Figure Legend: Single-cell mRNA sequencing from ILC2s collected from different tissues in the mouse reveals heterogeneity that may be aligned with tissue functionalities (Ricardo-Gonzalez et al, Nature Immunol 19:1093, 2018.)
In Memoriam

We wish to acknowledge Herb Sandler (1931-2019) and Marion Sandler (1930-2012), whose vision, leadership, inspiration and encouragement established the SABRE Center at UCSF to make the world better for persons with asthma. We remain committed to their quest.
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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 was 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 to accomplish our vision of a world free of asthma. The SABRE Center is made possible by the generous support of the Sandler Foundation.

Summary of Accomplishments over the Past Year

The SABRE Center continues to make innovative contributions to the understanding of asthma and allergic immunity and to nucleate an active asthma research enterprise within the greater UCSF scientific community. Comprised of four basic scientists, a population geneticist, two 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.

Notable accomplishments from SABRE Center members since the prior Report:

(1) The SABRE Program Project Grant ‘Exploring the biology of persistent type 2 airway niches in asthma’ was renewed by the NIH National Heart, Lung and Blood Institute with an outstanding score and funds of over $12 million in total costs over 5 years. Organized by John Fahy with Rich Locksley, Mark Ansel, Erin Gordon, and Prescott Woodruff, the PPG was top-scored at NHLBI for ‘a group of outstanding investigators who have made seminal contributions to the field of asthma pathogenesis.’
(2) John Fahy was awarded the European Respiratory Society Gold Medal in Asthma to be awarded in Madrid by the International Congress in September 2019. The 50,000 Euro award acknowledges worldwide leadership in asthma.
(3) The Asthma Collaboratory led by Esteban Burchard continues to identify genetic contributions from unplumbed African sequences and admixtures that generate disease risk for asthma and other prevalent diseases, including drug responsiveness, allergic rhinitis, pulmonary function, telomere protection and atrial fibrillation.
(4) In basic research, the Ansel lab pioneered recognition of the role of extracellular RNAs in allergic lung disease (Cell Rep 2019) and in standardizing technologies for their study (Cell 2019). The Allen lab clarified the off-target effects of a widely-used antibody in basic allergy research (JACI 2019) and contributed a definitive review of B cell biology (Cell 2019). The Locksley lab elucidated fate-mapping and single cell transcriptomics of ILC2s (Nature Immunol 2018; Immunity 2019); and the Shin lab defined the role of MARCH ubiquitinylation of MHC molecules in protecting dendritic cells from proteotoxicity (J Cell Biol 2018).
Overview – 2019

Richard M. Locksley, M.D.

The SABRE Center continues with its discovery-oriented mission towards deeper understanding of asthma that will guide innovative therapeutics. Major renovations of the UCSF Parnassus campus portend new research facilities built concurrent with the hospital rebuild by 2025, creating opportunities for re-configuration of SABRE research facilities within neighborhoods integrated with patient-centered investigative study in immunology, inflammation and lung diseases. Concurrently, we have invited Associate SABRE investigators into the research space on HSE2 while anticipating major changes to the research infrastructure at Parnassus over the next decade. SABRE is integrated well within all of the ongoing planning and allocation committees, and anticipates no impediments to continued productive engagement on the Parnassus site during this period of exciting re-configuration of the original UCSF campus. Scientific leadership includes participation and organizational activities for the 2020 Keystone Symposium on Asthma Immunobiology by the former American Asthma Foundation Scientific Board assembled by the Sandler Foundation, and organization of the 4th International Conference on Innate Lymphoid Cells in 2020.

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. Additional Associate Investigators with active laboratories on the SABRE Center floor include Drs. Erin Gordon, Mallar Bhattacharya, and Aparna Sundaram, who engage in collaborative work with SABRE investigators in addition to their primary research in aspects of lung biology 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, a member of the Executive Board, and Dr. Prescott Woodruff. SABRE investigators share quarterly lab and research meetings, and attend a monthly research conference. 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 for 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 (miRNA) 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 has developed a related research program to improve and expand characterization of inflammatory cells that infiltrate the airways in asthma. This work has motivated productive collaborations with ACRC investigators, including Dr. John Fahy, Dr. Prescott Woodruff, Dr. Laura Koth, Dr. Erin Gordon and Dr. Homer Boushey. One of his collaborative projects with Drs. Boushey and Lynch describes the bacterial biogeography of the airways in asthma, and uncovered unexpected relationships between specific bacterial genera and the abundance of eosinophils and certain inflammatory cytokines in the bronchial lavage fluid. Some of this work was published in the journal Microbiome in the past year, and more recent findings are part of a second manuscript. Dr. Ansel’s work in the NIH Director’s Office’s Extracellular RNA Communication Consortium was recently published in several articles in Cell and Cell Reports. Dr. Ansel co-authored the Consortium’s review of foundational knowledge and technologies for extracellular RNA research, and contributed two articles describing his laboratories discoveries in this field. His lab showed that T cells selectively and actively export small RNAs in vesicles upon immune activation. Furthermore, the airways are a rich source of extracellular RNAs encapsulated within vesicles that are secreted by airway epithelial cells and, in the setting of allergic inflammation, by T cells and other inflammatory cells that contribute to asthma pathology.

Altogether, Dr. Ansel contributed to 6 published manuscripts this year, and 8 others are in revision for publication. Dr. Ansel an established leader in his field. He hosted and spoke at a new Keystone Symposium on Transcription and RNA Regulation in Inflammation and Immunity in February. He also delivered invited lectures at the Midwinters Conference of Immunologists, and in Detroit, Sacramento, Miami and Hampton, Virginia. Dr. Ansel’s work has been recognized by substantial extramural grant support. He has continuing funding from an R01 grant from NHLBI, and an Exploratory/Developmental Research (R21) grant from the NIAID. The Ansel laboratory is currently populated by two graduate students, three postdoctoral fellows, two technicians, and one undergraduate researcher. All three postdoctoral fellows have external grant support: Ni-Ting Chiou recently won an American Association of Immunologists Intersect Fellowship for computational immunology; Kristina Johansson is supported by the Swedish Heart Lung Foundation and the Sweden-America Foundation; Marlys Fassett is supported by a fellowship from the Dermatology Foundation and is expected to receive an NIH K08 Career Development Award this spring. Her Dermatology Department funding also supports technician Suparna Roy. Dr. Ansel’s departed trainees have moved successfully into the next phase of their career as postdoctoral fellows, scientists at biotechnology companies, MD/PhD residents and fellows in research career tracks, and in three 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 avidly pursues studies using materials
collected from asthma patients in the Airway Clinical Research Center. He has worked with Dr. Woodruff, Dr. Fahy, Dr. Gordon and Dr. Boushey to improve and apply high-dimensional flow cytometry and mass cytometry (i.e.; CyTOF) analysis of human airway biospecimens. He works closely with Drs. Woodruff and 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.

In recognition of his success to date, Dr. Ansel was promoted to Professor of Microbiology & Immunology in 2018. He is very active in University service and leadership, and was named one of 150 recipients of UCSF’s 150th Anniversary Alumni Excellence Awards. He is the director of the UCSF Biomedical Sciences (BMS) graduate program and the principal investigator of the large NIH T32 training grant to support graduate student training. He is a member of the Parnassus Heights Master Plan Steering Committee and has organized faculty efforts to advocate for enhanced infrastructure to support basic disease-relevant research like that performed in the SABRE Center. He participates in teaching for 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. Dr. Shin seeks to exploit this understanding to develop novel therapeutics for treatment of immune-associated disorders including asthma. In previous years, Dr. Shin discovered that a protein named MARCH1 is a master regulator of membrane trafficking of the two immune-associated molecules MHCII and CD86 in dendritic cells. Both of these molecules play key roles in antigen-presenting function of dendritic cells and promotes immune stimulation as well as regulation. To uncover functional significance of MARCH1-dependent membrane trafficking, Dr. Shin’s group created several genetically modified mouse strains and examined immune phenotypes and susceptibility of immune-associated diseases of these animals. These studies revealed that MARCH1 plays a critical role for dendritic cells to generate regulatory T cells in the thymus and develop type 2 T helper (Th2) cell immunity in the airways. In collaboration with Dr. Cyster at UCSF and Dr. Riella at Harvard University, Dr. Shin also found that MARCH1 supports B cell activation in the germinal center and mediates regulation of alloimmunity during transplantation. These findings were published in high-profile journals including *Journal of Experimental Medicine, Journal of Cell Biology, and Nature Communications.* Dr. Shin also investigated the role of membrane trafficking of the high-affinity IgE receptor, FceRI, and found that this molecule mediates clearance of circulating IgE through cellular endocytosis by dendritic cells. Dr. Shin reported this finding in the *Journal of Clinical Investigation* and was invited to present these findings at the annual meeting of the American Academy of Allergy, Asthma and Immunology.

The NIH recognized Dr. Shin’s strong research program in the field of membrane trafficking in dendritic cells and recently awarded her R35 funding, a five-year funding mechanism launched by NIGMS that gives the principle investigator freedom to explore areas beyond the PI’s current research subject. Dr. Shin plans will use this to explore the role of MARCH1-dependent membrane trafficking in the development of allergic asthma and to tease out the exact mechanisms by which MARCH1 mediates Th2 cell immunity.
in the airways. Dr. Shin is additionally funded from the Department of Defense and the American Association of Immunologists.

Dr. Shin is a thesis supervisor of a fourth year BMS graduate student who was awarded an Initiative for Maximizing Student Development (IMSD) fellowship from the National Institute for General Medical Sciences (NIGMS). More recently, the student was also awarded a trainee abstract award from the American Association of Immunologists and a presenter award from the Federation of American Societies for Experimental Biology. Dr. Shin actively participates in training future scientists from under-represented minorities. She serves as a research and career mentor for Steven Gonzalez, a senior of San Francisco State University funded by the NIH minority training program, SF Build.

Dr. Shin is in active collaboration with a number of investigators in and outside UCSF. Of note, she works with Dr. Degrado in the Department of Pharmaceutical Chemistry at UCSF, who has strong expertise in structural analysis of membrane proteins. From this collaboration, Dr. Shin will determine the 3D-structure of MARCH1, uncover the molecular mechanism of action of this protein at the atomic level, and utilize this information to design small molecule inhibitors, which could comprise potential drugs for allergic diseases. Dr. Shin also collaborates with Dr. Earl at UCSF to define the specific molecular pathways MARCH1 regulates to promote Th2 cell immunity in the airway. This collaboration utilizes next-generation sequencing technology, and the data will be deposited to the SABRE RNA-seq Consortium to exchange ideas and develop further collaborations among SABRE investigators.

Chris Allen, Ph.D., joined the SABRE center eleven 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. He has two related studies that he hopes to publish soon, one on the specificity of IgE plasma cells in mouse models of asthma, and a second on how innate stimuli and cytokine signals regulate IgE responses. His 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 recently 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* last year. Dr. Allen also recently published a letter in *The Journal of Allergy and Clinical Immunology* showing how an antibody to the IgE receptor, FceRI, actually recognizes multiple Fcg 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 has just completed an R21 characterizing a population of lung macrophages involved in antigen capture. This is Dr. Allen’s second R01 award, and he was previously awarded an NIH Director’s New Innovator Award. 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 has mentored a PhD student who graduated last year with a thesis project focused on a population of macrophages that capture inhaled allergen that is then presented to T cells, which may trigger inflammation contributing to asthma, and he mentored a postdoc who completed a project studying the generation of IgE B cells in mouse models of asthma. Dr. Allen currently mentors two PhD students and will welcome a new postdoc and new PhD student to his lab for the 2019-20 academic year. 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 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 epithelial cell-fate determination, metabolic homeostasis, and local regulation of cytokine expression by adaptive Th2 cells. His laboratory discovered the association of allergic immune responses by the environmental polysaccharide chitin, a constituent of fungi and insects associated with human allergic sensitivity, and has explored the role of mammalian chitinases in regulating enzymatic breakdown of environmental chitins at mucosal barriers. He directs an active laboratory effort with 13 peer-reviewed publications, 5 reviews and 2 commentaries in 2017-2019.

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. Earlier this year, his laboratory discovered the role of succinate, a Krebs cycle intermediate and end-product of metabolism by intestinal protists and helminths, in activation of small intestinal tuft cells. 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 a 2019 NIH Workshop on the role of ILC2s in allergy and asthma. He is a member of the American Academy of Arts & Sciences, a Fellow in the American Academy of Microbiology, and a member of 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’. Postdoctoral trainees in his laboratory include recipients of a Cancer Research Institute Fellowship, a Fulbright Fellowship and an American Dermatology Research Fellowship. Recent postdoc graduates have moved into academic faculty positions at UCSF, University of Washington, Washington University St. Louis, and ETH Zurich (Swiss Federal Institute of Technology). His past UCSF MSTP graduate is a medical resident at UCSF this year, and his most recent MSTP graduate student was awarded an F30 Award from the NIH with a perfect score on his grant investigating the development of ILC2s. He is active in teaching graduate and medical students in immunology and infectious diseases. Dr.
Locksley and SABRE will organize and host the 4th International Conference on Innate Lymphoid Cells in San Francisco in the fall of 2020.

John Fahy, M.D. is a longstanding participant in 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 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 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 (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). 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. Dr. Fahy was recognized with the European Respiratory Society Gold Medal in Asthma in 2019 for his global leadership in asthma research and care.

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 5 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. 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, including steroid-unresponsive disease that constitutes a substantial health care issue, and 2) type 2 and non-type 2 inflammatory mechanisms in allied diseases such as COPD and chronic bronchitis. Non-type 2 pathways that he is investigating in asthma include airway epithelial ER stress and interferon-driven inflammation. Dr. Woodruff’s research program also includes studies of microRNA regulation of airway epithelial mucin production. Dr. Woodruff is PI of a NHLBI U01 grant designed to develop reference profiles for exRNAs across 12 different human body fluids, of the NHLBI SPIROMICS study of COPD and of the NHLBI RETHINC clinical trial in COPD. 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. He has an NHLBI K24 award which supports his mentoring of junior faculty and trainees and he will co-Chair the Keystone Symposium on Asthma organized from the former American Foundation for Asthma supported by the Sandler Foundation in 2020. 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 has become the largest annotated gene biorepository of minority children with asthma in the world. The Asthma Collaboratory is accessible to scientists seeking to examine genetic risk for variants in populations of interest or to extend findings made in animal models to explore potential mechanistic involvement in human asthma. The Asthma Collaboratory continues 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 Asthma Collaboratory has led efforts to identify genetic modifiers of drugs used in asthma that might contribute to the poorer response among ethnic populations. More recently, Dr. Burchard is leading efforts to find biomarkers for different subsets of asthma as defined by presentation or response to therapy. Dr. Burchard and the Asthma Collaboratory have leveraged these resources to obtain funding to perform whole genome sequence (WGS) analysis on 15,580 minority children with asthma and known aspects of drug response. These studies identified associations between albuterol bronchodilator drug response and social and environmental determinants of asthma and related outcomes. Most recently, they completed a large study of albuterol bronchodilator drug response in minority children with asthma using whole genome sequencing. The Asthma Collaboratory contributed clinical and genetic data from minority children to the NHLBI Trans-Omics for Precision Medicine (TOPMed) program. The imputation reference panel generated from TOPMed greatly improved the accuracy of genotype imputation in admixed populations when compared to the most commonly used reference panels based on the 1000 Genomes Project or the Haplotype Reference Consortium. The group also contributed aggregated summary statistics through TOPMed for inclusion in gnomAD, a publicly available open genome aggregation database for the general research community.

Genetic association studies of asthma have found most risk variants are non-coding, suggesting these variants affect regulatory regions controlling gene expression. Therefore, expression quantitative trait loci (eQTL) variants identified in asthma disease-involved tissues will likely be enriched for risk variants. The bronchial airway epithelium is central to asthma pathogenesis through the production of mucus that results in airway obstruction and immune signaling which leads to airway inflammation. The expense and safety concerns of performing bronchoscopies on children to collect bronchial airway epithelial brushings have impeded airway epithelial eQTL studies in children with asthma. Previously, the Asthma Collaboratory showed minimally-invasive nasal airway epithelial brushings can be collected from children, where they can serve as a proxy for
bronchial airway epithelium. They recruited a cohort of 698 minority children with nasal airway epithelial brushings to perform a cis-eQTL study. Current software for transcriptome-wide association studies (TWAS) uses public genotype-expression repositories like GTEx to impute gene expression levels from genotypes. However, since these repositories have predominantly European adult subjects, the imputation quality is largely underexplored in racially admixed populations and children. The Burchard Lab has studied the transethnic portability of gene expression prediction models. Using iplot whole blood RNA-Seq data from 39 African American children, they found that gene expression prediction models trained on European adult subjects have low performance on African American children (manuscript under review, https://doi.org/10.1101/552042).

The Asthma Collaboratory is the first team to quantify the performance of gene expression prediction models trained by simulated data with various degrees of admixture. These results will inform other researchers about the limits and considerations necessary when applying gene expression prediction models to diverse populations. In addition, the Asthma Collaboratory is currently using RNAseq data from nasal airway epithelial cells to construct predictive models for gene expression imputation for TWAS.

These efforts facilitate numerous collaborators and bolster the careers of junior trainees and faculty. The lab has been extremely productive with over 200 publications and >70 national and international collaborations. Data from these investigations helped young investigators generate 2 R01s (Blanca Himes, U. Penn and Ann Wu, Boston Children’s Hospital), 2 K99/R00s (Walter Eckalbar, UCSF and Andreas Neophytou, Colorado State), and 7 Career Development (K) Awards.

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 Genomics Core, under the guidance of Dr. Erle, to the Microscopy Core, under the guidance of Dr. Krummel, and to the Genetics Core, under the guidance of Dr. Burchard. The Genomics Core has led a number of technological innovations of importance to the Center, particularly in facilitating deep-sequencing efforts, single-cell RNAseq and cutting-edge epigenetic analyses, such as ATACseq methods. 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. 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 SABRE Center contributed to key technology acquisition over the past several years that continue to represent widely used and pivotal resources on campus. All of these acquisitions were made by leveraging to gain matching funds from additional sources. We continue to provide upkeep resources on an as-needed/as-justified basis, while continuing to look for new areas of need for technology development. In the Microscopy Core, SABRE contributed to the customization and roll-out of a Generation-3 2-photon microscope with 6 color and 2 laser capabilities; to acquisition of a spectral laser scanning confocal microscope and to an Alaris 3D printer that has become a workhorse for production of parts and custom adapters; to acquisition of a state-of-the-art SP8 Leica white-light microscope for multiple-color imaging that will greatly enhance lung tissue studies. Overall, the Microscopy Core supports not only core SABRE investigators, but 228 registered users across the UCSF campus; 53 new users have been trained since 2016. The Microscopy Core has brought lattice sheet microscopy and in-lung intravital imaging to the Parnassus campus, all supported by in-house custom software analysis programs. In short, SABRE funding is being leveraged to create campus-wide resources that are unavailable on most research campuses. The SABRE Center will continue to support technology in the Microscopy Core for the coming year, directed primarily at improving ‘Clarity’ techniques for opacification of lung tissues for imaging, development of sophisticated software analytical programs for data processing, and for enhanced imaging capacity using SPIM (selective plane illumination microscopy) imaging of whole lung.

The SABRE Center also provides leveraged support to the Genetics Core under the leadership of David Erle on the Mission Bay Campus. SABRE funds contributed to the purchase of several robotic instruments that substantially enhanced throughput, and to software development to enhance analytics. Single-cell RNAseq comprises a powerful new method for probing individual cells in complex tissues, and the Genetics Core has helped establish this rapidly for SABRE investigators, including members of the Locksley, Ansel and Fahy labs, and in studies of both mouse and human cells. This relatively small outlay has been leveraged many times over to provide cutting-edge, individualized, research opportunities on a time and cost scale amenable to rapid utilization across both Parnassus and Mission Bay sites. Due to the early successes of these approaches, we initiated a SABRE investigator-wide effort using RNAseq to generate a database of mouse and human lung immune and non-immune cells to serve as a common technical resource across these two species.

The final core outlay maintained by the SABRE Center is the Asthma Collaboratory, under the leadership of Dr. Burchard. 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. This resource is entirely available to members of SABRE, who work with Dr. Burchard to investigate potential ‘hits’ that could be mined for predictive or therapeutic purposes. This key resource is also made available campus-wide and is open, thus contributing a
major asthma resource to UCSF, but also to investigators worldwide who wish to collaborate using this genetic database.

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. We help support the use of the CyTof mass spectrometry instrument on Parnassus that has enabled new approaches to the study of human samples. We also contributed to a liquid mass spectrophotometer on the Parnassus campus to enable rapid analysis of lipids involved in inflammatory diseases, including asthma, where lipid mediators have been implicated in airway reactivity and other aspects of allergic disease. Our contributions were leveraged to enable purchase of these two instruments for over $1 million, and both are highly utilized by multiple laboratories, including SABRE-associated labs.

**SABRE Innovative Grants**

We have continued to support prior Innovative Grants this year. The first, from Ari Molofsky in the Department of Laboratory Medicine, involves a comprehensive microscopic and genetic evaluation of the niches occupied by ILC2s in diverse tissues in the mouse. The first results from this grant were recently published in Immunity, and a second manuscript will be submitted shortly. The second, from Bill DeGrado on the Mission Bay campus, works with Jeoung-Sook Shin on the crystal structure for MARCH1 ubiquitin ligases in order to find small drug inhibitors. Dr. Shin’s work has shown that deletion of this ubiquitin pathway in mouse dendritic cells can profoundly inhibit allergic inflammation in mouse models of allergic airways inflammation. We also contributed pilot funds to enhance collaborative interactions between SABRE Associates – Drs. Gordon, Battacharya and Sundaram – to create discovery opportunities in asthma research.

**SABRE RNA-seq Initiative**

Based on discussions hatched at the 2017 SABRE Retreat, we designated a fixed commitment of $40,000 to each core lab for use in bulk and single-cell RNA-sequencing of lung tissues in order to create a tissue bank for core use and dissemination among labs across UCSF and wider after publication. Initial requests included studies of mouse nasal and lung ILC2s and epithelial tuft cells (Locksley lab), human airway brushes (Fahy lab), human airway epithelial monolayers under various conditions (Woodruff lab), human nasal polyp tissues from patients with allergic polyposis (Gordon/Fahy labs), Ig-E-switched allergen-specific B cells in the mouse (Allen lab), human and mouse micro-RNA and RNA comparators (Ansel lab), and human drug-response outliers (Burchard lab). These data are beginning to accrue and have yielded valuable information for comparisons between the mouse and human as well as biologic insights that will continue to drive hypothesis-driven exercises. All of these data are established in the public science space with proper masking of human data. This initiative will be repeated in the
coming academic year as appropriate to proceed with timely follow-up of promising discoveries.

Airway Clinical Research Center

The Airway Clinical Research Center (ACRC) (see Figure) 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. 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 quickly and efficiently. The ACRC has 12 research coordinators, a part time nurse, and a data manager. The model for these staff is that individual coordinators take ownership of specific research studies and manage that 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 1200 subject visits per year. The ACRC supports multiple NIH research programs that involve human-based study of airway disease, as assisted by the following capacities and technologies:

Exam rooms: Eight spirometers (Jaeger Masterscope (2), nSpire HDpft 1000 (1), Sensormedics VMax22 (1), Medgraphics CPFS/D Spirometer (2), nSpire KoKo PFT (2).

**Bronchoscopy room:** Pentax Fiberoptic Bronchoscope Model #EB-1530T3 (2), Pentax Processor Model #EPM-3500, Welch Allyn ProPaq CS vital signs monitor.

**Biospecimen Processing room:** Smith Kline Beecham VanGuard V6500 centrifuge, Fisher Scientific centrifuge Model #228, Thermo Shandon Cytospin 4 cytocentrifuge, Reichert hemocytometer (2), Eppendorf 5810R refrigerated centrifuge, Lab Companion B5-06 shaking water bath, Fisher Scientific specimen refrigerator #97-915-1, Frigidaire refrigerator/freezer for medication storage, Sanyo -80 freezer MDF-U53VA, Sanyo -80 freezer MDF-U73VC, Forma Class II A2 Biological Safety Cabinet, TLS2200 Thermal Labeling System, barcode reader (2), Van Guard microscope.

Faculty in the ACRC have robust grant support from NIH and other sources. Current asthma grants leveraged from SABRE activities include:

1. **UG1HL139106 (9/23/2017 - 6/30/2023)** *Sequential, Multiple Assignment, Randomized Trial in Severe Asthma Protocol (SMART-SA).* Dr Fahy is PI; Dr Woodruff is co-I. UCSF leads a consortium that is one of 10 centers in the NHLBI's Precision Interventions for Severe and/or Exacerbation Prone Asthma (“PrecISE”) program. The UCSF consortium includes a subsite at UC Davis and two international subsites (Vancouver Canada and Leicester, UK).

2. **U19 AI 077439 (4/01/2018 - 3/31/2023)** *Understanding Asthma Endotypes* Dr Erle is PI. Dr Woodruff directs 1 of the 2 projects; 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. Studies will uncover new knowledge about mechanisms of asthma and help to pave the way for new treatments for this common disease.

3. **R01AI136962** 1/15/2018 – 12/31/2022. *Understanding the Molecular Genetic Mechanisms of Asthma Risk Loci: IL33, IL1RL1, and GSDMB.* This is Dr Gordon’s first RO1 and marks her successful transition from K to R funding.

**Active grants with ongoing funding:**
(i) R01 HL080414-05 *Mechanisms of mucus pathology in acute severe asthma.* Dr Fahy is PI. This RO1 focuses on mechanism of mucus pathology occurring during episodes of acute severe asthma.
(ii) PO1 HL128191: *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.

(iii) U10- HL109146: *Clinical and Molecular Phenotypes of Severe Asthma.* Severe Asthma Research Program (SARP). Dr Fahy is PI and Dr Woodruff is co-I. The grant is in NCE and a renewal is pending.

(iv) P01- HL107202: Program Project Grant, *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-IP on Dr Ansel’s project. The competitive renewal was awarded and funded through 2024.


(vi) U01 HL128952. *Redefining Therapy In Early COPD: RETHINC* (Woodruff).

(vii) R01 HL121774. *Functional Analysis of the Pulmonary Microbiome during COPD* (Woodruff Co-I).

The ACRC is also a resource for industry-supported clinical research in airway disease at UCSF. Recent industry sponsors have included Genentech, Boehringer Ingelheim, Pfizer and Roche. The hope is to expand this aspect of SABRE-industry interactions as a platform for successful movement of target identification and pathophysiology onwards to drug and therapeutic development pathways.

**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.

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 physician 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

SABRE Center investigators participate in the organization and content of the 2020 Keystone meeting on Asthma and in the 4th International Conference on Innate Lymphoid Cells, which will be held in San Francisco in October, 2020.

SABRE Retreat, 2017

SABRE labs, including postdocs and students, gathered at the UCSF Mission Bay campus for an all-day retreat at the Smith Cardiovascular Research building. Morning scientific sessions were followed by a lunch break and poster session before breakouts for faculty and trainee discussions. Suggestions coming out of the retreat included the proposal for technical initiatives that unite the labs across a shared resource, and led to the RNAseq Initiative project that was unveiled in Spring of 2018, and to initial discussions underpinning the SABRE Program Project grant that was re-submitted to the NIH. Over 100 hundred persons participated, and enthusiastically embraced a second retreat in the fall of 2019.

Human Upper Respiratory Tract Analysis

The SABRE Center established a scientific relationship with a UCSF surgical practice located at Mt. Zion campus with experience taking care of large number of patients with allergic nasal polyposis. These investigators, Drs. Andrew Goldberg and Steven Pletcher, faculty in the Department of Otolaryngology and Head and Neck Surgery at UCSF, have been examining the interactions of the nasal microbiome and allergy-associated immune cells in excised nasal polyps. We have worked through planning meetings, human use forms and other regulatory issues in order to establish formal collaborative relationships with these investigators and their research group. These nasal polyps provide a rich source of human epithelia, macrophages, eosinophils and ILC2s that collect in these tissues. A substantial number of these recurrent allergic nasal polyposis patients have severe asthma, thus establishing a patient base for further study, including in clinical intervention trials. While the working relationship continues to evolve, we continue to strengthen basic and clinical research interactions with this surgical group, which remains enthusiastic and receptive to our overtures. A postdoc, Benjamin Terrier, a Fulbright Scholar in the Locksley lab, worked regularly with this group investigating nasal upper airway epithelial cells involved in sensory perception to allergens. Dr. Terrier will return for the summer of 2019 to continue these studies. Dr. Erin Gordon in Pulmonary is continuing these studies while working closely with colleagues in the SABRE Center. The biosketches of Dr. Goldberg, Pletcher and Gordon are appended.

Successful competition for extramural support

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

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

“Growth in total extramural funding procured by core investigators reached over $15 million with renewal of the SABRE NIH Program Project Grant in 2019.”

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. These are catalogued in the individual Core and Program Reports.

Highlighted SABRE Center-supported manuscripts impacting asthma-related research in 2017-18


The Fahy lab developed multidetector computed tomography (MCDT) lung scans to enable safe detection of mucus plugs in airways of 146 patients with asthma and 22 controls. Remarkably, airway mucus plugs were present in almost 60% of asthma patient airways, as compared to 4.5% of controls. Numbers of mucus plugs correlated with severity of disease, increased eosinophilia and poor control on standard therapies. *In vitro* studies showed that eosinophil oxidants could crosslink cysteine thiols and stiffen mucus-like thiolated gels. Development of the radiographic technique has generated new hypotheses regarding the role of aberrant niches in sustaining type 2 immune responses in the lung that will be amenable to further testing in both animals and human patients.


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.


Short-acting beta-adrenergic receptor agonists, or SABAs, are the most widely used prescribed asthma medication, but contributions of background genetics to their efficacy has not been examined in African Americans with complex admixture. Using the large numbers of characterized genomes from African Americans, the Burchard lab was able to show that existing genetic contributions to SABA unresponsiveness, as generated predominantly using European donors, were not matched, whereas previously unrecognized genetic contributions came from newly described positions in the genomes. Further work in these diverse populations is clearly needed to ascertain full coverage and discovery of implicated sequences and their functional significance.

Ubiquitinylating ligases, particularly MARCH1 and sometimes MARCH8, regulate enzymatic decrease in membrane-associated MHCII complexes, thus regulating the duration of immune activation, but the consequence of such regulation has not been elucidated. In studying dendritic cells, the Shin lab showed that lack of MHCII ubiquitination and turnover led to accumulation of excessive MHCII in the plasma membrane, causing disruption of lipid rafts and tetraspanin-containing webs necessary for engaging and regulating T regulatory cell differentiation in the thymus and leading to proteotoxicity in the cells. Thus, the MARCH1 system represents a novel quality control mechanism by which dendritic cells maintain homeostasis of membrane domains necessary to support cellular health and Treg development. Understanding dendritic cell – Treg activation will be critical in asthma and allergic diseases, where regulatory T cell function is insufficient to restrict aberrant responses to otherwise innocuous environmental allergens.


A definitive review of advances in B cell and antibody biology addressing all the technologic accomplishments of recent years. Includes identification of areas for pressing study and rapid progress achieved in the genetic engineering of B cells for production of high-quality antibodies.


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 massive 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 have organized this report to review SABRE Center activities and update the core and leveraged technologies that focus on asthma-related research. We will 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 will follow this with a listing of the newly funded, pending or submitted grants and publications since the prior annual reports that reflect support from SABRE Center activities. We will
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. Plans for the coming year including addition of members with expertise in systems biology in order to reflect projected needs in this area in the future.

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
Departments of Medicine and Microbiology/Immunology

Zena Werb, Ph.D., Professor
Department of Anatomy

*ex officio
SCIENTIFIC ADVISORY BOARD
Susan Kaech, Ph.D.
Director of the Nomis Center for Immunobiology and Microbial Pathogenesis
The Salk Institute

Susan Kaech is a Salk Institute Professor, Director of the NOMIS Center for Immunobiology and Microbial Pathogenesis, and holder of the NOMIS Chair. Prior to this she was a Waldemar Von Zedtwitz Professor at Yale University in the Department of Immunobiology (2004-2018). Dr. Kaech did her postdoctoral work with Dr. Rafi Ahmed at Emory University (1999-2004) and received her PhD in Developmental Biology at Stanford University. She received her BS in Cellular and Molecular Biology at the University of Washington.

Dr. Kaech aims to understand how memory T cells are produced during infection and vaccination, how they function and why they can fail to induce long-term immunity during immunization. Her lab has been a leader in using genetic and molecular tools to identify the genes and signaling molecules involved in generating two specific types of memory T cells, CD4 and CD8, from precursor cells during both acute and chronic viral infections. She and her team discovered more than half a dozen important regulatory genes, as well as several types of key molecules called cytokines, which influence memory T cell development.

Dr. Kaech is also interested in how T cells are metabolically regulated, and how their differentiation and function can be altered by nutrient availability during infection and in tumors. In particular, she seeks to learn how T cell behavior is suppressed by tumors, in order to create better therapies for cancer using the body's own immune system—an innovative and rapidly moving field called cancer immunotherapy.

Dr. Kaech has been the recipient of numerous awards including the Damon Runyon-Walter Winchell Cancer Research Fellowship (1999), the Burroughs-Wellcome Foundation Award in Biomedical Sciences (2003), the Presidential Early Career Award for Scientists and Engineers (PECASE) (2007) and the Howard Hughes Medical Institute Early Career Scientist (2009).
Mitchell Kronenberg, Ph.D.
President and Scientific Director
LIAI - La Jolla Institute for Allergy & Immunology

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

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

Ruslan Medzhitov obtained his PhD from Moscow State University in 1993. He performed his postdoctoral studies with Charles A. Janeway Jr. at Yale University School of Medicine. In 1999, he joined the faculty of the Department of Immunobiology and is currently a Sterling Professor of Immunobiology at Yale University School of Medicine, and an Investigator of the Howard Hughes Medical Institute.

Dr. Medzhitov is a director of Food Allergy Science Initiative at the Broad Institute. He serves on the editorial boards of several scientific journals, on the Scientific Advisory Board of the IMP Institute, Vienna, on the National Advisory Board of the PEW Scholars Program, and on a Review Board of the Crick Institute, London.

His awards include the Searle Scholarship, the William B. Coley Award from the Cancer Research Institute, a Master of Arts Privatum from Yale University, the Emil von Behring Award, the AAI–BD Biosciences Investigator Award, Doctor Honoris Causae from Munich University and Utrecht University, the Blavatnik Award for Young Scientists, the Howard Taylor Ricketts Award, the Lewis S. Rosenstiel Award, the Shaw Prize in Life Science and Medicine, the Vilcek Prize in Life Sciences, the Else Kröner-Fresenius-Foundation inaugural international prize in immunology, and the inaugural Lurie Prize in the Biomedical Sciences. He is a member of the National Academy of Sciences, USA, a member of the National Academy of Medicine, USA, a foreign member of the Russian Academy of Sciences, and a fellow of the American Academy of Microbiology.
SABRE CENTER INVESTIGATORS
Richard M. Locksley, M.D.
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Investigator, Howard Hughes Medical Institute
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Quantitative Biosciences UCSF (QB3)
Virology & Microbial Pathogenesis
Howard Hughes Medical Institute

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

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 recently 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.

Publications


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, including RNA-binding proteins 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 small 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 human 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 define the molecular mechanisms that control miRNA homeostasis and extracellular release by lymphocytes, and determine how the miRNA repertoire is so dramatically remodeled during activation.

Selected Publications


7. Pua HH, Steiner DF, Patel S, Gonzalez JR, Ortiz-Carpena JF, Kageyama R, Chiou NT, Gallman A, de Kouchkovsky D, Jeker LT, McManus MT, Erle DJ, Ansel KM. MicroRNAs 24 and 27 Suppress Allergic Inflammation and Target a Network of


Esteban G. Burchard, MD, MPH
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Esteban González Burchard, M.D., M.P.H., is a physician-scientist with formal training and expertise in pulmonary medicine, epidemiology, molecular genetics, genetic and clinical research. He has led a large research program focusing on minority children and gene-environment interactions since 2001. Dr. Burchard serves 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. Esteban Burchard directs the Asthma Genetics Core Facility, now named the Asthma Collaboratory, which is now the largest annotated gene 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 20 publications in the past 2 years with numerous collaborators and trainees, and successful competition for extramural funding. 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


Sandler Asthma Basic REsearch Center  SABRE Investigators

**Fahy JV.** Epithelial cell-derived periostin: roles in TGFβ activation, collagen production and collagen elasticity in asthma. *Proc Natl Acad Sci USA*. 2010; 107:14170-5.


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

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

The specific objectives are as following.

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

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

**Selected Publications**


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
UCSF

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UCSF Box 0130, HSE-1305
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Website: Woodruff Lab [http://woodrufflab.ucsf.edu/]

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

The Bhattacharya laboratory is interested in understanding the molecular mechanisms by which lung macrophages contact and signal to other lineages under acute inflammatory conditions. The current research is focused on interactions between monocyte-derived macrophages and (1) fibroblasts during the fibrotic response to injury; (2) airway smooth muscle during allergen sensitization and challenge.

The specific objectives are as follows:

- Determine the functional and mechanistic role of macrophage contacts with fibroblasts after injury. The lung responds to sterile injury by forming a “fibrotic niche”—clusters of activated fibroblasts that deposit matrix proteins comprising scar. Monocyte-derived macrophages establish contacts with fibroblasts in the first few days after lung injury in mice and are necessary for establishment of the fibrotic niche. How macrophages activate fibroblasts is being investigated in vivo and in co-culture systems by deletion of candidate genes and by live imaging of macrophage-fibroblast interactions.

- Determine the effect of macrophages on airway contraction. Cx3cr1+ macrophages are known to occupy the conducting airways, but their function in airway hyperresponsiveness and asthma is not well understood. Live lung slice imaging of airway contraction and of calcium transients is being applied to probe the role of macrophage contacts with airway-resident cells, including airway smooth muscle, in contractile responses.

Selected Publications


Erin Gordon, M.D.
Assistant Professor
Division of Pulmonary and Critical Care Medicine
Department of Medicine
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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


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


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


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

Objective/Mandate

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

Strategic Goals

The efforts of this center are being directed toward improving imaging technologies for the normal and allergic lung. In 2019, 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 build a novel microscopy platform that enables spatial tagging of cells for downstream single cell RNA sequencing analysis. Called ‘ZipSeq’, this technology promises to be one that will revolutionize spatial transcriptomics of tissues as varied as lung to lymph node.
2. To complete the construction of the 4th generation of our homebuilt multiphoton microscope which will exceed current generation 3 capabilities and further drive development of custom software and hardware tools.
3. To incorporate the upcoming version (2.0) of Micro-Magellan, an open-source UCSF based Micro-Manager plugin, into our homebuilt 2-photon, light-sheet, and widefield microscopy systems.
4. To further integrate the open-source machine learning pixel-classification software Ilastik into data analysis pipelines.
5. To extend machine learning data analysis to the incoming Multiplexed Ion Beam Imaging (MIBI) system.
6. To continue elaborate the use of Lattice Light-Sheet Microscope to study dynamics of immune cells membranes and to create software tools to mine this rich data.
7. To extend the usage and utility of mouse lung imaging through continued development of minimally invasive intravital imaging methods and instrumentation.
8. 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.
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 Managing 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 167 unique users of the BIDC. Many users are trained on multiple instruments. These users represent 62 principal investigators or labs. These labs are drawn from 21 departments or organizational units.

In 2018, 149 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 trained users from the following labs.

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Recent Accomplishments

In 2018, scientifically:

1. Jordan Briscoe (BIDC, SRA) and Peter Baluk, Phd (McDonald Lab) imaged the vascular system of an entire cleared mouse lung on the Nikon AZ100 MacoConfocal microscope. This success makes available the study of vascular rearrangement during cancer drug treatment.

2. Austin Edwards (BIDC, Bioinformatics Programmer) successfully utilized the open-source machine learning pixel classification software Ilastik on H&E slices to identify individual cells and tissue structures in both normal and cancerous tissue.

3. John Eichorst (BIDC, Bioinformatics Programmer) developed image analysis algorithms and software designed for Lattice Light Sheet data to quantitatively examine areas of local high concentrations of proteins along the exterior of cells and compare clustering and colocalization between other populations of proteins on the cell surface.

4. Adam Fries (BIDC, Bioinformatics Programmer) updated Sortomato (custom-written Imaris extension used for object analysis) by making it compatible with Imaris 9.2. Additional features were added such as the ability to automatically sort populations based upon a Gaussian mixture model opposed to manual population identification previous required.

5. Adam Fries successfully adapted a published methodology to spectrally unmix populations of densely packed membrane stained cells to determine their location within tissues. The analysis routine has been applied to whole mouse lymph nodes.


7. The fourth generation homebuilt 2-photon microscope (Gen4) is nearing completion. The design of the microscope makes use of many electronics and optics from the now disbanded Gen1 and Gen2 2-photon microscopes and includes quality of live improvements such as increasing sample accessibility and workspace. The Gen4 features two IR laser sources and 6 PMT detectors similar to the Gen3 microscope, but improves upon the emission optical path; shortening the distance the far red light must travel thus improving signal. Sample stage designs include the ability for intravital imaging, live tissue, and fixed samples. Microscope control will be done through the latest iteration of Micro-Magellan; a Plugin developed at the BIDC and distributed through the open-source UCSF based Micro-Manager.

8. The Selective-Plane Imaging Microscope (SPIM) capabilities were expanded to include cleared tissue imaging. The microscope is a dual side-illuminated galvo-scanning light sheet fitted with a 20x long working distance objective and large array CMOS camera resulting in higher magnification and spatial resolution than is typical for comparable microscopes. With the addition of our FormLabs Form2 3D printer we are able to create custom clearing agent-resistant sample holders compatible with the microscope.

9. We supported a collaborative project between the Krummel lab and Eli-Lilly Company to study how an immuno-oncology therapeutic agent enhances the tumor killing ability of T cells. We used Lattice Light Sheet microscopy to investigate the interaction between T cells and antigen presenting cells under the influence an immune-oncology agent in real time. We found that the immune-oncology agent enhanced the binding of
the T cell to antigen presenting cells by solidifying the interface between the two, namely the immune synapse. Such enhancement of the immune synapse is believed to contribute to enhanced T cell effector functions. Our finding revealed the cellular process in which this immune-oncology agent boosted T cell antitumor immunity.

10. 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

In 2018 the BIDC added three more full time employees. SRA Taylor Shagam has been brought on board to assist in training people across a variety of our microscopes and instruments. She is also assisting in developing user’s data analysis pipelines and working to make the BIDC more efficient. Bioinformatics Programmer John Eichorst, PhD has been hired to take the lead on 4D analysis of data generated on our Lattice Light-Sheet microscope within the Eli-Lilly collaboration. He is primarily focused on 3D clustering of analytes on cell surfaces through time and 4D cell:cell interactions. Bioinformatics Programmer Austin Edwards was hired to expand our machine-learning capabilities for both high-dimensional data analysis and instrument control.

The BIDC upgraded 4 major pieces of equipment this year. The Nikon A1r Multi-Photon and Laser Scanning Confocal Microscope received a new workstation and a multi-version update to the instrument control software. The upgrade resulted in a more stable system and faster communication between instrument and computer. A fully enclosed incubation and atmosphere system was added to the Nikon AZ100 MacroConfocal Microscope. The microscope is now capable of doing multi-day timelapse imaging of large tissue specimens with single-cell resolution. The two Imaris licenses on the Analysis Workstations have been updated to the latest version 9.2. The newest version better handles large datasets, renders surfaces faster, and has improved tracking algorithms and data visualization features. The aging Alaris Objet 30 3D printer has been replaced with the more compact FormLabs Form2. Overall, the new system is simpler to use, has a lower operating cost, and makes accessible more printing materials than the Alaris while maintaining similar lateral and axial printing resolution.

Space

The primary residence of the BIDC is Medical Sciences S11, which includes an office for staff of 6 employees with an attached analysis suite fostering collaboration on analysis projects; wetlab space outfitted for sample preparation including a vibratome, compressitome, incubator, 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.
Funding

The following represent some of the grants that were funded in 2018, in part through our efforts and support:

Jody Baron:
- F31DK112607-03 – A critical role for group 3 innate lymphocytes in hepatitis B virus pathogenesis ([renewed 2019] 2017-2020)
- R01AI39762 - Identifying and modulating therapeutic targets in a model of hepatitis B (2018-2022)
- R01DK103735-01 - Clinical & Immunologic Study of Treatment Withdrawal in E-Ag Negative Hepatitis B ([renewed 2018] 2016-2021)

Aaron Fields:
- NIH R01AR070198 - Role of the cartilage endplate in spinal disc degeneration (2017-2022)

Mark Looney:

Ari Molofsky:
- UCSF PBBR New Frontier in Research - Exploring innate lymphocytes at the brain-immune interface (2017-2018)

Alex Smith (Verkman):
- A2018351S BrightFocus Foundation – AQP4 mislocalization and glucose hypometabolism in Alzheimer’s Disease (2018-2021)

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 develop a novel microscopy platform that enables spatial tagging of cells for downstream single cell RNA sequencing analysis. This microscope will combine standard imaging modalities with the capability to illuminate samples with spatially defined patterns of light for photo-uncaging using a digital micromirror device. In addition, we will seek to integrate a microfluidic pump system that allows for automated perfusion of DNA barcodes into the sample along with washes. Altogether, the final goal is to tie together imaging, spatially selective photo-uncaging, and wash steps to create a prototype device that accomplishes spatial barcoding of cells with minimal user input.

2. The construction of the Gen4 2P microscope is nearing completion. Many components and optics from the now disbanded Gen1 and Gen2 2P microscopes were incorporated into the Gen4 build. A new detection optical train has been implemented which limits the overall photon-path for all channels limiting high-angle photon scatter and increasing S/N. The building of Gen4 encourages a complementary expansion of features of the BIDC written open source Micro-Magellan software that is made available through the UCSF developed Micro-Manager platform.

3. Micro-Magellan is an instrument software control suite that was previously developed in the BIDC and runs through the Micro-Manager program developed at UCSF. A new
version (2.0) is planned to be released in 2019 and will have a much improved graphical user interface (GUI) along with a Python based scripting interface allowing for increased instrument control and flexibility for complex experiments. We plan to incorporate this software on our homebuilt 2P, SPIM, and widefield microscopy systems.

4. Ilastik is an open-source machine learning pixel classification software. Austin Edwards (Bioinformatics Programmer) previously showed that it is capable of highly accurate cell type identification in H&E stained normal and cancer tissue samples. In collaboration with the ImmunoProfiler Initiative (IPI), we plan on utilizing the “canned” machine learning algorithms within Ilastik in conjunction with shape identification and traditional correlated fluorescence microscopy data analysis to develop a high-throughput machine learning pipeline for normal vs cancerous tissue identifiers.

5. The Multiplexed Ion Beam Imaging (MIBI) system is scheduled to be installed at Parnassus Heights in Fall 2019. The system is capable of imaging up to 35 channels using heavy metal tagged antibodies instead of fluorescent probes. The BIDC will work closely with teams using the MIBI to create data analysis pipelines and machine-learning algorithms to maximize the high-dimensional utility of the instrument.

6. John Eichorst (Bioinformatics Programmer) will work to expand his Lattice Light Sheet data based protein clustering and colocalization software with the aim of correlating locations of the T-cell surface having different extents of convexity with the locations of various fluorescently labeled proteins. Ultimately, the goal is to understand the biological significance of the T-cell surface geometry and the organization of proteins on the surface.

7. Adam Fries (Bioinformatics Programmer) will work to develop and incorporate a spectral unmixing tool into the Imaris plugin Sortomato. The aim is for faster and more accurate cell identification in complex biological systems in 2P imaging, but can be adapted for other high-dimensional imaging systems with significant spectral overlap.

8. Jordan Briscoe will work to generate high dimensional methods to analyze ‘neighborhoods’ of immune cells in living tissue sections.

9. The Lattice Light Sheet Microscope (LLSM) user base continues to grow. Kyle Marchuk (Managing Director) and John Eichorst (Bioinformatics Programmer) will share the workload of running the microscope to increase throughput. The BIDC continues to actively develop tools and workflow improvements to increase the accessibility of the massive amount of data the LLSM generates. Additionally, the BIDC will continue to support the collaboration between the Eli-Lilly company and the Krummel lab in the investigation of T cell directed killing of tumor cells.

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 specialist Jordan Briscoe will lead the lung imaging pilots with a focus on improving intravital methods and instrumentation.

Current Equipment

Permanent Equipment:
1. *Gen3 custom built 2-photon: 6 color/2 lasers
2. *Gen4 custom built 2-photon: 6 color/2 lasers
3. * Nikon C1si spectral laser scanning confocal microscope
4. Nikon spinning-disk confocal with TIRF and photo-ablation (Wittman)
5. Nikon A1R Multiphoton and laser scanning confocal microscope
6. Nikon AZ100 MacroConfocal microscope
7. Zeiss large field of view spinning disk microscope (Yokogawa CSU-X1)
8. Zeiss TIRF microscope with IRM
9. Zeiss Cell Observer with Apotome (Nystul)
10. Zeiss AxioImager2 with Apotome
11. Zeiss AxioImagerA1 brightfield microscope
12. Leica SP5 laser scanning confocal microscope
13. IVIS Spectrum live animal imager (animal colony)
14. Selective-plane imaging microscope (SPIM) custom built: 3 lasers
15. Lattice Light-Sheet Microscope
16. *FormLabs 3D printer
17. *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 upgrade Imaris 9.2, 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 Immuno X/BIDC initiative

Principal Investigator, Vincent Chan, Ph.D., Senior Scientist & Chief Strategist

In the past year, SABRE has supported and participated in the Bakar ImmunoX Program, a new initiative on the Parnassus campus, which is jumpstarting a bevy of new projects that will benefit our scientific community. A sample of these includes:

- Inaugural Immuno“XX” Women in Immunology Symposium to highlight phenomenal female immunologists at UCSF (Oct 22)
- ImmunoX booths at Discovery Day at AT&T Park to engage and promote the understanding of immunology and basic science to a family-friendly audience (Nov 3)
- Ignite Short Talks & Happy Hours to introduce the research of new and prospective ImmunoX members to the community (Nov 9, Dec 7, Jan 11, Feb 15, & Mar 8)
- Reserved Journal Club slots for “X Files” to present clinical cases with immunological interest to the ImmunoX community (Nov 29)

Additionally, this initiative launched and received seven proposals for the first-ever call for ImmunoX Community Initiative Seed Grants to spur new ideas and involve more community participation. With a committee of eight technicians, work has begun in brainstorming to build a Technician Training Program to ensure the best research experience for them at UCSF.

As long-term planning for the UCSF CoLabs infrastructure begins, an ImmunoX CoProjects Pilot RFA will be released in early January to collect untapped samples and generate feasibility and diligence data for larger cohort studies.

As a result of the leadership and the momentum in this direction, additional donations were garnered to build even more bandwidth to support a “home base” for faculty in immunology-based research. Together with yearly annual subscriptions, it provides the momentum to deliver exceptional upgrades for the community.
SABRE RNAseq Consortia

Allen Lab

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

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

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

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

Ansel Lab

Accomplishments during prior funding period

High throughput RNA sequencing has transformed the way we study tissue heterogeneity, and the molecular programming of cell identity and function. In my lab, RNAseq has quickly become a staple of our research approach, used in every project and in a variety of ways. In the past year, we have expanded our use of small RNA sequencing in biochemical experiments that identify protein binding sites in messenger RNAs and noncoding RNAs. We used Argonaute-2 high throughput sequencing of RNA from crosslinking immunoprecipitation (Ago2 HITS-CLIP) to map the interactions between microRNAs, mRNAs, and long noncoding RNAs in T cells. The first analysis of these data is under revision at Cell Reports, and can be browsed on our new software tool for RNAseq data visualization at Thagomizer.ucsf.edu. By combining Ago2 HITS-CLIP with RNAseq gene expression analyses in T cells deficient in specific miRNAs, we discovered that abundant miRNAs coordinate enormous genetic networks by directly binding hundreds of target mRNAs simultaneously. The binding sites of less abundant miRNAs can be determined in a similar fashion by pairing Ago2 HITS-CLIP analyses in wildtype cells with matched cells lacking a single miRNA family. In the past year, we performed this analysis in T cells deficient for 4 different miRNA families, and for the first time in B cells as well. The latter analysis pointed us toward mRNA targets of miR-221/222 that may explain their regulation of immunoglobulin class switch recombination to IgG1 and IgE, the antibody isotype that drives allergic responses. We also used small RNAseq to identify novel tRNA fragments that are selectively exported by activated T cells (Chiou et al, Cell Reports 25: 3356-70, Dec 2018), and to determine the cell types that release microvesicles containing microRNAs into the airway lining fluid in allergic inflammation (Pua et al, Cell Reports 26:933-44, Jan 2019), and

In addition, we have used single cell RNA sequencing (scRNAseq) to identify the inflammatory cells that infiltrate skin, and explore the connections between these cells and the molecular cues that communicate with nerves to mediate itch sensation in atopic dermatitis and psoriasis. We also partnered with Prescott Woodruff’s laboratory to perform pilot experiments in preparation for an extensive characterization of airway infiltrating cells in a human segmental airway allergen challenge study that has been ongoing in his lab. Early experiments revealed that the bronchial lavage cells collected from allergen challenged airways are rich in eosinophils and/or neutrophils. These data are interesting, but they are also troublesome since both cell types are resistant to current scRNAseq protocols, and they reduce the data yield accordingly. Therefore, we developed a FACS sorting strategy to separate target cells from frozen airway specimens while excluding eosinophils and neutrophils.

Request for continuing support.

With a second year of support and our partnership with the Woodruff laboratory, we will be able to complete scRNAseq analysis of FACS- sorted cells from the entire library of banked airway samples in the airway challenge study, and to do so with paired single cell analysis of the T cell antigen receptor repertoire. We expect scRNAseq data from this unique experiment to provide novel insights into the acute response to airway allergens in subjects with asthma.
Burchard Lab

Accomplishments during prior funding period

Current transcriptome-wide association studies (TWAS) software uses public genotype-expression repositories like GTex to impute gene expression levels from genotypes. However, since these repositories have predominantly European adult subjects, the imputation quality is largely underexplored in admixed populations and children. Dr. Keys in Burchard Lab in collaboration with Dr. Gignoux have been studying the transethnic portability of gene expression prediction models. Using whole blood RNA-Seq data from 39 African American children, we found that gene expression prediction models based on European adult subjects have low performance on African American children (manuscript in preparation for AJHG). To our knowledge, we are the first team to quantify the performance of gene expression prediction models trained by simulated data with various degree of admixture. These results will inform other researchers about the limits and considerations necessary when applying gene expression prediction models to diverse populations.

Request for continuing support

In the prior funding period, we produced preliminary RNA-seq data that suggest transcriptomic profiles are ethnic-specific. Recent interest in genetic epidemiological studies with RNA-seq data stems from a failure to explain asthma heritability (estimates range widely).1-4 Despite the success of GWAS in identifying risk variants for asthma, these loci only account for a small proportion of disease risk. A complementary approach to identify disease variants is to first identify a set of genetic variants that affect gene expression. Using peripheral blood RNA gene expression, Price et al. demonstrated that differences in gene expression among African Americans of different ancestry proportions are consistent with gene expression differences between European and African populations.5 Leveraging local genetic ancestry to quantify the relative contributions of cis and trans regulation to human gene expression found that 12% of heritable variation in human gene expression was due to cis variants.5

We will employ a similar process in which local ancestry measured from whole genome data is integrated with RNA-seq data from 250 pediatric asthma cases of varying ancestry proportions to find genes and pathways differentially expressed for asthma and related traits. We hypothesize that the genetic determinants of gene expression that significantly explain phenotypic variability in asthma and related traits also vary substantially by genetic ancestry. We will test this hypothesis through two specific aims:

Aim 1: Identification of genes differentially expressed among pediatric asthma cases. We will sequence a total of 250 whole blood transcriptomes from African American children with asthma. Mapped and aligned RNA-seq read counts will be combined with high-resolution local ancestry estimates from existing WGS data to study the effects of ancestry on gene expression. We will investigate the effects of differentially expressed genes on asthma severity and related
traits. Finally, we will assess the portion of asthma heritability attributable to gene expression levels.

**Aim 2: Generation of population-specific gene expression imputation models for transcriptome-wide association studies (TWAS).** Current TWAS software uses public genotype-expression repositories to impute gene expression levels from summary statistics or genotypes. However, these repositories have predominantly European adult subjects. We found in the prior funding period that gene expression imputation models are population-specific. We will train new population-specific models of gene expression for whole blood TWAS. We will perform the first TWAS of pediatric asthma in admixed children. The prediction models will be available to other researcher to perform TWAS with genotype data.

**Impact:** We build on a history of successful integrative genomic analyses of pediatric asthma.6-8 We will produce highly accurate and freely distributable gene expression imputation models for general research use.

References:


Bulk RNA sequencing in the UCSF severe asthma cohort

Investigators: Michael Peters, Max Seibold (National Jewish Health), John Fahy

Background: UCSF is participating center in the NHLBI Severe Asthma Research Program. Participants with severe asthma and non-severe controls undergo detailed phenotyping at baseline including collection of induced sputum. UCSF is the core laboratory for the network for sputum RNA extraction and quality assurance, and UCSF investigators (Peters and Fahy) have been at the forefront in demonstrating the feasibility and utility of sputum cell RNA analysis (using qPCR) in studies of airway inflammation in asthma. Recently, Dr Fahy and Peters have collaborated with Max Seibold at NJH to perform whole genome sequencing on sputum cell RNA samples from a non-SARP (mild/moderate) asthma cohort from UCSF. We found gene expression co-networks that correlate with clinical features of asthma. For example, we found evidence for an “ultra high T2” subset of asthmatics characterized by uniformly high overexpression of dozens of genes related to type 2 inflammation. The ultra high T2 patients were relatively steroid resistant and had more severe asthma. Other notable findings included a finding that that older asthma patients are characterized by increases in a gene expression profile for CD11b+ CD103- dendritic cells. In addition, we noted a deficiency in airway cytotoxic CD8+ cell activity in T2-low asthmatics that is associated with obesity-related inflammation. In studying more severe patients in SARP, we hope to confirm and extend these preliminary data and identify additional unsuspected pathways and their consistency over time.

Proposal: To perform bulk RNAseq in 200 UCSF SARP asthma cell samples (sputum cell RNA samples from 40 patients at baseline, with repeat sputum from the same patients at year 1, year 2, and year 3).

High level analysis Plan:
Using data from a non-SARP (mild/moderate) asthma cohort from UCSF we have developed a data analysis workflow to identify gene co-expression networks within severe asthma (Figure 1). We propose to use this same workflow in the SARP. Specifically, we propose to identify gene expression co-networks using Weighted Gene Co-expression Network Analysis (WGCNA). Then using immune cell specific gene signatures identified in the immune response in silico (IRIS) database we will determine the immune cells that drive each WGCNA module. Using these co-expression networks that relates to specific immune cells we will then: i) Determine how co-expression networks correlate to clinical asthma phenotypes such as age, body mass index, Forced expiratory volume in 1 second (FEV1), and risk of developing asthma exacerbations, and ii) Determine the reproducibility of gene expression co-networks over time.
Gene Expression data

Identify Gene Expression Co-networks associated with clinical characteristics

Define asthma endotypes based upon: cell type, clinical, and gene expression characteristics

Determine how asthma endotype classification changes over one, two, and three years

Hierarchical clustering analysis

Co-expression analysis (WGCNA)

Immune cell enrichment analysis

Figure 1: Schematic of data analysis plan
SABRE RNAseq Consortia II

Locksley Lab

Accomplishments during prior funding period.

We proposed to assess heterogeneity of innate lymphoid cells across tissues of the mouse and during ontogeny using single-cell RNAseq (scRNAseq). The approach was facilitated through use of reporter mice engineered in the lab that allowed identification and enrichment of ILC2s to high purity. Our initial findings were published in Nature Immunology (Ricardo-Gonzalez et al., Tissue signal imprint ILC2 identify with anticipatory function. Nature Immunol 19:1093-99, 2018), and attracted an accompanying News & Views commentary (Zhu, Mysterious ILC2 tissue adaptation, Nature Immunol 19:1042-4, 2018) and substantial attention in the scientific community. The work reflects contributions from post-docs in my lab, but also bioinformatics support from the Institute for Human Genetics and the Lung Biology Center. We continue to mine data from this work, and a second manuscript has been reviewed and is in revision after submission to Immunity, spearheaded by a student in the lab together with postdocs and bioinformatics analysis and input (Lee et al, Layered ontogeny and in situ perinatal priming of tissue ILC2s, in revision for Immunity), which explores developmental aspects of ILC2 differentiation in tissues, including the lung.

Request for second year of support.

Based on success of our initial forays into this technology, we propose to extend our study to epithelial tuft cells in the upper and lower respiratory tract. Based on our identification of tuft cells as key mucosal sensory cells that are upstream of ILC2 activation in small intestine (Schneider et al., Cell 174: 271-84, 2018), we will extend our analysis in anticipation of uncovering unexpected mechanisms by which tuft cells sense environmental biologic signals and transmit information to tissue resident immune cells. Our discovery that tuft cells are the only epithelial cells that have the capacity to generate IL-25, cysteinyl leukotrienes and acetylcholine, all linked in various pathways to ILC2 activation, smooth muscle contraction and airway hyperresponsiveness, suggests that this analysis, facilitated by our genetic marking, fate-mapping and conditional deletion strategies for tuft cells in mice, will uncover unexpected pathways underpinning chronic airways allergic inflammation, and that these will extrapolate to relevant pathways in human disease. Although some scRNAseq approaches of these respiratory epithelia have been reported, none have evaluated the airway as a contiguous unit for transmission of respiratory elements to the innate immune system via tuft cells. Our systematic approach, together with the genetic tools available in my lab and the bioinformatics supports of the Human Genetics Institute and the Lung Biology Center, will enable rapid progress and novel discovery.

We have accomplished bulk RNAseq of epithelial tuft cells from multiple organs, attesting to our capacity to purify and analyze these rare cell types (Nadjsonbati et al., Immunity 49: 33-41, 2018). We anticipate one year of additional support will be necessary to complete these studies using scRNAseq approaches. As with our prior studies, sequencing data will be made openly available to the scientific community after publication.
SABRE RNAseq Consortia II

Shin Lab

Accomplishments during prior funding period

We have proposed to utilize RNA sequencing technology to define the molecular mechanisms by which MARCH1 conditions dendritic cells (DCs) to induce the production of IL-4 from naïve allergen-specific CD4 T cells during allergic sensitization. This proposal was built on our recent findings that MARCH1-deficient mice were completely resistant to developing Th2 inflammation, eosinophilia, airway hyper-reactivity, and IgE production upon exposure to the house dust mite (HDM) allergen and that these phenotypes were entirely attributed to MARCH1 deficiency in DCs (submitted to Immunity).

As proposed, we intratracheally challenged wild type and MARCH1-deficient mice with HDM, isolated DCs from the mediastinal lymph nodes, purified RNA from the isolated DCs, and performed a sequencing analysis. Four to five mice were used per strain, and littermates were used to control potential variation coming from environment. The sequencing yielded 372.6 billion total reads with an average of 74.1 % of these reads aligning uniquely to the mouse genome. Reads uniquely mapped to known mRNAs were used to assess expression changes between genes. Pairwise combinations were made between wild type and MARCH1-deficient samples using DESeq2. After filtering (FDR <0.05), we found that 236 genes were differentially expressed between wild type and MARCH1-deficient DCs. This is very exciting finding because it indicates MARCH1, an enzyme involved in post-translational modification of protein, is involved in the regulation of a large number of genes during allergic sensitization. These differentially expressed genes included some of tumor necrosis factor receptor super families, chemokines, and chemokine receptors that have been previously implicated in DC function of instructing T helper cell differentiation. Interestingly, several solute carrier transporters including SLC26a6, SLC4a8, SLC41a1, SLC9a8, and SLC27a3 were markedly deficient in DCs lacking MARCH1, suggesting a role of MARCH1 in regulating some metabolic pathways in DCs, which may play an important role for DCs to drive Th2 cell differentiation. A non-biased pathway analysis is on-going to define specific pathways that control Th2 cell priming in a MARCH1 dependent manner. We also started a kinetic analysis of gene expression changes to figure out the exact stages where the expression of each gene is regulated along the migration of DCs from the lungs to the draining lymph nodes.

Request for second year of support

Along the study of defining the specific role of MARCH1 in allergic asthma, we found that MARCH1 is not only important for priming Th2 cells during allergic sensitization but also important for evoking memory Th2 cell responses. More importantly, this role was also dependent on the expression of MARCH1 in DCs. This finding implicates a function of DCs in chronic asthma and a role of MARCH1 in executing this function. Therefore, we propose to extend our study to the understanding of the role of DCs and MARCH1 in chronic asthma. We already established a robust protocol of inducing HDM-dependent chronic asthma in mice. We also generated a mouse strain in which we can disable the expression of MARCH1 in an inducible manner. By using this mouse strain and single cell RNA sequencing technology, we will investigate how heterogeneous lung DCs are, how this heterogeneity is altered in chronic asthma, and whether MARCH1 is involved in this alteration contributing to chronic asthma.
SABRE RNAseq Consortia II

Woodruff Lab

Accomplishments during prior funding period.

We have an ongoing human segmental airway allergen challenge study that is ideal for single cell RNA-sequencing (scRNAseq) studies since we are obtaining both BAL cells and airway epithelial at baseline, after diluent challenge (control) and after allergen challenge (ClinicalTrials.gov Identifier: NCT02230189). Therefore, we can study both the immune cells recruited into the lung and the changes in the airway epithelial cell composition in response to a stereotypic allergic stimulus in well-characterized people with asthma. To date we have used SABRE funds to perform 2 pilot studies of scRNAseq in BAL cells and 2 pilot studies in epithelial brushings using the 10X Chromium platform at the UCSF Institute for Human Genetics. These pilot studies are required because the study of primary human cells does not yet have standardized protocols and because the complicated human study (with three sampling times in each of n=12 participants for BAL cells (total of 36 samples) and in each of n=5 for epithelial brushings (total of 15 samples)) have required us to freeze cells before analysis. The studies on BAL cells tested the yield of RNAseq data on the full range of inflammatory cells, with and without depletion of dead cells using magnetic beads. We found that we are able to acquire good data from T cells and dendritic cells but that granulocytes are largely lost (with or without dead cell depletion). Based on these results, our scientific goal for the BAL cell preparations will be to proceed with single cell TCR sequencing after flow sorting of T cells (in conjunction with Mark Ansel) from the BAL samples since this approach will be robust to the loss of granulocytes and will specifically leverage the allergen challenge design. Out pilot studies using airway epithelial cells before and after allergen challenge have yielded better quality data for the range of epithelial cells so far. Therefore, our scientific goal for the epithelial cell preparations will be to identify the effect of in vivo human allergen challenge on secretory cells (goblet cells), and, if possible, tuft cells and ionocytes, and the production of epithelial cytokines in response to allergen challenge in human asthma. This work will be synergistic with the studies that are ongoing in the Locksley Lab.

Request for second year of support.

A second year of support (and any remaining funds from the first year) will allow us to perform all of our planned studies with airway epithelial cell preparations described above and, by combining our efforts with the Ansel Lab, we expected to be able to complete the BAL cell analyses described above. The opportunity to perform these scRNAseq studies in human cells in this interventional study is invaluable because it should both provide novel insights and also serve as human correlation for investigations that are ongoing using model systems in the Ansel and Locksley laboratories. Our sequencing data will be made openly available to the scientific community after publication.
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.

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

**Figure 2.** Type 2 Gene Signature is increased in the sinus epithelium of CRS with asthma and nasal polyps (CR SwANP) compared to health and CRS without asthma and polyps (CR SwoANP).
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. Given this data, we expect that tuft cells are increased in the sinus epithelium in the context of type 2 inflammation. 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. The degree to which type 2 and tuft cell signatures correlate across airway epithelial sites in patients with asthma and NP is not known but is needed to understand the relationship between upper and lower airway responses in severe asthma.

In order to test this hypothesis and further characterize tuft cells throughout the human respiratory tract, we propose single cell sequencing of epithelial brushes from healthy controls (N=2-3) and subjects with NP and asthma (N=3-4). We propose the collection and single cell sequencing on the 10x platform from 4 anatomic sites of the same patients: proximal bronchial epithelium, nasal epithelium, sinus epithelium, and polyp epithelium. The ethmoid sinus is most commonly the site of origin of nasal polyps and we propose to sample both the sinus epithelium as well as the polyp epithelium, in order to better understand their precise location (a major limitation of published work). Understanding the anatomic position of tuft cells as well as their gene expression signatures in health and disease will enable us to further understand how the type 2 immune response is orchestrated in nasal polyposis and severe type 2 high asthma.

REFERENCES:

CONTRIBUTIONS TO RELEVANT SCIENTIFIC ACTIVITIES
# SABRE Asthma Research Conference Schedule 2019

**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>1/23/19</td>
<td>Prescott Woodruff, M.D.</td>
<td>MicroRNA regulation of airway epithelial mucus production</td>
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<tr>
<td>2/27/19</td>
<td>Vincent Auyeung</td>
<td>Roles for IRE1 paralogs and the unfolded protein response in asthma</td>
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<td>3/27/19</td>
<td>Hal Chapman, M.D.</td>
<td>Reversal of pro-fibrotic signaling in vivo in humans with fibrosis</td>
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<td>4/24/19</td>
<td>Andre Levchenko, Ph.D. (visiting scholar from Yale University)</td>
<td>Analysis of epithelial-smooth muscle interaction in broncospasm using a bronchi-on-a-chip model</td>
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<td>Lekshmi Santosh</td>
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<tr>
<td>12/31/18</td>
<td>Winter Holiday Break</td>
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<tr>
<td>01/07/19</td>
<td>Fellows Feedback</td>
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<tr>
<td>01/14/19</td>
<td>John Greenland</td>
<td>Ricky Wang</td>
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<tr>
<td>01/21/19</td>
<td>MLK Holiday</td>
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<tr>
<td>01/28/19</td>
<td>Visiting Professor - Nuala Meyer</td>
<td>Rupal Shah</td>
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<tr>
<td>02/04/19</td>
<td>Michael Peters</td>
<td>Nirav Bhakta</td>
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<tr>
<td>02/11/19</td>
<td>Visiting Professor - John Tsang</td>
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<tr>
<td>02/18/19</td>
<td>President's Day Holiday</td>
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<tr>
<td>02/25/19</td>
<td>Nikko Arger</td>
<td>Tien Peng</td>
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<tr>
<td>03/04/19</td>
<td>Visiting Professor - Jerry Krishnan</td>
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<tr>
<td>03/11/19</td>
<td>Elliot Naidus</td>
<td>Danny Calabrese</td>
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<tr>
<td>03/25/19</td>
<td>Panel Discussion</td>
<td>Carolyn Calfee</td>
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<tr>
<td>04/01/19</td>
<td>Vincent Auyeung</td>
<td>Tien Peng</td>
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<tr>
<td>04/08/19</td>
<td>Visiting Professor - Patricia Kritek</td>
<td>Lekshmi Santosh</td>
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<tr>
<td>04/15/19</td>
<td>Chris Berger</td>
<td>Chaz Langelier</td>
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<tr>
<td>04/29/19</td>
<td>Visiting Professor - Christina Barkauskas</td>
<td>Tien Peng</td>
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<tr>
<td>05/06/19</td>
<td>Nadia Herrera</td>
<td>Christina Yoon</td>
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<tr>
<td>05/20/19</td>
<td>ATS - (no conference)</td>
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<tr>
<td>05/27/19</td>
<td>Memorial Day holiday (no conference)</td>
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<tr>
<td>06/17/19</td>
<td>Bart Lambrecht (Ghent University)</td>
<td>John Fahy</td>
</tr>
<tr>
<td>Date</td>
<td>Speaker</td>
<td>Host</td>
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<tr>
<td>September 10</td>
<td>Dusan Bogunovic, <em>Icahn School of Medicine at Mount Sinai</em></td>
<td>Adrian Erlebacher</td>
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<tr>
<td>September 17</td>
<td>Felix Yarovinsky, <em>University of Rochester Medical Center</em></td>
<td>Julie Zikherman</td>
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<tr>
<td>September 24</td>
<td>James Crowe – <em>Vanderbilt University</em></td>
<td>Art Weiss</td>
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<tr>
<td>October 1</td>
<td>Joel Ernst, <em>UCSF</em></td>
<td>Anita Sil</td>
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<tr>
<td>October 8</td>
<td>Dana Philpott, <em>University of Toronto</em></td>
<td>Joanne Engel</td>
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<tr>
<td>October 15</td>
<td>Marco Colonna, <em>Washington University School of Medicine</em></td>
<td>Ari Molofsky</td>
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<tr>
<td>October 22</td>
<td>Camilla Forsberg, <em>U.C. Santa Cruz</em></td>
<td>Anthony DeFranco</td>
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<tr>
<td>October 29</td>
<td>Russell Vance, <em>UC, Berkeley</em></td>
<td>Nadia Roan</td>
</tr>
<tr>
<td>November 5</td>
<td>Ken Murphy, <em>Washington University School of Medicine</em></td>
<td>Jeoung-Sook Shin</td>
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<tr>
<td>November 19</td>
<td>Stefan Feske, <em>New York University School of Medicine</em></td>
<td>Cliff Lowell</td>
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<tr>
<td>December 3</td>
<td>Hilde Cheroutre, <em>La Jolla Institute for Allergy and Immunology</em></td>
<td>Melanie Ott</td>
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<tr>
<td>December 10</td>
<td>Claudia Kemper, <em>NIH: National Heart, Lung &amp; Blood Institute</em></td>
<td>Jody Baron</td>
</tr>
<tr>
<td>January 7</td>
<td>Greg Barton, <em>UC Berkeley</em></td>
<td>Mark Anderson</td>
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<tr>
<td>January 18</td>
<td>Gerard Eberl, <em>Institut Pasteur</em></td>
<td>Immunology Postdocs</td>
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<tr>
<td>February 4</td>
<td>Nicolas Chevrier, <em>University of Chicago</em></td>
<td>Rich Locksley</td>
</tr>
<tr>
<td>February 11</td>
<td>Gwen Randolph, <em>Washington University School of Medicine</em></td>
<td>Max Krummel</td>
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<tr>
<td>February 25</td>
<td>Jorge Henao-Mejia, <em>Perelman School of Medicine, University of Pennsylvania</em></td>
<td>Rich Locksley</td>
</tr>
<tr>
<td>March 4</td>
<td>Janelle Ayres, <em>Salk Institute for Biological Studies</em></td>
<td>Tiffany Scharschmidt</td>
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<tr>
<td>March 11</td>
<td>Megan Levings, <em>B.C. Children’s Hospital</em></td>
<td>Qizhi Tang</td>
</tr>
<tr>
<td>March 18</td>
<td>Niki Moutsopoulos, <em>NIH: National Institute of Dental and Craniofacial Research</em></td>
<td>Mark Ansel</td>
</tr>
<tr>
<td>March 25</td>
<td>Andrea Schietinger, <em>Memorial Sloan Kettering Cancer Center</em></td>
<td>Jeff Bluestone</td>
</tr>
<tr>
<td>April 1</td>
<td>Julie Blander, <em>Weill Cornell Medicine</em></td>
<td>Judith Hellman</td>
</tr>
<tr>
<td>April 8</td>
<td>Kristin Hogquist, <em>University of Minnesota</em></td>
<td>Jeroen Roose</td>
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<tr>
<td>April 15</td>
<td>Mark Shlomchik, <em>University of Pittsburgh</em></td>
<td>Jason Cyster</td>
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<tr>
<td>April 22</td>
<td>Ruslan Medzhitov, <em>Yale School of Medicine</em></td>
<td>Rich Locksley</td>
</tr>
<tr>
<td>April 29</td>
<td>Romina Goldszmid, <em>NIH: Center for Cancer Research</em></td>
<td>Matt Spitzer</td>
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<tr>
<td>May 6</td>
<td>Akiko Iwasaki, <em>Yale School of Medicine</em></td>
<td>Immunology Grad Students</td>
</tr>
<tr>
<td>May 13</td>
<td>Michel Nussenzweig, <em>Rockerfeller University</em></td>
<td>Zena Werb</td>
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<tr>
<td>May 20</td>
<td>Lora Hooper, <em>University of Texas Southwestern Medical Center</em></td>
<td>Averil Ma</td>
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</table>
ImmunoX Seminar Series
Monday 4/22, 9 AM, PARNASSUS, N-225

“Tissue Biology: Homeostasis and Disease”

Ruslan Medzhitov, PhD
Professor, Department of Immunobiology
Yale School of Medicine

Host: Rich Locksley
RECENT AND NEW PUBLICATIONS
SUPPORTED BY THE SANDLER ASTHMA BASIC RESEARCH CENTER
(2017-2019)
Christopher D.C. Allen, Ph.D.

K. Mark Ansel, Ph.D.


Mallar Bhattacharya, M.D., MSc.


Homer Boushey, M.D.


Harold Chapman, M.D.

Pres a M, Racine JJ, Dwyer JR, Lamont DJ, Ratti u JJ, Sarsani VK, Chen YG, Geurts A, Schmitz I, Stearns T, Allocco J, Chapman HD, Serreze DV. A Hypermorphic Nfkbid Allele


Kim KK, Sheppard D, Chapman HA. TGF-β1 Signaling and Tissue Fibrosis.
Anthony DeFranco, Ph.D.


William F. DeGrado


PMID: 30694671


PMID: 30449325


**David Erle, M.D.**

Eckalbar WL, **Erle DJ**. Singling out Th2 cells in eosinophilic esophagitis. *J Clin Invest.* 2019 Apr 8;130. pii: 128479. doi: 10.1172/JCI128479. eCollection 2019 Apr 8. PMID:30958801


**John Fahy, M.D.**


Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction.


PMID: 29400693


Internet-Based Monitoring in the Severe Asthma Research Program Identifies a Subgroup of Patients with Labile Asthma Control.


PMID: 29080709


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


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


**Erin Gordon, M.D.**


**Matthew Krummel, Ph.D.**


Ari Molofsky


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


**Dean Sheppard, M.D.**


Jeoung-Sook Shin


Aparna Sundaram, M.D.


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


Jonathan Weissman, Ph.D.


Prescott Woodruff


Fawzy A, Putcha N, Aaron CP, Bowler RP, Comellas AP, Cooper CB, Dransfield MT, Han MK, Hoffman EA, Kanner RE, Krishnan JA, Labaki WW, Paine R 3rd, Paulin LM, Peters...


ROP: dumpster diving in RNA-sequencing to find the source of 1 trillion reads across diverse adult human tissues.


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 (SAR) and the PrecISE Asthma Trials Network, and have successfully renewed the NIH Program Project Grant oriented around patients recruited to the UCSF Airways Clinical Research Center. Dr. Burchard has become a national leader in deconvoluting genomes from minority populations that suffer disproportionately from asthma. 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, reaching over $15 million in direct costs this year. Individual members have been recognized by national honor organizations, professional and scientific 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 SABRE Center continues to play a formative role in shaping opportunities for patient-oriented, disease-focused, basic research as the new Parnassus campus planning continues to accelerate. Although several options exist, visions of a multi-component structure housing a spectrum of immune-related diseases, including asthma and allergic diseases, but also autoimmune, inflammatory, transplantation and gene therapy, is being considered. Incorporating basic research, cutting-edge, discovery in close physical approximation to patients and patient material in efforts to improve information and biologics flow from ‘bench-to-bedside’ through rapid acquisition and implementation of progressive sequencing, proteomic and tissue engineering capacity remains a key piece of the plan, which would coincide with the buildout of the new hospital on the Parnassus site by 2025. This remains a major initiative for the future of the UCSF campus, and participation by the SABRE Center and its investigators in these efforts will remain imperative for the next several years. A number of SABRE faculty are involved in planning and resource allocation, and we anticipate playing a major contributing role going forward as SABRE positions itself to being a forward-looking contributor to the new campus.

Beyond integrating across campus sites, the SABRE Center is continuing efforts for outreach and integration. We continue to leverage state-of-the-art technology across the greater campus by seeding start-up and matching funds to achieve the greatest return for cutting-edge investments in basic science as applied to human biology and disease. We are close to hiring a full-time systems analyst for computation and handling of the large
amounts of sequencing data accumulated from mouse and human tissues. We look forward to continuing novel and unexpected discoveries made by laboratories at UCSF that will impact asthma and asthma-related research. The SABRE Center is planning a second strategic retreat in the fall to more thoughtfully prepare for the challenges faced by the Center during this period of growth and re-direction on the Parnassus campus.

As we approach our second decade at UCSF, our goal is to continue the trajectory established by 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. We look forward to continuing work and counsel with Jim, Susan, Steve and all the members of the Sandler Foundation. We are most grateful for the opportunity to respond to the challenge and look forward to discoveries that will have a lasting impact on the important human disease of asthma.
BIOGRAPHICAL SKETCHES
BIOGRAPHICAL SKETCHES

Christopher Allen, Ph.D.
K. Mark Ansel, Ph.D.
Nirav Rati Bhakta, M.D., Ph.D.
Mallar Bhattacharya, M.D., MSc.
Homer Boushey, M.D.
Esteban Burchard, M.D., M.P.H.
Harold Chapman, M.D.
Anthony DeFranco, Ph.D.
William DeGrado, Ph.D.
David Erle, M.D.
John Fahy, M.D., M.Sc.
James S. Fraser Ph.D.
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>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
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<tr>
<td>Massachusetts Institute of Technology</td>
<td>B.S.</td>
<td>06/2001</td>
<td>Biology</td>
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<tr>
<td>University of California, San Francisco</td>
<td>Ph.D.</td>
<td>06/2007</td>
<td>Biomedical Sciences</td>
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<tr>
<td>University of California, San Francisco</td>
<td>Postdoctoral</td>
<td>10/2007</td>
<td>Immunology</td>
</tr>
</tbody>
</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

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


A 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 Fc\(\gamma\) 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 solve the technical roadblocks in studying these cells, my lab generated a novel fluorescent reporter mouse to identify and track rare B cells and plasma cells that express IgE. We used this tool to study the genesis and fate of IgE-expressing B cells in the primary immune response to protein antigens and helminth infection. This analysis revealed that IgE-expressing B cells showed an increased propensity to undergo plasma cell differentiation, with limited participation in germinal centers, which limited the affinity and lifespan of the IgE antibody response in healthy mice. We recently revealed that these properties of IgE-expressing B cells, can be traced to constitutive activity of the IgE B cell receptor. This work provided a new understanding of the mechanisms responsible for regulating IgE antibody responses in vivo. For these studies, I designed the experiments, directed the research and helped collect and analyze the data. We also wrote a review based on these and other recent studies on the regulation of IgE-expressing B cells.


Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

R01 AI 130470-01A1  Allen, Christopher David Caballero (PI)  12/01/17 – 11/30/22
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

R21 AI130495-01A1 Allen, Christopher David Caballero (PI) 06/07/17-05/31/19
Function of bronchus-associated macrophages. The overall goal of this proposal is to characterize and determine the function of a population of macrophages proximal to the bronchial airways.
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 considered whether basophils contribute to antigen transport, to the enhancement of adaptive immunity, and to tissue damage and repair.
Role: PI
BIOGRAPHICAL SKETCH

NAME
K. Mark Ansel

eRA COMMONS USER NAME
anselm

POSITION TITLE
Associate Professor of Microbiology and Immunology

EDUCATION/TRAINING

INSTITUTION AND LOCATION | DEGREE | YEAR(s) | FIELD OF STUDY
--- | --- | --- | ---
Virginia Tech, Blacksburg, VA | B.S. | 1992-1996 | Biochemistry
University of California, San Francisco | Ph.D. | 1996-2001 | Biomedical Sciences
Immune Disease Institute, Harvard Medical School | 12/2007 | Immunology

Positions

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

Other Experience and Professional Memberships

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

Awards and Honors

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

Contribution to Science

1. We have developed sophisticated capabilities in single cell analysis in mouse and human biospecimens using flow cytometry (FACS) and mass cytometry (CyTOF). In collaboration with Dr. Fahy, Dr. Woodruff and sarcoidosis expert Dr. Laura Koth, we applied these tools to characterize inflammatory infiltrate in blood, bronchial lavage and induced sputum samples in human airway diseases. These experiments identified a small population of airway innate type 2 lymphocytes (ILC2) but led to the surprising finding that airway basophils are the major IL33-responsive cell type associated with molecular markers of allergic inflammation in asthma. Characterization of T helper cell subsets using cell surface markers revealed a marked increase in CCR6-expressing effector T cells in sarcoidosis, and subsequent transcription factor and cytokine intracellular FACS experiments showed that most of these cells were “Th17.1” cells and a major source of both IL-17 and the Th1 cytokine IFN-γ, a major driver of the immunopathology of sarcoidosis.


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


3. Helper T cells lacking all miRNAs exhibited 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 a ‘rescue screening’ technology to determine which miRNAs regulate T cell behaviors that can be observed in vitro and used it to test all of the reasonably abundantly expressed miRNAs for effects on T cell proliferation and differentiation. This led to the discovery that miR-29 potently inhibits Th1 cell differentiation through inhibition of a set of direct mRNA targets that include the related transcription factors T-bet and Eomesodermin. This same miRNA and several others that we have studied also regulate the differentiation of Th17 and T regulatory (Treg) cells. Recently, we have 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 miRNAs miR-24 and miR-27 potently inhibit Th2 responses in vitro and in vivo, and combined empirical and bioinformatic methods to identified a network of functionally relevant target mRNAs including some that encode well-known regulators of Th2 cell differentiation, such as GATA-3 and Ikaros, and others that represent novel players in Th2 biology.


4. 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.


5. We have also made important discoveries regarding the programming of follicular helper T (Tfh) cell development and cytokine production. My interest in Tfh cells goes back to my first publication as a graduate student in Jason Cyster's laboratory, in which we showed that activated T cells acquire expression of homing receptors that permits their migration into B cell areas of secondary lymphoid organs. More recently, we described the early kinetics of the upregulation of the transcriptional repressor BCL6, which is necessary and sufficient to direct Tfh cell differentiation. Drawing on knowledge and genetic tools generated during my postdoctoral studies, we also 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. Finally, we 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 directly inhibiting the transcription factor ROR-α, which otherwise induces a Th17/Th22-like gene expression program.


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

5R01HL109102 K Mark Ansel (PI) 08/01/2011 – 03/31/2020
National Heart, Lung, and Blood Institute
MicroRNA-Directed Pathway Discovery In Helper T Cell Driven Airway Inflammation
The major goal of this project is to identify and characterize the in vivo activity and molecular targets of miRNAs that regulate Th2 and Th17 cell functions relevant to asthma.
Role: PI

1R21AI128047-01A1 K Mark Ansel (PI) 05/10/2018 – 04/30/2020
National Institute of Allergy and Infectious Diseases
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.

1R01AI106923-04 Lukas Jeker (PI) 08/01/2014 - 07/31/2019
National Institute of Allergy and Infectious Diseases
The Role of Micrornas in Autoimmune Disease
The major goal of this project is to examine the molecular mechanisms by which miRNAs influence the balance between the stimulatory and inhibitory effects of helper T cells in autoimmunity.
Role: Co-investigator

5T32GM008568-22 Ansel (PI) 07/01/1995 – 06/30/2020
National Institute of General Medical Sciences
Predoctoral Training in Biomedical Sciences
This training grant supports BMS, an interdisciplinary PhD program that trains students for research careers investigating the molecular basis of tissue and organ function in human health and disease. The program offers an integrative curriculum that provides a foundation in cell biology, molecular biology and genetics as applied to research problems in metazoan development, physiology and disease. It provides opportunities for deep exposure to focus areas and intensive mentoring through small group discussion-style courses and technology workshops, as well as translational courses that incorporate discussion of patient cases.
Role: PI
BIOGRAPHICAL SKETCH

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

POSITION TITLE
Assistant Professor of Medicine

eRA COMMONS USER NAME
(BRANIR

EDUCATION/TRAINING

<table>
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<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
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<tr>
<td>Massachusetts Institute of Technology</td>
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<td>Electrical Engineering</td>
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<tr>
<td>Stanford University School of Medicine</td>
<td>MD</td>
<td>2006</td>
<td>Medicine</td>
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<tr>
<td>Stanford University School of Medicine</td>
<td>PhD</td>
<td>2006</td>
<td>Mol. and Cell Physiology</td>
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<tr>
<td>University of California, San Francisco</td>
<td>Internship</td>
<td>2007</td>
<td>Internal Medicine</td>
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<td>University of California, San Francisco</td>
<td>Residency</td>
<td>2008</td>
<td>Internal Medicine</td>
</tr>
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<td>University of California, San Francisco</td>
<td>Fellowship</td>
<td>2011</td>
<td>Pulmonary, Critical Care</td>
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<tr>
<td>University of California, San Francisco</td>
<td>Postdoctoral</td>
<td>2011</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
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
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

Nina Ireland Program for Lung Health 01/01/2017-12/31/2018 with extension
Understanding cellular sources of airway cytokines in interferon-high asthma
Role: PI

Sandler Asthma Basic Research Fund 06/01/14
Support for my role in the Airway Research Center, where I see study subjects and perform bronchoscopies.

Completed Research Support

A124693 Bhakta (PI) 01/01/15-01/01/16
SPIROMICS (Subpopulations and intermediate outcome measures in COPD study)
mRNA and miRNA profiling in epithelial brushings, sputum cell pellets, BAL fluid, bronchial wash, serum, plasma, and sputum supernatant on network-wide samples.
Role: Subcontract PI
# BIOGRAPHICAL SKETCH

<table>
<thead>
<tr>
<th>NAME</th>
<th>POSITION TITLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mallar Bhattacharya, M.D., M.Sc.</td>
<td>Assistant Professor of Medicine</td>
</tr>
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| eRA COMMONS USER NAME (credential, e.g., agency login) | BMALLAR |

## EDUCATION/TRAINING

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

### Positions and Employment

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

### Other Experience and Professional Memberships

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

### Honors

- **2008-2009**: Will Rogers Institute Fellowship
- **2000**: American Neurological Association Summer Fellowship
- **2000**: Pasteur Summer Research Fellowship for Medical Students
- **1997**: Member, Phi Beta Kappa Society, Harvard College Chapter
- **1994 -1998**: New York State Robert C. Byrd Honors Scholarship
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 macrophages that localize to sites of fibroblast accumulation after lung injury in mice and exert a profibrotic effect. As part of this project, working with outstanding computational collaborators Dvir Aran and Atul Butte, I have developed a novel tool named SingleR that annotates cellular identity in single cell RNA-seq by reference to bulk RNA-seq datasets of pure cell types. We used SingleR for unbiased hierarchical clustering of mouse lung macrophages in fibrosis, which yielded three main subtypes: interstitial macrophages; resident alveolar macrophages; and an intermediate, transitional cell with intermediate gene expression between alveolar and interstitial cells. Marker analysis by flow and immunofluorescence localized these transitional macrophages specifically to the fibrotic niche, and ablation using a subtype-specific Cre (Cx3cr1-CreERT2) driving diphtheria toxin revealed a profibrotic effect of the cellular subtype in the bleomycin model. Mechanistic studies attributed the profibrotic effect to macrophage secretion of Pdgf-aa, which supported fibroblast proliferation. These findings provide a new window on the repertory of macrophage signaling to the mesenchyme.


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

On-going Research Support

1R01HL131560-03 04/01/2016-03/31/2021
NHLBI
Title: The Regulation of RhoA Activation in Airway Smooth Muscle Role: PI

UCSF Nina Ireland Program for Lung Health 01/01/2019 – 12/31/2021
Title: Defining macrophage pro-fibrotic mechanisms in lung fibrosis. Role: PI

UCSF Resource Allocation Program 01/19/2019 – 12/31/2019
Title: Macrophage function in lung fibrosis Role: PI
Completed Research Support

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

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

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

UCSF Resource Allocation Program  02/01/2015 – 12/31/2016
Title: Integrin alpha-v beta-5 disrupts endothelial barrier function in acute lung injury
Role: PI

15BGIA22780001  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
Role: PI

UCSF Nina Ireland Program for Lung Health  01/05/2015 – 12/31/2016
Title: Integrin alpha-v beta-5 drives pulmonary vascular leak from ischemia-reperfusion in lung transplantation
Role: PI
BIOGRAPHICAL SKETCH

NAME
Homer A. Boushey, Jr., M.D.

POSITION TITLE
Professor of Medicine (Emeritus)

eRA COMMONS USER NAME
Boushey

EDUCATION/TRAINING

<table>
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<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
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<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>
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<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
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 (egs., 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.

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

eRA COMMONS USER NAME: Eburchard

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**EDUCATION/TRAINING**

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<tr>
<td>San Francisco State University, San Francisco, CA Stanford University School of Medicine, Stanford, CA</td>
<td>B.S.</td>
<td>1984-1990</td>
<td>Cellular &amp; Molecular Biology</td>
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<tr>
<td>Harvard School of Public Health, Boston, MA</td>
<td>Certificate</td>
<td>1997</td>
<td>Program in Clinical Effectiveness</td>
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<td>Brigham and Women's Hospital, Boston, MA</td>
<td>Resident</td>
<td>1995-1998</td>
<td>Internal Medicine</td>
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<td>University of California, San Francisco, SF, CA</td>
<td>Fellow</td>
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<td>Stanford University, Stanford, CA</td>
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<td>University of California, Berkeley</td>
<td>M.P.H.</td>
<td>2005-2006</td>
<td>Epidemiology</td>
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**Positions and Honors**

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

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<tr>
<td>1988, 1989</td>
<td>NCAA Div. II Academic All-American, Wrestling</td>
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<tr>
<td>2005–2010</td>
<td>RWJ Amos Medical Faculty Development Award</td>
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<tr>
<td>2008-2014</td>
<td>NIH Study Section Member, Genetics of Health and Disease (GHD)</td>
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<tr>
<td>2009</td>
<td>American Society of Clinical Investigation (ASCI), elected member</td>
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<td>2009</td>
<td>Guest Speaker, Tavis Smiley Show</td>
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<td>2010</td>
<td>Guest Speaker, NPR’s Science Friday, hosted by Ira Flatow</td>
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<tr>
<td>2011</td>
<td>Athletic Hall of Fame, San Francisco State University</td>
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<tr>
<td>2013</td>
<td>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.</td>
</tr>
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<td>2013</td>
<td>Guest Speaker, Smithsonian Institution National Museum of Natural History (NMNH)</td>
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</table>
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

Contributions to Science

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


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 ($\beta_2$AR) 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.

Complete List of Published Work in MyBibliography:

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.

U54MD009523 (PI: Marquez-Magana/Bibbins-Domingo) 09/26/14 - 06/30/19
NIH/NIMHD
Role: Subcontract Co-Investigator
San Francisco State University-Subcontract
Project title: “SF State BUILD: Enabling Students to Represent in Science”
Goal: Collaborative efforts between UCSF CVP and SFSU to enhance the academic qualifications of the underrepresented minority BUILD scholars and also promote faculty exchanges between the two institutions, thereby transforming both institutions, and strengthening the existing long-term partnership.
NIH
Role: Co-investigator
Project title: Defining a Comprehensive Reference Profile of Circulating Human Extracellular RNA
Goal: To profile extracellular RNAs in multiple body fluids from healthy individuals.

NIH-Subcontract (#2020100601)
Role: Subcontract PI
Project title: Genetic Control of Airway Epithelium Gene Expression in Childhood Asthmatics
Goal: To participate and advise the design, performance, interpretation of all proposed sequencing and genetic analyses.

NIH (Subcontract from Stanford University)
Role: Co-PI
Project title: Genes, Air Pollution, and Asthma severity in minority children
Goal: To understand the genetic basis of racial/ethnic differences in asthma severity and lung function. Results from this proposal will inform public health policy and clinical practice and aid in the mechanistic understanding of asthma severity (morbidity), which may lead to more targeted therapies.

NIH (Subcontract from Stanford University)
Role: Co-PI
Project title: Transcriptomic and Pharmacogenetic Asthma Endotypes in Minority Children
Goal: To understand the genetic basis of racial/ethnic differences in asthma severity and lung function, and to examine data from 4,379 minority children with asthma to determine how asthma endotypes influence response to albuterol and risk for severe asthma.

TRDRP
Project title: Tobacco Exposure and Asthma Disparity in Minority Children
Goal: To evaluate independent and collective contributions of IUS/SHS tobacco exposure, racial/ethnic differences, and epigenetic mediators predicting ICS responsiveness among African American and Latino children.
Integrative Analyses to Uncover Biological Mechanisms Mediating Gene Associations with Asthma Drug Response Among Minority Children.

Goal: To understand the biological basis of differential drug response that leads to observed racial/ethnic asthma disparities. In this proposal, we use two cloud-based apps we developed to identify functional biologic mechanisms of genes that are associated with racial/ethnic variation in asthma therapies.

Role: Subcontract PI

**Completed Research Support**

1R01HL117004-02S3 (PI: Burchard) 09/01/13 - 08/31/17
NIH/NHLBI
Role: PI
Project title: Pharmacogenomics of Bronchodilator Response in Minority Children with Asthma
Goal: To identify genetic variation that contributes to differences in bronchodilator drug response using whole genome sequencing of extreme traits.

R21ES24844-01 (PI: Burchard/Gauderman) 12/01/14 - 11/30/17
NIH/NIEHS
Role: Co-PI
Project title: Gene-Environment Analyses of Early Life Exposures and Asthma in Ethnically Diverse Children
Goal: To perform a GxE analysis of early life exposures secondhand tobacco smoke and air pollution vs. incident and prevalent asthma in five racially/ethnically diverse populations of children

1K12HL119997-01 Erle/Burchard (MPI). 09/01/2013 - 05/31/2018
NIH/NHLBI
UCSF Career Development Program in Omics of Lung Diseases
Goal: To launch the careers of an outstanding group of next generation scientists equipped to use omics approaches to help transform lung research and pulmonary medicine.
Role: Principal Investigator

24RT-0025 Burchard (PI). 07/01/2015 - 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

UM1 HG008901 Darnell (PI). 01/14/2016 - 11/30/2018
NIH/NHGRI
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.
NAME
Harold A. Chapman, M.D.

POSITION TITLE
Professor of Medicine

eRA COMMONS USER NAME
Halchapman

EDUCATION/TRAINING

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>YEAR(s)</th>
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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>
</tr>
<tr>
<td>Pulmonary Fellow, University of Utah Affiliated Hospitals, Salt Lake City, UT</td>
<td></td>
<td>1979</td>
<td>Pulmonary/Critical Care</td>
</tr>
</tbody>
</table>

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.

I led in vivo investigations of the role of epithelial mesenchymal transition (EMT) in pulmonary fibrosis and in the course of studying epithelial plasticity we discovered a population of lung epithelial progenitors expressing the integrin α6β4 capable of regenerative activity in vitro and in vivo in response to major injury. Follow-up studies led to the discovery that the actual stem/progenitor cells are relatively rare distal airway epithelial subpopulations devoid of mature lineage markers but capable of rapid proliferation and pluripotent differentiation in vivo. Their fates in vivo were recently found to be regulated by local lung hypoxia via its impact on Notch signaling.

A 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 to a novel therapeutic approach to attenuate fibrosis and the disease promoting effects of tissue stiffness by specifically targeting T SymbolRI kinase in lysyl oxidase-like 2 (LOXL2)-expressing cells, a fibroblast-specific pathway of TGFβ1 inhibition.

**References:**


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 to a novel therapeutic approach to attenuate fibrosis and the disease promoting effects of tissue stiffness by specifically targeting T SymbolRI kinase in lysyl oxidase-like 2 (LOXL2)-expressing cells, a fibroblast-specific pathway of TGFβ1 inhibition.


Recommended as exceptional (3 stars) by F1000.
Full reference list can be found at:

Research Support

Ongoing Research Support

R01HL128484-01 (Chapman HA PI) Epithelial Stem/Progenitor Cells in Repair of the Injured Lung
7/1/2015-6/30/2020

The major goals of this project are to define determinants of alveolar stem/progenitor cell differentiation after lung injury and identify the human equivalent of recently identified undifferentiated epithelial cells in the mouse lung parenchyma.

U01HL134766 (Chapman, HA PI) 9/1/2016-8/31/2023
Epithelial stem/progenitor cells as repair agents in diffuse alveolar damage.
This project describes a new therapeutic approach to lung repair that extends recent results in mice demonstrating that lung stem/progenitor cells can transplant and engraft in damaged lungs. The application is driven by the frustrating current state of pulmonary medicine that offers little more than supportive care in the management of acute respiratory failure and progressive fibrotic lung diseases. A group of investigators have come together to overcome the hurdles of stem/progenitor cell replacement therapy in humans.

RO1 HL142265-01A1 Chapman, HA PI 02/1/2019-1/13/2024
LOXL-2 dependent blockade of TGFβ1 signaling and lung fibrosis. The major objectives of this project are to define the structural basis for inhibition of TβRI/II kinase by a LOXL2-dependent trihydroxyphenolic metabolite(s). Second, to test the hypothesis that the trihydroxyphenolic EGCG limits and reverses fibrosis in both a chronic bleomycin mouse model in vivo and precision cut lung slices (PCLS) of IPF patient explants. And to execute a proof-of-principle pilot study in ILD patients with lung fibrosis, testing the hypothesis that oral EGCG will suppress lung Snail1 and pSmad3 accumulation and block collagen mRNA in vivo.

Recently Completed

U01 HL111054-01 Chapman HA, PI NIH/NHLBI Epithelial Progenitor Cells in Lung Repair and Regeneration 1/1/2012-12/31/2016
The specific aims of this project are (1) Test the hypothesis that differential expression of adhesion receptors underlies the capacity of epithelial subtypes to self-organize and promote repair. (2) Define the requirement for neuroendocrine cells (PNECS) and alveolar progenitor cells in maintenance and reconstitution of distal airway and alveolar cells following lung injury. (3) Analyze and further develop a novel, single cell in vivo lung organoid assay in kidney capsules in order to optimize the capacity of adult epithelial progenitor cells to generate functional respiratory units de novo.

PO1 HL108794 Sheppard PI, Chapman HA, project leader Targeting epithelial cells to treat pulmonary fibrosis. 8/1/2012-7/31/2017
The major goal of this project is to deliver one or more novel therapeutics based on recently identified regulators of EMT in lung epithelial cells for further drug development.
## BIOGRAPHICAL SKETCH

<table>
<thead>
<tr>
<th>NAME</th>
<th>Anthony L. DeFranco, Ph.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>eRA COMMONS USER NAME</td>
<td>DeFranco</td>
</tr>
<tr>
<td>POSITION TITLE</td>
<td>Professor, Department of Microbiology &amp; Immunology</td>
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### EDUCATION/TRAINING

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<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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### 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.
- **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.


**Research Support**

Active - none

Completed (last three 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

“BCR Regulation of Antibody Responses”
Principal Investigator: Anthony DeFranco
1 R56 AI108684-01A1  8/1/14-7/31/15 Agency: NIAID/NIH

“The role of Apobec3 enzymes in regulating marginal zone B cells”
Principal Investigator: Matthias Wabl (DeFranco co-investigator)
1R21 AI107101-01  8/1/13-7/31/15 Agency: NIAID

“Sensitized mouse genetic screen for amelioration of murine lupus-like autoimmune disease”
Principal Investigator: Anthony DeFranco
Agency: Program in Breakthrough Biomedical Research (UCSF internal) 7/1/13-12/31/15
NAME

William F. DeGrado

POSITION TITLE

Professor

EDUCATION/TRAINING

<table>
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<tr>
<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>
<td>Organic Chemistry</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 Zn^{2+}-binding peptides that adopt catalytically active cross-beta fibrils. This work has the potential to open new doors for the design of catalytic materials as well as implications concerning the evolution of life.


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.

\begin{itemize}
\end{itemize}

3) 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 \(\alpha\)II\(\beta\)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 idiopathic 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 \(\alpha\)II\(\beta\)3, 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}. 

\textsuperscript{185}
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. 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
NIH/NIGMS by R35GM122603
“A Multiscale Model of Protein Mediated Changes in membrane Morphology”
Dr. DeGrado’s lab is collaborating with Dr. Zhou and Dr. Grabe on computational modeling for membrane protein stability, and his lab helps determine membrane protein structure and orientation in the membrane for this project. Dr. DeGrado’s effort has been subsumed into the R35.

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

CHE-1709506 (Therien) 08/01/17—07/31/21
NSF/Duke University
“Collaborative Research: De novo Protein Constructs for Photosynthetic Energy Transduction”
This collaborative proposal aims to understand the essential design principles of photosynthetic energy transduction and storage. An integrated, multi-disciplinary approach focuses on peptide-synthetic cofactor complexes that undergo photoinduced charge-transfer reactions, where the protein matrix stabilizes the charge-separated state and guides the efficient separation of electrons and holes. A postdoc in DeGrado’s group works on the design of proteins that bind non-biological cofactors for energy transduction.
Role: Co-Investigator
P01 AG002132 (Prusiner) 06/16/15—03/31/20
NIH/NIA
“Degenerative and Dementing Diseases of Aging”
We seek to understand the assembly of prion precursors into oligomers and fibers and to correlate the formation of specific conformational forms with toxicity and transmissibility. A postdoc is shared with Jan Stoehr’s group (Assistant Professor, UCSF) to examine mouse models of infectivity of Aβ peptides.
Role: Co-Investigator

P01 HL040387 (Bennett) 05/16/14—04/30/19 1.1 Calendar
NIH/NHLBI/University of Pennsylvania
Controlling αIIbβ3 Function by Altering Its Energy Landscape”
We conduct conformational analysis of the protein gpIIb/IIIa, and analyze positions that specifically stabilize it in different activation states. Mutagenesis is used to stabilize or destabilize a given state. We work with the Bennett lab to correlate differences in biophysical properties with changes in adhesion and activation.

P01 HL120846 (Abrams, PI) 08/08/14—06/30/19
NIH/NHLBI/University of Pennsylvania
“Platelet signals and their interface with external environment”
The DeGrado lab’s work involves discovery of small molecules that allosterically regulate integrins through the HTS drug discovery center here at UCSF. Synthetic efforts will then be devoted to increasing their affinity and specificity for the desired target.
Role: Co-investigator

Completed

R01 AI097051 (Scott) 03/01/2012—02/29/16
NIH/NIAID Simon Fraser University
“Vaccines that Replicate the Neutralization-Competent Structure of gp41 MPER”
The DeGrado group’s effort focused on the design of DNA vaccines intended to induce neutralizing antibodies to HIV by presenting MPER of gp41 in an appropriate environment/conformation.
Role: Co-investigator

U54 HL119893 (Palazzolo) 09/26/16—07/31/17
NIH/NHLBI/UCLA
BRAID CENTER FOR ACCELERATED INNOVATION
The University of California Center for Accelerated Innovation, a consortium of the five UC medical campuses: UC Davis, UC Irvine, UC Los Angeles, UC San Diego, and UC San Francisco, is involved in a comprehensive program to transform new biomedical inventions by faculty and staff into highly effective medications, diagnostic tests and medical devices. Funds in DeGrado’s group are being used to synthesize and characterize integrin-binding small molecules.
BIOGRAPHICAL SKETCH

NAME
David J. Erle, M.D.

POSITION TITLE
Professor of Medicine

eRA COMMONS USER NAME
DJERLE

EDUCATION/TRAINING

<table>
<thead>
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<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
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<td>University of California, San Francisco, CA</td>
<td>M.D.</td>
<td>5/1984</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>
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<td>6/1988</td>
<td>Pulmonary Disease</td>
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<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
2019-2026  NHLBI Outstanding Investigator Award (R35)

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

Contributions to Science
1. 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.


2. 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.


b. Rüegg C, Postigo AA, Sikorski EE, Butcher EC, Pytela R, **Erle DJ**. Role of integrin $\alpha 4\beta 7/\alpha 4\beta P$ in lymphocyte adherence to fibronectin and VCAM-1 and in homotypic cell clustering. *J Cell Biol.* 1992; 117:179-89. PMID: 1372909; PMCID: PMC2289398.


3. 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.


4. 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.


5. 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, publications from genomics projects performed by members of my group or as collaborations between our core and other investigators include:


**Complete list of publications in MyBibliography:**


**Research Support**

R35 HL145235  Erle (PI)  02/15/2019-12/31/2026  
Airway epithelial cell gene regulation: new mechanisms and therapeutic strategies  
Fund Dr. Erle’s NHLBI research program (no specific aims, replaces two prior R01 grants).

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

R01 GM110251  McManus/Erle (MPI)  09/01/2014-08/31/2019 (NCE)  
Empiric Deconvolution of Functional RNA Elements  
The goal is to develop a set of novel tools allowing us to dissect millions of elements in an unbiased manner and potentially shed new insights into the regulation of gene expression and aid the discovery of novel therapeutics.  
Role: PI

U01 HL126492  Woodruff/Erle (MPI)  07/01/2014-06/30/2019  
Defining a Comprehensive Reference Profile of Circulating Human Extracellular RNA  
The goal is to profile extracellular RNAs in multiple body fluids from healthy individuals.  
Role: PI

T32 HL007185-41  Sheppard/Huang/Erle (MPI)  07/01/2017-06/30/2022  
Multidisciplinary Training Program in Lung Disease  
The goal is to support postdoctoral training of MDs and PhDs.  
Role: PI

1K12 HL119997-01Erle/Burchard (MPI)  09/01/2013-05/31/2019  
UCSF Career Development Program in Omics of Lung Diseases  
Overall project goal is to launch the careers of an outstanding group of next generation scientists equipped to use omics approaches to help transform lung research and pulmonary medicine.  
Role: PI

R01 DK112304  Koliwad/Hunt (MPI)  07/20/2017-04/30/2022  
Immunologic and Fat-Associated Predictors of Insulin Resistance in Treated HIV  
Identify specific immunologic pathways that mediate the increased risk of T2DM in treated HIV infection to identify targets for novel interventions.  
Role: Co-I
# 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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<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
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<th>FIELD OF STUDY</th>
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<tr>
<td>University College Dublin</td>
<td>MB BAO BCH</td>
<td>6/1985</td>
<td>Medicine</td>
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<tr>
<td>Trinity College Dublin</td>
<td>Internal Medicine</td>
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<td>University College Dublin</td>
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<td>University of California, San Francisco</td>
<td>M.D. (doctorate by thesis)</td>
<td>6/1997</td>
<td>Airway Inflammation</td>
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<td>University College Dublin</td>
<td>M.Sc.</td>
<td>6/2003</td>
<td>Molecular Medicine</td>
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<td>Trinity College Dublin</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.

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 perioestin 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.

A. Fahy JV, Wong HH, Geppetti P, Reis JM, Harris SC, Nadel, JA, Boushey HA. Effect of an NK-1 receptor antagonist (CP-99, 994) on hypertonic saline-induced


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).

1P01HL128191 (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).

1U10HL109146 (Fahy JV) 08/01/2011 - 7/31/2018 (NCE)

*Clinical and Molecular Phenotypes of Severe Asthma:* This U10 program grant funds our center and 6 others to conduct research into mechanisms of severe asthma using biospecimens collected from a highly characterized clinical cohort followed longitudinally for 3 years. Role: PI
**BIOGRAPHICAL SKETCH**

**NAME**  
James Solomon Fraser, Ph.D.

**POSITION TITLE**  
Assistant Professor

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

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<td>McGill University, Montreal, QC, Canada</td>
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**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)

- **2018 -**  
  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
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 Biology
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. 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.


5. Determining structures of protein mediating 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 (UCSF) 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, which can cause inflammation in the context of lung disease, and the hijacking of the proline isomerase CypA in lentiviral evolution.


Complete List of 46 Publications in MyBibliography:

Research Support
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.

Packard Fellowship for Science and Engineering Fraser (PI) 11/01/14 – 10/31/19
The David and Lucile Packard Foundation
The major goal of this project is to create and apply methods to examine non-Bragg (diffuse) scattering to define and study the importance of conformational dynamics in protein function.

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.

LFR-17-476732 Fraser (PI) 03/01/17 – 02/29/20
UC Lab Fees Research Program
Macromolecular movements by simulation and diffuse scatter
The goal of this project is to validate X-ray diffuse scattering data with molecular dynamics simulations. Fraser is the overall project director, overseeing coordination between sites (UCSD, UCI, UCR, LANL).

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.

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

NAME
Andrew N. Goldberg

POSITION TITLE
Research Investigator

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

EDUCATION/TRAINING

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>MM/YY</th>
<th>FIELD OF STUDY</th>
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<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>
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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**

**Ongoing Research Support**

Rebecca Susan Buffet Foundation  Goldberg (PI)  12/31/12-12/31/16

**Clinical Research in Otolaryngology**

Unrestricted grant for clinical research in otolaryngology. These funds are used to support the Division of Rhinology and Sinus Surgery for ongoing research principally in microbial ecology.

Mount Zion Health Fund, Innovations Funding for Education 2016 The Haile T. Debas Academy of Medical Educators

Goldberg (PI)

Teaching Observation Program (TOP)

Grant to study teaching observation in the operating room

**Completed Research Support** (selected)

American Rhinologic Society  Goldberg (PI)  06/30/2008 - 06/30/2009

Resident Research Grant  (mentored Fredrick Roediger)

Aspire Medical  Goldberg (PI)  7/1/04-6/30/05

A Cadaver Model of Obstructive Sleep Apnea

The goal of this project was the creation of a cadaver model of obstructive sleep apnea to evaluate changes in airway mechanics associated with specific surgical interventions.

Bristol-Myers  Machtay (PI)  7/1/97-6/30/01

A Phase II Trial of Combined Modality Therapy for Oropharyngeal Carcinoma (UPCC 11397)

The goal of this project was to examine multimodality treatment for oropharyngeal cancer.

Role: Co-Investigator
Biomechanical Basis for the Treatment of Sleep Apnea

The goal of this study was to compare anatomical structure in obstructive sleep apnea patients versus normals using multiple imaging techniques.
Role: Co-Investigator
BIOGRAPHICAL SKETCH

NAME
Erin Duncan Gordon

eRA COMMONS USER NAME
egordon1

POSITION TITLE
Assistant Professor

EDUCATION/TRAINING

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

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<tr>
<td>07/05-06/07</td>
<td>Resident Physician</td>
<td>University of California, San Diego</td>
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<tr>
<td>07/07-12/08</td>
<td>Clinical Fellow, Pulmonary/Critical Care</td>
<td>University of California, San Francisco</td>
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<tr>
<td>01/09-06/11</td>
<td>Research Fellow, Pulmonary/Critical Care</td>
<td>University of California, San Francisco</td>
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<tr>
<td>07/11-06/12</td>
<td>Clinical Instructor, Pulmonary/Critical Care</td>
<td>University of California, San Francisco</td>
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<tr>
<td>07/12-06/17</td>
<td>Adjunct Assistant Professor, Pulmonary/Critical Care</td>
<td>University of California, San Francisco</td>
</tr>
<tr>
<td>07/17-Present</td>
<td>Assistant Professor</td>
<td>University of California, San Francisco</td>
</tr>
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<td>Sandler Asthma Basic Research Center</td>
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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.


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.


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.

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.

Recently Completed Research Support

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.

U19 AI077439 Opportunity Fund Gordon (PI) 09/01/16-08/31/17
NIH-NIAID Role of Notch Signaling in Mucus Metaplasia in Asthma
The goal of this study is to explore the role of notch signaling in mucus metaplasia in type 2 low asthma.

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

NAME
Matthew Frederick Krummel, Ph.D

POSITION TITLE
Professor

eRA COMMONS USER NAME
Krummel

EDUCATION/TRAINING

<table>
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<tr>
<td>University of Illinois at Champaign-Urbana</td>
<td>B.S.</td>
<td>05/1989</td>
<td>Biology and Chemistry</td>
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<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
1987-1987 HHMI Summer Fellow, Neurobiology, UTHSC Dallas. Advisor: Dr. Flora Katz

Other Experience and Professional Memberships

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

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

Contribution to Science

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

   a.) Engelhardt, J.J., Boldajipour, B., Beemiller, P., Pandurangi, P., Sorensen, C., Werb, Z.,
Egeblad, M., Krummel, M.F. 2012. Marginating Dendritic Cells of the Tumor
Microenvironment Cross-Present Tumor Antigens and Stably Engage Tumor-Specific T
: Dissecting the Tumor Myeloid Compartment Reveals A Rare Antigen Presenting Critical for
Visualization of Immediate Immune Responses to Pioneer Metastatic Cells in the Lung.
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.

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.


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 II A 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.


cell amoeboid motility is modulated via myosin IIA-regulated adhesions. *Nat Immunol.* 11, 953-961. PMC2943564


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 ipilimumab, the first FDA approved immunotherapeutic in cancer, in 2011.


Complete List of PubMed-indexed Published Work:

Research support

Ongoing Research Support

R01 AI114787 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

R01 AI52116 Krummel (PI) 01/15/08-12/31/22
NIH Cytoskeletal Regulation of T cell Motility and Synaptic 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

R21CA191428 Krummel (PI) 01/01/15-12/31/16
NIH/NCI Cutting Edge Lineage Tracking of Tumor-Educated Immune Cells
The goal of this project is to devise novel lineage-tracking tools, taking advantage of photoconvertable tamoxifen derivatives and high resolution intravital imaging.

Role: PI

U54 CA163123-01 (Coussens, Krummel, Van't Veer: multi-PI) Coussens (PI) 09/01/11-08/30/16
NIH/NCI, Leukocyte Biomarkers for Predicting Human Breast Cancer Outcome
The goal of this project is to identify predictive biomarkers in human breast cancer, using genomic profiling of mouse and human breast cancer infiltrates and correlated analyses of outcome.

Role: PI (MPI)

U01 HL111054-01 (Chapman, Chuang, Krummel, multi-PI) (co-PI) Chapman (PI) 12/01/11-11/30/16
NHLBI, Epithelial Progenitor Cells in Lung Repair and Regeneration
This project will analyze the stem cells and events that take place during lung repair.

Role: co PI

U19 A1077439-06 Sheppard (PI) 04/01/08-03/31/18
NIH/NIAID, Program: IL-13 and IL-17 Dynamics in the Asthmatic Airway
Project 3: Dynamic Imaging of IL13/IL17 Immune Infiltrates in Asthma
In conjunction with Projects 1 and 2, this project will directly analyze the unfolding of asthmatic responses in the context of the intact airway epithelium. It develops cutting-edge imaging technologies in mouse, applies them to human samples via the Clinical Subject and Biospecimen core and significantly develops reagents and methods that will advance our capacity to study living human biopsies at the subcellular level.

Role: Project 3 Leader

R01 AI52116 Krummel (PI) 01/15/08-12/31/17
NIH
Myosin Motors in T cell Synapse Formation and Activation
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
**BIOGRAPHICAL SKETCH**

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

| eRA COMMONS USER NAME | LOCKSLEY |

**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 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</td>
</tr>
<tr>
<td>University of Washington, Seattle, WA</td>
<td></td>
<td>1980-83</td>
<td>Infectious Diseases Fellow</td>
</tr>
</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

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-\(\gamma\), 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.

Research Support

Howard Hughes Medical Institute 09/01/97 – 08/31/20 (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) 07/01/18 – 06/30/23
Parasite immunity orchestrated by type 2 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.

R01 HL128903    Locksley (PI) 07/01/15 – 04/30/19
Epithelial chitinase and lung homeostasis
The goal of the project is to examine the role of the epithelial chitinase, AMCase, in clearing insoluble chitin oligomers from environmental sources that are inhaled or aspirated into the lung.
Role: PI

P01 HL107202    Fahy (PI) 06/01/12 – 05/31/17 (NCE until 12/31/18)
Innate and adaptive immune responses in Th2-high asthma
The goal of this project is to focus on the role of ILC2 cells as proximal regulators of Th2 inflammation in the airway. This project proposes to characterize markers for these cells, delineate their role in allergic airway responses and collaborate with investigators in Project 3 to advance understanding of ILC2 cells in human asthma.
Role: PI, Project 1

Completed Research Support

R37 AI026918    Locksley (PI) 04/01/11-03/31/17
Parasite immunity orchestrated by Th2 cells
The major goal of this project was to identify the role of cytokine-producing cells, including Th2 cells, basophils and eosinophils, in mediating the immune response to parasitic helminths.
Role: PI
This grant has been since renewed as an R01.

R01 AI030663    Locksley (PI) 05/01/12 – 06/30/18
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 helminthes.
Role: PI
**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

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**EDUCATION/TRAINING**

<table>
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<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
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<th>FIELD OF STUDY</th>
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<tbody>
<tr>
<td>University of Texas, Austin</td>
<td>B.S.</td>
<td>05/1999</td>
<td>Molecular Biology</td>
</tr>
<tr>
<td>University of Michigan, Ann Arbor</td>
<td>M.D./Ph.D.</td>
<td>05/2007</td>
<td>Medicine/ Microbiology Immunology</td>
</tr>
<tr>
<td>University of California, San Francisco</td>
<td>Resident/Chief Resident</td>
<td>2007-2011</td>
<td>Laboratory Medicine</td>
</tr>
<tr>
<td>University of California, San Francisco</td>
<td>Clinical Fellow</td>
<td>2009-2010</td>
<td>Hematopathology,</td>
</tr>
<tr>
<td>University of California, San Francisco</td>
<td>Postdoctoral Fellow</td>
<td>2011-2015</td>
<td>Immunometabolism</td>
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**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, Departments of Laboratory Medicine and Micro/Immunology, UCSF

2015-  
Affiliate Professor, Diabetes Center, UCSF

2018-  
Assistant Professor in line, Dept of Laboratory Medicine
Honors/Awards

1995-1999 National Merit Finalist Scholarship, U. of Texas
1997 Fellowship, Howard Hughes Molecular Biology Summer Research, U. of Texas
1998-1999 Undergraduate Research Fellowship Award, U. of Texas
1999 The Dean’s Honored Graduate in Molecular Biology, U. of Texas
2002-2004 Predoctoral Fellowship, Genetics Training Grant, U. of Michigan
2004-2005 Frederick G. Novy Fellowship, Microbiology & Immunology, U. of Michigan
2006 Rackham Distinguished Dissertation Award Nominee, U. of Michigan
2006 Ward J. MacNeal Distinguished Dissertation Award, Microbiology/Immunology
2006 Alpha Omega Alpha (AOA) Medical Honors Society, U. of Michigan
2007 MD, *graduate with research distinction*, U. of Michigan
2009-2012 Molecular Medicine Research Fellowship, UCSF
2014 Mentored Clinical Scientist Research Career Development Award (K08)
2016-2019 Larry L. Hillblom Foundation Junior Investigator Award
2017 American Association of Immunology, Travel Award
2017 New Frontiers Research Awardee, UCSF Program for Breakthrough Biomedical Research
2017 Milstein Young Investigator 1st Place Winner, International Cytokine & Interferon Society

Professional Societies

2000-2001 American Medical Student Association, U of Michigan
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

We aim to define 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. As a postdoctoral fellow, 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. My independent work has focused on the positive and negative regulation of ILC2s by the cytokines IL-33 and IFN$\gamma$, and the relationship of tissue ILC2 with regulatory T cells (Treg). Our most recent findings have established a novel stromal niche for innate lymphocytes in the
lung and elsewhere that is required for their maintenance and activation (Jones, Dahlgren et al, Immunity, in press).


2. We aim to understand how innate immune cells and cytokines control normal central nervous system (CNS) development and go awry in neuropsychiatric disease. Our group, in collaboration with the Anna Molofsky lab, has defined a novel circuit whereby astrocyte-derived IL-33 promotes microglial activation and neuronal synapse engulfment during CNS development. Ongoing work aims to define how meningeal-resident lymphocytes including ILC2 impact CNS glia and neural circuit formation during brain development.


3. I have been involved in collaborative work to understand the role of and group 2 innate lymphoid cells in immunometabolism. 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. I have 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. This work has advanced our knowledge of the regulation and function of ILC2 in diverse homeostatic, therapeutic, and pathologic settings.


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. Surprisingly, 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.


injury from a split plateletpheresis unit. *Critical Care Medicine*, 40(8), 2488–2491. PMCID: PMC3733455


**Ongoing Research Support**

K08 DK101604 NIH/NIDDK (Molofsky, PI) 5/1/2014 - 3/31/2019
Regulation and function of allergic immune cells in visceral adipose tissue
The major goal of this career development award is to characterize the regulation and metabolic impact of adipose tissue lymphocytes associated with allergic immunity while supporting career and education development of the PI.

Larry L. Hillblom Foundation Startup Grant (Molofsky, PI) 8/1/2016 – 7/31-2019
Adipose tissue type 2 immunity in metabolic health and disease.
The major goal of this three-year startup grant is to begin to determine the cells and signals that regulate adipose tissue group 2 innate lymphoid cells (ILC2), developing strong preliminary data that can be utilized for R01 or equivalent funding.

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 for an R01, testing our hypothesis that lung ILC2 engage in a cross-talk with adventitial fibroblasts that regulate their development and function.

**Pending**

R01 NIH/NHLBI (Molofsky, PI)
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.

UCSF RAP Pilot for Junior Investigators (Molofsky, Co-PI)
Innate lymphocytes at the developing brain-immune interface.
The major goal of this one-year 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)
Defining lung lymphocyte niches in humans.
The major goal of this one-year pilot grant is to develop 3D imaging techniques for normal human lungs and begin to define human lung lymphocyte and stromal cell niches.
# 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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<th>INSTITUTION AND LOCATION</th>
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<th>FIELD OF STUDY</th>
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<tr>
<td>Massachusetts Eye and Ear Infirmary, Boston</td>
<td>Fellow</td>
<td>06/06</td>
<td>Rhinology</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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<tr>
<td>University of California, San Francisco</td>
<td>Intern</td>
<td>06/01</td>
<td>General Surgery</td>
</tr>
<tr>
<td>University of California, Los Angeles School of Medicine</td>
<td>MD</td>
<td>06/00</td>
<td>AOA</td>
</tr>
<tr>
<td>Yale University, New Haven CT</td>
<td>BS</td>
<td>06/95</td>
<td>Cum Laude, Molecular Biochemistry and Physics</td>
</tr>
</tbody>
</table>

---

## 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
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.
NAME
William E. Seaman, M.D.

POSITION TITLE
Emeritus, recalled, Professor of Medicine and of Microbiology and Immunology, UCSF

eRA COMMONS USER NAME
BSEAMAN

EDUCATION/TRAINING

<table>
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<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
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<tr>
<td>Princeton University, Princeton, NJ</td>
<td>A.B.</td>
<td>1964</td>
<td>English</td>
</tr>
<tr>
<td>Harvard Medical School, Boston, MA</td>
<td>M.D.</td>
<td>1969</td>
<td>Medicine</td>
</tr>
<tr>
<td>Massachusetts General Hospital, Boston, MA</td>
<td>Resident</td>
<td>1969-1971</td>
<td>Internal Medicine</td>
</tr>
<tr>
<td>Arthritis and Rheumatism Branch, NIAMDD, NIH Bethesda, MD</td>
<td>Fellow</td>
<td>1971-1974</td>
<td>Immunology and Rheumatology</td>
</tr>
<tr>
<td>Massachusetts General Hospital, Boston, MA</td>
<td>Chief Resident</td>
<td>1974-1975</td>
<td>Medicine</td>
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<tr>
<td>Massachusetts General Hospital, Boston, MA</td>
<td>Fellow</td>
<td>1976</td>
<td>Rheumatology</td>
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Positions and Honors

Academic Positions

1976 - 1984 Assistant Professor of Medicine, University of California, San Francisco
1978 - Present Staff Physician, San Francisco VA Medical Center
1981 - 1992 Chief, Arthritis/Immunology Section, San Francisco VA Medical Center
1984 - 1988 Associate Professor of Medicine, University of California, San Francisco
1988 - Present Professor of Medicine and of Microbiology and Immunology, University of California San Francisco
1992 - 1999 Chief, Medical Service, San Francisco VA Medical Center
1999 - 2015 Chief, Immunology section, San Francisco VA Medical Center
2011 - 2017 Associate Chair of Medicine for Research, UCSF

Other Positions

1999 - Present Research Director, American Asthma Foundation
1999 - 2003 NIH Study Section, Experimental Immunology
2000 - 2008 Director, Macrophage Biology Laboratory, Alliance for Cellular Signaling
2002 - 2005 President, Society for Natural Immunity

**Honors**

1964 AB cum laude
1969 MD cum laude
2007 Master, American College of Rheumatology

**Medical and Research Society Memberships and Board Certifications**

1973 to Present American College of Rheumatology
1974 American Board of Internal Medicine
1978 American Board of Rheumatology
1979 to Present American Federation for Clinical Research
1980 to Present American Association of Immunologist
1984 to Present American Society for Clinical Investigation
1994 to Present American Association of Physicians
1998 to Present Society for Natural Immunity
2001 to Present American Association for Cancer Research
2007 to Present International Bioiron Society
2007 to Present International Society of Neuroimmunology

**Editorships**

1985-1989 Associate Editor, Journal of Immunology
1989-1993 Section Editor, Journal of Immunology
2005 to 2016 Faculty of 1000

**15 Selected Peer-Reviewed Publications (of 94)**


**Research Support**

I closed my laboratory in 2014 and no longer have grant support.
BIOGRAPHICAL SKETCH

NAME
Dean Sheppard

POSITION TITLE
Professor of Medicine

eRA COMMONS USER NAME
sheppard

EDUCATION/TRAINING

<table>
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<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 Francisco</td>
<td>Fellow</td>
<td>7/78-6/81</td>
<td>Pulmonary</td>
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</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
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.

a) **Sheppard D**, Rozzo C, Starr L, Quaranta V, Erle DJ, Pytela R. Complete amino acid sequence of a novel integrin β subunit (β6) identified from epithelial cells using the polymerase chain reaction. *J Biol Chem* 1990; 265:11502-11507. PMID: 2365683


c) Palmer EL, Ruegg C, Ferrando R, Pytela R, **Sheppard D**. Sequence and tissue distribution of the integrin α9 subunit, a novel partner of β1 that is widely distributed in epithelia and muscle. *J Cell Biol* 1993; 123(5):1289-97. PMCID: PMC2119880

d) Yokosaki Y, Palmer EL, Prieto AL, Crossin KL, Bourdon MA, Pytela R, **Sheppard D**. The integrin α9β1 mediates cell attachment to a non-RGD site in the third fibronectin type III repeat of tenascin. *J Biol Chem* 1994; 269:26691-26696. PMID: 7523411

3. To better understand the in vivo relevance of members of the integrin family we had identified, my lab generated integrin subunit knockout mice and used the phenotypes we identified in those mice to identify novel integrin ligands and molecular pathways upstream and downstream of these integrins that contribute to development and disease. Through these studies we identified a completely unexpected role for integrins in activating latent TGFβ and showed that this pathway is important, though distinct effects on different responding cells, in experimental models of pulmonary fibrosis, emphysema, acute lung injury, allergic asthma and in modulating immune responses to tumors. These studies have stimulated substantial interest in potential anti-integrin therapeutics, including one humanized monoclonal antibody generated based on work in my lab that is now in phase 2 clinical trials for potential treatment of idiopathic pulmonary fibrosis and antibodies and small molecule inhibitors we have developed targeting the αvβ8, αvβ5, αvβ1 and α5β1 integrins that are in various stages of clinical development for treatment of severe asthma, fibrotic diseases, acute lung injury and for tumor immunotherapy.


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

1 HL145037 (Sheppard, co-PI) 10/1/18-9/30/22
NHI/NHLBI
Interventional targeting of IRE1alpha-TGFbeta signaling loop in pulmonary fibrosis
Role – co-PI, contact PI
Overall project goal – Elucidating the mechanisms of interaction between the ER stress response and TGFDbeta activation and signaling in initiation and progression of pulmonary fibrosis.
UH2 HL123423 (Sheppard, co-PI)  07/01/2014-06/30/2019
NIH/NHLBI
Treatment of pulmonary fibrosis with inhibitors of integrin alphavbeta1
Role: co-PD/PI, Contact PI
Overall project goal: Completing pre-clinical trials to develop a small molecule alphavbeta1 inhibitor to treat pulmonary fibrosis.

U54HL119893 CFDA 93.837 (Lee)  08/01/2016- 07/31/2018
NIH/NHLBI
UC BRAID Center for Advanced Innovation
Role: Co-PI, Contact PI of CAI funded project “Inhibition of abnormal airway smooth muscle contraction by inhibitors of the alpha5beta1 integrin”
Overall project goal: To develop either inhaled or orally available alpha5beta1 integrin inhibitors for treatment of severe asthma.

Sponsored Research Agreement (Sheppard)  08/01/2014- 07/31/2018
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)  12/07/2012-11/30/2018
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, contact 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>
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## EDUCATION/TRAINING

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<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
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<tr>
<td>Seoul National University, Seoul, Korea</td>
<td>BS</td>
<td>2/1993</td>
<td>Chemistry</td>
</tr>
<tr>
<td>Seoul National University, Seoul, Korea</td>
<td>MS</td>
<td>2/1995</td>
<td>Biochemistry</td>
</tr>
<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>
</tr>
<tr>
<td>Yale University, New Haven, CT</td>
<td>Postdoctoral</td>
<td>1/2008</td>
<td>Cell Biology</td>
</tr>
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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

### Honors and Awards

- **1999** The Best Research Student Award in the Department of Pathology, 9th Graduate Student Symposium, Duke University
- **2004** The Jane Coffin Childs Memorial Fund Research Fellowship Award
2009  Sandler Innovative Award in Asthma Research, Sandler Asthma Basic Research Center
2009  Cancer Research Institute Investigator Award
2010  American Heart Association Scientist Development Award
2016  AAI laboratory travel award
2018  AAI Careers in Immunology Fellowship Award

Contribution to Science

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

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


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.


b. Ma, JK, Platt MY, Eastham-Anderson, J, Shin, JS*, and Mellman, I*. MHC class II distribution in dendritic cells and B cells is determined by ubiquitin chain length, PNAS. 109:8820, 2012. Pubmed PMID: 22566640; PubMed Central PMCID: PMC3384207 *Shin, JS and Mellman, I contributed equally to this work


3. Endocytosis of FcεRI in dendritic cells

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

a. Shin, JS and Greer, AM. The role of FcεRI expressed in dendritic cells and monocytes, Cellular and Molecular Life Science, 72:2349, 2015. PubMed PMID: 25715742; PubMed Central PMCID: PMC4479177


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

09/05/2013 - 05/31/2019
R01 GM105800-01, National Institute of Health
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.

06/01/2018 – 11/30/2019
W81XWH1810110, Department of Defense
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.
BIOGRAPHICAL SKETCH

NAME
Aparna Bala Sundaram

POSITION TITLE
Assistant Professor of Medicine
Division of Pulmonary & Critical Care Medicine
Department of Medicine

eRA COMMONS USER NAME
ASUNDARAM

EDUCATION/TRAINING

<table>
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<tr>
<th>INSTITUTION AND LOCATION</th>
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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>
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<td>Medicine</td>
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<td>Northwestern University, Chicago IL</td>
<td>n/a</td>
<td>06/09</td>
<td>Internal Medicine</td>
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<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

Other Experience

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

Honors

1999-2003   National Merit Scholarship
1999-2006   Honors Program in Medical Education, Northwestern University
2006-2009   Resident Teaching Award, Northwestern University
2009-present American Board of Internal Medicine for Internal Medicine Certification
2011-present American Board of Internal Medicine for Pulmonary Diseases Certification
2012-present American Board of Internal Medicine for Critical Care Medicine Certification
2013       Respiratory Disease Young Investigators’ Forum Finalist, ARC
2014  Respiratory Structure and Function Abstract Scholarship, American Thoracic Society
2014-2015  Early Stage Investigator Award, NIH/NIAID AADCRC
2018  Invited lecturer, Use of Mouse Models to Develop Therapies for Human Lung Diseases, UCSF

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

Contributions to Science

I began my research training studying the effect of integrin 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.


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:

**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.

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.
UCSF Catalyst Award (PI). UCSF, ShangPharma Innovation. 2018-2020
Development of potent inhibitors of integrin α5β1 and α2β1 to treat smooth muscle contraction in asthma. This grant does not encompass I-domain inhibitors.

UC Center for Accelerated Innovation Technology Development Award (co-I)
UCSF, NHLBI. 2018-2020
Development of inhaled or oral inhibitors of integrin α2β1 to treat smooth muscle contraction in asthma. This grant does not encompass I-domain inhibitors.

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.

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.
BIOGRAPHICAL SKETCH

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

POSITION TITLE
Research Specialist

eRA COMMONS USER NAME

EDUCATION/TRAINING

<table>
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<tr>
<td>Xian Medical University, Xian, China</td>
<td>M.D.</td>
<td>12/82</td>
<td>Medicine</td>
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<tr>
<td>Xian Medical University, Xian, China</td>
<td>M.S.</td>
<td>12/85</td>
<td>Immunology</td>
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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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<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>
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<tr>
<td>University of Chicago</td>
<td>M.D.</td>
<td>05/1979</td>
<td>Medicine</td>
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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

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 (PLC\textsubscript{G1}), 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 PLC\textsubscript{G1} 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>
</thead>
<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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EDUCATION/TRAINING

<table>
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<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
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</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>
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Positions and Honors

<table>
<thead>
<tr>
<th>Year</th>
<th>Position</th>
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<tbody>
<tr>
<td>1993 - 1996</td>
<td>Postdoctoral Fellow, Yale University, Structural and Biochemical Studies of GroEL</td>
</tr>
<tr>
<td>1996 - 2000</td>
<td>Assistant Professor, University of California San Francisco, Departments of Cellular &amp; Molecular Pharmacology, and Biochemistry &amp; Biophysics</td>
</tr>
<tr>
<td>2000 - 2005</td>
<td>Assistant Investigator, Howard Hughes Medical Institute</td>
</tr>
<tr>
<td>2000 - 2003</td>
<td>Associate Professor, University of California San Francisco, Departments of Cellular &amp; Molecular Pharmacology, and Biochemistry &amp; Biophysics</td>
</tr>
<tr>
<td>2003 - Present</td>
<td>Professor, University of California San Francisco, Departments of Cellular &amp; Molecular Pharmacology, and Biochemistry &amp; Biophysics</td>
</tr>
<tr>
<td>2010-present</td>
<td>Vice-chair of Department of Cellular and Molecular Pharmacology, UCSF</td>
</tr>
<tr>
<td>2016-present</td>
<td>Presidents Advisory Committee of the Chan-Zuckerberg Biohub</td>
</tr>
</tbody>
</table>

Other Experience and Professional Memberships

Permanent Member, NIH Molecular Biology and Protein Processing Study Section (2004-2008); Reviewer, CDF-2 NIH study section (2001-2003, ad hoc); Member, NIH College of CSR Reviewers (2010); Juror, New York Academy of Sciences Blavatnik Awards for Young Scientists (2014-present); External Reviewer, Lawrence Berkeley National Lab, Physical Biosciences Division (2005); Member, Harvard Medical School Review Committee (2015). Head of the program committee for the 2016 annual meeting of the American Society of Cell Biology. Co-founder KSQ therapeutics.


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

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.

HR0011-17-2-0043 (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.

R21 NS101395 (Lim, Daniel)  4/1/2017 - 3/31/2019
NIH/NS
Functional long noncoding RNAs in human glioma
Our long-term goal is to develop highly specific and effective new therapies for the treatment of primary brain tumors including GBM. In pursuit of this goal, our immediate
The objective is to identify and pursue specific lncRNAs as therapeutic targets in human glioma.

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 (Doudna) 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 (Bivona) 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.

Recently Completed Research Support

NIH/NIA 5R01AG041826-05 (Weissman) 05/01/12 –04/30/18  
Human Gene Knockdowns that May Extend Lifespan  
The goal of this project is to screen for genes important in human aging.

R01 DA036858 (Lim/Qi/Weissman) 09/30/13 - 05/31/18  
NIH/NIDA  
Harnessing CRISPR for Targeted and Inducible Epigenomic Reprogramming  
Specific aims: 1) development of optimized genome-wide library of dCas9-targeted epigenetic modifiers; 2) using CRISPR to recruit epigenetic modifiers in a temporally controlled manner; 3) using CRISPR epigenetic toolbox to probe temporal and spatial dynamics of chromatin silencing.

NIH/NIGMS P50 GM102706 (Cate) 09/01/12 - 08/31/17  
Center for RNA Systems Biology  
This Center aims to use systems biological methods to discover the regulation of mRNA fate controlled by RNA structural elements in pre-mRNAs and mRNAs.  
Role: PI on UCSF Subcontract
**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>1971-73</td>
<td>Protein Chemistry</td>
</tr>
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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   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

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 CA199315-03. 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 human breast cancer.
  Role: PI

- NIH/NCI R01 CA190851-04. 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.
  Role: PI

- NIH/NCI R01 CA057621-25 Werb (PI) 04/01/13-08/31/19 NCE
  Role of Metalloproteinases in Mammary Gland Remodeling
  The goal of this grant is to determine functions of ECM-degrading proteinases and inhibitors in mammary epithelium during development and tumor progression.
  Role: PI

- NIH/NCI P30 CA082103-19 (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.
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>
<thead>
<tr>
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<th>DEGREE</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
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<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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<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>
</tr>
<tr>
<td>University of California, San Francisco</td>
<td>Fellow</td>
<td>07/98-02</td>
<td>Pulmonary/Critical Care</td>
</tr>
</tbody>
</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.

Innes AL*, Woodruff PG*, Ferrando RE, Donnelly S, Dolganov GM, Lazarus SC, Fahy JV. Epithelial mucin stores are increased in the large airways of smokers with airflow obstruction. Chest. 2006 Oct;130(4):1102-8. PMID: 17035444 *denotes authors contributed equally


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) 9/15/17-5/30/22
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.

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

U01 HL126493 (contact PI: Woodruff, Co-PI: Erle DJ). 8/1/14-4/30/19
NIH/Common Fund
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.

U19 AI077439 (Project leader: Woodruff, overall PI: Erle) 4/01/18-3/31/23
NIH/NIAID
Understanding Asthma Endotypes
To study the roles of interferon driven inflammation and airway epithelial ER stress in asthma.

U01 HL128952-01 (Co-PI Woodruff) 9/09/15-7/31/19
NIH/NHLBI
Redefining Therapy In Early COPD: RETHINC
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.
This study investigates a pathway that links inflammation, Gram negative bacterial overgrowth, mucus production and chronic bacterial colonization in COPD.

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.

To identify the roles of iH2 cells, IL-33 and miRNAs in local immune responses in the lung in asthma.

The goal of this project is to investigate molecular phenotypes and lectins that regulate mucus viscosity in severe asthma.

To determine the relationship between the airway microbiome and type 2 inflammation in asthma.

To identify subpopulations and intermediate outcome measures in COPD.

To determine the relationships between the airway microbiome and airway mucin and EGFR-pathway abnormalities in COPD.

To identify T-cell effector pathways that are present in COPD and correlate with progression of emphysema.