designed small molecule mimics of antimicrobial peptides based on matching the overall-physicochemical properties of this class of peptides. While our initial molecules were designed to test hypotheses concerning the features required for their membrane activity, our mimetics also showed promise in animal mouse models for treatment of drug-resistant *Staph. aureus.* This work led to the founding of PolyMedix, which developed brilacidin as an antimicrobial. Brilacidin was subsequently licensed to Innovation Pharma, and it is being tested in multiple phase II trial as an antibacterial (Clinical Trials NCT01211470, NCT020388, and NCT02324335) as well as SARS-CoV-2 infections (Clinical Trial NCT04784897).

a. Miller MW, Basra S, Kulp DW, Billings PC, Choi S, Beavers MP, McCarty OJ, Zou Z, Kahn ML, Bennett JS and **DeGrado WF**. Small-molecule inhibitors of integrin alpha2beta1 that prevent pathological thrombus formation via an allosteric mechanism. Proc Natl Acad Sci U S A. 2009;106(3):719-24. PMCID: 2625282. PubMed PMID 19141632
b. Reed NI, Jo H, Chen C, Tsujino K, Arnold TD, **DeGrado WF** and Sheppard D. The alphavbeta1 integrin plays a critical in vivo role in tissue fibrosis. Sci Transl Med. 2015;7(288):288ra79. PMCID: PMC4461057. PubMed PMID 25995225
c. Liu S, Ngo U, Tang XZ, Ren X, Qiu W, Huang X, **DeGrado W**, Allen CD, Jo H, Sheppard D and Sundaram AB. Integrin alpha2beta1 regulates collagen I tethering to modulate hyperresponsiveness in reactive airway disease models. J Clin Invest. 2021;131(12). PMCID: PMC8203456. PubMed PMID 33956668
d. Tew GN, Scott RW, Klein ML and **DeGrado WF**. De novo design of antimicrobial polymers, foldamers, and small molecules: from discovery to practical applications. Acc Chem Res. 2010;43(1):30-9. PMCID: 2808429. PubMed PMID 19813703

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=DeGrado%20WF[Author]&cauthor=true&cauthor_uid=7481798

BIOGRAPHICAL SKETCH

NAME: Erle, David Jacob

eRA COMMONS USER NAME (credential, e.g., agency login): DJERLE

POSITION TITLE: Professor of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Harvard College, Cambridge, MA	AB	05/1980	Biochemistry
University of California, San Francisco, CA	MD	05/1984	Medicine
University of California, San Francisco, CA	Resident	06/1987	Internal Medicine
University of California, San Francisco, CA	Fellow	06/1988	Pulmonary Medicine
University of California, San Francisco, CA	Postdoc	06/1990	Cell & Molecular Biology

Ongoing and recently completed projects:

R35 HL145235
Erle (PI)
04/15/19-02/28/26
Airway Epithelial Cell Gene Regulation: New Mechanisms and Therapeutic Strategies

U19 AI 077439
Erle (PI, Project 1 Leader)
04/01/18-03/31/23
Understanding Asthma Endotypes

Cystic Fibrosis Foundation URNOV19XX0
Urnov (PI); Role: UCSF subcontract PI
02/01/20-01/31/23
Advancing delivery of novel genome editing enzymes to correct orphan CF mutations

U19 AI 077439-13S1
Erle (PI)
05/08/20-03/31/22
UCSF COVID-19: Extended Immunophenotyping Studies

U19 AI 077439-13S2
Erle (PI)
05/08/20-03/31/22
UCSF COVID-19 Immunophenotyping Clinical Study and Core Laboratories

Highlighted Citations:

1. Bonser LR, Eckalbar WL, Rodriguez L, Shen J, Koh KD, Ghias K, Zlock LT, Christenson S, Woodruff PG, Finkbeiner WE, **Erle DJ**. The Type 2 Asthma Mediator IL-13 Inhibits SARS-CoV-2 Infection of Bronchial Epithelium. Am J Respir Cell Mol Biol. 2022 Jan 4. doi: 10.1165/rcmb.2021-0364OC. Epub ahead of print. PMID: 34982656
2. Sarma A, Christenson SA, Byrne A, Mick E, Pisco AO, DeVoe C, Deiss T, Ghale R, Zha BS, Tsitsiklis A, Jauregui A, Moazed F, Detweiler AM, Spottiswoode N, Sinha P, Neff N, Tan M, Serpa PH, Willmore A, Ansel KM, Wilson JG, Leligdowicz A, Siegel ER, Sirota M, DeRisi JL, Matthay MA; COMET Consortium, Hendrickson CM, Kangelaris KN, Krummel MF, Woodruff PG, **Erle DJ**, Calfee CS, Langelier CR. Tracheal aspirate RNA sequencing identifies distinct immunological features of COVID-19 ARDS. Nat Commun. 2021 Aug 26;12(1):5152. doi: 10.1038/s41467-021-25040-5. PMID: 34446707; PMCID: PMC8390461
3. van der Wijst MGP, Vazquez SE, Hartoularos GC, Bastard P, Grant T, Bueno R, Lee DS, Greenland JR, Sun Y, Perez R, Ogorodnikov A, Ward A, Mann SA, Lynch KL, Yun C, Havlir DV, Chamie G, Marquez C, Greenhouse B, Lionakis MS, Norris PJ, Dumont LJ, Kelly K, Zhang P, Zhang Q, Gervais A, Le Voyer T, Whatley A, Si Y, Byrne A, Combes AJ, Rao AA, Song YS, Fragiadakis GK, Kangelaris K, Calfee CS, **Erle DJ**, Hendrickson C, Krummel MF, Woodruff PG, Langelier CR, Casanova JL, Derisi JL, Anderson MS, Ye CJ; UCSF COMET consortium. Type I interferon autoantibodies are associated with systemic immune alterations in patients with COVID-19. Sci Transl Med. 2021 Sep 22;13(612):eabh2624. doi: 10.1126/scitranslmed.abh2624. Epub 2021 Aug 24. PMID: 34429372; PMCID: PMC8601717
4. Combes AJ, Courau T, Kuhn NF, Hu KH, Ray A, Chen WS, Chew NW, Cleary SJ, Kushnoor D, Reeder GC, Shen A, Tsui J, Hiam-Galvez KJ, Muñoz-Sandoval P, Zhu WS, Lee DS, Sun Y, You R, Magnen M, Rodriguez L, Im KW, Serwas NK, Leligdowicz A, Zamecnik CR, Loudermilk RP, Wilson MR, Ye CJ, Fragiadakis GK, Looney MR, Chan V, Ward A, Carrillo S; UCSF COMET Consortium, Matthay M, **Erle DJ**, Woodruff PG, Langelier C, Kangelaris K, Hendrickson CM, Calfee C, Rao AA, Krummel MF. Global absence and targeting of protective immune states in severe COVID-19. Nature. 2021 Mar;591(7848):124-130. doi: 10.1038/s41586-021-03234-7. Epub 2021 Jan 25. Erratum in: Nature. 2021 Aug;596(7872):E8. PMID: 33494096; PMCID: PMC8567458

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2020-	Director, UCSF CoLabs
2018-	Member, UCSF Institute for Human Genetics
2018-	Member, UCSF ImmunoX program
2017-	Associate Chair for Biomedical Research, UCSF Department of Medicine
2006-2011	Associate Director, UCSF Clinical and Translational Sciences Institute Bioinformatics Program
2004-	Professor of Medicine, UCSF
2000-2019	Director, Functional Genomics Core Facility, UCSF SABRE Center
1999-	Investigator, Cardiovascular Research Institute, UCSF
1998-2004	Associate Professor of Medicine, UCSF
1997-2001	UCSF/SFGH General Clinical Research Center (GCRC) Advisory Committee
1996-	Faculty, UCSF Immunology and Biomedical Sciences Graduate Programs
1992-1998	Assistant Professor of Medicine in Residence, UCSF
1990-1992	Adjunct Assistant Professor of Medicine, UCSF
1990-2018	Attending Physician, San Francisco General Hospital

1988-1990 Research Fellow, Lung Biology Center and Cardiovascular Research Institute, UCSF
1987-1988 Clinical Pulmonary Fellow, University of California Hospitals, San Francisco
1984-1987 Resident in Internal Medicine, University of California Hospitals, San Francisco

Other Experience and Professional Memberships

2014-2015 Chair, RCMB Assembly Nominating Committee, American Thoracic Society
2010- Editorial Board, *American Journal of Respiratory Cell and Molecular Biology*
2008-2012 NIH LCMI Study Section, member (chair, 2010-2012)
2005- NIH Special Emphasis Panels for Member Conflicts
2001-2004 RCMB Assembly Program Committee, American Thoracic Society
1999-2002 American Thoracic Society Scientific Advisory Council
1998-1999 RCMB Assembly Nominating Committee, American Thoracic Society
1996-1999 American Lung Association/American Thoracic Society Scientific Advisory Council
1988- Member, American Thoracic Society

Selected Honors

2019 NHLBI Outstanding Investigator Award (R35)
2018 Elected member, Association of American Physicians
1984 Alpha Omega Alpha, University of California, San Francisco, CA
1980 Magna cum laude, Harvard College, Cambridge, MA
1990-1993 Edward Livingston Trudeau Award of the American Lung Association
1977-1978 John Harvard Scholarship, Harvard College, Cambridge, MA
1977 Detur Prize, Harvard College, Cambridge, MA

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.
   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.

2. 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.

3. 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. In 2020, the core was incorporated into the UCSF CoLabs, a new model for collaborative research and team science at UCSF. I am the founding director of CoLabs, which is part of UCSF's Office of Research and provides a centralized home for integrating laboratories with experts and specialized equipment required for many studies performed at UCSF. Recent publications from Genomics Core and CoLabs projects include:
   a. 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
   b. 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.
   c. 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.
   d. Combes AJ, Courau T, Kuhn NF, Hu KH, Ray A, Chen WS, Chew NW, Cleary SJ, Kushnoor D, Reeder GC, Shen A, Tsui J, Hiam-Galvez KJ, Muñoz-Sandoval P, Zhu WS, Lee DS, Sun Y, You R, Magnen M, Rodriguez L, Im KW, Serwas NK, Leligdowicz A, Zamecnik CR, Loudermilk RP, Wilson MR, Ye CJ, Fragiadakis GK, Looney MR, Chan V, Ward A, Carrillo S; UCSF COMET Consortium, Matthay M, **Erle DJ**, Woodruff PG, Langelier C, Kangelaris K, Hendrickson CM, Calfee C, Rao AA, Krummel MF. Global absence and targeting of protective immune states in severe COVID-19. *Nature*. 2021 Jan 25. doi: 10.1038/s41586-021-03234-7. Epub ahead of print. PMID: 33494096. PMCID pending.

4. 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.

5. 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

BIOGRAPHICAL SKETCH

NAME: John V. Fahy

eRA COMMONS USER NAME (credential, e.g., agency login): johnfahy

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University College Dublin	MB BAO BCH	06/1985	Medicine
Trinity College Dublin	Internal Medicine (Residency)	06/1988	Internal Medicine
University College Dublin	Pulmonary Medicine (Medical Registrar)	06/1989	Pulmonary Medicine
University of California, San Francisco	Postdoctoral fellowship	06/1993	Pulmonary & Critical Care Medicine
University College Dublin	M.D. (doctorate by thesis)	06/1997	Airway Inflammation
Trinity College Dublin	MSc.	06/2003 (Sabbatical)	Molecular Medicine

Ongoing and recently completed projects:

R01 HL080414
Fahy (PI)
07/01/05-04/30/21 (NCE)
Mechanism of mucus pathology in asthma exacerbations

UG1 HL139106
Fahy (PI)
09/23/17-06/30/23
Sequential, Multiple Assignment, Randomized Trial in Severe Asthma Protocol (SMART-SA*)*

P01 HL107202
Fahy (PI)
08/01/12-06/30/24
Exploring the biology of persistent type 2 airway niches in asthma
Role: Overall PPG PI (Leader of project 3; Core leader - Administrative Core & the Human Subjects Core)

P01 HL128191
Fahy (PI)
09/01/16-07/31/21
Carbohydrate-based Therapy for Lung Disease
Role: Overall PPG PI (Project leader for project 3 and Core leader for the Administrative Core)

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

1989-1993	Fellow, Division of Pulmonary and Critical Care Medicine, UCSF.
1993-1998	Assistant Professor of Medicine, Division of Pulmonary and Critical Care Medicine, UCSF.
1999-2005	Associate Professor of Medicine, Division of Pulmonary and Critical Care Medicine, 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, UCSF.

Other Experience and Professional Memberships

1989-	Member, American Thoracic Society
2014-	Member, European Respiratory Society
2009- 2018	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	Elected member of the Association of American Physicians (AAP).
2017	American Thoracic Society (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).

Contributions to Science

1. 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. 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 type 2-high and type 2-low endotypes of asthma (publications A-C) as well as the recent identification of IL-6 high asthma (publication D).

   ***Impact*:** The impact of discovery of type 2-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 type 2-high and -low subgroups and clinical trials of inhibitors of type 2 cytokines are specifically targeting patients with type 2-high asthma.

   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**. T-helper type 2-driven inflammation defines major subphenotypes of asthma. Am J Respir Crit Care Med. 2009;180:388-95. PMCID: PMC2742757
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. PMCID: PMC2922596
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.** Alternative splicing of interleukin 33 and type 2 inflammation in asthma. Proc Natl Acad Sci U S A. 2016;113:8765-70. PMCID: PMC4978244
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. PMCID: PMC5007068

2. AIRWAY MUCUS PATHOLOGY

Background: Airway mucus is normally a lightly cross-linked gel that is easily transported out of the lung via the mucociliary escalator. This mucus gel becomes more elastic and harder to clear In lung disease, and mucus stasis then causes airflow obstruction and lung infection. Mucus pathology is a feature of all major lung disease especially asthma, COPD, and cystic fibrosis. The study of mucus in lung disease has been a major focus of my lab and my group has optimized multiple methodologies to apply to quantify mucus cells and mucin proteins in the airway and to quantify mucus plugging using image based scoring.

Central findings: My lab identified intelectin-1 is a prominent protein constituent of mucus plugs in eosinophilic asthma role (publication A) and proposed oxidative stress as a key driver of pathologic airway mucus gels in cystic fibrosis (publication B). I also led studies that uncovered prominent mucus plug phenotypes in severe forms of asthma and COPD that have been unsuspected based on cough and sputum symptoms (publications C and D).

Impact: There are few treatments targeting mucus pathology in lung disease despite the common occurrence of mucus-associated disease. My lab's focus on mechanisms of mucus gel pathology, on mucus phenotypes that can be identified using imaging, and on novel mucolytic treatment approaches are helping to advance precision-based treatment for mucus plugging in asthma and other lung diseases.

My role: I generate funding for studies of mucus pathology in my lab attract personnel to pursue studies of mucus pathology and guide specific research projects designed to reveal mechanism and test mucus-directed therapies. Key grants for this activity include R01HL080414 and P01HL128191.

a. Kerr SC, Carrington SD, Oscarson S, Gallagher ME, Solon M, Yuan S, Ahn JN, Dougherty RH, Finkbeiner WE, Peters MC, **Fahy JV**. Intelectin-1 is a prominent protein constituent of pathologic mucus associated with eosinophilic airway inflammation in asthma. Am J Respir Crit Care Med. 2014 Apr 15;189(8):1005-7. PMID: 24735037. PMCID: PMC4098098
b. Yuan S, Hollinger M, Lachowicz-Scroggins ME, Kerr SC, Daniel BM, Ghosh S, Erzurum SC, Willard B, Hazen SL, Huang X, Carrington SD, Oscarson S, **Fahy JV**. Oxidation Increases Mucin Polymer Cross-links to Stiffen Airway Mucus Gels. Science Translational Med. Sci Transl Med. 2015;7(276) 276ra27 PMCID: PMC4403633.
c. Dunican EM, Elicker BM, Gierada DS, Nagle SK, Schiebler ML, Newell JD, Raymond WW, Lachowicz-Scroggins ME, Di Maio S, Hoffman EA, Castro M, Fain SB, Jarjour NN, Israel E, Levy BD, Erzurum SC, Wenzel SE, Meyers DA, Bleecker ER, Phillips BR, Mauger DT, Gordon ED, Woodruff PG, Peters MC, **Fahy JV.** Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. J Clin Invest. 2018;128:997-1009. PMCID: PMC582487.
d. Dunican EM, Elicker BM, Henry T, Gierada DS, Schiebler ML, Anderson W, Barjaktarevic I, Barr RG, Bleecker ER, Boucher RC, Bowler RP, Christenson SA, Comellas A, Cooper CB, Couper D, Criner GJ, Dransfield M, Doerschuk CM, Drummond MB, Hansel NN, Han MK, Hastie AT, Hoffman EA, Krishnan JA, Lazarus SC, Martinez FJ, McCulloch CE, O'Neal WK, Ortega VE, Paine R 3rd, Peters S, Schroeder JD, Woodruff PG, **Fahy JV**. Mucus Plugs and Emphysema in the

Pathophysiology of Airflow Obstruction and Hypoxemia in Smokers. Am J Respir Crit Care Med. 2020 Nov 12. PMID: 33180550

3. NOVEL DRUGS FOR AIRWAY DISEASE

Background: Airway diseases such as asthma and COPD affect millions of patients and cause a significant public health care burden. Current treatments are suboptimal and new treatments are needed to alleviate the morbidity and mortality associated with these diseases. As new treatment targets are identified and novel inhibitors are developed, it is necessary to carefully conduct early phase proof of concept studies to determine the safety an efficacy of these new treatments. Choosing the right study design and the right study population for these early phase studies is critically important for the proper assessment of drug potential. I have used my expertise in clinical medicine, airway biology, and clinical research to help company's design and test new drugs for airway disease in early phase studies, including drugs directed against neurokinin (NK) receptors, IgE, selectins, and EGFR. Most recently, I have built an academic drug development program to bring a novel mucolytic to the clinic (see P01HL128191 below).

***Central findings*:** Although inhibition of NK-1, selectins, or EGFR did not have beneficial effects in clinical trials (publications A and B below), blocking IgE with a recombinant humanized monoclonal anti-IgE antibody (Omalizumab) proved effective in reducing early and late phase responses to inhaled allergen in patients with asthma (publication C).

***Impact*:** The Phase 1B study I led was pivotal in the drug development of Omalizumab and paved the way for later phase 2 and 3 trials of Omalizumab. This drug (marked as Xolair now has been in clinical use for 10 years, and it has helped many patients with asthma experience better asthma control.

***My role*:** Early in my career I worked closely on trial design, data analysis, and manuscript preparation with Homer Boushey (my mentor), and I was first author on our publications. Later, I have been the senior investigator contributing to trial design, data analysis and manuscript writing, while supervising and mentoring my junior colleagues. A key grant for this activity is P01HL128191.

a. **Fahy JV**, Wong HH, Geppetti P, Reis JM, Harris SC, Nadel, JA, Boushey HA. Effect of an NK-1 receptor antagonist (CP-99, 994) on hypertonic saline-induced bronchoconstriction and cough in male asthmatic subjects. Am J Respir Crit Care Med 1995;152:879-884. PMID: 7663799 DOI: 10.1164/ajrccm.152.3.7663799
b. Woodruff PG, Wolff M, Hohlfeld JM, Krug N, Dransfield MT, Sutherland ER, Criner GJ, Kim V, Prasse A, Nivens MC, Tetzlaff K, Heilker R, **Fahy JV.** Safety and efficacy of an inhaled epidermal growth factor receptor inhibitor in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2010;181:438-45. PMID: 20007923 DOI: 10.1164/rccm.200909-1415OC
c. **Fahy JV**, Fleming HE, Wong HH, Liu JT, Su JQ, Reimann J, Fick RB, Boushey HA. The effect of an anti-IgE monoclonal antibody-E25 on the early and late phase responses to allergen inhalation in asthmatic subjects. Am J Respir Crit Care Med 1997;155:1828-1834. PMID: 9196082.

Complete List of Published Work in MyBibliography:
https://pubmed.ncbi.nlm.nih.gov/?term=%22fahy+jv%22

BIOGRAPHICAL SKETCH

NAME: Fraser, James Solomon

eRA COMMONS USER NAME (credential, e.g., agency login): FRASERJA

POSITION TITLE: Professor of Bioengineering and Therapeutic Sciences

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
McGill University, Montreal, QC, Canada	B.Sc.	05/2005	Biology
University of California, Berkeley, CA	Ph.D.	12/2010	Molecular and Cell Biology

Ongoing and recently completed projects:

R01 GM123159
Fraser (PI)
12/01/17-11/31/22 (NCE)
Resolving ensemble averaged conformations by multi-temperature x-ray crystallography

R01 GM0517315
Holton (PI), Role: Co-Investigator
12/15/17-11/30/22
Eliminating Critical Systematic Errors In Structural Biology With Next-Generation Simulation

Highlighted Citations:

1. Wankowicz SA, de Oliveira SHP, Hogan DW, van den Bedem H, **Fraser JS**. Ligand binding remodels protein side chain conformational heterogeneity. *BioRxiv* 461269 [Preprint]. September 21, 2021. Available from: https://doi.org/10.1101/2021.09.21.461269.
2. Schuller M*, Correy GJ*, Gahbauer S*, Fearon D*, et al, von Delft F, Shoichet BK, **Fraser JS**, Ahel I. Fragment binding to the Nsp3 macrodomain of SARS-CoV-2 identified through crystallographic screening and computational docking. *Science Advances*. 2021. PMCID: PMC8046379.
3. Li Q*, Pellegrino J*, Lee DJ, Tran AA, Chaires HC, Wang R, Park JE, Ji K, Chow D, Zhang N, Brilot AF, Biel JT, van Zundert G, Borrelli K, Shinabarger D, Wolfe C, Murray B, Jacobson MP, Mühle E, Chesneau O, **Fraser JS**, Seiple IB. Synthetic group A streptogramin antibiotics that overcome Vat resistance. *Nature*. 2020. PMCID: PMC7546582
4. 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.

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2020- BioCARS P41 Resource, Advisory Board

2019- Faculty Scientist, Molecular Biophysics and Integrated Bioimaging Division, Lawrence Berkeley National Lab
2019- UCSF Biophysics Graduate Program, Associate Director
2018- PHENIX (Python-based Hierarchical ENvironment for Integrated Xtallography), Advisory Board
2018 Protein Society Annual Symposium, Co-Chair
2017- ALS-ENABLE P30 Resource, Deputy Director
2017- Quantitative Biosciences Institute of UCSF, Associate Director
2016- NIH CSR Ad hoc reviewer (Special Emphasis, Fellowships, TR01, DP2, etc)
2016- Relay Therapeutics, Consultant
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 (2017-2020), Vice President (2020-)
2015-2018 Linac Coherent Light Source (XFEL) Proposal Review Panel (BIO-C), Chair
2013- Assistant, Associate (2016), Full Professor (2020), Department of Bioengineering and Therapeutic Sciences, UCSF
2011-2012 QB3 at UCSF Faculty Fellow (Principal Investigator), Department of Cellular and Molecular Pharmacology, UCSF
2007-2012 Author of problems/solutions manual for physical biochemistry textbook "The Molecules of Life" (Garland Science, Authors: John Kuriyan, Boyana Konforti, David Wemmer)

Selected Honors

2020 W.H. and W.L. Bragg Prize (IUCr)
2020 Byers Award in Basic Science (UCSF)
2018 UCSF/Berkeley Sabbatical Exchange Fellowship (Host: Eva Nogales)
2014 Packard Fellow, The David and Lucile Packard Foundation
2014 Searle Scholar, Kinship Foundation
2014 Pew Scholar, Pew Charitable Trusts
2011 Nicholas Cozzarelli Prize for Best Dissertation in Molecular and Cell Biology (UCB)
2011 Forbes 30 under 30 Science
2010 EMBO Short Term Fellowship (Host: Dan Tawfik, Weizmann Institute, Israel)
2010 Warren DeLano Award for Structural Bioinformatics and Computational Biophysics
2007-2010 Natural Sciences and Engineering Research Council (Canada) Doctoral Fellowship
2007-2010 National Science Foundation Graduate Research Fellowship

Contributions 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 (using EMRinger and ensemble modeling) and through integrative approaches to discover new ligand binding sites.
   a. Eshun-Wilson 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. Keedy DA*, Hill ZB*, Biel JT, Kang E, Rettenmaier TJ, Brandao-Neto J, Pearce NM, von Delft F, Wells JA, **Fraser JS**. An expanded allosteric network in PTP1B by multitemperature crystallography, fragment screening, and covalent tethering. *eLife.* 2018. PMCID: PMC6039181.
   c. 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.

d. Barad BA, Echols N, Wang RY, Cheng Y, DiMaio F, Adams PD, **Fraser JS**. EMRinger: Side-chain-directed model and map validation for 3D Electron Cryomicroscopy. *Nature Methods*. 2015. PMCID: PMC4589481.

2. **Determining structures that influence microbial interactions**. I have a longstanding interest in microbiology, beginning from my undergraduate work with Alan Davidson (Toronto) on bacteriophage structure prediction that led to the surprising discovery of a class of mobile immunoglobulin domains. I have collaborated with the Zusman lab (UC Berkeley) to determine the structure of FrzS, a key signaling regulator of Myxococcus xanthus, with the Fischbach lab (Stanford) to determine how the gut microbiome produces the neurotransmitter tryptamine, and with the Tawfik lab (Weizmann Institute, Israel) to determine the role of epistasis in restricting antibiotic resistance mutations and the surprising assembly of counter-enzyme complexes. We are expanding this interest to include the interaction of human enzymes in degrading chitin molecules that can cause inflammation in the context of allergy and asthma (in collaboration with Richard Locksley and structure-based antibiotic design using cryoEM (in collaboration with Ian Seiple and Danica Fujimori).
   a. Tsai K, Stojković V, Lee DJ, Young ID, Szal T, Vazquez-Laslop N, Mankin AS, **Fraser JS,** Fujimori DG. Structural basis for context-specific inhibition of translation by oxazolidinone antibiotics. *BioRxiv* 455846 [**Preprint**]. August 10, 2021. Available from: https://doi.org/10.1101/2021.08.10.455846.
   b. Jayaraman V, Lee DJ, Elad N, Vimer S, Sharon M, **Fraser JS**, Tawfik DS. A counter-enzyme complex regulates glutamate metabolism in Bacillus subtilis. *Nat Chem Biol.* 2021. NIHMSID: NIHMS1747948
   c. Barad BA, Liu L, Diaz RE, Basillo R, Van Dyken SJ, Locksley RM, **Fraser JS**. Dissecting the chitinolytic activity of mammalian chitinases. *Protein Science*. 2020. PMCID: PMC7096708
   d. **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.

3. **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, the positioning of crucial water molecules in the flu ion channel M2, and the outcomes of protein design.
   a. Otten R*, Liu L*, Kenner LR, Clarkson MW, Mavor D, Tawfik DS, Kern D, **Fraser JS.** Rescue of conformational dynamics in enzyme catalysis by directed evolution. *Nature Communications.* 2018. PMCID: PMC5883053.
   b. Keedy DA*, Kenner LR*, Warkentin M*, Woldeyes RA*, et al, van den Bedem H, Thorne RE**, Fraser JS**. Mapping the Conformational Landscape of a Dynamic Enzyme by XFEL and Multitemperature Crystallography. *eLife*. 2015. PMCID: PMC4721965.
   c. **Fraser JS**, van den Bedem H, Samelson AJ, Lang PT, Holton JM, Echols N, Alber T. Accessing protein conformational ensembles by room-temperature X-ray crystallography. *PNAS*. 2011. PMCID: PMC3182744.
   d. **Fraser JS**, Clarkson MW, Degnan SC, Erion R, Kern D, Alber T. Hidden alternative structures of proline isomerase essential for catalysis. *Nature*. 2009. PMCID: PMC2805857.

4. **Developing new X-ray diffuse and time-resolved scattering experiments to probe correlated motions in proteins**. A major limitation of most biophysical techniques is the inability to directly reveal correlations in motions between distinct regions of macromolecules. Diffuse scattering has the potential to reveal these motions; however, we currently lack the ability to collect, integrate, and refine diffuse scattering data. Our long-term goal is to increase the information content of every X-ray diffraction experiment to reveal atomic level coupling at high resolution and improved models of

grouped flexibility at low resolution. We are also taking advantage of the new capabilities of next-generation X-ray free electron laser (X-FEL) light sources to perform radiation damage-free imaging of proteins and to watch how protein ensembles respond when perturbed by rapid temperature jumps using the X-FEL.

a. Dasgupta M, et al, **Fraser JS**, Wall ME, van den Bedem H, Wilson MA. Mix-and-inject XFEL crystallography reveals gated conformational dynamics during enzyme catalysis. *PNAS*. 2019. PMCID: PMC6926069
b. Thomaston JL, Woldeyes RA, et al, **Fraser JS**, DeGrado WF. XFEL structures of the influenza M2 proton channel: Room temperature water networks and insights into proton conduction. *PNAS*. 2017. PMCID: PMC5754760
c. Van Benschoten AH, Liu L, Gonzalez A, Brewster AS, Sauter NK, **Fraser JS**, Wall ME. Measuring and modeling diffuse scattering in protein X-ray crystallography. *PNAS*. 2016. PMCID: PMC4839442.
d. 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. *PNAS*. 2014. PMCID: PMC4273327.

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. Gordon DE, et al (~80 collaborators), **Fraser JS**, Gross JD, Sali A, Roth BL, Ruggero D, Taunton J, Kortemme T, Beltrao P, Vignuzzi M, García-Sastre A, Shokat KM, Shoichet BK, Krogan NJ. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* 2020. PMCID: PMC7431030
   b. Braberg H, Echeverria I, Bohn S, Cimermancic P, Shiver A, Alexander R, Xu J, Shales M, Dronamraju R, Jiang S, Dwivedi G, Bogdanoff D, Chaung KK, Hüttenhain R, Wang S, Mavor D, Pellarin R, Schneidman D, Bader JS, **Fraser JS**, Morris J, Haber JE, Strahl BD, Gross CA, Dai J, Boeke JD, Sali A, Krogan NJ. Genetic interaction mapping informs integrative structure determination of protein complexes. *Science*. 2020. PMCID: PMC7946025.
   c. Mavor D, et al (~30 student authors), **Fraser JS**. Determination of Ubiquitin Fitness Landscapes Under Different Chemical Stresses in a Classroom Setting. *eLife*. 2016. PMCID: PMC4862753
   d. Braberg H, et al, **Fraser JS**, Holstege FC, Hieter P, Guthrie C, Kaplan CD, Krogan NJ. From structure to systems: high-resolution, quantitative genetic analysis of RNA polymerase II. *Cell*. 2013. PMCID: PMC3932829

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/james.fraser.1/bibliography/public/

BIOGRAPHICAL SKETCH

NAME: Andrew N. Goldberg

eRA COMMONS USER NAME (credential, e.g., agency login): ANGOLDBERG

POSITION TITLE: Professor; Research Investigator

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	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 Surgery
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
Univeristy of Pennsylvania, Philadelphia, PA	MSCE	2003	Clinical Epidemiology

Ongoing and recently completed projects:

P01 HL107202
Fahy (PI)
07/01/19-03/31/24
Exploring the biology of persistent type 2 airway niches in asthma

R15 AI147148
Cope/Caporaso (MPI)
07/01/19-06/30/22
Determining the Role of the Upper and Lower Airway Microbiota as Drivers of Concomitant Inflammatory Responses in patients with Chronic Rhinosinusitis and Asthma

R01 AG062562
Geschwind (PI)
08/01/19-07/31/24
Tracking longitudinal change in presymptomatic genetic prion disease (TLC-Pre-gPrD)

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

1990-1992 Instructor, Otolaryngology - Head and Neck Surgery. Washington University School of Medicine. St. Louis, MO
1992-1993 Assistant Professor, Otolaryngology - Head and Neck Surgery. Washington University School of Medicine. St. Louis, MO

1993-2000	Assistant Professor, Otolaryngology - Head and Neck Surgery. University of Pennsylvania Medical School. Philadelphia, PA
1993-2000	Surgical Director, Penn Center for Sleep Disorders. University of Pennsylvania Medical School. Philadelphia, PA
2000-2006	Associate Professor, Otolaryngology - Head and Neck Surgery. University of California, San Francisco. San Francisco, CA
2004-Present	Director, Division of Rhinology and Sinus Surgery, Otolaryngology - Head and Neck Surgery. University of California, San Francisco. San Francisco, CA
2006-Present	Professor, Otolaryngology - Head and Neck Surgery. University of California, San Francisco. San Francisco, CA
2007-Present	Professor, Neurological Surgery. University of California, San Francisco. San Francisco, CA

Selected 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 Award, UCSF, Otolaryngology - Head and Neck Surgery

Contributions to Science

1. At present, my principle interest in research involves the application of basic science techniques in determining the causes of and treatment for chronic sinusitis and asthma. I have been involved in a number of research efforts that characterize inflammation and the microbial flora in the sinuses and lungs. We initally assembled a multidisciplinary team and hired Dr. Emily Cope to help develop this area of research. Our research collaboration has evolved to include basic scientists, rhinology faculty as well as faculty from microbiology, immunology and pulmonology**.** I am presently a co-investigator on a program project grant to study type II inflammation in the sinues and lungs. 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.
    e. Lee K, Pletcher SD, Lynch SV, **Goldberg AN**, Cope EK. Heterogeneity of Microbiota Dysbiosis in Chronic Rhinosinusitis: Potential Clinical Implications and Microbial Community Mechanisms Contributing to Sinonasal Inflammation. Front Cell Infect Microbiol. 2018 May 23;8:168.
    f. Pletcher SD, **Goldberg AN**, Cope EK. Loss of Microbial Niche Specificity Between the Upper and Lower Airways in Patients With Cystic Fibrosis. Laryngoscope. 2019 Mar 129(3):544-550.

2. 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.

Complete List of Published Work in MyBibliography:
https://pubmed.ncbi.nlm.nih.gov/?term=goldberg+an&sort=pubdate

BIOGRAPHICAL SKETCH

NAME: Erin Duncan Gordon, M.D.

eRA COMMONS USER NAME (credential, e.g., agency login): egordon1

POSITION TITLE: Sandler Distinguished Professor, Dept. of Medicine, University of California, San Francisco

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of California, Berkeley	BA	05/2001	Molecular and Cell Biology
University of Southern California	MD	05/2005	Medicine
University of California, San Diego		06/2007	Internal Medicine
University of California, San Francisco		06/2010	Pulmonary and Critical Care

Ongoing and recently completed projects:

R01 AI136962
Gordon (PI)
01/15/18-12/31/22
Understanding the Molecular Genetic Mechanisms of Asthma Risk Loci: IL33, IL1RL1, and GSDMB

P01 HL107202
Fahy (PI), Role: Co-I
09/01/19-05/31/24
Exploring the Biology of Persistent Type 2 Airway Niches in Asthma
ILC2 and Epithelial Cell Heterogeneity and Self-Sustaining Type 2 Airway Niches in Asthma (Sub-Project 1)

Highlighted Citations:

1. **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
2. **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
3. **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

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2017 – Present	Assistant Professor, Pulmonary, Critical Care, Allergy and Sleep Medicine, Sandler Asthma Basic Research Center, UCSF
2012 – 2017	Assistant Professor, Pulmonary, Critical Care, Allergy and Sleep Medicine, UCSF
2011 – 2012	Clinical Instructor, Pulmonary, Critical Care, Allergy and Sleep Medicine, UCSF
2009 – 2011	Research Fellow, Pulmonary, Critical Care, Allergy and Sleep Medicine, UCSF
2007 – 2008	Clinical Fellow, Pulmonary, Critical Care, Allergy and Sleep Medicine, UCSF
2005 – 2007	Resident Physician, Internal Medicine, UC San Diego

Selected Honors

2011	Ruth L. Kirschstein National Research Service Award
2005	American Medical Association Student Achievement Award – first ranked student, Class of 2005 USC SOM
2005	American Medical Women's Association Janet M. Glasgow Memorial Award – first ranked female student, Class of 2005 USC SOM
2005	Summa cum Laude, Keck School of Medicine, USC
2005	Merck Manual Award – awarded to the four highest ranking students in the basic sciences at USC SOM
2004	Alpha Omega Alpha, Gamma Chapter, Keck School of Medicine, USC – elected as a junior
2002 – 2005	Dean's Scholar – awarded to top 10% of students each year of medical school
2001 – 2005	Recipient of merit-based full tuition scholarship at Keck School of Medicine, USC
2001	Grace Fimognari Memorial Award – awarded to the highest achieving graduate in Molecular & Cell Biology, Biochemistry, University of California, Berkeley
2001	Phi Beta Kappa, University of California, Berkeley
2001	Graduate with Honors, University of California, Berkeley – awarded for undergraduate research thesis

Professional Societies

American Thoracic Society

Board Certification

2011	American Board of Internal Medicine, Critical Care Medicine
2010	American Board of Internal Medicine, Pulmonary Medicine
2008	American Board of Internal Medicine

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 who 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 Immunol, 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.

BIOGRAPHICAL SKETCH

NAME: Kotas, Maya

eRA COMMONS USER NAME (credential, e.g., agency login): mkotas

POSITION TITLE: Assistant Professor of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Yale University, New Haven, CT	BS	05/2005	Biomedical Engineering
Yale University, New Haven, CT	MS, M Phil	12/2009	Immunobiology
Yale University, New Haven, CT	PhD	05/2012	Immunobiology
Yale University, New Haven, CT	MD	05/2013	Medicine
New York Presbyterian – Columbia University, New York, NY	Residency	06/2015	Internal Medicine
University of California, San Francisco, CA	Fellowship	06/2018	Pulmonary & Critical Care
University of California, San Francisco, CA	Postdoctoral	06/2020	Immunology

Ongoing and recently completed projects:

Nina Ireland Program in Lung Health
Kotas (PI)
01/04/22-01/03/24
Understanding the Role of Airway Tuft Cells in Mucociliary Clearance in Cystic Fibrosis

A.P. Giannini Foundation
Kotas (PI)
07/01/20-06/30/23
Characterization of the type 2 immune circuit that regulates airway epithelial remodeling

F32 HL140868
Kotas (PI)
01/01/18-06/30/20
Role of ILC2s in lung maintenance and repair

Highlighted Citations:

1. **Kotas ME**, Medzhitov RM. (2015). Homeostasis, Inflammation, and Disease Susceptibility. Cell. 160(5):816-827. PMCID: PMC4369762
2. **Kotas ME**, Locksley RM. (2018). Why Innate Lymphoid Cells? Immunity 48(6): 1081-1090. PMCID: PMC6145487

3. **Kotas ME**, Dion J, Van Dyken, S, Ricardo-Gonzalez RR, Danel CJ, Taille C, Mouthon L, Locksley RM, Terrier B. (2021). A role for IL-33-activated ILC2s in eosinophilic vasculitis. JCI Insight 6(12)e143366. (doi: 10.1172/jci.insight.143366) PMCID: PMC8262498
4. **Kotas ME**, Mroz NM, Koga S, Liang HE, Schroeder AW, Ricardo-Gonzalez RR, Schneider C, Locksley RM. (2021). CISH constrains the tuft–ILC2 circuit to set epithelial and immune tone. Mucosal Immunology (doi: 10.1038/s41385-021-00430-6) PMID: 34290377

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2020 - present	Assistant Professor of Medicine, Div. of Pulmonary, Critical Care, Allergy and Sleep, UCSF
2020 - 2023	Fellow, A.P. Giannini Foundation
2020 - present	Attending Physician, COVID ICU, Zuckerberg San Francisco General Hospital
2020	Attending Physician, COVID ICU, New York Presbyterian—Cornell University
2020 - present	Attending Physician, Medical and Neurologic ICUs, Moffitt-Long Hospital, UCSF
2019 - present	Certification in Critical Care Medicine, American Board of Internal Medicine
2018 - 2020	HS Clinical Instructor, Division of Pulmonary and Critical Care Medicine, UCSF
2018 - present	Certification in Pulmonary Medicine, American Board of Internal Medicine
2017 - 2020	Postdoctoral Research Fellow, Laboratory of Richard Locksley, UCSF
2015 - 2018	Clinical Fellow, Division of Pulmonary and Critical Care Medicine, UCSF
2015 - 2020	Member, California Thoracic Society
2015 - 2020	Member, American Thoracic Society
2015 - present	Member, Physician and Surgeon Certificate, Medical Board of California
2015 - present	Diplomate, American Board of Internal Medicine
2013 - 2013	Resident Physician, New York Presbyterian – Columbia University Medical Center
2005 - 2013	Medical Scientist Training Program, Yale University
2008 - 2010	Teaching Fellow, “Human Biology”, Yale University

Selected Honors

2019	Above and Beyond Award, San Mateo Medical Center
2013	Marguerite Rush Lerner Writing Contest winner, Yale University
2013	Selma & Karl Folkers Prize in Biomedical Research, Yale University
2005	B.S. awarded cum laude, with Distinction in Biomedical Engineering, Yale University
2005	Allan D. Bromley Prize in Engineering, Yale University
2004	Member, Tau Beta Pi

Contributions to Science

1. Role of the immune system in regulating whole body metabolism: As a graduate student in Ruslan Medzhitov’s lab, I focused on the role of the immune system in diverse aspects of health and disease. In three first author publications, I reported on an iNKT-independent role for CD1d in lipid metabolism, a role for caspase-1 in orchestrating hepatic triglyceride flux, and a mechanism by which overnutrition leads to inflammation via Sirtuin-1. These studies helped to propel the field of immunometabolism and elucidate roles for the immune system that extend beyond immunity to microbes.
   a. **Kotas ME**, Lee H-Y, Gillum MP, Annicelli C, Guigni BA, Shulman GI, Medzhitov R. (2011) Impact of CD1d Deficiency on Metabolism. *PLoS ONE* 6(9): e25478. doi:10.1371/journal.pone.0025478. PMCID: PMC3183002.
   b. Gillum MP*, **Kotas ME***, Erion DM*, Kursawe R, Chatterjee P, Nead KT, Muise ES, Hsiao JJ, Frederick DW, Yonemitsu S, Banks AS, Qiang L, Bhanot S, Olefsky JM, Sears DD, Caprio S,

Shulman GI. (2011) SirT1 Regulates Adipose Tissue Inflammation. *Diabetes*. 60(12): 3235-45. PMCID: PMC3219953. ***equal contribution**.

c. **Kotas ME**, Jurczak MJ, Annicelli C, Gillum MP, Cline GW, Shulman GI, Medzhitov R. (2013) Role of caspase-1 in regulation of triglyceride metabolism. *Proc Natl Acad Sci*. 110(12): 4810-15. PMCID: PMC3607017.

d. Erion DM, Kotas ME, McGlashon J, Yonemitsu S, Hsiao JJ, Nagai Y, Iwasaki T, Murray SF, Bhanot S, Cline GW, Samuel VT, Shulman GI, Gillum MP. (2013) cAMP-responsive element-binding protein (CREB)-regulated transcription coactivator 2 (CRTC2) promotes glucagon clearance and hepatic amino acid catabolism to regulate glucose homeostasis. J Biol Chem. 288(22): 16167-76.

2. Innate type 2 defense of the mucosal barrier: Since joining the Locksley lab in January of 2017, I have explored type 2 biology at mucosal barriers, with a focus on the airway. I have leveraged the core expertise of the Locksley laboratory to study interactions between tuft cells and ILC2s in the airway—as well as exploring other tissue systems and disease models to understand key principles of mucosal immunity and of the biology of rare epithelial cell types. A close interaction between tuft cells and ILC2s is now well-described in intestinal tissue, but understanding of their biology in the airway is comparatively poor. My synthesis of the current body of literature on tuft cells and my own preliminary findings in this area are the basis for my current proposal. A manuscript that incorporates many of the preliminary data presented in this proposal and relates to the abstract listed in (B) has been submitted for peer review, and an invited review on tuft cell biology (Annual Review of Pathology) is in preparation.

   a. **Kotas ME**, Terrier B, Cope E, Goldberg A, Pletcher S, Seibold M, Moore C, Gordon E, Locksley RM. Development and Function of Airway Tuft Cells in Health and Disease. *American Thoracic Society.* May 17-22, 2019. (abstract).

   b. Roberto-Gonzalez RR, Kotas ME, Tenvooren I, Marquez DM, Fassett MS, Lee J, Daniel SG, Bittinger K, Diaz RE, Fraser JS, Ansel KM, Spitzer MH, Liang HE, Locksley RM. Type 2 innate immunity regulates hair follicle homeostasis to control Demodex pathosymbionts. BioRxiv [Preprint] March 30, 2021 (doi: 10.1101/2021.03.29.437438) *under revision after peer review.

   c. **Kotas ME**, Dion J, Van Dyken, S, Ricardo-Gonzalez RR, Danel CJ, Taille C, Mouthon L, Locksley RM, Terrier B. (2021) A role for IL-33-activated ILC2s in eosinophilic vasculitis. *JCI Insight* 6(12)e143366. (doi: 10.1172/jci.insight.143366) PMCID: PMC8262498.

   d. **Kotas ME**, Mroz NM, Koga S, Liang HE, Schroeder AW, Ricardo-Gonzalez RR, Schneider C, Locksley RM. (2021) CISH constrains the tuft–ILC2 circuit to set epithelial and immune tone. *Mucosal Immunology* (doi: 10.1038/s41385-021-00430-6) PMCID: PMC8528700.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1nE-cp1KGPFAk/bibliography/public/

BIOGRAPHICAL SKETCH

NAME: Krummel, Matthew F.

eRA COMMONS USER NAME (credential, e.g., agency login): Krummel

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Illinois High School, Urbana, Illinois		06/1985	
University College, London, England	Exchange Student	06/1988	Department of Chemistry
University of Illinois, School of Liberal Arts and Sciences	BS	06/1989	Honors Biology and. Chemistry.
University of California at Berkeley, Department of Molecular and Cell Biology	PhD	06/1995	Immunology

Ongoing and recently completed projects:

R01 CA197363
Krummel (PI)
03/15/17-02/28/22
Anti-Tumor Mechanisms of Intratumoral Stimulatory Dendritic Cells

R01 AI52116
Krummel (PI)
01/01/18-12/31/22
Spatiotemporal Control of T Cell Synapse Stabilization and Signaling

Highlighted Citations:

1. **Looney MR**, Thornton EE, Sen D, Lamm WJ, Glenny RW, **Krummel MF**. Stabilized imaging of immune surveillance in the mouse lung. Nat Methods 8(1):91-96, 2011. PMCID: PMC3076005.
2. Headley MB, Bins A, Nip A, Roberts EW, **Looney MR**, Gerard A, **Krummel MF**. Visualization of immediate immune responses to pioneer metastatic cells in the lung. Nature 531(7595):513-517, 2016. PMCID: PMC4892380
3. Lefrançais E, Ortiz-Muñoz G, Caudrillier A, Mallavia B, Liu F, Sayah DM, Thornton EE, Headley MB, David T, Coughlin SR, **Krummel MF**, Leavitt AD, Passegué E, **Looney MR**. The lung is a site of platelet biogenesis and a reservoir for haematopoietic progenitors. Nature 544(7648):105-109, 2017. PMCID: PMC5663284
4. Combes AJ, Courau T, Kuhn NF, Hu KH, Ray A …**Looney MR**,…**Krummel MF**. Global absence and targeting of protective immune states in severe COVID-19. Nature 591(7848):124-130, 2021. PMID: 33494096

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2018-present	Co-Founder and Inaugural Chair, ImmunoX Initiative, UCSF
2012-present	Professor, Department of Pathology, UCSF
2006-present	Faculty Director, Biological Imaging Development Center, UCSF
2006-2011	Associate Professor, Department of Pathology, UCSF
2001-2006	Assistant Professor, Department of Pathology, UCSF
1997-2001	Postdoctoral Fellow, HHMI, Stanford University. Advisor: Dr. Mark M. Davis
1996-1997	Postdoctoral Fellow, Dendritic Cell Biology, WEHI, Melbourne Australia. Advisors: Dr. Bill Heath and Dr. Ken Shortman
1989-1996	Graduate Research Assistant, MCB, UC Berkeley. Advisor: Dr. James Allison
1988-1988	Stagiare (Technician), UGM, UGM, Institut Pasteur. Advisors: Dr. Julian Davies
1987-1987	HHMI Summer Fellow, Neurobiology, UTHSC Dallas. Advisor: Dr. Flora Katz

Other Experience and Professional Memberships

2015-2017	Founder and CEO, Pionyr Immunotherapeutics
2008-present	Referee, European Research Council
2008-2009	Member: Board of Scientific Counselors, NIAID
2004-present	Ad hoc reviewer, US-Israeli Binational Science Foundation
2003-present	Ad hoc reviewer, Wellcome Trust
2002-present	Ad hoc member of study sections, NIH: CMIA, TTT, ImmunoOncology.

Selected 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
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

Contributions to Science

1. **An Archetype Theory of Immunobiology, from Cancer to COVID.** In the past eight years, my lab has invested heavily to test the hypothesis of and define the nature of archetypal immunobiology—collections of cells types, linked gene expression and spatial co-localization that define normal and diseased tissues. This includes our hypothesis, in this grant, that skewed myeloid biology alters infection and subsequence immune function, through stabilized feedback loops involved FcRs.
   a. Mujal AM, **Krummel MF**. Immunity as a continuum of archetypes. *Science*. 2019 364(6435):28-29. PMID: 30948539.
   b. Combes AJ, Courau T, Kuhn NF, Hu KH, Ray A … **Krummel MF**. Global absence and targeting of protective immune states in severe COVID-19. Nature. 2021 591(7848):124-130. PMID: 33494096
   c. Combes AJ, Samad B… **Krummel MF**. A Pan-Cancer Census of Dominant Tumor Immune Archetypes. BioRXIV 2021.04.26.441344
   d. 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

2. **Spatial and Real-time Dynamics of Immune Responses in Tissue and Lung.** Using combinations of custom-built multiphoton microscopes and matched stabilization methods, we have been able to understand immune responses directly in vital tissues. This has permitted us to understand normal neutrophil surveillance and the early stages of lung injury and direct antigen uptake, across the epithelium, by alveolar but not airway DC. We adapted and validated what is now called Precision Cut Lung Slices. Recently, we developed methods to 'Zipcode' cells while they are still within tissues for single cell spatial, demonstrating spatial gradients of gene expression in developing tumors and wounds.
   a. Engelhardt, J.J., Boldajipour, B., Beemiller, P., Pandurangi, P., Sorensen, C., Werb, Z., Egeblad, M., **Krummel, M.F**. Marginating Dendritic Cells of the Tumor Microenvironment Cross-Present Tumor Antigens and Stably Engage Tumor-Specific T Cells. Cancer Cell, 2012; 402-417. PMID: 22439936
   b. Looney, M.R., Thornton, E.E., Sen, D., Lamm, W.J., Glenny, R.W., **Krummel, M.F**. 2010. Stabilized imaging of immune surveillance in the mouse lung. Nat Methods. 2010. 8(1):91-6. PMID: 21151136
   c. Headley, M.R., Bins A., Nip A., Roberts E.W., Looney M., Gerard, A., **Krummel, M.F**. Visualization of Immediate Immune Responses to Pioneer Metastatic Cells in the Lung. Nature, 2016.531(7595):513-7. PMID: 26982733
   d. Hu KH, Eichorst JP, McGinnis CS, Patterson DM, Chow ED, Kersten K, Jameson SC, Gartner ZJ, Rao AA, **Krummel MF**. ZipSeq: barcoding for real-time mapping of single cell transcriptomes. Nat Methods., 2020. 17, 833–843. PMID: 32632238

3. **Identification of Reactive Archetypes in Tumor Immunology.** My laboratory has developed mouse models through which to image 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 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 and used the Immunoprofiler pipeline to show phenocopies of these in patient populations.
   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. PMID: 25446897
   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, 2016. PMID: 27424807
   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 24(8):1178-1191. 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 177(3):556-571. PMID: 30955881

4. **T cell sensitivity.** Combining our interest in optics and imaging, we have defined how T cells are so sensitive to antigens and effectively survey tissues—using active microvillar scanning and random-walk migration. We also discovered 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 356(6338)
   b. 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

c. 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
d. 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., 2010. 11, 953-961. PMC2943564

5. **Checkpoint Blockade and Myeloid Tuning.** My work demonstrated that 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 also demonstrated that this same antibody upregulated T cell responses in vivo serving as the method that we applied across multiple mouse models including augmenting anti-tumor immunity. Together with Jim Allison and Dana Leach, we patented CTLA-4 blockade, now 'Checkpoint Blockade' Therapy. The FDA approved anti-CTLA-4, as the first FDA approved 'checkpoint blockade' drug in cancer, in 2011 and this work formed the basis for the 2018 Nobel Prize in Medicine. In 2015, I similarly moved myeloid targets from the TME into a UCSF-associated startup and in 2020 we filed INDs and initiated Phase I trials in cancer patients using anti-TREM1 and anti-TREM2 antibodies we developed.
   a. **Krummel, M.F**. and Allison, J.P. CD28 and CTLA-4 deliver opposing signals which regulate the response of T cells to stimulation. J. Exp. Med., 1995. 182, 459-465
   b. Leach, D.R., **Krummel, M.F**. and Allison, J.P. 1996. Enhancement of antitumor immunity by CTLA-4 blockade. Science, 1996. 271, 1734-1736
   c. **Krummel, M.F**. and Allison, J.P. CTLA-4 engagement inhibits IL-2 accumulation and cell cycle progression upon activation of resting T cells. J. Exp. Med., 1996. 183, 2533-2540
   d. **Matthew Krummel**, Miranda Broz, Denise Wolf, Joshua Pollack, Mikhail Binnewies. Modulation of Stimulatory and Non-stimulatory Myeloid Cells. US Patent 20200017584

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=krummel+mf

BIOGRAPHICAL SKETCH

NAME: Locksley, Richard Michael

eRA COMMONS USER NAME (credential, e.g., agency login): Locksley

POSITION TITLE: Sandler Distinguished Professor, Dept. of Medicine, University of California, San Francisco

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Harvard College, Cambridge, MA	BA	06/1970	Biochemistry
University of Rochester Med, Rochester, NY	MD	06/1976	Medicine
University of California, San Francisco, CA		06/1980	Resident/Chief Resident
University of Washington, Seattle, WA		06/1983	Infectious Diseases Fellow

Ongoing and recently completed projects:

Howard Hughes Medical Institute
Locksley (PI)
09/01/97-08/31/25
Activation of Immunity

R01 AI026918
Locksley (PI)
07/01/88-04/30/23
Parasite Immunity Orchestrated by Type 2 Immune Cells

P01 HL107202
Fahy (PI), Role: Sub-Project 1 PI
08/15/12-07/31/24
Exploring the Biology of Persistent Type 2 Airway Niches in Asthma
ILC2 and Epithelial Cell Heterogeneity and Self-Sustaining Type 2 Airway Niches in Asthma (Sub-Project 1)

Highlighted Citations:

1. Ricardo-Gonzalez R.R., Van Dyken S.J., Schneider C., Lee J., Nussbaum J.C., Liang H-E., Vaka D., Eckalbar W.L., Molofsky A.B., Erle D.J., **Locksley R.M**. (2018). Tissue signals imprint ILC2 identity with anticipatory function. Nat Immunol. 19(10):1093-1099. PMCID: PMC6202223.
2. O'Leary C.E., Schneider C., **Locksley R.M**. (2019). Tuft Cells-Systemically Dispersed Sensory Epithelia Integrating Immune and Neural Circuitry. Annu Rev Immunol. 37:47-72. PMCID: PMC8352721.
3. Schneider C., Lee J., Koga S., Ricardo-Gonzalez R.R., Nussbaum J.C., Smith L.K., Villeda S.A., Liang H-E., **Locksley R.M**. (2019). Tissue-Resident Group 2 Innate Lymphoid Cells Differentiate by Layered Ontogeny and In Situ Perinatal Priming. Immunity. 50(6):1425-1438. PMCID: PMC6645687.

4. Kotas M.E., Moore C.M., Gurrola J.G. II, Pletcher S.D., Goldberg A.N., Alvarez R., Yamato S., Bratcher P.E., Shaughnessy C.A., Zeitlin P.L., Zhang I.H., Li Y., Montgomery M.T., Lee K., Cope E.K., **Locksley R.M.**, Seibold MA, Gordon ED. (2022). IL-13-programmed airway tuft cells produce PGE2, which promotes CFTR-dependent mucociliary function. JCI Insight. 7(13):e159832. PMCID: PMC9310525.

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2017 – Present	Member, National Advisory Committee, Pew Scholars Program in Biomedical Sciences
2016 – Present	Member, Albert Lasker Basic Medical Research Awards Jury
2003 – Present	Director, Sandler Asthma Basic Research Center, UCSF
2002 – 2005	Council, NIAID, National Institutes of Health
1998 – 2001	Member, Chair (2000-01), US-Japan Immunology Board, NIH
1997 – Present	Investigator, Howard Hughes Medical Institute, UCSF
1995 – 2001	Faculty, Assoc. of American Immunology Annual Course, Advanced Immunology
1995 – 2005	Council, Chair (1998), Midwinter Conference of Immunologists, Asilomar
1994 – 1999	Chair, Parasitology Pathogenesis Committee, WHO, Geneva
1991 – 1994	Co-Director, Immunology Section, Biology of Parasitism Course, Woods Hole, MA
1988 – 1993	Member and Chair (1991-93), Tropical Medicine and Parasitology Study Section, NIH
1986 – 2003	Chief, Division of Infectious Diseases, UCSF Medical Center, San Francisco, CA

Editorial Boards

Immunity, J Clin Invest, Immunology & Cell Biology

Selected Honors

2019	Univ of Rochester School of Medicine, Distinguished Alumnus
2019	AAI Distinguished Fellow (inaugural class)
2017	National Academy of Sciences
2017	Fellow, American Academy of Microbiology
2017	Inaugural William Paul Award for Cytokine Research, International Cytokine & Interferon Society
2014	Thomson Reuters ‘Top 1% highly cited researchers in immunology’
2006	R37 MERIT Award, NIAID/NIH
2005	American Academy of Arts & Sciences
2003	Sandler Distinguished Professorship
2003	Inspirational Teacher Award, UCSF class of 2006
2003	Distinguished Service Award, American Association of Immunologists
2001 – 2005	Ellison Medical Foundation Senior Scholar in Global Infectious Diseases
1994	Bailey K Ashford Medal, American Society Tropical Medicine and Hygiene
1994	Association of American Physicians
1992	Fellow, Infectious Diseases Society of America
1992 – 1997	Burroughs Wellcome Fund Scholar in Molecular Parasitology
1991	American Society for Clinical Investigation

Contributions to Science

1. My early work contributed to the discovery of T helper subsets, initially using the model of cutaneous leishmaniasis mediated by L. major in susceptible and resistant mice. Th subsets were discovered in studies of mouse T cell clones by Mosmann and Coffman in 1986, and my studies in 1987 were the first to report that infectious outcomes in vivo were mediated by disparate Th responses. My laboratory

discovered that interventions aimed at discrete cytokines, such as IL-4 and IFN-γ, at early time points following infectious challenges, could profoundly affect disease outcome by altering Th subset differentiation. These studies were extrapolated to multiple infectious and inflammatory diseases and served to coalesce studies targeting cytokines to alter disease outcomes. I was the PI for these studies.

a. **Locksley, R.M.**, Heinzel, F.P., Sadick, M.D., Holaday, B.J., Gardner, K.D. (1987). Murine cutaneous leishmaniasis. Susceptibility correlates with differential expansion of helper T-cell subsets. Ann Inst Pasteur/Immunol, 138:744-49.
b. Heinzel, F.P., Sadick, M.D., Holaday, B.J., Coffman, R.L., **Locksley, R.M.** (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 M.D., Heinzel, F.P., Holaday, B.J., Pu, R.T., Dawkins, R.S., **Locksley, R.M.** (1990). Cure of murine leishmaniasis with anti-IL-4 monoclonal antibody. Evidence for a T cell-dependent, IFN-γ-independent mechanism. J Exp Med, 171:115-27.
d. Reiner S.L., Wang, Z.E., Hatam, F., Scott, P., **Locksley, R.M.** (1993). Th1 and Th2 cell antigen receptors in experimental leishmaniasis. Science, 259:1457-60.

2. Having established critical roles for cytokines in mediating the business of immunity, my laboratory turned to studies of cytokine expression, reasoning that such study might reveal key pathways by which cytokine expression is turned on, off and regulated. We collaborated with the Rubin laboratory at UC Berkeley to further understanding of CNSs, or conserved noncoding sequences, which could be identified by sequence comparisons among many species, and which are now known to identify major enhancer, promoter and boundary elements that regulate cell-specific gene expression. These studies have been extrapolated to understanding major organizational aspects of gene expression in many cell types. I was the PI for all of these studies except for the collaboration with the Rubin laboratory, where I coordinated the immunologic aspects of that study to complement the genetics expertise of the Rubin lab.
    a. Bix M., **Locksley, R.M.** (1998). Independent and epigenetic regulation of the interleukin-4 alleles in CD4+ T cells. Science, 281:1352-54.
    b. Loots G.G., **Locksley, R.M.**, Blankespoor, C.M., Wang, Z-E., Miller, W., Rubin, E.M., Frazer, K.A. (2000). Identification of a coordinate regulator of interleukins 4, 13 and 5 by cross-species sequence comparisons. Science 288:136-40.
    c. Grogan J.L., Mohrs, M., Harmon, B., Lacy, D.A., Sedat, J.W., **Locksley, R.M.** (2001). Early transcription and silencing of cytokine genes underlie polarization of T helper cell subsets. Immunity, 14:205-15.
    d. Mohrs M., Blankespoor, C.M., Wang, Z-E., Loots, G.G., Afzal, V., Hadeiba, H., Shinkai, K., Rubin, E.M., **Locksley, R.M.** (2001). Deletion of a coordinate regulator of type 2 cytokine expression in mice. Nat Immunol, 2:842-47.

3. The regulation of cytokine expression was clearly a key determinant of the immune response, but the field lacked tools to study cytokine expression in situ. To this end, we developed reporter mice that faithfully mimicked cytokine expression in vivo while leaving the endogenous cytokines intact through use of viral IRES elements. These reagents revolutionized the capacity to study the immune system, which previously relied on isolating cells and re-stimulating in vitro. Key discoveries directly attributable to various strains of these mice include the discrete regulation of the duplicated genes, IL-4 and IL-13, in different types of lymphoid cells, including the production of IL-4 by follicular helper T cells; characterization of a tissue checkpoint mediated by epithelial cytokines important in the regulation of allergic immunity; and the identification of innate lymphoid cells that produce these cytokines (see area 4, below). Mouse strains generated in my laboratory are distributed to Jackson Laboratories for use by the scientific community, where they have been utilized in publications worldwide. I was PI for all of these contributions.
    a. Mohrs M., Shinkai, K., Mohrs, H., **Locksley, R.M.** (2001). Analysis of type 2 immunity in vivo with a biscistronic IL-4 reporter. Immunity, 15:303-11.
    b. Reinhardt R.L., Liang, H-E., **Locksley, R.M.** (2009). Cytokine-secreting follicular T cells shape the antibody repertoire. Nat Immunol, 10:385-93. PMCID: PMC2714053.
    c. Liang H-E., Reinhardt, R.L., Bando, J.K., Sullivan, B.M., Ho, I-C., **Locksley, R.M.** (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 S.J., Nussbaum, J.C., Lee, J., Molofsky, A.B., Liang, H-E., Pollack, J.L., Gate, R.E., Haliburton, G.E., Ye, C.J., Marson, A., Erle, D.J., **Locksley, R.M.** (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 located in tissues, where they contribute to early cytokine responses. We were one of three laboratories to call attention to the key role for these cells during biologic responses in vivo in 2010, and uncovered roles for these cells in migratory helminth infection and allergic challenge. My laboratory has investigated the development of these cells during embryogenesis, and their tissue-specific transcriptomic signatures using single-cell RNA sequencing. This continues to be a rapidly advancing field with implications for the understanding of tissue homeostasis and allergic immunopathology. 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 A.E., Liang, H-E., Sullivan, B.M., Reinhardt, R.L., Eisley, C.J., Erle, D.J., **Locksley, R.M.** (2010). Systemically dispersed innate IL-13-expressing cells in type 2 immunity. Proc Natl Acad Sci USA, 107:11489-94. PMCID: PMC2895098
    b. Nussbaum J.C., Van Dyken, S.J., von Moltke, J., Cheng, L.E., Mohapatra, A., Molofsky, A.B., Thornton, E.E., Krummel, M.F., Chawla, A., Liang, H-E., **Locksley, R.M.** (2013). Type 2 innate lymphoid cells control eosinophil homeostasis. Nature, 502:245-248. PMCID: PMC3795960
    c. Ricardo-Gonzalez R.R., Van Dyken, S.J., Schneider, C., Lee, J., Nussbaum, J.C., Liang, H-E., Vaka, D., Eckalbar, W.L., Molofsky, A.B., Erle, D.J., **Locksley, R.M.** (2018). Tissue signals imprint ILC2 identity with anticipatory function. Nature Immunol, 19:1093-9. PMCID: PMC6202223
    d. Schneider C., Lee, J., Koga, S., Ricardo-Gonzalez, R.R., Nussbaum, J.C., Smith, L.K., Villeda, S.A., Liang, H-E., **Locksley, R.M.** (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 epithelia 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 T.A., Liang, H-E., Tager, A.M., Luster, A.D., van Rooijen, N., Voehringer, D., **Locksley, R.M.** (2007). Chitin induces accumulation in tissue of innate immune cells associated with allergy. Nature, 447:92-96. PMCID: PMC2527589
    b. Van Dyken S.J., Liang, H-E., Naikawadi, R.P., Woodruff, P.G., Wolters, P.J., Erle, D.J., **Locksley, R.M.** (2017). Spontaneous chitin accumulation in airways and age-related fibrotic lung disease. Cell, 169:497-509. PMCID: PMC5444468
    c. von Moltke J., Ji, M., Liang, H-E., **Locksley, R.M.** (2016). Tuft cell-derived IL-25 regulates an intestinal ILC2- epithelial response circuit. Nature, 529:221-225. PMCID: PMC4830391
    d. Schneider C., O'Leary, C.E., von Moltke, J., Liang, H-E., Yan Ang, Q., Turnbaugh, P.J., Radhakrishnan, S., Pellizzon, M., Ma, A., **Locksley, R.M.** (2018). A metabolite-triggered tuft cell-ILC2 circuit drives small intestinal remodeling. Cell, 174:271-284. PMCID: PMC6046262

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/richard.locksley.1/bibliography/public/

BIOGRAPHICAL SKETCH

NAME: Molofsky, Ari Benjamin

eRA COMMONS USER NAME: ARIBMOLOSKY

POSITION TITLE: Associate Professor of Laboratory Medicine, University of California San Francisco

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	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	Residency/ Chief / Clinical Fellow	06/2011	Laboratory Medicine/ Hematopathology
University of California, San Francisco	Postdoctoral Fellow	09/2015	Immunology

Ongoing and recently completed projects:

R01 HL142701
Molofsky (PI)
09/01/19-08/31/23
Defining group 2 innate lymphoid cell lung niches.

R01 AI162806
Molofsky (PI)
01/11/22-01/10/27
Localization and function of tissue type 2 lymphocytes during mixed inflammation

UC Tobacco Related Disease Research Program
Molofsky (PI)
11/01/19-10/31/22
Regulation of lung type 2 immunity in tobacco smoke-related allergic asthma

R01 AI150191
Erlebacher (PI), Molofsky (Co-PI)
09/01/19-08/31/24
The IL-33/ILC2 axis in parturition

Highlighted Citations:

1. 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**. (2019). Adventitial stromal cells define group 2 innate lymphoid cell tissue niches. Immunity. PMCID: PMC6553479
2. Cautivo KM, CSteer CA, **Molofsky AB**. (2020). Immune outposts in the adventitia: One foot in sea and one on shore. *Curr. Opin. Immunol.* 64, 34–41
3. **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
4. 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 PMC6070131. *# co-corresponding*

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

1997-1999	Undergrad Research Fellow, Lab of Janice Fischer, PhD, Developmental Genetics, U. of Texas
1999-2007	Medical Scientist Training Program (MSTP), director Ron Koenig MD PhD, U. of Michigan
2001-2005	Graduate Student, Lab of Michele S. Swanson, PhD, U. 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, Depts of Laboratory Medicine, UCSF
2015-	Affiliate Professor, Diabetes Center & Microbiology/Immunology ImmunoX Program, UCSF
2019-	Associate Professor, tenured, UCSF Dept of Laboratory Medicine

Selected Honors

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 Award, International Cytokine & Interferon Society
2019	American Association of Immunology, Travel Award
2019	Nina Ireland Program for Lung Health Award

Professional Experience and Professional Memberships

2007-	College of American Pathologists, Member
2008-	American Society of Hematology (ASH), Member
2009-	Board licensed physician and surgeon, Medical Board of California, Clinical Pathology/Hematopathology
2011-	American Association of Immunologists (AAI), Member
2012-	International Clinical Cytometry Society, Member
2016-	International Cytokine and Interferon Society, Member

Contributions to Science

1. We aim to understand the regulation and function of tissue-resident lymphocytes in multiple systems, including models of normal tissue development and (re)modeling, infection, pathology, and aging. Our group's work has focused on the positive and negative regulation of ILC2s and Th2 lymphocytes, critical cells that organize type 2 'allergic' immune responses. Our studies helped define the regulation and sources of the cytokines IL-33 and IFNγ, and the relationship of tissue ILC2s with regulatory T cells (Treg). We have also defined a novel stromal mesenchymal cell niche for type 2 lymphocytes in multiple tissues that is required for their maintenance and activation. Our ongoing work focuses on understanding the cells and signals that control tissue lymphocytic niches and trafficking, including crosstalk between distinct 'flavors' of lymphocyte-driven immune responses (Cautivo et al, 2021, *Immunity, in press*).
   a. Dahlgren MW, Jones SW, Cautivo KM, Dubinin A, Ortiz-Carpena JF, Farhat S, Yu KS, Lee K, Wang C, Molofsky AV, Tward AD, Krummel MF, Peng T, **Molofsky AB**. Adventitial stromal cells define group 2 innate lymphoid cell tissue niches. *Immunity*, 2019. PMCID: PMC6553479
   b. Wu, D., **Molofsky, A. B**., Liang, H.-E., Ricardo-Gonzalez, R. R., Jouihan, H. A., Bando, J. K., Chawla, A., Locksley, R.M. (2011). Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. *Science*, *332*(6026), 243–247. PMCID: PMC3144160
   c. **Molofsky, A. B**., Nussbaum, J. C., Liang, H.-E., Van Dyken, S. J., Cheng, L. E., Mohapatra, A., Chawla, A., Locksley R.M. (2013). Innate lymphoid type 2 cells sustain visceral adipose tissue eosinophils and alternatively activated macrophages. *Journal of Experimental Medicine*, *210*(3), 535–549. PMCID: PMC3600903
   d. **Molofsky, A.B.**, Van Gool, F., Liang, H.-E., Van Dyken, S.J., Nussbaum, J.C., Lee, J., Bluestone, J.A., and Locksley, R.M. (2015). Interleukin-33 and Interferon-γ Counter-Regulate Group 2 Innate Lymphoid Cell Activation during Immune Perturbation. *Immunity* 43, 1-14. PMCID: PMC4512852

2. We aim to understand how immune cells and cytokines control normal central nervous system (CNS) development and go awry in neuropsychiatric disease. In collaboration with the Anna Molofsky lab, we have uncovered IL-33 as a novel cytokine that regulates microglial function, defining how astrocyte-derived IL-33 promotes microglial activation and neuronal synapse engulfment during CNS development. We have also helped define a hippocampal pathway by which neuronal-derived IL-33 regulates microglial function and extracellular matrix composition, ultimately regulating activity-dependent synapse remodeling. Our ongoing work aims to define how meningeal- and CNS-resident lymphocytes interact in their 'stromal niches' to impact glia and neural circuit formation and remodeling during brain development and CNS damage.
   a. Vainchtein, I.D., Chin, G., Cho, F.S., Kelley, K.W., Miller, J.G., Chien, E.C., Liddelow, S.A., Nguyen, P.T., Nakao-Inoue, H., Dorman, L.C., Akil, O., Joshita, S., Barres, B.A., Paz, J.T., **Molofsky, A.B**.[#], Molofsky, A.V.[#], 2018. Astrocyte-derived interleukin-33 promotes microglial synapse engulfment and neural circuit development. *Science* 359: 1269-1273, PMCID PMC6070131. *# co-corresponding*
   b. Nguyen, P.T., Dorman, L.C., Pan, S., Vainchtein, I.D., Han, R.T., Nakao-Inoue, H., Taloma, S.E., Barron, J.J., **Molofsky, A.B**., Kheirbek, M.A., Molofsky, A.V. (2020). Microglial Remodeling of the Extracellular Matrix Promotes Synapse Plasticity. Cell *182*, 388-403. PMCID: PMC7497728

3. We have engaged in a range of collaborative projects aim to understand the function and diversity of stromal 'niche' cells that regulate resident-lymphocytes in adipose tissue, lung, liver, and brain. We helped characterize the non-redundant roles of the epithelial cytokines IL-33, IL-25, and TSLP in activating lung ILC2s, as well as the contribution of type 2 allergic immunity to adipose tissue metabolic health and disease. We helped define the heterogeneity of tissue ILC2s from multiple organs. Using 3D imaging, we worked to delineate stromal cell heterogeneity and function in lung damage and fibrosis. Together, this collaborative work has advanced our knowledge of the regulation and function of tissue-immune niche interactions.
   a. Cassandras, M., Wang, C., Kathiriya, J., Tsukui, T., Matatia, P., Matthay, M., Wolters, P., **Molofsky, AB,** Sheppard, D., Chapman, H., et al. (2020). Gli1+ mesenchymal stromal cells form a pathological

niche to promote airway progenitor metaplasia in the fibrotic lung. *Nat Cell Biol* 2020 1295-1306. PMCID: PMC7642162.

b. Reyes de Mochel, N., Cheong, K.N., Cassandras, M., Wang, C., Krasilnikov, M., Matatia, P., **Molofsky, AB**, Campisi, J., and Peng, T. (2020). Sentinel p16-INK4a+ cells in the basement membrane form a reparative niche in the lung. BioRxiv 2020.06.10.142893.

c. Nussbaum JC, Van Dyken SJ, von Moltke J, Cheng LE, Mohapatra A, **Molofsky AB**, Thornton EE, Krummel MF, Chawla A, Liang HE, Locksley RM. (2013) Type 2 innate lymphoid cells control eosinophil homeostasis. *Nature* 502**,** 245–248. PMCID: PMC3795960

d. Ricardo-Gonzalez, R.R., Van Dyken, S.J., Schneider, C., Lee, J., Nussbaum, J.C., Liang, H.-E.E., Vaka, D., Eckalbar, W.L., **Molofsky, A.B.,** Erle, D.J., et al. (2018). Tissue signals imprint ILC2 identity with anticipatory function. *Nat Immunol 19*, 1093–1099. PMCID: PMC6202223

4. *L. pneumophila* is a model intracellular bacterium that alternates between an intracellular replicating phase and a transmissible 'virulent' phase and is causative agent of Legionnaire's disease. My graduate work in the laboratory of Michele S. Swanson focused on the molecular mechanisms regulating *Legionella pneumophila* replication and virulence. I discovered that flagellin, the major protein that comprises the flagellum, is the key cytoplasmic pathogen associated molecular pattern (PAMP) that macrophages recognize to restrict *L. pneumophila* replication. My work on macrophage innate recognition of flagellin was a seminal early work that helped launch the field of inflammasome biology and the study of pyroptotic cell death.

   a. **Molofsky, A.B.,** & Swanson, M.S. (2003). Legionella pneumophila CsrA is a pivotal repressor of transmission traits and activator of replication. *Mol Microbiol*, *50*(2), 445–461.

   b. **Molofsky, A.B.,** Shetron-Rama, L.M., & Swanson, M.S. (2005). Components of the Legionella pneumophila flagellar regulon contribute to multiple virulence traits, including lysosome avoidance and macrophage death. *Infection and immunity*, *73*(9), 5720–5734. PMCID: PMC1231111

   c. **Molofsky, A. B.,** Byrne, B. G., Whitfield, N. N., Madigan, C. A., Fuse, E. T., Tateda, K., & Swanson, M. S. (2006). Cytosolic recognition of flagellin by mouse macrophages restricts Legionella pneumophila infection. *The Journal of experimental medicine*, *203*(4), 1093–1104. PMCID: PMC1584282

5. As a Clinical Pathologist with specialization in Hematopathology, 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.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/14AY37wr6bCAj/bibliography/public/

BIOGRAPHICAL SKETCH

NAME: Dean Sheppard

eRA COMMONS USER NAME (credential, e.g., agency login): sheppard

POSITION TITLE: Professor of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Harvard College, Cambridge, MA	AB	06/1972	Social Studies
SUNY at Stony Brook, Stony Brook, NY	MD	06/1975	Medicine
Univ of Washington, Seattle, WA	Resident	06/1978	Internal Medicine
Univ of California, San Francisco, San Francisco	Fellow	06/1981	Pulmonary

Ongoing and recently completed projects:

R01 HL142568
Sheppard (PI)
04/01/20-03/31/24
Fibroblast heterogeneity in pulmonary fibrosis

R01 HL145037
Sheppard/Papa (MPI)
01/15/19-12/31/22
Interventional Targeting of the IRE1alpha-TGFbeta signaling loop in pulmonary fibrosis

R01 DK125858
Reiser (PI), Role: Subcontract PI
07/01/20-06/30/25
suPAR and renal fibrosis

ShangPharma Innovation, Inc
De Grado/Sheppard (MPI)
11/01/20-11/01/21
Inhibitors of Integrin Alpha 2 Beta 1 and Methods of Use

T32 HL007185
Sheppard/Erle/Huang (MPI)
07/01/12–06/30/22
Multidisciplinary training program in lung disease

UCSF Pfizer CTI Program
Sheppard (PI)
12/07/12-11/30/21
Targeting the $\alpha v\beta 8$ integrin for tumor immunotherapy

AbbVie Sponsored Research Agreement
Sheppard (PI)
08/15/14- 04/01/21
Characterizing molecular diversity of renal and hepatic fibroblasts in the setting of tissue fibrosis

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2009-present	Chief, Pulmonary, Critical Care, Allergy and Sleep Division, UCSF
1999-2004	Acting Director, Sandler Basic Asthma Research Center, UCSF
1997-2009	Associate Chair for Biomedical Research, Department of Medicine, UCSF
1992-present	Professor of Medicine, UCSF
1987-1992	Associate Professor of Medicine, UCSF
1986-present	Director, Lung Biology Center, UCSF
1981-1987	Assistant Professor of Medicine, University of California, San Francisco (UCSF)

Other Experience

2006-2009	Scientific Advisory Board, Parker B. Francis Foundation
2006-2008	Chair, Lung Injury and Repair Study Section
2004-present	Chair, OSMB, NHLBI Lung Tissue Consortium
2004-2008	Member, Lung Injury and Repair Study Section
2003-present	Editorial Board, Journal of Clinical Investigation
2000-2002	Chair, NHLBI Program Project Review Committee
1998-2002	Member, NHLBI Program Project Review Committee
1996-2007	Editorial Board, American Journal of Physiology; Lung Cell and Molecular Biology
1995-2002	Associate Editor, American Journal of Respiratory Cell and Molecular Biology

Selected Honors

2021	Elected Fellow, American Association for the Advancement of Science
2021	Lifetime Achievement in Mentoring Award, UCSF
2019	Christopher Spilios Memorial Lecture, Brigham and Women's Hospital
2017	Elected Member, American Academy of Arts and Sciences
2016	UCSF Faculty Lecture, Translational Science
2014	Harold and Marilyn Menkes Memorial Lectureship, Johns Hopkins University
2013	Listed as one of top 20 translational scientists in the world by Nature Biotechnology
2012	Frank Austen Visiting Professor, Brigham and Woman's Hospital
2010	McClennan Lecturer, University of Iowa
2007	Amberson Lecturer, American Thoracic Society
2006	Kass Medal, University of Nebraska
2005	McClement Lecturer, New York University
2004-2014	Robert Johnston Lecturer, Drexel University
2001	NIH Merit Award
2000	Roger Mitchell Lecturer, Aspen Lung Conference
1998	Jerome I. Flance Visiting Professor, Washington University
1996	Lifetime Scientific Achievement Award, American Thoracic Society

1995 Parker B. Francis Lecturer, Aspen Lung Conference
1995 Clean Air Award, American Lung Association of California
1992 Elected Member, Association of American Physicians
Elected Member, American Society for Clinical Investigation

Contributions 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. PMCID329638
    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. PMCID2462379

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. PMCID 2365683
    b. Busk M, Pytela R, **Sheppard D**. Characterization of the integrin $\alpha v\beta 6$ as a fibronectin-binding protein. J Biol Chem 1992; 267:5790-96. PMCID: 1532572
    c. Palmer EL, Rüegg C, Ferrando R, Pytela R, **Sheppard D**. Sequence and tissue distribution of the integrin $\alpha 9$ subunit, a novel partner of $\beta 1$ that is widely distributed in epithelia and muscle. J Cell Biol 1993; 123(5):1289-97. PMCID: 2119880
    d. Yokosaki Y, Palmer EL, Prieto AL, Crossin KL, Bourdon MA, Pytela R, **Sheppard D**. The integrin $\alpha 9\beta 1$ 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 and genome wide expression analysis 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, αvβ5 and αvβ1 integrins that are in various stages of clinical development for treatment of fibrotic diseases, acute lung injury and for tumor immunotherapy

a. Munger JS, Huang XZ , Kawakatsu H , Griffiths MJD, Dalton SL, Wu JF, Pittet JF, Kaminiski N, Garat C, Matthay MA, Rifkin DB, **Sheppard D**. The integrin αvβ6 binds and activates latent TGFβ1: a mechanism for regulating pulmonary inflammation and fibrosis. Cell 1999; 96:319-328. PMID: 10025398
b. Morris DG, Huang X, Kaminski N, Wang Y, Shapiro SD, Dolganov G, Glick, A, **Sheppard D**. Loss of integrin αvβ6-mediated TGFβ activation causes Mmp12-dependent emphysema. Nature 2003 422:169-173. PMID: 12634787
c. Travis MA, Reizis B, Melton AC Masteller E, Tang Q, Proctor J, Wang Y, Bernstein X, Huang X, Riechardt L, Bluestone J, **Sheppard D**. Loss of integrin αvβ8 on dendritic cells causes autoimmunity and colitis in mice. Nature 2007 449:361-365. PMCID: 2670239
d. Sundaram A, Chen C, Khalifeh-Soltani A, Atakilit A, Qiu W, Jo H, DeGrado W, Huang X, **Sheppard D**. Integrin alpha5beta1 as a novel target for airway hyperresponsiveness in asthma J. Clin Invest 2017 127:365-374 PMCID: 5199700

4. Having identified an integrin (αvβ6) that played an important role in activating TGFβ only in close proximity to contracting epithelial cells, we sought to determine whether there were other integrins that could also activate this growth factor in other contexts. We found that the αvβ8 integrin is an important activator of TGFβ in the context of antigen presentation by dendritic cells and that this process is essential for the generation of Th17 cells. Using mice we generated specifically lacking this integrin in dendritic cells we identified important roles for this process in models of multiple sclerosis and allergic asthma. We have subsequently found that there is another αv integrin on activated fibroblasts (αvβ1) that is critical to pathologic fibrosis in the lungs, liver and kidney. This work has led us to appreciation of the importance of multiple αv-containing integrins as potential therapeutic targets in a variety of immune-mediated and fibrotic diseases. This work also led us to further explore the mechanisms underlying fibrosis by using scRNAseq to identify novel populations of fibroblasts that play important roles in lung homeostasis and pathologic fibrosis.

a. Henderson NC, Arnold TD, Katamura Y, Giacomini MM, Rodriguez JD, McCarty JH, Ruminski PG, Griggs DW, Maher JJ, Iredale JP, Lacy-Hulbert A, Adams RH, **Sheppard D**. Selective αv integrin deletion identifies a core, targetable molecular pathway that regulates fibrosis across solid organs. Nature Medicine 2013 19:1617-1624 NIHMS495176, PMCID:3855865.
b. Reed NI, Jo H, Chen C, Tsujino K, Arnold TD, DeGrado WF, **Sheppard D**. The αvβ1 integrin plays a critical in vivo role in tissue fibrosis. Science Translational Medicine 2015 7:288-294. PMCID: 4461057
c. Arnold T, Lizama CO, Cautivo KM, Lin L, Qui H, Huang E, Lui C, Mukouyama Y, Reichardt L, Zovein AC, **Sheppard D**. Microglial dysmaturation and developmental neuromotor dysfunction result from impaired alphavbeta8-TGFbeta signaling J. Exp Med. 2019 216:900-915 PMCID: 6446869
d. Tsukui T, Sun K-H, Wetter JB, Wilson-Kanamori JR, Hazelwood LA, Henderson NC, Adams TS, Schupp JC, Poli SD, Rosas IO, Kaminski N, Matthay MA, Wolters PJ, **Sheppard D**. Collagen-producing lung cell atlas identifies multiple subsets with distinct localization and relevance to fibrosis Nature Communications, 2020:11:1920. PMCID: 7174390

A full listing of my publications is available at:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/41543684/?sort=date&direction=descending
http://profiles.ucsf.edu/dean.sheppard

BIOGRAPHICAL SKETCH

NAME: Sundaram, Aparna B

eRA COMMONS USER NAME (credential, e.g., agency login): asundaram

POSITION TITLE: Assistant Professor of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Northwestern University, Evanston IL	BS	06/2003	Biomedical Engineering
Northwestern University, Chicago IL	MD	06/2006	Medicine
Northwestern University, Chicago IL		06/2007	Internship
Northwestern University, Chicago IL		06/2009	Residency, Internal Medicine
University of California, San Francisco CA		06/2012	Fellowship, Pulmonary & Critical Care Medicine

Ongoing and recently completed projects:

UCSF
Sundaram (Co-PI)
2020-2022
UCSF InVent Fund

K08 HL124049-01
Sundaram (PI)
2015-2020
Role of Human Chymase in Smooth Muscle Contraction in Asthma

UCSF/ShangPharma
Sundaram (Co-PI)
2018-2020
UCSF Resource Allocation Program (RAP) Catalyst Award

Highlighted Citations:

1. Liu S, Ngo U, Tang X, Ren X, Qiu W, Huang X, DeGrado W, Allen C, Jo H, Sheppard D, **Sundaram A.** Integrin α2β1 regulates collagen I tethering to modulate hyperresponsiveness in reactive airway disease models. J Clin Invest. 2021 Jun. (PMC8203456)
2. **Sundaram A**, Chen C, Isik Reed N, Liu S, Ki Yeon S, McIntosh J, Tang YZ, Yang H, Adler M, Beresis R, Seiple IB, Sheppard D, DeGrado WF, Jo H. Dual antagonists of α5β1/αvβ1 integrin for airway hyperresponsiveness. Bioorg Med Chem Lett. 2020 Nov. (PMC7700746)
3. **Sundaram A**, Chen C, Khalifeh-Soltani A, Atakilit A, Ren X, Qiu W, Jo H, DeGrado W, Huang X, Sheppard D. Targeting integrin $\alpha_5\beta_1$ ameliorates severe airway hyperresponsiveness in experimental asthma. J Clin Invest. 2017 Jan. (PMC5199700)

4. **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. (PMC4347230) (*shared first-author)

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2020-present Associate Program Director, Molecular Medicine Pathway, Internal Medicine Residency, UCSF
2016-present Scientific Reviewer, Resource Allocation Program Technology Committee, UCSF
2016-2018 Member, Chancellor's Committee on the Status of Women, UCSF
2014-present Assistant Professor of Medicine, Division of Pulmonary and Critical Care Medicine, UCSF
2012-2014 Clinical Instructor, Division of Pulmonary and Critical Care Medicine, UCSF
2009-2012 Fellow, Pulmonary and Critical Care Medicine, UCSF
2007-present Member, American Thoracic Society
2007-2009 Resident, Internal Medicine, Northwestern University
2006-2007 Intern, Internal Medicine, Northwestern University

Honors

2014 Respiratory Structure and Function Abstract Scholarship, American Thoracic Society
2013 Respiratory Disease Young Investigators' Forum Finalist, ARC
2012-present American Board of Internal Medicine for Critical Care Medicine Certification
2011-present American Board of Internal Medicine for Pulmonary Diseases Certification
2009-2019 American Board of Internal Medicine for Internal Medicine Certification
2006-2009 Excellence in Teaching, Northwestern University
1999-2006 Honors Program in Medical Education, Northwestern University

Contributions to Science

1. 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. (PMC3266785)

2. Having gained mastery over a variety of techniques to dissect smooth muscle physiology and interrogate associated signaling pathways, I began to work on identifying novel pathways that contribute to airway narrowing using mouse models of asthma. I determined that the scaffold protein IQGAP1 regulates airway contraction by facilitating the interaction of RhoA and its regulator proteins. I also used the expertise I have developed in *in vitro, ex vivo, and in vivo* smooth muscle analysis to collaborate with a diverse group of researchers within UCSF to study novel regulators of airway smooth muscle physiology.

   Katsumoto TR, Kudo M, Chen C, **Sundaram A**, Callahan EC, Zhu JW, Lin J, Rosen CE, Manz BN, Lee JW, Matthay MA, Huang X, Sheppard D, Weiss A. The phosphatase CD148 promotes airway hyperresponsiveness through SRC family kinases. J Clin Invest. 2013 Apr 1. (PMC3635736)

Sundaram A*, Bhattacharya M*, Kudo M, Farmer J, Ganesan P, Khalifeh-Soltani A, Arjomandi M, Atabai K, Huang X, Sheppard D. IQGAP1-dependent scaffold suppresses RhoA and inhibits airway smooth muscle contraction. J Clin Invest. 2014 Oct 1. (PMC4347230) (*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. (PMC5267521)

Bulek K, Chen X, Parron V, **Sundaram A**, Herjan T, Ouyang S, Liu C, Majors A, Zepp J, Gao J, Dongre A, Bodaszewska-Lubas M, Echard A, Aronica M, Carman J, Garantziotis S, Sheppard D, Li X. IL-17A recruits Rab35 to IL-17R to mediate PKCα-dependent stress fiber formation and airway smooth muscle contractility. J Immunol. 2019 Mar 1. (PMC6379809)

3. 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 $\alpha_5\beta_1$. I described a similar phenomenon with integrin $\alpha_2\beta_1$ and its interaction with collagen I. 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.

   Sundaram A, Chen C, Khalifeh-Soltani A, Atakilit A, Ren X, Qiu W, Jo H, DeGrado W, Huang X, Sheppard D. Targeting integrin $\alpha_5\beta_1$ ameliorates severe airway hyperresponsiveness in experimental asthma. J Clin Invest. 2017 Jan. (PMC5199700)

   Sundaram A, Chen C, Isik Reed N, Liu S, Ki Yeon S, McIntosh J, Tang YZ, Yang H, Adler M, Beresis R, Seiple IB, Sheppard D, DeGrado WF, Jo H. Dual antagonists of α5β1/αvβ1 integrin for airway hyperresponsiveness. Bioorg Med Chem Lett. 2020 Nov. (PMC7700746)

   Liu S, Ngo U, Tang X, Ren X, Qiu W, Huang X, DeGrado W, Allen C, Jo H, Sheppard D, **Sundaram A.** Integrin α2β1 regulates collagen I tethering to modulate hyperresponsiveness in reactive airway disease models. J Clin Invest. 2021 Jun. (PMC8203456)

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1pkI5O8fJQW5K/bibliography/public/

BIOGRAPHICAL SKETCH

NAME: Wang, Zhi-En

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Research Specialist

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Xian Medical University, Xian, China	MD	12/1982	Medicine
Xian Medical University, Xian, China	MS	12/1985	Immunology

Highlighted Citations:

1. 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
2. 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
3. Cheng LE**, ZE Wang**, RM Locksley. (2010). Murine B cells regulate serum IgE levels in a CD23-dependent manner. *J Immunol* 185:5040-7
4. 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

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

1997 – Present	Research Specialist II, Howard Hughes Medical Institute (HHMI) San Francisco, CA
1994 – 1997	Senior Research Associate, Cell Genesys Inc., Foster City, CA
1991 – 1994	Research Fellow, University of California, San Francisco Department of Medicine
1990 – 1991	Research Fellow, Temple University School of Medicine, Philadelphia, PA
1989 – 1990	Cheng Scholar and Visiting Scientist, University of California, San Francisco, CA
1987 – 1989	Assistant Researcher and Lecturer, Xian University, Xian China
1986 – 1987	Research and Teaching Associate, Department of Microbiology and Immunology, Xian University, Xian, China

BIOGRAPHICAL SKETCH

NAME: Weiss, Arthur

eRA COMMONS USER NAME (credential, e.g., agency login): weissa

POSITION TITLE: Professor of Medicine and of Microbiology and Immunology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
John Hopkins University, Baltimore	BA	05/1973	Biology
University of Chicago	PhD	05/1978	Immunology
University of Chicago	MD	05/1979	Medicine

Ongoing and recently completed projects:

Howard Hughes Medical Institute
Weiss (PI)
07/01/85-08/31/22
Cell surface molecules and molecular events involved in human T cell activation

1R37 AI114575
Weiss (PI)
12/08/15-11/30/25
The cell and molecular mechanisms underlying CD28 costimulation

2P01 AI091580
Weiss (Program Leader and Project PI)
07/01/16-06/30/21 (NCE to 06/30/21; Resubmission of renewal awaiting funding decision)
Defining the Unique Properties of the Distinct Signaling Machinery Used by the TCR

Highlighted Citations:

1. Lo, W.-L., Shah, N.H., Rubin, S.A., Zhang, W., Horkova, H., Fallahee, I.R., Stepanek, O., Zon, L.I., Kuriyan, J., **Weiss A**. (2019). Slow phosphorylation of a tyrosine residue in LAT optimizes T cell ligand discrimination. Nature Immunology. 20(11),1481-1493. PMCID: PMC6858552.
2. Courtney, A.H., Shvets, A.A., Lu, W., Griffante, G., Mollenauer, M.N., Horkova, V., Lo, W.-L., Yu, S., Stepanek, O., Chakraborty, A., **Weiss, A**. (2019). CD45 functions as a signaling gatekeeper in T cells. Science Signaling. 12(604). pii: eaaw8151. PMCID: PMC6948007.
3. Shen, L., Matloubian, M., Kadlecek, T.A., **Weiss, A**. (2021). A disease-associated mutation that weakens ZAP70 autoinhibition enhances responses to weak and self-ligands. Science Signaling. 14(668):eabc4479. PMCID: PMC8009134.
4. Nguyen, T.T., Wang, Z.-E., Shen, L., Schroeder, A., Eckalbar, W., **Weiss, A**. (2021). Cbl-B deficiency prevents functional but not phenotypic T cell anergy. Journal of Experimental Medicine.

218(7):e20202477. PMCID: PMC8117209.

Positions, Scientific Appointments, and Honors

Positions

2002-2006 Director, Medical Scientist Training Program (MSTP), UCSF
1998-2005 Associate Director, The Rosalind Russell Medical Research Center for Arthritis, UCSF
1993-present Investigator, Howard Hughes Medical Institute, UCSF
1992-present Professor of Medicine, and of Microbiology and Immunology, UCSF
1991-present Ephraim P. Engleman Distinguished Professor of Rheumatology, UCSF
1989-1993 Associate Professor of Medicine, and of Microbiology and Immunology, UCSF
1989-1994 Associate Investigator, Howard Hughes Medical Institute, UCSF
1987-2011 Chief, Division of Rheumatology/Clinical Immunology, Department of Medicine, UCSF
1985-1989 Assistant Investigator, Howard Hughes Medical Institute, UCSF
1985-1989 Assistant Professor of Medicine, and of Microbiology and Immunology, UCSF
1984-1985 Instructor, Department of Medicine, Division of Rheumatology/Clinical Immunology, UCSF
1982-1985 Associate, Howard Hughes Medical Institute, UCSF
1982-1984 Fellow in Rheumatology/Clinical Immunology, UCSF
1980-1982 Resident, Department of Medicine, University of California, San Francisco (UCSF)
1979-1980 Postdoctoral Fellow, Swiss Institute for Experimental Cancer Research, Lausanne, Switzerland

Scientific Appointments

2013-2016 Chair, Section 43 (Immunology and Inflammation), National Academy of Sciences
2008-2009 President, American Association of Immunologists
2005-present Advisory Council, RIKEN Research Center for Integrative Medical Sciences
2003-2010 Council, American Association of Immunologists
2000-2002 Chair, Allergy and Immunology Study Section (NIH)
1999-2011 Chair, Scientific Advisory Board, American Asthma Foundation
1998-2002 Member, Allergy and Immunology Study Section (NIH)
1991-1992 President, Western Region of the American College of Rheumatology
1986-1991 Councilor, American Federation for Clinical Research

Honors

2021 Master, American College of Rheumatology
2019 AAI Distinguished Fellow, American Association of Immunologists
2019 The Eberly Distinguished Lecture, University of Pittsburgh School of Medicine
2019 Establishment of the Art Weiss Lectureship in Immunology and Rheumatology at UCSF
2019 William B. Coley Award for Distinguished Research in Basic Immunology, Cancer Research Institute
2018 Howard and Martha Holley Research Prize in Rheumatology
2017 Associate Member, European Molecular Biology Organization (EMBO)
2016 Frank and Shirley Fitch Lecture, University of Chicago
2016 Merit Award, NIAID, NIH
2016 Ephraim P. Engleman Memorial Lecture, American College of Rheumatology
2014 Nathan Zwaifler Lecture, UCSD
2012 Lifetime Achievement Award, American Association of Immunology
2012 UCSF Lifetime Achievement in Mentoring Award
2010 Dorothy Baugh Harmon Endowed Lectureship, Oklahoma Medical Research Foundation
2009 Ishizaka Lecture, La Jolla Institute for Allergy and Immunology
2009 46th Stuart Memorial Lecture, Brown University
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
2004 Member, National Academy of Sciences
2004 Fellow, American Academy of Microbiology
2004 Member, National Academy of Medicine (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
2003 Fellow, American Academy of Arts and Sciences
2001 American Association of Immunologist-Huang Foundation Meritorious Career Award
1998 Forty-First Faculty Research Lecturer, University of California, San Francisco
1997 Lee C. Howley Prize, Arthritis Foundation
1993 Junior Investigator Award, American Association of Immunologists
1990 Young Investigator Award, Western Society for Clinical Investigation
1990 Henry Kunkel Young Investigator Award, American College of Rheumatology

Contributions 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 $\alpha\beta$ 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 $\alpha\beta$ 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 based on the zeta chain that are currently used in cell-based tumor immunotherapy.

a. **Weiss A**, Stobo J. (1984). Requirement for the coexpression of T3 and the T cell antigen receptor on a malignant human T cell. Journal of Experimental Medicine. 160:1284-1299. PMCID: PMC2187507.
b. Ohashi P, Mak T, Van den Elsen P, Yanagi Y, Yasunobu Y, Calman A, Terhorst C, Stobo J, **Weiss A.** (1985). Reconstitution of an active surface T3/T-cell antigen receptor by DNA transfer. Nature. 316:606-609. PMCID: PMC4033759
c. Tan L, Turner J, **Weiss A**. (1991). Regions of the T cell antigen receptor α and β chains that are responsible for interactions with CD3. Journal of Experimental Medicine. 173:1247-1256. PMCID: PMC2118847.
d. Irving BA. **Weiss A**. (1991). The cytoplasmic domain of the T cell receptor ζ chain is sufficient to couple to receptor-associated signal transduction pathways. Cell. 64:891-901. PMCID: PMC1705867

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 that 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 a mAb against Tp44, later named CD28, could provide the second signal for Jurkat and 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. (1984). 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. Journal of Immunology. 133:123-128. PMCID: PMC6327821

b. **Weiss A**, Imboden J, Shoback D, Stobo J. (1984). Role of T3 surface molecules in human T cell activation: T3 dependent activation results in a rise in cytoplasmic free calcium. Proceedings of the National Academy of Science USA. 81:4169-4173. PMCID: PMC345390.
c. **Weiss A**, Manger B, Imboden J. (1986). Synergy between the T3/antigen receptor complex and Tp44 in the activation of human T cells. Journal of Immunology. 137:819-825. PMID:3088111
d. Fraser JD, Irving BA, Crabtree GR, **Weiss A**. (1991). Regulation of interleukin-2 gene enhancer activity by the T cell accessory molecule CD28. Science. 251:313-316. PMCID: PMC1846244

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 develope a model for TCR signaling whereby Lck and ZAP-70 interact with ITAMs in a sequential and ordered manner. This model has withstood more than 20 years of subsequent investigation.

a. Straus DB, **Weiss A**. (1992). Genetic evidence for the involvement of the lck tyrosine kinase in signal transduction through the T cell antigen receptor. Cell. 70:585-593. PMCID: PMC1505025
b. Chan AC, Iwashima M, Turck CW, **Weiss A**. (1992). ZAP-70: A 70kD protein tyrosine kinase that associates with the TCR ζ chain. Cell. 71:649-662. PMCID: PMC1423621
c. Chan AC, Kadlecek T, Elder ME, Filipovich AH, Kuo W-L, Iwashima M, Parslow TG, **Weiss A**. (1994). ZAP-70 deficiency in an autosomal recessive form of severe combined immunodeficiency. Science. 264:1599-1601. PMCID: PMC8202712
d. Iwashima M, Irving BA, van Oers NSC, Chan AC, **Weiss A**. (1994). Sequential interactions of the TCR with two distinct cytoplasmic tyrosine kinases. Science 263:1136-1139. PMCID: PMC25326545

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 using small molecule inhibition of a catalytic mutant of ZAP-70. We recently demonstrated that the slow phosphorylation by ZAP-70 of the PLCγ1 binding site in LAT is a critical step in ligand discrimination and may be a part of kinetic proofreading.

a. **Weiss A**, Koretzky G, Kadlecek, T. (1991). Stimulation of the T cell antigen receptor induces tyrosine phosphorylation of phospholipase Cγ1. Proceedings of the National Academy Science USA . 88:5484-5488. PMCID:_ PMC51901
b. Yablonski D, Kuhne MR, Kadlecek. T, **Weiss A**. (1998). Uncoupling of non-receptor tyrosine kinases from PLC-γ1 in a SLP-76-deficient T cell. Science. 281:413-416. PMCID: PMC9665884
c. Au-Yeung BB, Levin SE, Zhang C, Hsu L-Y, Cheng D, Killeen N, Shokat KM, **Weiss A**. (2010). A genetically selective ZAP-70 kinase inhibitor reveals requirements for catalytic function in Treg cells. Nature Immunology. 11:1085-1093. PMCID: PMC3711183.
d. Lo WL, Shah NH, Rubin SA, Zhang W, Horkova V, Fallahee IR, Stepanek O, Zon LI, Kuriyan J, **Weiss A**. (2019). Slow phosphorylation of a tyrosine residue in LAT optimizes T cell ligand discrimination. Nature Immunology. 20:1481-93. PMCID: PMC6858552

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**. (1990). Tyrosine phosphatase CD45 is essential for coupling of the T cell antigen receptor to the phosphatidylinositol second messenger pathway. Nature. 346:66-68. PMCID: PMC2164155
b. Zikherman J, Jenne C, Watson S, Doan K, Raschke W, Goodnow CC, **Weiss A**. (2010). CD45-Csk phosphatase-kinase titration uncouples basal and inducible T cell receptor signaling during thymic development. Immunity. 32:342-54. PMCID: PMC2865198
c. Tan Y-X, Manz BN, Freedman TS, Zhang C, Shokat KM, **Weiss A**. (2014). Inhibition of the kinase Csk in thymocytes reveals a requirement for actin remodeling in the initiation of full TCR signaling. Nature Immunology. 15:186-94. PMCID: PMC3946925
d. Courtney AH, Shvets AA, Lu W, Griffante G, Mollenauer M, Horkova V, Lo W-L, Yu S, Stepanek O, Chakraborty AK, **Weiss A**. (2019). CD45 functions as a signaling gatekeeper in T cells. Science Signaling. 12(604):eaaw8151. PMCID: PMC6948007

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/arthur.weiss.1/collections/51780518/public/

BIOGRAPHICAL SKETCH

NAME: Prescott G. Woodruff, MD

eRA COMMONS USER NAME (credential, e.g., agency login): woodruffp

POSITION TITLE: Professor of Medicine in Residence

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Wesleyan University, Middletown, CT	B.A.	05/89	Letters
Columbia College of Physicians & Surgeons, NY	M.D.	05/93	Medicine
Massachusetts General Hospital	Residency	07/93-96	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

Ongoing and recently completed projects:

U01 HL137880
Woodruff (PI)
09/15/17-05/30/22
NHLBI SPIROMICS II: Biological underpinnings of COPD heterogeneity and progression.

K24 HL137013
Woodruff (PI)
04/28/17-3/31/22
Mentoring Research in Precision Medicine for Lung Disease
(5 year renewal approved at NHLBI Council to start 4/1/2022)

R01 HL146002 MPI
Levy (Contact PI), Woodruff (PI)
10/1/19-07/24
Severe Asthma Research Program 4

U19 AI077439
Erle (PI), Woodruff (Project Leader)
04/01/18-03/31/23
Understanding Asthma Endotypes

R01 HL143998 MPI
Huang (Contact PI), Woodruff (PI)
09/15/19-07/31/23
Integrated Analysis of Microbial and Genomic data in Obstructive Lung Disease (I AM GOLD) Study

R01 HL121774
Huffnagle G (PI), Woodruff (Co-I)
01/01/17-08/31/20

Functional Analysis of the Pulmonary Microbiome during COPD

R35 HL138424
Erle (PI), Woodruff (Co-I)
02/15/19-12/31/26
Airway Epithelial Cell Gene Regulation: New Mechanisms and Therapeutic Strategies

P01 HL107202
Fahy (PI), Woodruff (Core Director)
09/01/19-07/31/24
Exploring the Biology of Persistent Type 2 Airway Niches in Asthma

Highlighted Citations:

1. **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
2. **Woodruff PG**, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, Koth LL, Arron JR, and Fahy JV. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med.* 2009;180(5):388-95
3. Christenson SA, van den Berge M, Faiz A, Inkamp K, Bhakta N, Bonser LR, Zlock LT, Barjaktarevic IZ, Barr RG, Bleecker ER, Boucher RC, Bowler RP, Comellas AP, Curtis JL, Han MK, Hansel NN, Hiemstra PS, Kaner RJ, Krishnanm JA, Martinez FJ, O'Neal WK, Paine R 3rd, Timens W, Wells JM, Spira A, Erle DJ, **Woodruff PG**. An airway epithelial IL-17A response signature identifies a steroid-unresponsive COPD patient subgroup. *J Clin Invest.* 2019 Jan 2;129(1):169-181. PMID: 30383540. PMCID: PMC6307967
4. Siddiqui S, Johansson K, Joo A, Bonser LR, Koh KD, Le Tonqueze O, Bolourchi S, Bautista RA, Zlock L, Roth TL, Marson A, Bhakta NR, Ansel KM, Finkbeiner WE, Erle DJ, **Woodruff PG**. Epithelial miR-141 regulates IL-13-induced airway mucus production. *JCI Insight*. 2021 Mar 8;6(5):PMID: 33682796. PMCID: PMC8021117.

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

1998 – 2002	Clinical and Research Fellow, Division of Pulmonary and Critical Care Medicine & Cardiovascular Research Institute, Department of Medicine
2002 – 2005	Assistant Adjunct Professor; Division of Pulmonary and Critical Care Medicine
2005 – 2010	Assistant Professor in Residence, Division of Pulmonary and Critical Care Medicine, Department of Medicine
2010 – 2014	Associate Professor in Residence, Division of Pulmonary and Critical Care Medicine, Department of Medicine
2014 – Present	Professor in Residence, Division of Pulmonary and Critical Care Medicine, Department of Medicine

Selected Honors

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

C. Contribution to Science

1. Molecular phenotyping of COPD and asthma using genomics. This work, which is based on gene expression studies of airway epithelial cells, 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. PMCID: PMC6307967
   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. PMCID: PMC4407484
   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 U S A. 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. Siddiqui S, Johansson K, Joo A, Bonser LR, Koh KD, Le Tonqueze O, Bolourchi S, Bautista RA, Zlock L, Roth TL, Marson A, Bhakta NR, Ansel KM, Finkbeiner WE, Erle DJ, **Woodruff PG**. Epithelial miR-141 regulates IL-13-induced airway mucus production. *JCI Insight*. 2021 Mar 8;6(5):PMID: 33682796. PMCID: PMC8021117.

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:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40802581/?sort=date&direction=descending