Progress
Report Year 21
July 2020
Figure Legend: Single cell RNA Sequencing of sinus epithelial brushes from 4 healthy controls and 5 nasal polyp patients reveals an expansion of MUC5AC+ secretory cells and mast cells. Rare cell types such as tuft cells (0.2-0.5% of the epithelium) are identified here and reveal a novel inflammatory gene signature in patients with nasal polyps.
In Memorium

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

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

Summary of Accomplishments over the Past Year

This year witnessed the SARV-CoV2 pandemic with its unprecedented impact on academic life, research and the health care system. SABRE labs were shuttered in March and only partially reopened in late May, and currently remains at a 25% limit in persons allowed in the lab at a given time. Animal breeding, sequencing studies, core activities, in-person conferences and seminars were suspended to minimize human contact and to redirect resources to COVID-19-related activities, generating opportunity that could only be met by the flexibility provided through SABRE funding. Thus, SABRE Center investigators continued to make contributions to the understanding of asthma and allergic disease, while also pivoting to address the impact on COVID-19 on patients with asthma, an emphasis that continues with the ongoing pandemic.

Notable accomplishments from SABRE Center members since the prior Report:

1. Esteban Burchard was awarded a $10 million grant from the NIH, designated PRIMERO, to study asthma development in a prospective cohort of 3000 mother-newborn pairs in Puerto Rico, where the prevalence and severity of asthma are among the highest in the world. Despite the pandemic, over 100 births have been enrolled and the study has already spawned additional NIH submissions to expand on this rich data set.
2. John Fahy used the NIH Severe Asthma Research Program repository to rapidly assess the expression of viral SARS-CoV-2 receptors on sputum cells of asthma patients as compared to controls, revealing a potential protective role for corticosteroids.
3. Mark Ansel, John Fahy, Prescott Woodruff and David Erle were among the UCSF consortium of immunologists and basic scientists uniting to form COMET as an NIH-partnered institutional commitment to apply next-gen sequencing, proteomics and cell analysis to better understanding of effects of COVID-19 on lung functions, including their impact on allergic lung diseases.
4. Among basic research contributions, the Allen lab discovered the role of IL-21 in inhibiting IgE class switch recombination in mouse and human B cells (JEM, 2020). The Locksley lab continued to elucidate mechanisms driving ILC2 biology, including extrusion from tissues in response to perturbation to mediate systemic effects (JEM, 2020). The Shin lab continued to explore the role of MARCH1 regulation in dendritic cells and effects on T cell differentiation (Nat Comm, 2018).
Overview – 2020

Richard M. Locksley, M.D.

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

The onset of the COVID-19 pandemic in late February began an unprecedented disruption of American society, including research, with non-essential research and clinical activities suspended at UCSF in March. Efforts were made to pivot to COVID-19-related activities, as permitted at 25% effort, and here the flexibility of SABRE support allowed a number of labs to move quickly to assess interactions between the virus, lung tissues, and among patients with asthma. These activities became unified to form COMET, a spontaneous integration of scientists across disciplines with clinicians to bring cutting-edge technologies to bear on understanding this new infectious disease. Boosted by our early commitment to single-cell RNAseq and related platforms, SABRE labs were able to contribute quickly to studies of viral receptors, cell phenotypes and transcriptomic signatures among patients, including those with airways disease, and these studies continue. With laboratories at UCSF cautiously expanding to 25% capacity in late May, we have slowly increased research across SABRE while adhering to the realities of the pandemic. SABRE members remain integrated across the leadership areas of UCSF in order to work quickly and supportively in this new environment while bringing projects back online to further our Mission. Scientific leadership on national and international scales included participation and organization of the 2020 Keystone Symposium on Asthma Immunobiology by the former American Asthma Foundation Scientific Board assembled by the Sandler Foundation to be held in Utah, and organization of the 4th International Conference on Innate Lymphoid Cells to be held in San Francisco. Both activities had to be postponed and will hopefully be held in 2021.

Investigators

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

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

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

As the COVID-19 pandemic swept across the world, pulmonologists, infectious disease experts, and immunologists at UCSF united to form COMET, a consortium capable of deploying established expertise to interrogate the immune phenotypes associated with COVID-19 disease pathology in a team science effort to accelerate discovery of biomarkers and therapies to ameliorate the disease and its impact on patients and society. Dr. Ansel’s role in COMET is to investigate the cellular heterogeneity and signaling status of immune and epithelial cells recovered from the airways of COVID-19 patients. In addition to leveraging the experience gained in Dr. Ansel’s prior studies of asthma, this work also directly benefits his ongoing asthma research, as it has provided access to airway biospecimens, closer collaboration with CyTOF expert Dr. Matt Spitzer, and urgency to rapidly develop and empirically test the technical and computational analysis pipelines to investigate airway diseases using this powerful technology.
Dr. Ansel is an established leader in his field. He contributed to 9 published manuscripts this year, and 8 others are in review or revision for publication. He has recently renewed funding from R01 and P01 grants from NHLBI, as well as Fastgrants and NIAID supplemental funding for his COVID-19 research. The Ansel laboratory is currently populated by three graduate students, two postdoctoral fellows, two technicians, and one undergraduate researcher. Postdoctoral fellow Kristina Johansson is supported by the Swedish Heart Lung Foundation and the Sweden-America Foundation; Marlys Fassett received a K08 Career Development Award this year; graduate student Didi Zhu was awarded a Hooper Foundation Fellowship; and Priscila Muñoz-Sandoval was awarded the Howard Hughes Medical Institute Gilliam Fellowship. Dr. Ansel’s departed trainees have moved successfully into the next phases of their careers as postdoctoral fellows, scientists at biotechnology companies, MD/PhD residents, fellows in research career tracks, and in four cases, as principal investigators of independent laboratories in the US and Germany where they have continued their work on cell programming in asthma.

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

Jeoung-Sook Shin, Ph.D., seeks to understand the molecular mechanisms by which dendritic cells contribute to immune homeostasis and diseases. The research goal of Dr. Shin’s laboratory is to better understand the molecular mechanism underlying antigen presenting function of dendritic cells and apply that understanding to the development of therapeutics for treatment of human diseases. In particular, Dr. Shin is interested in understanding the contribution of membrane trafficking to dendritic cell function in allergic asthma. Dr. Shin has found that the high affinity IgE receptor, which mediates activation of mast cells in allergic asthma, mediates endocytosis of IgE in dendritic cells contributing to IgE clearance, thus potentially mitigating allergy. Dr. Shin has also found that the endocytic pathway of the IgE receptor could be exploited to establish immune tolerance against the IgE-bound antigens. More recently, Dr. Shin has investigated the role of the ubiquitin ligase MARCH1 in dendritic cell function in allergic asthma. She and others had previously found that MARCH1 ubiquitinates the antigen presenting molecule MHCII and the costimulatory molecule CD86. Her recent studies indicate that ubiquitination of these molecules by MARCH1 conditions dendritic cells to prime allergen-specific naïve T cells for IL-4 production and drive development of IgE responses, airway inflammation, and airway hyper-reactivity. During this study, she generated a few genetically manipulated mouse strains and established mouse models of acute and chronic asthma sensitive to house dust mite allergens. These experimental tools
have been disseminated to wide scientific community including NIH and Canada to accelerate new discovery. More recently, she has launched into examination of the heterogeneity of lung dendritic cells involved in allergic asthma. This new project reveals that respiratory allergens are captured by three distinct dendritic cell subsets in the lungs. One of them is localized close to airway and highly endocytic and migratory while the others are not readily accessed from the airway and less endocytic and lung-resident. This finding implicates versatile roles of dendritic cells in allergic asthma and functional specialization of these subsets.

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

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

Chris Allen, Ph.D., joined the SABRE center twelve years ago as a UCSF Fellow. He was the first member of the UCSF Sandler Fellows Program (http://fellows.ucsf.edu/) who was selected to work on a specific human disease, in this case, asthma. This program enabled Dr. Allen to develop an independent research program combining his skills in cellular and molecular immunology with optical imaging capacities that have powered new insights in allergic inflammation. His primary research focuses on understanding the mechanisms that regulate the generation and fate of IgE-producing B cells and plasma cells. Surprisingly, this remains a poorly understood pathway of fundamental importance to the pathogenesis of allergy and asthma. Dr. Allen published his initial findings in *Immunity*, reporting his discovery that IgE heavy chains inherently drive plasma cell differentiation and the movement of B cells out of germinal centers, a process that may serve to limit somatic hypermutation and thus affinity. He followed up this work showing that the unusual properties of IgE-switched B cells are due to constitutive activity of the IgE B cell receptor, which he published in *eLife*. These findings will drive new hypotheses regarding mechanisms by which some allergic individuals develop high-affinity IgE, and these continue to be a major effort of his laboratory. Dr. Allen recently
published a paper in the *Journal of Experimental Medicine* regarding cytokine regulation of IgE responses, showing that IL-21 is a major factor limiting the generation of IgE B cells. Dr. Allen is about to submit a manuscript on how antigen is captured and presented to T cells in the lung by macrophages proximal to the bronchial airway epithelium, as well as two manuscripts on the activation and function of basophils, which are IgE effector cells. Dr. Allen’s generation of an IgE reporter mouse that permits the efficient tracking of IgE-switched B cells constitutes an important technical advance for the field and has been shared with numerous investigators, and Dr. Allen has published detailed protocols on how to use this reporter mouse to study IgE in the *Methods in Molecular Biology* book series. Dr. Allen has also developed methodology to characterize human IgE+ B cells. To facilitate mechanistic studies of human B cells, Dr. Allen has optimized approaches to genetically manipulate primary human B cells with CRISPR-Cas9 technology, which was published in the *Journal of Immunological Methods*. Dr. Allen also published a letter in *The Journal of Allergy and Clinical Immunology* showing how an antibody to the IgE receptor, FcepsilonRI, actually recognizes multiple Fcgamma receptors, which has led to significant confusion in the field regarding the functions of basophils, a type of IgE effector cell. Dr. Allen also published a review on recent advances in IgE biology for *Current Opinion in Immunology* and a comprehensive review on B cells in *Cell*. He continues to work closely with other investigators in the SABRE Center as he optimizes lung and immune cell imaging technologies that are applicable to broader use by other investigators on campus.

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

Dr. Allen was recruited to the Cardiovascular Research Institute (CVRI) at UCSF in 2012, when he joined the UCSF faculty as an Assistant Professor in the Department of Anatomy. Dr. Allen moved his laboratory to the Smith Cardiovascular Research Building on the Mission Bay campus in 2013, putting him in close proximity to other researchers working on the lung as well as advanced optical imaging techniques. He remains committed to investigations into the basic pathogenesis of asthma. Dr. Allen remains an active member of SABRE and participates in monthly and quarterly meetings with SABRE investigators on the Parnassus site. Dr. Allen continues to collaborate with SABRE members on research projects and as collaborators on recently submitted NIH grant proposals, including Dr. Ansel, Dr. Bhattacharya, and Dr. Sundaram. Dr. Allen recently contributed his expertise on IgE B cells to a study on microRNA regulation of B cell class switch recombination in Dr. Ansel’s lab, under review at the *Journal of Experimental Medicine*. 
Dr. Allen is currently mentoring three PhD students and a new postdoc in his lab. This postdoc is following up on the project of a previous PhD student in the lab, focused on a population of macrophages in the lung that capture inhaled allergen and present it to T cells, which may trigger inflammation contributing to asthma. Dr. Allen’s newest PhD student is following up on work from a previous postdoc regarding the generation of IgE B cells in mouse models of asthma, and another PhD student is working on the molecular pathways that control the genesis of IgE B cells. Dr. Allen has also mentored a medical student who worked for five years in his laboratory in various stints on the properties of human IgE B cells. This student began as a volunteer, and then was awarded UCSF Resource Allocation Program, Pathways to Explore summer fellowship, and then was recognized with a 2016-17 HHMI Medical Research Fellows award for a full year of research, followed by extended study through the Pathways program. In recognition of his significant contributions, his maintenance of extramural funding, and his service to UCSF, Dr. Allen was promoted to Associate Professor in 2018.

Richard Locksley, M.D., is Director of the SABRE Center, an immunologist and infectious diseases-trained physician who pursues basic studies of allergic immunity and asthma. His laboratory focuses on deeper understanding of the role for allergic cytokines in basal homeostasis, with a particular emphasis on group 2 innate lymphoid cells, or ILC2s, that have become of increasing interest in not only basic immune functions, but also in our understanding of human asthma. These studies have revealed previously unknown links with basal tissue health, metabolic homeostasis, and local regulation of cytokine expression by adaptive Th2 cells. His laboratory discovered the association of allergic immune responses by the environmental polysaccharide chitin, a constituent of fungi and insects associated with human allergic sensitivity, and has explored the role of mammalian chitinases in regulating enzymatic breakdown of environmental chitins at mucosal barriers. He directs an active laboratory effort with 10 peer-reviewed publications, 5 reviews and 3 commentaries in 2018-2020, with 3 additional manuscripts in various stages of revision after review.

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

John Fahy, M.D. is a longstanding participant in SABRE research and a formal faculty member in the SABRE Center for the past 7 years. He is a physician scientist with a primary appointment in the Division of Pulmonary and Critical Care Medicine (Department of Medicine and Cardiovascular Research Institute). He directs a mechanism-oriented clinical research program in airways disease that emphasizes studies in humans and in human-derived tissues and cells. For asthmatics with prominent airway type 2 inflammation (“type 2-high asthma”), his current research focuses on mechanisms underlying regional variation in type 2 inflammation in the lung and airway epithelial cell dysfunction in patients with “ultra-high” type 2 inflammation who are steroid-resistant and have mucus plugs and severe airflow obstruction. Dr Fahy’s lab is a leader in developing methods, applicable in humans that advance understanding for how pathologic mucus gels form in asthma (Figure). He leads a PO1 program in type 2 airway inflammation in asthma (with Drs. Locksley, Ansel and Woodruff), a translational PO1 program in academic drug discovery that aims to advance mucolytics to the clinic, and an RO1 program investigating mechanisms of airway inflammation and mucus pathology in acute severe asthma. In addition, he leads the UCSF center in the NHLBI-funded PrecISE program (biomarker driven clinical trials in severe asthma).

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

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

Prescott Woodruff, M.D., is Associate Director of the Airway Clinical Research Center, has been an integral member of the SABRE Center for the past 6 years and is a longstanding collaborator with other SABRE investigators. He is a physician-scientist with a primary appointment in the Department of Medicine, Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, where he is Vice-Chief for Research and in which he was awarded the Mentoring Award for 2020. His research interests are in asthma pathogenesis, genomics and translational studies, particularly in the field of precision medicine. His discoveries were among the earliest to identify biomarkers that permit segregation of asthma patients into categories likely to benefit from specific types of therapies that target type 2 inflammation mediated by the IL-4/IL-13 pathway. More recently, he has focused on 1) non-type 2 mechanisms of disease that may drive severe asthma, 2) type 2 and non-type 2 inflammatory mechanisms in allied diseases such as COPD and chronic bronchitis, and 3) immunophenotyping in critically ill patients with COVID-19 (through the new NIAID IMPACC Study). Dr. Woodruff’s research program also includes studies of microRNA regulation of airway epithelial mucin production. Dr. Woodruff is PI or multiple-PI of 1) the NHLBI Severe Asthma Research Program (4th iteration which started in 2019), 2) the NHLBI SPIROMICS study of COPD, 3) a NHLBI U01 grant designed to develop reference profiles for exRNAs across 12 different human body fluids, 4) the NHLBI RETHINC clinical trial in COPD, and 5) a NHLBI study of obstructive lung disease in patients living with HIV (the NIH “I AM GOLD”) Study and 6) a NHLBI K24 award which supports his mentoring of junior faculty and trainees. He is a co-investigator and/or project leader on three NIH-funded asthma grants, the NHLBI PRECISE adaptive clinical trial study in severe asthma, a NHLBI P01 directed by Dr. Fahy and a NIAID U19 directed by Dr. Erle. He serves on the Scientific Advisory Board for the NIAID Inner City Asthma Consortium. Finally, he is co-Chair the Keystone Symposium on Asthma in 2020 (delayed due to the pandemic) which was organized by the former American Foundation for Asthma and has been supported by the Sandler Foundation. Dr. Woodruff’s honors include election to membership in the American Society for Clinical Investigation.
Esteban G. Burchard, M.D., M.P.H., directs the UCSF Asthma Collaboratory, which contains the largest annotated gene biorepository of minority children with asthma in the world. Puerto Ricans have the highest asthma prevalence and mortality in the world and experience a disproportionate amount of early-life respiratory illnesses. (Wohlford et al. PLoS One 2020) In 2018, the NIH funded the Puerto Rican Infant Metagenomic and Epidemiologic study of Respiratory Outcomes (PRIMERO, U01HL138626) birth cohort study, which is designed to study the complex relationship between early-life respiratory viral infections and the development of recurrent respiratory wheeze and asthma in children. In February 2020, the first of 3,000 Puerto Rican mother-infant dyads across socioeconomic strata was recruited into PRIMERO. We will prospectively follow the infants through their first 5 years of life, collecting breast milk, maternal and neonatal cord blood, neonatal/infant nasal epithelium swabs for viral etiologies, and blood at birth, during respiratory illness, and at yearly clinical evaluations. PRIMERO offers the opportunity to study how socio-environmental factors such as race, genetic ancestry, family structure, and socioeconomic status (SES) affect the immunological profiles of mothers and their infants and further affect the child’s respiratory health. These prospective measures will establish the etiology of recurrent wheeze by identifying pathogenic trajectories and biomarkers that may predict lower respiratory tract illnesses, recurrent wheeze, and asthma. PRIMERO will uncover novel biological insights that can guide vaccine strategies and drug targets for recurrent wheeze and asthma.

PRIMERO is a natural progression and culmination of the research that the team has been conducting over the past 20 years. The buy-in and support from local institutions and authorities were also critical to establishing the birth cohort and are a testament to the substantial investment in political capital that Drs. Burchard and Rodríguez-Santana have made. Despite Puerto Rico’s Shelter in Place mandate, recruitment and specimen collection has continued during the COVID-19 pandemic and to date, the PRIMERO team have successfully recruited over 120 mother-infant dyads. Given the scale and complexity of the study (e.g., coordinating recruitment visits, study visits, and the unique procedures associated with each visit), the team developed an electronic record keeping software de novo to track these tasks for all 3,000 participants as they progress through each stage of the study. In addition, in 2019, the team established a state-of-the-art cell biology and sample processing laboratory at the recruitment hospital in Puerto Rico for the PRIMERO study. The laboratory, directed by co-Principal Investigator Dr. Rodríguez-Santana and co-supervised by Celeste Eng, manager of the UCSF Asthma Collaboratory for the last 16 years, is outfitted with BSL-2 biosafety cabinets, cell culture incubators, centrifuges, refrigerator, freezer, liquid nitrogen storage, and other laboratory equipment. In line with Dr. Burchard’s goal to make PRIMERO a university-wide resource, the Asthma Collaboratory has expanded PRIMERO to study SARS-CoV-2 and microbiome with other investigators within UCSF (Rutherford, Lynch, Chan, Ziv, and Halkias).

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

Core Activities and Technology Development

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

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

As part of the nimble nature of our technology support, SABRE has also contributed as part of leveraged equipment requests that contribute broadly to research efforts across the campus, including to investigators in SABRE labs. A number of instruments supported by SABRE matching funds, including CyTOF, liquid mass spectrophotometers and flow units remain in widespread use among many labs at UCSF. The dedication of a Microbiota Center under the leadership of Dr. Susan Lynch has created need for expansion of the gnotobiotic core supporting maintenance of germfree mice under the direction of Dr. Peter Turnbaugh. SABRE investigators, including Drs. Locksley, Allen and Ansel have all used the gnotobiotic core and realize its value in controlling and isolating microbiota that have profound effects on metabolism and organ function. With this in mind, SABRE has made a contribution to developing the gnotobiotic core to facilitate work in allergic and asthma diseases in a highly leveraged way that will work well for our access while supporting greater use of this technology across UCSF.

SABRE Associate Support

We contributed pilot funds to enhance collaborative interactions between SABRE Associates – Drs. Gordon, Battacharya and Sundaram – to create discovery opportunities in asthma research. These three young scientists have also generated terrific data with these resources and are already procuring independent grants and contributing to the SABRE Mission. Dr. Gordon, who is on a grant with Drs. Locksley and Fahy, obtained her own grants to further her interests in epithelial responses in asthma. Dr. Battacharya investigates lung injury, and has pivoted rapidly to address mechanisms by which COVID-19 mediates such devastating lung destruction. Lastly, Dr. Sundaram studies smooth muscle and its role in asthma pathogenesis, an incompletely studied area of research of much relevance to SABRE. We look forward to continue support with matching Innovative Grants to allow these talented young scientists to continue their outstanding trajectories. Each of their CVs has been included.

SABRE RNA-seq Initiative

Based on discussions hatched at the 2017 SABRE Retreat, we designated commitments to core labs for use in bulk and single-cell RNA-sequencing of airway tissues in order to create a tissue bank for core use and dissemination among labs across UCSF and wider after publication. Initial requests included studies of mouse nasal and
lung ILC2s and epithelial tuft cells (Locksley lab), human airway brushes (Fahy lab), human airway epithelial monolayers under various conditions (Woodruff lab), human nasal polyp tissues from patients with allergic polyposis (Gordon/Fahy labs), Ig-E-switched allergen-specific B cells in the mouse (Allen lab), human and mouse microRNA and RNA comparators (Ansel lab), and human drug-response outliers (Burchard lab). These data are beginning to accrue and have yielded valuable information for comparisons between the mouse and human as well as biologic insights that will continue to drive hypothesis-driven exercises. All of these data are established in the public science space with proper masking of human data. This initiative will be repeated in the coming academic year as appropriate to proceed with timely follow-up of these promising discoveries, some of which are noted in manuscripts highlighted below.

Airway Clinical Research Center

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

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

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

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

**ACRC Trainees:** The ACRC has provided a successful training environment for multiple trainees in the past, including Drs Woodruff, Gordon, Peters, Christenson, Dunican, and Bhakta. Current trainees include Anita Oh, M.D., Aartik Sarma, M.D., Elizabeth Yu, M.D., Brendan Huang, M.D., William Mckleroy, M.D. and Aaron Baugh, M.D.

**Current Active Funding**

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

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

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

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

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

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

7. **U10 HL109146 (07/01/2011 – 07/01/24)**: Clinical and Molecular Phenotypes of Severe Asthma. Severe Asthma Research Program (SARP). Dr Woodruff is PI and Dr Fahy is co-I. This multicenter grant is exploring molecular subtypes of asthma in a cohort of 4 patients with severe asthma.

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

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

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

11. **K24 HL137013 04/28/17-3/31/22** Mentoring Research in Precision Medicine for Lung Disease. Dr. Woodruff is PI. The goal of this grant is to enable Dr. Woodruff mentor students, fellows and junior faculty in patient oriented precision medicine related research in respiratory disease.

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

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

14. **R01 HL146002 (07/01/19-06/30/24)** SPIROMICS II Heart Failure Dr Woodruff is Co-I, PI is RG Barr. The goal of this study is to define the heart failure phenotypes associated with COPD using 4D MRI and exercise echo by leveraging the SPIROMICS study.
15. U01 HL126493 (8/01/14-4/30/19 in no cost extension): Defining a Comprehensive Reference Profile of Circulating Human Extracellular RNA (Woodruff, Erle). The goal of this study is to use RNA sequencing to establish the reference range of exRNAs as biomarkers in 12 different body fluids.

Communications, Training and Leadership Initiatives

SABRE is involved with ImmunoX leadership council at Parnassus, with Mark Ansel sitting as a representative on the council. John Fahy is involved with research and clinical planning on Parnassus. Richard Locksley organizes the basic immunology research seminars and is a Co-PI on the Gnotobiotic Initiative.

SABRE Center core scientists and the Director meet quarterly with translational scientists to further communication, planning and collaborative investigations of human asthma patients. Each of the core scientists is involved in ongoing or planned investigations with translational scientists in the ACRC, confirming that this serves as an important integrative unit for translational interests of the SABRE Center. We hold monthly research conferences for SABRE/ACRC investigators at the Parnassus site to promote interactions and collaborations.

National and International Meetings

Dr. Locksley and SABRE Center investigators participated in the organization and content of the 2020 Keystone meeting on Asthma and in the 4th International Conference on Innate Lymphoid Cells, planned for San Francisco, although both had to be postponed at least a year due to the SARVS-CoV-2 pandemic.

Human Upper Respiratory Tract Analysis

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

**Successful competition for extramural support**

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

We have maintained substantial procurement of external funds by the core SABRE investigators in support of their research efforts. This has occurred despite the difficult funding climate, and attests to the capacity of the Center to serve as a nidus for successful asthma basic research. We believe that building multicomponent research teams to take on difficult problems associated with asthma will prove a successful strategy for maintaining this funding momentum.

![SABRE External Funding - Directs](image)

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

Activities related to the SABRE Center resulted in publication of numerous manuscripts and contributions to many successfully awarded grants and fellowships of various types to investigators at UCSF. Despite our successes in competing for extramural resources, the flexibility of SABRE support is not matched by these types of grant monies.
Highlighted SABRE Center-supported manuscripts impacting asthma-related research in 2019-20


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


The Fahy lab used patient samples from the NIH SARP-3 (Severe Asthma Research Program-3) repository to assess which cells from airway samples expressed receptors critical for infection by SARV-CoV-2, the etiologic agent of COVID-19. Analyzing 330 SARP-3 asthma patient samples and 79 healthy controls, the authors used next generation sequencing to reveal significantly higher levels of the viral spike protein receptor, ACE2, and the trimming protease necessary for permissive entry, TMPRSS2, among asthma patients who were male, African American, and with diabetes, consistent with known risk factors for exacerbated disease. Levels in the remainder of samples did not differ from healthy controls, and patients on inhaled corticosteroids had lower transcripts, presaging later studies showing protection by glucocorticoids among patients with severe COVID-19. Although these studies are early and remain incomplete, they suggest that asthma alone may not constitute significant risk for severe disease, and inhaled steroids may offer some protection by regulating the levels of receptors and proteases on host cells.

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

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


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


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


Using a novel fate-mapping system, this study revealed the development and differentiation of group 2 innate lymphoid cells, or ILC2s, that have been implicated in allergic diseases. ILC2s in the mouse develop during fetal hematopoiesis, when cells are first deposited into tissues. Upon birth, ILC2s undergo proliferation in situ, and acquire
transcriptomes that are specific to the tissues in which they reside. As established by parabiosis and fate-mapping, ILC2s are largely tissue resident cells that appear to respond locally to local perturbations in ways matched to the metabolic and functional needs of each tissue. Over time, adult-derived cells slowly replace fetally derived ILC2s, and the functional capacity of these cells will require further study to assess their role in tissue health and disease.

Organization of the body of this Annual Report

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

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

Richard M. Locksley, M.D.

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

SABRE Center Executive Committee Members

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

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

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

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

William Seaman, M.D., Professor *
Department of Medicine

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

Art Weiss, M.D., Ph.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 opening up entirely new avenues for discovery.
Representative Publications

Christopher D. C. Allen, Ph.D.
Associate Professor
Cardiovascular Research Institute
Department of Anatomy
Sandler Asthma Basic Research Center

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

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

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

Selected Publications


K. Mark Ansel, Ph.D.
Professor, Department of Microbiology & Immunology
Sandler Asthma Basic Research Center of UCSF

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

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

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

Active projects in the laboratory focus on cellular and molecular analysis of allergic inflammation in asthma and atopic dermatitis, and the post-transcriptional regulatory networks that program immune cells involved in these diseases. We pioneered the study of miRNAs in immune cell differentiation and effector functions, and continue that work to leverage miRNA biology to uncover gene networks that program the cells that drive allergic airway inflammation in asthma. We also study the fate of miRNAs and other regulatory
RNAs in activated T cells and airway epithelial cells, as they are specifically regulated by transcription, processing, degradation and even secretion within extracellular vesicles. Recently, we developed a biochemical method for broadly interrogating the cis-regulatory transcriptome in living cells by mapping protein occupancy genome-wide at near-nucleotide resolution. We hypothesized that RBP occupancy in transcripts would be a marker of cis-regulatory activity, and this prediction was supported by a massively parallel reporter assay testing each of these site in primary T cells. We are now using GCLiPP together with other biochemical and genetic data to guide experimental dissection of transcripts involved in airway inflammation and allergic disease.

**Lab Objectives**

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

**Selected Publications**

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

Dr. Esteban Burchard directs the Asthma Genetics Core Facility, now named the Asthma Collaboratory, which is now the largest biorepository from minority populations with asthma in the world. The Asthma Biobank is open to reputable scientists seeking to assess genetic risk for variants in populations of interest or to extend findings made in animal models to suggest potential mechanistic involvement in human asthma. The Asthma Collaboratory has met continued goals to expand the numbers of patient samples; to extend the numbers of collaborators both nationally and internationally who use the database; and to continue to spearhead genetic studies in minority populations with asthma. The Burchard lab has led efforts to identify genetic modifiers of drugs used in asthma that might contribute to the poorer response in a number of ethnic populations and more recently is leading efforts to find biomarkers for different subsets of asthma as defined by presentation or response to therapy. These efforts have contributed to over 260 publications with more than 80 collaborators. Dr. Burchard served on President Obama’s Precision Medicine Initiative and has begun efforts to prepare a US-wide Asthma Genetics Consortium grant funded by the NIH.

Dr. Burchard’s team is taking a comprehensive approach to studying asthma and related phenotypes in minority children by focusing on genetic, social and environmental risk factors with the goal of creating innovative therapies and identifying targets for public health inventions. Dr. Burchard’s team was the first to leverage genetic ancestry to identify novel genetic and environmental risk factors for disease and poor drug response. Dr. Burchard’s laboratory recently completed the largest genome-wide association studies (GWAS) and
admixture-mapping scans of asthma in minority children and total IgE in the United States. Dr. Burchard and his team published the largest air pollution and genome-wide study of asthma in minority children. His research has been seminal in elucidating the pathogenesis of asthma and asthma related traits in minority populations.

Lab Objectives

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

Selected Publications


John V Fahy, M.D, M.Sc.
Professor, Department of Medicine and the Cardiovascular Research Institute CVRI)

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http://bms.ucsf.edu/directory/faculty/john-v-fahy-md-msc
UCSF Profiles: http://profiles.ucsf.edu/john.fahy

John Fahy, M.D. is a longstanding supporter of SABRE research and a formal faculty member in the SABRE Center for the past 6 years. He is a physician scientist with a primary appointment in the Division of Pulmonary and Critical Care Medicine (Department of Medicine and CVRI). He directs a mechanism-oriented clinical research program in airways disease that emphasizes studies in humans and in human-derived tissues and cells. For asthmatics with prominent airway type 2 inflammation (“type 2-high asthma”), his current research focuses on mechanisms underlying regional variation in type 2 inflammation in the lung and airway epithelial cell dysfunction in patients with “ultra-high” type 2 inflammation who are steroid-resistant and have mucus plugs and severe airflow obstruction. Dr Fahy’s lab is a leader in advancing understanding for how pathologic mucus gels form in asthma and other mucus-associated airway diseases. He leads a PO1 program in type 2 airway inflammation in asthma (includes Drs. Locksley, Ansel and Woodruff), a translational PO1 program in academic drug discovery that aims to advance mucolytic to the clinic, and an RO1 program investigating mechanisms of airway inflammation and mucus pathology in acute severe asthma. In addition, he leads the UCSF center in the NHLBI funded PrecISE program (biomarker driven clinical trials in severe asthma). Recent honors include election to AAP in 2016 and a Recognition Award for Scientific Accomplishments from the ATS in 2017.

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

ABNORMAL TYPE 2 IMMUNE RESPONSES IN HUMAN ASTHMA: The airway epithelium has emerged as an important regulator of innate and adaptive immune responses that result in type 2 allergic airway inflammation. My lab is specifically investigating epithelial mechanisms that contribute to upregulation of Th2 cytokines in the asthmatic airway. Our experimental approaches include gene and protein expression analysis of airway
epithelial brushings, biopsies, and secretions, and cell culture studies in airway epithelial cells from human donors. We collaborate with multiple other UCSF labs, including the Locksley, Ansel, and Woodruff labs, and the Seibold lab at National Jewish Healthy is a key non-UCSF collaborator.

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

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

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

Selected Publications
Jeoung-Sook Shin, Ph.D.
Associate Professor, Department of Microbiology & Immunology
Sandler Asthma Basic Research Center
University of California San Francisco

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

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

The specific objectives are as following.

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

2. **Determine the role of MARCH1 in dendritic cell function of driving T cell immunity.** Dendritic cells play an essential role in the development of specific T cell immunity to various antigens. Dendritic cell subset 1 drives cytotoxic T lymphocyte and T helper type 1 (Th1) immunity against virus, cancer, and intracellular bacteria or parasite whereas dendritic cell subset 2 drives Th17 immunity to fungi and extracellular bacteria and Th2 immunity to intestinal hookworm and allergens. The Shin laboratory is interested in finding out whether MARCH1 plays an important role in the development and maintenance of any specific types of T cell immunity.
3. **Determine the role of MARCH1 in immune-stimulatory diseases.** Many of immune-stimulatory diseases are associated with unregulated T cell immunity. Allergic diseases including allergic asthma are associated with strong Th2 immunity while certain autoimmune diseases such as multiple sclerosis are associated with strong Th1 and Th17 immunity. The Shin laboratory is interested in determining whether MARCH1 is involved in the development and exacerbation of these T cell-dependent immune-stimulatory diseases and if so, whether MARCH1 could serve as a therapeutic target for treatment of these diseases.

**Selected Publications**

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

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

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

These studies fall into three specific categories:

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

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

3) Clinical trials of novel therapeutic approaches.

Selected Publications


SABRE CENTER ASSOCIATES
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Selected Publications


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

Selected Publications


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


Andrew Schroeder, MPH
Bio Informatics Scientist
UCSF Genomics CoLab & Dept. of Pulmonology
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Andrew Schroeder is a Bio Informatics Scientist in the UCSF Genomics CoLab & Dept. of Pulmonology recruited to his position to build computational pipelines for next-generation sequencing analysis (e.g. RNA-seq and scRNA-seq). He is responsible for transcript quality, cell quality, differential gene expression analysis, single-cell developmental trajectory analysis, receptor-ligand analysis, pathway and gene ontology analysis. His background as a Research Data Analyst in the UCSF Medical Center was in analysis of high-throughput-omics and clinical data for 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 human subject data using R to predict human response to sound. His work was published in the Journal of Acoustical Society
https://asa.scitation.org/doi/abs/0.1121/1.5035683.

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

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

**Selected Publications**


Sandler Asthma Basic REsearch Center
Core Facilities

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

Objective/Mandate

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

Strategic Goals

The efforts of this center are being directed toward improving imaging technologies for the normal and allergic lung. In 2020, the core will focus on expanding use of new technologies, and continue to develop and elaborate custom built tools for image acquisition and analysis that have direct and indirect benefits to the lung imaging community.

1. To extend the usage and utility of mouse lung imaging through continued development of minimally invasive intravital imaging methods and instrumentation.
2. To provide ongoing technical and instrumentation support to the UCSF (and beyond) asthma community in order to put existing and emerging imaging technologies to practical use in the study of asthma.
3. To automate a novel microscopy platform in collaboration with the Krummel Lab that enables spatial tagging of cells for downstream single cell RNA sequencing analysis.
4. To incorporate the newly released Micro-Manager (open-source and UCSF based) Python extension Pycro-Manager, into our homebuilt 2-photon, light-sheet, spinning disk, and widefield microscopy systems.
5. To integrate additional open-source machine learning pixel-classification software such as Ilastik, DeepCell, StarDist, YaPiC, LabKit, and PyImageQualityRanking into the Multiplexed Ion Beam Imaging (MIBI) and other data analysis pipelines.
6. To extend the BIDC’s 3D cell surface morphology analysis program to include multi-channel comparison and correlation studies.
7. To develop in collaboration with Ophir Klein (UCSF) and Jeremy Green (King’s College, London) an automated epithelial cell identification and morphological characterization pipeline for cells undergoing the invagination process during organ development.
8. To upgrade and extend the capabilities of the selective-plane imaging microscope (SPIM) to include more simultaneous fluorophore imaging capabilities while simultaneously increasing the overall speed of the microscope.

9. To continue to develop in collaboration with the Molofsky lab 8+ color panels for tissue staining.

Organization

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

Current Usage

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

In 2019, 139 new user trainings were completed. All users received comprehensive training on Center instruments or image processing stations. Training is done on an individual basis and reflects the differences in each user’s experience, aptitude, and project needs. After initial training, BIDC staff continues to consult and assist with projects on an individual basis. We do not charge for our time through recharges, thus encouraging users to ask questions and request assistance as needed. Many projects evolve into collaborations. Within the past year we have specifically worked with users from the following labs.

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Recent Accomplishments

In 2019, scientifically:

1. John Eichorst (BIDC, Bioinformatics Programmer) in collaboration with the Krummel Lab built a novel microscopy platform that enables spatial tagging of cells for downstream single cell RNA sequencing analysis. This microscope combines standard imaging modalities with the capability to illuminate samples with spatially defined patterns of light for photo-uncaging using a digital micromirror device.

2. John Eichorst (BIDC, Bioinformatics Programmer) in collaboration with the Krummel Lab developed user-friendly software to correlate geometric features in 3D images of t-cells to areas on the exterior of the t-cells containing locally high fluorescence intensities (puncta). The work this past year involved calculating curvature along the cell’s exterior, locate and characterize protrusions based on curvature calculation and an optimization of a feature extraction method to locate puncta. The curvature program was generalized to an Imaris Extension.

3. Austin Edwards (BIDC, Bioinformatics Programmer), Katya Maidji and Joshua Vasquez (Vasquez Lab) developed analysis pipelines for granulomas infected with tuberculosis. Austin trained a machine learning classifier to segment bacteria in the tissue and also developed software to draw custom ROI overlays on the tissue and filter the segmentation results based on the ROIs.

4. Austin Edwards (BIDC, Bioinformatics Programmer), Jillian Jespersen and Jody Baron (Baron Lab) trained a machine learning classifier using Ilastik to segment the cells and classify them based on marker and have also developed a tool for spatially clustering cells and measuring the distance of these clusters to the nearest vessels innervating the tissue.
5. Austin Edwards (BIDC, Bioinformatics Programmer), Su-Yang Liu (Werb Lab), Stanley Tamaki (Flow CoLab), Mohammad Naser (BIOS), Maha Rahim and Matt Spitzer (Spitzer Lab) have been collaborating to develop an image acquisition, processing and analysis pipeline regarding the newly functional MIBI operating within the Flow CoLab. The in-depth assessments of state-of-the-art technologies for image segmentation and cell detection, such as DeepCell (deep learning) and Ilastik (multi-tool machine learning platform) have opened them up as tools within the BIDC.

6. Jordan Briscoe (BIDC, SRA and Ran Yu (Krummel Lab) successfully imaged the real-time infiltration of bispecific antibodies into live tumors through “leaky” blood vessels.

7. Kyle Marchuk (BIDC, Director) and Madelene Dahlgren (Molofsky Lab) have been refining an 8-color lung tissue staining panel for imaging on the Leica Sp8. The white light laser, user defined emission filters using an AOBS, and spectral unmixing software has made available high-dimensional imaging to the average user.

8. We continued to provide ongoing technical and instrumentation support to the asthma community at UCSF and beyond, in order to put existing and emerging imaging technologies to practical use in the study of asthma.

**Introduction of new people and equipment**

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

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

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

Recent publications

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


**Plans for the Coming Year**

1. The BIDC will continue to work with the Krummel lab to automate and expand their novel microscopy platform that enables spatial tagging of cells for downstream single cell RNA sequencing analysis. Automation with a user-friendly interface will allow for increased spatial location resolution and allow the technology to span to other microscopes within and outside the BIDC.

2. Pycro-Manager, a recently released Python interface for the UCSF developed open-source software Micro-Manager, will be integrated into our existing homebuilt microscope platforms. Pycro-Manager allows for n-dimensional acquisitions with user defined hooks and feedback loops (including machine learning) as well as the interface with non-microscopy related hardware. This software can greatly increase the opportunity for “smart-acquisitions” resulting in smaller files size and increased temporal resolution for events of interest.

3. The Multiplexed Ion Beam Imaging (MIBI) system is now online and producing high-dimensional images. The BIDC will work alongside our collaborators in developing and evaluating analysis pipelines. This includes the learning and understanding of recently published open-source software designed for cell segmentation and identification. Such packages include DeepCell, StarDist, YaPiC, LabKit, and PyImageQualityRanking. Understanding these packages helps make them available as tools for the rest of the BIDC community.

4. John Eichorst (BIDC, Bioinformatic Programmer) has developed a user-friendly interface for his software that evaluates the morphology of cell surfaces in the 3D. This software will be extended to evaluate features between channels including colocalization of puncta and other structures.

5. Kyle Marchuk (BIDC, Director), Ophir Klein (UCSF) and Jeremy Green (King’s College, London, UK) are working in collaboration on an automated pipeline for the 3D segmentation and morphological evaluation of epithelial cells undergoing tissue invagination during tissue development.

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

7. The BIDC will continue to work in collaboration with the Molofsky lab to develop 8+ color panels for cleared tissue imaging. Increasing the fluorophores per sample increases the information gathered per experiment thus increasing the efficiency of experiments. Analysis pipelines and software will be developed as needed.
Training and Integration with Sandler Program

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

Current Equipment

Permanent Equipment:
1. *Gen3 custom built 2-photon: 6 color/2 lasers
2. *Gen4 custom built 2-photon: 6 color/2 lasers
3. * Nikon C1si spectral laser scanning confocal microscope
4. Nikon spinning-disk confocal with TIRF and photo-ablation (Wittman)
5. Nikon A1R Multiphoton and laser scanning confocal microscope
6. Nikon AZ100 MacroConfocal microscope
7. Zeiss large field of view spinning disk microscope (Yokogawa CSU-X1)
8. Zeiss TIRF microscope with IRM
9. Zeiss Cell Observer with Apotome (Nystul)
10. Zeiss AxiolImager2 with Apotome
11. Zeiss AxiolImagerA1 brightfield microscope
12. Leica SP5 laser scanning confocal microscope
13. Leica SP8 laser scanning confocal microscope with white light laser
14. IVIS Spectrum live animal imager (animal colony)
15. Selective-plane imaging microscope (SPIM) custom built: 3 lasers
16. Lattice Light-Sheet Microscope
17. *FormLabs 3D printer
18. *Analysis stations: 4 custom built computers

* Indicates SABRE is a partial owner of this instrument.

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

We would like to acknowledge:
- Nikon for supplying a software key for the full image analysis version of NIS-Elements.
- Bitplane ‘Imaris’ for subsidizing the purchase of software and bestowing a ‘developer’ license.
ASTHMA RELATED RESEARCH PROJECTS
The ImmunoX Initiative

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

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

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

- Improve with Improv
- Movie Nights at Cole Hall
It has launched pioneering programs to benefit the community, including:

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

Allen Lab

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

Figure 1. t-SNE plots representing single cell RNAseq analysis (10x platform) of antigen-presenting cells in the lung following exposure to house dust mite (HDM) versus in the naïve state. Two samples of each type were processed, which displayed remarkable similarity.
In the next year, we have two major objectives to further elucidate the initiation of allergic immune responses in asthma.

1) We plan to expand our studies of the B cells that produce IgE, focusing this year on using RNAseq technology to gain insight into the mechanisms controlling the fate of IgE-expressing B cells. In particular, we will elucidate the gene expression profile of B cells that have already switched to IgE, whereas last year we focused on the gene expression profile of B cells that were undergoing class switch recombination to IgE. We have previously shown that IgE-switched B cells undergo enhanced plasma cell differentiation and poorly compete within germinal centers, where the generation of high affinity antibodies takes place (Yang et al. Immunity 2012). We have traced these distinct properties of IgE-switched B cells to the IgE B cell receptor (BCR), which has unique signaling properties even in the absence of ligand (Yang et al. eLife 2016). However, the molecular basis by which the IgE BCR controls the fate of these B cells is unknown. We will do RNAseq analysis in which we modulate BCR signaling with genetic mutants and/or pharmacological inhibitors and we will compare B cells expressing the IgE BCR to other BCRs (such as IgG1) in order to elucidate the genes affected by IgE BCR signaling. As an ancillary goal, we will continue to characterize the repertoire of variable regions of the B cell receptors expressed by IgE-expressing B cells induced in response to allergen exposure in the lung.

2) We and other groups have found that basophils, one of the two main types of IgE effector cells, accumulate in the lung in and in lymph nodes in response to some allergens. Studies in human patients have confirmed that basophils accumulate in the lungs of asthmatics with allergic inflammation. However, remarkably the true functions of basophils in these tissues remain poorly defined. Based originally on collaborative studies with Dr. Richard Locksley’s laboratory, which made genetic tools to visualize and manipulate basophils, we have been able to image basophils by two-photon microscopy and test the consequences of their elimination under various conditions. In doing so we have defined a lymph node model in which numerous basophils accumulate and orchestrate alternative activation of macrophages and recruitment of other cell types to inflammatory foci. We postulate that a similar role for basophils may occur in the lung in asthma. Of particular interest to our group is the activation of basophils by IgE/allergen in the lung and lymph nodes, as the impact of IgE-mediated activation in vivo is poorly defined and has not been characterized in gene expression studies thus far. We plan to use RNAseq to study the gene expression profile of basophils in these contexts to gain insights into their physiological roles. Co-isolation of other tissue cells (such as resident macrophages and stromal cells) and analysis in single-cell sequencing may also reveal gene expression changes following IgE-mediated activation of basophils, thus proving further insights into basophil function.
Single Cell Sequencing in Nasal Polyp Patients

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

Severe asthma accounts for approximately 10% of the disease burden, but nearly 50% of asthma costs. Understanding the molecular pathways that promote severe disease is critical to the development of novel therapeutics. One strategy is to study extreme phenotypes or outliers. In severe asthma, one extreme phenotype is nasal polyposis (NP). NP affects only 2-4% of the general population (1), but among patients with NP, 30-70% carry a diagnosis of asthma (2). Among all patients with chronic rhinosinusitis (CRS) the presence of NP is strongly associated with tissue type 2 inflammation. In 386 asthmatics enrolled in the Severe Asthma Research Program (SARP), we find that 19% of asthmatics suffer from NP. Asthmatics with NP have lower lung function (FEV1% 77.9±20.4 vs 71.3±17.9, p=0.011) and more exacerbations than asthmatics without NP (Fig 1). Understanding the relationship between upper and lower airway responses in patients with asthma and NP may hold the key to understanding the mechanisms that underlie airflow obstruction and exacerbations in severe asthma.
To explore this relationship between the upper and lower airway in nasal polyposis, we performed whole genome RNA sequencing in upper and lower airway brushes from patients undergoing endoscopic surgery for CRS. We collected epithelial brushes from patients with CRS without polyps or asthma, CRS with polyps and asthma, and subjects without CRS undergoing pituitary surgery (healthy). Our data demonstrates a type 2 gene expression signature which is increased in the **sinus epithelium** in subjects with NP and asthma (Fig 2). This gene expression module is characterized by increased IL13 signature genes (CDH26, SERPINB2, POSTN, CLCA1, SPDEF), basophil/mast cell genes (CPA3, GATA2, KIT) and the IL-33 and IL-25 receptors (IL1RL1, IL17RB). Recent studies in mice (3) demonstrate that master epithelial cytokines IL-33, TLSP, and IL-25, are critical upstream drivers of type 2 inflammation. These cytokines stimulate mast cells, basophils, ILC2, and Th2 cells to produce type 2 cytokines. The expression of these cytokines in human disease has been difficult to detect, likely due to a low level of basal expression and transient increases in expression. Our inability to characterize the timing and context of their expression in relationship to disease has hampered drug development efforts. Recently, restricted expression of IL-25 has been demonstrated in a rare chemosensory cell population called tuft cells (4). We hypothesize that tuft cells act as sensors of environmental
insults at the respiratory epithelial barrier. Characterizing these cells in humans has been limited by lack of consensus about markers and antibodies as well as their rarity. In preliminary data, we find a robust gene expression signature of tuft cells (POU2F3, TRPM5) in the type 2 gene expression module. These genes are increased markedly in the sinus epithelium only in patients with NP. Interestingly, augmented tuft cell-associated transcripts were not observed in the bronchial epithelium of these same patients; this may be explained by distal airway sampling (as tuft cells may be restricted to larger airways), or suggest a dissociation between the roles of tuft cells in type 2 inflammation in the sinus versus the lower airways.

In order to further study tuft cells in the context of nasal polyposis we performed single cell RNA sequencing on brushes obtained from 5 subjects with nasal polyps and 4 healthy control subjects. From this data, we identified 15 clusters of epithelial cells encompassing the spectrum of basal (cluster 0, 1, 2, 8, 9), secretory (3, 4, 6), goblet (6), and ciliated cells (11,12,13,14). The cell type percentages in each of these clusters was surprisingly similar between polyp and health with the exception of an increase in goblet cells. We were able to identify a population of rare cells in cluster 10 which contained markers of tuft cells and ionocytes. These cells were subclustered using hierarchical clustering and we identified a population of tuft cells with markers that included LRMP, KIT, AVIL, POU2F3, TRPM5. These cells were increased in number 2.5 fold in the polyp epithelium compared to healthy epithelium. We were even more surprised to identify a population of tuft cells within the polyps but not in the healthy controls which were strongly expressing BMX, GNG13, IL17RB. These tuft cells which we called “inflammatory tuft cells” appear also in the nasal epithelium of mice stimulated with IL-13. Given the importance of tuft cells as the producer of IL-25 as well as acetylcholine, prostaglandins, and leukotrienes, further investigations will focus on the function of this novel tuft cell subset.
REFERENCES:


CONTRIBUTIONS TO RELEVANT SCIENTIFIC ACTIVITIES
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<th>Date</th>
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<th>Host</th>
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<td>September 6</td>
<td>Chris Goodnow, <em>Garvan Institute of Medical Research</em></td>
<td>Jason Cyster</td>
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<tr>
<td>September 9</td>
<td>Wayne M. Yokoyama, <em>Washington University School of Medicine</em></td>
<td>Lewis Lanier</td>
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<td>September 16</td>
<td>Larry Fong, <em>UCSF</em></td>
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<td>John T. Harty, <em>University of Iowa</em></td>
<td>Nadia Roan</td>
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<td>Jimmie Ye, <em>UCSF</em></td>
<td>Lindsey Criswell</td>
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<td>October 7</td>
<td>Dan R. Littman, <em>NYU</em></td>
<td>David Wofsy</td>
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<td>October 14</td>
<td>Maxim N. Artyomov, <em>Washington University School of Medicine</em></td>
<td>Matthew Spitzer</td>
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<td>October 21</td>
<td>Bali Pulendran, <em>Stanford University</em></td>
<td>Jody Baron</td>
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<td>October 28</td>
<td>Marion Pepper, <em>University of Washington</em></td>
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<td>November 4</td>
<td>Francisco Quintana, <em>Harvard Medical School</em></td>
<td>Minnie Sarwal</td>
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<td>November 21</td>
<td>Karen E. de Visser, <em>Netherlands Cancer Institute</em></td>
<td>Kelly Kersten</td>
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<td>December 2</td>
<td>Marc K. Jenkins, <em>University of Minnesota</em></td>
<td>Mark Andersen</td>
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<td>December 9</td>
<td>Ram Savan, <em>University of Washington</em></td>
<td>Mark Ansel</td>
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<tr>
<td>January 6</td>
<td>Richard Flavell, <em>Yale School of Medicine</em></td>
<td>Zena Werb</td>
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<tr>
<td>January 13</td>
<td>Jean-Laurent Casanova, <em>Rockefeller University</em></td>
<td>Joel Ernst</td>
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<td>February 3</td>
<td>Nir Hocohen, <em>Harvard Medical School/MBI</em></td>
<td>Melissa Reeves</td>
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<tr>
<td>February 10</td>
<td>Jenny Ting, <em>University of North Carolina</em></td>
<td>Averil Ma</td>
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<tr>
<td>February 24</td>
<td>Paula M. Oliver, <em>University of Pennsylvania</em></td>
<td>Art Weiss</td>
</tr>
<tr>
<td>March 2</td>
<td>Vijay Kuchroo, <em>Harvard Medical School</em></td>
<td>ImmunoX Grad Students</td>
</tr>
<tr>
<td>March 9</td>
<td>Denise Monack, <em>Stanford University</em></td>
<td>Anthony DeFranco</td>
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<tr>
<td>March 16</td>
<td>Donna Farber, <em>Columbia University</em></td>
<td>Qizhi Tang</td>
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<td>March 23</td>
<td>Andrew Oberst, <em>University of Washington</em></td>
<td>Adrian Erlebacher</td>
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<td>March 30</td>
<td>Ken Murphy, <em>Washington University School of Medicine</em></td>
<td>Ari Molofsky</td>
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<tr>
<td>April 6</td>
<td>Jennifer Gommerman, <em>University of Toronto</em></td>
<td>Sergio Baranzini</td>
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<td>Galit Alter, <em>Harvard Medical School</em></td>
<td>Satish Pillai</td>
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<td>Dan Mucida, <em>Rockefeller University</em></td>
<td>Mary Helen Barcellos-Hoff</td>
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<td>April 27</td>
<td>Manuela Raffatellu, <em>U.C. San Diego</em></td>
<td>Tiffany Scharschmidt</td>
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<td>May 4</td>
<td>Rahul Satija, <em>NYU</em></td>
<td>Jimmie Ye</td>
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<td>May 11</td>
<td>K. Christopher Garcia, <em>Stanford University</em></td>
<td>ImmunoX Post Docs</td>
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<tr>
<td>May 18</td>
<td>Filip Swirski, <em>Harvard Medical School/MBI</em></td>
<td>Judith Hellman</td>
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### UCSF PULMONARY RESEARCH CONFERENCE 2019-2020
Mondays, 4:00 pm - Parnassus

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**Fellows Feedback Session 1**

- 01/06/20: Nirav Bhakta
- 01/13/20: Mike Podolsky
- 01/20/20: John Greenland
- 01/27/20: Franklin Heng
- 02/03/20: Shoshana Zha
- 02/10/20: Zimu Deng
- 02/17/20: Visiting Professor - Melanie Koenigshoff
- 02/24/20: Visiting Professor - Lorraine Ware (Vanderbilt)
- 03/02/20: Melia Magnen
- 03/09/20: Chris Berger
- 03/16/20: Daniah Beleford
- 03/23/20: Erica Farrand
- 03/30/20: Walter Eckalbar
- 04/06/20: Ram Naikawadi
- 04/13/20: Sam Oh
- 04/20/20: Paola Torre
- 04/27/20: Pratik Sinha
- 05/04/20: Michelle Yu
- 05/11/20: Daniah Beleford
- 05/18/20: Ram Naikawadi
- 05/25/20: Walter Eckalbar
- 06/01/20: Bhavika Kaul
- 06/08/20: Olivier Bernard
- 06/15/20: Eric Farrand

**Faculty Feedback and appreciation**

- 01/20/20: Nirav Bhakta
- 01/27/20: Mike Podolsky
- 02/03/20: John Greenland
- 02/10/20: Zimu Deng
- 02/17/20: Visiting Professor - Melanie Koenigshoff
- 02/24/20: Visiting Professor - Lorraine Ware (Vanderbilt)
- 03/02/20: Melia Magnen
- 03/09/20: Chris Berger
- 03/16/20: Daniah Beleford
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- 05/25/20: Walter Eckalbar
- 06/01/20: Bhavika Kaul
- 06/08/20: Olivier Bernard
- 06/15/20: Eric Farrand

**ATS - (no conference)**

**Memorial Day holiday (no conference)**

**Fellows Feedback Session 2**
### SABRE Asthma Research Conference Schedule 2020

**Location:** 513 Parnassus Avenue, HSE-402  
**Time:** 9:00-10:00AM  
**Day:** 4th Wednesday of each month (*except Wednesdays that fall on a UCSF holiday*)

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<td>K. Mark Ansel, Ph.D.</td>
<td>RNA regulation of effector and regulatory T cells</td>
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<td>3/25/20</td>
<td>Dean Sheppard</td>
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<tr>
<td>4/22/20</td>
<td>Jeoung-Sook Shin</td>
<td>Cancelled do to COVID-19</td>
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<td>5/27/20</td>
<td>John Fahy, M.D.</td>
<td>Update on mucus plugs in airway disease – clinical features, computer vision and mucolytics</td>
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<td>6/24/20</td>
<td>Ari Molofsky, M.D.</td>
<td>Rescheduled for November 25, 2020</td>
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<td>Esteban Burchard, M.D.</td>
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<td>Mallar Bhattacharya, M.D.</td>
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<td>Ari Molofsky, M.D.</td>
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“Predictive rules and altered cell states in the human immune system”

Nir Hacohen, PhD

Professor, Harvard Medical School
Director, Center for Cancer Immunotherapy, MGH
RECENT AND NEW PUBLICATIONS
SUPPORTED BY THE SANDLER ASTHMA BASIC RESEARCH CENTER
(2018-2020)
**Christopher D.C. Allen, Ph.D.**


**K. Mark Ansel, Ph.D.**


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


Duvall MG, Barnig C, Cernadas M, Ricklefs I, Krishnamoorthy N, Grossman

**Mallar Bhattacharya, M.D., MSc.**


**Homer Boushey, M.D.**


Esteban G, Burchard, M.D., M.P.H.


PMID: 31848607


**Harold Chapman, M.D.**


Schloss J, Ali R, Racine JJ, Chapman HD, Serreze DV, DiLorenzo TP. HLA-B*39:06 Efficiently Mediates Type 1 Diabetes in a Mouse Model Incorporating Reduced Thymic

Anthony DeFranco, Ph.D.


William F. DeGrado


**David Erle, M.D.**


**John Fahy, M.D.**


**James S. Fraser, Ph.D.**


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


Erin Gordon, M.D.


Matthew Krummel, Ph.D.


**Richard M. Locksley, M.D.**


Van Dyken SJ, Locksley RM. Chitins and chitinase activity in airway diseases.


**Ari Molofsky**


**Steven D. Pletcher, M.D.**


**Dean Sheppard, M.D.**


Thamsen M, Ghosh R, Auyeung VC, Brumwell A, Chapman HA, Backes BJ, Perara G, Maly DJ, Sheppard D, Papa FR. Small molecule inhibition of IRE1α kinase/RNase has anti-


**Jeoung-Sook Shin**


Aparna Sundaram, M.D.


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


PMID: 29915297


Jonathan Weissman, Ph.D.


Zena Werb, M.D.


Prescott Woodruff


Labaki WW, Gu T, Murray S, Curtis JL, Yeomans L, Bowler RP, Barr RG, Comellas AP, Hansel NN, Cooper CB, Barjaktarevic I, Kanner RE, Paine R 3rd, McDonald MN, Krishnan JA, Peters SP, Woodruff PG, O’Neal WK, Diao W, He B, Martinez FJ, Standiford TJ, Stringer KA, Han MK. Serum amino acid concentrations and clinical outcomes in smokers:


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

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

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

We believe that the SABRE Center has played a formative role in shaping the footprint for patient-oriented, disease-focused, basic research at UCSF. As such, this footprint has played out to assist an accelerated community scientific response to COVID-19 in the UCSF community. We continue to support a nimble, transformative research platform with the ability to move quickly as needed, and to position SABRE as an important component of the research efforts at all of the UCSF campuses to achieve the greatest return for cutting-edge investments in basic science as applied to human
biology and disease. We look forward to continuing novel and unexpected discoveries made by laboratories at UCSF that will significantly impact asthma and asthma-related research and alter the course of human disease.

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

Christopher Allen, Ph.D.
K. Mark Ansel, Ph.D.
Nirav Rati Bhakta, M.D., Ph.D.
Mallar Bhattacharya, M.D., MSc.
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Esteban Burchard, M.D., M.P.H.
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Anthony DeFranco, Ph.D.
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James S. Fraser Ph.D.
Andrew N. Goldberg, M.D., M.S.
Erin Gordon, M.D.
Matthew Krummel, Ph.D.
Richard Locksley, M.D
Ari B. Molofsky, M.D., Ph.D.
Steven D. Pletcher, M.D.
William Seaman, M.D.
Dean Sheppard, M.D.
Jeoung-Sook Shin, Ph.D
Aparna Sundaram, M.D.
Zhi-En Wang, M.D., M.S.
Arthur Weiss, M.D., Ph.D.
Jonathan Weissman, PhD.
Zena Werb, PhD.
Prescott Woodruff, M.D., M.P.H.
BIOGRAPHICAL SKETCH

NAME
Christopher David Caballero Allen, Ph.D.

POSITION TITLE
Assistant Professor of Anatomy and Investigator, Cardiovascular Research Institute & Sandler Asthma Basic Research Center

EDUCATION/TRAINING

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

Positions

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

Other Experience and Professional Memberships

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

Honors

1994 National Science Foundation Young Scholars Program Fellowship
1997 National Hispanic Scholar
1999 Academic Excellence Award, Office of Minority Education, Massachusetts Institute of Technology
2001 Whitehead Prize in Biomedical Research, Whitehead Institute and Massachusetts Institute of Technology
2001 Phi Beta Kappa, Massachusetts Institute of Technology
2001-2002 Regents Fellowship, University of California
2002-2007 Predoctoral Fellowship, Howard Hughes Medical Institute
2010 Top Cited Article 2008-2010, Seminars in Immunology
2012 NIH Director’s New Innovator Award, National Institutes of Health
2013 Research Award, Weston Havens Foundation
2016 Pew Biomedical Scholar, The Pew Charitable Trusts

Contribution to Science

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


A second major emphasis of my dissertation project in the laboratory of Jason Cyster was the study of the dynamic behavior of B cells within the germinal center. I established a model system for imaging the germinal center in intact lymph nodes by two-photon microscopy. This approach allowed me to visualize cell migration and interactions during the process of selection of high affinity B cells, for the first time. I analyzed the movements of germinal center B cells between dark and light zones and I characterized the interactions between B cells and T cells in the light zone. Based on these findings, we proposed a new model for the selection of high affinity B cells within the germinal center. This model was an important paradigm shift for the field and has since been corroborated by other groups.
I subsequently collaborated with a theoretical biologist to gain new insights on germinal center B cell migration by an extensive computational analysis of our dataset. This analysis revealed a previously unappreciated net migration of B cells from the dark zone to the light zone.


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


IgE antibodies play a major role in allergic responses underlying numerous diseases, yet little was known about the cells that produce these antibodies due to technical limitations. In order to overcome these roadblocks, my lab generated a novel fluorescent reporter mouse as well as an improved flow cytometry method to identify and track rare B cells and plasma cells that express IgE. We used these tools to study the genesis and fate of IgE-expressing B cells in primary immune responses to protein antigens and helminth infection. This analysis revealed that IgE-expressing B cells showed an increased propensity to undergo plasma cell differentiation and only transiently participated in germinal centers, which limited the affinity and duration of the IgE antibody response in healthy mice. We further revealed that these properties of IgE-expressing B cells can be traced to constitutive activity of the IgE B cell receptor. In a
collaborative study, we established that IgE responses were severely curtailed by haploinsufficiency of IL-4, suggesting that limited amounts of IL-4 are available in vivo to promote IgE class switch recombination. Conversely, we recently demonstrated that IL-21 is the major extrinsic factor that inhibits IgE class switch recombination in mouse and human B cells, whereas IFN-gamma, IL-10, and IL-6 were dispensable. Overall, our studies have provided critical new insights into understanding the mechanisms regulating IgE antibody responses in vivo. For these studies, I designed experiments, directed research, and helped collect and analyze data. We have also published a review and methods chapter related to these studies.


In the course of our above studies, we have devoted considerable effort to optimizing techniques for the genetic manipulation of B cells. We have developed an efficient protocol for retroviral transduction of primary mouse B cells and B cell lines, using a self-inactivating retrovirus in which gene expression can be directed by a ubiquitous or specific promoter. By inserting the EF1 ubiquitous promoter we achieved far more uniform expression than is normally observed with the gene expression driven by the viral long terminal repeat (LTR). Using CRISPR-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.


Complete List of Published Work in MyBibliography:  http://usa.gov/1rS9D69
**Additional Information: Research Support and/or Scholastic Performance**

**Ongoing Research Support**

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

The Pew Charitable Trusts Biomedical Scholar Award  
Allen, Christopher David Caballero (PI) 08/01/16–07/31/20  
Unraveling the mysteries of allergen specific IgE production  
The major goal of this project is to identify cell types and molecules involved in promoting the production of IgE in allergic responses versus the suppression of IgE in healthy individuals.  
Role: PI

**Completed Research Support**

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

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

R21 AI130495 Allen, Christopher David Caballero (PI) 06/07/17–05/31/19  
Function of bronchus-associated macrophages  
The overall goal of this proposal was to characterize and determine the function of a population of macrophages proximal to the bronchial airways.  
Role: PI
BIOGRAPHICAL SKETCH

NAME
K. Mark Ansel

eRA COMMONS USER NAME
anselm

POSITION TITLE
Associate Professor of Microbiology and Immunology

EDUCATION/TRAINING

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<td>Biochemistry</td>
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<td>9/2001</td>
<td>Biomedical Sciences</td>
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<td>Immune Disease Institute, Harvard Medical School</td>
<td></td>
<td>12/2007</td>
<td>Immunology</td>
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Positions

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

Other Experience and Professional Memberships

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

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

Contribution to Science

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


2. Helper T cells lacking all miRNAs exhibit defective proliferation and survival, as well as rapid and aberrant differentiation into effector cells with the ability to secrete inflammatory cytokines. This complex phenotype indicates significant contributions from many miRNAs and mapping specific regulatory impacts to individual miRNAs or families of related miRNAs remains one of the central pursuits of my laboratory and one of the major challenges for the field as a whole. We developed and deployed a ‘rescue screening’ technology to determine which miRNAs regulate various aspects of T cell proliferation and differentiation. This led to the discovery that miR-29 potently inhibits Th1 cell differentiation through inhibition of a functionally related set of direct
mRNA targets. We extended this approach to leverage our ability to assign biological functions to miRNAs and identify their direct target mRNAs as a means of directed pathway discovery. For example, we found that miR-24 and miR-27 potently inhibit Th2 responses and used combined empirical and bioinformatic methods to identify a network of functionally relevant target mRNAs, including well-known regulators of Th2 cell differentiation and others that represent novel players in Th2 biology. Biochemical approaches to target discovery further advanced our ability to define miRNA-directed gene expression networks.


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


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


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


**Research Support**

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

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

P01HL107202  Fahy (PI)  8/1/19-7/31/2024
Exploring the biology of persistent type 2 airway niches in asthma
This project aims to uncover tissue-immune checkpoints that lead to persistent airway type 2 inflammation and mucus plug formation in asthma. We will use image guided bronchoscopy, high-dimensional single cell analytics, and other experimental approaches to decode the regulatory networks that sustain severe disease.
Role: Project 2 Leader, Project 3 co-investigator
# BIOGRAPHICAL SKETCH

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<thead>
<tr>
<th>NAME</th>
<th>Nirav Rati Bhakta, M.D., Ph.D.</th>
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<td>POSITION TITLE</td>
<td>Assistant Professor of Medicine</td>
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## EDUCATION/TRAINING

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<td>SB</td>
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<td>Electrical Engineering</td>
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<td>Stanford University School of Medicine</td>
<td>MD</td>
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<td>PhD</td>
<td>06/2006</td>
<td>Mol. and Cell Physiology</td>
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<td>Postdoctoral</td>
<td>206/011</td>
<td>Asthma</td>
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## Positions and Employment

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

## Other Experience and Professional Memberships

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

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

Contribution to Science

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


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.


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


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


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.


Complete List of Published Work in MyBibliography:

**Research Support**

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

**U19 AI 077439** (PI: David J. Erle) 04/01/2018-03/31/2023
NIH/NIAID
Understanding Asthma Endotypes
Our Center is focused on understanding how airway epithelial cells are involved in causing different forms of asthma. Our studies will uncover new knowledge about mechanisms of asthma and help to pave the way for new treatments for this common disease.
Role: Core Leader

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

**R35 HL145235** (PI: David J. Erle) 01/01/2019-12/31/2026
NIH/NHLBI
Airway epithelial cell gene regulation: new mechanisms and therapeutic strategies
Epithelial cells line the airways and are important for maintaining lung health. Airway epithelial cell dysfunction is a key feature of asthma and other common airway diseases. This project will study how genes are regulated in airway epithelial cells and is designed to provide a scientific basis for designing new approaches to prevent, cure, or treat airway diseases. Role: Co-Investigator

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

POSITION TITLE
Assistant Professor of Medicine

EDUCATION/TRAINING

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<td>Biology &amp; Psychology</td>
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Positions and Employment

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

Other Experience and Professional Memberships

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

Honors

- 2008-2009: Will Rogers Institute Fellowship
- 2000: American Neurological Association Summer Fellowship
- 2000: Pasteur Summer Research Fellowship for Medical Students
- 1997: Member, Phi Beta Kappa Society, Harvard College Chapter
1994 – 1998 Dean’s List, Harvard College
1995, 97, 98 John Harvard Scholarship
1996 Harvard College Scholarship

**Contribution to Science**

1) Immune Determinants of Acute Lung Injury and Fibrosis: I have had a longstanding interest in the acute and chronic effects of lung injury. My earlier work focused on the role of alpha-v integrins in vascular leak during the acute phase of lung injury. Using mass spectrometry to identify novel integrin binding partners, I discovered the actin organizer and scaffold IQGAP1 as an effector of the endothelial barrier protective effects of beta-3 integrin. In recent work focusing on the fibrotic period of the wound healing response, I have used single cell mRNA sequencing to identify a subset of murine macrophages that localize to sites of fibroblast accumulation after lung injury and exert a pro-fibrotic effect. As part of this project, working with computational collaborators, I developed a tool (SingleR) that annotates cellular identity in single cell RNA-seq by reference to bulk RNA-seq datasets of pure cell types. This tool enabled clustering of cells revealing a transitional cell state of monocyte-derived macrophages acquiring lung resident identity within sites of fibroblast accumulation, i.e. the fibrotic niche. Our subsequent studies included cell ablation experiments that indicated the pro-fibrotic and activating effect of these macrophages on adjacent fibroblasts.


2) RhoA GTPase in Airway Hyperresponsiveness: The small GTPase RhoA has pro-contractile effects in airway smooth muscle and is therefore a potential therapeutic target in asthma. My interest in this pathway began with the discovery that the intracellular scaffold Iqgap1 suppresses RhoA activation in airway smooth muscle, leading to decreased contraction both at baseline and in murine allergic airway hyperresponsiveness. Mechanistically, we found
that Iqgap1 serves as a protein scaffold, supporting the function of the RhoGAP p190ARhoGAP to inhibit RhoA activation. My current R01 grant is focused on further studies in the RhoA pathway. In recent work, we performed a riboprofiling screen of airway smooth muscle genes that activate RhoA, known as RhoGEFs, with the rationale that they could be targeted for inhibition of bronchospasm. This screen led to the discovery of Arhgef12, which was also highly expressed in human airway smooth muscle. We then found that Arhgef12 is necessary for IL17A-induced airway contractility and allergic airway hyperresponsiveness in vivo. Arhgef12 thus represents a novel therapeutic target in severe asthma patients, a subset of whom have an IL17A-centric airway inflammatory signature.


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

Research Support

Ongoing Research Support

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

Completed Research Support

4K08HL114641-05 Role: PI 09/01/2012 – 06/30/2018
NHLBI
Title: IQGAP1 in vascular barrier regulation during acute lung injury
U54HL119893 Role: PI. 01/01/2018 – 06/30/2018
NHLBI
Title: Targeting ArhGEF12 in Asthma
UCSF Marcus Program for Precision Medicine Role: PI 04/01/2016 – 12/31/2017
Title: Microfluidic droplet capture for gene expression analysis of airway smooth muscle in asthma
UCSF Resource Allocation Program  Role: PI.  02/01/2015 – 12/31/2016  
Title: Integrin alpha-v beta-5 disrupts endothelial barrier function in acute lung injury  
15BGIA22780001  Role: PI.  01/01/2015 – 12/31/2016  
American Heart Association  
Title: Integrin alpha-v beta-5 is necessary for stress fiber formation and vascular leak during acute lung injury and sepsis  
UCSF Nina Ireland Program for Lung Health  Role: PI.  01/05/2015 – 12/31/2016  
Title: Integrin alpha-v beta-5 drives pulmonary vascular leak from ischemia-reperfusion in lung transplantation
# BIOGRAPHICAL SKETCH

<table>
<thead>
<tr>
<th>NAME</th>
<th>POSITION TITLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homer A. Boushey, Jr., M.D.</td>
<td>Professor of Medicine (Emeritus)</td>
</tr>
<tr>
<td>eRA COMMONS USER NAME</td>
<td></td>
</tr>
<tr>
<td>Boushey</td>
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## EDUCATION/TRAINING

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

## Positions and Honors

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

## Honors and Awards

- **1964**: Phi Beta Kappa
- **1967**: AOA
- **1964-1968**: Regents' Scholar
- **1968**: Gold-Headed Cane Recipient
- **1977**: H. J. Kaiser Award for Excellence in Teaching
- **1988, ’90, ’95, 99, 2000**: Faculty-Student Teaching Award for "An Outstanding Lecture"
- **1993**: Clean Air Award (Education/Research), American Lung Association, San Francisco
1993  California Medal, American Lung Association-California
1996  UCSF Alumnus of the Year Award
1997-2000 Bay Area’s Best Physicians, San Francisco Focus Magazine
2000  Medical Student Teaching Award: “An Outstanding Clinical Correlation Lecturer”

Contribution to Science

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


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

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


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


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


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


BIOGRAPHICAL SKETCH

NAME
Esteban González Burchard, M.D., M.P.H.
eRA COMMONS USER NAME: Eburchard

POSITION TITLE: Harry Wm. and Diana V. Hind Distinguished Professorship in Pharmaceutical Sciences, Schools of Pharmacy and Medicine, Departments of Bioengineering & Therapeutic Sciences and Medicine

EDUCATION/TRAINING

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

1995 – 1996 Intern in Medicine, Brigham & Women’s Hospital, Harvard Medical School, Boston, MA
1996-1998 Junior/Senior Resident in Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA
1998 – 2001 Fellow in Pulmonary and Critical Care Medicine, UCSF
2001 - Director, UCSF Asthma Collaboratory
2008 Director, UCSF Center on Genes, Environments & Health
2009 - Director, UCSF Clinical Pharmacology Training Program
2010 - Vice Chair, UCSF Department of Bioengineering & Therapeutic Sciences
2011 - Hind Distinguished Tenured Professor

Schools of Pharmacy & Medicine, UCSF

Selected Honors

1988, 1989 NCAA Div. II Academic All-American, Wrestling
2005–2010 RWJ Amos Medical Faculty Development Award
2008-2014 NIH Study Section Member, Genetics of Health and Disease (GHD)
2009 American Society of Clinical Investigation (ASCI), elected member
2009 Guest Speaker, Tavis Smiley Show
2010 Guest Speaker, NPR’s Science Friday, hosted by Ira Flatow
2011 Athletic Hall of Fame, San Francisco State University
2013 American Museum of Natural History (AMNH) documentary on Esteban Burchard and his research. This documentary was exhibited at the AMNH for two years and distributed to all U.S. public high schools.
2013 Guest Speaker, Smithsonian Institution National Museum of Natural History (NMNH)
2014 UCSF Medal. The UCSF Medal is UCSF’s most prestigious award, given to individuals who have made outstanding personal contributions in the areas associated with the University’s mission, goals and values.

2015 National Academy of Sciences, Engineering and Medicine, Committee on Incorporating 21st Century Science into Risk-Based Evaluations

2015 President Obama’s Precision Medicine Initiative, Advisory Committee to the Director Innovations in Health Equality – Lifetime Achievement Award

2016 Lifetime Achievement Award, American Thoracic Society, Innovations in Health Equality

2017 RWJ Amos Medical Faculty Development Program, National Advisory Committee

2018 Lifetime Achievement Award, National Medical Association (NMA), Allergy and Immunology Section. The NMA is the largest and oldest Black Medical Organization in the nation.

2018 Alumni Hall of Fame, San Francisco State University

2018 Apple Teaching Award

Contributions to Science

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


2. We demonstrated ethnic-specific differences in pharmacogenetic associations of bronchodilator drug responsiveness between Puerto Rican and Mexican children with asthma. I conceived the idea to test the beta 2 adrenergic receptor (β2AR) gene as part of the candidate gene list in the original GALA proposal.


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


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


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

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

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


Research Support

Ongoing Research Support

T32GM007546 (PI: Burchard) 07/01/08 - 06/30/20
NIH/NIGMS
Role: Co-PI
Project title: UCSF Clinical Pharmacology and Therapeutics Training Grant
Goal: To train physician, pharmacist and Ph.D. scientists in clinical and therapeutic actions of drugs in humans.

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

R56MD013312 Zaitlen/Burchard (MPI) 09/25/2018 - 09/24/2019
NIH/NIMHD
Project title: Epigenetics of Socio-Environmental Effects on Asthma in Minorities
Goal: (1) Perform whole genome methylation in a multi-ethnic cohort with existing genetics, transcriptomic, and socio-environmental measures; (2) Develop advanced computation methods needed to identify and characterize associations between epigenetic variation and socio-environmental asthma risk factors; (3) Establish approaches to uncover the causal relationships between socio-environmental factors, epigenetic variation, and asthma

Role: Principal Investigator

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

<table>
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<tr>
<th>NAME</th>
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<tr>
<td>Harold A. Chapman, M.D.</td>
<td>Professor of Medicine</td>
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<td>Halchapman</td>
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EDUCATION/TRAINING

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<tr>
<td>Tulane University</td>
<td></td>
<td>1968</td>
<td>Premedical</td>
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<tr>
<td>University of Alabama School of Medicine</td>
<td>M.D.</td>
<td>1972</td>
<td>Medicine</td>
</tr>
<tr>
<td>Residency in Internal Medicine, University of Utah Affiliated Hospitals, Salt Lake City, UT</td>
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<td>1975</td>
<td>Medicine</td>
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<tr>
<td>Associate Investigator, V.A. Medical Center, Salt Lake City, UT</td>
<td></td>
<td>1977</td>
<td>Infectious Disease</td>
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<tr>
<td>Pulmonary Fellow, University of Utah Affiliated Hospitals, Salt Lake City, UT</td>
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<td>1979</td>
<td>Pulmonary/Critical Care</td>
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Positions and Honors

1979-1985  Assistant Professor of Medicine, University of Utah, Department of Medicine, Salt Lake City, UT
1985      Associate Professor of Medicine, University of Utah, Department of Medicine, Salt Lake City UT
1985-1999 Associate Professor of Medicine, Harvard Medical School, Department of Medicine, Boston, MA
1992-1999 Physician, Brigham and Women's Hospital, Boston, MA
1992-1999 Associate Professor of Environmental Health, Harvard School of Public Health, Boston, MA
2000-2008 Chief, Division of Pulmonary and Critical Care Medicine, University of California, San Francisco
2000      Attending Physician, Moffitt-Long Hospital, University of California San Francisco
2000      Professor of Medicine, University of California, San Francisco
2000      Senior Member, Cardiovascular Research Institute, University of California San Francisco
1985-1990  Career Investigator Award, American Lung Association
1987  American Society for Clinical Investigation
1998  American Association of Physicians
2001-2012  MERIT Award, NIH/NHLBI

Ad Hoc member of various NIH study sections, including Chair and Co-Chair of two NIH study sections in the last three years. Permanent member NIH LRRI study section 2017-2023.

Editorial Boards
*Journal of Clinical Investigation*

**Contribution to Science**

The nature of the cells and proteases important to human emphysema was uncertain not very long ago, with almost all of the attention directed at neutrophils. However we developed and published data in the early 1980s that lung macrophages could be as or more important in elastin degradation. But believing that we did not know the important macrophage enzymes, we generated a human alveolar macrophage-derived DNA expression library to search for additional proteases. My colleagues and I were able to clone four new cysteine proteases from this library and then the group spent the next several years understanding their biology. We also shared the library with other investigators in the field, e.g. Steve Shapiro’s group used the library to clone human macrophage metallo-elastase. We found cysteine proteases with non-redundant functions in antigen presentation, bone collagen turnover, thymic development, and neuronal lysosomal lipofuscin degradation. Cathepsin S, the first enzyme characterized, proved to be a potent elastase and a critical enzyme in MHC class II maturation. Collaborating with geneticists, we were able to link two of the enzymes to human genetic disorders and inhibitors of one of these, cathepsin K, has recently proven effective in a phase III clinical trial for post-menopausal osteoporosis (Merck).


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.


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 α3β1, and Smad signaling. Disruption of this signaling pathway in vivo attenuated epithelial transition and fibrogenesis. The implication that epithelial transition is important to fibrogenesis was subsequently confirmed by Kevin Kim, independent in his own lab, using an epithelial-specific knockout of collagen 1.


A 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 Tβ RI kinase in lysyl oxidase-like 2 (LOXL2)-expressing cells, a fibroblast-specific pathway of TGFβ1 inhibition.


The project is recommended as exceptional (3 stars) by F1000


Full reference list can be found at:

Research Support

Ongoing Research Support

U01HL134766 Chapman, HA PI 09/01/2016-8/31/2023
Epithelial stem/progenitor cells as repair agents in diffuse alveolar damage.

This project describes a new therapeutic approach to lung repair that extends recent results in mice demonstrating that lung stem/progenitor cells can transplant and engraft in damaged lungs. The application is driven by the frustrating current state of pulmonary medicine that offers little more than supportive care in the management of acute respiratory failure and progressive fibrotic lung diseases. A group of investigators have come together to overcome the hurdles of stem/progenitor cell replacement therapy in humans.
# BIOGRAPHICAL SKETCH

**NAME**  
Anthony L. DeFranco, Ph.D.

**POSITION TITLE**  
Professor, Department of Microbiology & Immunology

**eRA COMMONS USER NAME**  
DeFranco

## EDUCATION/TRAINING

<table>
<thead>
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<th>DEGREE</th>
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<th>FIELD OF STUDY</th>
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<tbody>
<tr>
<td>University of California, Berkeley, CA</td>
<td>Ph.D.</td>
<td>10/1979</td>
<td>Biochemistry</td>
</tr>
<tr>
<td>National Institutes of Health, Bethesda, MD</td>
<td>Postdoctoral</td>
<td>8/1983</td>
<td>Immunology</td>
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</tbody>
</table>

## 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 Institute, MIT, Cambridge, MA

- **1994-present**  
  Professor, UCSF, Department of Microbiology & Immunology

- **1997-1998**  
  Sabbatical with Suzanne Cory, Walter and Eliza Hall Institute, Melbourne, Australia

- **1998-2004**  
  Scientific Advisory Board, Abgenix, Inc. Fremont, CA

- **1999-2009**  
  Chairman, Department of Microbiology & Immunology, UCSF

- **2012-**  
  Scientific Advisory Board, UCB Celtech, Slough, UK

- **2015-present**  
  Professor Emeritus of Microbiology & Immunology, UCSF (with continuing research and teaching activities)

## Honors

- **1974**  
  Dreyfuss Foundation Fellow

- **1975**  
  Phi Beta Kappa, Harvard University

- **1975-1978**  
  NSF Predoctoral Fellow

- **1979-1982**  
  Helen Hay Whitney Postdoctoral Fellow

- **1993**  
  2nd Rose Lieberman Lecturer, NIH

- **1994**  
  NIAID Merit Award

- **1997-1998**  
  NIH Fogarty Senior International Award
Contribution to Science

1). Mechanism of signal transduction by the BCR - A longstanding problem is how lymphocytes recognize the presence of the antigen that they recognize. We were the first (along with two other independent groups) to demonstrate that the BCR signals by inducing protein tyrosine phosphorylation (a). We demonstrated a number of features of the BCR signaling pathway, including the rapid tyrosine phosphorylation of Igα and Igβ of engaged receptors, activation of the PI 3-kinase pathway, and phosphorylation of PLC-γ2 as the mechanism of stimulation of PIP2 breakdown, as well as other findings. Some recent contributions are highlighted in the references cited here, including studies demonstrating that BCR signaling results in rapid release of ezrin from linkages to plasma membrane proteins, which facilitates membrane rearrangements that support BCR signaling (b), an analysis of the role of reactive oxygen species in BCR signaling, which disproved a long-standing model in the field (c), and studies in which BCR-induced diacylglycerol signaling to Erk was specifically enhanced by removal of the negative regulator DGKζ, which showed that Erk signaling is an important determinant of expansion of B cell numbers, especially at the plasmablast stage. In addition, the data strongly suggested that BCR affinity for antigen is primarily sensed by the B cell via the magnitude of Erk signaling (d).


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).


3). Analysis of Lyn-deficient mice as a murine model of lupus - Also in collaboration with Dr. Lowell, we have studied the autoimmunity that develops in Lyn-deficient mice. We have found that mice deficient in Lyn and Fyn have stronger lupus nephritis than do Lyn-/- mice, which probably reflects a role for Lyn in the homeostasis of the epithelial foot processes of the glomeruli (a). We showed that DCs contribute importantly to the autoimmune disease of Lyn-deficient mice by producing BAFF and stimulating interferon-γ production from T cells (b) and that DCs require MyD88-dependent signaling to promote inflammatory disease in this model (c). Selective deletion of Lyn in B cells also leads to lupus-like autoantibody production and lupus nephritis, indicating that B cell tolerance defects contribute to the lupus-like autoimmunity of Lyn-deficient mice (d). In studies nearing publication, we have found that combination of Lyn-deficiency with a hypomorphic allele of Aire, which is important for thymic expression of organ-specific autoantigens, results in spontaneous autoimmune uveitis, providing a model for multigenic autoimmune susceptibility. This project is the subject of the current application.


4). Roles of TLR signaling in dendritic cells and macrophages for the innate response to adjuvants and infections - To dissect the roles of TLRs in immune responses in vivo, we created a conditional allele of the TLR signaling component MyD88 with the Cre/loxP system, and verified its utility for deletion of MyD88 selectively in dendritic cells (DCs) (a). These studies showed that DCs are the major producers of inflammatory cytokines in the spleen following i.v. infusion of TLR ligands, and that splenic macrophages are a minor contributor. In collaborative studies with Felix Yarovinsky (UT Southwestern), we used these mice to demonstrate that infection with *Toxoplasma gondii* results in TLR-dependent IL-12 production by peritoneal DCs, which is critical for innate host defense by inducing infiltrating NK cells to make interferon-γ which in turn promotes killing of parasites by inflammatory monocytes (b). This was the first study to clearly demonstrate a critical role for type 1 innate immunity in control of *Toxoplasma* infection as previous studies had been interpreted in light...
of effects on the Th1 response, which is also essential to control of *Toxoplasma*. This work was primarily conducted in my lab by the first author, although Dr. Yarovinsky provided important support for these studies. This collaboration lead to two other important papers that were primarily conducted in Dr. Yarovinsky’s lab (4c and 5b). In contrast to the critical role of DCs in response to *Toxoplasma gondii* infection, in a murine malaria model, splenic red pulp macrophages were found to be critical for early cytokine production (4d). The conditional allele of *Myd88* was deposited with Jackson Lab soon after initial publication and is available to academic investigators for their studies.


5). TLR7/9 in B cells promote germinal center responses Although TLRs are not required for antibody responses, TLR ligands are excellent adjuvants. Previously, it was thought that TLR signaling in B cells promoted extrafollicular antibody responses, but we showed that TLR7 and TLR9 can strongly enhance GC responses to virus particles (5a). Subsequently, other groups showed that mice lacking TLR7 or MyD88 selectively in B cells fail to make a normal neutralizing antibody response against LCMV, Friend virus, or endogenous retroviruses, leading to poor control of these virus infections, thus demonstrating an important biological role of the pathway we first described. We showed that this mechanism is also required for production of anti-nuclear antibodies in the Lyn-deficient mouse model of lupus (5c) and we have recently dissected the cellular mechanisms of this response (5d). In addition, in collaboration with Dr. Yarovinsky we found that MyD88 function in B cells promotes the rapid IgM response to colonic bacteria following damage to colonic epithelium.


A complete list of my publications is available at:

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
Agency: NIH/NIAID

Completed (last 3 years)

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

NAME
William F. DeGrado

POSITION TITLE
Professor

EDUCATION/TRAINING

<table>
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<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
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<td>Kalamazoo College, Kalamazoo, MI</td>
<td>B.S.</td>
<td>02/1978</td>
<td>Chemistry</td>
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<td>University of California, San Francisco</td>
<td>Ph.D.</td>
<td>06/1981</td>
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Positions

1996-2011 Professor, Dept. of Biochemistry & Biophysics, University of Pennsylvania, Philadelphia, PA
2001-2003 President, The Protein Society
2011-present Professor, UCSF Department of Pharmaceutical Chemistry

Visiting Positions

1987 Sloan Visiting Lecturer of Chemistry, Dept. of Chemistry, Harvard University
1987-1989 Adjunct Professor, Department of Biophysics, Johns Hopkins Medical School
1991 Adjunct Professor, Departments of Biochemistry & Biophysics, University of Pennsylvania
2010-2011 Visiting professor, UCSF Department of Pharmaceutical Chemistry.

Honors

1988 du Vigneaud Award for Peptide Research
1989 Protein Society Young Investigator Award
1992 Eli Lilly Award in Biological Chemistry
1994 Fellow, American Association for the Advancement of Science
1998 Member, American Academy of Arts and Sciences
1999 Member, National Academy of Sciences (U.S.A.)
2003 Merrifield Award, (presented by the Peptide Society)
2008 Ralph F. Hirschmann Award in Peptide Chemistry (American Chemical Society)
2009 Makineni Award (APS)
Contribution to Science

1) Protein Design. In the 80’s our group began a new approach to probe protein conformation and function through the de novo design of proteins. At that time, proteins were seen as impossibly complex molecules whose structure could not be predicted or designed. We therefore adopted minimalist approach to protein design in which we set out to engineer sequences of the minimal complexity required for folding and a given function. Our group was the first to design and convincingly characterize a protein from scratch; a four-helix bundle. De novo protein design proved to be a useful method for probing the features required for forming secondary structures (e.g., O’Neil and DeGrado’s well-known thermodynamic scale of helix propensity), forming compact states known as “molten globules” and ultimately for forming well-packed native protein structures. This method was then used to design proteins that bound DNA, transition metals, and redox-active cofactors including both natural and non-natural porphyrins. For example, our group predicted the DNA-bound structures of the leucine zipper, HLH and related transcription factors before their high-resolution crystallographic structures were known, and we designed minimalist versions of the protein to illustrate the mechanisms by which they folded and recognized DNA in a sequence-specific manner. Also, our work on diiron proteins has resulted in proteins that catalyze a variety of two-electron processes. We also designed proteins that bind and coat various materials including carbon nanotubes, and proteins that bind a variety electrical and optical cofactors. Most recently, we demonstrated the design of catalytically active Zn²⁺-binding peptides that adopt catalytically active cross-beta fibrils. This work has the potential to open new doors for the design of catalytic materials as well as implications concerning the evolution of life.


2) Membrane protein design We also used minimalist design principles to delineate the features required for assembly and conduction of ion channels and also designed transmembrane, multi-porphyrin helical bundles that catalyze electron transfer through phospholipid membranes. Simultaneous with Engelman’s group, we also showed the role of polar amino acids in inducing association of transmembrane helices, and its role in a variety
of single-span membrane proteins\textsuperscript{5,6}. We also developed a computational approach to design peptides that target the transmembrane regions of membrane proteins in much the same way that antibodies are used to block protein-protein interactions in water-soluble proteins\textsuperscript{7}. In our most recent work\textsuperscript{8}, we also have designed helical bundles that use a Zn(II) gradient to drive the transport of protons up a concentration gradient (and vice versa). This work was particularly significant, as it was the first example of a designed membrane protein whose structure was determined at high resolution, as well as the complexity of the function achieved.


3) \textbf{Structure-based design of small molecule therapeutics.}

\textit{Integrins}. Our group has long been involved in the design of cyclic peptides small molecules as inhibitors of integrins to allow the interrogation of their roles in various biological processes. Early work on the integrins \(\alpha\)I\(\beta\)3 led to compounds that reached clinical trials. More recently, we explored the role of other integrins involved in platelet adhesion including \(\alpha\)v\(\beta\)3 and \(\alpha\)2\(\beta\)1 (a non-RGD collagen receptor). Since moving to UCSF, we have focused on the problem of fibrotic diseases including idiotypic pulmonary fibrosis (IPF). In collaboration with Dean Sheppard we have developed very potent integrin antagonists that inhibit activation of TGF-\(\beta\)1, and work in a variety of animal models of IPF and other fibrotic disorders\textsuperscript{9}. We also have had a long-standing collaboration with Joel Bennett on the activation of \(\alpha\)I\(\beta\)\(\beta\), particularly the role of its transmembrane helices\textsuperscript{7} and engagement of cytoplasmic proteins\textsuperscript{10}.

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

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4) Peptide-membrane interactions and development of mimics of host defense peptides

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


Complete List of Published Work in MyBibliography:

Research Support

R35 GM122603  05/01/17—04/30/22  6.0 Calendar
NIH/NIGMS
“Deciphering the relationship between structure, dynamics and function in helical bundle proteins”
Our lab uses de novo protein design to test the principles of protein structure and function – if we understand proteins we should be able to design them from scratch. We also study the structure and inhibition of M2, a transmembrane proton transporter from influenza A virus, which is the target of amantadine. Finally, we study transmembrane histidine kinases, which are used by bacteria to sense their environment.

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

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

CHE-1709506 (Therien)  08/01/17—07/31/21
NSF/Duke University
“Collaborative Research: De novo Protein Constructs for Photosynthetic Energy Transduction”
This collaborative proposal aims to understand the essential design principles of photosynthetic energy transduction and storage. An integrated, multi-disciplinary approach focuses on peptide-synthetic cofactor complexes that undergo photoinduced charge-transfer reactions, where the protein matrix stabilizes the charge-separated state and guides the efficient separation of electrons and holes. A postdoc in DeGrado’s group works on the design of proteins that bind non-biological cofactors for energy transduction.
Role: Co-Investigator
### BIOGRAPHICAL SKETCH

<table>
<thead>
<tr>
<th>NAME</th>
<th>POSITION TITLE</th>
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<tr>
<td>David J. Erle, M.D.</td>
<td>Professor of Medicine</td>
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### EDUCATION/TRAINING

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<td>University of California, San Francisco, CA</td>
<td>M.D.</td>
<td>5/1984</td>
<td>Medicine</td>
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<tr>
<td>University of California, San Francisco, CA</td>
<td>Resident</td>
<td>6/1987</td>
<td>Internal Medicine</td>
</tr>
<tr>
<td>University of California, San Francisco, CA</td>
<td>Fellow</td>
<td>6/1988</td>
<td>Pulmonary Disease</td>
</tr>
<tr>
<td>University of California, San Francisco, CA</td>
<td>Postdoc</td>
<td>6/1990</td>
<td>Cell &amp; Molecular Biology</td>
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### Positions

- **1984-1987**: Resident in Internal Medicine, University of California Hospitals, San Francisco
- **1987-1988**: Clinical Pulmonary Fellow, University of California Hospitals, San Francisco
- **1988-1990**: Research Fellow, Lung Biology Center and Cardiovascular Research Institute, UCSF
- **1990-1992**: Adjunct Assistant Professor of Medicine, UCSF
- **1990-present**: Attending Physician, San Francisco General Hospital
- **1992-1998**: Assistant Professor of Medicine in Residence, UCSF
- **1996-present**: Faculty, UCSF Immunology and Biomedical Sciences Graduate Programs
- **1997-2001**: UCSF/SFGH General Clinical Research Center (GCRC) Advisory Committee
- **1998-2004**: Associate Professor of Medicine, UCSF
- **1999-present**: Investigator, Cardiovascular Research Institute, UCSF
- **2000-present**: Director, Functional Genomics Core Facility, UCSF SABRE Center
- **2004-present**: Professor of Medicine, UCSF
- **2006-2011**: Associate Director, UCSF Clinical and Translational Sciences Institute Bioinformatics Program
- **2013-present**: Founder and Director, UCSF K12 Career Development Program in Omics of Lung Diseases
- **2017**: Associate Chair for Biomedical Research, UCSF Department of Medicine
- **2018-**: Member, UCSF Institute for Human Genetics
- **2018-**: Member, Immuno X program

### Other Experience and Professional Memberships

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

Honors
1977 Detur Prize
1980 Magna cum laude, Harvard College, Cambridge, MA
1984 Alpha Omega Alpha, elected
1990-1993 Edward Livingston Trudeau Award of the American Lung Association
2018 Elected member, Association of American Physicians
2019 NHLBI Outstanding Investigator Award (R35)

Contributions to Science

1. I have led a series of studies investigating how the cytokine interleukin-13 acts on cells in the airway to contribute to pathophysiologic changes that are important in a large subset of individuals with asthma. We used transgenic mouse modeling and human cell culture-based studies to demonstrate how IL-13, acting directly on airway epithelial cells, causes mucus metaplasia and airway hyperreactivity, two characteristic features of asthma. We identified many IL-13-induced genes and dissected out their contributions to disease. We have also collaborated closely with patient-based researchers to demonstrate the relevance of these pathways in humans with asthma. Antibodies against IL-13 are now in clinical trials for treatment of severe asthma.


Since founding the UCSF Sandler Asthma Basic Research Functional Genomics Core Facility in 2000, I have made extensive use of genomics approaches in my own work and in collaborative projects with many other investigators. Many studies listed elsewhere in this biosketch include genomics work performed in my lab. In addition, recent publications from genomics projects performed by members of my group or as collaborations between our core and other investigators include:
The goal of this research program is to understand the interactions between lung epithelial and mesenchymal cells in sufficient detail to deliver new therapeutic interventions in pulmonary fibrosis, a process without disease modifying therapies. This program is focused on further elucidation of mechanisms of a fibroblast-specific trihydroxyphenolic inhibitor of LOXL2 and TGFR1 with potent in vivo anti-fibrotic effects. We will test one of these, EGCG, in a proof of principle clinical trial. Data in press show reversal of a core set of pro-fibrotic tissue biomarkers in IPF patients given EGCG two weeks prior to diagnostic lung biopsy. The R35 mechanism allows us to integrate our capacity to attenuate fibrosis with the broader issue of defective epithelial regeneration in IPF, a competing process with fibrogenesis. This grant replaces two RO1s: R01HL128484-01 and HL142265-01A1.

**Recently Completed**

Sponsored Research Agreement Chapman HA, PI  01/01/2014-12/31/2016
Biogen Idec.

Elucidation of human lung cellular diversity and epithelial-mesenchymal interactions

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

The major goal of this project is to deliver one or more novel therapeutics based on recently identified regulators of EMT in lung epithelial cells for further drug development.

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

The specific aims of this project are (1) Test the hypothesis that differential expression of adhesion receptors underlies the capacity of epithelial subtypes to self-organize and promote repair. (2) Define the requirement for neuroendocrine cells (PNECS) and alveolar progenitor cells in maintenance and reconstitution of distal airway and alveolar cells following lung injury. (3) Analyze and further develop a novel, single cell in vivo lung organoid assay in kidney capsules in order to optimize the capacity of adult epithelial progenitor cells to generate functional respiratory units de novo.

R01 HL44712 Chapman HA, PI
NIH/NHLBI
Regulation of Integrin Function  01/01/1991 – 12/31/2014

The major goals of this project are to understand the molecular basis and importance of integrin function in promoting TGFβ1 signaling and pulmonary fibrosis. The hypothesis that epithelial to mesenchymal transition is an important component of pulmonary fibrosis, and regulated by integrins, is the main idea tested in this grant.


I have a strong interest in understanding basic mechanisms of post-transcriptional gene regulation in health and disease (especially asthma). We have developed novel massively parallel methods for functional annotation of 3’ UTRs and used these to identify novel regulatory elements in human 3’ UTRs. In asthma, we have identified changes in miRNA expression in airway epithelial cells in asthma and identified one pathway that contributes to these changes.


Mucosal epithelial cell biology is another major interest of the lab. There are 19 members of the protein disulfide isomerase (PDI) family of ER-resident proteins in humans but the roles of most of these remain poorly understood. Our discovery that the PDI family member AGR2 is induced in asthma led us to study the roles of AGR2 and its homolog AGR3. We produced Agr2−/− mice and used these to show that AGR2 is essential for mucus production in the intestine and is also important for allergen-induced mucus overproduction in a mouse model of asthma. Surprisingly, we found that the close AGR2 homolog AGR3 has a very different role in airway epithelium: it is expressed in ciliated cells rather than mucus cells and helps regulate ciliary beat frequency.


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 \( \beta 7 \) and the integrin \( \alpha 4\beta 7 \) heterodimer that directs lymphocyte trafficking to the intestine. Subsequent work by other investigators led to the development of the anti-integrin \( \alpha 4\beta 7 \) antibody vedolizumab as an FDA-approved treatment for inflammatory bowel disease.


Complete list of publications in MyBibliography:

**Research Support**

**Ongoing Research Support**

R35 HL145235 Erle (PI) 04/15/2019-02/28/2026

Airway Epithelial Cell Gene Regulation: New Mechanisms and Therapeutic Strategies

This project will study how genes are regulated in airway epithelial cells and is designed to provide a scientific basis for designing new approaches to prevent, cure, or treat airway diseases.

Role: PI

U19 AI 077439 Erle (PI) 04/01/2018-03/31/2023

Understanding Asthma Endotypes

Our Center is focused on understanding how airway epithelial cells are involved in causing different forms of asthma. Our studies will uncover new knowledge about mechanisms of asthma and help to pave the way for new treatments for this common disease.

Role: PI, project 1 leader
BIOGRAPHICAL SKETCH

NAME
John Vincent Fahy, M.D., M.Sc.

POSITION TITLE
Professor

eRA COMMONS USER NAME
johnfahy

EDUCATION/TRAINING

<table>
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<td>MB BAO BCH Internal Medicine (Residency)</td>
<td>6/1985</td>
<td>Medicine</td>
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<tr>
<td>Trinity College Dublin</td>
<td>Internal Medicine (Residency)</td>
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<td>University College Dublin</td>
<td>Pulmonary Medicine (Medical Registrar)</td>
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<td>Postdoctoral Fellowship</td>
<td>6/1993</td>
<td>Pulmonary/Critical Care Medicine</td>
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<td>University College Dublin</td>
<td>M.D. (doctorate by thesis)</td>
<td>6/1997</td>
<td>Airway Inflammation</td>
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<tr>
<td>Trinity College Dublin</td>
<td>M.Sc.</td>
<td>6/2003 (Sabbatical)</td>
<td>Molecular Medicine</td>
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Positions

1989-1993  Fellow, Division of Pulmonary and Critical Care Medicine, Department of Medicine (DOM) and Cardiovascular Research institute (CVRI), UCSF.

1993-1998  Assistant Professor of Medicine, Division of Pulmonary and Critical Care Medicine, DOM and CVRI, UCSF.

1999-2005  Associate Professor of Medicine, Division of Pulmonary and Critical Care Medicine, DOM and CVRI, UCSF.

2002-2003  Visiting Scholar, Trinity College Dublin and University College Dublin (sabbatical year)

2005-present  Professor of Medicine, Division of Pulmonary and Critical Care Medicine, DOM and CVRI, UCSF.

Other Experience and Professional Memberships

1989- Member, American Thoracic Society

2014- Member, European Respiratory Society

2009- Member, Organizing Committee - Transatlantic Airway Conference (TAC).

2012-2014 NIH Workshop: Primary prevention of lung disease - chair of asthma subcommittee.

2014 NIH Strategic Planning Working Group: Member, disease modification subcommittee.
2015  Ad hoc NIH Peer reviewer, Lung Cellular, Molecular Immunobiology Study Section

Honors

1990  Traveling Studentship in Medicine, National University of Ireland.
2009  Michael S. Stulbarg Endowed Chair in Pulmonary Medicine, UCSF.
2015  Scientific Accomplishment Award, American Thoracic Society, Allergy Immunology and Inflammation Assembly.
2016  Election to Association of American Physicians (AAP)
2017  ATS Recognition Awardees for Scientific Accomplishments.
2019  European Respiratory Society (ERS) Gold Medal in Asthma (the ERS presents this award annually to recognize excellence in the field of asthma research).

Contribution to Science

Molecular Phenotypes of Asthma

Background: Asthma is clinically heterogeneous, and previous concepts held that this heterogeneity could be explained by variability in the levels of type 2 (eosinophilic) inflammation in the airway. This concept has now been replaced by the view that asthma is not mechanistically homogenous and that different molecular mechanisms are responsible for disease expression in different subsets of patients. This realization has emphasized the importance of mechanism-oriented research in human subjects, and my lab has been at the forefront of mechanism-oriented studies that are designed to uncover molecular phenotypes of asthma.

Central findings: My initial work as a fellow and junior faculty member involved developing methods to non invasively study airway inflammation using analysis of induced sputum for cells and mediators of asthma (publication A below). I later extended this sputum-based work to cell and molecular analyses of other airway biospecimens, including epithelial brushings, bronchial mucosal biopsies, and bronchial lavage. By applying and optimizing rigorous analytic methods, including OMIC technologies to the analysis of these biospecimens, my lab had made major contributions to current understanding of disease heterogeneity in asthma. These findings have included the identification of Th2-high and Th2-low endotypes of asthma (publications A-D) as well as the recent identification of IL-6 high asthma (publication E).

Impact: The impact of discovery of Th2-high asthma by my lab in collaboration with Prescott Woodruff’s lab (UCSF) and Joe Arron’s group (Genentech) has been large. Asthma research now routinely segregates patients into Th2-high and low subgroups and clinical trials of Th2 inhibitors are specifically targeting patients with Th2-high asthma using biomarkers like periostin that I helped discover.

My role: I lead a large research group that is involved in mechanism-oriented research in asthma. My role is that of a senior investigator who manages a clinical research lab, generates funding, manages and mentors personnel, interprets data, writes papers, and sets the course for my group. Key grants for this activity include P01HL107202 and U10HL109146.


(II) Airway Mucosa Pathology

**Background:** Airway mucus is normally a lightly cross-linked gel that is easily transported out of the lung via the mucociliary escalator. In lung disease this mucus gel becomes more elastic and harder to clear and mucus stasis then causes airflow obstruction and lung infection. Mucus pathology is a feature of all major lung disease especially COPD, asthma and cystic fibrosis. The study of mucus in lung disease has been a major focus of my lab and my group has optimized multiple methodologies to apply to quantify mucus cells and mucin proteins in the airway. I am regarded as a world expert in mucus pathology in the lung (publication A).

**Central findings:** My lab has described the mucus cell and mucin gene abnormalities that occur in asthma COPD, and in CF (example in publication B) and revealed pathologic mechanisms by which mucus plugs form (publication C) and physiologic mechanisms by which mucins contribute to host defense (publication D).

**Impact:** There are few treatments targeting mucus pathology in lung disease despite the common occurrence of mucus-associated disease. My lab’s focus on studies in human lung disease using sputum samples in ex vivo experiments has been impactful in drawing attention to research approaches to answer mechanistic questions and to point to treatment strategies that might be easily applied.

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


(III) Novel Drugs for Airway Disease

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

**Central findings:** Although inhibition of NK-1, selectins, or EGFR did not have beneficial effects in clinical trials (publications A-C below), blocking IgE with a recombinant humanized monoclonal anti-IgE antibody (Omalizumab) proved effective in reducing early and late phase responses to inhaled allergen in patients with asthma (publication D). By revealing oxidation as a key mechanism of mucin cross-linking and mucus gel stiffness and the potential for thiol-based saccharide compounds to have therapeutic advantages over existing mucolytics, I have set the stage for a novel strategy for mucolysis in lung disease (publication E).

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

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


inhaled epidermal growth factor receptor inhibitor in chronic obstructive pulmonary disease. 


**Complete List of Published Work - UCSF Profiles:** [http://profiles.ucsf.edu/john.fahy#toc-id8](http://profiles.ucsf.edu/john.fahy#toc-id8)

**H Index (Google Scholar):** 71

**Research Support – Active**

5 R01 HL080414 (Fahy, JV) 07/01/05 - 04/30/20
*Mechanism of mucus pathology in asthma exacerbations:* The major goals of this project are to investigate how stiff mucus gels form in the airway to cause airway obstruction in acute severe asthma. Role: PI

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

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

1 P01HL128191 (Fahy, JV) 09/01/2016 - 07/31/2021
*Carbohydrate-based Therapy for Lung Disease:* This tPPG is advancing a program of research to bring a novel mucolytic treatment to the clinic for the treatment of mucus-associated diseases of the lung.
Role: Overall PPG PI (Project leader for project 3 and Core leader for the Administrative Core).
BIOGRAPHICAL SKETCH

NAME
James Solomon Fraser, Ph.D.

POSITION TITLE
Associate Professor of Bioengineering and Therapeutic Sciences

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

EDUCATION/TRAINING

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>MM/YY</th>
<th>FIELD OF STUDY</th>
</tr>
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<tbody>
<tr>
<td>McGill University, Montreal, QC, Canada</td>
<td>B.Sc.</td>
<td>5/2005</td>
<td>Biology</td>
</tr>
<tr>
<td>University of California, Berkeley, CA</td>
<td>Ph.D.</td>
<td>12/2010</td>
<td>Molecular and Cell Biology</td>
</tr>
</tbody>
</table>

Positions

2011-2012 QB3 at UCSF Fellow (Principal Investigator)
Department of Cellular and Molecular Pharmacology, UCSF
California Institute of Quantitative Biosciences (QB3)

2013-Present Assistant Professor
Department of Bioengineering and Therapeutic Sciences, UCSF
California Institute of Quantitative Biosciences (QB3)

2016 - Consulting Professor
Department of Photon Science
SLAC National Accelerator Laboratory

2016 - Associate Professor
Department of Bioengineering and Therapeutic Sciences, UCSF
California Institute of Quantitative Biosciences (QB3)

2019 - Faculty Scientist
Molecular Biophysics and Integrated Bioimaging Division
Lawrence Berkeley National Lab

2007-2012 Author of problems and solutions manual for physical biochemistry textbook “The Molecules of Life” (Garland Science, Authors: John Kuriyan, Boyana Konforti, David Wemmer)

2008-2009 Assistant to Professor Howard Schachman for NIH Ethics Training (MCB 293C)

2013-2015 Advanced Light Source Proposal Review (Structural Biology), Panel Member

2015-2018 Linac Coherent Light Source (XFEL) Proposal Review Panel (BIO-C), Chair

2016- Beamline 8.3.1. at the Advanced Light Source, Head of Participating Research Team

2016- ASAPbio (Accelerating Science and Publication in biology) Board of Directors, Treasurer

2016- Relay Therapeutics, Consultant

2017- Quantitative Biosciences Institute of UCSF, Associate Director

2017- ALS-ENABLE P30 Resource, Deputy Director

2017- Collaboration for Structural Simulations and Scattering, Project Director

2018 Protein Society Annual Symposium, Co-Chair
2018- PHENIX (Python-based Hierarchical ENvironment for Integrated Xtallography), Advisory Board
2019 UCSF Biophysics Graduate Program, Associate Director

Honors and Awards

2001-2005 Canadian Millennium Excellence Undergraduate Scholarship
2004 NSERC Undergraduate Summer Research Award (Mentor: Alan Davidson)
2006-2007 Natural Sciences and Engineering Research Council (Canada) Postgraduate Fellowship
2007-2010 Natural Sciences and Engineering Research Council (Canada) Doctoral Fellowship
2007-2010 National Science Foundation Graduate Research Fellowship
2010 EMBO Short Term Fellowship (Host: Dan Tawfik, Weizmann Institute, Israel)
2010 Warren DeLano Award, Structural Bioinformatics and Computational B
2011 Nicholas Cozzarelli Prize for Best Dissertation in Molecular and Cell Biology (UCB)
2011 Forbes 30 under 30 Science
2014 Searle Scholar, Kinship Foundation
2014 Pew Scholar, Pew Charitable Trusts
2014 Packard Fellow, The David and Lucille Packard Foundation
2017-2018 Raymond and Beverly Sackler UCSF/Berkeley Sabbatical Exchange (Host: Eva Nogales)

Contribution to Science

1. Identifying hidden alternative conformations of proteins in biophysical data. We study proteins as conformational ensembles. Although X-ray crystallography is an ensemble experiment, the results are typically summarized with a single static structure. As a graduate student, and now in my own lab, we have developed software to discover the structural ensembles present in the crystal. The ensemble nature of proteins highlighted by this work feeds into all of our mechanistic studies that interpret the functional effects of mutations, that characterize designed and artificially evolved proteins, or that seek to modulate protein function with small molecules. We are expanding this direction to include modeling and validating protein structural data generated by cryoelectron microscopy, through EMRinger and collaborations with Gabe Lander’s lab on ensemble modeling, and through integrative approaches to discover cryptic sites.


2. Creating multi-temperature X-ray data collection methods to inform mechanistic studies. We recognized that the standard practice of cryocooling crystals could distort protein conformations. In
both larger surveys and isolated mechanistic studies, we have demonstrated the value of room temperature data collection for revealing the structural basis of protein conformational dynamics, leading to new insights into the enzymes PTP1B, CypA, H-Ras, and DHFR, and increasing connections to dynamics studies from NMR and simulations. Additionally, we have identified how temperature can bias small molecule discovery, leading some fragment sites inaccessible at cryogenic temperatures, and the positioning of crucial water molecules in the flu ion channel M2.


3. Developing new X-ray diffuse scattering and X-FEL experiments to probe correlated motions in proteins. A major limitation of most biophysical techniques is the inability to directly reveal correlations in motions between distinct regions of macromolecules. Diffuse scattering has the potential to reveal these motions; however, we currently lack the ability to collect, integrate, and refine diffuse scattering data. We are tackling each of these problems directly with collaborators: Michael Wall, Nicholas Sauter, Tom Terwilliger, and Paul Adams. Our long-term goal is to increase the information content of every X-ray diffraction experiment to reveal atomic level coupling at high resolution and improved models of grouped flexibility at low resolution. We are also taking advantage of the new capabilities of next-generation X-ray free electron laser (X-FEL) light sources to perform radiation damage-free imaging of proteins. Our long term goal is to watch how protein conformational ensembles respond when perturbed by rapid temperature jumps using the X-FEL.


4. **Determining structures that influence microbial-host interactions.** I have a longstanding interest in microbiology, beginning from my undergraduate work with Alan Davidson (Toronto) on bacteriophage structure prediction that lead to the surprising discovery of a class of mobile immunoglobulin domains. I have collaborated with the Zusman lab (UC Berkeley) to determine the structure of FrzS, a key signaling regulator of Myxococcus xanthus, with the Fischbach lab (Stanford) to determine how the gut microbiome produces the neurotransmitter tryptamine, and with the Tawfik lab (Weizmann Institute, Israel) to determine the role of epistasis in restricting antibiotic resistance mutations. We are expanding this interest to include the interaction of human enzymes in degrading chitin molecules that can cause inflammation in the context of allergy and asthma, the hijacking of the proline isomerase CypA in lentiviral evolution, and structure-based antibiotic design using cryoEM.


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.


Complete List of 46 Publications in MyBibliography:

Research Support

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

R01 GM123159  Fraser (PI)  12/01/17 – 11/31/21
NIH/NIGMS
Resolving ensemble averaged conformations by multi-temperature x-ray crystallography
The objective of this research program is to experimentally access and computationally model multi-scale heterogeneity in allosteric protein-ligand complexes.

P30 GM0519206  Adams (PI)  07/01/17 – 06/30/22
NIH/NIGMS
ALS Efficiently Networking Advanced Beam Line Experiments (ALS-ENABLE)
Fraser administers the project as Deputy Director of Macromolecular Crystallography and performs outreach. Fraser is the deputy project director, overseeing the crystallography component of the project.

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

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

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

<table>
<thead>
<tr>
<th>NAME</th>
<th>Andrew N. Goldberg</th>
</tr>
</thead>
<tbody>
<tr>
<td>POSITION TITLE</td>
<td>Research Investigator</td>
</tr>
<tr>
<td>eRA COMMONS USER NAME (credential, e.g., agency login)</td>
<td>ANGOLDBERG</td>
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### EDUCATION/TRAINING

<table>
<thead>
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<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>MM/YY</th>
<th>FIELD OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston University, Boston, MA</td>
<td>BA</td>
<td>1982</td>
<td>Mathematics</td>
</tr>
<tr>
<td>Boston University, Boston, MA</td>
<td>MD</td>
<td>1985</td>
<td>Medicine</td>
</tr>
<tr>
<td>Los Angeles County-Harbor/UCLA Medical Center, Torrance, CA</td>
<td>Intern</td>
<td>1986</td>
<td>General Medicine</td>
</tr>
<tr>
<td>University of Pittsburgh, School of Medicine Eye &amp; Ear Hospital, Pittsburgh, PA</td>
<td>Residency</td>
<td>1990</td>
<td>Otolaryngology, Head and Neck Surgery</td>
</tr>
<tr>
<td>National Cancer Institute, Center for Epidemiology and Biostatistics, Philadelphia, PA</td>
<td>Fellow</td>
<td>1996</td>
<td>Clinical Epidemiology of Cancer</td>
</tr>
<tr>
<td>University of Pennsylvania, Philadelphia, PA</td>
<td>MS</td>
<td>2003</td>
<td>Clinical Epidemiology</td>
</tr>
</tbody>
</table>

### Positions

- **2007-Present** Professor, Neurological Surgery, University of California, San Francisco
- **2006-Present** Professor, Otolaryngology - Head and Neck Surgery, University of California, San Francisco
- **2000-2006** Associate Professor, Otolaryngology, Head and Neck Surgery, University of California, San Francisco
- **1993 – 2000** Assistant Professor, Otolaryngology, Head and Neck Surgery University of Pennsylvania Medical School, Philadelphia, PA
- **1992 – 1993** Assistant Professor, Otolaryngology, Head and Neck Surgery, Washington University School of Medicine, St. Louis, MO
- **1990 – 1992** Instructor, Otolaryngology, Head and Neck Surgery, Washington University School of Medicine, St. Louis, MO

### Honors

- **1989** George C. Schein, MD Research Award
  University of Pittsburgh, School of Medicine
- **1993** Resident Appreciation Award
  Washington University of St. Louis, Department of Otolaryngology, Head and Neck Surgery
- **2002** Distinction in Teaching Award, Honorable Mention
  UCSF Academic Senate
- **2002** Roger Boles Resident Teaching Award
  UCSF Otolaryngology, Head and Neck Surgery
Contribution to Science

My principle interest in research involves the application of basic science techniques in determining the causes of and treatment for chronic sinusitis. I have been involved in a number of research efforts that characterize the microbial flora in the sinuses. Initially, culture-based techniques were used and subsequently, non-culture-based techniques. We have assembled a multidisciplinary team and hired Dr. Emily Cope to help develop this area of research. We have created a mouse model of sinusitis and have been able to duplicate the clinical and histologic pattern seen in humans in this model. At this point, we have published a manuscript that outlines our technique and a manuscript has also been published that combines our genetic information on the microbiome with animal and clinical data. In this manuscript, we discuss a new etiology for chronic sinusitis that may lead to interventions for treatment. We presently are submitting a manuscript that proposes categories of sinotypes for sinus infection and begins to delineate pathways for chronicity in sinus infection. The research is unique, and we have been recognized as leaders in the field because of our work.


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.


**Research Support**

P01 HL107202 (Fahy) Co-Investigator 07/01/2019 03/31/2024

Exploring the biology of persistent type 2 airway niches in asthma $1,615,416 total

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

R15 (Cope/Caporaso MPI) Co-Investigator 07/01/2019 06/30/2022

Determining the Role of the Upper and Lower Airway Microbiota as Drivers of Concomitant Inflammatory Responses in patients with Chronic Rhinosinusitis and Asthma. $300,000 total

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

R01 AG062562-01 (Geschwind) Co-Investigator 08/01/2019 07/31/2024

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

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

<table>
<thead>
<tr>
<th>NAME</th>
<th>POSITION TITLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erin Duncan Gordon</td>
<td>Assistant Professor</td>
</tr>
</tbody>
</table>

| eRA COMMONS USER NAME | egordon1                |

## EDUCATION/TRAINING

<table>
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<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>YEAR(s)</th>
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<tbody>
<tr>
<td>University of California, Berkeley</td>
<td>B.A.</td>
<td>05/01</td>
<td>Molecular &amp; Cell Biology</td>
</tr>
<tr>
<td>University of Southern California</td>
<td>M.D.</td>
<td>05/05</td>
<td>Medicine</td>
</tr>
<tr>
<td>University of California, San Diego</td>
<td>Board Cert. in Medicine 2009</td>
<td>07/05-06/07</td>
<td>Internal Medicine</td>
</tr>
<tr>
<td>University of California, San Francisco</td>
<td>Pulmonary 2010 Critical Care 2011</td>
<td>07/07-06/10</td>
<td>Pulmonary &amp; Critical Care</td>
</tr>
</tbody>
</table>

### Positions

- **07/05-06/07**  Resident Physician, Internal Medicine, University of California, San Diego
- **07/07-12/08**  Clinical Fellow, Pulmonary/Critical Care, University of California, San Francisco
- **01/09-06/11**  Research Fellow, Pulmonary/Critical Care, University of California, San Francisco
- **07/11-06/12**  Clinical Instructor, Pulmonary/Critical Care, University of California, San Francisco
- **07/12-06/17**  Assistant Professor, Pulmonary/Critical Care, University of California, San Francisco
- **07/17-Present**  Assistant Professor, Pulmonary/Critical Care, University of California, San Francisco, Sandler Asthma Basic Research Center

### Honors

- Ruth L. Kirschstein National Research Service Award, 01/11.
- American Medical Association Student Achievement Award – first ranked student, Class of 2005 USC SOM (05/05).
- American Medical Women’s Association Janet M. Glasgow Memorial Award – first ranked female student, Class of 2005 USC SOM (05/05).
- Summa cum Laude, Keck School of Medicine, USC (05/2005).
Merck Manual Award – awarded to the four highest ranking students in the basic sciences at USC SOM (05/05).
Alpha Omega Alpha, Gamma Chapter, Keck School of Medicine, USC – elected as a junior (05/04).
Dean’s Scholar – awarded to top 10% of students each year of medical school (May 2002, 2003, 2004, 2005).
Recipient of merit-based full tuition scholarship at Keck School of Medicine, USC (05/01-05/05).
Grace Fimognari Memorial Award – awarded to the highest achieving graduate in Molecular & Cell Biology, Biochemistry, University of California, Berkeley (05/01).
Phi Beta Kappa, University of California, Berkeley (05/01).
Graduate with Honors, University of California, Berkeley – awarded for undergraduate research thesis (05/01).

Professional Societies

American Thoracic Society

Board Certification

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

Contributions to Science

1. IL-33 is a key upstream driver of type 2 inflammation in mouse models of asthma. The biology surrounding its activity as an extracellular cytokine remains unclear however. Full length IL-33 is a nuclear protein produced by the airway epithelial cell, and the mechanism of release is unknown. It has been postulated that release occurs in the context of epithelial cell death; however, cell death is not a prominent feature in most asthmatics including many mild asthmatics that display evidence of airway type 2 inflammation. I have discovered a novel mechanism of IL-33 release from epithelial cells which involves alternative splicing of IL-33 RNA transcripts. Specifically, a deletion of exons 3 and 4 (Δexon 3,4) is the second most abundant IL-33 transcript in the human airway epithelial cell (following the full length transcript). Its protein product is biologically active and localizes to the cell cytoplasm. Upon overexpression, this transcript produces a protein, which is released from the cell in a calcium dependent fashion, distinct from the biology of full length IL-33. Finally, among a cohort of mild-moderate asthmatics, only this Δexon 3,4 transcript variant is positively associated with airway type 2 inflammation, while the full-length IL-33 transcript is not. These findings are described in a manuscript, which was recently published in the Proceedings of the National Academy of Science. I am the first author of this publication; I conceived of the experiments, generated the proteins products of the alternatively spliced transcripts, demonstrated their biological activity in vitro, overexpressed them in primary airway epithelial cells and an airway epithelial cell line, and wrote the manuscript.

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

2. The ST2/IL1RL1 gene is among the most replicated asthma genetic associations documented to date; however, it remains unclear how genetic polymorphisms in this gene confer disease risk and how they relate to the major disease endotype, type 2 high asthma. The IL1RL1 gene produces two gene transcripts from two distinct promoters via alternative splicing. One transcript encodes the membrane bound receptor for IL-33 while the other transcript encodes a soluble receptor, which inhibits IL-33 activity. In mouse models, IL-33 induces airway type 2 inflammation. I discovered two distinct genetic signals in the IL1RL1 gene that are associated with circulating plasma levels of the soluble ST2 protein. However, in circulating blood cells there is no evidence of genetic control of gene expression at these loci. Instead, there is strong genetic control at one locus, rs1420101, of sST2 protein and gene expression in human airway epithelial cells. Moreover, this and another locus rs11685480 both demonstrate strong control over the gene expression of sST2 in distal lung tissue. I further demonstrated that these two independent genetic effects are consistent with the use of different promoters in different cell types. Airway epithelial cells use only the proximal promoter while lung alveolar epithelial cells equally use both the distal and proximal promoters. I have shown that these two SNP blocks demonstrate an additive effect on circulating soluble ST2 levels among asthmatics further suggesting their independent effects. We are currently performing fine mapping using DNA sequencing to narrow down the causative SNP and using Crispr-Cas9 technology to determine the causative SNP in vitro. Finally, I have demonstrated that these two SNPs are associated with the type 2 high asthma endotype. These results are described in a recently published manuscript in Journal of Clinical Investigation Insight. I am the first author of this publication, and I conceived of the study, performed all of the airway epithelial cell culture, sST2 ELISA, sST2 gene expression by Taqman PCR, analyzed the data and wrote the manuscript.


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

3. Asthma is a heterogeneous disease, which is variably heritable within families. While genome wide association studies have been successful in discovering common risk alleles for asthma, only a small portion of the heritability is accounted for by these variants. This has been termed “missing heritability,” and many possible explanations have been proposed to
account for it including rare variants, structural variants such as copy number variation, and genetic risk due to interaction effects. Interaction effects encompass both gene-gene interactions as well as gene-environment interactions and are likely to explain a large majority of this genetic risk; however, they are difficult to capture in traditional epidemiological studies. Because asthma is a heterogeneous disease, with the largest subgroup demonstrating evidence of airway type 2 inflammation, we have explored gene-gene interactions within airway epithelial cells by exposing cells to the type 2 cytokine IL-13. We hypothesize that genetic variants in IL-13 responsive genes account for the variable response of the epithelium to IL-13 stimulation. Specifically, individuals may display varying degrees of tissue remodeling, mucus hyperplasia, airway fibrosis, or eosinophilic or mast cell infiltrates depending on the degree to which the epithelium can orchestrate such responses in the presence of IL-13. In order to examine this type of interaction, I have taken a novel approach by culturing airway epithelial cells from over 140 unique donors at air liquid interface and stimulating these cells with IL-13. I have performed RNA sequencing before and after IL-13 stimulation and DNA SNP arrays on these donors. We find over 2000 significant expression quantitative trait loci (eQTL), many of which are revealed only upon stimulation with IL-13. As proof of the validity of our experimental design, we find strong eQTL for at least nine known asthma genome wide association study loci, including HLA-DQB1, GSDMB, ORMDL3, and TSLP. Moreover, for many of these loci including GSDMB, ORMDL3 and TSLP, no one has demonstrated an eQTL in the airway epithelium, which is the primary site of dysfunction in asthma. We are currently preparing this data for publication this fall.


Research Support

Ongoing Research Support

R01AI136962    Gordon (PI)   01/15/2018-12/31/2022
NIH/NIAID
Understanding the Molecular Genetic Mechanisms of Asthma Risk Loci: IL33, IL1RL1, and GSDMB. The goal of this study is to explore novel genetic mechanisms that influence the development of type 2 inflammation, the most common disease pathology, in asthma.

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

Recently Completed Research Support

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

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

A1077439    Opportunity Fund    Gordon (PI)   09/01/16-08/31/17
NIH-NIAID
Role of Notch Signaling in Mucus Metaplasia in Asthma
The goal of this study is to explore the role of notch signaling in mucus metaplasia in type 2 low asthma.

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

**NAME**  
Matthew Frederick Krummel, Ph.D

**POSITION TITLE**  
Professor

**eRA COMMONS USER NAME**  
Krummel

<table>
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<td>University of Illinois at Champaign-Urbana</td>
<td>B.S.</td>
<td>05/1989</td>
<td>Biology and Chemistry</td>
</tr>
<tr>
<td>University of California at Berkeley</td>
<td>Ph.D.</td>
<td>05/1995</td>
<td>Immunology</td>
</tr>
<tr>
<td>University College, London England</td>
<td>Exchange Student</td>
<td>06/1988</td>
<td>Dept of Chemistry</td>
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</tbody>
</table>

**Positions**

- 2018-Present: Co-founder and Inaugural Chair, UCSF ImmunoX Initiative, UCSF
- 2012-Present: Professor, Department of Pathology, University of California at San Francisco
- 2006-present: Faculty Director, Biological Imaging Development Center, University of California at San Francisco
- 2006-2011: Associate Professor, Department of Pathology, University of California at San Francisco
- 2001-2006: Assistant Professor, Department of Pathology, University of California at San Francisco
- 1997-2001: Postdoctoral Fellow, HHMI, Beckman Institute, Stanford University. Advisor: Dr. Mark M. Davis
- 1996-1997: Postdoctoral Fellow, Dendritic Cell Biology, Walter and Eliza Hall Institute, Melbourne Australia. Advisors: Dr. Bill Heath and Dr. Ken Shortman
- 1995-1996: Postdoctoral Fellow, MCB, UC Berkeley. Advisor: Dr. James P. Allison
- 1989-1995: Graduate Research Assistant, MCB, UC Berkeley. Advisor: Dr. James Allison
- 1988-1988: Stagiare (Technician), UGM, UGM, Institut Pasteur. Advisors: Dr. Julian Davies and Dr. Tom Holt

**Other Experience and Professional Memberships**

- 2002-present: Ad hoc member of study sections, NIH: CMIA (formerly Aly), TTT
- 2003-present: Ad hoc reviewer, Wellcome Trust
- 2004-present: Ad hoc reviewer, US-Israeli Binational Science Foundation
- 2008-2009: Member: Board of Scientific Counselors, NIAID
2008-present  Referee, European Research Council

Honors
2016  Robert E. Smith Endowed Chair in Experimental Pathology
2013  Pediatrics FLAG Mentorship Award, University of California, San Francisco
2009  Fellow of the American Asthma Foundation
2005  Leukemia and Lymphoma Foundation, Career Award
2004  Cancer Research Institute, Investigator Award
down-regulation associated with CTLA-4 signaling
1997  NRSA Postdoctoral Fellowship, National Institutes of Health
1996  Postdoctoral Fellowship, Juvenile Diabetes Foundation International
1989  Luce scholars competition finalist, Henry Luce Foundation
1986  James scholar, University of Illinois
1985  Illinois State Scholar, National Merit scholar, Westinghouse Science Award

Contribution to Science

1.  Direct Imaging of Immune Subversion in Solid Tumors and Identification of Immune Stimulatory
Pathways and Antigen-presenting cells. My laboratory has developed mouse models through
which to study the T cell-APC dynamics within spontaneous tumors in living animals. This has
allowed us to track antigen-presentation pathways and to identify sites and APC subsets involved
in immune subversion. Recently, we used this combined with 11-color flow cytometry to isolate a
rare antigen-presenting cell that is required for T cell mediated tumor rejection and which is
present in most tumors at very low levels.

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

Kaisho, T., Bogunovic, D., Bhardwaj, N., and Krummel, M.F. 2016. Critical Role for
CD103+/CD141+ Dendritic Cells bearing CCR7 for Tumor Antigen Trafficking and Priming
of T cell Immunity in Melanoma. Cancer Cell. PMC in progress.

Kumar R, Rosenblum MD, Alvarado MD, Wolf DM, Bogunovic D, Bhardwaj N,
Daud AI, Ha PK, Ryan WR, Pollack JL, Samad B, Asthana S, Chan V, Krummel
MF. A natural killer-dendritic cell axis defines checkpoint therapy-responsive tumor
microenvironments. Nat Med. 2018 Aug;24(8):1178-1191. doi: 10.1038/s41591-018-
0085-8. Epub 2018 Jun 25. PMID: 29942093

Ruhlman MK, Kersten K, Abushawish MA, Spasic M, Giurintano JP, Chan V, Daud
AI, Ha P, Ye CJ, Roberts EW, Krummel MF. Unleashing Type-2 Dendritic Cells to
Drive Protective Antitumor CD4+ T Cell Immunity. Cell. 2019 Apr 18; 177(3):556-
571.e16. PMID: 30955881

2.  Vital and Intravital Imaging of Immune Responses in the Lung. My laboratory has developed
intravital imaging methods for assessment of immune responses directly in tissues. Using
combinations of custom-built multiphoton microscopes and matched stabilization methods, we
have been able to understand immune responses directly in fully ventilated lungs. This has permitted us to understand normal neutrophil surveillance and the early stages of lung injury. Additionally, it has permitted a direct study of dendritic cell functions in the lungs. This demonstrated direct antigen uptake, across the epithelium, by alveolar but not airway DC. Further, it allowed us to demonstrate that these DC cluster near the reactive airway and re-stimulate T cells there. We’ve applied this method to track myeloid cell differentiation in allergy and recently adapted this to track mast cell probing of vessels in the trachea. We’ve also applied this method to understand nematode interactions with the immune system in the lung.


d. Boldajipour B, Nelson A, Krummel MF. Tumor-infiltrating lymphocytes are dynamically desensitized to antigen but are maintained by homeostatic cytokine. JCI Insight. 2016 Dec 8;1(20): e89289. PMCID:PMC5135268.


3. Dynamic Imaging of Immune Synapse Assembly in vitro and in vivo. My laboratory and I have defined the dynamics of immune synapse assembly, starting with the relationship of TCR and CD4 clustering and centralization to the onset of calcium signaling. We pioneered imaging of the TCR complex visualized in T cells within T cell-zones of vital lymph nodes by multiphoton microscopy. We defined how TCRs could signal while T cells are still moving across the APC surface. And, we’ve defined synaptic assembly between neighboring activating T cells, for the sharing of cytokine signals.


4. Identification of Key Cytoskeletal Regulators of T cell motility and arrest. My laboratory defined the key roles for Myosin IIA in facilitating optimal migration in T cells as well as its phosphorylation as part of the T cell ‘stop’ signal. We also identified the unconventional septin cytoskeleton as a key player in T cell shape and motility. Most recently, we demonstrated that the unconventional Myosin Myo1c is necessary for random turning and thereby provides optimal surveillance strategy for antigen-detection.


5. Identification of CTLA-4 as an Inhibitor of T cell Responses and Modulation to Regulate Immunity In vivo. My work as a graduate student demonstrated that both CD4 and CD8 T cells express a homolog of the costimulatory molecule CD28, CTLA-4, after activation. I generated mouse antibodies to these and demonstrated that engagement of CTLA-4 by antibodies or by its ligand resulted in dampening of T cell responses. I subsequently injected this antibody into mice and demonstrated that this could be used to block this pathway and thus up regulate T cell responses in vivo. This served as a generalized method that we applied across multiple mouse models including augmenting anti-tumor immunity. This work was led to a patent for CTLA-4 blockade in cancer and immunization and has now become ‘Checkpoint Blockade’ Therapy. The FDA approved anti-CTLA-4, also known as Yervoy or ipilulumab, the first FDA approved immunotherapeutic in cancer, in 2011.


Complete List of PubMed-indexed Published Work:
Research support

Ongoing Research Support

R01 AI52116    Krummel (PI).  01/01/18-12/31/22
NIH, Spatiotemporal Control of T Cell Synapse Stabilization and Signaling
The major goals of this project are to analyze MyoIIA regulation during T cell motility and synapse formation. This includes mutational analyses as well as generation and analyses of knockout animals.
Role: PI

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

1R01CA197363 Krummel (PI) 03/15/17-02/28/22
NIH/NCI, Anti-Tumor Mechanisms of Intratumoral Stimulatory Dendritic Cells
The goal of this project is to study the generation and function of rare stimulatory dendritic cell populations in mouse and human tumors, with emphasis on determining the flow of antigens from tumors towards pathways that stimulate T cells.
Role: PI

U01CA217864    Balmain, Krummel, Weiss (PI)  8/17/17-07/31/22
NIH/NCI, Integrating targeted and immunotherapy to treat genetically heterogeneous cancers.
The goal of this project is to perform crispr screens in monocytes and T cells to identify genes associated with tumor entry and function in two distinct tumor types. Will use genetic or pharmacological perturbation of newly generated candidate genes involved in metabolic stress and ros-induced DNA damage to increase mutation load and antigen abundance in a tumor-specific manner, leading to improved responses to IMT. Will also exploit gene expression networks to identify druggable targets and pathways that augment immune responses.
Role: co PI

Consortia of Pharma Companies Krummel (PI) 01/1/2015 - 12/31/2019
UCSF Immunoprofiler. (immunoprofiler.org)
This is funding of consortia of laboratories, initiated by Krummel Lab, for a project designed to profile the immune composition, localization, and gene-expression of hundreds of human tumors from multiple cancer indications. Funds largely drive a UCSF campus-wide clinical project designed to generate a common database of immune profiles.
Role: PI
# BIOGRAPHICAL SKETCH

<table>
<thead>
<tr>
<th>NAME</th>
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</tr>
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<tbody>
<tr>
<td>Richard M. Locksley, M.D.</td>
<td>Sandler Distinguished Professor, Department of Medicine, University of California, San Francisco</td>
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<tr>
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<tr>
<td>Locksley</td>
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## EDUCATION/TRAINING

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<th>INSTITUTION AND LOCATION</th>
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<tbody>
<tr>
<td>University of Rochester, Rochester, NY</td>
<td>M.D.</td>
<td>1976</td>
<td>Medicine</td>
</tr>
<tr>
<td>University of California, San Francisco, CA</td>
<td></td>
<td>1976-80</td>
<td>Resident, Chief Resident Infectious Diseases Fellow</td>
</tr>
<tr>
<td>University of Washington, Seattle, WA</td>
<td></td>
<td>1980-83</td>
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</tbody>
</table>

## Positions and Honors

- **1986-2003** Chief, Division of Infectious Diseases, UCSF Medical Center, San Francisco, CA
- **1988-93** Member and Chair (1991-93), Tropical Medicine and Parasitology Study Section, NIH
- **1991-94** Co-Director, Immunology Section, Biology of Parasitism Course, Woods Hole, MA
- **1994-99** Chair, Parasitology Pathogenesis Committee, WHO, Geneva
- **1995-05** Council, Chair (1998), Midwinter Conference of Immunologists, Asilomar
- **1995-01** Faculty, Association of American Immunology Annual Course, Advanced Immunology
- **1997-** Investigator, Howard Hughes Medical Institute, UCSF
- **1998-01** Member, Chair (2000-01), US-Japan Immunology Board, NIH
- **2002-05** Council, NIAID, National Institutes of Health
- **2003 -** Director, Strategic Asthma Basic Research Center, UCSF
- **2016 -** Member, Albert Lasker Basic Medical Research Awards Jury
- **2017 -** Member, National Advisory Committee, Pew Scholars Program in Biomedical Sciences

## Editorial Boards

- Immunity, Journal Clinical Investigation, Immunology & Cell Biology, Annual Review Immunology
Honors

American Society for Clinical Investigation, 1991; Burroughs Wellcome Fund Scholar in Molecular Parasitology, 1992-97; Fellow, Infectious Diseases Society of American, 1992; Association of American Physicians, 1994; Bailey K Ashford Medal, American Society Tropical Medicine and Hygiene, 1994; Ellison Medical Foundation Senior Scholar in Global Infectious Diseases, 2001-05; Distinguished Service Award, American Association of Immunologists, 2003; Inspirational Teacher Award, UCSF class of 2006; Sandler Distinguished Professorship, 2003; American Academy of Arts & Sciences, 2005; R37 MERIT Award, NIAID/NIH, 2006; Thomson Reuters ‘Top 1% highly cited researchers in immunology’, 2014; 1st William Paul Award for Cytokine Research, International Cytokine & Interferon Society, 2017; Fellow, American Academy of Microbiology, 2017; National Academy of Sciences, 2017; AAI Distinguished Fellow (inaugural class), 2019; University of Rochester School of Medicine, Distinguished Alumnus, 2019.

 Contribution to Science

1. My early contributions contributed to the discovery of T helper subsets, initially using the model of cutaneous leishmaniasis mediated by L. major in susceptible and resistant mice. Th subsets were discovered in studies of mouse T cell clones by Mosmann and Coffman in 1986, and my studies in 1987 were the first to report that disease outcomes in vivo were mediated by disparate types of Th responses. My laboratory also discovered that interventions aimed at discrete cytokines, such as IL-4 and IFN-g, at early time points following infectious challenges, could profoundly affect disease outcome through alterations in Th subset differentiation in situ. These studies were extrapolated to multiple infectious and inflammatory diseases and served to coalesce studies targeting cytokines to alter disease outcomes. I was the PI for all of these contributions.

   
   
   

2. Having established critical roles for cytokines in mediating the business of immunity, my laboratory turned to studies of cytokine expression, reasoning that such study might reveal key pathways by which cytokine expression is turned on, off and regulated. We collaborated with the Rubin laboratory at UC Berkeley to further understanding of what are now called CNSs, or conserved noncoding sequences, which could be identified by sequence comparisons among many species, and which are now known to identify major enhancer,
promoter and boundary elements that regulate cell-specific gene expression. These studies have been extrapolated to understanding major organizational aspects of genetic expression in a variety of cell types, as well as in cancer. I was the PI for all of these studies except for the collaboration with the Rubin laboratory, where I coordinated the immunologic aspects of that study to complement the genetics expertise of the Rubin lab.


3. The regulation of cytokine expression was clearly a key determinant of the immune response, but the field lacked tools to study cytokine expression in situ. To this end, we developed reporter mice that faithfully mimicked cytokine expression in vivo while, through the use of viral IRES elements, leaving the endogenous cytokines themselves intact. These reagents have revolutionized the capacity to study the immune system, which previously relied on isolating cells and re-stimulating in vivo in order to reveal their effector capacity. Key discoveries directly attributable to various strains of these mice include the discrete regulation of the duplicated genes, IL-4 and IL-13, in different types of lymphoid cells, including the production of IL-4 by follicular helper T cells; characterization of a tissue checkpoint mediated by epithelial cytokines important in the regulation of allergic immunity; and the identification of innate lymphoid cells that produce these cytokines (see area 4, below). Mouse strains generated in my laboratory are distributed to Jackson Laboratories for use by the scientific community, where they have been utilized in many publications. The strategy we introduced is now widely used in the scientific community. I was PI for all of these contributions.


4. The ability to identify cytokine-producing cells in vivo allowed us to identify Group 2 innate lymphoid cells, or ILC2s, as innate lymphocytes that are located in tissues, where they contribute to early cytokine responses. We were one of three laboratories to call attention to the key role for these cells during biologic responses in vivo in 2010, and uncovered roles for these cells in migratory helminth infection and allergic challenge. My laboratory has investigated the development of these cells during embryogenesis, and their tissue-specific transcriptomic signatures using single-cell RNAseq. This continues to be a rapidly advancing field with implications for the understanding of tissue homeostasis and allergic immunopathology, including in human disease. I was the PI for all of the primary studies and took part in the nomenclature meetings chaired by Dr. Spits for the scientific community.


5. The discovery of ILC2s that expressed type 2 cytokines in situ generated questions regarding upstream activation signals and downstream targets of effector output from these cells. These approaches have revealed unsuspected circuits by which ILC2s communicate with epithelial cells in different organs to sustain homeostasis. In lung, ILC2 output elevates chitinase production by a subset of epithelial club cells to enhance degradation of non-soluble chitin fragments from the environment; mice without epithelial chitinase develop spontaneous accumulation of chitin fragments and, over time, lung fibrosis. In small intestine, we discovered that epithelial tuft cells are the source of IL-25, which is released in response to luminal succinate generated by protozoan protist fermentation. IL-25 activates ILC2s to alter crypt stem cell outputs to increase secretory cells, including goblet cells and tuft cells, thus explaining the intestinal remodeling induced by these organisms. I was PI for all of these studies.


d. Schneider C, CE O’Leary, J von Moltke, HE Liang, Q Yan Ang, PJ Turnbaugh, S Radhakrishnan, M Pellizzon, A Ma, RM Locksley. 2018. A metabolite-triggered tuft...


**Research Support**

Howard Hughes Medical Institute 09/01/97-08/31/25 (budgeted annually)

*Activation of Immunity*

The goals of this project are to uncover new strategies to optimize host defense and tissue preservation in response to immunopathologic responses to infectious, allergic and inflammatory challenges. HHMI support is critical in generating and maintaining mouse strains necessary for these studies. Support from HHMI pays Dr. Locksley’s salary.

Role: PI

R01 AI026918 Locksley (PI) 05/01/18-04/30/23
Parasite immunity orchestrated by type 2 immune cells
The goals of this grant are to explore the mechanisms driving the tuft cell – ILC2 circuit in the intestinal tract in response to luminal parasitic infection, with emphasis on metabolic and dietary effects on microbiota.

P01 HL107202 Fahy (PI) 09/19-08/24
Exploiting crosstalk between tuft cells and group 2 ILC2s for tissue homeostasis and disease
Role: PI, Project 1; Innate type 2 cells and tuft cells in allergic lung disease
The goals of this grant are to define characteristics of epigenetically altered sites where allergic pathologies recur in patients and animal models of allergic upper airways disease.

T291P0554 Fraser (PI); Locksley – collaborator 09/19-08/21
University of California Tobacco-Related Disease Research Program/High Impact Pilot Program
Engineered proteins to reverse chitin buildup and fibrotic lung disease
The goals of this project are to optimize chitinolytic activity of AMCase in order to accelerate the capacity for chitin breakdown in lung tissue.

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

**Completed Research Support**

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

NAME
Ari Benjamin Molofsky, M.D., Ph.D.

POSITION TITLE
Assistant Professor, Department of Laboratory Medicine, University of California, San Francisco

eRA COMMONS USER NAME
ARIBMOLOSKY

EDUCATION/TRAINING

INSTITUTION AND LOCATION | DEGREE | YEAR(s) | FIELD OF STUDY
--- | --- | --- | ---
University of Texas, Austin | B.S. | 05/1999 | Molecular Biology
University of Michigan, Ann Arbor | M.D./Ph.D. | 05/2007 | Medicine/ Microbiology Immunology
University of California, San Francisco | Resident/Chief Resident | 2007-2011 | Laboratory Medicine
University of California, San Francisco | Clinical Fellow | 2009-2010 | Hematopathology,
University of California, San Francisco | Postdoctoral Fellow | 2011-2015 | Immunology

Positions and Employment

1997-1999 Undergrad Research Fellow, Lab of Janice Fischer, PhD, Developmental Genetics, University of Texas
1999-2007 Medical Scientist Training Program (MSTP), director Ron Koenig MD PhD, University of Michigan
2001-2005 Graduate Student, Lab of Michele S. Swanson, PhD, University of Michigan Micro/Immunology
2007-2009 Laboratory Medicine Resident/Chief Resident, Dept. Chair Clifford Lowell MD PhD, UCSF
2009-2010 Clinical Fellow, Hematopathology, program director Joan Etzell, MD, UCSF
2010-2011 Laboratory Medicine Resident, 3rd year, Dept. Chair Clifford Lowell MD PhD, UCSF
2011-2015 Research Fellow (80% time), Lab of Richard M. Locksley, MD, HHMI, UCSF
2011-2013 Clinical Instructor (20% time), Hematology Section, Dept. of Laboratory Medicine, UCSF
2013-2015 Assistant Adjunct Professor (20% time), Hematology Section, Dept. of Lab Medicine, UCSF
2015- Assistant Professor in Residence, Department of Laboratory Medicine, UCSF
2015- Affiliate Professor, Diabetes Center, UCSF
2018- Associate Professor in line, Dept of Laboratory Medicine

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Honors/Awards

1995-1999 National Merit Finalist Scholarship, U. of Texas
1997 Fellowship, Howard Hughes Molecular Biology Summer Research, U. of Texas
1998-1999 Undergraduate Research Fellowship Award, U. of Texas
1999 The Dean’s Honored Graduate in Molecular Biology, U. of Texas
2002-2004 Predoctoral Fellowship, Genetics Training Grant, U. of Michigan
2004-2005 Frederick G. Novy Fellowship, Microbiology & Immunology, U. of Michigan
2006 Rackham Distinguished Dissertation Award Nominee, U. of Michigan
2006 Ward J. MacNeal Distinguished Dissertation Award, Microbiology/Immunology
2006 Alpha Omega Alpha (AOA) Medical Honors Society, U. of Michigan
2007 MD, graduate with research distinction, U. of Michigan
2009-2012 Molecular Medicine Research Fellowship, UCSF
2014 Mentored Clinical Scientist Research Career Development Award (K08)
2016-2019 Larry L. Hillblom Foundation Junior Investigator Award
2017 American Association of Immunology, Travel Award
2017 New Frontiers Research Awardee, UCSF Program for Breakthrough Biomedical Research
2017 Milstein Young Investigator, International Cytokine & Interferon Society
2019 Nina Ireland Progra for Lung Health Award

Professional Societies

2001-2003 MSTP Program Activities Committee, Recruiting Coordinator, U of Michigan
2007- College of American Pathologists, Member
2008- American Society of Hematology (ASH), Member
2009- Board licensed physician and surgeon, Medical Board of California
2011- American Association of Immunologists (AAI), Member
2012- International Clinical Cytometry Society, Member
2016- International Cytokine and Interferon Society, Member

Contribution to Science

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


2. We aim to understand how innate immune cells and cytokines control normal central nervous system (CNS) development and go awry in neuropsychiatric disease. In collaboration with the Anna Molofsky lab, we have defined a novel circuit where astrocyte-derived IL-33 promotes microglial activation and neuronal synapse engulfment during CNS development. Our ongoing work aims to define how meningeal-resident lymphocytes, including group 2 innate lymphoid cells, impact CNS glia and neural circuit formation during brain development.


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


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


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


5. As a Clinical Pathologist and Hematopathologist, my clinical work focuses on diagnosing benign and neoplastic disorders of blood and immune cells. In the clinical arena, I have a limited but active role in teaching and clinical research, publishing several case reports and reviews. I have a particular interest in the use of flow cytometry in benign and neoplastic hematology.


D. Additional Information: Research Support and/or Scholastic Performance
Ongoing Research Support

R01 NIH/NHLBI (Molofsky, PI) 9/1/2019 – 8/31/2023
Defining group 2 innate lymphoid cell lung niches.
The major goal of this five-year R01 is to define the micro-anatomic niches of mouse lung ILC2, including their development, regulation, and response to infections.

Tobacco Related Disease Research Program (Molofsky, PI) 11/1/2019 – 10/31/2022
Regulation of lung type 2 immunity in tobacco smoke-related allergic asthma
The major goal of this grant is to define the impact of tobacco smoke on lung type 2 immune niches in mouse models of allergic asthma.

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

Nina Ireland Program for Lung Health (Molofsky, PI) 1/2019 – 12/2020
Defining lung lymphocyte niches in humans.
The major goal of this pilot grant is to develop 3D imaging techniques for normal human lungs and begin to define human lung lymphocyte and stromal cell niches.

Liver Center Pilot Grant (Molofsky, PI) 3/2019-2/2020
Defining liver type 2 lymphocyte niches with 3D imaging
The major goal of this pilot grant is to define the localization and stromal interactions of liver group 2 innate lymphoid cells at rest and during models of NASH and fibrosis.

Completed Research Support

R56HL142701-01 NIH/NHLBI (Molofsky, PI) 9/1/2018 – 8/31/2019
Defining group 2 innate lymphoid cell lung niches.
The major goal of this one-year ‘bridge’ grant is to continue to generate preliminary and supporting data testing our hypothesis that lung ILC2 engage in a cross-talk with adventitial stromal cells that regulate their development and function.
BIOGRAPHICAL SKETCH

NAME
Steven D. Pletcher

POSITION TITLE
Associate Professor: Otolaryngology – Head and Neck Surgery

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

EDUCATION/TRAINING

<table>
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<td>Massachusetts Eye and Ear Infirmary, Boston</td>
<td>Fellow</td>
<td>06/06</td>
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<tr>
<td>University of California, San Francisco</td>
<td>Resident</td>
<td>06/05</td>
<td>Otolaryngology-Head and Neck Surgery</td>
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<td>University of California, San Francisco</td>
<td>Intern</td>
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<td>University of California, Los Angeles School of Medicine</td>
<td>MD</td>
<td>06/00</td>
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<tr>
<td>Yale University, New Haven CT</td>
<td>BS</td>
<td>06/95</td>
<td>Cum Laude, Molecular Biochemistry and Physics</td>
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Positions and Honors

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

Other Experience and Professional Memberships

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

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

Contribution to Science

1. The majority of my current research effort focuses on the role of the sinus microbiome in chronic rhinosinusitis. Our research group produced one of the first major papers in this area with a variety of critical findings:
   1) Diverse microbial communities are present in the sinuses of healthy patients,
   2) CRS is associated with a loss of microbial diversity, but not an increased microbial burden
   3) A newly identified microbial pathogen (C. tuberculostearicum) produces inflammation consistent with sinusitis when introduced into the murine nasal cavity
   4) Development of murine sinonasal inflammation is accelerated when the native microbiome is perturbed through antibiotic treatment
   5) Co-instillation of a commensal microbe (L sakeii) prevents C. tuberculostearicum induced inflammatory changes

Since publication of this 2012 paper, we have investigated the biogeography of microbial communities, fungal contributions to the sinus microbiome, dominant pathogenic species within the sinus microbiome of CRS patients, and continued to develop our mouse model for evaluation of microbial communities in sinusitis. These investigations have resulted in 2 publications currently under review and are multiple manuscripts in preparation.

Prior to and concomitant with this line of research I have led studies related to rheologic properties of sinonasal mucus and novel steroid deposition methods for treatment of CRS with nasal polyposis.

Research Support

On-going Research Support

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

Completed Research Support

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

NAME
Dean Sheppard
POSITION TITLE
Professor of Medicine
eRA COMMONS USER NAME
sheppard

EDUCATION/TRAINING

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
</tr>
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<tr>
<td>Harvard College, Cambridge, MA</td>
<td>AB</td>
<td>6/72</td>
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<tr>
<td>SUNY at Stony Brook, Stony Brook, NY</td>
<td>MD</td>
<td>6/75</td>
<td>Medicine</td>
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<tr>
<td>University of Washington, Seattle, WA</td>
<td>Resident</td>
<td>7/75-6/78</td>
<td>Internal Medicine</td>
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<tr>
<td>University of California, San Francisco, San</td>
<td>Fellow</td>
<td>7/78-6/81</td>
<td>Pulmonary</td>
</tr>
</tbody>
</table>

Positions

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

Other Experience

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

Honors and Awards

Elected member, American Society for Clinical Investigation, 1992
Elected member, Association of American Physicians, 1995
Clean Air Award, American Lung Association of California, 1995
Parker B. Francis Lecturer, Aspen Lung Conference, 1996
Lifetime Scientific Achievement Award, American Thoracic Society, 1998
Jerome I. Flance Visiting Professor, Washington University, 2000
Roger Mitchell Lecturer, Aspen Lung Conference, 2001
NIH Merit Award, 2004-2014
Robert Johnston Lecturer, Drexel University, 2005
McClement Lecturer, New York University, 2006
Kass Medal, University of Nebraska, 2007
Amberson Lecturer, American Thoracic Society, 2010
McClenann Lecturer, University of Iowa, 2012
Frank Austen Visiting Professor, Brigham and Woman’s Hospital, 2013
Listed as one of top 20 translational scientists in the world by Nature Biotechnology, 2013
Harold and Marilyn Menkes Memorial Lectureship, Johns Hopkins University, 2014
UCSF Faculty Lecture, Translational Science, 2016
Elected Member, American Academy of Arts and Sciences, 2017

Contribution to Science

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


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.


3. To better understand the in vivo relevance of members of the integrin family we had identified, my lab generated integrin subunit knockout mice and used the phenotypes we identified in those mice to identify novel integrin ligands and molecular pathways upstream and downstream of these integrins that contribute to development and disease. Through these studies we identified a completely unexpected role for integrins in activating latent TGFβ and showed that this pathway is important, though distinct effects on different responding cells, in experimental models of pulmonary fibrosis, emphysema, acute lung injury, allergic asthma and in modulating immune responses to tumors. These studies have stimulated substantial interest in potential anti-integrin therapeutics, including one humanized monoclonal antibody generated based on work in my lab that is now in phase 2 clinical trials for potential treatment of idiopathic pulmonary fibrosis and antibodies and small molecule inhibitors we have developed targeting the αβ8, αβ5, αβ1 and αβ1 integrins that are in various stages of clinical development for treatment of severe asthma, fibrotic diseases, acute lung injury and for tumor immunotherapy.


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


A full listing of my publications is available at:
http://profiles.ucsf.edu/dean.sheppard

**Research Support**

RO1 HL145037 (Sheppard) 1/15/2019-12/31/2022
NIH/NHLBI
Interventional Targeting of the IRE1alpha-TGFbeta signaling loop in pulmonary fibrosis
Role: Co-PI, Contact PI
Overall project goal – Determining the mechanisms of cross talk between the unfolded protein response and TGFbeta activation and signaling that drives pulmonary fibrosis
Sponsored Research Agreement (Sheppard)  
08/01/2014- 07/31/2020  
AbbVie  
Characterizing molecular diversity of renal and hepatic fibroblasts in the setting of tissue fibrosis  
Overall project goal: Discovery of novel biomarkers and therapeutic targets for hepatic fibrosis from single cell RNAseq  

UCSF Pfizer CTI Program (Sheppard).  
12/07/2012-11/30/2019  
Pfizer, Inc  
Targeting the αvβ8 integrin for tumor immunotherapy  
Overall project goal: The goal of this proposal is to develop humanized monoclonal antibodies to the αvβ8 integrin for immunotherapy of human tumors. This project with Pfizer is focused on developing a clinical candidate and not on the basic biology underlying the effects of αvβ8 in tumors, which is the focus of the current proposal  

T32 HL007185 (Sheppard)  
07/01/2012–06/30/2022  
NIH/NHLBI  
Multidisciplinary training program in lung disease  
Role: Program Co-PI  
Overall project goal: This is a training grant to train future leaders in basic, clinical and translational pulmonary science. There are 13 annual training slots on this grant.
**BIOGRAPHICAL SKETCH**

<table>
<thead>
<tr>
<th>NAME</th>
<th>POSITION TITLE</th>
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<tbody>
<tr>
<td>Jeoung-Sook Shin, Ph.D.</td>
<td>Associate Professor</td>
</tr>
</tbody>
</table>

| eRA COMMONS USER NAME | SHINJS |

### EDUCATION/TRAINING

<table>
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<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
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<tr>
<td>Duke University, Durham, NC</td>
<td>Ph.D.</td>
<td>5/2002</td>
<td>Pathology</td>
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<tr>
<td>Duke University, Durham, NC</td>
<td>Postdoctoral</td>
<td>8/2003</td>
<td>Pathology</td>
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<tr>
<td>Yale University, New Haven, CT</td>
<td>Postdoctoral</td>
<td>1/2008</td>
<td>Cell Biology</td>
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</table>

### Professional Positions

- **1996** Research Associate, Cheong-Am Biotech, Seoul, Korea
- **2008-2014** Assistant Professor, University of California San Francisco, Dept. of Microbiology, Immunology & Sandler Asthma Basic Research Center
- **2014-present** Associate Professor, University of California San Francisco, Dept. of Microbiology, Immunology & Sandler Asthma Basic Research Center

### Professional Memberships

- **2008-2009** American Thoracic Society, member
- **2010-Present** American Association of Immunologists, member
- **2008-Present** Adhoc reviewer for Journal of Cell Biology, Journal of Experimental Medicine, PNAS, European Journal of Immunology, ACS Chemical Biology, The Wellcome Trust Research Training Fellowship Program, and KSEA Young Investigator Award
- **2017** NIH study section ZRG1 IMM-T90
- **2017-Present** Treasurer, Association of Korean Immunologists in America
- **2019** NIH study section ZRG1 F70-U20
- **2019** NIH study section ZRG1 IMM-T57

### Honors and Awards

- **1999** The Best Research Student Award in the Department of Pathology, 9th Graduate Student Symposium, Duke University
- **2004** The Jane Coffin Childs Memorial Fund Research Fellowship Award
- **2009** Sandler Innovative Award in Asthma Research, Sandler Asthma Basic Research Center
Contribution to Science

1. Role of MARCH1 in dendritic cell and B cell function

Although MARCH1 mediates ubiquitination and endocytosis of MHCII and CD86 in antigen presenting cells, its functional role was unclear. We found that this ubiquitin ligase plays an important role in dendritic cell selection of regulatory T cells. The mechanism involved MARCH1-dependent ubiquitination of MHCII, which was required for thymic dendritic cells to preserve functional integrity of the plasma membrane microdomain that facilitates activation of engaged thymocytes. We also found that MARCH1-dependent MHCII ubiquitination is required for germinal center B cells to effectively exchange MHCII-loaded peptide and mature into high-affinity antibody producing cells. I served as the primary investigator, co-investigator, or principle investigator in these studies.


2. Ubiquitination of MHCII and CD86

It is well known that dendritic cells regulate the surface expression of MHCII during maturation, however its molecular mechanism has been elusive. My colleagues and I found that MHCII is ubiquitinated in dendritic cells, this ubiquitination mediates MHCII endocytosis and lysosomal degradation controlling the surface level of MHCII, and the ubiquitination is down-regulated during maturation of dendritic cells resulting in the accumulation of MHCII at cell surface. More recently, we found that MHCII ubiquitination plays a significant role for dendritic cells to mediate regulatory T cell development in the thymus. This finding results in a significantly improved...
understanding of the functional role of MHCII ubiquitination. It also reveals a significant contribution of dendritic cells to regulatory T cell development and the underlying mechanism. I served as the primary investigator, co-investigator, or principle investigator in all these studies.


3. Endocytosis of FcεRI in dendritic cells

The expression of the high affinity IgE receptor in human dendritic cells has been known for more than two decades, but its functional role is not clearly understood. My colleagues and I found that this receptor mediates cellular entry and degradation of circulating IgE, thus promoting serum IgE clearance. We also found that this pathway of IgE entry results in dendritic cell presentation of IgE-bound antigens to naïve T cells and that this presentation results in development of antigen-specific T cell tolerance. These findings reveal the functional role of the IgE receptor expressed in DCs and also suggest that this receptor could be therapeutically targeted to develop tolerance to disease-causing allergens or auto-antigens. I served as the principle investigator in these studies.


4. Endocytosis mediated by caveolae and lipid raft

Caveolae and lipid raft have been known as the endocytic membrane domain that mammalian cells utilize to take up nutrients from outside. However, whether this domain could be exploited by microbes for host invasion had not been known. My colleagues and I found that the fimbriated uropathogenic *E. coli* exploits this membrane domain to enter mouse mast cells and epithelial cells and reside in a compartment protected from proteolytic degradation. These findings prompted other investigators in the field, resulting in a series of findings that caveolae and lipid raft are utilized by a broad array of microbes including virus and parasite to invade various types of host cells. I served as the primary investigator or co-investigator in this study as shown below.


Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/1zW5inwS0Ljkk/bibliography/46542569/public/?sort=date&direction=ascending

Research Support

Ongoing Research Support
R35GM131702, National Institute of Health. 06/01/2019 - 03/31/2024
Shin, Jeoung-Sook (PI)
Mechanism and function of membrane trafficking in dendritic cells
The goal of this project is to define the molecular mechanism underlying MARCH1 ubiquitin ligase activity and identify new substrates of MARCH1.

Completed Research Support During Last Three Years
R01GM105800, National Institute of Health. 09/05/2013 - 05/31/2019
Shin, Jeoung-Sook (PI)
Role of MARCH1 E3 ubiquitin ligase in thymic dendritic cell function
The major goal of this project is to identify the specific molecular mechanisms by which dendritic cells mediate clonal deletion and regulatory T cell differentiation in the thymus.

W81XWH1810110, Department of Defense. 06/01/2018 – 11/30/2019
Shin, Jeoung-Sook (PI)
Assessing the candidacy of MARCH1 as a therapeutic target for treatment of asthma
The goals of this project are to determine the role of MARCH1 in the effectuation phase of allergic asthma and identify the specific motif of mouse CD83 transmembrane domain that binds to MARCH1.

NIH/NCATS UL1TR001872-A127552, National Institute of Health. 02/01/2017 – 05/31/2018
Shin, Jeoung-Sook (PI)
Development of a small molecule inhibitor of MARCH1 for treatment of asthma
The goal of this project is to develop tool compounds to be used for the validation of the hypothesis that asthma is improved by inhibiting MARCH1.
# BIOGRAPHICAL SKETCH

<table>
<thead>
<tr>
<th>NAME</th>
<th>POSITION TITLE</th>
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</thead>
<tbody>
<tr>
<td>Aparna Bala Sundaram</td>
<td>Assistant Professor of Medicine</td>
</tr>
<tr>
<td>eRA COMMONS USER NAME</td>
<td>Division of Pulmonary &amp; Critical Care Medicine</td>
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<td>Department of Medicine</td>
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## EDUCATION/TRAINING

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<tr>
<td>Northwestern University, Evanston IL</td>
<td>BS</td>
<td>06/03</td>
<td>Biomedical Engineering, Honors Program in Medical Education</td>
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<tr>
<td>Northwestern University, Chicago IL</td>
<td>MD</td>
<td>06/06</td>
<td>Medicine</td>
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<tr>
<td>Northwestern University, Chicago IL</td>
<td>n/a</td>
<td>06/09</td>
<td>Internal Medicine</td>
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<tr>
<td>University of California, San Francisco CA</td>
<td>n/a</td>
<td>06/12</td>
<td>Pulmonary &amp; Critical Care Medicine</td>
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## Positions and Employment

- **2006-2007** Intern, Internal Medicine, Northwestern University
- **2007-2009** Resident, Internal Medicine, Northwestern University
- **2009-2012** Fellow, Pulmonary and Critical Care Medicine, UCSF
- **2012-2014** Clinical Instructor, Division of Pulmonary and Critical Care Medicine, UCSF
- **2014-present** Assistant Professor of Medicine, Division of Pulmonary and Critical Care Medicine, UCSF
- **2020-present** Associate Program Director, Molecular Medicine Pathway, Internal Medicine Residency, UCSF

## Other Experience

- **2016-present** Scientific Reviewer, Resource Allocation Program Technology Committee UCSF
- **2016-present** Member, Chancellor’s Committee on the Status of Women, UCSF

## Honors

- **1999-2003** National Merit Scholarship
- **1999-2006** Honors Program in Medical Education, Northwestern University
- **2006-2009** Resident Teaching Award, Northwestern University
- **2009-present** American Board of Internal Medicine for Internal Medicine Certification
- **2011-present** American Board of Internal Medicine for Pulmonary Diseases Certification
- **2012-present** American Board of Internal Medicine for Critical Care Medicine Certification
Professional Societies

2007-present Member of American Thoracic Society, Respiratory Cell & Molecular Biology Assembly Member

Contributions to Science

I began my research training studying the effect of integrin β6 subunit knockout mice on experimental models of allergic asthma. Integrin β6 plays an important role in activating latent TGFβ, and mice lacking integrin β6 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.


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.


(*shared first author)


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 α5β1. This novel therapeutic approach to reduce airway contraction by inhibiting cellular tethering to the matrix enhances the effect of currently available bronchodilators, and has led to the filing of two patents and further collaborations with investigators in the chemistry department to continue pre-clinical studies for integrin α5β1 as well as other integrins and cadherins that I have identified with therapeutic potential.


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

**Research Support**

**Ongoing**

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

UCSF Resource Allocation Program (RAP) Catalyst Award (co-PI). 2018 – 2020
UCSF/ShangPharma
The major goal of this project is to design and screen more potent and specific small molecule inhibitors of integrin alpha2 beta1.
Recently Completed

T32 HL 7185-34  2009 – 2012
NIH/NHLBI
This is a training grant provided to the University of California, San Francisco during the fellowship training period in the Division of Pulmonary and Critical Care Medicine.

F32 HL112588-01 (PI)  2012 – 2014
NIH/NHLBI
Regulation of Allergic Asthma by TGF-β-induced Modulation of mMCP-1 and mMCP-4
The major goals of this project are: To determine whether mMCP-1 and mMCP-4 modulate airway hyperreactivity 1) through effects on the adjacent epithelium or through direct effects on smooth muscle cells and 2) whether their effect is upstream or downstream of changes in intracellular calcium concentration.

5U19 AI070412-09 ESI (PI)  2014-2015
NIH/NIAID
Role of Human Chymase in Smooth Muscle Contraction
This early stage investigator award is dedicated to studying the convergence of pathways between chymase and integrin ligation in smooth muscle modulation of airway contraction and allergen challenge.

Resource Allocation Program (RAP) Shared Instrument Award (PI)  2016-2017
UCSF
Funding to purchase new muscle bath system to serve as a core for measurement of contractility with capacity for higher throughput screening.

Nina Ireland Program for Lung Health, Innovative Grant Program (PI)  2017-2019
UCSF
Investigating the mechanisms of smooth muscle tension transmission via cell-matrix and cell-cell connections.
BIOGRAPHICAL SKETCH

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

POSITION TITLE
Research Specialist

eRA COMMONS USER NAME

EDUCATION/TRAINING

<table>
<thead>
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<tr>
<td>Xian Medical University, Xian, China</td>
<td>M.D.</td>
<td>12/82</td>
<td>Medicine</td>
</tr>
<tr>
<td>Xian Medical University, Xian, China</td>
<td>M.S.</td>
<td>12/85</td>
<td>Immunology</td>
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</tbody>
</table>

Positions and Honors

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

Selected Peer-reviewed Publications


BIOGRAPHICAL SKETCH

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

POSITION TITLE
Professor of Medicine and of Microbiology and Immunology

eRA COMMONS USER NAME
weissa

EDUCATION/TRAINING

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<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
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<th>FIELD OF STUDY</th>
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<tr>
<td>John Hopkins University, Baltimore</td>
<td>B.A.</td>
<td>05/1973</td>
<td>Biology</td>
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<tr>
<td>University of Chicago</td>
<td>Ph.D.</td>
<td>05/1978</td>
<td>Immunology</td>
</tr>
<tr>
<td>University of Chicago</td>
<td>M.D.</td>
<td>05/1979</td>
<td>Medicine</td>
</tr>
</tbody>
</table>

Positions and Employment

1979-1980 Postdoctoral Fellow, Swiss Institute for Experimental Cancer Research, Lausanne, Switzerland
1980-1982 Resident, Department of Medicine, University of California, San Francisco (UCSF)
1982-1984 Fellow in Rheumatology/Clinical Immunology, UCSF
1982-1985 Associate, Howard Hughes Medical Institute, UCSF
1984-1985 Instructor, Department of Medicine, Division of Rheumatology/Clinical Immunology, UCSF
1985-1989 Assistant Investigator, Howard Hughes Medical Institute, UCSF
1985-1989 Assistant Professor of Medicine, Microbiology and Immunology, UCSF
1987- Chief, Division of Rheumatology/ Clinical Immunology, Department of Medicine, University of California, San Francisco
1989-1993 Associate Professor or Medicine, Microbiology and Immunology, UCSF
1989-1994 Associate Investigator, Howard Hughes Medical Institute, UCSF
1991- Ephraim P. Engleman Distinguished Professor of Rheumatology, UCSF
1992- Professor of Medicine, Microbiology and Immunology, UCSF
1993- Investigator, Howard Hughes Medical Institute, UCSF
1998-2005 Associate Director, The Rosalind Russell Medical Research Center for Arthritis, UCSF
2002-2006 Director, Medical Scientist Training Program (MSTP), UCSF
2007-2010 Co-Director, Institute for Molecular Medicine, UCSF

Other Experience and Professional Memberships

1986-1991 Councilor, American Federation for Clinical Research
1991 President, Western Region of the American College of Rheumatology
1998-2002 Member, Allergy and Immunology Study Section (NIH)
1999-2011 Chair, Scientific Advisory Board, American Asthma Foundation
2000-2002 Chair, Allergy and Immunology Study Section (NIH)
2003-2010 Council, American Association of Immunologists
2008-2009 President, American Association of Immunologists
2005-2012 Advisory Council, RIKEN Research Center for Allergy & Immunology
   Yokohama, Japan
2013- Chair, Section 43 (Immunology and Inflammation), National Academy of Sciences

Honors
1990 Young Investigator Award, Western Society for Clinical Investigation
1990 Henry Kunkel Young Investigator Award, American College of Rheumatology
1993 Junior Investigator Award, American Association of Immunologists
1997 Lee C. Howley Prize, Arthritis Foundation
1998 Forty-First Faculty Research Lecturer, University of California, San Francisco
2001 American Association of Immunologist-Huang Foundation Meritorious Career Award
2003 Fellow, American Academy of Arts and Sciences
2004 Member, National Academy of Sciences
2004 Fellow, American Academy of Microbiology
2004 Member, Institute of Medicine
2004 Distinguished Investigator Award, American College of Rheumatology
2004 Walter Bauer Visiting Professor in Rheumatology, Massachusetts General Hospital
2004 Bridget Ogilvie Lecture, University of Dundee, Scotland
2004 Sue Kim Hansen Lecture, Boston University School of Medicine
2005 Dan H. Campbell Memorial Lecture, Midwinter Conference of Immunologists, Asilomar, CA
2005 Visiting Professor, Harvard Medical School Rheumatology Division
2005 Beirne B. Carter Lecture in Immunology, University of Virginia
2005 Dan H. Campbell Memorial Lecture, Midwinter Conference of Immunologists, Asilomar, CA
2006 Keynote Speaker, American Association of Immunologists, Advanced Immunology Course
2009 Ishizaka Lecture, La Jolla Institute for Allergy and Immunology
2009 46th Charles A. Stuart Memorial Lecture, Brown University
2010 Dorothy Baugh Harmon Endowed Lectureship, Oklahoma Medical Research Foundation
2012 Lifetime Achievement Award, American Association of Immunologists
2012 UCSF Lifetime Achievement in Mentoring Award
2014 Nathan Zwaifler Lecturer, UCSD
2016 Frank and Shirley Fitch Lecture, University of Chicago
2016 Merit Award, NIAID, NIH
2016 Ephraim P. Engleman Memorial Lecture, American College of Rheumatology
2017 Associate Member, European Molecular Biology Organization
2018 Howard and Martha Holley Research Prize in Rheumatology
2019 AAI Distinguished Fellow, American Association of Immunologists
2019 William B. Coley Award for Distinguished Research in Basic Immunology, Cancer Research Inst.
2019 Establishment of the Arthur Weiss Lectureship in Rheumatology and Immunology, UCSF
Contribution to Science

1. The Oligomeric TCR Complex. The T cell antigen receptor (TCR) was identified by others during my postdoctoral studies. As a postdoctoral fellow and junior faculty member I focused on the oligomeric complexity of the TCR. Taking advantage of the Jurkat T cell leukemic line as an experimental model, I used somatic cell genetics to show, in collaborative studies with Tak Mak’s group, that the TCR αβ heterodimer had a requisite association with the CD3 complex for cell surface expression. My group first showed the transmembrane domains as the basis for the interaction of the αβ heterodimer with CD3. This led us to show that the zeta chain cytoplasmic domain, when transferred to another heterologous receptor (CD8), could confer upon that receptor the signaling capability of the TCR. The latter experiment was the inspiration for chimeric antigen receptors that are currently used in cell-based tumor immunotherapy.

d. Irving BA. Weiss A. The cytoplasmic domain of the T cell receptor ζ chain is sufficient to couple to receptor-associated signal transduction pathways. *Cell* 1991. 64:891-901.

2. The Two Signals Required for T cell Activation. In the early 1980's little was known about the signaling events that were required for T cells to become activated. Using the Jurkat leukemic T cell line, while a postdoc in the Stobo lab, I showed that two signals were required for IL-2 transcription. One signal was provided by the TCR and the other by a second signal which could be mimicked by phorbol esters, which at that time were known to activate PKC. Using a calcium sensitive dye, John Imboden and I showed that stimulation of the TCR/CD3 complex in Jurkat could induce calcium increases and calcium ionophores and phorbol esters could mimic the two signals required for IL-2 transcription. This led us to search for physiologic stimuli that could provide the second signal required for IL-2 production. We found that mAbs against Tp44, later named CD28, as a molecule that could provide the second signal for Jurkat or for normal human T cell activation. We identified a region in the IL-2 upstream regulatory region that was responsive to CD28 signals, distinguishing it from typical NFAT sites that were responsive to TCR signals. This CD28 response element proved to be a composite binding site for c-Rel and AP-1.


3. The Tyrosine Kinases that Initiate TCR Signaling. The mechanism by which the TCR signaled to increase calcium was unknown. Some speculated that G-proteins were involved and some that tyrosine phosphorylation was involved. We took a somatic cell genetic approach and isolated TCR signaling mutants from the Jurkat T cell leukemic line. The first of these, J. CaM1 proved to be deficient in the Src family kinase Lck. At the same time, we attempted to understand how the TCR zeta chain mediated a signal via a conserved motif ultimately called the immunoreceptor tyrosine-based activation motif (ITAM). We found that stimulated zeta interacted with a 70 kDa tyrosine phosphoprotein, which we purified and cloned as ZAP-70. The importance of ZAP-70 has been substantiated by the severe combined
immunodeficiency that results from inactivating mutations. This led us to develop a model for TCR signaling whereby Lck and ZAP-70 interacted with ITAMs in a sequential and ordered manner. This model has withstood more than 20 years of subsequent investigation.

4. TCR Signaling Mechanisms. The consequences of TCR signaling by the proximal kinases demanded the identification of key substrates and the pathways they activated. We were among the first to show that TCR stimulation led to phosphorylation of phospholipase C gamma1 (PLCγ1), providing a mechanism for TCR-induced calcium increases and PKC activation. Subsequently, using two of our somatic cell Jurkat mutants, we demonstrated that the adaptors LAT and SLP-76, substrates of ZAP-70 were critically important for TCR signaling leading to PLCγ1 activation and most other downstream pathways, i.e., calcium increases, PKC activation, and Ras/MAPK pathways. The critical importance of ZAP-70 in activating these pathways and most T cell responses was further validated using a chemical genetic approach towards small molecule inhibition of a catalytic mutant of ZAP-70.


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.


Complete List of Published Work in My Bibliography:


Research Support

Ongoing Research Support

Howard Hughes Medical Institute, Weiss (PI) 07/01/85-08/31/22
Cell surface molecules and molecular events involved in human T cell activation.
The goal is to study cell surface molecules and molecular events involved in T cell activation. HHMI personnel (1 student, 1 postdoc and 4 technicians) focus on structure of the TCR and the ZAP-70 protein tyrosine kinase.
Role: Principal Investigator

2P01AI091580-06
NIH/NIAID (Program Leader A. Weiss) 07/01/2016-06/30/2021
Defining the Unique Properties of the Distinct Signaling Machinery Used by the TCR
The goals of this project are to understand the unique properties that define the tyrosine phosphorylation signaling and Ras pathways immediately downstream of the TCR.
Role: Principal Investigator (Project #1)

1R37AI114575
NIH/NIAID Weiss (PI) 12/08/15-11/30/2020
The cell and molecular mechanisms underlying CD28 costimulation
The goals of this project are to understand the molecular signaling machinery that mediates CD28 costimulation in T cells.
Role: Principal Investigator

1R01AI13841-01A1 07/01/18-06/30/23
NIH/NIAID (Sub-PI, A. Weiss)
Novel Roles for the DNA Damage Response Kinase CHK1 in TCR/ITAM Signaling
The goals of this project are to understand how CHK1 inhibitors influence proximal TCR signaling mechanism, with an emphasis on the activities of the proximal kinases, Lck and Zap70.

2017195 10/01/18-09/30/19
United States – Israel (Co-PI, A. Weiss)
Binational Science Foundation
Molecular Gating of T Cell Responsiveness by the Gads Adaptor Protein
The goal of this project is to understand how dimerization of the Gads adaptor protein may regulate LAT-dependent TCR signaling.
BIOGRAPHICAL SKETCH

<table>
<thead>
<tr>
<th>NAME</th>
<th>POSITION TITLE</th>
</tr>
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<tbody>
<tr>
<td>Jonathan S. Weissman, Ph.D.</td>
<td>Professor, University of California San Francisco Investigator, Howard Hughes Medical Institute</td>
</tr>
<tr>
<td>eRA COMMONS USER NAME</td>
<td>WEISSMAN</td>
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</table>

EDUCATION/TRAINING

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvard University</td>
<td>A.B.</td>
<td>06/1988</td>
<td>Physics</td>
</tr>
<tr>
<td>Massachusetts Institute of Technology</td>
<td>Ph.D.</td>
<td>05/1993</td>
<td>Physics</td>
</tr>
</tbody>
</table>

Positions and Honors

1993 - 1996 Postdoctoral Fellow, Yale University, Structural and Biochemical Studies of GroEL
1996 - 2000 Assistant Professor, University of California San Francisco, Departments of Cellular & Molecular Pharmacology, and Biochemistry & Biophysics
2000 - 2005 Assistant Investigator, Howard Hughes Medical Institute
2000 - 2003 Associate Professor, University of California San Francisco, Departments of Cellular & Molecular Pharmacology, and Biochemistry & Biophysics
2003 - Present Professor, University of California San Francisco, Departments of Cellular & Molecular Pharmacology, and Biochemistry & Biophysics
2010-present Vice-chair of Department of Cellular and Molecular Pharmacology, UCSF
2016-present Presidents Advisory Committee of the Chan-Zuckerberg Biohub

Other Experience and Professional Memberships

Permanent Member, NIH Molecular Biology and Protein Processing Study Section (2004-2008); Reviewer, CDF-2 NIH study section (2001-2003, ad hoc); Member, NIH College of CSR Reviewers (2010).
External Reviewer, Lawrence Berkeley National Lab, Physical Biosciences Division (2005);


Scientific Advisory Board: NIH, Amyloid Diseases (2005-2007); Proteostasis Therapeutics (2009-2013); Merck Research Labs (2010-2013), Helen Hay Whitney Foundation (2013-present); Stowers Institute for Medical Research (2016-present) Amgen (2016-present), Princeton Department of Molecular Biology (2015-present), KSQ Therapeutics, (2015-present), Stowers Institute for Medical...
Research, Chair (2016-present, Chair since 2017), Tenaya Therapeutics (2018-present), Maze Therapeutics (2018-present), Venture Partner, 5AM Ventures (2018-present).

Honors and Awards

1988  Summa Cum Laude in Physics, Harvard University
1988  National Science Foundation Pre-doctoral Fellowship
1996  David and Lucile Packard Fellowship
1997  Searle Scholars Program Fellowship
2004  Irving Sigal Young Investigator Award, Protein Society
2008  Raymond & Beverly Sackler International Prize in Biophysics
2009  Alexander M. Cruikshank Lecturer, Gordon Research Conference on Stress
2009  Elected to the National Academy of Sciences
2010  David Perlman Award Lecturer of the ACS Division of Biochemical Technology (BIOT)
2010  Fellow, American Academy of Microbiology
2011  Don Summers Memorial Lecturer, University of Utah Bioscience Symposium
2012  Richard A. Scott, M.D. Lecturer, Center for Genetic Medicine, Northwestern University
2013  Marshall Nirenberg Lecturer, National Institutes of Health (NIH)
2013  Bashour Distinguished Lecturer, University of Texas Southwestern Medical Center
2013  Max Planck Distinguished Seminar, Max Planck Institute (MPI) for Developmental Biology
2014  Cedars-Sinai Medical Center Research Day 2014 Lecturer, Cedars-Sinai Medical Center
2014  Academic Senate Faculty Research Lecturer in Basic Science, University of California San Francisco (UCSF)
2015  12th Annual Albert L. Lehninger Lecturer, Johns Hopkins University
2016  Frank H. Westheimer Prize Lecture, Harvard University
2017  Frederic M. Richards Lecture, Yale University
2017  Election to EMBO Membership (European Molecular Biology Organization), Theodor Bucher Medal Lecture at the 2017 FEBS meeting, Jerusalem
2019  T.Y. Shen Lecturer, MIT
2020  Ira Herskowitz Award from the Genetic Society of America

Contribution to Science

Development of CRISPRi/CRISPRa. While the catalog of mammalian transcripts and their expression levels in different cell types and disease states is rapidly expanding, our understanding of their function lags behind. We present a robust technology enabling systematic investigation of the cellular consequences of repressing or inducing individual transcripts. We identify rules for specific targeting of transcriptional repressors (CRISPRi), typically achieving 90-99% knockdown with minimal off-target effects, and activators (CRISPRa) to endogenous genes via endonuclease-deficient Cas9. Together they enable modulation of gene expression over a ~1000-fold range. Using these rules, we construct and validate genome-scale CRISPRi and CRISPRa libraries that enable systematic analysis of gene function including both essential and nonessential as well as long noncoding RNAs. Our results establish CRISPRi and CRISPRa as powerful tools that provide rich and complementary information for mapping complex pathways. We have now adapted this approach to allow the large-scale analysis of double knockdowns. This enables the systematic search for synthetic lethal interactions that will inform the rational design of combination drug therapies. We are broadly applying the CRISPRi/a approach to understanding disease mechanisms, defining drug targets, and
even potentially treating disease by reversibly regulating gene expression without permanently altering patients’ DNA.


Development of Ribosome Profiling: We developed a ribosome profiling approach based on deep-sequencing of ribosome-protected fragments that makes it possible to determine the rate of translation with a depth, speed and accuracy that rivals or exceeds existing approaches for following mRNA levels. We have applied these techniques to address a number of fundamental questions including: (1) Development of ribosome profiling protocols for a wide variety of eukaryotic and prokaryotic organisms. (2) Uses of ribosome profiling to globally monitor when chaperones, targeting factors or processing enzymes engage nascent chains. (3) Development of a strategy for monitoring subcellular translation. (4) Position-specific ribosome profiling to decipher the driving force and biological consequences underlying the choice of synonymous codons. (5) Use of ribosome profiling to define the protein coding potential of complex genomes.


Systematic analysis of the Endoplasmic reticulum (ER). As a rule, proteins that enter the secretory pathway fold within the ER. The ER establishes and maintains a highly specialized environment optimized for folding. Understanding how this is accomplished is a major focus of our research. Major recent findings include the following: Identification of Yos9 as a sugar sensor of misfolded proteins. Discovery of a novel branch of the metazoan UPR, termed RIDD, involving targeted mRNA destruction. Identification of the GET pathway: a conserved system responsible for the biogenesis of tail-anchored membrane proteins. Discovery of a molecular caliper mechanism for determining the
length of very long-chain fatty acids. Identification of the Orm family of proteins as critical mediators of sphingolipid homeostasis.


Mechanism of prion propagation: My lab has used the yeast [PSI+] prion to elucidate the principles of prion-based inheritance. Most notably, we developed an approach for producing distinct infectious (prion) conformation of the yeast Sup35 prion protein. We showed that when introduced into yeast, these distinct infectious conformations led to distinct strains of the [PSI+] prion. This work provided the first and still the most direct demonstration of the protein only hypothesis of prion propagation and established that prion strains results from distinct self-propagating infectious conformations.


Full List of Published Work:

Research Support

Howard Hughes Medical Institute (Weissman) 10/01/00 - 08/31/24
Prion-Based Inheritance, Protein Folding, and Analysis of Cellular Systems
This grant supports our studies of how cells insure that proteins fold into their correct shape, as well as the role of protein misfolding in disease and normal physiology.

HR0011-19-2-0007 (Weissman) 04/01/2019 – 03/31/2023
DOD Defense Advanced Res Projects Agency (DOD DARPA)
An IND-Enabling Platform for CBRN Threat Protection via Transient, RNA-guided, Targeted Epigenome Editing In Vivo
This grant proposes to build a vertically integrated, target-agnostic, and IND-enabling platform for clinic-ready, transient, RNA-guided, targeted epigenome editing in vivo. We will deploy this platform to develop an experimental therapeutic for prophylactic or post-exposure protection of hematopoiesis and the gastrointestinal (GI) tract from high-dose radiation exposure.

HR0011-17-2-0043 (Doudna) 04/01/17–03/31/2021
DARPA
Next-Generation CRISPR and anti-CRISPR Tools and Delivery Systems for Safely Engineering the
Genome and Epigenome
This grant proposes to develop next generation CRISPR tools for editing the genome, epigenome and transcriptome with application as advanced anti-viral therapeutics. This grant also proposes to identify, characterize, refine and implement natural and engineered anti-CRISPR agents as a means of controlling the activity of dual use gene editing platforms.

1U01 CA217882-01 (MPI: McManus, Bandyopadhyay, Bivona, Weissman) 07/01/2017-06/30/2022 NIH/NCI
The Cancer Target Discovery and Development Network at UCSF
The goal of this proposal is directly to bridge the gap between the enormous volumes of data generated by the comprehensive molecular characterization of a number of cancer types– and the ability to use these data for the development of human cancer therapeutics.

1RM1 HG009490-01 (PI: Doudna; Co-Investigator: Weissman) 08/08/2017 – 05/31/2022 NIH/NHGRI
Center for Genome Editing and Recording
The major goals of this project are to create technologies to enable robust, comprehensive exploration of genes and genetic pathways responsible for human disease.

1U54 CA224081-01 (PI: Bivona; Co-investigator: Weissman) 9/1/2017-8/31/2022 NIH/NCI
Bay Area Team Against Resistance
The Bay Area Team Against Resistance U54 Project (BATAR-UP) is an interdisciplinary effort of investigators to apply their knowledge and expertise to dissect the molecular and cellular basis of incomplete response and resistance to current treatments and to identify new treatment strategies to better neutralize or eliminate residual disease and prevent resistance.

2019-203762 (Weissman) 8/01/2019-3/31/2020
Chan Zuckerberg Initiative
Lineage Tracer Supplement #2
This work will develop methods for permanently recording cell state changes in DNA in a compact manner that can be read out in single cell format using droplet-based single cell RNA-seq.

1 R01 NS113429-01 (Wang) 2/1/2020-1/31/2025 NIH/NINDS
Molecular Pathogenesis of Hereditary Hemorrhagic Telangiectasia
The main objective is to establish a novel HHT2-AVM mouse model, with which to identify molecular regulators crucial for AVM pathogenesis, using both a targeted approach and unbiased genome-wide expression profiling.
BIOGRAPHICAL SKETCH

NAME
Zena Werb, Ph.D.

POSITION TITLE
Professor of Anatomy

eRA COMMONS USER NAME
werbzena

EDUCATION/TRAINING

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

Positions

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

Editorial Board Memberships

1983-1985 Journal of Cell Biology
1982-1987 American Journal of Physiology
1985-2004 Journal of Experimental Medicine
1990-2001 Science
1999-Present Matrix Biolog
1999-Present Neoplasia
2000-2009 Cell
2001-Present Developmental Cell
2001-Present Cancer Cell
2002-2006 Molecular Biology of the Cell
2007-2009 Genes & Development
2009-Present Current Opinion in Cell Biology
2010-Present  Guest Editor, Proc. National Academy Science, USA
2010-Present  Member, Editorial Board, Disease Models and Mechanisms

Professional Memberships

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

Scientific Leadership (selected)

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

Honors

1996    FASEB Excellence in Science Award
1998    Rothschild/Mayent Fellowship, Institut Curie
2002    Elected Member, Institute of Medicine
2003    Elected Fellow, American Academy of Arts and Sciences
2003    Doctor of Medicine (honoris causa), University of Copenhagen
2006-2007  Alexander von Humboldt Foundation (Germany) Research Award
2007    E.B. Wilson Medal, American Society for Cell Biology
2009    Colin Thomson Memorial Medal, AICR
2010    Elected Member, National Academy of Sciences
2010    American Society for Cell Biology, Women in Cell Biology Senior Award
2011    John H. Blaffer Lecture, M.D. Anderson Cancer Center, Research Award
2011 McAllister Lecture, Pathology Grand Rounds, Yale Medical School, New Haven CT
2012 Keynote Lecture, International Assoc. for Breast Cancer Research Conference
2014 Detlev Bronk Alumni Lecture, Rockefeller University, New York
2014 Billingham Lecture, University of Texas Southwestern, Dallas, TX
2014 Curie-Servier Lecture, Paris, France
2015 UCSF Lifetime Achievement in Mentoring Award, San Francisco, CA
2015 University College, University of Toronto, Alumni of Influence Award, Toronto, Canada
2016 Keynote speaker, American Association of Anatomists Annual Meeting, San Diego CA
2016 Keynote speaker, Gordon Research Conference Plasminogen Activation, Extracellular Proteolysis
2016 Doctor of Medical Science (honoris causa), National Cheng Kung University, Tainan, Taiwan
2016 Inaugural Fellow, American Society for Cell Biology
2018 Distinguished Role Model Award, Northwestern University, Evanston
2018 AACR Distinguished Lectureship in Breast Cancer Research Award, San Antonio Breast Cancer Symposium, San Antonio, TX
2020 Suffrage Science Award, Life Sciences category, MRC London Institute of Medical Sciences

Contribution to Science

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

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


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


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


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

Complete List of My Published Work in PubMed:

Research Support

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

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

NIH/NCI P30 CA082103-20  (Ashworth, PI) 05/08/99 - 05/31/23
(Werb, Assoc. Director for Basic Science)
Cancer Center Support Grant – Senior Leadership
The Cancer Center Support Grant provides support for administration and infrastructure for the UCSF Helen Diller Family Comprehensive Cancer Center.

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

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

**NAME**  
Prescott Gurney Woodruff, M.D., M.P.H.

**POSITION TITLE**  
Associate Professor of Medicine in Residence

**eRA COMMONS USER NAME**  
woodruffp

### EDUCATION/TRAINING

<table>
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<th>DEGREE</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
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<tbody>
<tr>
<td>Wesleyan University, Middletown, CT</td>
<td>B.A.</td>
<td>5/1989</td>
<td>Letters</td>
</tr>
<tr>
<td>Columbia College of Physicians &amp; Surgeons, NY</td>
<td>M.D.</td>
<td>5/1993</td>
<td>Medicine</td>
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<tr>
<td>Massachusetts General Hospital</td>
<td>Residency</td>
<td>7/93-1996</td>
<td>Internal Medicine</td>
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<tr>
<td>Harvard School of Public Health</td>
<td>M.P.H.</td>
<td>06/98</td>
<td>Epidemiology</td>
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<tr>
<td>Brigham and Women’s Hospital</td>
<td>Fellow</td>
<td>07/97-98</td>
<td>Respiratory</td>
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<tr>
<td>University of California, San Francisco</td>
<td>Fellow</td>
<td>07/98-02</td>
<td>Pulmonary/Critical Care</td>
</tr>
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</table>

**Positions and Honors**

1998-2002  
Clinical and Research Fellow, Pulmonary/Critical Care Medicine & Cardiovascular Research Institute, Department of Medicine, University of California San Francisco, San Francisco, CA

2002-2005  
Assistant Adjunct Professor; University of California San Francisco

2005-2010  
Assistant Professor in Residence, Pulmonary/Critical Care Medicine, Department of Medicine and CVRI, University of California San Francisco

2010-2014  
Associate Professor in Residence, Division of Pulmonary and Critical Care Medicine, Department of Medicine and CVRI, University of California San Francisco

2014-present  
Professor in Residence, Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of California San Francisco

**Honors**

1993  
Alpha Omega Alpha, Columbia College of Physicians and Surgeons, NY, NY

2012  
Elected to Membership, American Society for Clinical Investigation

**Contribution to Science**

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


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


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


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).


**Complete List of Published Work in MyBibliography (137 Publications):**

**Research Support**

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

NHLBI
SPIROMICS II: Biological underpinnings of COPD heterogeneity and progression.
To establish the biological underpinnings of COPD heterogeneity, progression and exacerbations using the SPIROMICS cohort.

K24 HL137013 (PI Woodruff) 04/28/17-3/31/22

Mentoring Research in Precision Medicine for Lung Disease
To mentor students, fellows and junior faculty in patient-oriented precision medicine related research in respiratory disease.

R01 HL146002 MPI (Contact PI Levy, PI Woodruff) 10/1/2019-7/2024

Severe Asthma Research Program 4
To study immunometabolic phenotypes in adult severe asthma and disease

U19 AI077439 (Project leader: Woodruff, overall PI: Erle) 04/01/18-3/31/23

Understanding Asthma Endotypes
To study the roles of interferon driven inflammation and airway epithelial ER stress in asthma.

R01 HL143998 MPI (Contact PI Huang, PI Woodruff) 09/15/2019-07/31/202

Integrated Analysis of Microbial and Genomic data in Obstructive Lung Disease (I AM GOLD) Study
To study the mechanisms underlying the increased risk of COPD with HIV infection in an ongoing international longitudinal multi-center study of HIV-associated COPD in Uganda and San Francisco.
Functional Analysis of the Pulmonary Microbiome during COPD
This study investigates a pathway that links inflammation, Gram negative bacterial overgrowth, mucus production and chronic bacterial colonization in COPD.

Airway Epithelial Cell Gene Regulation: New Mechanisms and Therapeutic Strategies
Our overall goals are to identify genomic elements that are important in airway epithelial cell differentiation in asthma and to develop approaches for targeting these elements.

Exploring the Biology of Persistent Type 2 Airway Niches in Asthma
To identify mechanisms of persistence of T2 inflammation in airway niches relevant to asthma.

Integrated Analysis of Microbial and Genomic data in Obstructive Lung Disease (I AM GOLD) Study
This study investigates mechanisms underlying the increased risk of COPD with HIV infection in an ongoing international longitudinal multi-center study of HIV-associated COPD in Uganda and San Francisco.

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

Defining a Comprehensive Reference Profile of Circulating Human Extracellular RNA
The goal of this study is to use RNA sequencing to establish the reference range of exRNAs as biomarkers in 12 different body fluids.

Redefining Therapy in Early COPD: RETHINC (in no cost extension)
To determine whether current and former smokers with preserved spirometry and respiratory symptoms will respond to inhaled bronchodilator therapy with improvement of their symptoms in a randomized controlled trial.

Completed Research Support

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