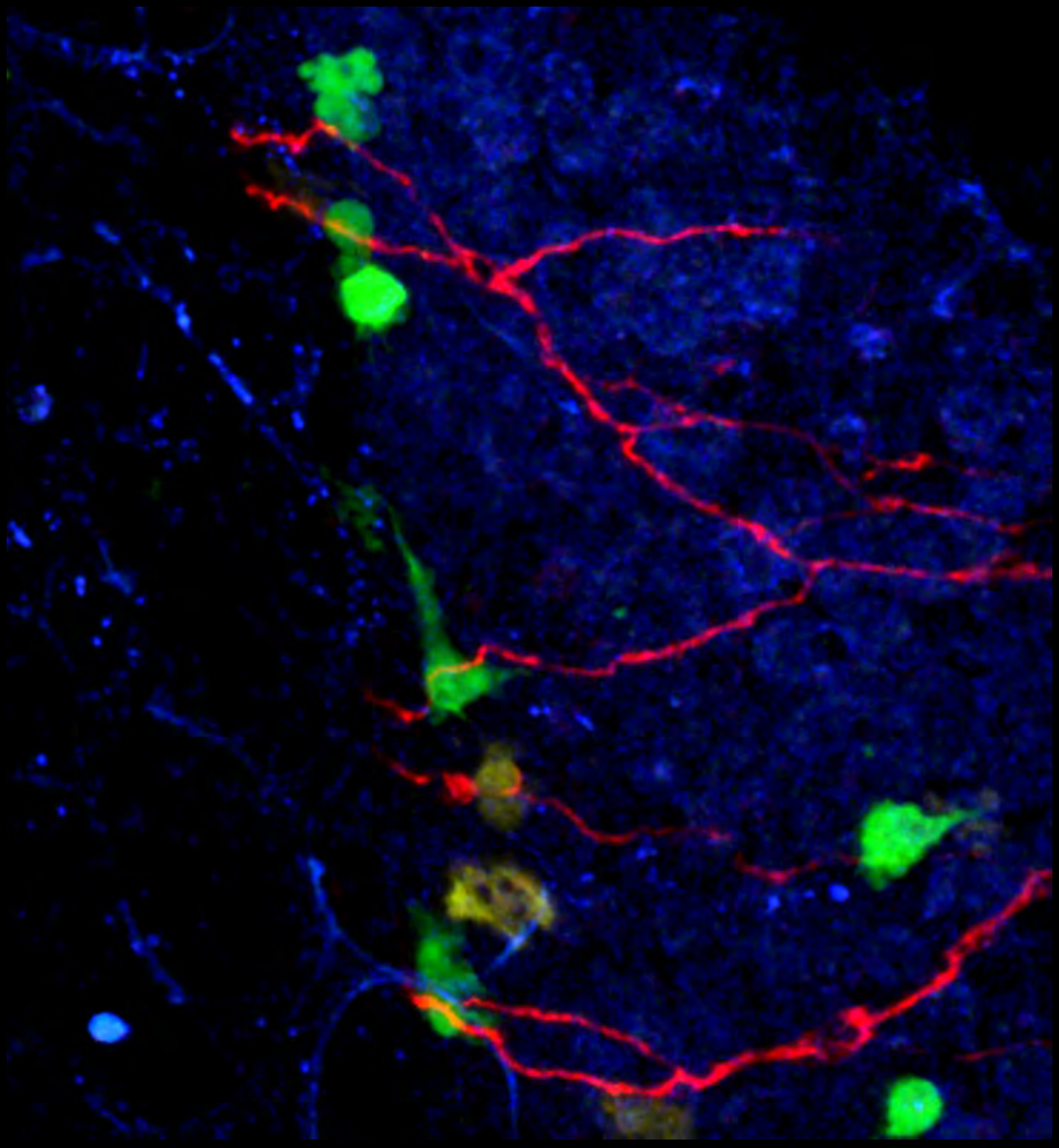
Sandler Asthma Basic REsearch Center

University of California, San Francisco



Progress Report

Year 24

2023

Figure Legend: Two-photon microscopy showing the innervation of a bronchial airway and associated cells that capture inhaled allergens and promote local type 2 inflammation. Bronchus-associated macrophages (green) and dendritic cells (yellow) are visible in proximity to nerve fibers (red). The airway epithelium is shown in blue. Image provided by Christopher Allen. The Allen Lab in the SABRE center applies advanced imaging techniques in studies of asthma. Related research is published in: Tang XZ *et al*. (2022) *eLife* 11:e63296

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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. Since 2014, the SABRE Center has been 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

As the UCSF research environment shifts towards normalizing after the pandemic, SABRE Center investigators continue to make contributions to the understanding of asthma and allergic diseases while helping to address the impact of COVID-19 on lung function, particularly among patients with asthma.

Notable accomplishments from SABRE Center members over the 2022-23 period:

(1) The Allen laboratory is focused on the intricacies of the tonically signaling IgE receptor on B cells and plasma cells that plays a dominant role in human allergy, asthma and anaphylaxis. In studies published in eLife and JEM, the lab used in vivo imaging to characterize subepithelial airway macrophages that play a key role in activating tissue Th2 cells and potentially in passing antigen to dendritic cells and also revealed that antigen-induced cross-linking of BCRs on IgE^+ plasma cells initiates apoptosis to limit the response. Importantly, mutations that attenuate BCR signaling cause greater IgE-mediated responses, suggesting potentially important genetic contributions to allergic diseases like asthma.

(2) The Ansel laboratory worked with the Woodruff group to discover a nonredundant role for the microRNA family mi-15/16 in maintaining T regulatory cell (Treg) function. In the absence of these micro-RNAs, effector ex-Tregs functionally develop and worsen type 2 inflammation in mouse models of allergic airways disease revealing a novel pathway necessary to sustain Treg suppressive capacity and limit lung inflammation.

(3) The Fahy and Woodruff labs led an investigation of the role of obesity and insulin resistance using individuals enrolled in the NIH NHLBI Severe Asthma Research cohort. Although over half of the cohort has obesity, only half of these have insulin resistance. Unexpectedly, insulin resistance rather than obesity alone correlated with decline in lung function and poor response to therapy, raising questions whether a strategy based around greater glucose control might improve airway inflammation and disease progression.

(4) The Locksley laboratory contributed two comprehensive reviews outlining the current knowledge and key future research directions in tuft cell development and in type 2 immunity.

Overview – 2023

Richard M. Locksley, M.D.

The SABRE Center presents a discovery-oriented mission towards deeper understanding of asthma that will serve to 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 UCSF research and national research organizations to establish increasing recognition for contributions to asthma research.

Easing of the COVID-19 pandemic has begun to open supply chain and personnel bottlenecks that have limited non-COVID-related research for over 2 years. In the interim, 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. Studies of new variants, vaccine responses and long-COVID continue, although currently with less participation by SABRE labs. Live scientific conferences were re-instigated and SABRE investigators organized the 4th International Conference on Innate Lymphoid Cells that was held with record attendance in September 2022 in Hawaii.

Investigators

The pandemic impacted many SABRE personnel. Dr. Jeoung-Sook Shin left UCSF to return to Seoul, South Korea, to join the Immunology 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. Burchard has taken a leave of absence for personal reasons over the past year and has yet to return to lead the Asthma Collaboratory which is continuing under direction of his assistant researchers. Dr. Fahy and Woodruff direct the Airway Clinical Research Center (ACRC) at Parnassus. Dr. Woodruff is thriving in the second year of 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. A prior postdoc in the Locksley laboratory, Dr. Maya Kotas, will join this group in the SABRE Center in the coming year. A Bioinformatics Specialist, Andrew Schroeder, MPH, remains to help with large

datasets and development of novel analytic tools to support next-generation 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. After loss of in-house meetings during the pandemic, SABRE investigators are reinvigorating shared quarterly lab and research meetings and 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 at the time 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 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 support these activities.

Chris Allen, Ph.D., joined the SABRE center fifteen years ago as a former UCSF Sandler Fellow (http://fellows.ucsf.edu/) studying asthma. The primary focus of his research program is 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. 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*. In studies in both human and mouse B cells of the cytokine regulation of IgE responses, Dr. Allen showed that IL-21 is a major factor limiting the generation of IgE B cells, published in the *Journal of Experimental Medicine*. Dr. Allen also previously 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*. Recently, Dr. Allen published a paper in the *Journal of Experimental Medicine* revealing a mechanism for the elimination of IgE plasma cells by B cell receptor signaling. This work has important implications for curtailing the production of pathogenic IgE and understanding the mechanisms of allergen immunotherapy. 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*.

Dr. Allen's research group has also contributed to broader studies of the mechanisms responsible for the initiation of allergic inflammation. Dr. Allen 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 Fc-gamma receptors, which has led to significant confusion in the field regarding the functions of basophils, a type of IgE effector cell. Dr. Allen is submitting two manuscripts providing new insights into the activation and function of basophils. Dr. Allen also recently published a paper in *eLife*, in which his advanced imaging techniques revealed how inhaled allergens are captured and presented to T cells in the lung by macrophages proximal to the bronchial airway epithelium. 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. For example, he 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 also contributed significantly to Dr. Bhattacharya's imaging studies of macrophage-fibroblast crosstalk in lung injury, with a paper published in *Frontiers in Immunology*.

Dr. Allen has attracted substantial extramural funding to support his studies. He was recently awarded a new NIH R21 on the cellular origin of IgE recall responses. He is in the process of renewing an R01 focusing on the role of B cell receptor signaling in the regulation of IgE responses. He recently completed an R21 on 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. Dr. Allen 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 is currently mentoring a PhD student, a postdoc, and two postbaccalaureate scholars in his lab. The PhD student has established a role for ligation of the B cell receptor in the induction of cell death in IgE plasma cells. The postdoc is studying the cellular basis for IgE responses after re-exposure to allergens and following up on studies of IgE-mediated functions of basophils in allergic inflammation. Dr. Allen continues mentoring a postbaccalaureate researcher who was selected as a scholar in the UCSF PROPEL (Post-baccalaureate Research Opportunity to Promote Equity in Learning) and NIH-funded PREP (Postbaccalaureate Research Education Program). This PROPEL/PREP scholar is studying the role of the cytokine signaling adapter STAT3 in regulating IgE class switch recombination, a critical step in the generation of IgE B cells. Dr. Allen also previously mentored an undergraduate from UC Berkeley who has

now joined his laboratory full time for postbaccalaureate studies, focused on genomic analysis of the molecular regulation of IgE class switch recombination. Dr. Allen previously 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 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 SARS-CoV-2 RNA vaccines were 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 circuits that program 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 circuits 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 used this experience to contribute to the rapid research mobilization to understand and combat COVID-19 as part of the COMET consortium. Dr. Ansel also shares an ImmunoX CoProject grant with sarcoidosis expert Dr. Laura Koth and the UCSF Co-Labs to combine single cell protein, RNA and epigenetic assays to uncover the inflammatory underpinnings of this common yet understudied lung disease that disproportionately affects young women of African descent. Recent work in asthma, conducted in collaboration with Dr. Woodruff and Dr. Nirav Bhakta, revealed clonal populations of allergen-responsive Th2 cells present in both the airways and circulation.

Dr. Ansel is an established leader in his field. He contributed to 8 published manuscripts this year and is guest editor for a special issue of *RNA Biology* focused on “RNA and the Immune Response: From Mechanisms to Clinical Applications”. He has ongoing funding from R01 and P01 grants from NHLBI.

The Ansel laboratory team includes two postdoctoral fellows, one graduate student, and three technicians including two post-bac scholars in the UCSF PROPEL program. Both Benjamin Wheeler and Didi Zhu were awarded the Hooper Foundation Fellowship, and Priscila Muñoz-Sandoval has been supported by a prestigious Howard Hughes Medical Institute Gilliam Fellowship, and recently received the UC President’s Dissertation Year 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 six cases, as principal investigators of independent laboratories in the US, Sweden and Germany where they have continued their work on cell programming in allergy and asthma.

Dr. Ansel is active in university service and leadership. He co-founded ImmunoX and is Chair of the Leadership Committee. He also 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. In these roles and during his seven-year tenure as faculty director of the UCSF Biomedical Sciences (BMS) graduate program, he championed and spearheaded initiatives to enhance diversity, equity and inclusion in the UCSF research community. He organized successful 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.

Although PRIMERO remains active, Dr. Burchard has taken a leave of absence from UCSF and the SABRE Center for personal reasons. We will update his status and the PRIMERO studies upon his return.

John Fahy, M.D. is a longstanding participant in SABRE research and a formal faculty member in the SABRE Center for the past 10 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 in 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 rheologic studies of the biophysical properties of human airway mucus gels, to analysis of the size, shape, and location features of mucus plugs in computed tomography lung images from patients with asthma.

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

- He leads a P01/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, or 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
- He leads an 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 site in the Severe Asthma Research program (Prescott Woodruff is site PI).

Dr. Fahy's 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. In addition, UCSF honored Dr. Fahy by awarding him the 10th Annual Faculty Research Lecture in Translational Science in 2021.

Richard Locksley, M.D., is Director of the SABRE Center, an immunologist and infectious diseases-trained physician who pursues basic studies of allergic immunity and asthma. His laboratory focuses on deeper understanding of the role for allergic cytokines in basal homeostasis, with a particular emphasis on group 2 innate lymphoid cells, or ILC2s, that are 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 9 peer-reviewed publications, 6 open repository contributions, and 4 invited reviews and commentaries during 2021-2023.

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 held in Hawaii in

2022 and he is helping organize the 5th ILC conference at Cambridge University in the UK in 2024.

Prescott Woodruff, M.D., is Associate Director of the Airway Clinical Research Center, has been an integral member of the SABRE Center for the past 9 years and is 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. His research interests are in asthma pathogenesis, genomics and translational studies, particularly in the field of precision medicine. His discoveries were among the earliest to identify biomarkers that permit segregation of asthma patients into categories likely to benefit from specific types of therapies that target type 2 inflammation mediated by the IL-4/IL-13 pathway. More recently, he has focused on non-type 2 inflammation in severe asthma and mechanisms of pathological mucus production in asthma. In particular, he identified a micro-RNA (miR-141) that regulates airway epithelial mucus production and which can be therapeutically targeted using an inhaled synthetic oligonucleotide (Siddiqui, *JCI Insight* 2021). He also has an active research program in chronic obstructive pulmonary disease (COPD). Dr. Woodruff is PI or multiple-PI of (1) the NHLBI Severe Asthma Research Program (4th iteration which started in 2019), (2) the NHLBI SPIROMICS study of COPD, (3) the NHLBI RETHINC clinical trial in COPD and (4) a NHLBI 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 membership in the American Society for Clinical Investigation and the Association of American Physicians.

Core Activities and Technology Development

A key element 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, we phased out some of these activities and re-directed resources to individual technology-enhancing procurements on an as-needed basis. This policy reflects both recommendations from our outside Scientific Advisory Board as well as initiatives reflected in the Strategic Plan. We 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 focuses on 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 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.

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. 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. We will also be bringing a new Aria flow cytometer with sorting capacity for human samples that will be available for SABRE investigators.

SABRE Associate Support

We support collaborative interactions between SABRE Associates – Drs. Gordon, Battacharya 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. Battacharya

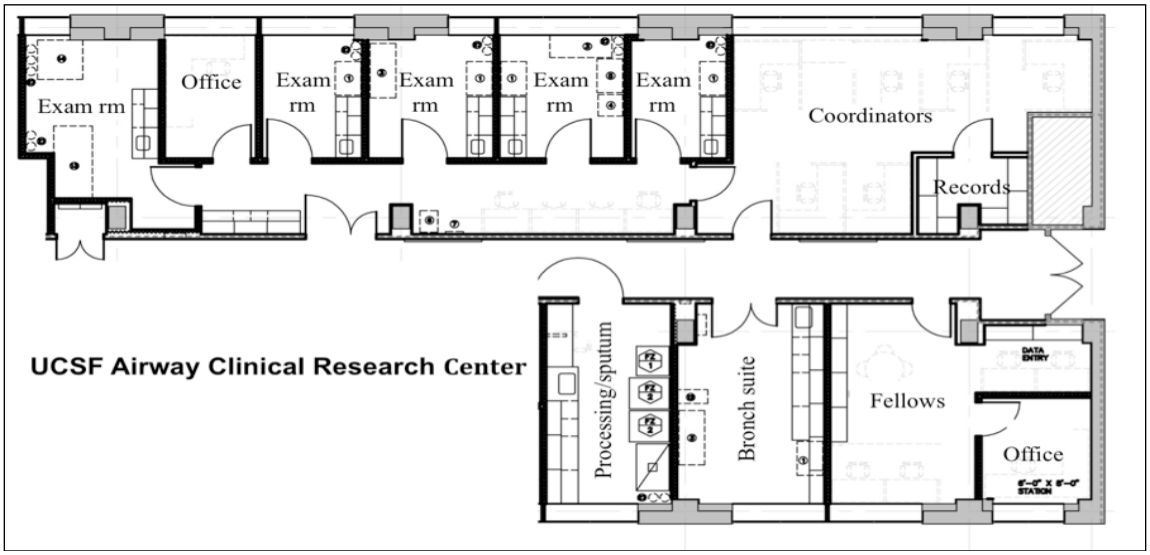
investigates lung injury, pivoted to address mechanisms by which COVID-10 mediates lung destruction, and received an NIH R01 to study pathways resulting in lung fibrosis. Dr. Sundaram studies smooth muscle and its role in asthma pathogenesis, an incompletely studied area of research of much relevance to SABRE. We look forward to continuing to support to allow these new Associates to continue their outstanding trajectories. Dr. Maya Kotas, a pulmonologist post-doc from the Locksley lab, will occupy independent space in the SABRE Center beginning in the next academic year. 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, and a data 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, Bhakta, and Peters. Drs Gordon, Christenson, Bhakta have faculty positions at UCSF and Dr Peters is currently a Global Development Lead/Senior Director of clinical development at Gilead Sciences. Current trainees include Aartik Sarma, M.D., Brendan Huang, M.D., Aaron Baugh, M.D. Jonathan Witonsky, M.D., Clarus Leung, M.D., and Omar Farooqui, 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 secured funding from NIH to develop thiol-modified carbohydrates as novel inhaled mucolytic drugs and this work led to the spin-out of Aer Therapeutics to further advance this technology to the clinic. Dr Fahy's mucolytic program is augmented by biomarker discovery research that has developed and validated image (CT lung)-based mucus plug quantification measures as predictive and monitoring biomarkers 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 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) 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 - 6/30/2024**) *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. **U01 HL146002 (9/23/2019 - 6/30/2024)** *Immunometabolic phenotypes in adult severe asthma and disease progression*. *Severe Asthma Research Program (SARP).* Dr. Woodruff is PI and Dr. Fahy is co-I. This multicenter grant is exploring molecular subtypes of asthma in a cohort of patients with severe asthma. The focus is on assessments focused on underlying genetic, inflammatory mechanisms and metabolic dysfunction that enable, promote and/or predict disease progression.

4. **U19 AI077439 (4/1/2018 - 3/31/2023)** *Understanding Asthma Endotype.* **(4/1/2023-3/31/2028)** *Immune-driven Airway Epithelial Dysfunction in Muco-obstructive Asthma*. Dr. David Erle is PI and Dr. Woodruff directs 1 of the 2 projects while Dr. Fahy is a co-I on Dr. Erle's grant. This NIAID/AADCRC grant is focused on understanding how airway epithelial cells are involved in causing different forms of asthma.

5. **Genentech TSK-020586 (12/15/2020 - 12/15/2023**) *The COMET+ Study: Deep phenotyping study of COVID+ and COVID- ARDS.* 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 - 2/28/2023)** *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 (7/1/2022 - 6/31/2027)** *Phenotypic and biological features of mucus plugs in asthma*. Dr Fahy is PI for this longstanding R01 that is exploring mechanism of mucus pathology in asthma.

9. **U01 HL137880 (9/15/2017 - 5/31/2024)** *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. This project is currently in a no cost extension as the NIH prepares an RFA for a competitive renewal.

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. **R01 HL146002 (7/1/2019 - 6/30/2024)** *SPIROMICS II Heart Failure.* Dr Woodruff is co-I, PI is RG Barr. This study is designed to define the heart failure phenotypes associated with COPD using 4D MRI and exercise echo by leveraging the SPIROMICS study.

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 (5/1/2020-4/30/2025)** *Understanding the Origins of Early COPD.* Dr. Woodruff is co-I, PI is Fernando J. Martinez. This grant will establish a longitudinal cohort of patients with "early COPD" and identify the pathophysiologic changes in the lung that predispose smokers to develop *bona fide* COPD that is associated with overt airflow obstruction.

Communications, Training and Leadership Initiatives

SABRE is 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 organized the basic immunology research seminars in 2019-21 and is a Co-PI on the Gnotobiotic Initiative and Member of the Flow Cytometry Consortium at Parnassus. Prescott Woodruff helped organize the COMET NIH-Genentech-UCSF Consortia for study of COVID patients and re-organized the submitted second-generation request, which includes SABRE support for airway specimen collection and patient study. He was appointed as the Head of the Division of Pulmonary, Critical Care, Allery & Sleep Medicine at UCSF last year.

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, was finally held on September 2022 in Hawaii in conjunction with the International Cytokine and Interferon Society Meetings. The 4th ILC meeting had the largest attendance among all prior ILC meetings and Dr. Locksley will help with planning the 5th ILC meeting in Cambridge, England, in 2024.

Human Upper Respiratory Tract Analysis

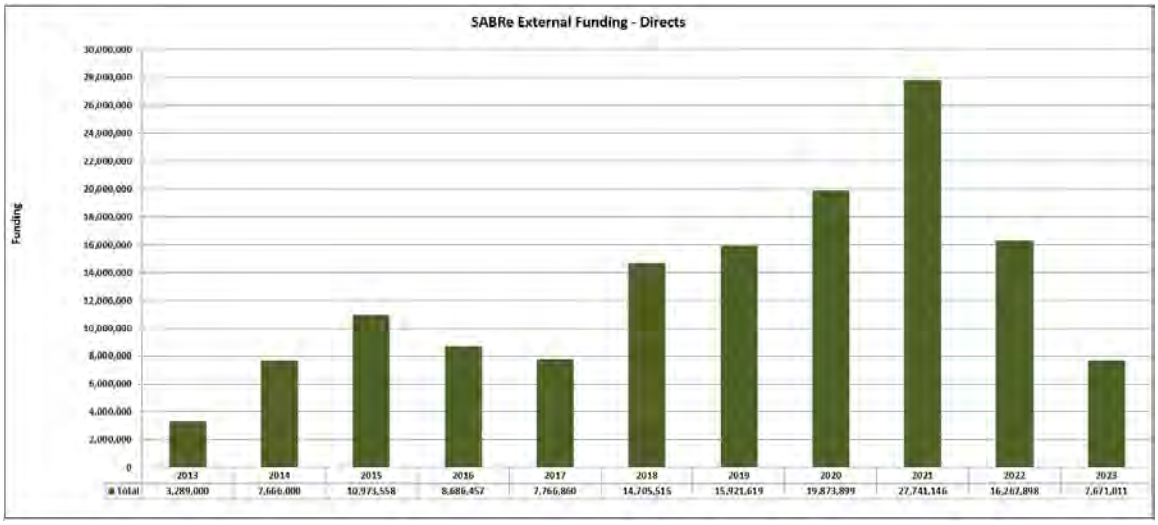
The SABRE Center works with the UCSF surgical practice located at Mt. Zion campus with experience taking care of large number of patients with allergic nasal polyposis. Drs. Andrew Goldberg and Steven Pletcher in the Department of Otolaryngology and Head and Neck Surgery at UCSF have been examining interactions of the nasal microbiome and allergy-associated immune cells in excised nasal polyps. We have established 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. After postdoc, Benjamin Terrier, a Fulbright Scholar in the Locksley lab, started work with this group investigating nasal upper airway epithelial cells involved in sensory perception to allergens, this is now continued by Maya Kotas, a postdoc in the Locksley lab, who will move into independent space in the SABRE Center in the fall. 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.

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.

We have maintained substantial procurement of external funds by the core SABRE investigators in support of their research efforts. Although diminished by ~$11 million in 2022, this was largely driven by expiration of a large NIH Center Grant to Dr. Woodruff. We have also

omitted the Burchard lab support while he is on leave from UCSF. 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. Dr. Burchard has been on leave since 2022.

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 research in 2022-23

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 nasal 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 activated during polyp formation.

Johansson K, JD Gagnon, S Zhou, MS Fassett, AW Schroeder, R Kageyama, RA Baustista, H Pham, PG Woodruff, KM Ansel. 2023. An essential role for miR-15/16 in Treg suppression and restriction of proliferation. *bioRxiv* 2023.03.26.533356 (preprint).

Regulatory T cells, or Treg, are crucial in restraining effector T cell function, thus limiting off-target damage to host tissues. The Ansel and Woodruff teams identified a key microRNA family – mi-15/16 – that functions nonredundantly in sustaining Treg function. In the absence of these miRNAs, expression of key proteins involved in Treg function, including FOXP3, CD25, CTLA4 and PD-1, is altered, resulting in emergence of a Treg effector population unable to restrain type 2 inflammation in a mouse model of allergic airways disease. Enforcing mi-15/16 in FOXP3 Tregs sustains their suppressive phenotype and reveals a novel pathway for regulation of Treg function.

Molofsky AB, RM Locksley. 2023. The ins and outs of type 2 innate and adaptive immunity. *Immunity* 56:704-722.

A comprehensive review of the state of the field that emphasizes the overlapping risks for allergic disease driven by developmental windows for immune and tissue differentiation, integrity of tissue niches for immune cells and genes that alter elaboration of cytokines and growth factors. Together, these factors integrate to control responses to environmental exposures post-birth, primarily driven by microbial constituents from bacteria, viruses, fungi and parasites, that can create lasting risks for allergic pathology through life.

Peters MC, ML Schiebler, JC Cardet, MW Johansson, R Sorkness, MD DeBoer, ER Bleecker, DA Meyers, M Castro, K Sumino, SC Erzurum, MC Tattersall, JG Zein, AT Hastie, W Moore, BD Levy, E Israel, BR Phillips, DT Mauger, SE Wenzel, ML Fajt, SK Koliwad, LC Denlinger, PG Woodruff, NN Jarjour, JV Fahy, NHLBI Severe Asthma Research Program-3. 2022. The impact of insulin resistance on loss of lung function and response to treatment in asthma. *Am J Respir Crit Care Med* 206:1096-1106.

Co-association of obesity and asthma is common but dissociation of the metabolic derangement, including insulin resistance, from body weight is unclear. Here, the Fahy and Woodruff teams worked with patient cohorts and colleagues from the NHLBI SARP to more closely examine the 55% of the SARP cohort with obesity, half of whom had insulin resistance. Comparing these groups revealed that decline in lung function and poor responses to therapy were associated with the degree of insulin resistance but not with the degree of obesity. These studies emphasize the inter-relationship of type 2 inflammation and metabolic dysregulation, and further studies are warranted to determine whether aggressive attempts to diminish insulin resistance improves airway inflammation.

Tang XZ, LSM Kreuk, C Cho, RJ Metzger, Allen CDC. 2022. Bronchus-associated macrophages efficiently capture and present soluble inhaled antigens and are capable of local Th2 cell activation. *Elife* 11:e63296.

Mechanisms by which inhaled allergens are processed and presented by host cells to induce allergic Th2 responses that accompany asthma remain incompletely defined. The Allen team used two-photon imaging of mouse lung to reveal allergen uptake by subepithelial CD11c+CX3CR1+MHC II+ interstitial macrophages beneath bronchial epithelia that were prominent at airway branch points, which represent areas where inhaled particles collect. Subepithelial bronchial macrophages, or BAMs, had extended interactions with Th2 cells that promoted cytokine production but also interacted with migratory dendritic cells. Thus, BAMs may represent a crucial macrophage population resident at airway branchpoints that traps, processes and presents antigens to effector Th2 cells while also transferring antigens to recruited DCs.

Wade-Vallance AK, Z Yang, JB Libang, MJ Robinson, DM Tarlinton, CDC Allen. 2023. B cell receptor ligation induces IgE plasm cell elimination. *J Exp Med* 220:e20220964.

In continuing careful studies of IgE, the Allen lab demonstrates that IgE+ plasma cells are eliminated in vivo by canonical signaling through the B cell receptor and in vitro through induction of apoptosis. These studies illuminate the pathways that impose regulation of the IgE receptor, which the Allen lab had previously shown is a tonically signaling receptor and inform mechanisms like anti-IgE monoclonal antibody approaches and immunotolerance used to control reactive IgE+ plasma cells.

Organization of the body of this Annual Report

We structured 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 additional campus asthma-oriented research projects and provide updates of seminar speakers at conferences for which we lend support. We summarize the Financial Report for the Program. Finally, we outline strategies for the coming years and append 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. 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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Departments of Medicine and Microbiology/Immunology

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

Hal Chapman, M.D., Professor
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John V. Fahy, M.D., Professor
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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 revealing entirely new avenues for discovery.

Selected Publications

1. Molofsky AB, **RM Locksley**. 2023. The ins and outs of innate and adaptive type 2 immunity. Immunity 56:704-722. PMCID: PMC10120575

2. Kotas ME, CE O'Leary, **RM Locksley**. 2023. Tuft cells: context- and tissue-specific programming for a conserved cell lineage. *Annu Rev Pathol* 18:311-335.
3. Ricardo-Gonzalez RR, ME Kotas, CE O'Leary, K Singh, W Damsky, C Liao, E Arouge, I Tenvooren, DM Marquez, AW Schroeder, JN Cohen, MS Fassett, J Lee, SG Daniel, K Bittinger, RE Diaz, JS Fraser, N Ali, KM Ansel, MH Spitzer, H-E Liang, **RM Locksley**. 2022. Innate type 2 immunity controls hair follicle commensalism by Demodex mites. *Immunity* 55:1891-1908.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. Kotas ME, **RM Locksley**. 2018. Why Innate Lymphoid Cells? *Immunity* 48:1081-1090.
10. Schneider C, CE O'Leary, J von Moltke, H-E Liang, Q Yan Ang, PJ Turnbaugh, S Radhakrishnan, Michael Pellizzon, A Ma, **RM Locksley**. 2018. A metabolite-triggered tuft cell-ILC2 circuit drives small intestinal remodeling. *Cell* 174:271-284.
11. 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.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.
17. **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 also serves as the Assistant Director for Diversity, Equity, and Inclusion in the Cardiovascular Research Institute. 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 faculty position in the Smith Cardiovascular Research Building on the UCSF Mission Bay campus.

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. Wade-Vallance AK, Yang Z, Libang JB, Robinson MJ, Tarlinton DM, **Allen CDC.** (2023) B cell receptor ligation induces IgE plasma cell elimination. *J Exp Med,* 220(4):e20220964. PMCID: PMC9997509.
2. Tang XZ, Kreuk LSM, Cho C, Metzger RJ, **Allen CDC.** (2022) Bronchus-associated macrophages are positioned for soluble antigen capture from the airway lumen and are capable of local Th2 cell activation. *eLife,* 11:e63296. PMCID: PMC9560158.
3. Bhattacharyya A, Torre P, Yadav P, Boostanpour K, Chen TY, Tsukui T, Sheppard D, Muramatsu R, Seed RI, Nishimura SL, Jung JB, Tang XZ, **Allen CDC**, Bhattacharya M.

(2022). Macrophage Cx43 Is Necessary for Fibroblast Cytosolic Calcium and Lung Fibrosis After Injury. *Front Immunol*, 13:880887. PMCID: PMC9134074.

4. **Allen CDC** (2022) Features of B Cell Responses Relevant to Allergic Disease (Review). *J Immunol*, 208(2):257-66. PMCID: PMC10054180.
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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 and the incoming Director of the Bakar ImmunoX Initiative, a UCSF initiative to harness immunology to improve human health. His laboratory in the Sandler Asthma Basic Research Center focuses on RNA circuits that regulate immunity.

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. We developed a biochemical method (called GCLiPP) for broadly interrogating the cis-regulatory transcriptome in living cells by mapping protein occupancy genome-wide at near-nucleotide resolution, and showed that RBP occupancy within transcripts marks cis-regulatory activity. We are now using GCLiPP together with other biochemical and human genetic data to guide experimental dissection of transcripts involved in 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. Johansson K, Gagnon JD, Zhou S, Fassett MS, Schroeder AW, Kageyama R, Bautista RA, Pham H, Woodruff PG, **Ansel KM.** An essential role for miR-15/16 in Treg suppression and restriction of proliferation. bioRxiv. 2023 Mar 26:2023.03.26.533356. Preprint.
2. Burnett CE, Okholm TLH, Tenvooren I, Marquez DM, Tamaki S, Munoz Sandoval P, Willmore A; UCSF COMET Consortium; Hendrickson CM, Kangelaris KN, Langelier CR, Krummel MF, Woodruff PG, Calfee CS, Erle DJ, **Ansel KM**, Spitzer MH. Mass cytometry reveals a conserved immune trajectory of recovery in hospitalized COVID-19 patients. Immunity. 2022 Jul 12;55(7):1284-1298.e3.
3. Pua H, **Ansel KM**. RNA regulation in immunity. *Immunol Rev*. 2021 Nov;304(1):5-9.
4. Johansson K, Woodruff PG, **Ansel KM**. Regulation of airway immunity by epithelial miRNAs. *Immunol Rev*. 2021 Nov;304(1):141-153.
5. Wigton EJ, Mikami Y, McMonigle RJ, Castellanos CA, Wade-Vallance AK, Zhou SK, Kageyama R, Litterman A, Roy S, Kitamura D, Dykhuizen EC, Allen CDC, Hu H, O'Shea JJ, **Ansel KM.** 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.
6. 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
7. 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
8. 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

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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 7 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. His current asthma-related 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.
- mechanisms underlying lung dysfunction in obesity-related metabolic disease. One component in this research area is leadership of a clinical trial studying the safety and efficacy of an IL-6 inhibitor (Clazakizumab) in “IL6-high” asthma patients (a study that is a part of the NHLBI PrecISE trial network).

Dr. Fahy leads multiple NIH supported grants related to asthma, as follows:

- a P01/PPG program in type 2 airway inflammation in asthma (includes Drs. Locksley, Ansel, Gordon and Woodruff);
- a P01/tPPG program (wrapping up this year), which developed a novel inhaled mucolytic drug treatment for mucus plug-associated lung diseases (including asthma and COPD). The intellectual property from this tPPG grant was recently licensed by UCSF to Aer Therapeutics, a life sciences company founded by Dr Fahy (https://aertherapeutics.com);
- two R01 programs, one investigating mechanisms of airway inflammation and mucus pathology in acute severe asthma and the other exploring mechanisms driving airway dysfunction in asthma patients with obesity-related metabolic disease;
- a UG1 program in which Dr Fahy leads the joint UCSF/UC-Davis PrecISE center for biomarker driven clinical trials in severe asthma.

Recent honors for Dr Fahy include election to AAP in 2016, a Recognition Award for Scientific Accomplishments from the ATS in 2017, and the UCSF Faculty Research Lecture in Translational Science in 2020.

Selected Publications

1. Gitlin I, **Fahy JV.** Mucus secretion blocked at its source in the lungs. Nature. 2022 Mar;603(7903):798-799.
2. Peters MC, Schiebler ML, Cardet JC, Johansson MW, Sorkness R, DeBoer MD, Bleecker ER, Meyers DA, Castro M, Sumino K, Erzurum SC, Tattersall MC, Zein JG, Hastie AT, Moore W, Levy BD, Israel E, Phillips BR, Mauger DT, Wenzel SE, Fajt ML, Koliwad SK, Denlinger LC, Woodruff PG, Jarjour NN, **Fahy JV**. The Impact of Insulin Resistance on Loss of Lung Function and Response to Treatment in Asthma.Am J Respir Crit Care Med. 2022 Nov 1;206(9):1096-1106.
3. **Fahy JV,** Locksley RM. Making Asthma Crystal Clear. N Engl J Med. 2019 08 29; 381(9):882-884. PMID: 31461600
4. Lachowicz-Scroggins ME, Dunican EM, Charbit AR, Raymond W, Looney MR, Peters MC, Gordon ED, Woodruff PG, Lefrançais E, Phillips BR, Mauger DT, Comhair SA, Erzurum SC, Johansson MW, Jarjour NN, Coverstone AM, Castro M, Hastie AT, Bleecker ER, Fajt ML, Wenzel SE, Israel E, Levy BD, **Fahy JV.** Extracellular DNA, Neutrophil Extracellular Traps, and Inflammasome Activation in Severe Asthma. Am J Respir Crit Care Med. 2019 May 01; 199(9):1076-1085. PMID: 30888839. PMCID: PMC6515873
5. Lambrecht BN, Hammad H, **Fahy JV.** The Cytokines of Asthma. Immunity. 2019 Apr 16; 50(4):975-991. PMID: 30995510
6. Peters MC, Kerr S, Dunican EM, Woodruff PG, Fajt ML, Levy BD, Israel E, Phillips BR, Mauger DT, Comhair SA, Erzurum SC, Johansson MW, Jarjour NN, Coverstone AM, Castro M, Hastie AT, Bleecker ER, Wenzel SE, **Fahy JV**. Refractory airway type 2 inflammation in a large subgroup of asthmatic patients treated with inhaled corticosteroids. J Allergy Clin Immunol. 2019 Jan; 143(1):104-113.e14. PMID: 29524537. PMCID: PMC6128784
7. 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 Mar 01; 128(3):997-1009. PMID: 29400693. PMCID: PMC5824874
8. 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 08 02; 113(31):8765-70. PMID: 27432971. PMCID: PMC4978244
9. 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 interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. Lancet Respir Med. 2016 07; 4(7):574-584. PMID: 27283230. PMCID: PMC5007068
10. Yuan S, Hollinger M, Lachowicz-Scroggins ME, Kerr SC, Dunican EM, Daniel BM, Ghosh S, Erzurum SC, Willard B, Hazen SL, Huang X, Carrington SD, Oscarson S, **Fahy JV.** Oxidation increases mucin polymer cross-links to stiffen airway mucus gels. Sci Transl Med. 2015 Feb 25; 7(276):276ra27. PMID: 25717100. PMCID: PMC4403633

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Prescott Woodruff is a Professor of Medicine and Chief of the Division of Pulmonary, Critical Care, Allergy and Sleep Medicine in the Department of Medicine at UCSF. 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. Han MK, Ye W, Wang D, White E, Arjomandi M, Barjaktarevic IZ, Brown SA, Buhr RG, Comellas AP, Cooper CB, Criner GJ, Dransfield MT, Drescher F, Folz RJ, Hansel NN, Kalhan R, Kaner RJ, Kanner RE, Krishnan JA, Lazarus SC, Maddipati V, Martinez FJ, Mathews A, Meldrum C, McEvoy C, Nyunoya T, Rogers L, Stringer WW, Wendt CH, Wise RA, Wisniewski SR, Sciurba FC, **Woodruff PG**; RETHINC Study Group. Bronchodilators in Tobacco-Exposed Persons with Symptoms and Preserved Lung Function. *N Engl J Med*. 2022 Sep 29;387(13):1173-1184. PMID: 36066078; PMCID: PMC9741866.
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3. Baugh AD, Shiboski S, Hansel NN, Ortega V, Barjakteravic I, Barr RG, Bowler R, Comellas AP, Cooper CB, Couper D, Criner G, Curtis JL, Dransfield M, Ejike C, Han M, Hoffman E, Krishnan J, Krishnan JA, Mannino D, Paine Iii R, Parekh T, Peters S, Putcha N, Rennard S, Thakur N, **Woodruff PG**. Reconsidering the Utility of Race-Specific Lung Function Prediction Equations. *Am J Respir Crit Care Med*. 2021 Dec 16. PMID: 34913855
4. 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.
5. 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.
6. 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).
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. Current research employs mouse and human cellular models to determine how monocyte-derived macrophages regulate fibrosis. Recent work has focused on macrophage-fibroblast crosstalk in lung injury and fibrosis.

Selected Publications

1. **Bhattacharya, M.** Insights from Transcriptomics: CD163+ Profibrotic Lung Macrophages in COVID-19. *American Journal of Respiratory Cell and Molecular Biology.* Online ahead of print. https://doi.org/10.1165/rcmb.2022-0107TR**.**
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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

1. Kotas ME, Patel NN, Cope EK, Gurrola JG 2nd, Goldberg AN, Pletcher SD, Seibold MA, Moore CM, **Gordon ED**. IL-13-associated epithelial remodeling correlates with clinical severity in nasal polyposis. *J Allergy Clin Immunol*. 2023 May;151(5):1277-1285. doi: 10.1016/j.jaci.2022.12.826. Epub 2023 Feb 2. PMID: 36736797.
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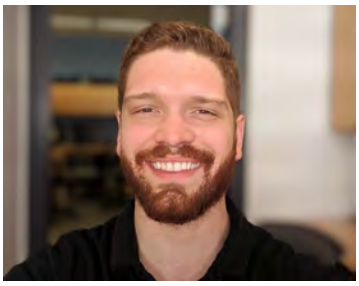

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Andrew Schroeder is a Bioinformatics Scientist in the UCSF Genomics CoLab & Dept. of Pulmonology where he builds computational pipelines for next-generation sequencing analysis (e.g. RNA-seq and scRNA-seq). He is responsible for transcript quality, cell quality, differential gene expression analysis, single-cell developmental trajectory analysis, receptor-ligand analysis, and pathway and gene ontology analysis. His background as a Research Data Analyst at the UCSF Medical Center was in the analysis of high-throughput-omics and clinical data for biomarker 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, Virginia where he trained machine learning algorithms on repeated measures of 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 a previous internship in Biostatistics and Machine Learning at the National Human Genome Research Institute of the NIH in Baltimore, Maryland and was a Graduate Research Assistant at Washington University, St. Louis Institute for Public Health, St. Louis, Missouri where he compared neoadjuvant chemotherapy drug regimens using statistical methods.

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

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

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

The Sundaram laboratory is interested in understanding the molecular mechanisms by which airway smooth muscle cells respond to allergic inflammation and regulate force transmission in chronic airways disease. Current research is focused on understanding the role of cell-matrix and cell-cell tethering in regulating force in smooth muscle, and the role of pro-inflammatory stimuli in regulating integrin activation in adherent cells. Finally, using a combination of in vitro screening, ex vivo validation, in vivo modeling, and advanced microscopy, the Sundaram lab also advances a pipeline for academic drug discovery to bring 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

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4. Del Cid JS, Reed NI, Molnar K, Liu S, Dang B, Jensen SA, DeGrado W, Handford PA, Sheppard D, **Sundaram AB**. A disease-associated mutation in fibrillin-1 differentially

regulates integrin-mediated cell adhesion. *J Biol Chem*. 2019 11 29; 294(48):18232-18243. PMID: 31640988.

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7. Tsvetanova NG, Trester-Zedlitz M, Newton BW, Riordan DP, **Sundaram AB**, Johnson JR, Krogan NJ, von Zastrow M. G Protein-Coupled Receptor Endocytosis Confers Uniformity in Responses to Chemically Distinct Ligands. *Mol Pharmacol*. 2017 Feb; 91(2):145-156. PMID: 27879340.
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.

SUPPORT TO FACULTY ASSOCIATES

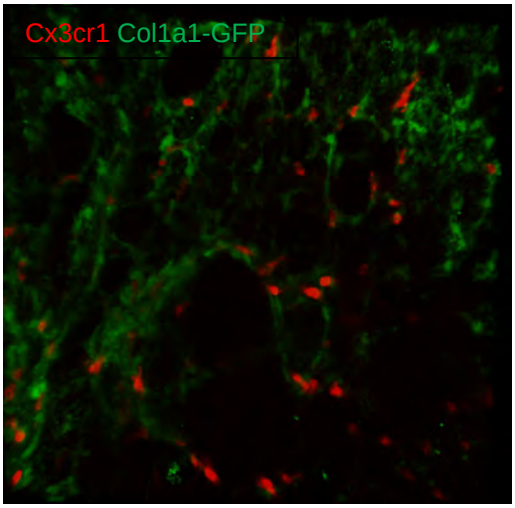
Macrophage-smooth muscle interactions in the allergic airway

Drs. Aparna Sundaram and Mallar Bhattacharya are UCSF investigators with neighboring laboratories in the Sandler Asthma Basic Research Center in HSE-201. The Sundaram Lab focuses on force transmission pathways in airway smooth muscle, and the Bhattacharya Lab is interested in lung macrophage function during inflammation and injury. Starting with a collaboration during their fellowship training in the Sheppard Lab, Drs. Sundaram and Bhattacharya have an established track record of collaborating on airway-focused projects (Bhattacharya et al. JCI PMID: 25271629).

Proposed Use of Funds

Research

Drs. Sundaram and Bhattacharya are grateful to have the opportunity to use SABRE funds to build further scientific interactions between our labs. The photomicrograph to the right is a multiphoton image acquired by the Bhattacharya lab showing that at steady state, Cx3cr1+ macrophages can be found surrounding airways in the lung. They increase markedly in the setting of disease and bear an inflammatory profile. Recently, Dr. Chris Allen, also a SABRE investigator, described the immune function of these cells vis-à-vis dendritic cells (Tang et al. *Elife* PMID: 36173678). How they may regulate other cells in the niche, such as fibroblasts and smooth muscle cells, is not currently known.



Drs. Sundaram and Bhattacharya request use of the SABRE funds to support research efforts by their respective lab members for a collaborative project focused on exploring the effect of Cx3cr1+ macrophages on airway smooth muscle function. Using macrophage ablation and macrophage-specific gene deletion approaches in acute and chronic airway allergic hyperresponsiveness models, the Sundaram and Bhattacharya Labs will test whether Cx3xr1+ macrophages or their secreted inflammatory mediators regulate airway contractility.

Benefit to larger SABRE Community

This project will be an exciting exploration of airway biology relevant to asthma and synergizes the expertise of both Drs. Sundaram and Bhattacharya. Beyond this, we believe this proposal will encourage and amplify opportunities for cross-collaborative interactions among other SABRE investigators with expertise in the biology of dendritic cells, macrophages, epithelial cells, smooth muscle, and chemosensory cells in the lung, as well as those with translational expertise and access to human asthma biopsy samples. Both Drs. Sundaram and Bhattacharya along with other SABRE investigators regularly attend and present at monthly SABRE asthma conferences, which provide an unparalleled forum for discussion of new science and establishing cross-collaborative efforts among SABRE investigators.

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.

Strategic Goals

The efforts of this center are being directed toward improving imaging technologies for the normal and allergic lung. In 2023, 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 continue to expand the capabilities of the recently completed homebuilt ZipSeq spatialtransciptomics microscope to include protocols for more tissue types, including lung.
4. To collaborate in developing an imaging workflow to detect cell populations responsible in lung fibrosis using multiplexed immunohistochemistry and fluorescence microscopy.
5. To study a rare population of progenitor cells thought to be found in lung tissue using the Resolve spatial transcriptomics imaging platform.
6. To leverage a highly multiplexed immunofluorescent kidney biopsy panel to train a deep learning semantic segmentation model to accurately annotate kidney compartments on H&E images. This technique is generalizable to lung tissue.
7. To develop an immunohistochemistry panel to investigate the interaction between cells types in mouse breast tumors.
8. To improve our microscope benchmarking and criteria tracking capabilities using an Argolight patterned fluorescence slide and the accompanying Daybook software.

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 2022, there were 269 unique users of the BIDC. Many users are trained on multiple instruments. These users represent 109 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 173 new user trainings in 2022. 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.

Alba, Diana	Harwell, Corey	Pomerantz, Jason
Alvarez-Buylla, Arturo	Hebrok, Matthias	Prakash, Arun
Anderson, Mark	Hervey-Jumper, Shawn	Rajkovic, Aleksandar
Atabai, Kamran	Ho, Sunita	Raleigh, David
Bapat, Sagar	Huang, Eric	Razani, Bahram
Barber, Diane	Jan, Taha	Reiter, Jeremy
Baskin, Laurence	Kim, Eunsun	Roose, Jeroen
Bhattacharya, Mallar	Klein, Ophir	Rosenblum, Michael
Bhushan, Anil	Knox, Sarah	Rosenbluth, Jennifer
Blelloch, Robert	Koliwad, Suneil	Rowitch, David
Bush, Jeff	Kriegstein, Arnold	Roybal, Kole
Chang, Tammy	Krummel, Matthew	Sarwal, Minnie
Chapman, Hal	Ku, Gregory	Scharschmidt, Tiffany
Chavali, Srinivas Manideep	Kutys, Matthew	Schneider, Rich

Chen, Jennifer	Laird, Diana	Schrepfer, Sonja
Cleary, Simon	L'etoile, Noelle	Selleri, Licia
Combes, Alexis	Lim, Daniel	Sneddon, Julie
Crouch, Elizabeth	Locksley, Richard	Solomon, David
Cyster, Jason	Looney, Mark	Springer, Matthew
Debnath, Jay	Lowell, Clifford	Tang, Qizhi
DenBesten, Pamela	Ma, Averil	Tlsty, Thea
Desai, Tejal	MacKenzie, Tippi	Vaisse, Christian
Deuse, Tobias	Maher, Jackie	Valdearcos Contreras, Martin
Dumont, Sophie	Maltepe, Emin	Vasquez, Joshua
Eckalbar, Walter	Manoli, Devanand	Wagner, Daniel
Erle, David	Marcucio, Ralph	Waterfield, Michael
Fahy, John	Molofsky, Ari	Weaver, Valerie
Fattahi, Seyedeh Faranak	NSFCCC Marshall Lab	Weiner, Orion
Fisher, Susan	Nystul, Todd	Wiita, Arun
Floor, Stephen	O'Farrell, Patrick	Willenbring, Holger
Gardner, James	Panagiotakos, Georgia	Wittmann, Torsten
Gartner, Zev	Paredes, Mercedes	Wolters, Paul
Gaw, Stephanie	Pati, Shibani	Xu, Allison
German, Mike	Peng, Tien	Ye, Chun
Goga, Andrei	Perera, Rushika	Yeghiazarains, Yerem
Gordon, Erin	Piao, Xianhua	Zhang, Yan
Habelitz, Stefan		

Recent Accomplishments

In 2022, scientifically:

1. Harrison Wismer (BIDC, Research Data Analyst) worked with Sunita Ho's lab (UCSF) to develop a Radial Profile Plugin using the napari software in Python. The plugin allows users to draw custom ROIs around cells/regions of interest and automatically calculates the radial profile for each custom ROI. Though not part of the program, an external script was also created to call peaks in the signals output from the plugin.
2. 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.
3. Mohammad Naser (BIDC, Microscopy Specialist) in collaboration with Alexis Combes' lab (UCSF) and Michel Kattah's lab (UCSF) piloted a spatial transcriptomics project with Nanostring to generate 1000-plex image-data of colorectal tumor through the Immunoprofiler Initiative (IPI).
4. Austin Edwards (BIDC, Bioinformatics Programmer) in collaboration with Stefani Spranger's lab (MIT) completed an analysis of Treg, dendritic cell, and CD8T cell interactions in tumor

draining lymph nodes within lung and subcutaneous tumors. A paper detailing this work was submitted and published in *Immunity* [1].

5. Austin Edwards in collaboration with Sunita Ho's lab (UCSF) imaged and analyzed the organic matrix on kidney stone samples. A paper detailing this work was submitted and accepted to *ACS Nanoscience Au* [2].
6. We continued to provide ongoing technical and instrumentation support to the asthma community at UCSF and beyond, in order to put existing and emerging imaging technologies to practical use in the study of asthma.

[1]. Zagorulya M., et al. Tissue-specific abundance of interferon-gamma drives regulatory T cells to restrain DC1-mediated priming of cytotoxic T cells against lung cancer. *Immunity.* 56(2), **2023**

[2] Bai, et al. Organic matrix derived from host-microbe interplay contributes to pathological renal biomineralization. *ACS Nanoscience Au*. **In press.**

Introduction of new people and equipment

New hire Harrison Wismer joined the BIDC in October 2022 to help fill John Eichorst's role who left the BIDC in Fall 2021. Harrison is a recent graduate from University of California, Santa Cruz with a degree in Bioinformatics. He will be responsible for conducting new user trainings, performing much of the microscope benchmarking program, and working on analysis projects internally and in collaboration with the BIDC userbase.

The BIDC grew considerably in July 2022. The Broad Center Microscopy Core (BCMC) located within the IRM building is now managed and maintained by the BIDC. As the financial situation is rectified and finalized over the next year, the microscopes will be transferred administratively to the BIDC and the BCMC will cease to exist. The microscopes will stay in their current locations and the Broad Center for Regenerative Medicine and Stem Cell Research will become a major supporter of the BIDC. The microscopes are now accessible to all BIDC users through the BIDC's established onboarding and training protocols. All current BIDC users now have access to two additional Leica Sp5 laser scanning confocal microscopes (one inverted, one upright configuration), one Leica Sp8 laser scanning confocal with a white-light laser (inverted configuration), one Leica THUNDER Imager (inverted configuration), and one Keyence self-contained microscope.

Additionally, as part of the merger process, the BCMC purchased a new Stellaris 5 laser scanning confocal microscope (inverted configuration). This microscope is a simple yet excellent confocal option for traditional 4-channel fluorescence panels. The microscope has the traditional 405 nm, 488 nm, 561 nm, and 640 nm laser lines for excitation as well as the acousto-optical beam splitter for tunable emission channels sent to 3 of the next-generation Hybrid Detectors. Important software modules include the Dye Assistant for quick experiment setup and the Navigator module for large volume exploration and acquisition.

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. Within the Medical Sciences building and the Health Sciences Tower West, the BIDC maintains microscopes at 5 different sites including behind the animal barrier. The BIDC also maintains 5 microscopes across the 4 "Pods" of the Broad Center of Regenerative Medicine building.

Plans for the Coming Year

1. Mohammad Naser is collaborating with Mallar Bhattacharya's lab (UCSF) to develop an imaging workflow to detect a particular cell population responsible in *lung fibrosis* using a multiplexed immunohistochemistry panel and fluorescence microscopy.
2. Harrison Wismer and Mohammad Naser are working with the Mark Looney lab (UCSF) on a spatial transcriptomics project looking for a rare and previously unstudied population of progenitor cells thought to be found in *lung tissue*. This utilizes the Resolve imaging platform and involves image segmentation, expression filtering, and neighborhood analysis for cells of interest.
3. Harrison Wismer and Austin Edwards are working with Zoltan Laszik (UCSF) on a project hoping to leverage a highly multiplexed immunofluorescent kidney biopsy panel to train a deep learning semantic segmentation model to accurately annotate kidney compartments (tubules, vessels, glomeruli, interstitium) on H&E images. To accomplish this, a *generalizable* pipeline was created involving image registration, generation of mIF whole slide annotations, tiling of annotations for training, and training of a model in Tensorflow. Once validated, the pipeline will be applicable other tissues such as the *lung*.
4. Mohammad Naser in collaboration with Krummel lab (UCSF) is developing an immunohistochemistry panel to investigate the interaction between cell types in mouse breast tumors.
5. The BIDC has a published schedule for maintenance and benchmarking of the microscope catalog (https://bidc.ucsf.edu/microscope-maintenance), and has recently purchased an Argolight patterned fluorescence slide and the accompanying Daybook software, which will give more a more in-depth characterization of each microscope and allow for a faster diagnosis of any issues that arise. The implementation of this workflow will primarily be led by Harrison Wismer.

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. Nikon spinning-disk confocal with TIRF and photo-ablation (Wittman)
3. Nikon spinning-disk confocal with inline super-resolution and optogenetics
4. Nikon A1R Multiphoton and laser scanning confocal microscope
5. Nikon AZ100 MacroConfocal microscope
6. Zeiss TIRF microscope with IRM
7. Zeiss Cell Observer with Apotome (Nystul)
8. Zeiss AxioImager2 with Apotome
9. Zeiss AxioImagerA1 brightfield microscope
10. Leica SP5 inverted laser scanning confocal microscope (x2)
11. Leica SP5 upright laser scanning confocal microscope
12. Leica SP8 upright laser scanning confocal microscope with white-light laser
13. Leica SP8 inverted laser scanning confocal microscope with white-light laser
14. Leica Stellaris 5 inverted laser scanning confocal microscope
15. Leica THUNDER Imager inverted widefield
16. Keyence microscope 4 fluorescence channels plus brightfield
17. IVIS Spectrum live animal imager (animal colony)
18. Selective-plane imaging microscope (SPIM) custom built: 3 lasers
19. Lattice Light-Sheet Microscope
20. *FormLabs 3D printer
21. Alveole PRIMO Micropatterning System
22. Scienion SCIFLEXARRAYER s3
23. *Precisionary Compresstome VF 310-02 Vibrating Microtome
24. Leica VT1000S Vibratome
25. *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, LivingImage, Matlab, NIS-Elements, Zen, LAS X, QuPath, GraphPad Prism, FIJI, R, and Python.

We would like to acknowledge:

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

CONTRIBUTIONS TO RELEVANT SCIENTIFIC ACTIVITIES

2022-2023 ImmunoX Seminar Series

Time: 9:00 a.m. Location: N-225 or Zoom

Date	Speaker	Host
9/5/22	NO SEMINAR - Labor Day	
9/12/22	Diane Mathis, Harvard Medical School	Mark Anderson
9/19/22	Judith Ashouri-Sinha, UCSF	Gabi Fragiadakis
9/26/22	Christopher Barnes, Stanford University	Renuka Nayak
10/3/22	Roberto Ricardo-Gonzalez, UCSF	Rich Locksley
10/10/22	Roberta Pelanda, University of Colorado, Anschutz	Julie Zikherman
10/17/22	Maziar Divangahi, McGill International TB Centre	Babak Javid
10/24/22	Ben Youngblood, St. Jude Children's Research Hospital	Rachel Rutishauser
10/31/22	Juliana Idoyaga, Stanford University	James Gardner
11/7/22	Carolina Barillas-Mury, NIAID	Melanie Ott
11/14/22	Jun Huh, Harvard Medical School	Adrian Erlebacher
11/21/22	Carla Nowosad, NYU	Hilde Schjerven
11/28/22	NO SEMINAR - Thanksgiving	
12/5/22	NO SEMINAR - Christmas	
12/12/22	NO SEMINAR - Christmas	
12/19/22	NO SEMINAR - Christmas	
12/26/22	NO SEMINAR - Christmas	
1/2/23	NO SEMINAR - New Years	
1/9/23	Soumya Raychaudhuri, Harvard Medical School	Sara Suliman
1/16/23	NO SEMINAR - MLK Day	
1/23/23	Pam Schwartzberg, NIAID	Jay Debnath
1/30/23	NO SEMINAR - Midwinter Conference of Immunologists	
2/6/23	Weiping Zou, University of Michigan	Sagar Bapat
2/13/23	Elaine Hsiao, UCLA	Peter Turnbaugh
2/20/23	NO SEMINAR - President's Day	

2/27/23	Aviv Regev, Genentech	Mallar Bhattacharya
3/6/23	Special Lectureship in Honor of Arthur Weiss Gillian Griffiths, Cambridge University	Eric Huang
3/13/23	Julia Carnevale, UCSF	Mark Ansel
3/20/23	NO SEMINAR	
3/27/23	Gianna Hammer, Duke University	Tiffany Scharschmidt
4/3/23	Andrés Hidalgo, CNIC/Yale University	Mark Looney
4/10/23	Rafi Ahmed, Emory University	Art Weiss
4/17/23	Kory Lavine, Washington University	Javid Moslehi
4/24/23	Stephanie Eisenbarth, Northwestern University	Jason Cyster
5/1/23	NO SEMINAR	
5/8/23	Susan Lynch, UCSF	Justin Eyquem
5/15/23	Kate Fitzgerald, University of Massachusetts Medical School	Maggie Feeney
5/22/23	Michela Locci, University of Pennsylvania	Tony DeFranco
5/29/23	NO SEMINAR - Memorial Day	
6/5/23	Alice Kamphorst, Icahn School of Medicine at Mount Sinai	Alexis Combes

2022-23 Pulmonary Research Conference Schedule

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

Date	Research	Research	Moderator
09/05/22	**HOLIDAY - LABOR DAY**		
09/12/22	Prescott Woodruff	Neeta Thakur	Claude Chapman
09/19/22	Paul Wolters	Maya Kotas	Prescott Woodruff
09/26/22	Tien Peng	Daniel Calabrese	Mallar Bhattacharya
10/03/22	Shoshana Zha	Nancy Allen	John Greenland
10/10/22	**HOLIDAY: INDIGENOUS PEOPLE'S DAY**		
10/17/22	Alison DeDent	Jon Singer	Shoshana Zha
10/24/22	Brian Graham	Simon Cleary PhD Mark Looney	Mehrdad Arjmandi
10/31/22	Jeff Fineman	Nabora Reyes PhD Tien Peng	Mallar Bhattacharya
11/07/22	**PULMONARY RESEARCH RETREAT**		
11/14/22	Ari Molofsky	Farshid Moussavi-Harami Mark Looney	John Greenland
11/21/22	Rahul Kumar	Melia Magnen PhD Mark Looney	Prescott Woodruff
11/28/22	Visiting Professor Francesca Polverino Baylor University		Will Mckleroy
12/05/22	**FELLOW FEEDBACK SESSION #1**		
12/12/22	**HOLD FOR HOLIDAY PARTY**		
12/19/22	**F1 FELLOW FEEDBACK SESSION #1**		
12/26/22	**HOLIDAY - WINTER BREAK**		
01/02/23	**HOLIDAY - NEW YEAR'S DAY OBSERVED**		
01/09/23	Sanjeev Datar	Aaron Baugh MD, Dean Sheppard Lab	Prescott Woodruff
01/16/23	**HOLIDAY - MLK JR. DAY**		
01/23/23	**HOLIDAY - Lunar New Year**		
01/30/23	**CANCELED**		
02/06/23	Visiting Professor Kathleen Barnes Colorado Center for Personal		Claude Chapman
02/13/23	Tony Shum	Preeti Yadav PhD Mallar Bhattacharya	John Greenland
02/20/23	**HOLIDAY - PRESIDENT'S DAY**		
02/27/23	**ACGME Survey Session**		
03/06/23	Nicholas Arger	Tatsuya Tsukui	Mallar Bhattacharya
03/13/23	Visiting Professor Bob Dickson University of Michigan School of I		Carolyn Calfee
03/20/23	**CANCELED**		
03/27/23	**SFUSD SPRING BREAK**		
04/03/23	Laurence Huang	Jinyoung Lee PhD Tien Peng	Shoshana Zha
04/10/23	Ricky Wang	Santosh Kurra	Claude Chapman
04/17/23	Visiting Professor Jon Kropski Vanderbilt University		Paul Wolters
04/24/23	Carolyn Calfee	Leah Witt	Mehrdad Arjmandi
05/01/23	**Byers Award Lecture**		
05/08/23	**F2/F3 FELLOW FEEDBACK SESSION #2**		
05/15/23	**ATS**		
05/22/23	**F1 FELLOW FEEDBACK SESSION #2**		
05/29/23	**HOLIDAY - MEMORIAL DAY**		
06/05/23	**FACULTY FEEDBACK & APPRECATION**		
06/12/23	**Visiting Professor Fernando Martinez Weill Cornell RESCHEDULE FOR 2023-24**		
06/19/23	**HOLIDAY - JUNETEENTH**		
06/26/23	**GRADUATION**		

SABRE Asthma Research Conference Schedule 2022-2023

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
10/26/22	Mallar Bhattacharya (Bhattacharya Lab)	Macrophage-Fibroblast Interactions in Lung Fibrosis
11/23/22	*No conference*	*Thanksgiving Break*
12/28/22	*No conference*	*Winter Break*
1/25/23	*No conference*	*Cancelled*
2/22/23	John Fahy (Fahy Lab)	Radiographic and Pathologic Features of Airway Mucus Plugs in Asthma
3/22/23	Aparna Sundaram (Sundaram Lab)	IL-13 and IL-17A Activate β1 Integrin to Enhance Force Transmission in Airway Smooth Muscle
4/26/23	Erin Gordon (Gordon Lab)	Non-Canonical Inflammasome Modulates Interleukin-33 Secretion and Type 2 Immunity
5/24/23	*No conference*	*Cancelled*
6/28/23	*No conference*	*Summer Break*
7/26/23	*No conference*	*Summer Break*
8/23/23	Rich Locksley (Locksley Lab)	TBA
9/27/23	Prescott Woodruff (Woodruff Lab)	TBA

RECENT AND NEW PUBLICATIONS SUPPORTED BY THE SANDLER ASTHMA BASIC RESEARCH CENTER (2021-2023)

Christopher D.C. Allen, Ph.D.

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K. Mark Ansel, Ph.D.

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Looking to the Future

Richard M. Locksley, M.D.

The SABRE Center regained momentum after the pandemic slowdown and continues to push our mission to advance basic research discoveries in asthma. Recent foundational insights include aspects of innate lymphoid cell biology, regulation of IgE, roles for microRNAs in critical signaling hubs driving asthma pathway, lung and nasal sinus epithelial cell biology, and the role of mucus plugs as potentially causal biomarkers for patients at increased risk for asthma morbidity and mortality.

SABRE investigators participated in the UCSF COMET consortium to meet 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. 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 asthma risk factors. SABRE investigators continue 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 biomarkers and outcomes for academic and industry trials.

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 an important role in shaping the footprint for patient-oriented, disease-focused, basic research at UCSF within 'Discovery Zones' that propose to re-organize investigative laboratories around distinct themes, each traversing the space from basic research to translational aspects of disease and aligned closely with studies 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 increase access to human tissues and furthering cutting-edge technologic advances. We continue to strive to be a nimble, transformative research platform with the ability to pivot 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 locating 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 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 1-2 years of preparation and preliminary data prior to submission but we are confident that the quality of the science and the intensity of investigator interactions will enhance likelihood of success. At the same time, we have consolidated administrative support to a single position to maximize available finances for 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 past decade of the SABRE Center in our mission to understand and ultimately conquer asthma. These challenges we take seriously to honor the extraordinary vision of the Sandler family and Sandler Foundation in committing resources to asthma basic research at UCSF. 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.

Hong-Erh Liang, Ph.D., M.S.

Richard Locksley, M.D

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

Roberto Ricardo-Gonzalez, 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 AI 154335
Allen (PI)
01/21/21-12/31/22
Molecular basis for the regulation of IgE class switch recombination by IL-21 and STAT3

R01 AI 130470
Allen (PI)
11/20/17-10/31/22
Regulation of IgE responses by B cell receptor signaling

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. Wade-Vallance AK, Yang Z, Libang JB, Robinson MJ, Tarlinton DM, **Allen CDC**. B cell receptor ligation induces IgE plasma cell elimination. J Exp Med. 2023 Apr 3;220(4):e20220964. PubMed PMID: 36880536. PubMed Central PMCID: PMC9997509.
2. Tang XZ, Kreuk LSM, Cho C, Metzger RJ, **Allen CDC**. Bronchus-associated macrophages are positioned for soluble antigen capture from the airway lumen and are capable of local Th2 cell activation. eLife. 2022 Sep 29;11:e63296. PubMed PMID: 36173678. PubMed Central PMCID: PMC9560158.
3. 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.
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. PubMed 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, I studied the migration dynamics of B cells in 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 then 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**, 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. **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.
c. **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
d. 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.

2. 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 short-lived 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. We have also 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 are dispensable. In more recent work, we determined that ligation of the IgE B cell receptor induced the elimination of IgE plasma cells. Overall, our studies have provided critical new insights into understanding the mechanisms regulating IgE antibody responses in vivo, which have further elaborated on in reviews and a methods chapter.
   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. 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
   d. Wade-Vallance AK, Yang Z, Libang JB, Robinson MJ, Tarlinton DM, **Allen CDC**. B cell receptor ligation induces IgE plasma cell elimination. J Exp Med. 2023 Apr 3;220(4):e20220964. PubMed PMID: 36880536. PubMed Central PMCID: PMC9997509.

3. In the course of our above studies on IgE, 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.

4. 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 also demonstrated that an antibody widely used to deplete mouse basophils, MAR-1, unexpectedly binds to Fcγ receptors on tissue macrophages and monocytes, potentially explaining discrepancies between the results reported by antibody-mediated versus genetic methods of basophil depletion in mice.
   a. Sullivan BM, Liang HE, Bando JK, Wu D, Cheng LE, McKerrow JK, **Allen CDC***, Locksley RM*. Genetic analysis of basophil function in vivo. Nat Immunol. 2011 Jun;12(6):527-35. PubMed PMID: 21552267; PubMed Central PMCID: PMC3271435. *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.

5. In situ studies of the lung may provide important new insights into the mechanisms of allergic airway inflammation and lung repair. In order to understand how allergic airway inflammation is induced in the lung, my laboratory studied how inhaled antigens are captured and presented near the bronchial airways. By two-photon microscopy, we revealed that soluble inhaled antigens are captured by a population of macrophages localized around the bronchial airways and enriched at airway bifurcations. These bronchus-associated macrophages remained lung resident, processed and presented antigen on MHC class II, and interacted with effector Th2 cells. We also determined that dendritic cells localized near the airways engaged in extensive interactions with bronchus-associated macrophages that had captured inhaled soluble antigen. This work has provided important new insights into the mechanism of antigen capture and presentation near the bronchial airways. In collaborative studies, my laboratory also contributed to the development of a method to quantify airway narrowing and airway smooth muscle shortening in the trachea by two-photon microscopy. This technique demonstrated the importance of integrin-mediated cell matrix tethering in the mechanism of force transmission in airway contraction induced by IL-13, which is relevant to airway hyperresponsiveness in asthma. I also contributed my imaging expertise and assisted with microscopy for a recent study of the communication between macrophages and fibroblasts in the lung after injury in a model of lung fibrosis. These studies took advantage of dynamic imaging of calcium flux by two-photon microscopy to determine the functional outcome of this cellular communication.
   a. Liu S, Ngo U, Tang XZ, Ren X, Qiu W, Huang X, DeGrado W, **Allen CDC**, 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. PubMed PMID: 33956668; PubMed Central PMCID: PMC8203456.

b. Bhattacharyya A, Torre P, Yadav P, Boostanpour K, Chen TY, Tsukui T, Sheppard D, Muramatsu R, Seed RI, Nishimura SL, Jung JB, Tang XZ, **Allen CDC**, Bhattacharya M. Macrophage Cx43 Is Necessary for Fibroblast Cytosolic Calcium and Lung Fibrosis After Injury. Front Immunol. 2022 May 12;13:880887. PubMed PMID: 35634278; PubMed Central PMCID: PMC9134074.
c. Tang XZ, Kreuk LSM, Cho C, Metzger RJ, **Allen CDC**. Bronchus-associated macrophages are positioned for soluble antigen capture from the airway lumen and are capable of local Th2 cell activation. eLife. 2022 Sep 29;11:e63296. PubMed PMID: 36173678. PubMed Central PMCID: PMC9560158.

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)*	Completion Date MM/YYYY	FIELD OF STUDY
Virginia Tech, Blacksburg, VA	BS	05/1996	Biochemistry
University of California San Francisco, San Francisco, CA	PhD	09/2001	Biomedical Sciences
Immune Disease Institute, Harvard Medical School	Postdoctoral	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
05/08/20-08/31/22 (NCE)
UCSF COVID-19: Extended Immunophenotyping Studies

FastGrants2020
Ansel, Spitzer (co-PIs)
05/01/20-04/30/22
High Dimensional Analysis of the Inflammatory Cytokine Storm in COVID-19

Highlighted Citations:

1. Johansson K, Gagnon JD, Zhou S, Fassett MS, Schroeder AW, Kageyama R, Bautista RA, Pham H, Woodruff PG, **Ansel KM.** An essential role for miR-15/16 in Treg suppression and restriction of proliferation. bioRxiv. 2023 Mar 26:2023.03.26.533356. doi: 10.1101/2023.03.26.533356. Preprint. PMID: 36993421.
2. Wigton EJ, Mikami Y, McMonigle RJ, Castellanos CA, Wade-Vallance AK, Zhou SK, Kageyama R, Litterman A, Roy S, Kitamura D, Dykhuizen EC, Allen CDC, Hu H, O'Shea JJ, **Ansel KM.** 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. doi: 10.1084/jem.20201422. PMID: 34586363.
3. Johansson K, Woodruff PG, **Ansel KM.** Regulation of airway immunity by epithelial miRNAs. Immunol Rev. 2021 Nov;304(1):141-153. doi: 10.1111/imr.13028. PMID: 34549450.

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2023 – Present	Director, ImmunoX Initiative, UCSF
2021 – Present	Visiting Professor InFLAMES, University of Turku, Finland
2018 – Present	Professor, Department of Microbiology & Immunology, UCSF
2008 – Present	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

2022 – Present	Board Member, Solving for Science
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 – Present	Reviewing Editor, Science Signaling
2007 – Present	Member, International Cytokine Society
2006 – Present	Member, American Association of Immunologists
1998 – Present	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. We interrogate RNA circuits that govern gene expression and cell identity. We optimized a robust RNA interactome capture assay, Global CrossLinking Protein Purification (GCLiPP), that generates transcriptome-wide maps of RNA binding protein occupancy in living cell lines and primary cells. We intersect these protein occupancy maps with human genetic data and use CRISPR-based reverse genetics to discover and investigate key cis-regulatory elements that mediate post-transcriptional gene regulation in lymphocytes. A massively parallel reporter assay detected deeply conserved patterns of regulatory activity across 26,000 protein-occupied sequences from T cells. These experiments revealed strong correlations between nucleotide content, local RNA folding potential, and transcript destabilization. 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; 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. Taylor KE, **Ansel KM**, Marson A, Criswell LA, Farh KK. PICS2: next-generation fine mapping via probabilistic identification of causal SNPs. Bioinformatics. 2021 Sep 29;37(18):3004-3007. PubMed PMID: 33624747; PMCID: PMC8528038.
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.

2. 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. PMID: 23382546; 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. PMID: 30566862; 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. PMID: 30673615; PMCID: PMC6365014

3. 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, Zhou SK, Kageyama R, Litterman A, Roy S, Kitamura D, Dykhuizen EC, Allen CDC, Hu H, O'Shea JJ, **Ansel KM**. 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; PMCID: PMC8485858.
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, Kageyama R, Chiou NT, Gallman A, de Kouchkovsky D, Jeker LT, McManus MT, Erle DJ, **Ansel KM**. 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.

4. 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; PMCID: PMC8021117.
    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.

5. We have also made important contributions to the understanding of RNA regulation of immune tolerance and autoimmunity. MicroRNAs regulate central tolerance through effects on thymocyte selection, and also control peripheral T cell tolerance by modulating costimulation and Treg cell activity. We showed that the miR-17~92 cluster of miRNAs is essential to specify the identity of Tfh cells, which otherwise acquire an inflammatory Th17/Th22-like gene expression program. We then mapped the cluster's inhibitory effect on Th17 cell differentiation to miR-18. This proposal will expand our exploration of RNA circuits in autoimmune disease.
    a. 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.

b. Montoya MM, Maul J, Singh PB, Pua HH, Dahlström F, et al. A Distinct Inhibitory Function for miR-18a in Th17 Cell Differentiation. J Immunol. 2017 Jul 15;199(2):559-569. PMID: 28607111 PMCID: PMC5508756
c. Schaffert SA, Loh C, Wang S, Arnold CP, Axtell RC, et al. mir-181a-1/b-1 Modulates Tolerance through Opposing Activities in Selection and Peripheral T Cell Function. J Immunol. 2015 Aug 15;195(4):1470-9. PMID: 26163591; PMCID: PMC4763610.
d. Simpson LJ, **Ansel KM**. MicroRNA regulation of lymphocyte tolerance and autoimmunity. J Clin Invest. 2015 Jun;125(6):2242-9. PMID: 26030228 PMCID: PMC4497751.

Complete List of Published Work in My Bibliography:
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

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). PMC8021117.
2. Nakada EM, Bhakta NR, Korwin-Mihavics BR, Kumar A, Chamberlain N, Bruno SR, Chapman DG, Hoffman SM, Daphtary N, Aliyeva M, Irvin CG, Dixon AE, Woodruff PG, Amin S, Poynter ME, Desai DH, Anathy V. Conjugated bile acids attenuate allergen-induced airway inflammation and hyperresponsiveness by inhibiting UPR transducers. JCI Insight. 2019 May 2;4(9):e98101. PMC6538331
3. 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.

Positions, Scientific Appointments, and Honors

Positions and Employment

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

Other Experience and Professional Memberships

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

Honors

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

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 can assist 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. This collaborative work 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 & Psych. (Neuroscience)
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 07/01/2021 – 06/30/2025
Title: Targeting ATP receptor P2rx4 for pulmonary fibrosis.
Role: PI
Goals: This project will test whether ATP effluxed via connexin hemichannels by monocyte-derived macrophages leads to activation of fibroblasts via the ATP receptor P2rx4.

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

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022 Reviewer, Israel Science Foundation, Research Grants Program
2022 Reviewer, UK Medical Research Council, Research Grants Program
2021- Investigator, UCSF Bakar Aging Research Institute
2019- Associate Professor, Department of Medicine, Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, UCSF
2012-2019: Assistant Professor, Department of Medicine, Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, UCSF
2010-2012: Instructor, Department of Medicine, Division of Pulmonary and Critical Care Medicine, UCSF
2010- Diplomate, Critical Care Medicine Certification, American Board of Internal Medicine
2009- Diplomate, Pulmonary Medicine Certification, American Board of Internal Medicine
2007-2010: Fellow, Pulmonary/Critical Care Medicine, UCSF
2007-2017 Diplomate, Internal Medicine Certification, American Board of Internal Medicine
2007- Member, American Thoracic Society
2004-2007: Resident, Internal Medicine, Johns Hopkins Hospital, Baltimore, MD

2002-2003: Fellow, Ruth L. Kirschstein Medical Student National Research Service Award, Fred Hutchison Cancer Research Center, Seattle, WA
1998-1999: Honorary Frank Knox Memorial Fellow (awarded by Harvard University), Oxford, UK

Honors

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

C. 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. (2013) Effective treatment of mouse sepsis with an inhibitory antibody targeting integrin αvβ5. ***Critical Care Medicine***. 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. ***American Journal of Respiratory and Critical Care Medicine***. 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. ***American Journal of Physiology: Lung Cell and Molecular Physiology***. 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 focused on the role of macrophage-derived ATP in driving fibroblast responses after injury.
   a. 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.
   b. 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.
   c. 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***. 322(3):L495-L502. PMID: 35107021. PMCID: PMC8917922.
   d. Bhattacharyya A, Torre P, Yadav P, Boostanpour K, Chen TY, Tsukui T, Sheppard D, Muramatsu R, Seed RI, Nishimura SL, Jung JB, Tang XZ, Allen CDC, Bhattacharya M. (2022) Macrophage Cx43 Is Necessary for Fibroblast Cytosolic Calcium and Lung Fibrosis After Injury. ***Frontiers in Immunology***. May 12;13:880887. PMID: 35634278. PMCID: PMC9134074.

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 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 lung fibrosis and survival studies for this work. A second project 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. ***Nature Communications*****. 12,** 6309. PMID: 34728633. PMCID:PMC8563941.

A complete list of my publications is available at:
https://www.ncbi.nlm.nih.gov/myncbi/1hyab8c8hE3A_/bibliography/public/

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 YYYY	FIELD OF STUDY
Tulane University	----	1968	Premedical
University of Alabama School of Medicine	M.D.	1972	Medicine
Residency in Internal Medicine, University of Utah Affiliated Hospitals, Salt Lake City, UT		1975	Medicine
Associate Investigator, V.A. Medical Center, Salt Lake City, UT		1977	Infectious Disease
Pulmonary Fellow, University of Utah Affiliated Hospitals, Salt Lake City, UT		1979	Pulmonary/Critical Care

Positions and Honors

Positions

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 proven effective in a phase III clinical trial for post-menopausal osteoporosis (Merck). Unfortunately, off target vascular effects prevented its approval as a drug.

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, and 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.

5. After moving to UCSF I focused my lab on epithelial biology and in particularly pulmonary fibrosis as a disorder of great, unmet medical need and a logical extension of my prior work in matrix biology. I led in vivo investigations of the role of epithelial mesenchymal transition (EMT) in pulmonary fibrosis and in the course of studying epithelial plasticity we discovered a population of lung epithelial progenitors expressing the integrin α6β4 capable of regenerative activity in vitro and in vivo in response to major injury. Follow-up studies referenced below led to the discovery that the actual stem/progenitor cells are relatively rare distal airway epithelial subpopulations low in mature lineage markers, identifiable in mice by high levels of the Class I antigen H2K-1, and capable of rapid mobilization, proliferation, and pluripotent differentiation in vivo. In humans we have recently identified Type II cells as much more plastic than that of mice, capable of transdiifferentiation and expansion as metaplastic basal cells after major injury. So, in mice airway progenitors mobilize and migrate into alveoli. In humans, alveolar Type II cells transdifferentiate and execute early lung repair locally. My lab now is comprised of mainly PhD trainees and research faculty. We are committed to a mechanistic understanding of the cellular basis of alveolar regeneration after lung injury.

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. Lineage-negative Progenitors Mobilize to Regenerate Lung Epithelium after Major Injury. ***Nature*** 2015 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), and Vaughan AE. Local lung hypoxia determines epithelial fate decisions during alveolar regeneration. ***Nature Cell Biology*** 2017, 19(8):904-914. PMCID: PMC5600325

3. Kathiriya J, Brumwell, AN, Jackson JR, Tang X, Chapman HA. Distinct airway epithelial stem cells hide among club cells but mobilize to promote alveolar regeneration. ***Cell Stem Cell.*** 2020, 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), and Peng T. Human alveolar Type 2 epithelium transdifferentiates into metaplastic KRT5+ basal cells. ***Nature Cell Biology***. 2022, 24(1):10-23.

Full reference list can be found at:
http://www.ncbi.nlm.nih.gov/sites/myncbi/harold.chapman.1/bibliograpahy/40691690/public/?sort=date&direction=ascending

Research Support

Ongoing Research Support

U01HL134766 Chapman, HA PI 09/01/2016-8/31/2023
Epithelial stem/progenitor cells as repair agents in diffuse alveolar damage.
This project describes a new therapeutic approach to lung repair that extends recent results in mice demonstrating that lung stem/progenitor cells can transplant and engraft in damaged lungs. The application is driven by the frustrating current state of pulmonary medicine that offers little more than supportive care in the management of acute respiratory failure and progressive fibrotic lung diseases. A group of investigators have come together to overcome the hurdles of stem/progenitor cell replacement therapy in humans.

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

R61/R33 HL158540. Chapman, HA Co-PI 06/1/2022-5/31/2026
Dose ranging study of oral epigallocatechin-3-gallate (EGCG) given daily for 12 weeks to patients with Idiopathic Pulmonary Fibrosis (IPF) evaluating safety, PK interactions with standard of care drugs, and biomarkers of drug effect. EGCG is being investigated for the treatment of idiopathic pulmonary fibrosis (IPF). The rationale for evaluation the safety and biomarkers of EGCG as a treatment for IPF comes from effects demonstrated on mechanisms believed to be important for the pathophysiology of the condition. The rationale for these studies is the extensive prior pre-clinical data in mice that the trihydroxyphenolic EGCG is efficacious in attenuating pulmonary fibrosis by blocking collagen cross-linking and the pro-fibrotic pathway mediated by TGFβ1 signaling. More compelling are data demonstrating that in humans EGCG is safe and capable of blocking lung tissue pro-fibrotic signaling when given two weeks prior to diagnostic surgical biopsy

of pulmonary fibrosis patients, many of whom were subsequently diagnosed with IPF (Chapman HA et al, NEJM 382:11, 2020). However, EGCG has never been given for longer than two weeks to IPF patients and interactions with FDA drugs approved for treatment of IPF patients are unknown.

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	A.B.	06/1975	Biochem. Sci.
Univ. California, Berkeley, CA	Ph.D.	10/1979	Biochemistry
National Institutes of Health, Bethesda, MD	postdoctoral	8/1983	Immunology

Positions and Honors

Positions

1972 - 1975	Undergraduate research, laboratory of Dr. Jack Strominger. HLA antigens.
1976 - 1979	Graduate research, laboratory of Dr. Daniel E. Koshland, Jr. Bacterial chemotaxis.
1979 - 1983	Postdoctoral research, laboratory of Dr. William E. Paul. B cell activation.
1983 - 1988	Assistant Professor, UCSF, Department of Microbiology & Immunology,
1988 - 1994	Associate Professor, UCSF, Department of Microbiology & Immunology
1989- 1990	Sabbatical with David Baltimore, Whitehead Insititute, MIT, Cambridge, MA
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)

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-present); NIH ad hoc grant reviewer (average 2+ reviews per year, 2005-2013); 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-present (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.

Contribution to Science

1. Mechanism of signal transduction by the BCR
A longstanding problem is how lymphocytes recognize the presence of the antigen that they recognize. We were the first (along with two other independent groups) to demonstrate that the BCR signals by inducing protein tyrosine phosphorylation (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. This project is the subject of the current application.

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 AL, and Lowell CA. (2013). Hyperactivated MyD88 signaling in dendritic cells, through specific deletion of Lyn kinase, causes severe autoimmunity and inflammation. Proc. Natl. Acad. Sci. USA. 110: E3311-20. PMC3761623

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 and F. Yarovinsky (2011). Critical coordination of innate immune defense against *Toxoplasma gondii* by dendritic cells responding via their Toll-like receptors. Proc. Natl. Acad. Sci USA 108: 278-283. PMC3017180.

4c. Raetz,M, Hwang, S-H, Wilhelm, C, Kirkland, D, Benson, A, Sturge, C, Mirpuri, J, Vaishnava, S, Hou, B, DeFranco, AL, Gilpin, CJ, Hooper, LV, Yarovinsky, F. (2013). Parasite-induced Th1 cells promote intestinal dysbiosis via IFN-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, Anthony L. DeFranco (2011). Selective utilization of Toll-like receptor and MyD88 signaling in B cells for enhancement of the anti-viral germinal center response. Immunity 34: 375-84. 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 m-myc and mTORC1 activity in germinal center B lymphocytes. Immunohorizons 3: 389-401. PMCID: PMC6738343.

A complete list of my publications is available at:
http://www.ncbi.nlm.nih.gov/sites/myncbi/anthony.defranco.1/bibliography/41142681/public/?sort=date&direction=ascending

Research Support

Active

"Organ-specific autoimmunity resulting from two genetic defects in tolerance"
Principal Investigator: Anthony DeFranco, 2.4 calendar mo. effort
1R01 AI138479-01
3/1/18-2/28/23.
Agency: NIH/NIAID

Completed (last 3 years)

1. "B cell TLRs and Germinal Centers"
Principal Investigator: Anthony DeFranco, 1.2 calendar mo. effort
1R21AI117378-01
7/1/15-6/30/17
Agency: NIH/NIAID

BIOGRAPHICAL SKETCH

NAME: William F. DeGrado

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	B.S.	05/1977	Chemistry
University of Chicago, Chicago, IL	Ph.D.	1981	Organic Chemistry

Positions, Scientific Appointments, and Honors

Professional Experience:

1981-1990 Research Chemist, CR&D, DuPont Company, Wilmington, DE
1990-1992 Research Leader, CR&D, DuPont Company, Wilmington, DE
1992-1994 Research Fellow, R&D, The DuPont Merck Pharmaceutical Company, Wilmington, DE
1994-1996 Senior Director, R&D, The DuPont Merck Pharmaceutical Company, Wilmington, DE
1996-2011 Professor, Dept. of Biochemistry & Biophysics, University of Pennsylvania, Philadelphia, PA
2011-present Professor, UCSF Department of Pharmaceutical Chemistry

Visiting Positions:

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

Honors:

1988 du Vigneaud Award for Peptide Research
1989 Protein Society Young Investigator Award
1992 Eli Lilly Award in Biological Chemistry (American Chemical Society)
1994 Fellow, American Association for the Advancement of Science
1998 Member, American Academy of Arts and Sciences
1999 Member, National Academy of Sciences (U.S.A.)
2003 Merrifield Award, (presented by the Peptide Society)
2008 Ralph F. Hirschmann Award in Peptide Chemistry (American Chemical Society)
2009 Makineni Award (APS)
2014 Member, National Academy of Inventors (U.S.A.)
2015 Stein & Moore Award (Protein Society)
2016 Max T. Rogers Award Lecture (Mich. State); Distinguished Visiting Professor (FSU).
2016 Max Perutz Memorial Lecture (Weizmann Institute, Israel)
2017 Distinguished Alumnus Award (Kalamazoo College).
2018 Cope Scholar Award (American Chemical Society, Organic Division).
2018 M. Goodman Memorial Prize (American Chemical Society, Biological Division).
2020 John Scott Inventor award from City of Philadelphia and American Philosophical Society.

Other experience and Professional Memberships

Assoc. Editor Proteins: Structure, Function, Genetics (’88-90); Journal of Peptide Research (97-00) Assoc. Ed. Current Res. in Prot. Chem. (89), Guest Editor Cur. Op. Struct. Bio (odd years 99-13); Guest Editor Chem. Rev. (99).

Editorial Advisory Boards Proteins (90-08); JACS (88-95); JMR (88-01); J. Peptide Research (98-**Present**); Protein Engineering (89-**Present**); Protein Science (90-95); Biochem. (94-97); Prot. Pep. Lett (94-98), Acc. Chem Res. (99-09), J. Comb. Chem. (98-02); Cur. Opinion Chem. Bio. (99-**Present**); Structure (99-**Present**), 1988-1995.

Prof. Societies President, The Protein Society (01-03); Council, The Protein Society (00-04); various committees for NAS and AAAS.

Inst. Boards Chair SAB Institute for Neurdegeneration (UCSF); Member Cardiovascular Inst. (UCSF); Member SAB (Inst. of Human Virology; U. of MD).

Contributions to Science

1) Protein Design. When our group first pioneered de novo protein design, proteins were seen as impossibly complex molecules whose structure could not be predicted or designed. We therefore adopted a minimalist approach to protein design in which we set out to engineer sequences of the minimum complexity required for folding and a given function. Our group was the first to design and convincingly characterize proteins from scratch – three-helix and four-helix bundles. De novo protein design proved useful for probing the features required for forming secondary structures (e.g., O'Neil and DeGrado's well-known thermodynamic scale of helix propensity), compact states known as "molten globules" and ultimately well-packed native protein structures. This method was then used to design proteins that bound DNA, transition metals, and redox-active cofactors, including both natural and non-natural porphyrins. Our work on di-metal proteins has deepened our understanding of how a protein creates an environment to tune the activity of its metal ion cofactors. We have shown how small changes to ligand environment convert a protein from an oxidase to a hydroxylase. We also designed Zn^{2+}-binding peptides that adopt catalytically active cross-beta fibrils, with potential to open new doors for the design of catalytic materials as well as implications concerning the evolution of life. We also designed proteins that bind and coat various materials, including carbon nanotubes and proteins that bind a variety electrical and optical cofactors. We reported the first example of a protein that stabilizes organic radicals for weeks in aqueous solution.

Most recently, we have developed methods for precise design of proteins that bind small molecule drugs and organic metal cofactors, providing the first example of structurally verified successful designs of small molecule binding proteins (without the need of extensive experimental screening or directed evolution). Key to these achievements were new concepts for protein design. We showed how to couple the favorable packing of the hydrophobic core to the active site to achieve tight binding. We also invented a new element of structure, the van der Mer, which links the position of the backbone of an amino acid to potential interacting groups, in much that rotamers map positions of sidechain atoms to the backbone. This concept has enabled rapid and accurate sampling of interactions in proteins.

[1] Grigoryan, G., Kim, Y. H., Acharya, R., Axelrod, K., Jain, R. M., Willis, L., Drndic, M., Kikkawa, J. M., and DeGrado, W. F. (**2011**) Computational design of virus-like protein assemblies on carbon nanotube surfaces, ***Science*** *332*, 1071-1076. PMC3264056

[2] Ulas G, Lemmin T, Wu Y, Gassner GT and DeGrado WF (**2016**) Designed metalloprotein stabilizes a semiquinone radical. ***Nature Chemistry*** 8:354-9. PMC4857601.

[3] Polizzi, N, Wu, Y., Lemmin, T, Maxwell, A, Zhang, SQ, Rawson, J., Beratan, DN, Therien, M.J., DeGrado, WF. (**2017**) De novo design of a hyperstable, non-natural protein-ligand complex with sub-Å accuracy. ***Nature Chemistry*** 9:1157-1164. PMC5859929

[4] Polizzi, N, DeGrado, WF. (**2020**) A defined structural unit enables de novo design of small-molecule–binding proteins. ***Science*** 369:1227-1233. PMCID PMC7526616

2) Membrane protein design. We used minimalist design principles to delineate the features required for assembly and conduction of ion channels, and we then used these principles to design TM, multi-porphyrin helical bundles that catalyze electron transfer through phospholipid membranes. Simultaneous with Engelman's group, we showed the role of polar amino acids in inducing association of transmembrane helices, and their role in membrane protein folding and assembly. We have elucidated a sequence-specific code for recognition of TM helices in membranes, and used it to design peptides that target the TM regions of membrane proteins. We also have designed helical bundles that use a Zn(II) gradient to drive the transport of protons up a concentration gradient (and vice versa). This work was particularly significant, as it was the first example of a designed membrane protein whose structure was determined at high resolution. Most recently, we focused on defining the role of van der Waals packing in driving folding in membrane environments, and in so doing we design a highly robust hyperstable transmembrane 5-helix bundle, which is an excellent scaffold for design of functional membrane proteins.

[1] Yin, H., Slusky, J. S., Berger, B. W., Walters, R. S., Vilaire, G., Litvinov, R. I., Lear, J. D., Caputo, G. A., Bennett, J. S., and DeGrado, W. F. (**2007**) Computational design of peptides that target transmembrane helices, **Science** *315*, 1817-1822.

[2] Fong KP, Zhu H, Span LM, Moore DT, Yoon K, Tamura R, Yin HH, DeGrado WF and Bennett JS (**2016**) Directly Activating alphaIIbbeta3 Initiates Outside-In Signaling by Causing alphaIIbbeta3 Clustering. ***J Biol Chem***. doi: 10.1074/jbc.M116.716613. PMCID PMC4882439.

[3] Joh, N. H., Wang, T., Bhate, M. P., Acharya, R., Wu, Y., Grabe, M., Hong, M., Grigoryan, G., and DeGrado, W. F. (**2014**) De novo design of a transmembrane Zn^{2+}-transporting four-helix bundle, ***Science*** *346*, 1520-1524. PMC4400864.
[4] Mravic M, Thomaston JL, Tucker M, Solomon PE, Liu L and DeGrado WF. Packing of apolar side chains enables accurate design of highly stable membrane proteins. **Science. 2019**;363:1418-1423. doi: 10.1126/science.aav7541. PubMed PMID: 30923216.

3) Structure/Function of the M2 proton channel from influenza A virus. Our early work with the groups of Robert Lamb and Larry Pinto established the overall fold and mechanism of the M2 proton channel, which is the target of the anti-influenza drugs, amantadine and rimantadine. We first proposed the transporter-like and His-shuttle mechanisms, which are now widely accepted. A decade later our group's crystallographic[9] and solution NMR structures provided direct support for these mechanisms. These structures defined the drug-binding site and explained how mutations led to amantadine-resistance. We have solved extremely high-resolution (1.05 Å) crystal structures of M2's pore, and studied the structure at room temperature using XFEL radiation. These structures showed well-defined water-wires for conduction of protons through the length of the pore, leading to the critical His37 proton-shuttling residue. Beyond the medical importance of M2, these studies provide important insight into the structure of water in confined spaces and its contribution to proton conduction throughout biology. My group also 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). Based on our proposed conductance mechanism, we designed novel small molecules that inhibit known clinically problematic mutants.

[1] 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.
[2] 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.
[3] 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. doi: 10.1073/pnas.1705624114. PubMed PMID: 28835537.
[4] Thomaston JL, Polizzi NF, Konstantinidi A, Wang J, Kolocouris A and DeGrado WF. Inhibitors of the M2 Proton Channel Engage and Disrupt Transmembrane Networks of Hydrogen-Bonded Waters. **J Am Chem Soc.** 2018;140(45):15219-15226. Epub 2018/08/31. doi: 10.1021/jacs.8b06741. PubMed PMID: 30165017.

4) Small molecule mimics of antimicrobial peptides, and transmembrane signaling in bacteria. Antimicrobial peptides are an essential component of innate immunity in all higher organisms. In early work we used minimalist peptide and foldamer design to engineer idealized versions of antimicrobial peptides, thereby showing that a basic amphiphilic helix was necessary and sufficient for their activities. Ultimately, we designed small molecules that were more potent and less toxic to animals than the parent antimicrobial peptides. One such compound, licensed to the company Innovation Pharma, successfully completed two phase II clinical trials (in humans) for highly drug-resistant *Staphylococcal aureus* infections, and it is moving into phase III studies. Our recent work in this area focused on the mechanisms by which bacteria respond to antimicrobial peptides as part of their own defense against the innate response of the host. We identified a group of bacterial histidine kinases and their corresponding response regulators that orchestrate the response to antimicrobial agents (in Gram positive and negative bacteria). Our primary focus now is to understand the mechanism by which signals are propagated across a membrane. We used integrative structural modeling to piece together the first experimental structure of a histidine kinase, and a large collection of mutants to examine the mechanism of signal transduction.

[1] Tew GN, Scott RW, Klein ML and DeGrado WF (**2010**) De novo design of antimicrobial polymers, foldamers, and small molecules: from discovery to practical applications. **Acc Chem Res** 43:30-9. PMC2808429
[2] Molnar, K. S., Bonomi, M., Pellarin, R., Clinthorne, G. D., Gonzalez, G., Goldberg, S. D., Goulian, M., Sali, A., and DeGrado, W. F. (**2014**) Cys-Scanning Disulfide Crosslinking and Bayesian Modeling Probe the Transmembrane Signaling Mechanism of the Histidine Kinase, PhoQ, ***Structure*** *22*, 1239-1251. PMC4322757
[3] Bhate MP, Lemmin T, Kuenze G, Mensa B, Ganguly S, Peters JM, Schmidt N, Pelton JG, Gross CA, Meiler J and DeGrado WF. Structure and Function of the Transmembrane Domain of NsaS, an Antibiotic Sensing Histidine Kinase in Staphylococcus aureus. **J Am Chem Soc. 2018**;140(24):7471-7485. doi: 10.1021/jacs.7b09670. PubMed PMID: 29771498.
[4] Clark IC, Mensa B, Ochs CJ, Schmidt NW, Mravic M, Quintana FJ, DeGrado WF and Abate AR. Protein design-scapes generated by microfluidic DNA assembly elucidate domain coupling in the bacterial histidine

kinase CpxA. **Proc Natl Acad Sci U S A. 2021**;118(12). Epub 2021/03/17. doi: 10.1073/pnas.2017719118. PubMed PMID: 33723045.

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	A.B.	05/1980	Biochemistry
University of California, San Francisco, CA	M.D.	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 projects:

R35 HL145235
Erle (PI)
04/15/2019-02/28/2026
Airway Epithelial Cell Gene Regulation: New Mechanisms and Therapeutic Strategies

U19 AI 077439
Erle (PI, Project 1 Leader)
03/01/2018-02/28/2028
Immune-driven Airway Epithelial Dysfunction in Muco-obstructive Asthma

U19 AI 077439-13S1
Erle (PI)
05/08/2020-03/31/2024
UCSF COVID-19: Extended Immunophenotyping Studies

U19 AI 077439-13S2
Erle (PI)
05/08/2020-03/31/2024
UCSF COVID-19 Immunophenotyping Clinical Study and Core Laboratories

Cystic Fibrosis Foundation URNOV19XX0
Urnov (PI); Role: UCSF subcontract PI
02/01/2020-01/31/2023 (NCE pending)
Advancing delivery of novel genome editing enzymes to correct orphan CF mutations

Citations:

1. 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.
2. 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.
3. Bonser LR, **Erle DJ**. The airway epithelium in asthma. *Adv Immunol*. 2019;142:1-34. PubMed PMID:31296301.
4. Koh KD, Bonser LR, Eckalbar WL, Yizhar-Barnea O, Shen J, Zeng X, Hargett KL, Sun DI, Zlock LT, Finkbeiner WE, Ahituv N, **Erle DJ**. Genomic characterization and therapeutic utilization of IL-13-responsive sequences in asthma. *Cell Genomics.* 2023; 3:100229. PMID: 36777184. PMCID: PMC9903679.

Positions, Scientific Appointments, and Honors

Positions and Employment

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

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. 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.
    c. 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.
    d. 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 Severe Acute Respiratory Syndrome Coronavirus 2 Infection of Bronchial Epithelium. *Am J Respir Cell Mol Biol.* 2022 Apr;66(4):391-401. doi: 10.1165/rcmb.2021-0364OC. PMID: 34982656. PMCID: PMC8990122.

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 produce *Agr2*$^{-/-}$ mice which we used 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. We have also developed new tools for gene targeting and analysis of human bronchial epithelial cells.

    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. 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.
    d. Bonser LR, Koh KD, Johansson K, Choksi SP, Cheng D, Liu L, Sun DI, Zlock LT, Eckalbar WL, Finkbeiner WE, **Erle DJ**. Flow-Cytometric Analysis and Purification of Airway Epithelial-Cell Subsets. *Am J Respir Cell Mol Biol.* 2021 Mar;64(3):308-317. doi: 10.1165/rcmb.2020-0149MA. PMID: 33196316 PMCID: PMC7909335.

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 related to allergy and lung disease 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 gene regulation in health and disease (especially asthma). We 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 studies performed in close collaboration with the Woodruff lab, we have identified changes in miRNA expression in airway epithelial cells in asthma and effects of those changes on IL-13-induced mucus production. We have also integrated genomics approaches such as scRNA-seq, scATAC-seq, and ChIP-seq to identify DNA regulatory elements important in epithelial responses to IL-13 and have shown that an IL-13-regulated secretory cell-selective enhancer is critical for goblet cell induction and can be re-purposed as part of a CRISPRi gene therapy approach for mucus plugging.

   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. 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. PMCID: PMC8021117.
   d. Koh KD, Bonser LR, Eckalbar WL, Yizhar-Barnea O, Shen J, Zeng X, Hargett KL, Sun DI, Zlock LT, Finkbeiner WE, Ahituv N, **Erle DJ**. Genomic characterization and therapeutic utilization of IL-13-responsive sequences in asthma. *Cell Genomics.* 2023; 3:100229. PMID: 36777184. PMCID: PMC9903679.

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 $\beta7$ and the integrin $\alpha4\beta7$ heterodimer that directs lymphocyte trafficking to the intestine. Subsequent work by other investigators led to the development of the anti-integrin $\alpha4\beta7$ 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 ($\beta7$) 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 $\alpha4\beta7/\alpha4\beta P$ 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 $\alpha4\beta7$, 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 $\alpha 4\beta 7$-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

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:

(i) R01 HL080414; Fahy (PI); 07/01/05 - 04/30/27. *Phenotypic and biological features of mucus plugs in asthma.* The major goals of this project are to investigate the clinical and biological features of pathologic mucus plugs in asthma.

(iv) R01 HL164787; Fahy (PI) 8/22/2022 – 5/31/2026. *Evaluating the Impact of Metabolic Dysfunction on Asthma Pathology and Physiology*. The major goals of this project are to investigate how systemic inflammation and metabolic dyfunction cause airway dysfunction in asthma.

(iii) P01 HL107202; Fahy (PI); 8/22/2019 – 7/31/2024. *Exploring the biology of persistent type 2 airway niches in asthma* - I lead this PPG program which is investigating the molecular underpinnings of persistent type 2 inflammation in asthma.

(iv) UG1 HL139106; Fahy (PI); 9/23/2017 - 6/30/2023. *Precision Interventions for Severe and/or Exacerbation-Prone Asthma (PrecISE) Network* - I lead the UCSF center in this network which is conducting biomarker informed clinical trials in severe asthma.

(v) U01HL146002 Fahy (co-I); Woodruff (PI). 9/23/2019 - 6/30/2024. *Immunometabolic phenotypes in adult severe asthma and disease progression.* I lead the clinical phenotyping of component of the UCSF center component of this U01 which has an overarching aim to advance understanding of disease endotypes in asthma.

Positions Scientific Appointments and Honors

(i) Positions and Scientific Appointments

2009 - present Michael S. Stulbarg Endowed Chair in Pulmonary Medicine, UCSF.
2005-present Professor of Medicine, Division of Pulmonary and Critical Care Medicine, UCSF.
2002-2003 Visiting Scholar, Trinity College Dublin and University College Dublin (sabbatical year)

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

(ii) Honors

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
2020	UCSF Academic Senate: 10th Annual Faculty Research Lecture in Translational Science

Contributions to Science

(I) 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. 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
C. 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
D. Lachowicz-Scroggins ME, Dunican EM, Charbit AR, Raymond W, Looney MR, Peters MC, Gordon ED, Woodruff PG, Lefrançais E, Phillips BR, Mauger DT, Comhair SA, Erzurum SC, Johansson MW, Jarjour NN, Coverstone AM, Castro M, Hastie AT, Bleecker ER, Fajt ML, Wenzel SE, Israel E, Levy BD, **Fahy JV.** Extracellular DNA, Neutrophil Extracellular Traps, and Inflammasome Activation in Severe Asthma. Am J Respir Crit Care Med. 2019;199:1076-1085. PMCID: PMC6515873.

(II) 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. 2021;203:957-968. PMCID: PMC8048745.

(III) NOVEL DRUGS FOR AIRWAY DISEASE

Background: Airway diseases such as asthma and COPD affect millions of patients and cause a significant public health care burden. Current treatments are suboptimal and new treatments are needed to alleviate the morbidity and mortality associated with these diseases. As new treatment targets are identified and novel inhibitors are developed, it is necessary to carefully conduct early phase proof of concept studies to determine the safety and 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.

(iv) Complete List of Published Work - https://pubmed.ncbi.nlm.nih.gov/?term=%22fahy+jv%22;

H Index (Google Scholar): 91

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:

R35 GM145238
Fraser (PI)
09/01/22-08/31/27
Discovering and Manipulating Macromolecular Conformational Ensembles

Key Citations

1. Wankowicz SA, de Oliveira SHP, Hogan DW, van den Bedem H, **Fraser JS**. Ligand binding remodels protein side chain conformational heterogeneity. *eLife.* 2022. PMCID: PMC9084896
2. Correy GJ, Kneller DW, Phillips G, Pant S, Russi S, Cohen AE, Meigs G, Holton JM, Gahbauer S, Thompson MC, Ashworth A, Coates L, Kovalevsky A, Meilleur F, **Fraser JS**. The mechanisms of catalysis and ligand binding for the SARS-CoV-2 NSP3 macrodomain from neutron and x-ray diffraction at room temperature. *Science Advances.* 2022. PMCID: PMC9140965.
3. 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
4. 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

Positions, Scientific Appointments, and Honors

2022- Vice Dean - Research, School of Pharmacy, UCSF
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 Parental leave (August-December)
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
2016 Parental leave (January-April)
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)

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 macromolecules in biophysical data**. We study proteins and RNA as conformational ensembles. Although X-ray crystallography is intrinsically 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 by 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. *NSMB*. 2022. PMCID: PMC8906282
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. *Nature Chem Biol.* 2022. PMCID: PMC8810680
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. Wolff AM, Nango E, Young ID, Brewster AS, Kubo M, Nomura T, Sugahara M, Owada S, Barad BA, Ito K, Bhowmick A, Carbajo S, Hino T, Holton JM, Im D, O'Riordan LJ, Tanaka T, Tanaka R, Sierra RG, Yumoto F, Tono K, Iwata S, Sauter NK, Fraser JS, Thompson MC. Mapping Protein Dynamics at High-Resolution with Temperature-Jump X-ray Crystallography. 2022. *Preprint on BioRxiv:* doi.org/10.1101/2022.06.10.495662

b. 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
c. 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
d. 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

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 100 Publications 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

Positions and Honors

Positions

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.

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 clinical and translational research to investigate 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. 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.

g. Kotas ME, Moore CM, Gurrola Ii JG, Pletcher SD, Goldberg AN, Alvarez R, Yamato S, Bratcher PE, Shaughnessy CA, Zeitlin PL, Zhang IH, Li Y, Montgomery MT, Lee K, Cope EK, Locksley RM, Seibold MA, Gordon ED. IL-13-programmed airway tuft cells produce PGE2, which promotes CFTR-dependent mucociliary function. JCI Insight. 2022 May 24:e159832. doi: 10.1172/jci.insight.159832.

h. Kotas ME, Patel NN, Cope EK, Gurrola JG, Goldberg AN, Pletcher SD, Seibold MA, Moore CM, Gordon ED. IL-13-associated epithelial remodeling correlates with clinical severity in nasal polyposis. J Allergy Clin Immunol. 2023 Feb 2;S0091-6749(23)00141-0. doi: 10.1016/j.jaci.2022.12.826. Online ahead of print.

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.

Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

1. P01 HL107202 (Fahy) Co-Investigator

07/01/2019 03/31/2024

Exploring the biology of persistent type 2 airway niches in asthma

$ 1,615,416 total

This project aims to uncover the key tissue-immune checkpoints that lead to persistent airway type 2 inflammation and mucus plug formation in asthma. We will use novel experimental approaches including image guided bronchoscopy and high-dimensional single cell analytics to decode the regulatory networks that sustain severe disease. NIH/NHLBI

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2. R15 (Cope/Caporaso MPI) Co-Investigator

07/01/2019 06/30/2022 (one year NCE)

Determining the Role of the Upper and Lower Airway Microbiota as Drivers of Concomitant Inflammatory Responses in patients with Chronic Rhinosinusitis and Asthma.

$ 300,000 total

This project focuses on characterizing the airway bacterial microbiome and metabolome CRS patients with asthma. Mechanistic in vitro studies of CRS/asthma associated metabolites will uncover specific microbial mechanisms that exacerbate host inflammatory responses in the upper and lower airways. Role: Co-Investigator. NIH/NIAID

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3. R01 AG062562-01 (Geschwind) Co-Investigator

08/01/2019 07/31/2024

Tracking longitudinal change in presymptomatic genetic prion disease (TLC-Pre-gPrD) $ 600,112 total

The overarching goal of this proposal is to track the PreSx phase of gPrD to identify biomarkers for treatment trials. JIT response relates to this grant. NIH/NIA

BIOGRAPHICAL SKETCH

NAME: Erin Duncan Gordon, M.D.

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

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
University of California, Berkeley	B.A.	05/2001	Molecular and Cell Biology
University of Southern California	M.D.	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:

1. ***Mechanisms of IL-33 secretion****:* We discovered a novel mechanism of IL-33 secretion from airway epithelial cells triggered by intracellular LPS and involving caspase 4 /11 and the airway microbiome, using human airway cells genetically modified by CRISPR-Cas9 and genetically modified mice. This work is an important advance in the field. It demonstrates that airway epithelial cells regulate IL-33 secretion (rather than IL-33 being released passively during cell death). It also answers an age-old question about how the microbiome influences type 2 inflammation in asthma.
2. ***Tuft cell derived PGE2 alters airway functions in type 2 inflammation:*** Using single cell RNA sequencing, we found that tuft cells are increased in the epithelium in nasal polyposis (NP), and they adopt a novel transcription state and secrete PGE2. PGE2 induces CFTR chloride currents, organoid swelling and accelerates mucocilliary clearance. Finally, we find evidence that tuft cell signatures and PGE2 transcriptional activation are increased in both NP and asthma. This is a significant advance in demonstrating a non-IL-13 mechanism of disease in type 2 inflammation which could be targeted therapeutically.
3. ***IL1RL1/IL33*** **SNP mapping**: *IL1RL1* and *IL33* genetic variants are strongly associated with asthma in large genome wide association studies. We previously discovered that *IL1RL1* genetic variants are associated with lung and blood levels of soluble ST2 and risk of type 2 high asthma. We performed DNA sequencing and mapped our genetic association to 3 SNP LD blocks. Using CRISPR-KRAB (DNA inhibition) targeting associated SNPS, we mapped the causal variants to 2 SNP blocks and determined their effect on gene expression in primary airway epithelial cells alone and in combination. We have taken a similar approach to determine causal variants in the IL33 gene locus. A manuscript is in preparation.
4. ***Type 2 and type 17 cross-regulation in asthma and nasal polyposis (NP):*** We have found that type 2 inflammation and IL17 activation of the airway epithelium co-occur in large number of asthmatics and patients with NP. Dupilumab is increasingly used to control symptoms in patients with these diseases. IL17 driven neutrophilia is not abrogated in animal models of IL4R blockade. We are exploring the cell types that make IL17 in animal models using the SMART17 reporter and in humans using single cell sequencing. We are determining the effects on IL17 signaling and neutrophilia in patients on dupilumab.

Since I established my lab in 2017, I have faced extraordinary circumstances that merit additional consideration. In 2017, my 3-year-old son Seth was diagnosed with rhabdomyosarcoma which is a rare and aggressive childhood malignancy. If detected early, it has a 90% 5-year survival rate but requires 14-cycles of chemotherapy and 6 weeks of radiation. We detected Seth's cancer when it was only 1 cm and had not spread. He completed treatment and has been in remission for 6 years. He is a healthy 9-year-old, but the

circumstances of his treatment required that I take Family Medical Leave, including a 6-week stay in Seattle to receive proton radiation. These events had a significant impact on the productivity of my laboratory.

Shortly thereafter, I was informed that the risk of breast cancer is higher in women whose children have rhabdomyosarcoma. Early surveillance resulted in the discovery of carcinoma in situ. In 2018, I had an uneventful mastectomy and reconstruction.

In 2020, the COVID pandemic had a significant impact on the ability to carry out human based translational research. For this reason, I pivoted back to mouse work using institutional startup funds. This was an easy transition given my prior post-doctoral work examining the *Postn*-/- mouse (PMCID: PMC3271792) and assistance from the Locksley lab in protocol development. I obtained the *Casp11* and *Gsdmd* -/- mouse strains (JAX) to examine their role in IL-33 secretion and type 2 inflammation. This work is a manuscript in preparation. I also obtained the SMART17 and IL4R knockout strains from the Locksley lab for the preliminary data presented in this application.

These circumstances impacted my productivity but did not deter me from my goal of developing therapeutics for asthma, running a successful academic laboratory, and training the next generation of scientists. My lab published seven papers during this difficult time and is on track to publish several more this year. **Given my track record of success during extraordinary circumstances, I was promoted on time to Associate Professor in the Department of Medicine in 2021.**

1. Kotas ME, Patel NN, Cope EK, Gurrola JG, Goldberg AN, Pletcher SD, Seibold MA, Moore CM, **Gordon ED.** Interleukin-13 associated epithelial remodeling correlates with clinical severity in nasal polyposis. JACI. 2023. Epub 2023/02/04. doi: 10.1016/j.jaci.2022.12.826. PMID: 36736797. PMCID: pending.
2. Kotas ME, Moore CM, Gurrola J, Pletcher SD, Goldberg AN, Alvarez R, Yamato S, Bratcher PE, Shaughnessy CA, Zeitlin PL, Zhang I, Li Y, Montgomery MT, Lee K, Cope EK, Locksley RM, Seibold MA, **Gordon ED.** IL-13-programmed airway cells produce PGE2, which promotes CFTR-dependent mucociliary function. JCI Insight, 2022, May 24: e159832. doi: 10.1172/jci.insight.159832. PMID: 35608904. PMCID: PMC9310525
3. **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
4. **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
5. **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

Ongoing and recently completed projects that I would like to highlight include:

R01AI136962 Gordon (PI) 01/15/18-12/31/22
NIH/NIAID
Understanding the Molecular Genetic Mechanisms of Asthma Risk Loci: IL33, IL1RL1, and GSDMB.
The goal of this study is to explore novel genetic mechanisms that influence the development of type 2 inflammation, the most common disease pathology, in asthma.

P01HL107202 Fahy (PI) 09/01/19-05/31/24
NIH/NHLBI
Exploring the biology of persistent type 2 airway niches in asthma.
The goal of this program project grant is to uncover the tissue and immune requirements for persistent type 2 inflammation in human asthma including the role of ILC2, tuft cells, mucus plug formation, and epigenetic reprogramming of immune and epithelial cells.
Role: Co-investigator

U19 K08HL114645-04 Gordon (PI) 08/04/13-05/31/18
NIH-NHLBI
The function and regulation of IL-33 in the airway epithelium in asthma
The goal of this study is to understand the role of IL-33 and its receptor ST2 in the induction of type 2 inflammation in human asthma.

Nina Ireland Program Gordon (PI) 01/01/17-12/31/18
Gaining Mechanistic Insight into Severe Asthma Through the Study of Extreme Phenotypes: Nasal Polyposis
The goal of this study is to explore the whole transcriptome epithelial response to IL-13 in sinus epithelium of patients with nasal polyposis compared to healthy subjects.

AI077439 Opportunity Fund Gordon (PI) 09/01/16-08/31/17
NIH-NIAID
Role of Notch Signaling in Mucus Metaplasia in Asthma
The goal of this study is to explore the role of notch signaling in mucus metaplasia in type 2 low asthma.

PFIZER Seibold/Fahy/Gordon (Co-PI) 07/01/13-11/30/16
QB3-UCSF Pfizer Collaboration
A Precision Medicine Approach to IL-33 Inhibition in Asthma
The goal of this project is to identify a subgroup of asthma patients with evidence of active IL-33 activity and identify possible genetic, protein, or gene expression biomarkers to identify this population.

B. Positions and Honors

Positions

2021-present	Associate Professor in residence, UCSF, DOM, Pulmonary and Critical Care Medicine
2021-present	Board Member, Nina Ireland Program for Lung Health, UCSF
2020-present	Member of UCSF Committee on Faculty Equal Opportunity
2018-2021	Ad hoc NIAID Special Emphasis Panel HAMI ZRG1 57
2017-2021	Assistant Professor in residence, UCSF, DOM, Pulmonary and Critical Care Medicine
2020	Ad hoc NIH Reviewer SBIR ZRG1 CVRS-J11
2020-present	UCSF Internal Medicine Resident Selection Committee
2018- present	UCSF Biomedical Sciences Graduate Student Admissions Committee
2017-present	UCSF College of Bench Scientists
2017-2020	UCSF Pulmonary Research Conference Organizing Committee
2017-present	Member Women in Pulmonary Advocacy Group, UCSF
2013-2017	Clinical Instructor, UCSF Pulmonary and Critical Care
2010-2013	Research Fellow, UCSF, Pulmonary Critical Care, with Dr. John Fahy

Honors
Ruth L. Kirschstein National Research Service Award 2011
American Medical Association Achievement Award 2005
American Medical Women's Association Award 2005
Summa cum Laude, Keck School of Medicine, USC 2005
Merck Manual Award – awarded to the highest-ranking student in the basic sciences at USC SOM 2005
Alpha Omega Alpha, Gamma Chapter, Keck School of Medicine, USC 2004
Dean's Scholar USC SOM 2002, 2003, 2004, 2005
Recipient of merit-based full tuition scholarship at Keck School of Medicine, USC 2001
Grace Fimognari Memorial Award –Molecular & Cell Biology, Biochemistry, UC, Berkeley 2001
Phi Beta Kappa, University of California, Berkeley 2001
Graduate with Honors, University of California, Berkeley 2001

Professional Societies
American Thoracic Society.

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

C. Contributions to Science

1. **Tuft cells produce PGE2 which regulates CFTR-dependent mucociliary clearance in the airway.** Using single cell sequencing from epithelial brushes from nasal polyps, we find an increase in tuft cells. These tuft cells adopt a novel transcriptional phenotype consistent with increased PGE2 synthetic machinery and secretion. In a mouse model of IL-13 driven airway remodeling, we find an increase in tuft cells and the same transcriptional activation state. Mice deficient in tuft cells (*Pou2f3*-/-) display reduced PGE2 levels in the airway in response to IL-13 activation. Airway epithelial cells treated with PGE2 display increased CFTR dependent fluid secretion, chloride channel activity and mucociliary clearance. The airway in asthma and nasal polyposis displays an activation signature of both IL-13 and PGE2.
   a. Kotas ME, Moore CM, Gurrola J, Pletcher SD, Goldberg AN, Alvarez R, Yamato S, Bratcher PE, Shaughnessy CA, Zeitlin PL, Zhang I, Li Y, Montgomery MT, Lee K, Cope EK, Locksley RM, Seibold MA, **Gordon ED.** IL-13-programmed airway tuft cells produce PGE2, which promotes CFTR-dependent mucociliary function. JCI Insight, 2022, May 24: e159832. doi: 10.1172/jci.insight.159832. Online ahead of print. PMID: 35608904. PMCID: PMC Journal-In process.

2. **IL-33 is secreted from airway epithelial cells in a regulated fashion**. IL-33 is a key upstream driver of type 2 inflammation. The biology surrounding its secretion remains unclear. Full length IL-33 is a nuclear protein without a signal sequence, and the mechanism of release is unknown. It is postulated that release occurs in the context of epithelial cell death; however, cell death is not a prominent feature in most asthmatics. I discovered a novel mechanism of IL-33 release involving alternative splicing of IL-33 RNA transcripts. A deletion of exons 3 and 4 (∆exon 3,4) is the most abundant IL-33 splice variant in the human airway. Its protein product is biologically active and localizes to the cytoplasm. This transcript produces a protein which is released from the cell in a calcium dependent fashion, distinct from full length IL-33. Among mild-moderate asthmatics, only this ∆exon 3,4 transcript variant is positively associated with airway type 2 inflammation. We have extended these data, showing that IL-33 (∆exon 3,4) is also secreted in a GSDMD and Casp4/11 dependent fashion in response to intracellular LPS. Mice deficient in *Casp11* or *Gsdmd* are protected from papain induced lung eosinophilia and have reduced BAL IL-33 levels. This finding is dependent on the microbiome. These results are in preparation for publication.
   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

3. ***IL1RL1* and *IL33* genetic variants regulate airway epithelial gene expression to drive type 2 inflammation.** The ST2/*IL1RL1* gene is among the most replicated asthma genetic associations; however, it remains unclear how genetic polymorphisms in this gene confer disease risk. 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. 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. This and a second locus rs11685480 demonstrate control over gene expression of sST2 in the lung. These two SNP blocks demonstrate an additive effect on circulating soluble ST2 levels among asthmatics, suggesting their independent effects. We have fine mapped the locus to narrow down the causative SNP and have used Crispr-Cas9KRAB to determine the causative SNP in vitro. These results are described in a recently published manuscript in *Journal of Clinical Investigation Insight*.
   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

4. **The airway epithelium regulates type 2 inflammation.** Asthma is a heterogeneous disease with variable inflammatory profiles, but type 2 inflammation is the dominant biology. It is characterized by production of type 2 cytokines IL4, 5, and 13 within the respiratory tract by innate lymphoid type 2 cells (ILC2), Th2 cells, mast cells, and basophils. Tissue infiltrates are characterized by eosinophils, and the epithelium displays increased goblet cells and mucus hypersecretion. The airway epithelium plays a key role in orchestration of the initiation, amplification, and resolution of these immune responses. During the initiation, the airway epithelium secretes IL-33, IL-25, and TSLP, which induce type 2 cytokine production from innate and adaptive immune cells. In response to IL-13 stimulation, the epithelial composition is altered leading to an expansion of goblet cells. Transcriptional changes alter epithelial mucus which traps and clear allergens. The epithelium alters its secreted products in an attempt to return to homeostasis. It is incompletely understood how the epithelium senses danger signals to initiate response to allergens and how it later directs the resolution of inflammation. My research seeks to understand the broad range of epithelial responses in type 2 inflammation including the secretion of sST2 (IL33 inhibitor) and IL-33 and the production of mucus and inflammatory peptides such as periostin.

a. Dunican EM, Elicker BM, Gierada DS, Nagle SK, Schiebler ML, Newell JD, Raymond WW, Lachowicz-Scroggins ME, Di Maio S, Hoffman EA, Castro M, Fain SB, Jarjour NN, Israel E, Levy BD, Erzurum SC, Wenzel SE, Meyers DA, Bleecker ER, Phillips BR, Mauger DT, **Gordon ED**, Woodruff PG, Peters MC, Fahy JV; 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. doi: 10.1172/JCI95693. Epub 2018 Feb 5. PMCID: PMC5824874
b. 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
c. **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

5. **Human airway epithelial cell function in health and disease**. My lab has expertise in culture and genetic manipulation of primary airway epithelial cells. We culture cells at air liquid interface and organoid and commonly use CRISPR-Cas9, CRISPR-Krab, CRISPR-SAM to silence or activate genes in these cells. We use lentivirus to infect and select cells prior to 2D and 3D culture. Using conditionally reprogramming (mitomycin treated fibroblasts and ROCK inhibition) we are able to passage cells multiple times allowing for efficient genetic modification and differentiation. We have banked airway cells from over 200 donor tracheas and multiple lower airway and upper airway brushes from patients with asthma and nasal polyps. These cells have been valuable to other investigators studying asthma, lung transplant, and COVID19.

a. Dugger DT, Calabrese DR, Gao Y, Deiter F, Tsao T, Maheshwari J, Hays SR, Leard L, Kleinhenz ME, Shah R, Golden J, Kukreja J, **Gordon ED**, Singer JP, Greenland JR. Lung Allograft Epithelium DNA Methylation Age Is Associated With Graft Chronologic Age and Primary Graft Dysfunction Front Immunology. 2021 Oct 7;12:704172. doi: 10.3389/fimmu.2021.704172. eCollection 2021. PMCID: PMC8528961
b. Dugger DT, Fung M, Zlock L, Caldera S, Sharp L, Hays SR, Singer JP, Leard LE, Golden JA, Shah RJ, Kukreja J, **Gordon E**, Finkbeiner W, Kleinhenz ME, Langelier C, Greenland JR. Cystic Fibrosis Lung Transplant Recipients Have Suppressed Airway Interferon Responses during *Pseudomonas* Infection. Cell Rep Med. 2020 Jul 21;1(4):100055. doi: 10.1016/j.xcrm.2020.100055. PMCID: PMC7402593
c. Lachowicz-Scroggins ME, Dunican EM, Charbit AR, Raymond W, Looney MR, Peters MC, **Gordon ED**, Woodruff PG, Lefrançais E, Phillips BR, Mauger DT, Comhair SA, Erzurum SC, Johansson MW, Jarjour NN, Coverstone AM, Castro M, Hastie AT, Bleecker ER, Fajt ML, Wenzel SE, Israel E, Levy BD, Fahy JV. Extracellular DNA, Neutrophil Extracellular Traps, and Inflammasome Activation in Severe Asthma Am J Respir Crit Care Med. 2019 May 1;199(9):1076-1085. doi: 10.1164/rccm.201810-1869OC. PMCID: PMC6515873
d. 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. doi: 10.1111/cea.13015. Epub 2017 Sep 26. PMID: 28833774

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)	END DATE MM/YYYY	FIELD OF STUDY
Yale University, New Haven, CT	BS	05/2005	Biomedical Engineering
Yale University, New Haven, CT	M.S., 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 research support:

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

A.P. Giannini Foundation (not assigned)
Kotas (PI)
07/01/20-08/31/22
Characterization of the type 2 immune circuit that regulates airway epithelial remodeling

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

U19 AI 070535-16 (IOF ESI)
Broide (PI)
09/01/21-06/30/23
Defining the role of epithelial prostaglandin E2 in allergic airway disease

K08 HL155490
Kotas (PI)
09/01/22-08/31/27
Understanding the role of tuft cells in allergic airway disease

Citations:

a. **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. PMCID: PMC8262498
b. **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* 14(6):1295-1305. PMCID: PMC8528700.
c. **Kotas ME***, Moore CM*, Gurrola JG, Pletcher SD, Goldberg AN, Alvarez R, Yamato S, Bratcher PE, Shaughnessy CA, Zeitlin PL, Zhang I, Li Y, Montgomery MT, Lee K, Cope EK, Locksley RM, Seibold MA, Gordon ED (2022) IL-13-programmed airway tuft cells produce PGE2, which promotes CFTR-dependent mucociliary function. *JCI Insight* 7(13). PMCID: PMC9310525. *equal contribution
d. **Kotas ME***, O'Leary CE*, Locksley RM. (2023) Tuft Cells: Context- and Tissue-Specific Programming for a Conserved Cell Lineage. *Annu. Rev. Pathol*. 18:311-335. PMID: 36351364. *equal contribution

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 - 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

Honors

2022	Burroughs Wellcome Foundation Career Award For Medical Scientists
2022	American Thoracic Society Science and Innovation Center Rising Stars of Research Award
2022	Parker B. Francis Fellow
2020 - 2023	A.P. Giannini Foundation Fellow
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

Contribution to Science

Role of the immune system in regulating nutrient 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. PMCID: PMC3668772

Regulation and tissue roles of type 2 innate lymphocytes: Type 2 innate lymphocytes (ILC2s) are specialized producers of type 2 cytokines such as IL-5 and IL-13 that are positioned and enriched in peripheral (rather than lymphoid) tissues starting during fetal development, and are poised to direct immune responses to tissue perturbation. Building on the core expertise and tools developed by my postdoctoral mentor, Dr. Locksley, I have examined roles for ILC2s in tissue homeostasis and allergic immunopathology. Through my own work and in collaboration with others, I have described protective roles for ILC2s in anti-parasitic immunity in the gut and skin through modulation of epithelial barrier function, as well as the potential for pathologic dysregulation induced of ILC2s by epithelial cytokines. Because interaction between tuft cells and ILC2s is well-described in intestinal tissue, this work directly dovetails with my interest in epithelial biology during type 2 responses, further described in the next section.

a. **Kotas ME**, Locksley RM. (2018) Why Innate Lymphoid Cells? *Immunity* 48(6): 1081-1090. PMCID: PMC6145487.
b. **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. PMCID: PMC8262498
c. **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* PMCID: PMC8528700
d. Roberto-Gonzalez RR, **Kotas ME**, O'Leary CO, Singh K, Damsky W, Liao C, Arouge E, Tenvooren I, Marquez DM, Schroeder AW, Cohen JN, Fassett MS, Lee J, Daniel SG, Bittinger K, Diaz RE, Fraser JS, Ali N, Ansel KM, Spitzer MH, Liang HE, Locksley RM. (2022) Innate type 2 immunity controls hair follicle commensalism by Demodex mites. *Immunity* 55, 1-18. PMCID: PMC9561030

Role of tuft cells in type 2 defense of the mucosal barrier: Tuft cells are rare epithelial cells that are now known to act as sentinels for type 2 immune activation in the gut. However, while they are found throughout the conducting airways, a unified understanding of their biology in the airway is lacking. In addition to collaborative efforts that have revealed a homeostatic role for tuft cells in controlling biliary inflammation and explored their ectopic development after severe lung injury, we discovered that airway tuft cells become altered by type 2 inflammation in the human airway, and increase secretion of prostaglandin E2 to activate neighboring epithelial secretion in paracrine fashion. In addition to the following, an recently-published invited review on tuft cell biology is highlighted in section A.

a. O'Leary CE, Sbierski-Kind J, **Kotas ME**, Wagner JC, Liang HE, Schroeder AW, de Tenorio JC, von Moltke J, Ricardo-Gonzalez RR, Eckalbar WL, Molofsky A, Schneider C, Locksley RM. (2022) Bile acid-sensitive tuft cells regulate biliary neutrophil influx. *Science Immunology* 7(69):eabj1080. PMCID: PMC9166270.
b. **Kotas ME***, Moore CM*, Gurrola JG, Pletcher SD, Goldberg AN, Alvarez R, Yamato S, Bratcher PE, Shaughnessy CA, Zeitlin PL, Zhang I, Li Y, Montgomery MT, Lee K, Cope EK, Locksley RM, Seibold MA, Gordon ED (2022) IL-13-programmed airway tuft cells produce PGE2, which promotes CFTR-dependent mucociliary function. *JCI Insight* 7(13). PMCID: PMC9310525. *equal contribution

c. Barr J, Gentile ME, Lee S, **Kotas ME**, Fernanda de Mello Costa M, Holcomb NP, Jaquish A, Palashikar G, Soewignjo M, McDaniel M, Matsumoto I, Margolskee R, Von Moltke J, Cohen NA, Sun X, Vaughan AE. (2022) Injury-induced pulmonary tuft cells are heterogenous, arise independent of key Type 2 cytokines, and are dispensable for dysplastic repair. *Elife* 8(11). PMCID: PMC9553214.
d. **Kotas ME**, Patel NN, Cope EK, Gurrola JG, Goldberg AN, Pletcher SD, Seibold MA, Moore CM, Gordon ED. (2023) IL-13-associated epithelial remodeling correlates with clinical severity in nasal polyposis. *JACI* S0091-6749(23)00141-0. doi: 10.1016/j.jaci.2022.12.826. (online ahead of print) PMID: 36736797

A complete list of my publications is available at:
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 California at Berkeley, Department of Molecular and Cell Biology	Ph.D.	06/1995	Immunology
University of Illinois, School of Liberal Arts and Sciences	B.S.	06/1989	Honors Biology and. Chemistry.
University College, London, England	Exchange Student	06/1988	Department of Chemistry
University of Illinois High School, Urbana, Illinois		06/1985	

Highlighted Citations:

a. 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 PMCID: PMC7891292

a) Binnewies M,…**Krummel MF**. Unleashing Type-2 Dendritic Cells to Drive Protective Antitumor CD4+ T Cell Immunity. **Cell.** 2019 177(3):556-571. PMID: 30955881

b) Roberts, E.W. … **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,…**Krummel MF**. A natural killer-dendritic cell axis defines checkpoint therapy-responsive tumor microenvironments. **Nat Med.** 2018 24(8):1178-1191. PMID: 29942093

d) Broz M, … **Krummel MF**: Dissecting the Tumor Myeloid Compartment Reveals Rare Antigen Presenting Cells Critical for T cell Immunity. **Cancer Cell,** 2014 26(5):638-52. PMID: 25446897

Positions, Scientific Appointments, and Honors

Positions and Employment

2018-present Co-Founder and Inaugural Chair, ImmunoX Initiative, UCSF
2016 Visiting Sabbatical Professor, Mediterranean Institute for Advanced Studies, Aix-Marseille University, France
2012-present Professor, Department of Pathology, UCSF
2008-9 Visiting Sabbatical Professor, Institut Curie, Paris, France
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, WEHI, Melbourne Australia. Advisor: Dr. Ken Shortman
1989-1996 Graduate Research Assistant, MCB, UC Berkeley. Advisor: Dr. James Allison
1988-1988 Stagiare (Technician), UGM, Institut Pasteur. Advisor: Dr. Julian Davies
1987-1987 HHMI Summer Fellow, Neurobiology, UTHSC Dallas. Advisor: Dr. Flora Katz

Other Experience and Professional Memberships

2021-present Co-Founder and Member of SolvingForScience.org, devoted to culture change in science
2021-present Co-Founder of Foundery Innovations|Immune Studios, a novel Venture Studio for Immunotherapy development, at the academic interface
2020-present Faculty advisory to ImmunoDiverse, a UCSF organization dedicated to racial equity
2019-present Faculty advisory to IgEquity, a UCSF organization dedicated to gender equity
2018-present Faculty, Irving Cancer Foundation summer mentoring course for junior faculty
2017-present Faculty, SITC 'Sparkathon' mentoring course for rising postdocs and new faculty
2018-present Scientific Advisory Board, Allen Institute of Immunology, Seattle
2018-2022 Member, Parker Institute for Cancer Immunotherapy (resigned)
2016-present Member of the European Academy for Tumor Immunology (EATI)
2015-2017 Founder and CEO, Pionyr Immunotherapeutics, San Francisco (acquired, Gilead)
2008-present Advisory Board, Immunity
2005-present Member, AAAS, AACR, AAI (intermittent)
2002-present Reviewer for Science, Cell, Nature, Immunity, Cancer Cell, JEM, JCB, JCI, PNAS, Nature Immunology, Nature Cell Biology, Nature Methods, Science Immunology JI, and various others
2002-present Ad hoc study sections (multiple, yearly) for NIH, NCI, Wellcome Trust, US-Israeli Binational Science Foundation, Starr Cancer Consortium, European Research Council, CRI, and others.

Honors

2020 Emerson Collective, Dial Fellowship.
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

C. Contributions to Science

2. **Critical Immune Components in Tumors.** 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 PMCID: PMC4254577
   b. Roberts, E.W., Broz, M.L., Binnewies, M., Headley, M.B., Nelson, A.E., Wolf, D.M., Kaisho, T., Bogunovic, D., Bhardwaj, N., and Krummel, M.F. 2016. Critical Role for CD103+/CD141+ Dendritic Cells bearing CCR7 for Tumor Antigen Trafficking and Priming of T cell Immunity in Melanoma. **Cancer Cell,** 2016. PMID: 27424807 PMCID: PMC5374862
   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 PMCID: PMC6475503
   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 PMCID: PMC6954108

3. **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 PMCID: PMC8567458
   c. Combes AJ, Samad B… Krummel MF. A Pan-Cancer Census of Dominant Tumor Immune Archetypes. **Cell.** 2022;185(1):184-203 e19. Epub 2021/12/29. doi: 10.1016/j.cell.2021.12.004. PubMed PMID: 34963056 PMCID: PMC8862608

4. **Spatial and Real-time Dynamics of Immune Responses in Tissues.** 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 PMCID: PMC3311997
   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 PMCID: PMC3076005
   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 PMCID: PMC4892380
   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 PMCID: PMC7891292

5. **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). PMCID: PMC6364556
   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 PMCID: PMC2139496
   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. PMCID: PMC2943564

6. **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, anti-TREM2, and anti-MARCO reagents 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. PMCID: PMC2192127
   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. PMID: 8596936
   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. PMCID: PMC2192613
   d. Matthew Krummel, Miranda Broz, Denise Wolf, Joshua Pollack, Mikhail Binnewies. *Modulation of Stimulatory and Non-stimulatory Myeloid Cells.* **US Patent** 20200017584
   e.

Complete List of Published Works: (165 total, 33840 total citations h-index 75)

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

PATENTS ISSUED OR PENDING

1. J.P. Allison, D.R. Leach, and M.F. Krummel. *Blockade of Lymphocyte Down-Regulation Associated with CTLA-4 Signaling.* US Patent 5,855,887, 5,811,097. 1996,8. Licensed to Medarex and subsequently BMS, 1998,2011
2. M.F. Krummel, Miranda Broz, Denise Wolf, Mikhail Binnewies and Josh Pollack. *Modulation of stimulatory and non-stimulatory myeloid cells.* US Patent 10,428,143 Licensed to Pionyr Immunotherapeutics. 2017
3. M.F. Krummel, and K.H. Hu, *Single Cell Mapping and Transcriptome Analysis.* Patent Publication number: 20210198722. License in progress with Narwhal Bio.

BIOGRAPHICAL SKETCH

NAME: Liang, Hong-Erh

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

POSITION TITLE: Adjunct Professor, 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
National Taiwan University, Taipei, Taiwan	BS	06/1990	Biochemistry
National Taiwan University, Taipei, Taiwan	MS	06/1992	Immunology
Johns Hopkins University, School of Medicine	PhD	06/2002	Molecular Biology

Ongoing projects that I have been associated as key personnel include:

R01 AI026918 (this is the competitive renewal for this grant)
Richard Locksley (PI)
07/01/88-04/30/23
Parasite Immunity Orchestrated by Type 2 Immune Cells

P01 HL107202 (this grant will not be renewed)
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)

Citations:

1. Kotas , M.E., R.M. Locksley. (2018). Why innate lymphoid cells? Immunity 48:1081-1090. PMCID: PMC6145487
2. Vivier, E., Artis, D., Colonna, M., Diefenbach, A., Di Santo, J.P., Eberl, G., Koyasu, S. Locksley, R.M., McKenzie, A.N.J., Rebius, R.F., Powrie, F., Spits, H. (2018). Innate lymphoid cells: 10 years on. Cell 174:1054-1066
3. 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
4. Schneider, Cl, O'Leary, C.E., Locksley, R.M. (2019). Regulation of immune responses by tuft cells. Nature Rev Immunol 19:584-593. PMCID: PMC8331098

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021-present	Adjunct Professor, Medicine, UCSF
2015 – 2021	Associate Adjunct Professor, Medicine, UCSF
2009 – 2015	Assistant Adjunct Professor, Medicine, UCSF
2004 – 2009	Research Associate, (PI: Dr. Richard Locksley), Howard Hughes Medical Institute
2002 – 2003	Postdoctoral Researcher, (PI: Dr. Mark S. Schlissel), University of California, Berkeley
1999 – 2002	Graduate Student Researcher, (PI: Dr. Mark S. Schlissel), University of California, Berkeley

1994 – 1996 Research Assistant, Academia Sinica, Taipei, Taiwan, Institute of Molecular Biology
1992 – 1994 First Lieutenant Medical Officer, R.O.C. Army

Professional Memberships
The American Association of Immunologists (AAI)

Honors
2002 Phi Beta Kappa
1992 IMB Student Thesis Award, Institute of Molecular Biology, Academia Sinica

Contributions to Science

1. **Genetic Analysis of Mouse Inflammatory Models and Innate Lymphoid Cell Biology**
   Development of reagents that have enabled the ability to interrogate the immune system *in vivo*, especially for the type 2 immune response, we have successfully marked type 2 innate lymphoid cells (ILC2) ideal for flow cytometric and histological examinations. We achieved specific ablation of these cells *in vivo* through genetic means. This led us to establish the indispensable role for ILC2-derived interleukin 5 (IL-5) and IL-13 in the control of eosinophil homeostasis. ILC2 thus serve as a convergent sensor of both the circadian rhythm and food/nutrient intake which has long been associated with the rhythmic blood eosinophil fluctuation. We have also implicated these cells in the response to chitin and identified the upstream epithelial cell-derived cytokines necessary for ILC2 activation. To further elucidate the upstream ILC2-activating signal, we marked one of the canonical epithelial cytokine genes, IL-25, through which we can gain a deeper understanding of the spatial and temporal control between the tissue damage and ILC2 activation. To expand our inflammatory models, we recently marked ILC3 cells by generating an allele specific for its effector cytokine, IL-22. Making these cells visible and ablatable *in vivo* again proves it to be an invaluable tool for studying gut lymphoid organogenesis, pathological inflammatory conditions and the host response to microbiota.
   Using the same approach, with a panel of 8 targeted reporter alleles covering almost all the type 2 cytokine genes (il4, 5, 9 and 13), we have elucidated the molecular distinction between the tissue Th2 cells and TFH cells in draining lymph nodes based on their divergent expression pattern of the type 2 cytokines.
   a. **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
   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

2. **Genetic Analysis of Mouse Tuft Cell Biology**
   Through the development of various genectically modified mouse strains, we discovered that tuft cells, a specialized epithelial cell type found in many mucosal sites, is the exclusive source of IL-25 in mouse. We have also elucidated the tightly regulated immune-epithelial cell cross-talk mediated by a tuft cell/IL-25, ILC2/IL-13 and intestinal stem cell (iSC) circuit which is intimately involved in monitoring whole body energy intake, specific nutrient metabolism and gut microbiota sensing. We are actively pursuing the underlying mechanisms in homeostasis and during pathologic settings.
   a. von Moltke J, Ji M, **Liang HE**, Locksley RM. Tuft-cell-derived IL-25 regulates an intestinal ILC2-epithelial response circuit. Nature. 2016 Jan 14; 529(7585):221-5. PMID: 26675736.
   b. Schneider C, Lee J, Koga S, Ricardo-Gonzalez RR, Nussbaum JC, Smith LK, Villeda SA, **Liang HE**, Locksley RM. Tissue-Resident Group 2 Innate Lymphoid Cells Differentiate by Layered

Ontogeny and In Situ Perinatal Priming. Immunity. 2019 06 18; 50(6):1425-1438.e5. PMID: 31128962. PMCID: PMC6645687

c. O'Leary CE, Sbierski-Kind J, Kotas ME, Wagner JC, **Liang HE**, Schroeder AW, de Tenorio JC, von Moltke J, Ricardo-Gonzalez RR, Eckalbar WL, Molofsky AB, Schneider C, Locksley RM. Bile acid-sensitive tuft cells regulate biliary neutrophil influx. Sci Immunol. 2022 Mar 04; 7(69):eabj1080. PMID: 35245089. PMCID: PMC9166270

3. **Functional Studies of Basophils in Type 2 Immunity and Allergic Skin Inflammation**
As a component of the innate immune cell compartment, basophils have poorly understood functions. They have been linked to the development of T helper type 2 immunity during parasite infection and allergic inflammation. We created a reporter mouse, Basoph8, whose basophils can be specifically marked by the YFP-IRES-hCre-targeted MCPT8 gene and can be deleted by genetically crossing with the ROSA26-DTa deleter strain. In a helminth infection model, we have successfully identified that basophils are a major source of early IL-4 but not IL-13 in affected tissues albeit they exert little or no effect on Th2 priming and lung ILC2 activation. Recently, we extended the applications of Basoph8 deleter strain and the conditional basophil-specific IL-4/13 deficient mice to show that basophils, when activated through their surface FceR, produce IL-4 and activate blood vessel endothelial cells which in turn upregulate VCAM followed by eosinophilic attraction and transmigration. Thus we established that IgE-activated basophils are endothelial gatekeepers for eosinophils which has implications for studying the allergen/IgE-mediated allergic skin inflammation.
    a. **Liang HE**, Sullivan BM, Bando JK, Wu D, Cheng LE, McKerrow JK, Allen CD, Locksley RM. Genetic analysis of basophil function in vivo. Nat Immunol. 2011 Jun; 12(6):527-35.
    b. Cheng LE, Sullivan BM, Retana LE, Allen CD, **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. PMID: 25779634.
    c. Laurence E. Cheng, Brandon M. Sullivan, Lizett E. Retana, Christopher D.C. Allen**, Hong-Erh Liang**, Richard M. Locksley. IgE-activated basophils regulate eosinophil tissue entry by modulating endothelial function. The Journal of Cell Biology. 2015 Mar 30; 208(7):2087oia41.

Complete List of Published Work:
https://pubmed.ncbi.nlm.nih.gov/?term=%28Liang+HE%5BAuthor%5D%29+AND+%28Locksley+RM%5BAuthor%5D%29&sort=pubdate

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

Highlighted Citations:

1. Molofsky AB, RM Locksley. 2023. The ins and outs of innate and adaptive type 2 immunity. Immunity 56:704-722. PMC10120575
2. Kotas , M.E., R.M. Locksley. (2018). Why innate lymphoid cells? Immunity 48:1081-1090. PMC6145487
3. Vivier, E., Artis, D., Colonna, M., Diefenbach, A., Di Santo, J.P., Eberl, G., Koyasu, S. Locksley, R.M., McKenzie, A.N.J., Rebius, R.F., Powrie, F., Spits, H. (2018). Innate lymphoid cells: 10 years on. Cell 174:1054-1066
4. 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. PMC8352721

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
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 among the first reporting that infectious outcomes were mediated by disparate Th subsets. 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 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, University of California San Francisco

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Texas, Austin	BS	05/1999	Molecular Biology
University of Michigan, Ann Arbor	MD/PhD	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

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, Steer CA, **Molofsky AB**. (2020). Immune outposts in the adventitia: One foot in sea and one on shore. *Curr. Opin. Immunol.* **64**, 34–41.
3. Cautivo, KM, Matatia, PR, Lizama, CO, Mroz, NM, Dahlgren, MW, Yu, X, Sbierski-Kind, J, Taruselli, MT, Brooks, JF, Wade-Vallance, A, Caryotakis, SE, Chang, AA, Liang, HE, Zikherman, J, Locksley, RM, & **Molofsky, AB.** (2022). Interferon gamma constrains type 2 lymphocyte niche boundaries during mixed inflammation. *Immunity*, *55*(2), 2022. PMCID: 35139352.
4. Vainchtein ID, Chin G, Cho FS, Kelley KW, Miller JG, Chien EC, Liddelow SA, Nguyen PT, Nakao-Inoue, H, Dorman, LC, Akil O, Joshita S, Barres, BA, Paz, JT, **Molofsky, AB**[#], Molofsky, A.V.[#], 2018. Astrocyte-derived interleukin-33 promotes microglial synapse engulfment and neural circuit development. *Science* 359: 1269-1273, PMCID PMC6070131. *# co-corresponding*

Active research support to highlight:

R01 NIH/NHLBI (Molofsky AB, PI) 9/1/2019 – 8/31/2023
Defining group 2 innate lymphoid cell lung niches.
The major goal of this study is to define the micro-anatomic niches and pathophysiologic role of mouse lung ILC2s, including their development, regulation, and response to infections.

R01 NIH/NIAID (Molofsky AB, PI) 01/11/2022 - 01/10/2027
Localization and function of tissue type 2 lymphocytes during mixed inflammation
The major goal of this project is to define how type 1 and type 2 tissue lymphocytes are cross regulated during settings of mixed inflammation in the lung and liver.

R01 NIH/NINDS (Molofsky AB, PI; Molofsky AV, Co-PI) 04/01/2021- 03/31/2027
Meningeal type 2 immunity in cortical synapse remodeling during brain development and injury
The major goal of this project is to define how group 2 innate lymphoid cells (ILC2s) in the brain meninges are activated to regulate synapse formation during early post-natal life and reactivated after brain damage.

Positions, Scientific Appointments, and Honors

Positions and Employment

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, UCSF
2010-2011	Laboratory Medicine Resident, 3rd year, Dept. chair Clifford Lowell MD PhD, UCSF
2011-2015	Research Fellow (80% effort), Lab of Richard M. Locksley, MD, HHMI, UCSF
2011-2013	Clinical Instructor (20%), Hematology Section, Dept. of Laboratory Medicine, UCSF
2013-2015	Assistant Adjunct Professor (20%), Hematology Section, Dept. of Lab Medicine, UCSF
2015-2019	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

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
2021	UCSF Medical School 'Foundations Curriculum" Teaching Award.
2022	Most 'Highly Cited Researchers' over past decade, top 1%, Clarivate.

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 and Hematopathology
2011-	American Association of Immunologists (AAI), Member
2012-	International Clinical Cytometry Society, Member
2016-	International Cytokine and Interferon Society (ICIS), Member
2022-	Co-Organizer of Innate Lymphoid Cell International Conference, Hawaii (ILC4 2022)
2021-	American Thoracic Society (ATS), Member

Contributions to Science

1. Our group studies the regulation and function of tissue-resident lymphocytes in multiple systems, including models of normal tissue development and (re)modeling, infection, pathology, and aging. We initially focused on the positive and negative regulation of ILC2s and Th2 lymphocytes, critical tissue 'type 2 lymphocytes' that organize type 2 allergic immune responses. Our studies helped define the regulation and sources of the cytokines IL-33 and IFNγ and their impacts respective positive and negative impacts on tissue type 2

lymphocytes, as well as the relationship of tissue ILC2s with regulatory T (Treg) cell subset(s). We identified a stromal (fibroblast) cell niche at natural tissue borders for type 2 lymphocytes that regulates their maintenance and activation. Our recent 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.

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: 6553479
b. Cautivo KM, Matatia PR, Lizama CO, Mroz NM, Dahlgren MW, Yu X, Sbierski-Kind J, Taruselli MT, Brooks JF, Wade-Vallance A, Caryotakis SE, Chang AA, Liang HE, Zikherman J, Locksley RM, **Molofsky AB** (2022). Interferon gamma constrains type 2 lymphocyte niche boundaries during mixed inflammation. *Immunity*, *55*(2), 2022. PMCID: 35139352
c. **Molofsky AB**, Van Gool F, Liang H-E, Van Dyken SJ, Nussbaum JC, Lee, JW, Bluestone JA, Locksley RM. Interleukin-33 And Interferon-Gamma Counter-Regulate Group 2 Innate Lymphoid Cell Activation During Immune Perturbation. *Immunity* 43, 161–174 (2015). PMCID: 26092469
d. **Molofsky, AB**, Nussbaum, JC, Liang, H-E, Van Dyken, SJ, Cheng, LE, Mohapatra, A, Chawla, A, Locksley RM (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

2. We have studied how immune cells and cytokines control normal central nervous system (CNS) development and go awry in neuropsychiatric disease. In collaboration with the AV 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 peripheral-, meningeal- and CNS-resident lymphocytes interact in their local neuroimmune niches to impact glia and neural circuit formation and remodeling during CNS development and central/peripheral damage.

a. Vainchtein ID, Chin G, Cho FS, Kelley KW, Miller JG, Chien EC, Liddelow SA, Nguyen PT, Nakao-Inoue H, Dorman LC, Akil O, Joshita S., Barres BA, Paz JT, **Molofsky AB**[#], Molofsky AV[#], 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, AB**, Kheirbek, M.A., Molofsky, A.V. (2020). Microglial Remodeling of the Extracellular Matrix Promotes Synapse Plasticity. *Cell 182*, 388-403. PMCID: PMC7497728
c. Han RT, Vainchtein ID, Schlachetzki, JCM, Cho FS, Dorman LC, Ahn E, Kim DK, Barron JJ, Nakao-Inoue H, **Molofsky AB**, Glass CK, Paz JT, Molofsky AV. (2022). Microglial pattern recognition via IL-33 promotes synaptic refinement in developing corticothalamic circuits in mice. *J. Exp. Med.* **220** (2). PMCID pending.
d. Kuhn JA, Vainchtein ID, Braz J, Hamel K, Bernstein M, Craik V, Dahlgren MW, Ortiz-Carpena J, **Molofsky AB**, Molofsky AV, Basbaum AI. 2021. Regulatory t-cells inhibit microglia-induced pain hypersensitivity in female mice. *Elife* **10**, 1–17 (2021). PMCID: 34652270.

3. We have engaged in collaborative projects to understand the function and diversity of tissue stromal 'niche' cells that regulate resident-lymphocytes in adipose tissue, lung, liver, and brain. Using volumetric imaging, we have worked with the T. Peng lab to delineate stromal cell heterogeneity and function in lung damage and fibrosis. We have found that dysregulated lung adventitial stromal niches are associated with human COPD/emphysema and are both necessary and sufficient to drive emphysematous changes in mouse models of this disease. In the skin, we have found that Th2-interacting fascial fibroblasts, a type of border 'universal' fibroblast, engages in a bi-directional dialogue with skin Th2 cells and impacts skin wound repair. These collaborative works have advanced our knowledge of 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: 7642162.
b. Reyes NS, Krasilnikov M, Allen NC, Lee JY, Hyams B, Zhou M, Ravishankar S, Cassandras M, Wang C, Khan I, Matatia P, Johmura Y, **Molofsky AB**, Matthay M, Nakanishi M, Sheppard D, Campisi J, Peng T.

(2022). Sentinel p16-INK4a+ cells in the basement membrane form a reparative niche in the lung. *Science* 378(6616):192-201. PMCID 36227993.

c. Wang C, Hyams B, Allen NC, Cautivo K, Monahan K, Zhou M, Dahlgren MW, Lizama CO, Matthay M, Wolters P, **Molofsky AB[#],** and Peng T[#] (2023) Dysregulated tissue niche potentiates resident lymphocytes to suppress an interferon-sensitive stem cell reservoir in emphysema. *Immunity*, *in press, PMCID pending. # co-corresponding*

d. Boothby IC, Kinet MJ, Boda DP, Kwan EY, Clancy S, Cohen JN, Habrylo I, Lowe MM, Pauli M, Yates AE, Chan JD, Harris HW, Neuhaus IM, McCalmont TH, **Molofsky AB**, Rosenblum MD. (2021). Early-life inflammation primes a T helper 2 cell-fibroblast niche in skin. *Nature*, Nov;599(7886) PMCID: 34707292.

4. We have helped characterize the non-redundant roles of the tissue cytokines IL-33, IL-25, and TSLP in activating tissue ILC2s and Th2s and downstream type 2 immunity, as well as the contribution of type 2 immunity to adipose tissue metabolic health and disease. We helped define the heterogeneity and functions of tissue ILC2s from multiple organs, including recent work on the role of a type 2 immune pathway that govern murine parturition (birth).

a. 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

b. Ricardo-Gonzalez RR, Van Dyken SJ, Schneider C, Lee J, Nussbaum JC, Liang H-E, Vaka D, Eckalbar WL, **Molofsky AB,** Erle DJ, Locksley RM. (2018). Tissue signals imprint ILC2 identity with anticipatory function. *Nat Immunol 19*, 1093–1099. PMCID: PMC6202223

c. O'Leary CE, Sbierski-Kind J, Kotas ME, Wagner JC, Liang HE, Schroeder AW, de Tenorio JC, von Moltke J, Ricardo-Gonzalez RR, Eckalbar WL, **Molofsky AB**, Schneider C, Locksley RM. (2022) Bile acid-sensitive tuft cells regulate biliary neutrophil influx. Sci Immunol. Mar 4;7(69) PMCID: 35245089.

d. Siewiera J, McIntyre T, Cautivo KM, Mahiddine K, Rideaux D, **Molofsky AB**, Erlebacher A. (2023). Circumvention of luteolysis reveals parturition pathways in mice dependent upon innate type 2 immunity. *Immunity*, in press. PMCID pending.

5. *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

A full list of my publications is available at: My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/14AY37wr6bCAj/bibliography/public/

BIOGRAPHICAL SKETCH

NAME: Ricardo Gonzalez, Roberto Rafael

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

POSITION TITLE: Assistant 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 Puerto Rico Mayaguez	B.S.	06/2001	Industrial Biotechnology
Stanford University	M.D., Ph.D.	06/2011	Immunology
Brigham and Women's Hospital	Internship	06/2012	Internal Medicine
University of California San Francisco	Residency	06/2015	Dermatology
University of California San Francisco	Postdoc	12/2020	Immunology

Ongoing and recently completed projects:

K08 AR075880 (NIH/NIAMS)
Ricardo-Gonzalez (PI)
09/24/2019-08/31/2024
Elucidating the Role of Type 2 Immunity in Skin Homeostasis

Not assigned (CZ Biohub)
Ricardo-Gonzalez (PI)
03/01/2022-02/28/2027
Chan Zuckerberg Biohub Investigator
Harnessing the therapeutic potential of innate lymphoid cells

RWJF 74257
Ricardo-Gonzalez (PI)
07/01/2017-05/31/2022
Robert Wood Johnson Foundation - Harold Amos Medical Faculty Development Program Award
Study of innate lymphoid cells in skin health and disease

Highlighted Citations:

1. **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. *Nature Immunology*. 2018 Sep 10. doi: 10.1038/s41590-018-0201-4. PMID: 30201992.
2. Schneider C, Lee J, Koga S, **Ricardo-Gonzalez RR**, Nussbaum JC, Smith LK, Villeda SA, Liang HR, Locksley RM. Layered ontogeny and in situ perinatal priming of tissue ILC2s. *Immunity.* 2019 May 14. pii: S1074-7613(19)30199-2. doi: 10.1016/j.immuni.2019.04.019. PMID:.31128962
3. **Ricardo-Gonzalez RR**, Schneider C, Liao C, Lee J, Liang HE, Locksley RM. Extrusion of activated ILC2s from tissues disseminates type 2 immunity via circulation. *J Exp Med*. 2020 Apr 6;217(4). doi: 10.1084/jem.20191172. PMID: 32031571
4. **Ricardo-Gonzalez RR**, Kotas ME, O'Leary CE, Singh K, Damsky W, Liao C, Arouge E, Tenvooren I, Marquez DM, Schroeder AW, Cohen JN, Fassett M, Lee J, Daniel SG, Bittinger K, Díaz RE, Fraser JS, Ansel M, Spitzer M, Liang HE, Locksley RM. Innate Type 2 Immunity Controls Hair Follicle Commensalism by *Demodex* Mites. *Immunity*. 2022 Aug 30:S1074-7613(22)00378-8. doi: 10.1016/j.immuni.2022.08.001. Online ahead of print. PMID: 36044899

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021-	Assistant Professor in Residence, UCSF Department of Dermatology and Microbiology and Immunology (by courtesy), San Francisco, CA
2017-	Co-chair, UCSF Department of Dermatology Diversity Committee
2016-	Dermatologist, UCSF Department of Dermatology, San Francisco, CA
2015-	Fellow, American Academy of Dermatology
2014-2020	Postdoctoral Research Fellowship, Laboratory of Dr. Richard Locksley, UCSF
2012-2015	Dermatology Residency, UCSF Department of Dermatology, San Francisco, CA
2012-	California Physician and Surgeon Medical License
2011-2012	Internal Medical Internship, Brigham and Women's Hospital, Boston, MA
2002-2011	Medical Scientist Training Program, Stanford University, Palo Alto, CA
2001-2002	Research Technician, Dana Farber Cancer Institute, Boston, MA

Honors

2022	Montagna Symposium on the Biology of Skin Travel Award
2022	Victor Newcomer Research Award, Pacific Dermatologic Association
2022	Chan Zuckerberg Biohub Investigator
2021	Milstein Travel Award & Milstein Abstract Award, International Cytokine & Interferon Society Annual Meeting, Cardiff, United Kindom
2019	Best Poster Award, European Society for Investigative Dermatology, 49th Annual Meeting, Bordeaux, France
2018	International Travel Award, Selected for Oral Presenation, 3rd International Innate Lymphoid Cells Meeting, Tokyo, Japan
2018	International Travel Award, Oral presentation, International Investigative Dermatology Meeting, Orlando, FL
2018	International Travel Award, Next Generation Immunology Cell Symposia, Rehovot, Israel
2017	Robert Wood Johnson Foundation Amos Medical Faculty Development Award
2016	Dermatology Foundation Research Career Development Award
2016	A.P. Giannini Foundation Postdoctoral Fellowship
2015	American Academy of Dermatology Resident Jeopardy, 2nd Place (UCSF Team)
2014	Medical Dermatology Society Mentorship Award
2009	Best Poster Award, Stanford Medical Student Research Symposium
2006	Walter J. Gores Award for Excellence in Teaching, Stanford University Commencement
2005-2009	NIH NRSA Predoctoral Fellowship, National Institute of Allergy and Infectious Diseases
2003-2005	Hispanic Scholarship Fund/Pfizer Graduate Fellow
1999	Oral Presentation Winner, 1999 National Minority Research Symposium, Phoenix, AZ
1999-2000	Mayo Clinic Minority Scholars
1999-2000	Hispanic Scholarship Fund Undergraduate Scholarship
1997-2000	Honor Scholarship of the Faculty of Arts And Sciences, UPR-Mayaguez

Contributions to Science

1. Elucidating the role of type 2 immunity in metabolism.

My first significant contribution to science was in describing the role of type 2 immunity in metabolic homeostasis. As a graduate student in Ajay Chawla's laboratory, we discovered that alternatively activated macrophages (AAMs) depend on peroxisome proliferator-activated receptors (PPARs) and are critical for the maintenance of adipose tissue homeostasis. While it is now well accepted that the immune system is a critical regulator of metabolic homeostasis, ours were among the first such reports, and helped ignite the new field of "immunometabolism." Additionally, we demonstrated that type 2 signaling was critical in the liver for the maintenance of glucose and lipid homeostasis. In collaboration with Dr. Richard Locksley, my postdoctoral research mentor, we uncovered the association and relationships between eosinophils and AAMs in healthy adipose tissue. Together, these studies served to propel the field of immunometabolism

and demonstrated the importance of type 2 immunity in protection from inflammation-associated obesity and metabolic syndrome.

a. Odegaard JI*, **Ricardo-Gonzalez RR***, Goforth MH, Morel CR, Subramanian V, Mukundan L, et al. Macrophage-specific PPARgamma controls alternative activation and improves insulin resistance. *Nature*. 2007 Jun 28;447(7148):1116–20. PMID: 17515919. *These authors contributed equally to this work.

b. Odegaard JI*, **Ricardo-Gonzalez RR***, Red Eagle A, Vats D, Morel CR, Goforth MH, et al. Alternative M2 activation of Kupffer cells by PPARdelta ameliorates obesity-induced insulin resistance. *Cell Metabolism*. 2008 Jun;7(6):496–507. PMID: 18522831. *These authors contributed equally to this work**.**

c. **Ricardo-Gonzalez RR**, Red Eagle A, Odegaard JI, Jouihan H, Morel CR, Heredia JE, et al. IL-4/STAT6 immune axis regulates peripheral nutrient metabolism and insulin sensitivity. *Proc Natl Acad Sci USA*. 2010 Dec 28;107(52):22617–22. PMID: 21149710

d. Wu D, Molofsky AB, Liang H-E, **Ricardo-Gonzalez RR**, Jouihan HA, Bando JK, et al. Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. *Science*. 2011 Apr 8;332(6026):243–7. PMID: 21436399

2. ILC2s in homeostasis, development, and inflammation.

My interest in type 2 immunity and understanding how it is critical to allergic tissue inflammation and homeostasis led me to seek additional training to develop a deeper understanding on how the type 2 circuit is integrated into tissue physiology. In Dr. Richard Locksley's laboratory at UCSF, I helped to identify tissue-specific transcriptional differences of type 2 innate lymphoid cells (ILC2s), including skin ILC2s, a cell type whose role in homeostasis and disease has been poorly characterized. Using reporter mice for type 2 cytokines (IL-5, IL-13) that were generated in our laboratory and combining these reporter mice with mice deficient in epithelial cytokines, we discovered that ILC2s have unique signatures in different tissues, independent of signaling by the ILC2-activating cytokines IL-25, IL-33, and TSLP. Critically, these findings suggest tissue-specific homeostatic cues and functionality that extend beyond well-known activating signals. We also showed that skin ILC2s respond to IL-18 in homeostasis and that ILC2s were unaltered in number and homeostatic function in germ-free mice. In addition, we found that ILC2s appear in multiple organs in late gestation, including skin, and that ILC2 activation and priming occurred in the post-natal development and associated with the acquisition of tissue-specific transcriptomes. Also, we found that activated ILC2s can enter the circulation after infection with the migratory helminth *Nippostrongylus brasiliensis*, and that these circulatory ILC2s are heterogeneous populations extruded from distinct tissues that are dependent on alarmins matched to the receptor profile of the specific tissue ILC2s.

a. **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. *Nature Immunology*. 2018 Sep 10. doi: 10.1038/s41590-018-0201-4. PMID: 30201992. *These authors contributed equally to this work**.**

b. Schneider C, Lee J, Koga S, **Ricardo-Gonzalez RR**, Nussbaum JC, Smith LK, Villeda SA, Liang HR, Locksley RM. Layered ontogeny and in situ perinatal priming of tissue ILC2s. *Immunity.* 2019 May 14. pii: S1074-7613(19)30199-2. doi: 10.1016/j.immuni.2019.04.019. PMID:.31128962

c. **Ricardo-Gonzalez RR***, Schneider C*, Liao C, Lee J, Liang HE, Locksley RM. Extrusion of activated ILC2s from tissues disseminates type 2 immunity via circulation. *J Exp Med*. 2020 Apr 6;217(4). doi: 10.1084/jem.20191172. PMID: 32031571. *These authors contributed equally to this work.

d. **Ricardo-Gonzalez RR**, Molofsky AB, Locksley RM. ILC2s - development, divergence, dispersal. *Curr Opin Immunol.* 2022 Feb 14; 75:102168. PMID: 35176675

3. Elucidating the function of tissue-resident immune cells in skin homeostasis and disease.

My continued interest in the role of type 2 immunity in tissue homeostasis has focused my current work in understanding the homeostatic functions of immune cells in tissue and how perturbations in these cells lead to aberrant inflammation and disease. As a practicing dermatologist, I am particularly interested in the role of type 2 immunity in the skin. As mentioned above, I have observed that ILC2s in the skin have a unique tissue signature, and are responsive to IL-18. In work completed since I transitioned to

independence and that was recently accepted for publication, I found that type 2 immunity is critical for the maintenance of normal immune skin tone, epidermal homeostasis, and the appropriate immune response to *Demodex*, a skin ectoparasite present in all mammals. In addition to examining the role of ILC2s in the skin, I have collaborated in studies related to the discovery that regulatory T cells in the skin play a significant role in augmenting the function of epithelial stem cells and on several studies investigating how ILCs can be associated with pathology or repair across tissues. I am also collaborating with other scientists at UCSF and at other academic institutions in the US to advance our understanding of how skin inflammation can influence immune cell activation and effector function.

a. **Ricardo-Gonzalez RR***, Kotas ME, O'Leary CE, Singh K, Damsky W, Liao C, Arouge E, Tenvooren I, Marquez DM, Schroeder AW, Cohen JN, Fassett M, Lee J, Daniel SG, Bittinger K, Díaz RE, Fraser JS, Ansel M, Spitzer M, Liang HE, Locksley RM. Innate Type 2 Immunity Controls Hair Follicle Commensalism by Demodex Mites. *Immunity*. 2022 Aug 26:S1074-7613(22)00378-8. doi: 10.1016/j.immuni.2022.08.001. Online ahead of print. PMID: 36044899. *Co-corresponding authors.

b. Bielecki P, Riesenfeld SJ, Hütter JC, Triglia ET, Kowalczyk MS, **Ricardo-Gonzalez RR**, Amezcua Vesely MC, Kroehling L, Biton M, Muus C, Ludwig LS, Christian E, Tao L, Kedaigle AJ, Steach HR, Yaghoubi P, Dionne D, Jarret A, McGee HM, Porter CBM, Licona-Limon P, Bailis W, Jackson RP, Gagliani N, Locksley RM, Regev A, Flavell RA. Inflammation drives diverse skin-resident innate lymphoid cells into convergent pathogenic effectors. *Nature.* 2021 Apr; 592:128-132. PMID: 33536623

c. Liu Y, Wang H, Taylor M, Cook C, Martínez-Berdeja A, North JP, Harirchian P, Hailer AA, Zhao Z, Ghadially R, **Ricardo-Gonzalez RR**, Grekin RC, Mauro TM, Kim E, Choi J, Purdom E, Cho RJ, Cheng JB. Classification of human chronic inflammatory skin disease based on single-cell immune profiling. *Sci Immunol.* 2022 Apr 15; 7(70):eabl9165. PMID: 35427179

d. O'Leary CE, Sbierski-Kind J, Kotas ME, Wagner JC, Liang HE, Schroeder AW, de Tenorio JC, von Moltke J, **Ricardo-Gonzalez RR**, Eckalbar WL, Molofsky AB, Schneider C, Locksley RM. Bile acid-sensitive tuft cells regulate biliary neutrophil influx. *Sci Immunol.* 2022 Mar 04; 7(69):eabj1080. PMID: 35245089

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1f9mtqh86yssHX/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

Positions, Scientific Appointments, and Honors

Positions and Employment

2009-2022	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
1986-2022	Director, Lung Biology Center, UCSF
1981-1987	Assistant Professor of Medicine, University of California, San Francisco (UCSF)

Honors

2022	Elected Fellow, American Association for the Advancement of Science
2021	Lifetime Achievement in Mentoring Award, UCSF
2017	Elected Member, American Academy of Arts and Sciences
2016	UCSF Faculty Lecture, Translational Science
2013	Listed as one of top 20 translational scientists in the world by Nature Biotechnology
2007	Amberson Lecturer, American Thoracic Society
2001	NIH Merit Award
1996	Lifetime Scientific Achievement Award, American Thoracic Society
1995	Clean Air Award, American Lung Association of California
1992	Elected Member, Association of American Physicians
1988	Elected Member, American Society for Clinical Investigation

Contribution to Science

1. Early in my career I focused on the effects of common air pollutants and occupational exposures on airway function in susceptible people, especially people with asthma. My work identified the potent effects of even short-term exposure of patients with mild asthma to low concentrations of the air pollutant sulfur dioxide. This work played an important role in re-evaluating National and California air pollution standards. I also developed a small animal model of occupational asthma induced by toluene diisocyanate and identified the important role of afferent airway C fibers in regulating responses to this important industrial pollutant.

a) Sheppard D, Wong SC, Uehara CF, Nadel JA, Boushey HA. Lower threshold and greater bronchomotor responsiveness of asthmatic subjects to sulfur dioxide. Am Rev Respir Dis 1980; 122:873-878. PMID: 7458061
b) Sheppard D, Saisho A, Nadel JA, Boushey HA. Exercise increases sulfur dioxide-induced bronchoconstriction in asthmatic subjects. Am Rev Respir Dis 1981; 123:486-491. PMID: 7235370
c) Sheppard D, Thompson JE, Scypinski L, Dusser D, Nadel JA, Borson DB. Toluene diisocyanate increases airway responsiveness to substance P and decreases airway neutral endopeptidase. J Clin Invest 1988; 81:1111-1115. 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 (β6) 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 αvβ6 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 α9 subunit, a novel partner of β1 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 α9β1 mediates cell attachment to a non-RGD site in the third fibronectin type III repeat of tenascin. J Biol Chem 1994; 269:26691-26696. PMID: 7523411

3. To better understand the in vivo relevance of members of the integrin family we had identified, my lab generated integrin subunit knockout mice and used the phenotypes we identified 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 2017127:365-374 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 and in the maturation of microglia. 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) Kudo M, Melton AC, Chen C, Engler M, Huang KE, Ren X, Wang Y, Bernstein X, Li J, Atabai K, Huang X, Sheppard D. IL-17A produced by αβ T cells drives airway smooth muscle contraction. Nature Medicine 2012 18:547-554. PMID:22388091
d) 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

5. Over the past few years the lab has increasingly focused on the roles that stromal cells play in normal tissue homeostasis and how these processes go awry in the development of acute and chronic diseases. To take full advantage of the power of single cell RNA sequencing we put considerable effort into developing methods to capture all of the stromal cells from healthy and diseased murine and human lungs. This effort allowed us to characterize the remarkable heterogeneity of lung fibroblasts, with unique molecular subsets present in unique anatomic positions in healthy lungs and several new molecular states that emerge in response to lung injury and in diseased human lungs. Remarkably, most of these subsets are conserved between mouse and human. With this information in mind we are developing a suite of novel tools that allow us to purify, mark, delete or genetically manipulate these diverse populations and to determine how these cells communicate with adjacent epithelial cells immune cells. We have also established collaborations with several other labs to advance understanding of the roles each subset plays in lung health and disease.
a) 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. PMID: 32317643
b) Alsamman S, Christenson S, Segal J, Ayad N, Hu JK-H, Sedki M, Rubino PR, Ghoshal S, Ferreira DDS, Ma H-Y, Wei L, Chung RT, Mattias A, Fuchs B, Weaver V, Mullen AC, Sheppard D*, Chen JY* (co-senior authors). Targeting Acid Ceramidase Inhibits YAP/TAZ Signaling to Reduce Fibrosis. Science Translational Medicine 2020 12:eeay8798. PMID:32817366
c) Auyeung VC, Downey MS, Thamsen M, Wenger TA, Backes, BJ, Sheppard D*, Papa FR*. (*equal contributions as senior authors) IRE1α drives lung epithelial progenitor dysfunction to establish a niche for pulmonary fibrosis. Am J Physiol Lung Mol Cell Physiol. 2022 322:L564-580. PMID: 35170357
d) Reyes N, Krasilnikov M, Allen NC, Lee JY, Hyams B, Zhou M, Ravishankar S, Cassandras M Wang C, Khan I, Matatia P, Johmura Y, Molofsky A, Matthay M, Nakanishi M, Sheppard D, Campisi J, and Peng

T. Sentinel p16INK4a+ cells in the basement membrane form a reparative niche in the lung. Science, 2022, 378:192-201 PMID 36227993

BIOGRAPHICAL SKETCH

NAME: Sundaram, Aparna B

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

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
Northwestern University, Evanston IL	BS	06/03	Biomedical Engineering
Northwestern University, Chicago IL	MD	06/06	Medicine
Northwestern University, Chicago IL	n/a	06/07	Internship
Northwestern University, Chicago IL	n/a	06/09	Residency, Internal Medicine
University of California, San Francisco CA	n/a	06/12	Fellowship, Pulmonary & Critical Care Medicine

Ongoing and recently completed projects:

ALA P0558571 (PI) 2022 – 2024
American Lung Association
The goals of this project are to explore the biology of cadherin-11 in regulation of allergic responses in asthma.

R61/R33 HL163725 (PI) 2022 – 2025
NIH/NHLBI
The major goal of this project is to develop potent and specific small molecule inhibitors of integrin alpha2 beta1.

UCSF InVent Fund (co-PI) 2020 – 2022
UCSF
The major goal of this project is to design and screen more potent and specific small molecule inhibitors of integrin alpha5 beta1.

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

Citations:

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)

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)

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*, 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

2022-present Associate Professor of Medicine, Division of Pulmonary and Critical Care Medicine, UCSF
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
2014-2022 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)

A full list of my publications can be found at:
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 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	B.A.	05/1973	Biology
University of Chicago	Ph.D.	05/1978	Immunology
University of Chicago	M.D.	05/1979	Medicine

Ongoing and recently completed projects that I would like to highlight include:

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)
12/08/15-11/30/2025
The cell and molecular mechanisms underlying CD28 costimulation

Nora Eccles Treadwell Foundation
Weiss (PI)
01/01/22-06/30/25
Identifying and Characterizing the T Cell Antigen Receptor Signaling Threshold for Arthritis Development

2P01 AI091580
Weiss (Program Leader and Project PI)
07/01/2016-06/30/2021 (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. 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.
2. 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.

3. 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.
4. Lu, W., Helou, Y. A., Shrinivas, K., Liou, J., Au-Yeung, B. B., **Weiss, A.** (2023). The phosphatidylinositol-transfer protein Nir3 promotes PI(4,5)P_2 replenishment in response to TCR signaling during T cell development and survival. *Nature Immunology*, *24*(1), 136–147. PMCID: PMC9810531.

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
1993-2022 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

Current Industry Relationships
Nurix Therapeutics, Co-Founder and Scientific Advisory Board
BlueSphere Bio, Scientific Advisory Board
BRIDgene Biosciences, Scientific Advisory Board
Genentech, Scientific Review Board
IMIDomics, Immunology Advisory Board
Jasper Therapeutics, Scietific Advisory Board

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://pubmed.ncbi.nlm.nih.gov/collections/51780518/?sort=pubdate

BIOGRAPHICAL SKETCH

NAME: Prescott G. Woodruff, MD, MPH

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

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
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 that I would like to highlight include:

NIH/NHLBI K24 HL137013 (PI Woodruff) 04/28/17-3/31/27
Mentoring Research in Precision Medicine for Lung Disease
To mentor students, fellows and junior faculty in patient oriented precision medicine related research in respiratory disease (5 year Renewal, to begin 2022, already submitted and scored in a funding range).

NIH/NHLBI R01 HL146002 (MPI Woodruff, PI Levy) 9/23/19-6/30/24
Immunometabolic phenotypes in adult severe asthma and disease progression
The major goal of this project is expand the comprehensive phenotyping of subjects with severe asthma that was begun in SARP III with additional biologic sampling and further longitudinal assessments focused on underlying genetic, inflammatory mechanisms and metabolic dysfunction that enable, promote and/or predict disease progression.

NIH/NIAID U19 AI077439 (Project leader Woodruff, PI Erle) 4/01/18-3/31/28
Understanding Asthma Endotypes
This proposal seeks to identify molecular phenotypes (endotypes) of asthma and understanding how these endotypes contribute to disease pathophysiology.

NIH/NHLBI U01 HL137880 (PI Woodruff) 09/15/17-5/31/22
NHLBI SPIROMICS II: Biological underpinnings of COPD heterogeneity and progression. In NCE
To establish the biological underpinnings of COPD heterogeneity, progression and exacerbations using the SPIROMICS cohort.

Most Relevant 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). PMID: 33682796.

2. 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.

3. **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

4. **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

Positions and Honors

Positions and Scientific Appointments

2022-present	Chief, Division of Pulmonary, Critical Care, Sleep and Allergy, Department of Medicine, UCSF
2021	Co-Chair Keystone Symposium on "Asthma: New Discoveries and Therapies in the Age of COVID"
2020-present	Executive Committee Member, UCSF COVID-19 Multi-Phenotyping for Effective Therapies (COMET) study
2019 -2021	Associate Editor, American Journal of Respiratory Critical Care Medicine
2019-present	Faculty, UCSF Bakar ImmunoX Program
2018-2022	Vice Chief for Research, Division of Pulmonary and Critical Care Medicine, Department of Medicine
2018-present	Chair, NHLBI SPIROMICS Steering Committee and Executive Committee
2018-present	NIH/NIAID Scientific Advisory Board, Inner City Asthma Consortium
2017-present	Director, UCSF Pulmonary Precision Medicine Core Laboratory
2017-present	Investigator, UCSF Sandler Asthma Basic Research Center (SABRE)
2017	NIH/NIAID Scientific Review Group ZAI1 TC-I (S3), U19 Review Panel
2016	Associate Editor, Journal of Clinical Investigation, Insight
2016	Chair, NHLBI/ATS Asthma COPD Overlap Syndrome Workshop
2014-present	Professor of Medicine, Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Department of Medicine, UCSF
2013	NIH/NHLBI Special Emphasis Review Panel ZRG1 EMNR-N (55)
2011 - 2013	Chair, Section on Genetics and Genomics, American Thoracic Society
2011	Faculty, UCSF Biomedical Sciences Graduate Program
2011	NIH/NHLBI Special Emphasis Review Panel ZRG1 EMNR-N (55)
2010-2014	Associate Professor of Medicine, Division of Pulmonary and Critical Care Medicine, Department of Medicine, UCSF
2010-2012	American Thoracic Society, Scientific Advisory Board
2010	NIH/NHLBI Special Emphasis Review Panel ZHL1 CSR-W (S1)
2009	Investigator, UCSF Cardiovascular Research Institute (CVRI)
2009	NIH/NHLBI Special Emphasis Review Panel ZHL1 CSR-D (O1)
2008-present	Associate Director, UCSF Airway Clinical Research Center

2005-2010	Assistant Professor of Medicine, Division of Pulmonary and Critical Care Medicine, UCSF
1998-2002	Clinical and Research Fellow, Division of Pulmonary and Critical Care Medicine & Cardiovascular Research Institute, Department of Medicine, UCSF
1997-1998	Research Fellow, Channing Laboratory, Brigham and Women's Hospital

Honors

2022	Elected to Membership, Association of American Physicians
2020	Faculty Mentoring Award, UCSF Division of Pulmonary, Critical Care, Sleep and Allergy
2012	Elected to Membership, American Society for Clinical Investigation
1993	Alpha Omega Alpha, Columbia College of Physicians and Surgeons, NY, NY

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

2. 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

3. 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.

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), as well as a trial showing that dual bronchodilator therapy does not relieve symptoms in tobacco-exposed persons with preserved lung function.
   a. Han MK, Ye W, Wang D, et al…, **Woodruff, PG**. Bronchodilators in Tobacco-Exposed Persons with Symptoms and Preserved Lung Function. N Engl J Med 2022 Sep 29;387(13):1173-1184..
   b. Criner GJ, Connett JE, Aaron SD, Albert RK, Bailey WC, Casaburi R, Cooper JA Jr, Curtis JL, Dransfield MT, Han MK, Make B, Marchetti N, Martinez FJ, Niewoehner DE, Scanlon PD, Sciurba FC, Scharf SM, Sin DD, Voelker H, Washko GR, **Woodruff PG**, Lazarus SC; the COPD Clinical Research Network and the Canadian Institutes of Health Research. Simvastatin for the Prevention of Exacerbations in Moderate-to-Severe COPD. N Engl J Med. 2014 Jun 5;370(23):2201-10. PMCID: PMC4375247
   c. 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

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