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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 five basic scientists supported by advanced technology cores and linked with the larger scientific community through Center Grants and Program Projects focused around asthma research. With maturation, the Center aligned in 2014 with the Airway Clinical Research Center (ACRC) at UCSF to facilitate increased focus on and integration with studies in patients. 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 in establishing an active asthma research enterprise within the greater UCSF scientific community. Comprised of four basic scientists, a population geneticist and two translational scientists, the Center has networked across the greater UCSF research and the national asthma research organizations to establish increasing recognition for contributions to asthma research.

Notable accomplishments from SABRE Center members over the past 12 months:
(1) Drs. Fahy and Woodruff described a new severe asthma endotype characterized by recurrent mucus plugging, poor drug control, and a high Th2-associated profile. These patients have a high incidence of recurrent nasal polyposis and were recognized through use of low-dose multidetector-CT radiography for diagnosis and follow-up (JCI 2018). Dr. Woodruff was part of an NIH study of airway mucins as markers for chronic bronchitis syndromes, which can overlap with asthma phenotypes (NEJM 2017).
(2) In the genetics realm, where ancestry has marked effects on the course and treatment of asthma, the Burchard Asthma Collaboratory Data Bank contributed to elucidation of origins of native populations in Patagonia, the last colonized area of the New World. Native Patagonians were identified as an anciently established Siberian descendent that divided into two primary clades, which were independently introgressed by subsequent waves of seafaring Southeast Asian and European populations (PNAS 2018). Such findings will assist in parsing out the complex genetics of allergy in highly admixed New World populations.
(3) In basic research, the Ansel lab established the microRNA landscape of ILC2s with the Locksley lab, opening up new interventional strategies (J Exp Med 2017); the Shin lab defined the role of MARCH ubiquitinylation of MHC molecules in protecting dendritic cells from proteotoxicity (J Cell Biol 2018); the Allen lab established efficient genetic engineering in human B cells using CRISPR/Cas9 (J Immunol Meth 2018); and the Locksley lab followed up their discovery of the role of epithelial tuft cells in type 2 immunity by defining the succinate receptor on tuft cells as a key luminal sensor that drives ILC2 activation in small intestine, a novel discovery (Cell 2018).

Overview – 2018

Richard M. Locksley, M.D.

The SABRE Center continues to move forward in its discovery-oriented mission towards deeper understanding of asthma that will guide innovative therapeutics. Plans for recruitment of an additional faculty member have been put on hold while the Parnassus site develops long-range re-development efforts centered around the need for a hospital re-build by 2025. With that centerpiece, plans for consolidation of immunology programs within more expansive efforts centered around precision medicine and bioengineered deliverables centered at Parnassus have raised the possibility of integrating the SABRE Center within a centralized immunology and tissue effort aimed at centralizing the basic and translational scientific disciplines at the Parnassus site. That being said, it remains a period of substantial transition, and opportunities are likely to change as the landscape becomes better defined over the coming 5 years.

This begins the last year of the American Asthma Foundation, including the final annual San Francisco scientific meeting this past May, which constituted a key mechanism for introducing SABRE investigators into a national consortia of scientists devoting substantial time to asthma research. Despite the phase-out, the many interactions and collaborations that have been established through this mechanism will enable continuing scientific cooperation among a number of these groups across the country for many years. Part of our efforts to re-build a greater research community have involved reinstitution of UCSC-wide innovative projects in order to generate new mechanisms for interactions and progress. This continues aspects of the Strategic Plan instituted 4 years ago and aimed at redirecting aspects of the organizational and budget structure to facilitate a conduit from basic science pathway discovery to validation in humans and identification of forward strategies. A second approach spearheaded by the AAF Scientific Board was to establish a Keystone meeting that will occur in 2019, which will be centered around asthma and allergy, with broad representation by investigators supported by AAF. SABRE members will also participate.

Investigators

The SABRE Center consists of the Director, Dr. Locksley; three core basic science faculty - Drs. Allen, Ansel, and Shin; and three core translational scientists - Drs. Fahy and Woodruff, who direct the Airway Clinical Research Center 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. The SABRE Center is integrated with the Airway Clinical Research Center (ACRC) under the leadership of Dr. John Fahy, who has become a member of the Executive Board, and Dr. Prescott Woodruff. All 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. A competitive renewal for this grant has been submitted. The SABRE Center has evolved into an active research constituent on the UCSF campus with the role of generating new basic understanding and potential therapeutic approaches to asthma. We here 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, particularly 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 Dsr. Fahy, Woodruff, Laura Koth, Erin Gordon and 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 inflammatory cytokines in bronchial lavage fluid. Another publication in the *Journal of Experimental Medicine* extended Dr. Ansel's work on the miRNA miR-19a, which is specifically upregulated in T cells from the airways of asthmatic subjects and strongly promotes cytokine production by Th2 cells. This new work, conducted in collaboration with Dr. Locksley's laboratory, showed that miR-19 promotes cytokine production and allergic airway inflammation mediated by type 2 innate lymphocytes (ILC2s) through an overlapping but non-identical downstream gene regulatory network. Altogether, Dr. Ansel contributed to 6 published manuscripts this year, and 7 others are in revision. Dr. Ansel is an established leader in his field. He delivered invited lectures in Philadelphia, Massachusetts, Washington D.C., Florida, San Francisco and Stanford, and he will host a new Keystone Symposium in February of 2019.

Dr. Ansel's work has been recognized by substantial extramural grant support. He has continuing funding from a recently renewed R01 grant from NHLBI, and a new Exploratory/Developmental Research (R21) grant from the NIAID. Dr. Ansel participates as a Project Leader in the NIH Program Project Grant of SABRE Investigators, and he is a Project Leader in a U19 project grant led by Dr. Robert Blelloch as part of the NIH Director's Office's Extracellular RNA Communication Consortium (http://commonfund.nih.gov/Exrna/index). Dr. Ansel's role in this program is to uncover how and why RNAs are released from cells into body fluids, particularly in the context of allergic lung inflammation.

The Ansel laboratory is currently populated by three graduate students, three postdoctoral fellows, one technician, and two undergraduate researchers. Graduate student John Gagnon is supported by a National Science Foundation Graduate Research Fellowship. Postdoctoral

fellow Adam Litterman is a recipient of the prestigious CRI Irvington Fellowship, and Marlys Fassett is supported by a fellowship from the Dermatology Foundation. Dr. Fassett has a pending NIH K08 Career Development Award application. Dr. Ansel's departed trainees have moved successfully into the next phase of their career as postdoctoral fellows, MD/PhD residents in research career tracks, and in three cases, as principal investigators of independent laboratories in the US and Germany. Most recently, Dr. Heather Pua departed to start her own laboratory at Vanderbilt University Medical Center, where she will continue to expand her research on the molecular regulation of asthma pathology. 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 investigators in the SABRE Center and throughout UCSF.

In recognition of his success to date, Dr. Ansel will be promoted to Professor of Microbiology & Immunology in 2018. He is 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 a large NIH T32 training grant to support graduate student training. He participates in teaching for medical, dental and graduate students, and directs the immunology course for the Doctor of Pharmacy program at UCSF.

Dr. Jeoung-Sook Shin, PhD., is studying the molecular mechanisms underlying antigen-presenting function of dendritic cells with the ultimate goal of developing novel therapeutics for treatment of immune-associated allergic diseases. Current research is focused on understanding how the ubiquitin ligase membrane-associated RING-CH1 (MARCH1) contributes to dendritic cell function in induction of T cell immunity. She has previously found MARCH1 supports dendritic cell function in selecting regulatory T cells by maintaining homeostasis of plasma membrane domains that strengthen dendritic cell engagement required for the activation of thymocytes. More recently, she found that MARCH1 plays an indispensable role in the development of airway allergic immunity and asthma by supporting dendritic cell function necessary for the priming and development of Th2 cells in vivo by protecting dendritic cells from proteotoxicity. She is currently assessing the candidacy of MARCH1 as a therapeutic target for treatment of allergic asthma by using a novel mouse strain that deletes MARCH1 expression in an inducible manner and by exploiting the endogenous antagonist of MARCH1, CD83. It appears that the single tyrosine residue localized in the middle of the transmembrane domain of CD83 plays a crucial role in MARCH1 antagonizing activity. How this tyrosine interferes with MARCH1 activity is under active investigation.

Dr. Shin has published 7 peer-reviewed research papers and 3 invited reviews over the past five years. She served as a member of an NIH Study Section for mucosal immunology, allergy, and asthma. Dr. Shin received her first R01 grant from NIH in 2013; her renewal

application is pending. She was recently awarded a Discovery award from the Department of Defense, which will support her study on the role of MARCH1 in asthma. She was also awarded a Career Development Fellowship Award from the American Association of Immunologists.

Dr. Shin is serving as a thesis supervisor for a BMS graduate student. This student was awarded the Initiative for Maximizing Student Development (IMSD) fellowship from the National Institute for General Medical Sciences (NIGMS). More recently, he was 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 is an active collaborator with investigators in and outside UCSF. She has worked with Dr. Erle in the SABRE Genomic Core to better understand the transcriptional regulation associated with dendritic cell function in the thymus, which resulted in a recent publication in Journal of Immunology. She is also collaborating with Dr. William DeGrado in the Department of Pharmaceutical Chemistry at UCSF to define the three-dimensional structure of MARCH1 and develop a small molecule inhibitor of the protein.

Chris Allen, Ph.D., joined the SABRE center ten 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. Dr. Allen has also recently developed methodology to characterize human IgE+ B cells. To facilitate mechanistic studies of human 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* this year. Dr. Allen also published a review on recent advances in IgE biology for *Current Opinion in Immunology*. 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 has continued to attract substantial extramural funding to support his studies. In the past year, he was awarded two new grants from the NIH: an R01 focusing on the role of B cell receptor signaling in the regulation of IgE responses, and an R21 to characterize a population of macrophages that captures allergen in the lungs. This is Dr. Allen's second R01 award, and he was previously awarded an NIH Director's New Innovator Award.

In late 2012, Dr. Allen was recruited to the Cardiovascular Research Institute (CVRI) at UCSF, where 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. When Dr. Allen moved to Mission Bay, he recruited a postdoc, a technician, and his first graduate student who was funded by the Singapore's Agency for Science, Technology and Research (A*STAR). Dr. Allen's first graduate student is due to graduate this summer. In 2014, Dr. Allen recruited a second graduate student, and in the past few weeks, Dr. Allen recruited a third student to his laboratory, both students in the Biomedical Sciences program. Dr. Allen has also mentored a medical student who worked for the past five years in his laboratory in various stints. 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 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.

Richard Locksley is an infectious diseases-trained M.D. who pursues basic studies of allergic immunity using a variety of animal models. His recent focus has been 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 cytokines implicated in 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 17 peer-reviewed publications, 4 reviews and 2 commentaries in 2016-2018.

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 that mediates 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 a member of the National Advisory Committee for the Pew Scholars Program in Biomedical Sciences. 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. His laboratory is supported by HHMI and by grants from the NIH, and he directs one of the subprojects for the SABRE Center PPG under the direction of Dr. Fahy. Postdoctoral trainees in his laboratory include recipients of 2 NIH K08 awards, a Swiss Foundation Fellowship, a Fulbright Fellowship and an American Dermatology Research Fellowship. Recent postdoc graduates have moved into faculty positions at UCSF, University of Washington, and Washington University St. Louis, and scientific positions at Merck and the Allen Brain Institute in Seattle. 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 both graduate and medical students in immunology and infectious diseases.

John Fahy, M.D., is a longstanding supporter of SABRE research and a formal faculty member in the SABRE Center for the past 5 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. In other studies in severe asthma, he is investigating how airways are injured by non-type 2 inflammatory mediators that originate outside the lung in obese and older patients with systemic IL-6 inflammation. Finally, Dr Fahy's lab is a leader in advancing understanding for how pathologic airway mucus gels form, and his lab has recently discovered that oxidative processes associated with airway inflammation drive mucin cross-linking and mucus gel stiffening. Dr Fahy leads a PO1 program in type 2 airway inflammation in asthma

(includes Drs. Locksley, Ansel and Woodruff), a PO1 mucolytic drug discovery program that targets covalent disulfide mucin cross-links, and an RO1 program investigating mechanisms of airway inflammation and mucus pathology in acute severe asthma. He is the PI of the UCSF center in the NHLBI Severe Asthma Research Program (SARP) and the PI of the UCSF center in the NHLBI PrecISE Asthma Trials Network. Recent honors include election to AAP in 2016 and a Recognition Award for Scientific Accomplishments from the ATS in 2017.

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 4 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 inflammatory mechanisms in allied disease such as COPD and chronic bronchitis. Non-type 2 pathways that he is investigating in asthma include interferon-driven inflammation and airway epithelial ER stress. 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 and of the NHLBI SPIROMICS study of COPD. He is a co-investigator and/or project leader on three NIH-funded asthma grants, the NHLBI Severe Asthma Research Program, a NHLBI P01 directed by Dr. Fahy and a NIAID U19 directed by Dr. Erle, and a member of the NHLBI Pulmonary Trials Consortium. He serves on the Scientific Advisory Board for the NIAID Inner City Asthma Consortium and is director of a community outreach program in San Francisco which brings asthma and COPD education to patients in the Southeastern Health Clinic, which serves inner-city, underserved populations in Bayview-Hunters Point. 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 from 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 has continued 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. More recently, he 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 Esteban group contributed clinical and genetic data from minority children to the NHLBI Trans-Omics for Precision Medicine (TOPMed) program. The 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 Burchard lab showed minimally-invasive nasal airway epithelial brushings can be collected from children, where they can serve as a proxy for bronchial airway epithelium. They recently recruited a cohort of 698 minority children with nasal airway epithelial brushings to perform a cis-eQTL study.

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, 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 provided 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 core support 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. David Erle, to the Microscopy Core, under the guidance of Dr. Max 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. Summaries of the activities of these three Cores, which continue to be supported by the Center, are included in this report.

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. 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 have 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 the only 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 funded two Innovative Grants this year, each with the ability for a second-year request. 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 (see Cover photo). The first results from this grant have resulted

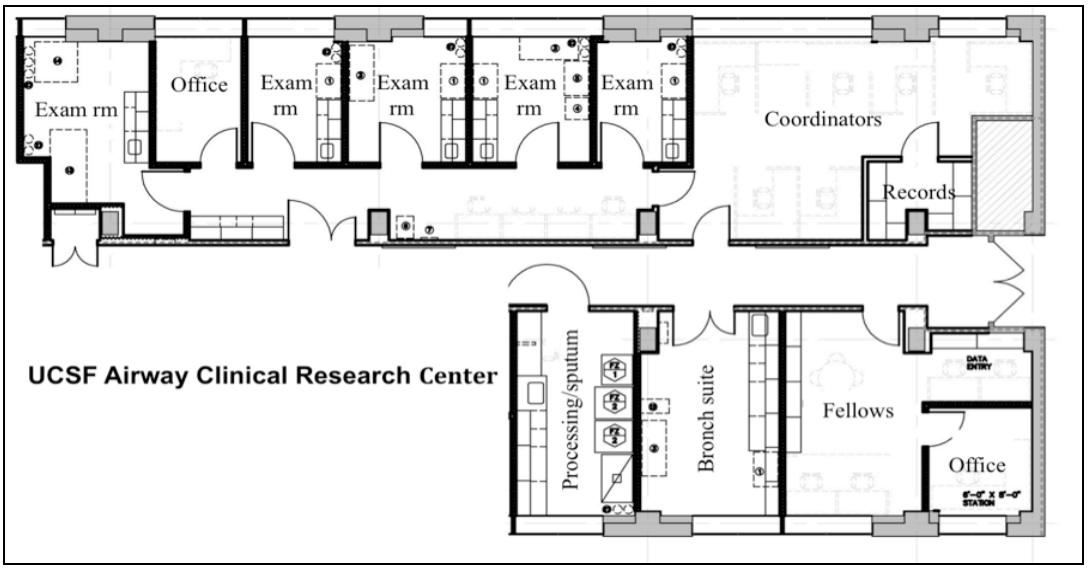
in a submitted manuscript which is under review at Immunity. The second, from Bill DeGrado on the Mission Bay campus, will work with Jeoung-Sook Shin on the crystal structure for MARCH1 ubiquitin ligases in order to find small drug inhibitors. Dr. Shin's work has shown that deletion of this ubiquitin pathway in mouse dendritic cells can profoundly inhibit allergic inflammation in mouse models of allergic airways inflammation. These Innovative Grants in the past have proven highly useful in pulling additional scientists into the asthma field, and we look forward to assessing the success of the reinstitution of this program. Plans are to continue to request proposals for the coming year. The two current proposals are included in this Report.

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). Some of these data are beginning to accrue and should yield valuable information for comparisons between the mouse and human as well as biologic insights that will continue to drive hypothesis-driven exercises. Following publication, all of these data will be established in the public science space with proper masking of human data.

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.

Equipment in ACRC includes:
Exam rooms: Eight spirometers (Jaeger Masterscope (2), nSpire HDpft 1000 (1), Sensormedics VMax22 (1), Medgraphics CPFS/D Spirometer (2), nSpire KoKo PFT (2). Devilbiss UltraNeb 99 ultrasonic nebulizer (2), Nouvag UltraNeb ultrasonic nebulizer (2), NuAire NU-810-SPEC.
Biohood sputum induction booths (2). Devilbiss PulmoAide compressor nebulizer (Rooms 1333, 1329A, 1329E), IsoTemp 205 water bath, Fisher Scientific Stereomaster Zoom Microscope Model #12-562-1, Niox Mino nitric oxide (NO) monitor, ECG machines (2) HP Pagewriter Xli and Burdick Eclipse LE, Nellcor pulse oximeter (2), Welch Allyn Sure Temp Plus (2), SM DSM-2 micro-dosimeter, Salter Labs Dosimeter (2), Tanita Scale, stadiometer, Bedfont Micro+ Smokerlyzer carbon monoxide (CO) monitors (2), Omron HEM-907XL blood pressure monitor.

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. Three asthma grants have been funded within the past year:

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. *Innate and Adaptive Immune Responses in Th2-high Asthma.* Dr Fahy is overall PI and a project leader and Drs. Locksley and Ansel also lead projects. Dr Woodruff leads a core and is co-I on Dr Ansel's project. The grant is in NCE and a competitive resubmission is awaiting review later this fall.

(v) U01 HL126493. *Defining a Comprehensive Reference Profile of Circulating Human Extracellular RNA* (Woodruff, Erle).

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

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

3. Training awards for physician scientists studying asthma and COPD.
The Airway Center provides key space and other resources to support four MD scientists who have current K awards. These physician scientists are: Erin Gordon, M.D., Nirav Bhakta, M.D., Ph.D., Stephanie Christenson, M.D., and Michael Peters, M.D. (also has a Parker B. Francis fellowship).

4. Non-NIH grants:
(i) COPD Foundation, Inc. Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS)(Woodruff)

(ii) Other: ACRC is 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.

Interactions and Communications

SABRE Center core scientists and the Director meet quarterly with Dr. Fahy and colleagues to further communication, planning and collaborative investigations of human asthma patients. Each of the core scientists is already 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 continue to hold monthly research conferences for SABRE/ACRC investigators at the Parnassus site to promote interactions and collaborations.

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 all enthusiastically embraced a second retreat in the fall of 2018.

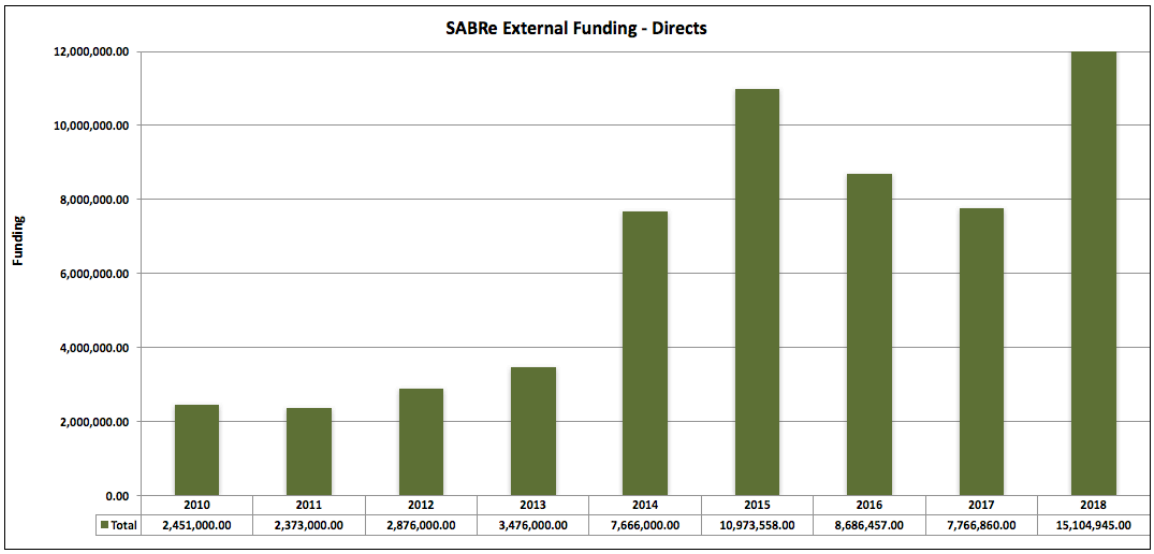
Human Upper Respiratory Tract Analysis

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 in the Locksley lab, Benjamin Terrier, worked regularly with this group investigating nasal upper airway epithelial cells involved in sensory perception to allergens. 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 these evidence-based metric achievements over this 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 accumulated extramural funds by SABRE investigators – Drs. Cheng, Fahy and Woodruff joined in 2014; Drs. Liu and Cheng were recruited elsewhere in 2015.

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

Dunican EM, BM Elicker, DS Gierada ME, SK Nagle, ML Schiebler, JD Newell, WW Raymond, ME Lachowicz-Scroggins, S Di Maio, EA Hoffman, M Castro, SB Fain, NN Jarjour, E Israel, BD Levy, SC Erzurum, SE Wenzel, DA Meyers, ER Bleecker, BR Phillips, DT Mauger, ED Gordon, PG Woodruff, MC Peters, JV Fahy; National Heart Lung and Blood Institute (NHLBI) Severe Asthma Research Program. 2018. Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. J Clin Invest 128:997-1009.

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.

Mangul S, HT Yang, N Strauli, F Gruhl, HT Porath, K Hsieh, L Chen, T Daley, S Christenson, A Wesolowska-Anderson, R Spreafico, C rios, C Eng, AD Smith, RD Hernandez, RA Ophoff, JR Santana, EY Lavanon, PG Woodruff, E Burchard, MA Siebold, S Shifman, E Eskin, N Zaitlen. 2018. ROP: dumpster diving in RNA-sequencing to find the source of 1 trillion reads across diverse human tissues. Genome Biology 19:36 (http://doi.orfg/10.1186/s13059-018-1403-7).

High-throughput RNA-sequencing has provided an unprecedented exploration of gene expression in human tissues, but unmapped reads, which comprise 10-20% of sequences, are usually discarded. Here, investigators at UCSF worked to create Read Origin Protocol, or ROP, a tool for findings the source of all reads secured from tissue reads. ROP uncovered diversity in immune system genes, including TCRs and BCRs, and revealed microbiome sequences in diverse tissues. SABRE investigators used ROP to demonstrate decreased BCR and TCR diversity in blood from asthma patients, illustrating the capacity of ROP to reveal functional data when applied to existing RNA-deq data bases. ROP is an open-access program. (https://github.com/smangul1/rop/wiki)

Singh PB, HH Pua, HC Happ, C Schneider, J von Moltke, RM Locksley, D Baumjohann, KM Ansel. 2017. MicroRNA regulation of type 2 innate lymphoid cell homeostasis and function in allergic inflammation. J Exp Med 214:3627-3643.

MicroRNAs constitute important components of gene expression that work by regulating whole networks in coordinate ways in order to promote cell effector function and cell fate decisions, and can direct efforts for drug interventions by elucidating key nodes in gene expression pathways. Here, the Ansel lab used ILCs rigorously defined by reporter alleles generated in the Locksley lab to discover miRNAs involved in ILC2 cytokine expression. The miR-17-82 cluster was identified as a key regulator of lung ILC2 proliferation and cytokine production in response to papain, and was necessary for optimal generation of type 2 cytokines in response to IL-33 and TSLP in vitro. The findings reinforce the important of miRNAs in elaboration of cytokines implicated in allergic disease, and suggest that strategies targeting such pathways may represent areas for therapeutic discovery.

Oh J, JSA Perry, H Pua, N Irgrens-Moller, S Ishido, CS Hsieh, Shin JS. 2018. MARCH1 protects the lipid raft and tetraspanin web from MHCII proteotoxicity in dendritic cells. *J Cell Biol* 217:1395-1410.

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.

Wu CM, TL Roth, Y Baglaenko, DM Ferri, P Brauer, JC Zuniga-Pflucker, KW Rosbe, JE Wither, A Marson, Allen CDC. 2018. Genetic engineering in primary human B cells with CRISPR-Cas9 ribonucleoproteins. *J Immunol Methods* 457:33-40.

Genome editing is moving forward rapidly, but mechanism for targeting primary human B cells remain limited. Here, the Allen lab used electroporation of CRISPR-Cas9 ribonucleoproteins to achieve efficient gene targeting in primary human B cells. The authors achieved both knock-out and nucleotide editing by co-delivery of oligonucleotide templates for homology directed repair. This reveals a powerful new technology for human B cell editing that may be important for both functional genetic studies but also for engineering B cell therapeutics.

Schneider C, CE O'Leary, J von Moltke, H-E Liang, Q Yan Ang, PJ Turnbaugh, S Radhakrishnan, Michael Pellizzon, A Ma, RM Locksley. 2018. A metabolite-triggered tuft cell-ILC2 circuit drives small intestinal remodeling. *Cell* 174:271-284.

The discovery of a role for tuft cells in type 2 immunity in 2016 in the Locksley lab drove efforts to uncover pathways that activate these cells at mucosal sites, since activation lies upstream of ILC2 stimulation and elaboration of type 2 cytokines. In small intestine, tuft cells were activated directly by succinate and the succinate receptor, which leads to elaboration of IL-25 and ILC2 activation in the lamina propria. Succinate is a metabolic end-product of the hydrogenosome, mitochondria-like organelles of the protist Tritrichomonas, which inhabit most mouse colonies; related organisms infect many invertebrate and vertebrate species, including humans. In a comprehensive series of experiments, Schneider et al. showed that complex fibers in chow are metabolized to short chain fatty acids and succinate by Tritrichomonas, and that chronic tuft cell activation leads to small bowel lengthening and hypertrophy. The resultant small bowel remodeling impedes further infestation by helminths, consistent with concomitant immunity, and suggesting an evolved mutualism by which vertebrates respond to chronic intestinal parasitism. Current efforts are examining systemic effects on lung immunity and aspects of sensory transduction by tracheal and nasal epithelial tuft cells, which express the succinate receptor but also other G protein-coupled receptors associated with sensory detection.

Organization of the body of this Annual Report

We organized this report to review the 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 summarize the Financial Report for the Program. Finally, we outline the strategies for the coming years and append the current biographical summaries of the members, awardees and participants in the SABRE Center at UCSF.

We thank the Sandler family for their vision and support in creating and sustaining the SABRE Center. Support for high-risk, open-ended, basic science is difficult to procure in the current funding and fiscal climate. As noted in the overview above, we can identify many examples where support from the SABRE Center has been leveraged greatly to achieve substantial gains for the scientific and academic study of asthma at UCSF. We are most grateful for the continued support of the Sandler Foundation.

Executive Committee

Richard M. Locksley, M.D.

The goals of the SABRE Center are to drive innovation in basic asthma research. We pursue this goal from a core scientific group dedicated to the study of asthma, by promoting access to state-of-the-art technologies required to drive the research, and by facilitating opportunities for interactions with translational and clinical investigators studying asthma patients. The Executive Committee is constituted to provide the Director with counsel regarding issues of scope, direction and execution. The Executive Committee plays a role in overseeing progress of SABRE Center faculty and provides oversight in sustaining progress towards the overall goals of the Center. 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, Ph.D., is currently the Director of the Nomis Center for Immunobiology and Microbial Pathogenesis at the Salk Institute. Her research focus is in understanding 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. 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, inflammation and in tumors. In particular, she seeks to learn how T cell behavior is suppressed by tumors, and this can be used for innovative therapies for cancer using the body's own immune system.

Prior to joining the Salk Institute Dr. Kaech was Professor in the Department of Immunobiology at Yale University from 2015 to 2018 and a Howard Hughes Medicial Institute Early Career Scientist from 2009 to 2015. She received her Ph.D. in Developmental Biology from Stanford University in 1998 and her B.S. in Cellular and Molecular Biology from the University of Washington, Seattle in 1993.

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 Immunolog*y. 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.
Professor, Departments of Medicine and
Microbiology & Immunology
Investigator, Howard Hughes Medical Institute

UCSF
513 Parnassus Avenue
Medical Sciences, S-1032B, Box 0795
San Francisco, CA 94143-0795

Tel: 415-476-3087
Fax: 415-502-5081
Website: http://sabre.ucsf.edu/locksleylab/
Programs:
Immunology Graduate Program
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

1. **Locksley RM**. 2010. Asthma and allergic inflammation. *Cell* 140:777-83.
2. Wu D, AB Molofsky, HE Liang, RR Ricardo-Gonzalez, HA Jouihan, JK Bando, A Chawla, **RM Locksley**. 2011. Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. *Science* 332:243-7.
3. Nussbaum JC, SJ Van Dyken, J von Moltke, LE Cheng, A Mohapatra, AB Molofsky, EE Thornton, MF Krummel, A Chawla, H-E Liang, **RM Locksley**. 2013. Type 2 innate lymphoid cells control eosinophil homeostasis. *Nature* 502:245-8.
4. Lee M-W, JI Odegaard, L Mukundan, Y Qui, AB Molofsky, JC Nussbaum, K Yun, **RM Locksley**, A Chawla. 2015. Activated type 2 innate lymphoid cells regulate beige fat biogenesis. *Cell* 160:74-87.
5. von Moltke J, M Ji, H-E Liang, **RM Locksley**. 2016. Tuft cell-derived IL-25 regulates an intestinal ILC2-epithelial response circuit. *Nature* 529:221-5.
6. Van Dyken SJ, JC Nussbaum, J Lee, AB Molofsky, H-E Liang, JL Pollack, RE Gate, GE Haliburton, CJ Ye, A Marson, DJ Erle, **RM Locksley**. 2016. A tissue checkpoint regulates type 2 immunity. *Nat Immunol* 17:1381-7.
7. Lechner AJ, IH Driver, J Lee, CM Conroy, A Nagle, **RM Locksley**, JR Rock. 2017. Recruited monocytes and type 2 immunity promote lung regeneration following pneumonectomy. *Cell Stem Cell* 21:120-134.
8. Van Dyken SJ, H-E Liang, R Naikawadi, P Woodruff, P Wolters, D Erle, **RM Locksley**. 2017. Spontaneous chitin accumulation in airways and age-related fibrotic lung disease. *Cell* 169:497-509.
9. Sui P, DL Wiesner, X Jinhao, Y Zhang, J Lee, SJ Van Dyken, A Iashua, C Yu, BS Klein, **RM Locksley**, G Deutsch, X Sun. 2018. Pulmonary neuroendocrine cells amplify allergic asthma responses. *Science* 360: eean8546. DOI: 10.1126/science.aan8546..
10. Miller CN, I Proekt, J von Moltke, KL Wells, AR Rajpurkar, H Wang, K Rattay, IS Khan, TC Metzger, JL Pollack, AC Fries, WW Lwin, EJ Wigton, AV Parent, B Kyewski, DJ Erle, KA Hogquist, LM Steinmetz, **RM Locksley**, MS Anderson. 2018. Thymic tuft cells promote an IL-4-enriched medullary microenvironment and shape thymocyte development. *Nature* (in press).
11. Schneider C, CE O'Leary, J von Moltke, H-E Liang, Q Yan Ang, PJ Turnbaugh, S Radhakrishnan, Michael Pellizzon, A Ma, **RM Locksley**. 2018. A metabolite-triggered tuft cell-ILC2 circuit drives small intestinal remodeling. *Cell* 174:271-284.
12. Kotas ME, **RM Locksley**. 2018. Why ILCs? *Immunity* 48:1081-1090.
13. Nadjsombati MS, JW McGinty, MR Lyons-Cohen, JB Jaffe, L DiPeso, C Schneider, CN Miller, JL Pollack, GA Nagana Gowda, DJ Erle, MS Anderson, **RM Locksley**, D Raftery, J von Moltke. 2018. Detection of succinate by intestinal tuft cells triggers a type 2 innate immune circuit. *Immunity* 49:33-41.
14. Vivier E, D Artis, M Colonna, A Diefenbach, JP Di Santo, G Eberl, S Koyasu, **RM Locksley**, ANJ McKenzie, RF Mebius, F Powrie, H Spits. 2018. Innate lymphoid cells: ten years on. *Cell* (in press).
15. Ricardo-Gonzalez RR, SJ Van Dyken, C Schneider, J Lee, JC Nussbaum, H-E Liang, D Vaka, WL Eckalbar, AB Molofsky, DJ Erle, **RM Locksley**. 2018. Tissue signals imprint ILC2 identity with anticipatory function. *Nature Immunol* (in press).

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

CVRI Box 3122
555 Mission Bay Blvd S.
San Francisco, CA 94143
Tel: 415-476-5178

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.

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

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9. Sullivan B.M., Liang H.E., Bando J.K., Wu D., Cheng L.E., McKerrow J.K., ***Allen C.D.C.**, *Locksley R.M. (2011). Genetic analysis of basophil function *in vivo*. *Nature Immunology*, 12(6), 527-535. *co-corresponding author. PMCID: PMC3271435.
10. Steiner D.F., Thomas M.F., Hu J.K., Yang Z., Babiarz J.E., **Allen C.D.C.**, Matloubian M., Blelloch R., Ansel K.M. (2011). MicroRNA-29 Regulates T-Box Transcription Factors and Interferon-γ Production in Helper T Cells. *Immunity*, 35(2), 169-181. PMCID: PMC3361370.
11. Yang Z., Sullivan B.M., **Allen C.D.C.** (2012). Fluorescent *in vivo* detection reveals that IgE^+ B cells are restrained by an intrinsic cell fate predisposition. *Immunity*, 36(5), 857-872.
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K. Mark Ansel, Ph.D.
Associate Professor, Department of Microbiology & Immunology
Sandler Asthma Basic Research Center of UCSF

513 Parnassus Avenue
UCSF Box 0414, HSE-1001E
San Francisco, CA 94143
Tel: 415-476-5368
Fax: 415-502-4995

Websites: Ansel Lab [http://ansel.ucsf.edu]
Biomedical Sciences Graduate Program [http://bms.ucsf.edu/directory/faculty/k-mark-ansel-phd]

Mark Ansel is an Associate 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. 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, 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, 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 mostly focus on posttranscriptional regulation of gene expression by miRNAs and RNA binding proteins. We study how individual miRNA families regulate helper T cell differentiation and immune function, as well as the regulation

of the miRNA pathway itself during immune responses. We developed a screening technology that allows us to rapidly determine which miRNAs regulate distinct T cell behaviors, and a high throughput pipeline for determining miRNA expression patterns in small clinical samples. In addition, we discovered that T cells reset their miRNA repertoire upon activation. This rapid change in miRNA expression appears to be critical to allow T cells to change their gene expression programs and develop effector functions.

Lab Objectives

1) To determine how the expression and function of miRNAs contributes to the pathogenic properties of T cells in human asthma.
2) To define the molecular mechanisms that control miRNA homeostasis, and determine how the miRNA repertoire is so dramatically remodeled during T cell activation.
3) To map the cis-regulatory activity of the transcriptome and reveal the trans-acting RNA binding proteins and miRNA mediators of post-transcriptional regulation.

Selected Publications

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2. Montoya MM, Maul J, Singh PB, Pua HH, Dahlström F, Wu N, Huang X, **Ansel KM***, Baumjohann D*. A Distinct Inhibitory Function for miR-18a in Th17 Cell Differentiation. *J Immunol*. 2017 Jul 15;199(2):559-569.
3. Pua HH, Steiner DF, Patel S, Gonzalez JR, Ortiz-Carpena JF, Kageyama R, Chiou NT, Gallman A, de Kouchkovsky D, Jeker LT, McManus MT, Erle DJ, **Ansel KM**. MicroRNAs 24 and 27 Suppress Allergic Inflammation and Target a Network of Regulators of T Helper 2 Cell-Associated Cytokine Production. *Immunity*. 2016 Apr 19;44(4):821-32.
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11. Baumjohann D and **Ansel KM**. MicroRNA regulation of T cell differentiation and plasticity. *Nat Rev. Immunol***.** 13:666-78 (2013)
12. Baumjohann D, Clingan JM, de Kouchkovsky D, Bannard O, Bluestone JA, Matloubian M, **Ansel KM*,** Jeker LT*. The microRNA cluster miR-17~92 is essential for follicular helper T cell differentiation. *Nat Immunol.* 14:840-8 (2013) (*co-corresponding authors)
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Esteban G. Burchard, MD, MPH
Harry Wm. and Diana V. Hind Distinguished Professor in Pharmaceutical Sciences II
Professor, Department of Bioengineering & Therapeutic Sciences and Medicine

1550 4th St. 5th FL
UCSF Box 2911, RM 584B
San Francisco, CA 94143
Tel: 415-514-9677
Fax: 415-514-4365

Website: Asthma Collaboratory [https://pharm.ucsf.edu/burchard]

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 annoted 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 differents 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

1. White MJ, Risse-Adams O, Goddard P, Contreras MG, Adams J, Hu D, Eng C, Oh SS, Davis A, Meade K, Brigino-Buenaventura E, LeNoir MA, Bibbins-Domingo K, Pino-Yanes M, **Burchard EG**. Novel genetic risk factors for asthma in African American children: Precision Medicine and the SAGE II Study. *Immunogenetics*. 2016 May 3. PubMed PMID: 27142222.
2. Oh SS, Galanter J, Thakur N, Pino-Yanes M, Barcelo NE, White MJ, de Bruin DM, Greenblatt RM, Bibbins-Domingo K, Wu AH, Borrell LN, Gunter C, Powe NR, **Burchard EG**. Diversity in Clinical and Biomedical Research: A Promise Yet to Be Fulfilled. *PLoS Med*. 2015 Dec 15; 12(12):e1001918. PubMed PMID: 26671224; PubMed Central PMCID: PMC4679830
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5. McGarry ME, Castellanos E, Thakur N, Oh SS, Eng C, Davis A, Meade K, LeNoir MA, Avila PC, Farber HJ, Serebrisky D, Brigino-Buenaventura E, Rodriguez-Cintron W, Kumar R, Bibbins-Domingo K, Thyne SM, Sen S, Rodriguez-Santana JR, Borrell LN, **Burchard EG**. Obesity and Bronchodilator Response in African-American and Hispanic Children and Adolescents with Asthma. *Chest.* 2015 Mar 5. PMID: 25742612

6. 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
7. Medical research: Missing patients. **Burchard EG**. *Nature*. 2014 Sep 18; 513 (7518):301-2. PMID: 25230631
8. 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.
9. Nishimura, K.K., Galanter, J.M., (19 Authors), **Burchard, E.G** Early Life Air Pollution and Asthma Risk in Minority Children: The GALA II & SAGE II Studies. *AJRCCM*. 2013 Aug. 1; 188(3):309-18. PMID: 23684070. PMCID: PMC3778732
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13. **Burchard EG**, Avila PC, (23 authors), Silverman EK; Lower Bronchodilator Responsiveness in Puerto Rican than in Mexican Asthmatic Subjects. *AJRCCM*. 2004; 169(3):386-92. PMID: 14617512

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

513 Parnassus Avenue
UCSF Box 0130, HSE-1307
San Francisco, CA 94143
Tel: 415-476-9940
Fax: 415-476-5712

Fahy Lab Website: http://www.cvri.ucsf.edu/~fahy/
Biomedical Sciences Graduate Program
http://bms.ucsf.edu/directory/faculty/john-v-fahy-md-msc
UCSF Profiles: http://profiles.ucsf.edu/john.fahy

John Fahy is a Professor in the Department of Medicine and the CVRI. He is a medical graduate of University College Dublin and completed fellowship training in pulmonary and critical care medicine at UCSF. His laboratory in the Sandler Asthma Basic Research Center focuses on mechanism-oriented clinical studies of airway inflammation and mucus pathology in asthma and other airway diseases.

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

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

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

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

Lab Objectives

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

Selected Publications

1. **Fahy JV**, Fleming HE, Wong HH, Liu JT, Su JQ, Reimann J, Fick RB, Boushey HA. The effect of an anti-IgE monoclonal antibody-E25 on the early and late phase responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med* 1997; 155:1828-1834.
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Jeoung-Sook Shin, Ph.D.
Associate Professor, Department of Microbiology & Immunology
Sandler Asthma Basic Research Center
University of California San Francisco

513 Parnassus Ave, HSE-201
San Francisco, CA 94143-0414
Tel: 415-476-5451
Fax: 415-476-3939
email: jeoung-sook.shin @ ucsf.edu

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. Thus, MARCH1 is involved in 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

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fibrotic lung diseases and Th2-high asthma. *PLoS ONE*, Jun 9(6): e99084, 2014
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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

513 Parnassus Avenue
UCSF Box 0130, HSE-1305
San Francisco, CA 94143
Tel: 415-514-2061
Fax: 415-502-7814

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

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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 2018, the core will focus on expanding use of new technologies, and continue to develop and elaborate custom built tools for image acquisition and analysis.

1. To open our Selective-Plane Imaging Microscope (SPIM) to the community and develop general acquisition and post-acquisition protocols for whole organ/organism imaging.
2. To construct the 4^{th} generation of our homebuilt multiphoton microscope which will exceed current capabilities and drive further development of custom software and hardware tools.
3. To incorporate high-dimensional 7^{+}-color imaging with machine learning data analysis for cell identification and interaction.
4. To extend the capabilities of the Lattice Light-Sheet Microscope (LLSM) to meet the needs of the growing user base.
5. To extend the usage and utility of mouse lung imaging through continued development of minimally invasive intravital imaging methods and instrumentation.
6. 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 Center (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 now 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 155 unique users of the BIDC. Many users are trained on multiple instruments. These users represent 56 principal investigators or labs. These labs are drawn from 19 departments or organizational units.

In 2017, 95 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.

Anderson
Baraqban
Barber
Baskin
Bhushan
Bluestone
Chang
Chen
Erlebacher
Fahy
Fields
Fong
Gartner
Hebrok
Kajimura
Krummel
Ku
Laird
Lin
Locksley
Looney
Lue
Ma
Marcucio
Marson
McManus
Molofsky
Noble
Nystul
Peng
Peterlin
Rinaudo
Rosenblum
Rubenstein
Rugerro
Sall
Schneider
Schrepfer
Shin
Solomon
Spitzer
Springer
Tang
Tward
Villeda
visiting scholar
Wang
Weaver
Weiss
Werb
Xu

Recent Accomplishments

In 2017, scientifically:

1. The Selective-Plane Imaging Microscope (SPIM) has been completed and is open to the community for pilots. The microscope is a dual side-illuminated galvo-scanning light sheet fitted with a 20x long working distance objective resulting in higher magnification and spatial resolution than is typical for comparable microscopes. Both live and fixed *Drosophila melanogaster* organs have been imaged in multiple colors using agarose plug support. Designs to include cleared organ imaging have been incorporated into the sample preparation pipeline.
2. The fourth generation 2-photon microscope (Gen4) was designed, funded, and space was allocated. The design of the microscope is such that it not only makes use of many of the parts (electronics and optics) from the now disbanded Gen1 and Gen2 microscopes, but improves on the optical path and features of the current cutting edge Gen3 design. A major improvement includes a split detection optical train to minimize the length of the photon path, while still including 6 PMT detectors. Sample stage design will again include the ability for intravital imaging, live tissue, and fixed samples while improving accessibility and workspace. 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.
3. Adam Fries (BIDC Specialist) created custom analysis software in Matlab as an extension of the 3D rendering software Imaris, which will lead to a publication in early March. This software was designed to characterize the time-dependent spatial distribution of germ cells in the ovarian environment once implantation has occurred. A second project, which builds on our contribution to a 2016 Development publication (doi:10.1242/dev.144386), includes a custom Matlab extension in Imaris to measure the angular relationship between luminal glands of the uterus, the lumen, and the implantation site of the eggs. This project is nearing completion and the script is in its final testing phase.
4. Adam Fries found a two-step custom analysis solution for a researcher trying to characterize the interactions between three types of immune cells in the lung. The solution includes a custom script executed in FIJI to perform the image processing and performs the quantification of the image data in Python.
5. Adam Fries wrote custom analysis in R using the spatstat library to measure whether the nearest neighbor relationship between immune cells in the thymus occurred more than randomly. This analysis has led to a paper that was submitted to Nature and is in the revisions phase.
6. We fostered collaboration between the company Amgen to develop methods for real-time tracking of antibody entry and dispersion in tumor, lung and other tissues to understand the dynamics that underpin the effectiveness and limitations of immune therapies.
7. The Lattice Light-Sheet Microscope user base was expanded through 7 pilot projects leading to 4 major users. As a result, the microscope is (limited, due to the availability of the necessary expertise, to) collecting data (up to 1 Tb/day) two full days a week.

The post-collection data pathway has been refined to quickly place the usable data into the users' hands. To correct for channel registration issues (both mechanical and fundamental), a processing program has been written so that a user can quickly adjust a three-dimensional (3D) overlay and the computer will re-assign the coordinates of the data resulting in 3D spatially aligned channels with 1 pixel accuracy.

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

Introduction of new equipment, and training

This year the BIDC has absorbed the microscopes from the Diabetes Center into the subscription model allowing for more efficient training of users and bookkeeping/billing. The addition includes one laser scanning confocal microscope, one optical Apotome microscope, and one Brightfield microscope. The BIDC is now maintaining an additional TIRF microscope recently opened to the community from the Krummel lab. The selective-plane imaging microscope (SPIM) has been completed to the extent that is now open to 'pilots' for the next few months as protocols are finalized. Money and space have been allocated for the construction of the Gen4 homebuilt multi-photon laser scanning confocal microscope set to take place in the first half of 2018.

Space

The primary residence of the BIDC is Medical Sciences S11, which includes an office for staff 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 2017, in part through our efforts and support:

1) Mark Looney: Nina Ireland Program in Lung Health Award
2) Matthew Krummel: RAP award
3) Alan Verkman: NEI competitive renewal

Recent publications

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

1. Cai, En, Kyle Marchuk, Peter Beemiller, Casey Beppler, Matthew G. Rubashkin, Valerie M. Weaver, Audrey Gérard, et al. 2017. "Visualizing Dynamic Microvillar Search and Stabilization during Ligand Detection by T Cells." Science 356 (6338): eaal3118. doi:10.1126/science. aal3118.
2. Theodore L Roth, Ruby Yu, Eric Shifrut, Joseph Hiatt, et al. 2017. "Correction of autoimmune IL2RA mutations in primary human T cells using non-viral genome targeting." bioRxiv. doi: https://doi.org/10.1101/183418.
3. Marrah Lachowicz-Scroggins, Erin Gordon, Agata Wesolowska-Andersen, Nathan Jackson, Hannah MacLeod, Louis Sharp, Matt Sun, Max Seibold, John V Fahy. "Cadherin-26 (CDH26) Regulates Airway Epithelial Cell Cytoskeletal Structure and Polarity." Nature: Cell Discovery. Accepted December 15, 2017. In Proofing.
4. Lefrançais E, Ortiz-Muñoz G, Caudrillier A, Mallavia B, Liu F, Sayah DM, Thornton EE, Headley MB, David T, Coughlin SR, Krummel MF, Leavitt AD, Passegué E, Looney MR. "The lung is a site of platelet biogenesis and a reservoir for haematopoietic progenitors". Nature. 2017 March 22. Doi:10.1038/nature21706 [Epub ahead of print]. PMID: 28329764
5. Smith AJ, Yao X, Dix JA, Jin BJ, Verkman AS. "Test of the 'glymphatic' hypothesis demonstrates diffusive and aquaporin-4-independent solute transport in rodent brain parenchyma." Elife. 2017 Aug 21;6. doi: 10.7554/eLife.27679.
6. Wong PT, Roberts EW1, Tang S, Mukherjee J, Cannon J, Nip AJ, Corbin K, Krummel MF, Choi SK. "Control of an Unusual Photo-Claisen Rearrangement in Coumarin Caged Tamoxifen through an Extended Spacer." ACS Chem Biol. 2017 Apr 21;12(4):1001-1010. doi:10.1021/acschembio.6b00999.
7. Alex J. Hughes, Hikaru Miyazaki, Maxwell C. Coyle, et al. "Engineered Tissue Folding by Mechanical Compaction of the Mesenchyme." Developmental Cell 44, 1–14, January 22, 2018. doi:10.1016/j.devcel.2017.12.004
8. Lefrançais E., Mallavia B., Zhuo H, Calfee C., Looney M. "The maladaptive role of neutrophil extracellular traps in antibacterial host defense in the lung". JCI Insight (In Press)

Plans for the Coming Year

1. A major project for the BIDC in the upcoming year will be to get the Gen4 2P microscope online. We will incorporate many electrical components and optics from the now disbanded Gen1 and Gen2 microscopes into the Gen4 shortening the time to full implementation. A new detection optical train will be machined, which will shorten the photon path length to detector and increase S/N for longer wavelengths compared to Gen3. Additional improvements will include more access to the stage/sample area, an alignment camera, and optional future additions such as visible lasers and laser ablation modules. 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.

2. In the next year we will work to expand the user base of the Selective-Plan Imaging Microscope (SPIM) to include fixed, live, and cleared whole organ/organism imaging. With the growing base we will work to incorporate additional features and 'quality-of-live' improvements. A major push will be to develop a seamless post-processing pipeline to quickly make accessible the large quantity of generated data. A complementary project will include developing and making available on our website a library of known fluorophores, which can be used with different clearing agents to minimize experimental optimization time.
3. With the growing success of the Lattice Light-Sheet Microscope (LLSM), more data is being generated that needs to be processed. The current channel registration tool used to compensate for mechanical and fundamental misalignment is limited to a manual visual inspection and can only achieve 1-pixel accuracy. The program will be expanded to include automated non-biased alignment using fixed multi-color fiducial markers to reach sub-pixel accuracy. Additionally, this and other post-processing tools will be expanded to include 'batch' processing and be moved from the CPU to the GPU to increase processing speed. BIDC Specialist Kyle Marchuk will continue to work to grow the user base and expand the microscope's capabilities with users' needs. Additionally, we have entered collaboration with the company Eli-Lilly to study T cell directed killing of tumor cells. This project supplies resources to develop new 4-dimensional cell:cell interaction analysis that will translate beyond this specific project.
4. As more of our instruments expand to generate high-dimensional data, we continue to develop state of the art machine learning algorithms to automate analysis, building on the open source software previously developed in the BIDC for the visualization of large data sets. Analysis will not only include cell type identification, but also learn to recognize different forms of cell:cell interactions.
5. Adam Fries (BIDC Specialist) will focus on implementing user-friendly, widely applicable clustering algorithms to analyze data currently being generated by BIDC users. His work will focus on collaborations with users, to design custom solutions to ever evolving analysis problems raised by the cutting edge imaging techniques we support.
6. In the next year, Jordan Briscoe (BIDC specialist) will continue to develop methods for real-time tracking of antibody entry and dispersion in tumor, lung and other tissues to understand the dynamics that underpin the effectiveness and limitations of immune therapies.

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 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. *Alaris 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 Imaris, 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

NIAID Asthma and Allergic Diseases Cooperative Research Center
Principal Investigator, David Erle

Objective

This Center grant is focused on understanding asthma endotypes.

Projects

The center is composed of 2 projects and 1 human subjects core that supports both projects. The Center successfully competed for a new five-year cycle for 2018-2023.

A. Specific Aims

Project 1, Asthma endotypes: Mechanisms and consequences for airway epithelium and mucus
Aim 1. Understand how differences in airway epithelial cell responses to IL-13 contribute to type 2-high asthma susceptibility and severity.
Aim 2. Identify changes in airway epithelial secretory cells and mucus that lead to mucostasis and airway obstruction in asthma.
Aim 3. Define an airway epithelial ER stress signature and determine how the IRE1 ER stress pathway contributes to type 2 and IFN responses in airway epithelial cells.
Project 2: Beyond the type 2-high endotype: Interferons and epithelial ER stress in asthma
Aim 1. Using longitudinal studies, determine the clinical significance of interferon-driven inflammation and airway epithelial ER stress in asthma.
Aim 2. Using randomized trials, determine whether interferon-driven inflammation and airway epithelial ER stress are resistant to and predict poor response to existing asthma therapies.
Aim 3. Using murine models, determine whether specific inhibition of airway epithelial ER stress improves AHR, inflammation and mucus production.

B. Studies and Results

Over the past two decades, work from many centers, including our own, has led to a better understanding of the diversity of molecular phenotypes (endotypes) and clinical features of asthma. Investigators from our AADCRC have made fundamental contributions to the understanding of type 2 and other immune responses, cell and molecular biology of airway cells, and pathophysiologic mechanisms leading to airway obstruction. In addition, we have played leading roles in development of clinical tools for relating findings from cell and animal model systems to the pathophysiology of asthma in humans. The identification of type 2 asthma as a prevalent endotype in both mild and severe asthma has led to studies assessing the utility of established and new therapies in this group. While substantial progress

has been made, an important subset of individuals with type 2 asthma have severe disease despite treatment. Non-type 2 asthma also accounts for a substantial proportion of individuals with asthma, including those with severe disease. Pathogenic mechanisms responsible for asthma in these individuals are less well understood, and this remains an important problem. There is therefore an urgent need to better understand the mechanisms underlying asthma endotypes and develop new therapeutic targets appropriate for these endotypes. Based on recent work from our Center and others, we propose three overarching hypotheses that serve as the focus for this renewal: 1) type 2 and IFN-driven asthma are persistent endotypes that may interact to increase asthma severity, 2) type 2 asthma susceptibility and severity relates to both heightened IL-13-driven epithelial production and tethering of MUC5AC leading to airway obstruction, and 3) ER stress is a feature in both type 2- and IFN-driven airway inflammation that is not effectively treated by existing therapies and targeting the IRE1 ER stress response pathway will inhibit airway inflammation and obstruction.

In this first year of the new cycle, we are building on prior published studies and preliminary results to test these hypotheses. With the exception of the use of pre-clinical mouse models to evaluate a novel therapeutic approach in Aim 3 of Project 2, the remainder of our program constitutes human subjects research or utilizes human primary cells. The Projects will both benefit from extensive support from a Clinical Subject and Biospecimen Core, which will conduct a human study and make biospecimens and clinical data available for detailed studies.

C. Significance

The identification of the role of type 2 cytokines, especially IL-13, as a driver of pathology in a large subset of asthma has been critical and represents an important step toward personalizing therapy for asthma. However, available therapies are not always successful for treating type 2 asthma and an important type 2 asthma group has severe disease that persists despite aggressive therapy. Non-type 2 mechanisms that cause asthma are far less well understood and many with type 2-low asthma respond poorly to corticosteroids and other mainstays of asthma treatment. Our major goals, therefore, are to discover new molecular mechanisms that are important in type 2 and other forms of asthma and in so doing to identify novel targets and therapeutic strategies.

Training and Integration with Sandler Program

This Center grant provides training in basic and applied biology of asthma for approximately 6 post-doctoral fellows and 2 junior faculty students working in the labs of the project and core directors. The Asthma SCOR grant and U19 Center grant that preceded this program has already provided training for several scientists who now lead their own laboratories engaged in asthma-related research and we expect a similar outcome from this new Center. The leaders of Projects and the Core are already actively involved in SABRE. SABRE support helped establish core labs (Mouse Physiology, Genomics) and provided other funding that have been important for the development and success of the Center. Supplementary grants provided through this center grant have supported 6 junior faculty members, Nirav Bhakta,

Aparna Sundaram, Erin Gordon, Stephanie Christenson, Walter Eckalbar (2017-2018), and Marquitta White (2018-2019) who are just launching careers focused on translational and basic research in asthma.

SABRE RNAseq Consortia
Richard M. Locksley Lab

We are interested in heterogeneity of innate lymphoid cells in the lung and upper respiratory tract, particularly ILC2s, which express cytokines of clear importance to the pathogenesis of asthma and atopic diseases. In preliminary experiments, we have uncovered a subset of lung ILC2s that are responsive to IL-18 rather than IL-33, as typical for most lung ILC2s. We will use our reporter mice with knockin alleles for Arginase-1 and IL-5 to permit high confidence sorting of ILC2s from the skin, pharynx, upper and lower airways, small intestine, visceral adipose and bone marrow.

For single-cell RNA sequencing (scRNAseq), ILC2s are prepped and sorted into ice-cold 0.5% BSA in PBS and processed through the Chromium Single Cell 3' v2 Library Kit (10X Genomics) per the manufacturer's protocol. Preliminary experiments have established sample yields of 5,000 to 25,000 cells from each tissue, resulting in 400-11,600 single cells for analysis from each tissue. The cells are partitioned into Gel Beads in Emulsion in the instrument, where cell lysis and barcoded reverse transcription of RNA occurrs, followed by amplification, shearing and 5' adaptor and sample index attachment. Libraries are sequenced on an Illumina HiSeq 4000. Single Cell 3' libraries use standard Illumina sequencing primers for both sequencing and index reads. They are run using paired-end sequencing with single indexing where Read1 is 26 cycles and Read 2 is 98 cycles. The resulting bcl files will be de-multiplexed using bcl2fastq2.1.7v and, the resultant paired-end fastq files are aligned to the mm10 transcriptome (ftp://ftp.ensembl.org/pub/release-84/fasta/mus_musculus/dna/Mus_musculus.GRCm38.dna.primary_assembly.fa.gz, ftp://ftp.ensembl.org/pub/release-84/gtf/mus_musculus/Mus_musculus.GRCm38.84.gtf.gz) using STAR aligner which come packaged in Cellranger toolkit (version 2.0.0) provided by 10X Genomics. Cellranger aggr is used to aggregate multiple libraries.

We anticipate novel findings that will lay the ground for similar approaches using human cells acquired through lavage and biopsy of airways. These experiments in the mouse will established bone fide markers that we will use to guide translation to the human cells. All of our results will be made available to the larger SABRE consortium, and after publication to the general scientific community.

SABRE RNAseq Consortia
Christopher D.C. Allen Lab

We are interested in the mechanisms that initiate allergic inflammation in the lung, which is a major driver of asthma pathogenesis in numerous patients. Upon inhalation of allergens to which an individual is sensitized, such as house dust mite, recognition by IgE antibodies triggers the degranulation of mast cells and basophils, releasing potent inflammatory mediators. In addition, allergen components are captured by antigen presenting cells that activate T cells, leading to the release of cytokines that promote allergic inflammation and airway smooth muscle hypercontractility. Surprisingly, the cellular interactions and molecular signals leading to the initiation of allergic inflammation in the lung remain poorly defined. We will 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:

1) IgE antibodies specific for allergens are produced by IgE plasma cells, yet the B cells from which these are derived, and the factors leading to their generation, have been poorly characterized.
    a. We have identified conditions that favor or inhibit the generation of IgE-expressing B cells, yet the downstream molecular pathways regulating IgE class switch recombination are not well understood. To identify candidate genes, we will treat B cells with stimuli to promote or inhibit IgE class switch recombination, and then isolate RNA for bulk RNAseq analysis.
    b. We have developed tools to specifically identify and sort rare IgE-expressing B cells, which will enable us to analyze their distinct gene expression profile compared with B cells expressing other isotypes. As an ancillary goal, we will characterize the repertoire of immunoglobulin genes expressed by IgE-expressing B cells induced in response to allergen exposure in the lung.
2) We have identified a population of resident interstitial macrophages located proximal to the bronchial airways that take up allergen components from the airway lumen. In our imaging studies, these macrophages appear distinct in morphology and behavior from other cell types, such as dendritic cells and recruited monocyte-derived cells. However, the distinct functional roles of these cell types remain unclear, and the ability to distinguish resident from infiltrating cells by flow cytometry remains limited. We have developed an approach to isolate these cell types from the lung with fluorescent lineage tracing to distinguish infiltrating from resident cells. In order to fully characterize these heterogeneous populations, we will do single cell RNAseq analysis on the 10X platform with cells isolated from the lungs at baseline versus after exposure to allergen.

We will initiate these studies with mouse models and then follow up key findings with human cells. Taken together, these approaches will help us understand the molecular profile of key cell types involved in triggering allergic inflammation in the lung in asthma. We anticipate that our work will identify numerous gene candidates for further study, which we will follow up by targeted approaches such as CRISPR gene modification.

SABRE RNAseq Consortia
K. Mark Ansel Lab

Helper T effector (Teff) cells of the Th2 cell subset were first implicated in asthma over 25 years ago, and biologic therapies targeting their type 2 cytokine products IL-5, IL-13 and IL-4 have proven efficacious in the clinic. However, it has been hard to demonstrate a robust increase in airway Th2 cell frequency among T cells in asthma. This may be due in part to technical difficulty in detecting and defining the pathologic Th2 cells in inflamed airways. Alternatively, other cells, such as T regulatory (Treg) cells may make a bigger contribution than previously understood. We hypothesize that allergic asthma pathology reflects local imbalances between cytokine-producing cells and a corresponding subset of specialized suppressive Tregs. Treg heterogeneity has been the subject of intense interest, yet it remains poorly defined. Complete absence of Tregs causes early onset fatal multi-organ autoimmunity and allergic disease symptoms in humans and mice. Our preliminary data and recent published reports indicate that a CCR6 and RORγt expressing Treg cell subset may play a key role in suppressing airway inflammation. These findings provide some hints about a functionally specialized Treg subset that suppresses allergic inflammation, and warrant a full accounting of Teff and Treg heterogeneity in human asthma.

We will use single cell RNA sequencing (scRNA-seq) to molecularly define the heterogeneity of airway helper T cells. Treg and Teff cells will be analyzed together by FACS-sorting CD4+CD45RO+ T cells from blood and bronchial lavage from asthmatic subjects. Biospecimens from subjects with asthma will be obtained from the UCSF Airway Tissue Bank through collaboration with Dr. Prescott Woodruff. scRNA-seq libraries will be prepared using the 10X Genomics Chromium platform in the UCSF Institute for Human Genetics Genomics Core. Current practices in the core yield approximately 10,000 cells per sample with greater than 50,000 raw reads per cell using paired-end sequencing. To reduce costs, cell-doublets and batch effects, we will use the Demuxlet software package to computationally deconvolute pooled samples from unrelated individuals using SNPs private to each individual. All of our results will be made available to the larger SABRE consortium, and after publication to the general scientific community.

These experiments will establish an unbiased account of the range of T cell subtypes that populate the airways in asthma. We expect to uncover novel markers of Treg and Teff cell subsets that can be incorporated into mass cytometry panels for analysis of larger subject cohorts. scRNA-seq analysis of airway Treg heterogeneity may reveal a more precisely defined functional subset, and establish a molecular definition of cells that can moderate or even reverse the inflammation that drives asthma pathology.

SABRE RNAseq Consortia
Esteban Burchard Lab

Genetic and environmental risk factors for asthma and drug response are modified by race/ethnicity. We demonstrated that genetic ancestry, a proxy for genetic variation, can be leveraged to identify genetic risk factors for, and improve clinical accuracy in, the diagnosis of lung disease.

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). 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. 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.
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 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: Determine the transethnic portability of 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, since these repositories have predominantly European adult subjects, the imputation quality is largely underexplored in admixed populations and children. We will perform the first TWAS of pediatric asthma in admixed children. We will compare predicted and measured expression levels and assess the quality of current imputation tools. Finally, we will train new population-specific models of gene expression in whole blood TWAS.
Impact: We build on a history of successful integrative genomic analyses of pediatric asthma. We will produce highly accurate and freely distributable gene expression imputation models for general research use.

We will use SABRE funding to offset sample processing and analyses.

SABRE RNAseq Consortia
John Fahy Lab

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+ T 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.

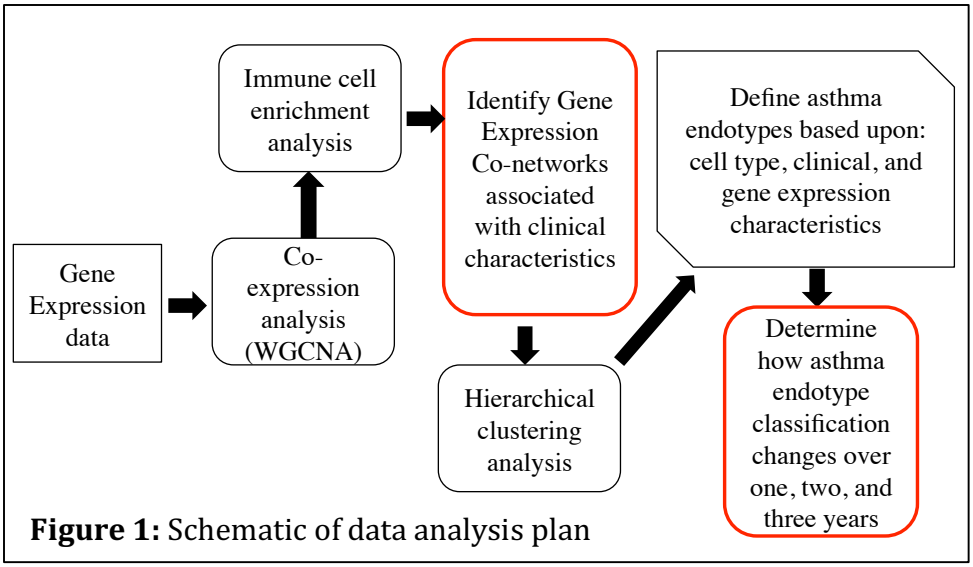

Figure 1: Schematic of data analysis plan

SABRE RNAseq Consortia
Jeoung-Sook Shin Lab

We are interested in understanding the molecular mechanism by which dendritic cells supports the development of type 2 immunity, the immunity that brings airway eosinophilia and IgE production in patients with allergic asthma. We have recently found that dendritic cells depend on a ubiquitin ligase named membrane-associated RING-CH1 (MARCH1) to initiate and maintain type 2 immunity against house dust mite allergen, the most common cause of allergic asthma. By employing RNA sequencing analysis, we will investigate how MARCH1 affects transcriptional changes of dendritic cells in response to house dust mite allergens.

Wild type and MARCH1-deficient mice will be intratracheally challenged with house dust mite allergens. At various time points, dendritic cells will be isolated from the lungs and the lung-draining lymph nodes via fluorescence-activated cell sorting. RNAs will be isolated, sequenced, and compared between wild type and MARCH1-deficient dendritic cells. This analysis will elucidate how dendritic cells change their transcriptome profile in response to house dust mite allergens and reveal which specific changes are made dependent on MARCH1. Subsequent analysis will include identification of the specific changes that promote type 2 immunity. These studies may lead to the identification of novel molecular pathways that play a crucial role in allergic asthma and provide scientific basis for the development of novel therapeutics.

SABRE RNAseq Consortia
Prescott Woodruff Lab

ScRNAseq to identify epithelial cell heterogeneity in asthma after allergen challenge

We have an ongoing human allergen challenge study (the ACE study) in which allergic asthmatics undergo bronchoscopy before and 1 day after lung segmental allergen challenge and airway epithelial brush samples are obtained at baseline, after diluent challenge and after allergen challenge. This study provides an opportunity to comprehensively assess the changes in airway epithelial cell heterogeneity that occur in asthma after allergen challenge (with two control samples). We have already done one round of scRNAseq in airway epithelial brushings from a human bronch with help from David Erle using the 10x platform and we have shown that we can freeze the cell prep and do library prep at a later point in time (makes booking time and batching analyses much easier). We continue to work with David Erle on this and he would be interested in participating in this project with me, including participating in discussion of data analysis approaches.

Specific hypotheses we test include:

- Goblet cell numbers are increased at 24 hours after allergen challenge and pseudolineage analysis can be used show they derive largely from other secretory cells (club cells).
- Tuft cells are present in human airway brushings.
- There are two distinct populations of tuft cells (based on prelim data in mice presented recently by Jay Rajagopal)
- Allergen challenge expands one or both of these tuft cell populations as compared to baseline or diluent challenge
- A distinct and relatively rare CFTR-high population of epithelial cells is present in human airway epithelial brushings (again based on prelim data in mice presented recently by Jay Rajagopal)
- Other hypotheses that Rich, David and others might propose before we do these experiments, to guide analyses

Comprehensive scRNAseq could also identify new hypotheses to test in follow-up studies.

CONTRIBUTIONS TO RELEVANT SCIENTIFIC ACTIVITIES

2017 SABRe Retreat – June 14, 2017
Smith Cardiovascular Research Building at Mission Bay
8am-3pm

8:00-8:30 am Coffee and pastries[SC-159]:

8:30-8:45 am Opening Remarks (Speaker: Chris Allen) [SC-159]:

8:45-10:00 am Ten-Minute Talks (+5 minutes for Q&A) Part 1[SC-159]:

- 8:45-8:55 Nirav Bhakta (Woodruff Lab), "Airway Epithelial ER Stress in asthma"
- 9:00-9:10 Priti Singh (Ansel Lab), "MicroRNA regulation of ILC2 homeostasis and function in allergic lung inflammation"
- 9:15-9:25 Carlos Castellanos (Shin Lab), "The role of MARCH1 in allergic immunity in the lung"
- 9:30-9:40 Marquitta White (Burchard Lab), "Whole Genome Sequencing of Bronchodilator Drug Response in Minority Children with Asthma"

9:45-10:00 am Coffee Break [SC-159]:

10:00-11:00 am Ten-Minute Talks (+5 minutes for Q&A) Part 2 [SC-159]:

- 10:00-10:10 Luke Bonser (Erle Lab), "Investigating airway epithelial reprogramming in asthma"
- 10:15-10:25 Benjamin Terrier (Locksley Lab), "Characterisation of epithelial and innate lymphoid cells in nasal cavity"
- 10:30-10:40 Marrah Lachowicz-Scroggins (Fahy Lab), "Characterization of DNA-High Neutrophilic Asthma"
- 10:45-10:55 Emily (Xin-Zi) Tang (Allen Lab), "Antigen Presenting Cells at the Airways"

11:00-12:30 pm Lunch [Spark Social SF]:

12:30-1:30 pm Poster Sessions [Lobby of SCVRB]:

1:30-2:30 pm Faculty/PI Roundtable Discussions [SC-341]:

1:30-2:30 pm Trainee Roundtable Discussions [SC-159]:

1 Group Leader from each lab to lead discussions

- Burchard Lab: Sam Oh
- Woodruff Lab: Sana Siddiqui
- Erle Lab: Luke Bonser
- Ansel Lab: Heather Pua
- Fahy Lab: Marrah Lachowicz-Scroggins
- Locksley Lab: Steve Van Dyken

2:30-3:00pm Present Round Table Findings / Closing Remarks [SC-159]:

SABRE Asthma Research Conference Schedule 2018

Location: 513 Parnassus Avenue, HSE-402

Time: 9:00- 10:00AM

Day: 4th Wednesday of each month (**except Wednesdays that fall on a UCSF holiday*)

Date	Presenter	Title
1/24/18	Mark Ansel	*The rich of life of RNA - lessons from the immune system*
2/28/18	Ari Molofsky, M.D.	*Exploring group 2 innate lymphoid cell tissue niches*
3/28/18	cancelled	
4/25/18	Walter Eckalbar	*Single cell transcriptomics of airway epithelial cell differentiation and response to asthma mediators*
6/27/18	Erin Gordon	*The biology of asthma associated genetic loci: IL33, IL1RL1, GSDMB*
7/27/18		*Summer Break*
8/23/18		*Summer Break*
9/26/18	Tien Peng	
10/24/18	Esteban Burchard	
11/28/18	Chis Allen	

UCSF PULMONARY RESEARCH CONFERENCE 2017-2018
Mondays, 4:30 pm - Parnassus

Date	Talk 1 (Clinical)	Talk 2 (Basic)	Moderator	Location
09/18/17	Jessica Tsui	Mark Ansel	Prescott Woodruff	HSW-301
09/25/17	Mallar Bhattacharya	Sreelakshmi Vasudevan	Prescott Woodruff	CL-220
10/02/17	Michelle Yu	Kamran Atabai	Prescott Woodruff	HSW-301
10/09/17	**Francis McCormack, Visiting Professor**		Meshell Johnson	HSW-300
10/16/17	John Greenland	Carolyn Calfee	Prescott Woodruff	HSW-300
10/23/17	Tien Peng	Hal Collard	Prescott Woodruff	HSW-301
10/30/17	***CVRI Retreat***			
11/06/17	Jonathan Budzik	Ram Naikawadi	Carolyn Calfee	HSW-301
11/13/17	***Pulmonary & Critical Care Research Retreat***			
11/20/17	Luke Bosner	Nick Kolaitis	Prescott Woodruff	HSW-301
11/27/17	Sana Siddiqui		Tien Peng	HSW-301
12/04/17	Sam Oh	Sheila Musharoff		HSW-301
12/11/17	**Zea Borok, Visiting Professor**		Michael Matthay	HSW-301
12/18/17	Priya Shete	Farzad Moazed	Carolyn Calfee	HSW-303
01/08/18	***Fellows Feedback***			
01/15/18	***MLK Day Holiday***			
01/22/18	***cancelled for Fellows Meeting***			
01/29/18	Jenna Nguyen	Aida Venado-Estrada	Tien Peng	S-214
02/05/18	**Marsha Wills-Karp, Visiting Professor**		Troy Shum	S-214
02/12/18	Meena Subramanian	Carolyn Hendrickson	Carolyn Calfee	S-214
02/19/18	***President's Day Holiday***			
02/26/18	Michael Peters	Brett Ley	Erin Gordon	S-214
03/05/18	Emila Patrick		Erin Gordon	S-214
03/12/18	**Monica Kraft, Visiting Professor**		Prescott Woodruff	S-214
03/19/18	Nirav Bhakta	Chaoqun Wang	Tien Peng	S-214
03/26/18	Stephanie Christenson	Carlo Follo	Tien Peng	S-214
04/02/18	Mallar Bhattacharya	Juan Caraballo	Mallar Bhattacharya	HSW-303
04/09/18	Aga Looney	Maya Kotes	Mallar Bhattacharya	HSW-303
04/16/18	**Anne Dixon, Visiting Professor**		Nirav Bhakta	HSW-303
04/23/18	Soledad Reyes de Mochel	Marquitta White		HSW-303
04/30/18	Joshua Vasquez	Walter Eckalbar		HSW-303
05/07/18	Erica Farrand	Marrah Lachowicz-Scroggins	Nirav Bhakta	HSW-303
05/14/18	Nikko Arger	Deepti Gupta		HSW-303
05/21/18	***ATS - (no conference)***			
05/28/18	***Memorial Day holiday (no conference)***			
06/04/18	**Marlene Rabinovitch, Visiting Professor**			HSW-303
06/11/18	***Fellows Feedback***			

Immunology Seminar Series
2017-2018 Schedule
Mondays, 9 am - Room: N-225

Date	Speaker	Host
September 11	Gary Nolan, *Stanford University*	Cliff Lowell
September 18	Marc Jenkins, *University of Minnesota*	Art Weiss
September 25	*Immunology Retreat – no seminar*	
October 2	Matthew Albert, *Genentech*	Mark Ansel
October 9	Joseph C. Sun, *Memorial Sloan Kettering Cancer Center*	Jody Baron
October 16	Dan Stetson, *University of Washington*	Immunology Grad Students
October 23	Facundo Batista, *Ragon Instutute of MGH, MIT & Harvard*	Jeroen Rosse
October 30	Jose Conejo-Garcia, *Moffitt Cancer Center*	Adrian Erlebacher
November 6	Sharon Evans, *Croswell Park Cancer Institute*	Steven Rosen
November 13	Albert Bendelac, *University of Chicago*	Rich Locksley
November 27	Susan Schwab, *New York University School of Medicine*	Kole Roybal
December 4	Tom Wynn, *Pfizer*	Ari Molofsky
December 11	Boris Reizis, *New York University*	Averil Ma
December 18	Rafi Ahmed, *Emory University*	Jeff Bluestone
January 8	Thomas Gajewski, *University of Chicago*	Kole Roybal
January 22	Jonathan Kipnis, *University of Virginia*	Judith Hellman
February 5	Nick Haining, *Harvard*	Alex Marson
February 12	Ken Cadwell, *New York University School of Medicine*	Ajay Chawla
February 26	Terri Laufer, *Perelman School of Medicine*, *University of Pennsylvania*	Julie Zikherman
March 5	Hongbo Chi, *St. Jude Children's Research Hospital*	Shomi Sanjabi
March 12	Michel C. Nussenzweig, *Rockefeller University*	Immunology Post Docs
March 19	Satish Pillai, *UCSF*	
March 26	Paul Kubes, *University of Calgary*	Zena Werb
April 2	Ron Germain, *NIH*	Jason Cyster
April 9	Michael Brenner, *Harvard*	Art Weiss
April 16	Jeroen Roose, *UCSF*	
April 23	Peter Savage, *University of Chicago*	Adrian Erlebacher
April 30	Ananda Goldrath, *UC San Diego*	Mark Anderson
May 7	Miriam Merad, *Mount Sinai*	Jeoung-Sook Shin
May 14	Denise Monack, Stanford	Anita Sil
May 21	Padmanee Sharma, *University of Texas*	Lewis Lanier

SEMINAR

University of California, San Francisco
Department of Microbiology and Immunology

Immunology Seminar Series

"Origin and Specificity of Intestinal IgA in homeostatic conditions"

Albert Bendelac, MD, PhD

The University of Chicago

Monday, November 13, 2017

9:00am, Parnassus, N-225

Host: Rich Locksley

Livestream | ▪ SPONSORS | Gladstone Institute of Virology & Immunology ▪
Rosalind Russell Medical Research Center for Arthritis ▪ Sandler Asthma Basic Research Center, SABRE
INFORMATION (415) 502-1961 http://immunology.ucsf.edu/immunology-seminar-series
Live stream and archive available (UCSF MyAccess login required)
Tweet questions to @ImmunologyUcsf

RECENT AND NEW PUBLICATIONS SUPPORTED BY THE SANDLER ASTHMA BASIC RESEARCH CENTER (2016-2018)

Christopher D.C. Allen, Ph.D.

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Looking to the Future

Richard M. Locksley, M.D.

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

The SABRE Center is playing a role in assessing opportunities 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 goal, which would coincide with the buildout of the new hospital on the Parnassus site by 2025. This remains a key 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.

Beyond integrating across campus sites, the SABRE Center is continuing efforts for outreach and integration. We re-invigorated the Innovative Grants program as a mechanism to reach into new research areas across the UCSF scientific community. In the past, this has resulted in a number of important breakthrough accomplishments, and has led to some young investigators remaining in research fields relevant to asthma. Our initial outreach has been met with substantial enthusiasm, and we look forward to continuing novel and unexpected discoveries made by laboratories at UCSF new to asthma-related research.

We have been aided immensely by our Review Board – Drs. Kronenberg, Marrack and Wilson – up to this point, and we are extremely grateful for their candid guidance and expertise. We look forward to continued input from Dr. Kronenberg, but also our new Board members, Drs. Medzhitov and Kaech. The SABRE Center is beginning plans for a 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.

Our goal is to continue the trajectory established over the first decade of the SABRE Center in our mission to understand and ultimately conquer asthma. These challenges we take seriously for the future in order to honor the extraordinary vision of the Sandler family and Sandler Foundation in committing resources to asthma basic research at UCSF. 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.
Homer Boushey, M.D.
Esteban Burchard, M.D., M.P.H.
George Caughey, M.D.
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.
Xiaozhu Huang, M.D., M.S.
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
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	POSITION TITLE
Christopher David Caballero Allen, Ph.D.	Assistant Professor of Anatomy and Investigator, Cardiovascular Research Institute & Sandler Asthma Basic Research Center

EDUCATION/TRAINING

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

Positions

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

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b. Haynes NM, **Allen CDC**, Lesley R, Ansel KM, Killeen N, Cyster JG. Role of CXCR5 and CCR7 in follicular Th cell positioning and appearance of a programmed cell death gene-1high germinal center-associated subpopulation. *J Immunol*. 2007 Oct 15; 179(8): 5099-108. PubMed PMID: 17911595.
c. Green JA, Suzuki K, Cho B, Willison LD, Palmer D, **Allen CDC**, Schmidt TH, Xu Y, Proia RL, Coughlin SR, Cyster JG. The sphingosine 1-phosphate receptor $S1P_2$ maintains the homeostasis of germinal center B cells and promotes niche confinement. *Nat Immunol*. 2011 Jun 5; 12(7): 672-80. PubMed PMID: 21642988; PubMed Central PMCID: PMC3158008.
d. Bannard O, Horton RM, **Allen CDC**, An J, Nagasawa T, Cyster JG. Germinal center centroblasts transition to a centrocyte phenotype according to a timed program and

depend on the dark zone for effective selection. *Immunity*. 2013 Nov 14; 39(5): 912-24. PubMed PMID: 24184055; PubMed Central PMCID: PMC3828484.

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

a. **Allen CDC**, Okada T, Tang HL, Cyster JG. Imaging of germinal center selection events during affinity maturation. *Science*. 2007 Jan 26; 315(5811): 528-31. PubMed PMID: 17185562.
b. **Allen CDC**, Okada T, Cyster JG. Germinal-center organization and cellular dynamics (Review). *Immunity*. 2007 Aug; 27(2): 190-202. PubMed PMID: 17723214; PubMed Central PMCID: PMC2242846.
c. Beltman JB, **Allen CDC**, Cyster JG, de Boer RJ. B cells within germinal centers migrate preferentially from dark to light zone. Proc *Natl Acad Sci U S A*. 2011 May 24; 108(21): 8755-60. PubMed PMID: 21555569; PubMed Central PMCID: PMC3102384.

Basophils are innate immune cells that are activated through IgE, yet their functional role in the immune response has been poorly understood and controversial. I achieved the first dynamic imaging of basophils in the lungs and lymph nodes by two-photon microscopy after infection with helminth parasites or immunization with a protease allergen. Using a reporter mouse generated by Richard Locksley's laboratory, I found that basophils did not interact with T cells during the priming phase of the immune response in lymph nodes, indicating that basophils do not serve as major antigen presenting cells. However, basophils did form repetitive, sustained interactions with T cells during the effector phase of the immune response in the lungs, a site in which T cells were shown to activate basophils to secrete IL-4 that contributed to helminth immunity. I also contributed my imaging expertise to the study of IgE-mediated basophil function in eosinophil recruitment in a mouse model of contact dermatitis.

a. Sullivan BM, Liang HE, Bando JK, Wu D, Cheng LE, McKerrow JK, **Allen CDC***, Locksley RM*. Genetic analysis of basophil function in vivo. *Nat Immunol*. 2011 Jun; 12(6): 527-35. PubMed PMID: 21552267; PubMed Central PMCID: PMC3271435. *Co-corresponding author
b. Cheng LE, Sullivan BM, Retana LE, **Allen CDC**, Liang HE, Locksley RM. IgE-activated basophils regulate eosinophil tissue entry by modulating endothelial

function. *J Exp Med*. 2015 Apr 6; 212(4): 513-24. PubMed PMID: 25779634; PubMed Central PMCID: PMC4387286.

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 date. We also wrote a review based on these and other recent studies on the regulation of IgE-expressing B cells.

a. Yang Z, Sullivan BM, **Allen CDC**. Fluorescent in vivo detection reveals that IgE(+) B cells are restrained by an intrinsic cell fate predisposition. *Immunity*. 2012 May 25; 36(5): 857-72. PubMed PMID: 22406270.
b. Yang Z, Robinson MJ, **Allen CDC**. Regulatory constraints in the generation and differentiation of IgE-expressing B cells (Review). *Curr Opin Immunol*. 2014 Jun; 28:64-70. PubMed PMID: 24632082; PubMed Central PMCID: PMC4069329.
c. Yang Z, Robinson MJ, Chen X, Smith GA, Taunton J, Liu W, **Allen CDC.** Regulation of B cell fate by chronic activity of the IgE B cell receptor. *eLife*. 2016 Dec 9; 5 pii: e21238 PubMed PMID: 27935477; PubMed Central PMCID: PMC5207771.
d. Robinson MJ, Prout M, Mearns H, Kyle R, Camberis M, Forbes-Blom EE, Paul WE, **Allen CDC**, Le Gros G. IL-4 Haploinsufficiency Specifically Impairs IgE Responses against Allergens in Mice. *J Immunol*. 2017 Jan 23; PubMed PMID: 28115531. NIHMSID: NIHMS840227.

Complete List of Published Work in MyBibliography: http://usa.gov/1rS9D69

Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

R01 AI 130470-01A1 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**	POSITION TITLE Associate Professor of Microbiology and Immunology
eRA COMMONS USER NAME anselm	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Virginia Tech, Blacksburg, VA	B.S.	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

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-	International Predoctoral Fellows Reviewer, Howard Hughes Medical Institute
2012-2015	Ad hoc reviewer, NIH CMIB study section
2012-	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

I pioneered the study of microRNA (miRNA) regulation of the immune system during my postdoctoral training. At that time, miRNAs were still a very recently discovered class of regulatory molecules, and their expression and activity in mammalian biology was virtually unknown. Together with a group of collaborators, I reported the first description of miRNA expression programs in purified cell populations (as opposed to complex tissues) and their dynamic regulation during immune cell activation, as well as the first description of the global requirements for miRNAs in mature helper T cells. We also published concurrently with two other groups the finding that a single miRNA can be required to support normal mammalian physiology (in our case, the requirement for miR-155 in humoral immunity and T cell responses). These early studies established the importance of miRNAs in immune regulation and presented many new avenues for investigation.

a. Monticelli S*, **Ansel KM***, Xiao C*, Socci ND*, Krichevsky AM, et al. MicroRNA profiling of the murine hematopoietic system. *Genome Biol*. 2005; 6(8): R71. PubMed PMID: 16086853; *PubMed Central PMCID*: PMC1273638. *equal contribution

b. Muljo SA*, **Ansel KM*,** Kanellopoulou C*, Livingston DM, Rao A, et al. Aberrant T cell differentiation in the absence of Dicer. *J Exp Med.* 2005 Jul 18; 202(2): 261-9. PubMed PMID: 16009718; *PubMed Central PMCID*: PMC2212998. *equal contribution

c. Thai TH, Calado DP, Casola S, **Ansel KM**, Xiao C, et al. Regulation of the germinal center response by microRNA-155. *Science*. 2007 Apr 27; 316(5824): 604-8. PubMed PMID: 17463289.

d. Baumjohann D, **Ansel KM**. MicroRNA-mediated regulation of T helper cell differentiation and plasticity. *Nat Rev Immunol.* 2013 Sep; 13(9): 666-78. PMID: 23907446; PMCID: PMC3980848.

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 targt 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 bioinformatics methods identified a network of functionally relevant target mRNAs including some that encode well-known regulatorsof Th2 cell differentiation, such as GATA-3 and Ikaros, and others that represent novel players in Th2 biology.

a. Steiner DF, Thomas MF, Hu JK, Yang Z, Babiarz JE, et al. MicroRNA-29 regulates T-box transcription factors and interferon-γ production in helper T cells. Immunity. 2011 Aug 26; 35(2): 169-81. PubMed PMID: 21820330; PubMed Central PMCID: PMC3361370.

b. Warth SC, Hoefig KP, Hiekel A, Schallenberg S, Jovanovic K, Klein L, Kretschmer K, **Ansel KM**, Heissmeyer V. Induced miR-99a expression represses Mtor cooperatively with miR-150 to promote

regulatory T-cell differentiation. *EMBO J*. 2015 May 5; 34(9): 1195-213. *PubMed PMID*: 25712478; *PubMed Central PMCID*: PMC4426480.

c. Pua HH, Steiner DF, Patel S, Gonzalez JR, Ortiz-Carpena JF, Kageyama R, Chiou NT, Gallman A, de Kouchkovsky D, Jeker LT, McManus MT, Erle DJ, **Ansel KM**. MicroRNAs 24 and 27 suppress allergic inflammation and target a network of regulators of T helper-2-cell-associated cytokine production. *Immunity*. 2016 Feb (*in press*)

d. Simpson LJ, **Ansel KM**. MicroRNA regulation of lymphocyte tolerance and autoimmunity. *J Clin Invest*. 2015 Jun; 125(6): 2242-9. *PubMed PMID*: 26030228; *PubMed Central PMCID*: PMC4497751.

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

a. Seumois G, Vijayanand P, Eisley CJ, Omran N, Kalinke L, et al. An integrated nano-scale approach to profile miRNAs in limited clinical samples. *Am J Clin Exp Immunol*. 2012 Nov 30; 1(2): 70-89. PubMed PMID: 23304658; PubMed Central PMCID: PMC3538381.

b. Simpson LJ, Patel S, Bhakta NR, Choy DF, Brightbill HD, et al. A microRNA upregulated in asthma airway T cells promotes TH2 cytokine production. *Nat Immunol*. 2014 Dec; 15(12): 1162-70. *PubMed PMID*: 25362490; *PubMed Central PMCID*: PMC4233009.

c. Pua HH, **Ansel KM**. MicroRNA regulation of allergic inflammation and asthma. *Curr Opin Immunol*. 2015 Oct; 36:101-8. *PubMed PMID*: 26253882; *PubMed Central PMCID*: PMC4593751.

d. Singh PB, Pua HH, Happ HC, Schneider C, von Moltke J, Locksley RM, Baumjohann D, **Ansel KM.** MicroRNA regulation of type 2 innate lymphoid cell homeostasis and function in allergic inflammation. *J Exp Med.* 2017 Dec; 214(12): 3627-43. PMID: 29122948; PMC in process

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 to 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.

a. Baumjohann D, Okada T, **Ansel KM**. Cutting Edge: Distinct waves of BCL6 expression during T follicular helper cell development. *J Immunol.* 2011 Sep 1;187(5):2089-92. PMID: 21804014.
b. Vijayanand P, Seumois G, Simpson LJ, Abdul-Wajid S, Baumjohann D, et al. Interleukin-4 production by follicular helper T cells requires the conserved Il4 enhancer hypersensitivity site V. *Immunity.* 2012 Feb 24; 36(2): 175-87. PMID: 22326582; PMCID: PMC3288297.
c. Baumjohann D, Kageyama R, Clingan JM, Morar MM, Patel S, et al. The microRNA cluster miR-17~92 promotes TFH cell differentiation and represses subset-inappropriate gene expression. *Nat Immunol.* 2013 Aug; 14(8): 840-8. PMID: 23812098; PMCID: PMC3720769.
d. Montoya MM, Maul J, Singh PB, Pua HH, Dahlström F, Wu N, Huang X, **Ansel KM*,** Baumjohann D*. A Distinct Inhibitory Function for miR-18a in Th17 Cell Differentiation. *J Immunol.* 2017 Jul 15; 199(2): 559-569. PMID: 28607111; PubMed Central PMCID: PMC5508756.

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.

a. Baumjohann D, **Ansel KM**. Tracking early T follicular helper cell differentiation in vivo. *Methods Mol Biol.* 2015; 1291:27-38. PMID: 25836299; PMCID: PMC4558195.
b. Gordon ED, Simpson LJ, Rios CL, Ringel L, Lachowicz-Scroggins ME, et al. Alternative splicing of interleukin-33 and type 2 inflammation in asthma. *Proc Natl Acad Sci U S A*. 2016 Aug 2; 113(31):8765-70. PMID: 27432971; PMCID: PMC4978244.
c. Ramstein J, Broos CE, Simpson LJ, **Ansel KM,** Sun SA, et al. IFN-γ-Producing T-Helper 17.1 Cells Are Increased in Sarcoidosis and Are More Prevalent than T-Helper Type 1 Cells. *Am J Respir Crit Care Med*. 2016 Jun 1; 193(11): 1281-91. PMID: 26649486; PMCID: PMC4910899.

Complete List of Published Work in MyBibliography: http://1.usa.gov/18fo0rz

Research Support

Ongoing Research Support

2012/08/15-2017/05/31
5P01HL107202-02, National Heart, Lung, and Blood Institute
K Mark Ansel (PI)
Innate and Adaptive Immune Responses in Th2-High Asthma
Project 2: Role of miRNAs in Th2-Driven inflammation in Asthma
Project 3: Mechanisms of airway Th2 inflammation in asthma
The major goal of this PPG is to elucidate cellular and molecular mechanisms underlying the initiation and maintenance of Th2-high asthma. The goals of Project 2 are to identify miRNAS that regulate helper T cell functions relevant to asthma, to discover asthma associated T cell miRNA expressions patterns in clinical samples, and to determine the mRNA targets and in vivo role of miR-29 in a mouse model of asthma. My role

in aim 3 is immunophenotyping of innate and adaptive immune cells in airway biospecimens in human asthma. Role: Project 2 Leader, Project 3 Co-Leader

2012/08/15-2017/05/31 (NCE)
5P01HL107202, National Heart, Lung, and Blood Institute
John Fahy (PI)
Innate and Adaptive Immune Responses in Th2-High Asthma
Project 2: Role of miRNAs in Th2-Driven inflammation in Asthma
Project 3: Mechanisms of airway Th2 inflammation in asthma
The major goal of this PPG is to elucidate cellular and molecular mechanisms underlying the initiation and maintenance of Th2-high asthma. The goals of Project 2 are to identify miRNAS that regulate helper T cell functions relevant to asthma, to discover asthma associated T cell miRNA expressions patterns in clinical samples, and to determine the mRNA targets and in vivo role of miR-29 in effector T cells. My role in aim 3 is immunophenotyping of innate and adaptive immune cells in airway biospecimens in human asthma. Role: Project 2 Leader, Project 3 Co-Leader

2013/09/01-2018/08/31
1U19CA179512-01, National Cancer Institute
Robert Blelloch (PI)
In Vivo Regulated Release and Function of Extracellular Small RNAs
Project 1: Ex-miRNA Release by Immune Cells and its Functional Consequences This U19 Center's long-term goal is to uncover paradigms of extracellular small RNA function in health and disease and apply those paradigms to clinically relevant settings including biomarker discovery and therapeutic intervention. As leader of Project 1, I will conduct studies to test the central hypothesis that immune cells release ex-miRNAs in response to inflammatory stimuli, and that this process is critical for their immune function.
Role: Project 1 Leader

2014/08/01-2019/07/31
1R01AI106923-02, National Institute of Allergy and Infectious Diseases
Lukas Jeker (PI)
The Role of Micrornas in Autoimmune Disease
The major goal of this project is to examine the molecular mechanisms involved in the regulation of Treg/TFH differentiation and function by the miR-17~92 cluster. The studies should promote our understanding of the complex biological processes by which miRNAs influence the balance between the stimulatory and inhibitory effects of TFH and Tregs, respectively, in autoimmunity. My role is to help in experiments that compare the target genes of miR-17~92 miRNAs in TFH and Tregs.
Role: Co-investigator

1995/07/01-2020/06/30
5T32GM008568-22, National Institute of General Medical Sciences
Ansel (PI)
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 (credential, e.g., agency login) BHANIR	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Massachusetts Institute of Technology	SB	1998	Electrical Engineering
Stanford University School of Medicine	MD	2006	Medicine
Stanford University School of Medicine	PhD	2006	Mol. and Cell Physiology
University of California, San Francisco	Internship	2007	Internal Medicine
University of California, San Francisco	Residency	2008	Internal Medicine
University of California, San Francisco	Fellowship	2011	Pulmonary, Critical Care
University of California, San Francisco	Postdoctoral	2011	Asthma

Positions and Employment

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

Honors

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

Professional Memberships

2016 to present	Associate Scientific Advisor for Science Translational Medicine, over a period of one year, I am writing eight editorial pieces that will appear in the journal.
11/2007 - present	American College of Physicians, Associate Member
8/2008 - present	American Thoracic Society, Trainee
7/2011- 7/2014	American College of Chest Physicians, Affiliate Member
2/2008 – present	California Medical License
08/2009	Board Certification in Internal Medicine by the ABIM
11/2011	Board Certification in Pulmonary Medicine by the ABIM
11/2012	Board Certification in Critical Care Medicine by the ABIM

Contribution to Science

I've 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.

Bhakta NR, Solberg OD, Nguyen CP, Nguyen CN, Arron JR, Fahy JV, Woodruff PG. A qPCR-based metric of Th2 airway inflammation in asthma. *Clin Transl Allergy*. 2013 Jul 17; 3(1): 24, PMC3724712.

Greer AM, Matthay MA, Kukreja J, **Bhakta NR**, Nguyen CP, Wolters PJ, Woodruff PG, Fahy JV, Shin JS. Accumulation of BDCA1$^+$ dendritic cells in interstitial fibrotic lung diseases and Th2-high asthma *PLoS One*. 2014 Jun 10; 9(6): e99084. doi: 10.1371/journal.pone.0099084. eCollection 2014. *PubMed PMID*: 24915147; *PubMed Central PMCID*: PMC4051692.

Peters MC, Mekonnen ZK, Yuan S, **Bhakta NR**, Woodruff PG, Fahy JV. Measures of gene expression in sputum cells can identify TH2-high and TH2-low subtypes of asthma. *J Allergy Clin Immunol.* 2014 Feb; 133(2): 388-94. PMC3981552.

Durack J, Lynch SV, Nariya S, **Bhakta NR**, Beigelman A, Castro M, Dyer AM, Israel E, Kraft M, Martin RJ, Mauger DT, Rosenberg SR, Sharp-King T, White SR, Woodruff PG, Avila PC, Denlinger LC, Holguin F, Lazarus SC, Lugogo N, Moore WC, Peters SP, Que L, Smith LJ, Sorkness CA, Wechsler ME, Wenzel SE, Boushey HA, Huang YJ. Features of the bronchial bacterial microbiome associated with atopy, asthma, and responsiveness to inhaled corticosteroid treatment. *J Allergy Clin Immunol*. 2016 Nov 10. In press (available online at http://dx.doi.org/10.1016/j.jaci.2016.08.055).

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.

Solberg OD, Ostrin EJ, Love MI, Peng JC, **Bhakta NR**, Hou L, Nguyen C, Solon M, Nguyen C, Barczak AJ, Zlock LT, Blagev DP, Finkbeiner WE, Ansel KM, Arron JR, Erle DJ, Woodruff PG. Airway Epithelial miRNA Expression is Altered in Asthma. *Am J Respir Crit Care Med* 186(10): 965-74. 2012.

Levänen B, **Bhakta NR**, Torregrosa Paredes P, Barbeau R, Hiltbrunner S, Pollack JL, Sköld CM, Svartengren M, Grunewald J, Gabrielsson S, Eklund A, Larsson BM, Woodruff PG, Erle DJ, Wheelock AM. Altered microRNA profiles in bronchoalveolar lavage fluid exosomes in asthmatic patients. *J Allergy Clin Immunol.* 2013 Mar; 131(3): 894-903.e8. PMID: 23333113

Simpson LJ, Patel S, **Bhakta NR**, Choy DF, Brightbill HD, Ren X, Wang Y, Pua HH, Baumjohann D, Montoya MM, Panduro M, Remedios KA, Huang X, Fahy JV, Arron JR, Woodruff PG, Ansel KM. A microRNA upregulated in asthma airway T cells promotes TH2 cytokine production. *Nat Immunol*. 2014 Dec; 15(12): 1162-70. *PubMed PMID*: 25362490; PubMed Central PMCID: PMC4233009.

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

Koth LL, Solberg OD, Peng JC, **Bhakta NR**, Nguyen CP, Woodruff PG. Sarcoidosis blood transcriptome reflects lung inflammation and overlaps with tuberculosis. *Am J Respir Crit Care Med*. 2011. 184: 1154-1163. 2011. PMC3262024.

Su R, Li MM, **Bhakta NR**, Solberg OD, Darnell EP, Ramstein J, Garudadri S, Ho M, Woodruff PG, Koth LL. Longitudinal analysis of sarcoidosis blood transcriptomic signatures and disease outcomes. *Eur Respir J*. 2014 Oct; 44(4):985-93. PMID: 25142485.

Lawson DA, **Bhakta NR**, Kessenbrock K, Prummel KD, Yu Y, Takai K, Zhou A, Eyob H, Balakrishnan S, Wang CY, Yaswen P, Goga A, Werb Z. Single-cell analysis reveals a stem-cell program in human metastatic breast cancer cells. *Nature*. 2015 Oct 1; 526(7571):131-5. PMC4648562.

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

Phipatanakul W, Mauger DT, Sorkness RL, Gaffin JM, Holguin F, Woodruff PG, Ly NP, Bacharier LB, **Bhakta NR**, Moore WC, Bleecker ER, Hastie AT, Meyers DA, Castro M, Fahy J, Fitzpatrick A, Gaston BM, Jarjour NN, Levy BD, Peters SP, Teague WG, Fajt M,

Wenzel SE, Erzurum SC, Israel E. Effects of Age and Disease Severity on Systemic Corticosteroid Responses in Asthma. *Am J Respir Crit Care Med*. 2016 Dec 14. PMID: 27967215.

Denlinger LC, Phillips BR, Ramratnam S, Ross K, **Bhakta NR**, Cardet JC, Castro M, Peters SP, Phipatanakul W, Aujla S, Bacharier LB, Bleecker ER, Comhair SA, Coverstone A, DeBoer M, Erzurum SC, Fain SB, Fajt M, Fitzpatrick AM, Gaffin J, Gaston B, Hastie AT, Hawkins GA, Holguin F, Irani AM, Israel E, Levy BD, Ly N, Meyers DA, Moore WC, Myers R, Opina MT, Peters MC, Schiebler ML, Sorkness RL, Teague WG, Wenzel SE, Woodruff PG, Mauger DT, Fahy JV, Jarjour NN. Inflammatory and Comorbid Features of Patients with Severe Asthma and Frequent Exacerbations. *Am J Respir Crit Care Med*. 2017 Feb 1;195(3):302-313. PMID: 27556234.

Duvall MG, Barnig C, Cernadas M, Ricklefs I, Krishnamoorthy N, Grossman NL, **Bhakta NR**, Fahy JV, Bleecker ER, Castro M, Erzurum SC, Gaston BM, Jarjour NN, Mauger DT, Noel PJ, Wenzel SE, Comhair SA, Coverstone AM, Fajt ML, Hastie AT, Johansson MW, Peters MC, Phillips BR, Israel E, and Levy B. Natural Killer Cell-Mediated Inflammation Resolution Is Disabled In Severe Asthma. *Sci Immunol.* 2017 Mar 10; 2(9). (available online at https://doi.org/10.1126/sciimmunol.aam5446)

With my PhD thesis advisor, I built a two-photon microscope to study T cell development: the optics and micro-controllers to guide/scan the laser, the alignment of the laser into the microscope, the chamber to keep tissue warm, humidified and oxygenated. I wrote the scripts for image analysis. I bred all of the mice and performed all tissue harvesting, labeling and imaging experiments. The techniques we developed continue to be used by immunologists to study signaling and motility of immune cells in their native environments.

Bhakta NR, Oh DY, Lewis RS. Intracellular calcium oscillations control thymocyte motility during positive selection in the three-dimensional thymic environment. *Nature Immunology* 6: 143-151. 2005.

Bousso P, **Bhakta NR**, Lewis RS, Robey E. Dynamics of thymocyte-stromal cell interactions visualized by two-photon microscopy. *Science* 296: 1876-80. 2002.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/nirav.bhakta.1/bibliography/47340518/public/?sort=date&direction=descending

Research Support

Ongoing 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).

R01 HL131560 Bhattacharya (PI) 06/01/16-05/3/21

The Regulation of RhoA Activation in Airway Smooth Muscle
This award will provide 10% salary support for me and funds for a bronchoscopy study that I am the PI on in order to fulfill Aim 3 of Dr. Bhattacharya's R01 grant.
Role: Co-Investigator

Marcus Program Seeding Bold Ideas Award (MP-SBI) 04/01/16-03/31/17
Microfluidic droplet capture for gene expression analysis of airway smooth muscle in asthma.
Role: co-PI

Nina Ireland Program for Lung Health 01/01/17-12/31/17
Understanding cellular sources of airway cytokines in interferon-high asthma
Role: PI

Sandler Asthma Basic Research Fund 06/01/14
The purpose of this fund is to provide non-discretionary money to support for my work as an investigator in the UCSF Airway Research Center, where I see study subjects and perform research bronchoscopies.

Completed Research Support

F32 HL110720 Bhakta (PI) 01/01/12-12/31/12
Using signatures of T-helper cell inflammation to phenotype human asthma
The overall goals of the project funded in part by this NRSA were to establish a Th17-driven epithelial gene expression signature in mild-to-moderate asthmatics, use the signature to identify a subset of asthmatics with Th17-driven inflammation, and discover whole blood gene expression markers of Th17-driven inflammation. I have been the PI on this project, designing, performing, and interpreting experiments with advice from my primary mentor Dr. Prescott Woodruff.
Role: PI

U19 AI070412 Baseman (PI) 04/01/13-03/31/14
Studies on airway extracellular miRNA in human asthma
The studies in this proposal are intended to determine the mode of packaging of extracellular airway microRNAs and whether this is altered in human asthma, and through in vitro studies on human airway epithelial cells to test the hypothesis that these cells are a major contributor to these airway extracellular miRNAs. The results from these investigations will inform the best use of extracellular miRNAs as biomarkers of distinct asthma phenotypes, and lay a foundation for future studies that ask what role they may play in disease pathogenesis.
Role: Sub-contract PI

R01 AI100082 McCune (PI) 08/21/12-06/30/14
Layering of the Human Immune System, viral infections, and childhood asthma
The studies of this proposal address the possibility that sequential "layering" of fetal-type and adult-type T cells and myeloid cells may occur, that different children may be born with varying admixtures of the two, and that such variability may underlie susceptibility to viral respiratory infections and asthma after birth.
Role: Co-Investigator

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

NAME **Homer A. Boushey, Jr., M.D.**	POSITION TITLE Professor of Medicine (Emeritus)
eRA COMMONS USER NAME Boushey	

EDUCATION/TRAINING

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

Positions and Honors

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

Honors and Awards

1964	Phi Beta Kappa
1967	AOA
1964-1968	Regents' Scholar
1968	Gold-Headed Cane Recipient
1977	H. J. Kaiser Award for Excellence in Teaching
1988, ’90, ’95, 99, 2000	Faculty-Student Teaching Award for "An Outstanding Lecture"
1993	Clean Air Award (Education/Research), American Lung Association, San Francisco

1993	California Medal, American Lung Association-California
1996	UCSF Alumnus of the Year Award
1997-2000	Bay Area's Best Physicians, San Francisco Focus Magazine
2000	Medical Student Teaching Award: "An Outstanding Clinical Correlation Lecturer"

Contribution to Science

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

a. **Boushey HA**, Richardson PS, Widdicombe JG. Reflex effects of laryngeal irritation on the pattern of breathing and total lung resistance. *J Physiol* (Lond) 1972; 224:501-513.
b. Holtzman MJ, Cunningham JH, Sheller JR, Irsigler GB, Nadel JA, **Boushey HA**. Effect of ozone on bronchial reactivity in atopic and non-atopic subjects. *Am Rev Respir Dis* 1979; 120:1059-1067.
c. Seltzer J, Bigby BG, Stulbarg M, Holtzman MJ, Nadel JA, Ueki IF, Leikauf GD, Goetzl EJ, **Boushey HA**. O3-induced change in bronchial reactivity to methacholine and airway inflammation in humans. *J Appl Physiol* 1986; 60:1321-1326.
d. Sheppard D, Wong WS, Uehara CF, Nadel JA, **Boushey HA**. Lower threshold and greater bronchomotor responsiveness of asthmatic subjects to sulfur dioxide. *Am Rev Respir Dis* 1980; 122:873-878.

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

a. Fahy JV, Liu J, Wong H, **Boushey HA**. Analysis of cellular and biochemical constituents of induced sputum after allergen challenge: A method for studying allergic airway inflammation. *J Allergy Clin Immunol* 1994; 93:1031-1039.
b. Fahy JV, Kim KW, Liu J, **Boushey HA**. Prominent neutrophilic inflammation in sputum from subjects with asthma exacerbation *J Allergy Clin Immunol* 1995;95(4):843-852.
c. Fahy JV, Wong H, Liu J, **Boushey HA**. Comparison of samples collected by sputum induction and bronchoscopy from asthmatic and healthy subjects. *Am J Respir Crit Care Med* 1995; 152:53-58
d. Fahy JV, Fleming HE, Wong HH, Liu JT, Su JQ, Reimann J, Fick RB, **Boushey HA**. The effect of an anti-IgE monoclonal antibody on the early and late phase responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med* 1997; 155:1828-1834.

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

a. Lazarus SC, **Boushey HA**, Fahy JV, Chinchilli VM, Lemanske RF Jr, Sorkness CA, Kraft M, Szefler SJ. Long-Acting beta2-Agonist Monotherapy vs. Continued Therapy With Inhaled Corticosteroids in Patients With Persistent Asthma. *JAMA*. 2001 (20): 2583-2593.
b. **Boushey HA**, Sorkness CA, King TS, Sullivan SD, Fahy JV, Lazarus SC, Daily versus as-needed corticosteroids for mild persistent asthma" *New Eng EJ Med*. 2005; 352(15) 1519-28.
c. Stoloff SW, **Boushey HA**, "Severity, Control, and Responsiveness in Asthma" *J Allergy Clin Immunol* 2006; 117(3): 544-48.
d. Calhoun WJ, Ameredes BT, King TS, Icitovic N, Bleecker ER, Castro M, Cherniack RM, Chinchilli VM, Craig T, Szefler SJ, Wasserman SI, Walter MJ, Wechsler ME, **Boushey HA**; Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT Trial. *JAMA*. 2012 Sep 12; 308(10): 987-9

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

a. Wang D, Coscoy L, Zylberberg M, Avila PC, **Boushey HA**, Ganem D, DeRisi JL.Microarray-bsed detection and genotyping of viral pathogens *Proc Natl Acad Sci USA*. 2002; 99(24): 15687-92.
b. Kistler A, Avila PC, Rouskin S, Wang D, Ward T, Yagi S, Schnurr D, Ganem D, DeRisi J, and **Boushey HA**. "Pan-viral Screening of Respiratory Tract Infections in Adults with and without Asthma Reveals Unexpected Coronavirus and Human Rhinovirus Diversity." *Journal of Infectious Diseases*; 2007; 196(6): 817-825c.
c. Lopez-Souza N, Favoreto S, Wong H, Ward T, Yagi S, Schnurr D, Finkbeiner WE, Dolganov GM, Widdicombe JH, **Boushey HA**, Avila PC. In vitro susceptibility to

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

d. Lachowicz ME, **Boushey HA**, Widdicombe JH. Interleukin-13 induced mucous metaplasia increases susceptibility of human aireay epithelium to rhinovirus infection. *Amer J. Resp Cell & Molec Biol*, Jan., 2010 doi: 10.1165/rcmb.2009-0244OC

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

a. Huang YJ, Nelson CE, Brodie EL, DeSantis TZ, Baek MS, Liu J, Woyke T, Allaier M, Bristow J, Wiener-Kronish JP, Sutherland ER, King TS, Icitovic N, Martin RJ, Calhoun WJ, Castro M, Denlinger LC, Dimango E, Kraft M, Peters SP, Wasserman SI, Wechsler ME, **Boushey HA**, and Lynch SV. Airway microbiota and bronchial hyperresponsiveness in patients with sub-optimally controlled asthma. *JACI* 2011; 127:372-381
b. Lynch SV, Wood RA, **Boushey HA**, Bacharier LB, Bloomberg GR, Kattan M, O'Connor GT, Sandel MT, Calatroni A, Matsui E, Johnson CC, Lynn H, Visness CM, Jaffee KF, Gergen PJ, Gold DR, Wright RJ, Fujimura K, Rauch M, Busse WW, Gern JE. Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children. *J Allergy Clin Immunol*. 2014; 134(3): 593-601.
c. Huang YJ, Sethi S, Murphy T, Nariya S, **Boushey HA**, Lynch SV. Airway microbiome dynamics in exacerbations of chronic obstructive pulmonary disease. *J Clin Microbiol*. 2014; 52(8): 2813-23.
d. Huang YJ, **Boushey HA**. The microbiome in asthma. *J Allergy Clin Immunol*. 2015; 135(1): 25-30. (PMCID: PMC4287960)

BIOGRAPHICAL SKETCH

NAME **Esteban González Burchard, M.D., M.P.H.**	POSITION TITLE: Harry Wm. and Diana V. Hind Distinguished Professorship in Pharmaceutical Sciences, Schools of Pharmacy and Medicine, Departments of Bioengineering & Therapeutic Sciences and Medicine
eRA COMMONS USER NAME: Eburchard	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
San Francisco State University, San Francisco, CA	B.S.	1984-1990	Cellular & Molecular Biology
Stanford University School of Medicine, Stanford, CA	M.D.	1990-1995	Medicine
Harvard School of Public Health, Boston, MA	Certificate	1997	Program in Clinical Effectiveness
Brigham and Women's Hospital, Boston, MA	Resident	1995-1998	Internal Medicine
University of California, San Francisco, SF, CA	Fellow	1998-2001	Pulmonary & Critical Care Medicine
Stanford University, Stanford, CA		2001-2002	Genetic Epidemiology
University of California, Berkeley	M.P.H.	2005-2006	Epidemiology

Positions and Honors

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

Selected Honors

1988, 1989	NCAA Div. II Academic All-American, Wrestling
2005–2010	RWJ Amos Medical Faculty Development Award
2008-2014	NIH Study Section Member, Genetics of Health and Disease (GHD)
2009	American Society of Clinical Investigation (ASCI), elected member
2009	Guest Speaker, Tavis Smiley Show
2010	Guest Speaker, NPR's Science Friday, hosted by Ira Flatow
2011	Athletic Hall of Fame, San Francisco State University
2013	American Museum of Natural History (AMNH) documentary on Esteban Burchard and his research. This documentary was exhibited at the AMNH for two years and distributed to all U.S. public high schools.
2013	Guest Speaker, Smithsonian Institution National Museum of Natural History (NMNH)

2014	UCSF Medal. The UCSF Medal is UCSF's most prestigious award, given to individuals who have made outstanding personal contributions in the areas associated with the University's mission, goals and values.
2015	National Academy of Sciences, Engineering and Medicine, Committee on Incorporating 21st Century Science into Risk-Based Evaluations
2015	President Obama's Precision Medicine Initiative, Advisory Committee to the Director Innovations in Health Equality – Lifetime Achievement Award
2016	Lifetime Achievement Award, American Thoracic Society, Innovations in Health Equality
2017	RWJ Amos Medical Faculty Development Program, National Advisory Committee

Contributions to Science

1. I conceived the GALA 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 160 manuscripts from this study. We demonstrated that Puerto Rican children have lower drug response to albuterol than Mexican children.

    a. **Burchard EG**, Avila PC, (23 authors), Silverman EK; Lower Bronchodilator Responsiveness in Puerto Rican than in Mexican Asthmatic Subjects. *AJRCCM*. 2004; 169(3): 386-92. PMID: 14617512

2. We demonstrated ethnic-specific differences in pharmacogenetic associations of bronchodilator drug responsiveness between Puerto Rican and Mexican children with asthma. I conceived the idea to test the beta 2 adrenergic receptor (β_2AR) gene as part of the candidate gene list in the original GALA proposal.

    a. Choudhry S., Ung N, (28 authors**), Burchard EG**. Pharmacogenetic Differences in Response to Bronchodilators between Puerto Rican and Mexican Asthmatics. *AJRCCM*. 2005; 171(6):563-70 PMID: 15557128

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

    a. Seibold MA, Reese TA (21 authors), **Burchard EG.** Differential enzymatic activity of common haplotypic versions of the human acidic Mammalian chitinase protein. *JBC*. 2009; 284(29): 19650-8 PMCID: PMC2740590

4. We identified a significant inverse relationship between African ancestry and forced expiratory volume at one second (FEV_1) and forced vital capacity (FVC) in CARDIA participants. These relationships were also observed among African American subjects in HABC and CHS. In predicting lung function, the ancestry-based model demonstrated as much as a 15% improvement in the diagnosis of lung disease when compared to the current clinic standard. In children with asthma, the ancestry-based models reclassified asthma severity (based on percent predicted FEV_1) in 4-5% of African American participants. Current predictive equations, which rely on self-identified race alone misclassify (misdiagnose) lung function among African American subjects. Incorporating ancestry into normative equations improves lung function estimates and more accurately categorize disease

severity. I conceived the idea to test genetic ancestry and lung function. Students, fellows and staff from my lab, whom I have hired and trained, did the analyses.

a. Kumar R*, Seibold MA*, Aldrich MCF*, Williams KL*, (23 authors), **Burchard EG**.*Equal contributions. Genetic ancestry in lung-function predictions. *NEJM*. 2010 Jul 22; 363(4): 321-30. PMCID: PMC2922981

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

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

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

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/esteban.burchard.1/bibliography/41458007/public/?sort=date&direction=ascending Note: A more accurate publicly available list is available at UCSF Profiles:http://profiles.ucsf.edu/esteban.burchard#toc-id9

Research Support

Ongoing Research Support

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

UM1 HG008901 (Darnell) 01/14/16-11/30/18
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.

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.

U01HL125493 (PI: Erle/Woodruff) 07/01/14 - 06/30/19
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.

R01Hl128439 (Seibold) 08/15/15 - 05/30/20
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.

1R01MD010443 (Burchard/Seibold) 04/22/16 -12/31/20
NIMHD
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 aide in the mechanistic understanding of asthma severity (morbidity), which may lead to more targeted therapies.

U01HG009080 (Bustamante and Burchard) 05/02/16 - 03/31/20
Role: Co-PI
NIH (Subcontract from Stanford University)
Center for Multi- and Trans-ethnic Mapping of Mendelian

Goal: To develop new methods, study designs and computational tools to comprehensively identify risk and protective variants for a variety of phenotypes with different disease architectures in ethnically diverse populations.

1R01HD085993 - 01 (Wu) 07/1/16 - 06/30/21
Role: Subcontract PI
Project title: Age-Dependent Pharmacogenomics of Asthma Treatment (ADAPT)
Goal: to elucidate response to the two most commonly used medications for asthma, inhaled steroids and β_2-agonists. This research employs existing genetic, genomic, and metabolomics data from clinical trial and real-life populations.

R01HL135156 (Seibold) 09/01/16 - 08/31/21
NIH/NHLBI
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.

27IR-0030 (Burchard) 04/01/18-03/31/21
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.

R01HL141992 (Himes) 05/01/18-04/30/20
NIH/NHLBI
Subcontract from University of Pennsylvania
Project Title: 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.

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

BIOGRAPHICAL SKETCH

NAME **George H. Caughey**	POSITION TITLE Professor of Medicine
eRA COMMONS USER NAME gcaughey	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Arizona State University	BS	1975	Chemistry
Stanford University School of Medicine	MD	1979	Medicine
Pennsylvania Hospital/UPenn		1982	Internal Medicine
University of California, San Francisco		1986	Pulmonary Medicine

Positions and Honors

1988-92	Assistant Professor, Dept. of Medicine, UCSF
1988-98	Associate Staff, Cardiovascular Research Institute, UCSF
1992-98	Associate Professor, Dept. of Medicine, UCSF
1992	Molecular Medicine Program Faculty, UCSF
1996	Member of UCSF Graduate Program in Biomedical Sciences
1998	Professor, Dept. of Medicine, UCSF
1999	Investigator, Cardiovascular Research Institute, UCSF
2002	Member, UCSF Cancer Center and Center for Neurobiology of Digestive Disease
2004	Named recipient of the Julius and Lillian Nadel Endowed Chair of Medicine
2004-17	Chief of Pulmonary and Critical Care and Sleep Medicine, San Francisco VA Medical Center
2012-14	Associate Chief of Research and Academic Affairs, Medical Service San Francisco VAHCS

Honors and Awards

1974	American Chemical Society Outstanding Undergraduate Award, ASU
1975	Phi Beta Kappa and Merck Award in Chemistry, ASU
1986	NIH Clinical Investigator Award
1992	American Lung Association Career Investigator Award
1992	Electee to American Society for Clinical Investigation
2000	Electee to American Association of Physicians
2010	Electee to Collegium Internationale Allergologicum

Contributions to Science

1. Genetics and biology of mast cell granule proteases. The lab obtained the first complete primary structure of a mast cell tryptase, the most abundant protein product of human mast cells. It also was the first to determine the complete structure of human mast cell chymase (the major chymotryptic protease) and collaborated to crystallize human pro-chymase, leading to the first structure of the pro-form of an inflammatory cell serine protease and revealing a unique mechanism of controlling activity prior to activation. The lab revealed the single-gene nature of the human chymase locus and the multi-gene nature of the human tryptase locus, discovered α-tryptase deficiency, and was the first to purify, clone and characterize mastins, the principal tryptase-like enzymes of mammalian basophils. We co-discovered a transmembrane version of mast cell tryptase (γ-tryptase), and revealed its evolutionary relationship to epithelial proteases like prostasin and marapsin (which we also discovered), and showed that cathepsin C-null mice are deficient in active forms of one or more chymases and tryptases. Using combinatorial methods, we identified novel substrates and inhibitors of tryptases, chymases, cathepsin G, and mastin. We made highly cited discoveries concerning their actions on peptides, proteins, cells and airway tissues, including mitogenic and secretagogue activity, non-ACE-mediated generation of angiotensin II, and activation of MMP9 and remodeling pathways. These discoveries have provided rationales for hypothesizing roles for these proteases in disease pathogenesis and host defense.

a. Vanderslice P, Ballinger SM, Tam EK, Goldstein SM, Craik CS, & **Caughey GH**. Human mast cell tryptase: multiple cDNAs and genes reveal a multigene protease family. *Proc Nat Acad Sci* USA 87:3811-5, 1990.
b. b.) Soto D, Malmsten C, Blount JL, Muilenberg DJ & **Caughey GH**. Genetic deficiency of human mast cell γ-tryptase. *Clin Exp Allergy* 32:1000-6, 2002.
c. c.) Raymond WW, Ruggles Waugh S, Craik CS, & **Caughey GH**. Albumin is a substrate of human chymase: prediction by combinatorial peptide screening and development of a selective inhibitor based on the cleavage site. *J Biol Chem* 278:34517-24, 2003.
d. Trivedi NN, Tamraz B, Chu C, Kwok PY, & **Caughey GH**. Human subjects are protected from mast cell tryptase deficiency despite frequent inheritance of loss-of-function mutations. *J Allergy Clin Immunol* 124:1099-105, 2009; PMC2783561.
e. Raymond WW, Trivedi NN, Makarova A, Ray M, Craik CS, & **Caughey GH**. How immune peptidases change specificity: Cathepsin G gained tryptic function but lost efficiency during primate evolution. *J Immunol* 185:5360-8, 2010; PMC3954857.
f. **Caughey GH**. Mast cell proteases as pharmacological targets. *Eur J Pharmacol* 778:44-55, 2016.
g. Carlson RJ, Arkwright PD, Hong C, Agama S, Wilson TM, Tucker S, Zhang Y, McElwee JJ, Pao M, Golver SC, Rothenberg ME, Hohman RJ, Stone KD, **Caughey GH**, Heller T, Metcalfe DD, Biesecker LG, Schwartz LB, & Milner JD. Elevated basal serum tryptase identifies a multisystem disorder associated with increased alpha tryptase copy number. *Nat Genet* 48:1564-9, 2016.

Cysteine cathepsins in lung inflammation and host defense. My laboratory used mice deficient in dipeptidylpeptidase I (cathepsin C) and cathepsin L to yield new insights concerning the roles of these cysteine proteases in inflammatory responses to infection, host defense, cytokine processing, serine protease activation, lung surfactant collectin metabolism, and survival from septic peritonitis and gram-negative pneumonia. The laboratory pioneered the use of $Kit^{W\text{-}sh}/Kit^{W\text{-}sh}$ mice as models of mast cell deficiency, incorporating these mice into innovative strategies to explore mast cell-specific roles of cathepsins and of cathepsin-activated proteases.

a. Wolters PJ, Muilenburg D, Pham CTN, Ley TJ, & **Caughey GH**. Dipeptidylpeptidase I is essential for *in vivo* activation of mast cell chymases, but not tryptases. *Journal of Biological Chemistry* 276:18551-6, 2001.
b. Mallen-St. Clair J, Pham CTN, Villalta SA, **Caughey GH**, & Wolters PJ. Mast cell dipeptidyl peptidase I mediates survival from sepsis. *Journal of Clinical Investigation* 113:628-34, 2004.
c. Wolters PJ, Mallen-St. Clair J, Lewis CC, Villalta SA, Baluk P, Erle DJ, & **Caughey GH**. Tissue-selective mast cell reconstitution and differential lung gene expression in mast cell-deficient $Kit^{W\text{-}sh}/Kit^{W\text{-}sh}$ sash mice. *Clinical and Experimental Allergy* 35:82-8, 2005.
d. Xu X, Greenland JR, Baluk P, Adams A, Bose O, McDonald DM, & **Caughey GH.** Cathepsin L protects mice from mycoplasmal infection and is essential for lymphangiogenesis. *American Journal of Respiratory Cell and Molecular Biology* 187:417-23, 2013.

2. Neutrophil proteases and histamine. The lab made highly cited observations concerning neutrophil elastase and cathepsin G, including identification of secretagogue and proteoglycanase activity, inactivation of surfactant apoproteins, and genetic mutations that altered human cathepsin G activity and function. Our discovery that neutrophils inducibly produce histamine in mice with pneumonia drew press attention because of the suggested link between infectious and allergic inflammation.

a. Xu X, Zhang D, Zhang H, Wolters PJ, Killeen NP, Sullivan BM, Locksley RM, Lowell CA, & **Caughey GH**. Neutrophil histamine contributes to inflammation in mycoplasma pneumonia. *Journal of Experimental Medicine* 203:2907-17, 2006.
b. Raymond WW, Trivedi NN, Makarova A, Ray M, Craik CS, & **Caughey GH**. How immune peptidases change specificity: Cathepsin G gained tryptic function but lost efficiency during primate evolution. *Journal of Immunology* 185:5360-68, 2010.
c. Xu X, Zhang H, Song Y, Lynch SV, Lowell CA, Wiener-Kronish JP, & **Caughey GH**. Strain-dependent induction of neutrophil histamine production and cell death by *Pseudomonas aeruginosa*. *Journal of Leukocyte Biology* 91:275-84, 2012.

Surface proteases of airway epithelium. My laboratory made seminal observations concerning the role of the lipid-anchored epithelial protease prostasin in regulating airway flux of salt and water, providing the first proof that prostasin activates the epithelial sodium channel ENaC in human airway epithelial cells. These and subsequent discoveries provided the rationale for development of inhaled, prostasin-inhibiting antiproteases as inhaled therapeutic agents in cystic fibrosis.

a. Tong ZY, Illek B, Bhagwandin VK, Verghese GM, & **Caughey GH**. Prostasin, membrane-anchored serine peptidase, regulates sodium currents in JME/CF15 cells, a cystic fibrosis epithelial cell line. American Journal of Physiology*: Lung Cellular and Molecular Physiology* 287:L928-35, 2004.
b. Verghese GM, Gutknecht MF, & **Caughey GH**. Prostasin regulates epithelial monolayer function: cell-specific Gpld1-mediated secretion and role of the GPI anchor. *American Journal of Physiology: Cell Physiology* 291:C1258-70, 2006.
c. Nimishakavi S, Besprozvannaya M, Raymond WW, Craik CS, Gruenert DC, & **Caughey GH**. Activity and inhibition of prostasin and matriptase on apical and basolateral surfaces of human airway epithelial cells. *American Journal of Physiology: Lung Cellular and Molecular Physiology* 303:L97-106, 2012.
d. Nimishakavi S, Raymond WW, Gruenert DC, & **Caughey GH**. Divergent inhibitor susceptibility among lumen-accessible tryptic proteases. *PLoS One* 2015 Oct 20; 10(10): e0141169; PMC4612780.

Lung transplantation. My laboratory generated the first large-scale human observations concerning the meaning and value of identifying lymphocytic bronchitis in endobronchial biopsies of lung allograft recipients. We also developed an immunophenotyping assay of bronchoalveolar lavage specimens that distinguishes rejection from infection in lung allograft recipients.

a. Xu X, Golden JA, Dolganov G, Jones KD, Donnelly S, Weaver T, & **Caughey GH**. Transcript signatures of lymphocytic bronchitis in lung allograft biopsies. *Journal of Heart and Lung Transplantation* 24:1055-66, 2005.
b. Greenland JR, Jones KD, Hays SR, Golden JA, Urisman A, Jewell NP, **Caughey GH**, & Trivedi NN. Association of large-airway lymphocytic bronchitis with bronchiolitis obliterans syndrome. *American Journal of Respiratory and Critical Care Medicine* 187:417-23, 2013.
c. Greenland JR, Xu X, Sayah DM, Liu FC, Jones KD, Looney MR, & **Caughey GH**. Mast cells in a murine ischemia-reperfusion model of primary graft dysfunction. *Respiratory Research* 15:95 (1-9), 2014.
d. Greenland JR, Jewell NP, Gottschall M, Trivedi NN, Kukreja J, Hays SR, Singer JP, Golden JA, & **Caughey GH**. Bronchoalveolar lavage cell immunophenotyping facilitates diagnosis of lung allograft rejection. *American Journal of Transplantation* 14:831-40, 2014.
e. Greenland JR, Wong CM, Ahuja R, Wang A, Uchida C, Golden JA, Hays SR, Leard LE, Raja R, Singer JP, Kukreja J, Wolters PJ, **Caughey GH**, & Tang Q. Donor-reactive regulatory T cell frequency increases during acute cellular rejection of lung allografts. *Transplantation* 100:2090-8, 2016; PMC5030122.

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

Research Support

Ongoing Research Support

Julius and Lilian Nadel Endowed Chair of Pulmonary Medicine Caughey (PI) 07/01/2004-
Supports research in mast cell proteases and airway biology
Role: Recipient/PI

VHA CSR&D IK2CX001034 Greenland (PI) 04/01/2015-03/31/2020
"Immune Mechanisms of Large-airway Lymphocytic Bronchitis"
The research goals are to explore the immune basis and clinical significance of lymphocytic airway inflammation in human recipients of lung allografts. Role: Principal Mentor

DVA Shared Equipment (ShEEP) Grant Caughey (Co-PI) 07/01/2014-
This award enables deep DNA sequencing on the San Francisco VA campus by funding purchase of an Illumina NextSeq 500 and Bioinformatics Pipeline system shared by 4 VA-based PIs.
Role: Co-PI

Completed Research Support

P01 HL024136 Caughey (PI) 05/11/2010-3/31/2016 (NCE)
"Evolving Microenvironments in Airway Inflammation"
Project 1 goals are to determine roles of secreted proteases in airway inflammation.
Role: PI/Project 1 Leader/Administrative Core Leader

Nina Ireland Program in Lung Health Tang (PI) 01/1/2013-12/31/2015
"Alloimmune Monitoring of Lung Transplant Recipients"
The goals of this project were to identify tests that anticipate and detect graft dysfunction in lung allograft recipients.

Hooper Foundation Bhagwandin (Post-doctoral Fellow) 06/01/2012-05/31/2014
"Roles of c-Kit in Lung Cancer Initiation and Progression"
The goals of this project were to explore the influence of proto-oncogene c-Kit on lung cancer using c-Kit-deficient mice and models of bronchogenic carcinoma.
Role: Research Supervisor/Mentor

BIOGRAPHICAL SKETCH

NAME **Harold A. Chapman, M.D.**	POSITION TITLE Professor of Medicine
eRA COMMONS USER NAME Halchapman	

EDUCATION/TRAINING

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

Positions and Honors

1979-1985	Assistant Professor of Medicine, University of Utah, Department of Medicine, Salt Lake City, UT
1985	Associate Professor of Medicine, University of Utah, Department of Medicine, Salt Lake City UT
1985-1999	Associate Professor of Medicine, Harvard Medical School, Department of Medicine, Boston, MA
1992-1999	Physician, Brigham and Women's Hospital, Boston, MA
1992-1999	Associate Professor of Environmental Health, Harvard School of Public Health, Boston, MA
2000-2008	Chief, Division of Pulmonary and Critical Care Medicine, University of California, San Francisco
2000	Attending Physician, Moffitt-Long Hospital, University of California San Francisco
2000	Professor of Medicine, University of California, San Francisco
2000	Senior Member, Cardiovascular Research Institute, University of California San Francisco

1985-1990 Career Investigator Award, American Lung Association
1987 American Society for Clinical Investigation
1998 American Association of Physicians
2001-2011 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 not very long ago uncertain, with almost all of the attention directed at neutrophils. However we developed and published data in the early 1980s that lung macrophages could be as or more important in elastin degradation. But believing that we did not know the important macrophage enzymes, we generated a human alveolar macrophage-derived DNA expression library to search for additional proteases. My colleagues and I were able to clone four new cysteine proteases from this library and then my group spent the next several years understanding their biology. We also shared the library with other investigators in the field, e.g. Steve Shapiro's group used the library to clone human macrophage metallo-elastase. We found cysteine proteases with non-redundant functions in antigen presentation, bone collagen turnover, thymic development, and neuronal lysosomal lipufuscin degradation. Cathepsin S, the first enzyme characterized, proved to be a potent elastase and a critical enzyme in MHC class II maturation. Collaborating with geneticists, we were able to link two of the enzymes to human genetic disorders and inhibitors of one of these, cathepsin K, has recently proven effective in a phase III clinical trial for post-menopausal osteoporosis (Merck).

a. Shi GP, Munger JS, Meara JP, Rich DH, **Chapman HA**. Molecular cloning and expression of human alveolar macrophage cathepsin S, an elastinolytic cysteine protease *J Biol Chem* 1992 15; 267:7258-62.
b. Riese R, Wolf P, Bromme D, Natkin L, Villadangos JA, Ploegh H and **HA Chapman.** Essential role for cathepsin S in MHC Class II-associated invariant chain processing and antigen presentation *Immunity* 1996; 4:357-366.
c. Gelb BD, Shi GP, **Chapman HA** Jr, Desnick RJ. Pycnodysostosis, a lysosomal disease caused by cathepsin K deficiency. *Science* 1996; 273:1236-1238.
d. Wealds SE, Lee BL, Lau L, Wickliffe KE, Shi GP, **Chapman HA**, Barton GM The ectodomain of Toll-like receptor 9 is cleaved to generate a functional receptor. *Nature* 2008 Dec 4; 456(7222): 658-62.
e. Tang CH, Lee JW, Galvez MG, Robillard L, Mole SE, **Chapman HA**. Murine cathepsin F deficiency causes neuronal lipofuscinosis and late-onset neurological disease. *Mol Cell Biol*. 2006; 26: 2309-16.

The nearly century-long observation that urokinase/plasmin activity is higher in tumors than surrounding normal tissues generated great interest in the nature of urokinase activators and

their function in cell migration. In studying urokinase activity in macrophages I discovered and reported for the first time that a cell-bound form of urokinase exists and proposed this focused protease activity to the immediate cell surface, thereby promoting invasion. This observation led to the subsequent identification of the urokinase receptor (uPAR). Although my group did not clone the receptor initially we did then identify the receptor as also an adhesion receptor for vitronectin, directly linking adhesion and protease activity. The crystal structure of uPAR confirmed the dual nature of the receptor. Subsequently we described the interaction of uPAR with several integrins, further connecting focal protease activation with cell attachment and motility. These studies spawned numerous subsequent studies examining the interplay between uPAR, matrix proteins, and adhesion receptors in cancer biology, establishing an important role for uPAR in tumor invasion.

f. **Chapman HA** Jr, Vavrin Z, Hibbs JB Jr. Macrophage fibrinolytic activity: Two pathways of plasmin formation by intact cells and an inhibitor of plasminogen activator. *Cell* 1982; 28:653-662.
g. Wei Y, Waltz D, Rao N, Drummond R, Rosenberg S, **Chapman HA**. Identification of the urokinase receptor as an adhesion receptor for vitronectin. *J Biol Chem*, 1994; 209:32380-32388.
h. Wei Y, Lukasev M, Simon DI, Bodary SC, Rosenberg S, Doyle MV, **Chapman HA**. Regulation of integrin function by the urokinase receptor. *Science* 1996; 273:1551-1555.
i. Wei Y, Yang X, Quimei Liu, Wilkins JA, and **Chapman HA**. Role for caveolin and urokinase receptors in integrin-mediated adhesion and signaling. *J Cell Biol* 1999; 144:1285-1294.

Although epithelial mesenchymal interactions are well known to influence extracellular matrix remodeling, the role of epithelial plasticity in this biology in the lung had been largely undefined. I asked the question of whether epithelial to mesenchymal transition (EMT) occurs in vivo in the lung in the context of injury and, if so, does this contribute importantly to pulmonary fibrosis. Using lineage labeling in vivo we discovered that epithelial cells express mesenchymal genes during fibrogenesis and activation of this pathway required extracellular matrix-induced TGFβ1 activation. These results inspired a series of studies examining the influence of integrin receptors on TGFβ1 signaling ultimately linking β-catenin-rich cell:cell contacts, integrin α3β1, and Smad signaling. Disruption of this signaling pathway in vivo attenuated epithelial transition and fibrogenesis. The implication that epithelial transition is important to fibrogenesis was subsequently confirmed by Kevin Kim, independent in his own lab, using an epithelial-specific knockout of collagen 1.

a. Kim KK, Kugler MC, Wolters PJ, Robillard L, Galvez MG, Brumwell AN, Sheppard D, **Chapman HA**. Alveolar epithelial cell mesenchymal transition develops *in vivo* during pulmonary fibrosis and is regulated by the extracellular matrix. *Proc Natl Acad Sci* 2006; 103(35): 13180-5. Epub 2006 Aug 21
b. Kim KK, Wei Y, Szekeres C, Kugler MC, Wolters PJ, Hill ML, Frank JA, Brumwell AN, Wheeler SE, Kreidberg JA, **Chapman HA**. Epithelial cell alpha3beta1 integrin links beta-catenin and Smad signaling to promote myofibroblast formation and pulmonary fibrosis. *J Clin Invest*. 2009 Jan; 119(1): 213-24. doi: 10.1172/JCI36940.

c. Kim Y, Kugler MC, Wei Y, Kim KK, Li X, Brumwell AN, **Chapman HA**. Integrin alpha3beta1-dependent beta-catenin phosphorylation links epithelial Smad signaling to cell contacts. *J Cell Biol.* 2009 Jan 26; 184(2): 309-22.
d. Xi Y, Wei Y, Sennino, Ulsamer A, Kwan I, Brumwell AN, Tan K, Aghi MK, McDonald DM, Jablons DM, **Chapman HA**. Identification of pY654-β-catenin as a critical co-factor in hypoxia-inducible factor-1α signaling and tumor responses to hypoxia *Oncogene* 2013, Dec 17. 2(42): 5048-57. PMID: 23246962

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. Follow-up studies led to the discovery that the actual stem/progenitor cells are rare epithelial subpopulations devoid of mature lineage markers but capable of rapid proliferation and pluripotent differentiation in vivo in response to major injury. More recent studies have further defined the origins of these epithelial stem/progenitor cells and the importance of local lung hypoxia in determining their differentiation fate. Further defining these cells in human lungs and exploring their capacity to improve lung function by transplantation remains a very active area for investigation in the lab.

a. **Chapman HA**, Li X, Alexander JP, Brumwell A, Lorizio W, Tan K, Sonnenberg A, Wei Y, Vu T. Integrin α6β4 identifies an adult distal lung epithelial population with regenerative potential in mice. *J Clin Invest*. 2011, 121:2855-62.
b. Vaughan AE, Brumwell A, Xi Y, Gotts J, Brownfield DG, Treutlein B, Tan K, Tan V, Liu F, Looney MR, Matthay M, Rock J, **Chapman HA**. Lineage-negative Progenitors Mobilize to Regenerate Lung Epithelium after Major Injury. *Nature* 2015 517(7536):621-5. PMID: 25533958
c. Xi Y,Kim T, Brumwell AN, Driver I, Wei Y, Tan V, Jackson J, Xu J, Lee DK, Gotts J, Matthay M, Shannon JM, **Chapman HA** (corresponding author), and Vaughan AE. Local lung hypoxia determines epithelial fate decisions during alveolar regeneration. *Nature Cell Biology* 2017, Aug;19(8):904-914. PMID: 28737769.

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

Research Support

Ongoing Research Support

R01HL128484-01 (Chapman HA PI) Epithelial Stem/Progenitor Cells in Repair of the Injured Lung 7/1/2015-6/30/20

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.

Sponsored Research Agreement Chapman HA, PI 1/1/2017-6/30/2018
Pliant Therapeutics
Elucidation of mechanisms by which trihydroxyphenols regulate TGF 1 signaling.

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.

Sponsored Research Agreement Chapman HA, PI 1/1/2014-12/31/2016
Biogen Idec. Elucidation of human lung cellular diversity and epithelial-mesencyhmal interactions

R01 HL44712 Chapman HA, PI NIH/NHLBI
Regulation of Integrin Function 1/1/1991 – 12/31/2014
The major goals of this project are to understand the molecular basis and importance of integrin function in promoting TGFβ1 signaling and pulmonary fibrosis. The hypothesis that epithelial to mesenchymal transition is an important component of pulmonary fibrosis, and regulated by integrins, is the main idea tested in this grant.

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Anthony L. DeFranco, Ph.D.	Professor,
eRA COMMONS USER NAME	Department of Microbiology & Immunology
DeFranco	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Harvard University, Cambridge, MA	A.B.	6/1975	Biochem. Science
University of California, Berkeley, CA	Ph.D.	10/1979	Biochemistry
National Institutes of Health, Bethesda, MD	Postdoctoral	8/1983	Immunology

Positions

1972-1975	Undergraduate research, laboratory of Dr. Jack Strominger. HLA antigens.
1976-1979	Graduate research, laboratory of Dr. Daniel E. Koshland, Jr. Bacterial chemotaxis.
1979-1983	Postdoctoral research, laboratory of Dr. William E. Paul. B cell activation
1983-1988	Assistant Professor, UCSF, Department of Microbiology & Immunology,
1988-1994	Associate Professor, UCSF, Department of Microbiology & Immunology
1989-1990	Sabbatical with David Baltimore, Whitehead Insititute, MIT, Cambridge, MA
1994-present	Professor, UCSF, Department of Microbiology & Immunology
1997-1998	Sabbatical with Suzanne Cory, Walter and Eliza Hall Institute, Melbourne, Australia
1998-2004	Scientific Advisory Board, Abgenix, Inc. Fremont, CA
1999-2009	Chairman, Department of Microbiology & Immunology, UCSF
2012-	Scientific Advisory Board, UCB Celtech, Slough, UK
2015-present	Professor Emeritus of Microbiology & Immunology, UCSF (with continuing research and teaching activities)

Honors

1974	Dreyfuss Foundation Fellow
1975	Phi Beta Kappa, Harvard University
1975-1978	NSF Predoctoral Fellow
1979-1982	Helen Hay Whitney Postdoctoral Fellow
1993	2nd Rose Lieberman Lecturer, NIH
1994	NIAID Merit Award
1997-1998	NIH Fogarty Senior International Award

Contribution to Science

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

a. Gold, M.R., D.A. Law and **A.L. DeFranco**. (1990) Stimulation of protein tyrosine phosphorylation by the B lymphocyte antigen receptor. *Nature* 345: 810-813.
b. Gupta, N., B. Wollscheid, J.D. Watts, B. Scheer, R. Aebersold, and **A.L. DeFranco** (2006). Quantitative proteomic analysis of B cell lipid rafts reveals that ezrin regulates antigen receptor-mediated lipid raft dynamics. *Nature Immunol*. 7: 625-633.
c. Wheeler, M.L., and **A.L. DeFranco** (2012). Prolonged production of reactive oxygen species in response to BCR stimulation promotes B cell activation and proliferation. *J. Immunol*. 189: 4405-4416. PMC3515638.
d. Wheeler ML, Dong MB, Brink R, Zhong X-P, and **DeFranco AL**. (2013). Diacylglycerol kinase zeta limits B cell antigen receptor-induced ERK signaling and the early antibody response. *Sci. Signaling* 6 (297): ra91. PMC4128120.

2). Role of Lyn in inhibitory signaling in B cells - In a long-standing collaboration with Dr. Clifford Lowell (UCSF), we have studied the function of the protein tyrosine kinase Lyn in B cells in vitro and in vivo. Lyn is a member of the Src-family of tyrosine kinases, which at the time were implicated in the initiation of antigen receptor signaling in T cells and B cells. We found that Lyn did indeed participate in the initiation of BCR signaling, but that it was redundant with the other Src family kinases expressed in B cells (primarily Fyn and Blk), a conclusion later confirmed by Tarakhovsky, who made the Lyn-/-Fyn-/-Blk-/- triple KO. Importantly, we found that Lyn is uniquely responsible for enabling the function of the inhibitory receptors CD22 and FcγRIIb, and therefore in its absence BCR signaling was of much greater magnitude after the first few minutes (2a, 2b). We subsequently found that the inhibitory function of the Lyn-CD22-Shp1 pathway is much greater in mature B cells than in immature B cells (2c). This finding is likely relevant to the striking breakdown in B cell tolerance in Lyn-deficient mice, which spontaneously develop a strong lupus-like autoimmunity (see next category). Indeed, selective deletion of Lyn in B cells was shown to be sufficient for lupus-like autoantibody production and lupus nephritis, indicating that B cell tolerance defects contribute importantly to the lupus-like autoimmunity of Lyn-deficient mice (3d).

a. Chan, V.W.F., F. Meng, P. Soriano, **A.L. DeFranco**, and C.A. Lowell (1997). Characterization of the B lymphocyte populations in Lyn-deficient mice and the role of Lyn in signal initiation and downregulation. *Immunity* 7: 69-81.

b. Chan, V.W.F., C.A.Lowell, and **A.L. DeFranco** (1998). Defective negative regulation of antigen receptor signaling in Lyn-deficient B lymphocytes. *Curr. Biol.* 8: 545-553.
c. Gross, A.J., J.R. Lyandres, A.K. Panigrahi, E., T.L. Prak, and **A.L. DeFranco** (2009). Developmental acquisition of the Lyn-CD22-SHP-1 inhibitory pathway promotes B cell tolerance. *J. Immunol*. 182: 5382-92. PMC2840041.
d. Lamagna, C., Y. Hu, **A.L. DeFranco**, and C.A. Lowell (2014). B cell-specific loss of Lyn kinase leads to autoimmunity. *J. Immunol*. 192: 919-928. PMC3900234

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

a. Yu, C.C.K., T.S.B. Yen, C.A. Lowell, and **A.L. DeFranco** (2001). Lupus-like kidney disease in mice deficient in Src-family protein tyrosine kinases Lyn and Fyn. *Curr. Biol.* 11:34-38.
b. Scapini, P., Y. Hu, C.L. Chu, T.S. Migone, **A.L. DeFranco**, M.A. Cassatella, and C.A. Lowell (2010). Myeloid cells, BAFF, and IFN-γ establish an inflammatory loop that exacerbates autoimmunity in Lyn-deficient mice. *J. Exp. Med*. 207: 1757-73. PMC2916124
c. Lamagna C, Scapini P, Van Ziffle J, Hou B, **DeFranco AL**, and Lowell CA. (2013). Hyperactivated MyD88 signaling in dendritic cells, through specific deletion of Lyn kinase, causes severe autoimmunity and inflammation. *Proc. Natl. Acad. Sci. USA*. 110: E3311-20. PMC3761623
d. Proekt, I., Miller, C.N., Jeanne, M., Fasano, K., Moon, J.J., Lowell, C.A., Gould, D.B., Anderson, M.S., and **DeFranco, A.L**. (2016). LYN- and AIRE-mediated tolerance checkpoint defects synergize to trigger organ-specific autoimmunity. *J. Clin. Invest*. 126: 3758-3771. doi: 10.1172/JCI84440.

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

conducted in Dr. Yarovinsky's lab (4c and 5b). In contrast to the critical role of DCs in response to *Toxoplasma gondii* infection, in a murine malaria model, splenic red pulp macrophages were found to be critical for early cytokine production (4d). The conditional allele of *Myd88* was deposited with Jackson Lab soon after initial publication and is available to academic investigators for their studies.

a. Hou, B., B. Reizis, and **A.L. DeFranco** (2008). Toll-like receptors activate innate and adaptive immunity using dendritic cell-dependent and -independent mechanisms. *Immunity* 29: 272-82. PMC2847796.
b. Hou, B., A. Benson, L. Kuzmich, **A.L. DeFranco** and F. Yarovinsky (2011). Critical coordination of innate immune defense against *Toxoplasma gondii* by dendritic cells responding via their Toll-like receptors. *Proc. Natl. Acad. Sci USA* 108: 278-283. PMC3017180**.**
c. Raetz,M, Hwang, S-H, Wilhelm, C, Kirkland, D, Benson, A, Sturge, C, Mirpuri, J, Vaishnava, S, Hou, B, **DeFranco, AL**, Gilpin, CJ, Hooper, LV, Yarovinsky, F. (2013). Parasite-induced Th1 cells promote intestinal dysbiosis via IFN-dependent elimination of Paneth cells. *Nat. Immunol*. 14: 136-142. PMC3552073.
d. Lee, L.M., Ji, M., Sinha, M., Dong, M.B., Ren, X., Wang, Y., Lowell, C.A., Ghosh, S., Locksley, R.M., and **DeFranco, A.L**. (2016). Determinants of divergent adaptive immune responses after airway sensitization with ligands for Toll-like receptor 5 or Toll-like receptor 9. PLoS ONE in press.

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

a. Hou, B., P. Saudan, G. Ott, M.L. Wheeler, M. Ji, L. Kuzmich, L.M. Lee, R.L. Coffman, M.F. Bachmann, **Anthony L. DeFranco** (2011). Selective utilization of Toll-like receptor and MyD88 signaling in B cells for enhancement of the anti-viral germinal center response. *Immunity* 34: 375-84. PMC3064721
b. Kirkland, D., A. Benson, J. Mirpuri, R. Pifer, B. Hou, **A.L. DeFranco**, F. Yarovinsky (2012). B cell-intrinsic MyD88 signaling prevents the lethal dissemination of commensal bacteria during colonic damage. *Immunity* 36: 228-238. PMC3288553
c. Hua, Z., A.J. Gross, C. Lamagna, N. Ramos-Hernandez, P. Scapini, M. Ji, H. Shao, C.A. Lowell, B. Hou and **A. L. DeFranco** (2014). Requirement for MyD88 signaling in B cells and dendritic cells for germinal center anti-nuclear antibody production in Lyn-deficient mice. *J. Immunol.* 192: 875-885. PMC4101002.
d. Rookhuizen, D.C. and **A.L. DeFranco** (2014). Toll-like receptor 9 signaling acts on multiple elements of the germinal center to enhance antibody responses. *Proc. Natl. Acad. Sci USA* 111: E3224-33. PMC4128120.

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

Research Support

Active - none

Completed (last three years)

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

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

3. "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

4. "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

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
William F. DeGrado	Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Kalamazoo College, Kalamazoo, MI	B.S.	02/1978	Chemistry
University of California, San Francisco	Ph.D.	06/1981	Organic Chemistry

Positions

1981-1990	Research Chemist, CR&D, DuPont Company, Wilmington, DE
1990-1992	Research Leader, CR&D, DuPont Company, Wilmington, DE
1992-1994	Research Fellow, R&D, The DuPont Merck Pharmaceutical Company, Wilmington, DE
1994-1996	Senior Director, R&D, The DuPont Merck Pharmaceutical Company, Wilmington, DE
1996-2011	Professor, Dept. of Biochemistry & Biophysics, University of Pennsylvania, Philadelphia, PA
2001-2003	President, The Protein Society
2011-present	Professor, UCSF Department of Pharmaceutical Chemistry.

Visiting Positions

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

Honors

1988	du Vigneaud Award for Peptide Research
1989	Protein Society Young Investigator Award
1992	Eli Lilly Award in Biological Chemistry
1994	Fellow, American Association for the Advancement of Science
1998	Member, American Academy of Arts and Sciences
1999	Member, National Academy of Sciences (U.S.A.)
2003	Merrifield Award, (presented by the Peptide Society)
2008	Ralph F. Hirschmann Award in Peptide Chemistry (American Chemical Society)
2009	Makineni Award (APS)
2014	Member, National Academy of Inventors (U.S.A.)

2015 Stein & Moore Award (Protein Society)
2016 Max Perutz Memorial Lecture (Weizmann Institute, Israel)
2017 Distinguished Alumnus Award (Kalamazoo College).
2018 Cope Scholar Award (American Chemical Society, Organic Division).
2018 M. Goodman Memorial Prize (American Chemical Society, Biological Division).

Contribution to Science

Conformational strains and misfolding of tau and A The spreading of protein misfolding pathology by a prion mechanism is implicated in the etiology of many neurodegenerative diseases. By accessing a cross-β conformation, amyloidogenic proteins involved in neurodegenerative disease (such as PrP, Aβ, tau, and α- synuclein) are able to capture and convert soluble monomeric proteins into joining the fibril conformation, thus spreading by protein-only transmission. Recent studies have begun to define fibril structures, but the precise molecular conformations of the fibrils found in disease are still not known. Further complicating structural studies is the transient nature of oligomeric steps preceding fibril formation, making it difficult to gain any structural information on the conformations that may be most closely implicated in disease toxicity. Additionally, mutations to Aβ are known to cause early-onset disease, but the structural changes to the fibril that result from these amino acid changes are not understood. We have characterized conformational strains encoded by disease-associated mutations in Aβ (fibril formation kinetics, EM, fibril stability, solid-state NMR, fiber diffraction), and correlated them with their transmissibility in mouse models. These experiments have shown that certain familial mutants associated with early-onset AD and related diseases form kinetically dominant seeds that can impose their misfolded conformations on that of WT protein in heterozygotes. We also have defined the minimal sequence and active conformational nucleus that defines the self-propagating misfolding of tau. The microtubule-binding region, spanning residues 244-372, reproduces much of the aggregation behavior of tau in cells and animal models. Further dissection of the amyloid-forming region to 31 residues led to a peptide that induced aggregation of tau244-372 in cells. X-ray fiber diffraction, hydrogen-deuterium exchange and solids NMR studies map the beta-forming region to a 25-residue sequence. Current work is focused on using these methods to examine conformational strains of full-length tau isoforms associated with various diseases.

1. Stöhr, J.W., Wu, H., Nick, M., Wu, Y., Bhate, M., Condello, C., Johnson, N., Rodgers, J., Lemmin, T., Acharyraya, S., Becker, J., Robinson, K., Kelly, M.J.S., Gai, F., Stubbs, G., Prusiner, S.B., **DeGrado, W.F**. (2017) A 31-residue peptide induces aggregation of tau's microtubule-binding region in cells. *Nature Chemistry*, Sep;9(9):874-881
2. PMC5759337.
3. Wang, T., Jo, H., **DeGrado, W**., Hong, M. (2017) Water Distribution, Dynamics and Interactions with Alzheimer's β-Amyloid Fibrils Investigated by Solid-State NMR. *J. Amer. Chem. Soc.* 139, 6242-52, PMC5149419
4. Elkins MR, Wang T, Nick M, Jo H, Lemmin T, Prusiner SB, **DeGrado WF**, Stohr J and Hong M. (2016) Structural Polymorphism of Alzheimer's beta-Amyloid Fibrils as Controlled by an E22 Switch: A Solid-State NMR Study. *J Am Chem Soc*. 138, 9840-52. PMCID: PMC5149419.
5. Rufo CM, Moroz YS, Moroz OV, Stohr J, Smith TA, Hu X, **DeGrado WF** and Korendovych IV. (2014) Short peptides self-assemble to produce catalytic amyloids. *Nat Chem*. 6, 303-9. PMC3996680.

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.

1. Bryson, J. W., Betz, S. F., Lu, H. S., Suich, D. J., Zhou, H. X., O'Neil, K. T., and **DeGrado, W. F.** (1995) Protein design: a hierarchic approach, *Science 270*, 935-941.
2. Grigoryan, G., Kim, Y. H., Acharya, R., Axelrod, K., Jain, R. M., Willis, L., Drndic, M., Kikkawa, J. M., and **DeGrado, W.F.** (2011) Computational design of virus-like protein assemblies on carbon nanotube surfaces, *Science 332*, 1071-1076. PMCID: PMC3264056
3. Rufo, C. M., Moroz, Y. S., Moroz, O. V., Stohr, J., Smith, T. A., Hu, X., **DeGrado, W.F.,** and Korendovych, I. V. (2014) Short peptides self-assemble to produce catalytic amyloids, *Nature chemistry 6*, 303-309. PMCID: PMC3996680
4. Polizzi, N, Wu, Y., Lemmin, T, Maxwell, A, Zhang, SQ, Rawson, J., Beratan, DN, Therien, M.J., **DeGrado, WF.** (**2017**) De novo design of a hyperstable, non-natural protein-ligand complex with sub-Å accuracy. *Nature Chemistry* doi:10.1038/nchem.2846. PMC ID in progress.

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. 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. More recently, 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.

1. Choma, C., Gratkowski, H., Lear, J. D., and **DeGrado, W.F.** (2000) Asparagine-mediated self-association of a model transmembrane helix, *Nature Struct. Biol. 7*, 161-166.
2. Gratkowski, H., Lear, J. D., and **DeGrado, W.F.** (2001) Polar sidechains drive the association of model, transmembrane peptides., *Proc. Natl. Acad. Sci. U.S.A. 98*, 880-885. PMCID: PMC14678
3. Yin, H., Slusky, J. S., Berger, B. W., Walters, R. S., Vilaire, G., Litvinov, R. I., Lear, J. D., Caputo, G. A., Bennett, J. S., and **DeGrado, W.F.** (2007) Computational design of peptides that target transmembrane helices, *Science 315*, 1817-1822.
4. Joh, N. H., Wang, T., Bhate, M. P., Acharya, R., Wu, Y., Grabe, M., Hong, M., Grigoryan, G., and **DeGrado, W.F.** (2014) De novo design of a transmembrane Zn(2)(+)-transporting four-helix bundle, *Science 346*, 1520-1524. PMCID: PMC4400864

Structure-based design of small molecule therapeutics

Integrins. Our group has long been involved in the design of cyclic peptides small molecules as inhibitors of integrins to allow the interrogation of their roles in various biological processes. Early work on the integrins αvβ1 led to compounds that reached clinical trials. More recently, we explored the role of other integrins involved in platelet adhesion including αvβ3 and α2β1 (a non-RGD collagen receptor). Since moving to UCSF we have focused on the problem of fibrotic diseases including idiotypic pulmonary fibrosis (IPF). In collaboration with Dean Sheppard we have developed very potent integrin antagonists that inhibit activation of TGF-β1, and work in a variety of animal models of IPF and other fibrotic disorders. We also have had a long-standing collaboration with Joel Bennett on the activation of αIIbβ, particularly the role of its transmembrane helices [7] and engagement of cytoplasmic proteins.

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 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.

1. Reed, N. I., Jo, H., Chen, C., Tsujino, K., Arnold, T. D., **DeGrado, W.F.,** and Sheppard, D. (2015) The αvβ1 integrin plays a critical in vivo role in tissue fibrosis., *Science, Translational Medicine* 7, 288ra279.
2. Moore, D. T., Nygren, P., Jo, H., Boesze-Battaglia, K., Bennett, J. S., and **DeGrado, W.F.** (2012) Affinity of talin-1 for the beta3-integrin cytosolic domain is modulated by its phospholipid bilayer environment, *Proc Natl Acad Sci USA* 109, 793-798. PMCID: PMC3271903
3. Stouffer, A. L., Acharya, R., Salom, D., Levine, A. S., Di Costanzo, L., Soto, C. S., Tereshko, V., Nanda, V., Stayrook, S., and **DeGrado, W.F.** (2008) Structural basis for the function and inhibition of an influenza virus proton channel, *Nature* 451, 596-599. PMCID: PMC3889492
4. Wang, J., Wu, Y., Ma, C., Fiorin, G., Wang, J., Pinto, L. H., Lamb, R. A., Klein, M. L., and **DeGrado, W.F.** (2013) Structure and inhibition of the drug-resistant S31N mutant of the M2 ion channel of influenza A virus, *Proc Natl Acad Sci USA* 110, 1315-1320. PMCID: PMC3557100

5) *Development of chemical tools and probes of protein structure, dynamics, and interactions.* My graduate work with E. T. Kaiser and F. Kezdy, which was used for synthesis of protected peptides and is still in use for various types of combinatorial chemistry today. As an independent investigator, I continued an interest in peptide chemistry and developed the photo-affinity amino acid, p-benzoyl-phenylalanine (Bpa) that is widely used today. This amino acid was used to probe the mechanism by which peptides interact with calmodulin binds its target enzymes[17], leading to models that proved to be predictive of later high-resolution structures. Our work on the development of methods to follow protein folding and conformational change, continued through long collaborations with the groups of Feng Gai and the late Robin Hochstrasser. For example, with Gai we introduced use of nitrile-containing amino acids as vibrational and fluorescent probes of protein interactions and folding including the widely used 4-cyano-phenylalanine, and with Hochstrasser we performed the first single-molecule measurements of protein folding by fluorescence microscopy, and we solved the structure of a transmembrane helical dimer using two-dimensional IR spectroscopy.

1. O'Neil, K. T., and **DeGrado, W.F.** (1990) How calmodulin binds its targets: sequence independent recognition of amphiphilic a-helices, *Trends in Biochem. Sci.* 15, 59-64.

2. Getahun, Z., Huang, C. Y., Wang, T., De Leon, B., **DeGrado, W.F.**, and Gai, F. (2003) Using nitrile-derivatized amino acids as infrared probes of local environment, *J Am Chem Soc* 125, 405-411.
3. Jo, H., Culik, R. M., Korendovych, I. V., **DeGrado, W.F.**, and Gai, F. (2010) Selective incorporation of nitrile-based infrared probes into proteins via cysteine alkylation, *Biochemistry 49*, 10354-10356. PMCID: PMC3999665
4. Remorino, A., Korendovych, I. V., Wu, Y., **DeGrado, W.F.**, and Hochstrasser, R. M. (2011) Residue-specific vibrational echoes yield 3D structures of a transmembrane helix dimer, *Science* 332, 1206-1209. PMCID: PMC3295544

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

Research Support

R35 GM122603 05/01/17—04/30/22 6.0 Calendar
NIH/NIGMS $410,983 ADC
"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.

CHE-1413295 08/01/17—07/31/21 0.18 Calendar
NSF/Duke University (Therien) $78,864 ADC
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 is employed toward this goal, and focuses on the computational design of peptide-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.

UH2 HL123423-01 (Sheppard/DeGrado) 07/01/16—06/30/19 0.5 Calendar
NIH/NHLBI $265,658 ADC
"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.

P01 HL040387 (Bennett) 05/16/14—04/30/19 1.1 Calendar
NIH/NHLBI/University of Pennsylvania $102,700 ADC
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.

BIOGRAPHICAL SKETCH

NAME **David J. Erle, M.D.**	POSITION TITLE Professor of Medicine
eRA COMMONS USER NAME DJERLE	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Harvard College, Cambridge, MA	A.B.	5/1980	Biochemistry
University of California, San Francisco, CA	M.D.	5/1984	Medicine
University of California, San Francisco, CA	Resident	6/-1987	Internal Medicine
University of California, San Francisco, CA	Fellow	6/1988	Pulmonary Disease
University of California, San Francisco, CA	Postdoc	6/1990	Cell & Molecular Biology

Positions

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

Other Experience and Professional Memberships

1988-	Member, American Thoracic Society
1996-1999	American Lung Association/American Thoracic Society Scientific Advisory Council

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

Honors

1977	Detur Prize
1977, 1978	John Harvard Scholarship
1980	Magna cum laude, Harvard College, Cambridge, MA
1984	Alpha Omega Alpha, elected
1990-1993	Edward Livingston Trudeau Award of the American Lung Association

Contributions to Science

1. I have a longstanding interest in the cell and molecular biology of airway epithelial cells. In studies performed using mouse models, cultured human cells, and materials from human subjects, we analyzed the functions of key mediators (IL-13, EGFR ligands), receptors (EGFR, IL-4/IL-13 receptors), and transcription factors (STAT6, FOXA2, and FOXA3) in these cells. Relevant contributions in this area include:
   a. Kuperman DA, Huang X, Koth LL, Chang GH, Dolganov GM, Zhu Z, Elias JA, Sheppard D, **Erle DJ**. Direct effects of interleukin-13 on epithelial cells cause airway hyperreactivity and mucus overproduction in asthma. *Nat Med.* 2002; 8:885-9. PMID: 12091879.
   b. Woodruff PG, Boushey HA, Dolganov GM, Barker CS, Yang YH, Donnelly S, Ellwanger A, Sidhu SS, Dao-Pick TP, Pantoja C, **Erle DJ**, Yamamoto KR, Fahy JV. Genome-wide profiling identifies epithelial cell genes associated with asthma and with treatment response to corticosteroids. *Proc Natl Acad Sci USA*. 2007; 104:15858-63. PMID: 17898169; PMCID: PMC2000427.
   c. Park SW, Verhaeghe C, Nguyenvu LT, Barbeau R, Eisley CJ, Nakagami Y, Huang X, Woodruff PG, Fahy JV, **Erle DJ**. Distinct roles of FOXA2 and FOXA3 in allergic airway disease and asthma. *Am J Respir Crit Care Med* 180:603-10, 2009. PMCID: PMC2753788.
   d. Bonser LR, Zlock L, Finkbeiner W, **Erle DJ**. A heterogenous mucus gel impairs mucociliary transport in asthma. *J Clin Invest* 2016; 126:2367-71. PMID: 27183390; PMC4887179.

2. 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. Examples of ongoing NIH-funded projects include a subcontract to an NHLBI R01 grant (PI: Dr. Keoki Williams) that involves sequencing of >1000 human blood samples from participants with asthma and controls and an Extracellular RNA Communication Program U01 grant (from the NIH Common Fund, PIs: Woodruff and Erle) that involves sequencing of 3000 extracellular

biofluid samples. 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:

a. Kuperman DA, Lewis CC, Woodruff PG, Rodriguez MW, Yang YH, Dolganov GM, Fahy JV, **Erle DJ**. Dissecting asthma using focused transgenic modeling and functional genomics. *J Allergy Clin Immunol* 116:305-311, 2005.
b. McErlean P, Berdnikovs S, Favoreto S, Shen J, Biyasheva A, Barbeau R, Eisley C, Barczak A, Ward T, Schleimer RP, **Erle DJ**, Boushey HA, Avila PC. Asthmatics with exacerbation during acute respiratory illness exhibit unique transcriptional signatures within the nasal mucosa. *Genome Med.* 2014; 6:1. PMID: 24433494. PMCID: PMC3971347
c. Minagawa S, Lou J, Seed RI, Cormier A, Wu S, Cheng Y, Murray L, Tsui P, Connor J, Herbst R, Govaerts C, Barker T, Cambier S, Yanagisawa H, Goodsell A, Hashimoto M, Brand OJ, Cheng R, Ma R, McKnelly KJ, Wen W, Hill A, Jablons D, Wolters P, Kitamura H, Araya J, Barczak AJ, **Erle DJ**, Reichardt LF, Marks JD, Baron JL, Nishimura SL. Selective targeting of TGF-β activation to treat fibroinflammatory airway disease. *Sci Transl Med.* 2014; 6:241ra79. PMID: 24944194.
d. Van Dyken SJ, Liang HE, Naikawadi RP, Woodruff PG, Wolters PJ, **Erle DJ**, Locksley RM. Spontaneous Chitin Accumulation in Airways and Age-Related Fibrotic Lung Disease. *Cell*. 2017 Apr 20;169(3):497-509.e13. doi: 10.1016/j.cell.2017.03.044. PubMed PMID: 28431248.

3. Recent and ongoing work in the lab focuses on understanding basic mechanisms of post-transcriptional gene regulation in health and disease (especially asthma). We have developed a novel massively parallel method for functional annotation of 3' UTRs (fast-UTR) and used this to identify many novel regulatory elements in human 3' UTRs. In asthma, we have identified changes in miRNA expression in airway epithelial cells in asthma and identified one pathway that contributes to these changes.
   a. Solberg OD, Ostrin EJ, Love MI, Peng JC, Bhakta NR, Hou L, Nguyen C, Solon M, Nguyen C, Barczak AJ, Zlock LT, Blagev DP, Finkbeiner WE, Ansel KM, Arron JR, **Erle DJ***, Woodruff PG*. Airway epithelial miRNA expression is altered in asthma. *Am J Respir Crit Care Med.* 2012; 186:965-74. PMID: 22955319; PMCID: PMC3530212. *, equal contributions.
   b. Levänen B, Bhakta NR, Torregrosa Paredes P, Barbeau R, Hiltbrunner S, Pollack JL, Sköld CM, Svartengren M, Grunewald J, Gabrielsson S, Eklund A, Larsson BM, Woodruff PG, **Erle DJ**, Wheelock ÅM. Altered microRNA profiles in bronchoalveolar lavage fluid exosomes in asthmatic patients. *J Allergy Clin Immunol.* 2013; 131:894-903. PMID: 23333113; PMCID: PMC4013392.
   c. Zhao W, Pollack JL, Blagev DP, Zaitlen N, McManus MT, **Erle DJ**. Massively parallel functional annotation of 3' untranslated regions. *Nat Biotechnol*. 2014; 32:387-91. PMID: 24633241; PMCID: PMC3981918.
   d. Zhao W, Siegel D, Biton A, Le Tonqueze O, Zaitlen N, Ahituv N, **Erle DJ**. CRISPR-Cas9 mediated functional dissection of 3'-UTRs. *Nucleic Acids Res* 2017, in press.

1. 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, both of which are expressed in epithelial cells. We produced *Agr2*$^{-/-}$ mice and used these to show that AGR2 is essential for mucus production in the intestine and is also important for allergen-induced mucus overproduction in a mouse model of asthma. Surprisingly, we found that the close AGR2 homolog AGR3 has a very different role in airway epithelium: it is expressed in ciliated cells rather than mucus cells and helps regulate ciliary beat frequency.

a. Park SW, Zhen G, Verhaeghe C, Nakagami Y, Nguyenvu LT, Barczak AJ, Killeen N, **Erle DJ**. The protein disulfide isomerase AGR2 is essential for production of intestinal mucus. *Proc Natl Acad Sci USA*. 2009; 106:6950-5. PMID: 19359471; PMCID: PMC2678445.
b. Schroeder BW, Verhaeghe C, Park SW, Nguyenvu LT, Huang X, Zhen G, **Erle DJ**. AGR2 is induced in asthma and promotes allergen-induced mucin overproduction. *Am J Respir Cell Mol Biol.* 2012; 47:178-85. PMID: 22403803; PMCID: PMC3423459.
c. Bonser LR, Schroeder BW, Ostrin LA, Schmid N, Olson JL, Salathe M, **Erle DJ**. The Endoplasmic Reticulum Resident Protein AGR3. Required for Regulation of Ciliary Beat Frequency in the Airway. *Am J Respir Cell Mol Biol.* 2015; 53:536-43. PMID: 25751668; PMCID: PMC4742895

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 β7 and the integrin α4β7 heterodimer that directs lymphocyte trafficking to the intestine. Subsequent work by other investigators led to the development of the anti-integrin α4β7 antibody *vedolizumab as an* FDA-approved treatment for inflammatory bowel disease.

a. **Erle DJ**, Rüegg C, Sheppard D, Pytela R. Complete amino acid sequence of an integrin β7 subunit (β7) identified in leukocytes. *J Biol Chem.* 1991; 266:11009-16. PMID: 2040616.
b. Rüegg C, Postigo AA, Sikorski EE, Butcher EC, Pytela R, **Erle DJ**. Role of integrin α4β7/α4βP in lymphocyte adherence to fibronectin and VCAM-1 and in homotypic cell clustering. *J Cell Biol*. 1992; 117:179-89. PMID: 1372909; PMCID: PMC2289398.
c. **Erle DJ**, Briskin MJ, Butcher EC, Garcia-Pardo A, Lazarovits AI, Tidswell M. Expression and function of the MAdCAM-1 receptor, integrin α4β7, on human leukocytes. *J Immunol*. 1994; 153:517-28. PMID: 7517418.
d. Pachynski RK, Wu SW, Gunn MD, **Erle DJ**. Secondary lymphoid-tissue chemokine (SLC) stimulates integrin α4β7-mediated adhesion of lymphocytes to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) under flow. *J Immunol.* 1998; 161:952-6. PMID: 9670974.

Complete list of publications in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/12KO9xu_bEz/bibliography/40107757/public/?sort=date&direction=ascending

Research Support

Ongoing Research Support

R01 HL138424 Erle (PI) 08/01/2017-06/30/2021
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: PI

R01 HL124285-01 Erle (PI) 07/01/2014-06/30/2019 (with NCE)
Massively Parallel Identification of Causative 3' UTR Variants in Asthma. The goal is to identify 3' UTR variants that alter gene expression and risk of asthma. Role: PI

R01 GM110251 McManus/Erle (MPI) 09/01/2014-08/31/2018
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

U19 AI 077439 Sheppard (PI) 04/01/2013-03/31/2018
IL-13 and IL-17 Dynamics in the Asthmatic Airway
Overall project goal is to determine how immune cells producing IL-13 and IL-17 specifically modulate contractile responses of airway smooth muscle and the relevance of these pathways to human asthma.
Role: Project 1 Leader

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 HL119997-01 Erle/Burchard (MPI) 09/01/2013-05/31/2018
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

Completed Research Support

Henry Ford Health System Erle (subcontract PI) 02/01/2014-01/31/2018
Subcontract to R01 HL118267, PI Williams
Combined Transcriptomics and Genomics to Find Asthma Genes in Admixed Populations
Goal is to perform RNA-Seq for transcript profiling of blood cells in asthma.
Role: Subcontract PI

BIOGRAPHICAL SKETCH

NAME **John Vincent Fahy, M.D., M.Sc.**	POSITION TITLE Professor
eRA COMMONS USER NAME johnfahy	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University College Dublin	MB BAO BCH	6/1985	Medicine
Trinity College Dublin	Internal Medicine (Residency)	6/1988	Internal Medicine
University College Dublin	Pulmonary Medicine (Medical Registrar)	6/1989	Pulmonary Medicine
University of California, San Francisco	Postdoctoral Fellowship	6/1993	Pulmonary/Critical Care Medicine
University College Dublin	M.D. (doctorate by thesis)	6/1997 2003	Airway Inflammation
Trinity College Dublin	M.Sc.	6/2003 (Sabbatical year)	Molecular Medicine

Positions

1989-1993	Fellow, Division of Pulmonary and Critical Care Medicine, Department of Medicine (DOM) and Cardiovascular Research institute (CVRI), UCSF.
1993-1998	Assistant Professor of Medicine, Division of Pulmonary and Critical Care Medicine, DOM and CVRI, UCSF.
1999-2005	Associate Professor of Medicine, Division of Pulmonary and Critical Care Medicine, DOM and CVRI, UCSF.
2002-2003	Visiting Scholar, Trinity College Dublin and University College Dublin (sabbatical year)
2005-present	Professor of Medicine, Division of Pulmonary and Critical Care Medicine, DOM and CVRI, UCSF.

Other Experience and Professional Memberships

1989-	Member, American Thoracic Society
2014-	Member, European Respiratory Society
2009-	Member, Organizing Committee - Transatlantic Airway Conference (TAC).
2012-2014	NIH Workshop: Primary prevention of lung disease - chair of asthma subcommittee.
2014	NIH Strategic Planning Working Group: Member, disease modification subcommittee.
2015	Ad hoc NIH Peer reviewer, Lung Cellular, Molecular Immunobiology Study Section

Honors

1990	Traveling Studentship in Medicine, National University of Ireland.
2009	Michael S. Stulbarg Endowed Chair in Pulmonary Medicine, UCSF.
2015	Scientific Accomplishment Award, American Thoracic Society, Allergy Immunology and Inflammation Assembly.
2016	Election to Association of American Physicians (AAP)
2017	ATS Recognition Awardees for Scientific Accomplishments.

Contribution to Science

Molecular Phenotypes of Asthma
Background: Asthma is clinically heterogeneous, and previous concepts held that this heterogeneity could be explained by variability in the levels of type 2 (eosinophilic) inflammation in the airway. This concept has now been replaced by the view that asthma is not mechanistically homogenous and that different molecular mechanisms are responsible for disease expression in different subsets of patients. This realization has emphasized the importance of mechanism-oriented research in human subjects, and my lab has been at the forefront of mechanism-oriented studies that are designed to uncover molecular phenotypes of asthma.
Central findings: My initial work as a fellow and junior faculty member involved developing methods to non invasively study airway inflammation using analysis of induced sputum for cells and mediators of asthma (publication A below). I later extended this sputum-based work to cell and molecular analyses of other airway biospecimens, including epithelial brushings, bronchial mucosal biopsies, and bronchial lavage. By applying and optimizing rigorous analytic methods, including -OMIC technologies to the analysis of these biospecimens, my lab had made major contributions to current understanding of disease heterogeneity in asthma. These findings have included the identification of Th2-high and Th2-low endotypes of asthma (publications A-D) as well as the recent identification of IL-6 high asthma (publication E).
Impact: The impact of discovery of Th2-high asthma by my lab in collaboration with Prescott Woodruff's lab (UCSF) and Joe Arron's group (Genentech) has been large. Asthma research now routinely segregates patients into Th2-high and low subgroups and clinical trials of Th2 inhibitors are specifically targeting patients with Th2-high asthma using biomarkers like periostin that I helped discover.
My role: I lead a large research group that is involved in mechanism-oriented research in asthma. My role is that of a senior investigator who manages a clinical research lab, generates funding, manages and mentors personnel, interprets data, writes papers, and sets the course for my group. Key grants for this activity include P01HL107202 and U10HL109146.

A. Woodruff PG, Modrek M, Choy DF, Guiquan J. Abbas AR, Ellwanger A, Koth LL, Arron JR, Fahy JV. *TH2-driven inflammation defines major sub-phenotypes of asthma.* Am J Respir Crit Care Med. 2009; 180:388-95.
B. Sukhvinder SS, Yuan S, Innes AL, Kerr S, Woodruff PG, Solon M, Hou L, Muller SL, **Fahy JV.** *Epithelial cell-derived periostin: roles in TGF activation, collagen production and collagen elasticity in asthma.* PNAS 2010; 107:14170-5.
C. Fahy JV. *Type 2 inflammation in asthma; Present in most, absent in many*. Nat Rev Immunol. 2014; 15:57-65.

D. Gordon ED, Simpson LJ, Rios CL, Ringel L, Lachowicz-Scroggins ME, Peters MC, Wesolowska-Andersen A, Gonzalez JR, MacLeod HJ, Christian LS, Yuan S, Barry L, Woodruff PG, Ansel KM, Nocka K, Seibold MA, **Fahy JV.** *Alternative splicing of interleukin 33 and type 2 inflammation in asthma*. Proc Natl Acad Sci U S A. 2016 Aug 2; 113(31): 8765-70.
E. Peters MC, McGrath KW, Hawkins GA, Hastie AT, Levy BD, Israel E, Phillips BR, Mauger DT, Comhair SA, Erzurum SC, Johansson MW, Jarjour NN, Coverstone AM, Castro M, Holguin F, Wenzel SE, Woodruff PG, Bleecker ER, **Fahy JV.** *Plasma IL6 levels, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts.* Lancet Respiratory Medicine 2016:4:574-84
F. Gordon ED, Palandra J, Wesolowska-Andersen A, Ringel L, Rios CL, Lachowicz-Scroggins ME, Sharp LZ, Everman JL, MacLeod HJ, Lee JW, Mason RJ, Matthay MA, Sheldon RT, Peters MC, Nocka KH, Fahy JV, Seibold MA. *IL1RL1 asthma risk variants regulate airway type 2 inflammation.* JCI Insight. 2016 Sep 8; 1(14): e87871.

(II) Airway Mucas Pathology

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

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

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

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

A. **Fahy JV**, Dickey B. *Airway Mucus - Function and Dysfunction*. *NEJM*. 2010; 363: 2233.
B. Ordoñez CL, Khashayar, R, Wong HH, Ferrando R, Wu R, Hyde DM, Hotchkiss JA, Zhang Y, Novikov A, Dolganov G, **Fahy JV**. *Mild and moderate asthma is associated with goblet cell hyperplasia and abnormalities in mucin gene expression*. *Am J Resp Crit Care Med* 2001; 163:517-523.
C. Innes AL. Carrington SD, David J. Thornton DJ, Kirkham S, Dougherty RH, Raymond WW, Caughey GH, Muller SJ, **Fahy JV**. *Ex vivo sputum analysis reveals impairment*

of protease-dependent mucus degradation by plasma proteins in acute asthma. *Am J Respir Crit Care Med.* 2009; 180:203-10. PMCID: PMC2724713.
Dunican EM, Elicker BM, Gierada DS, Nagle SK, Schiebler ML, Newell JD, Raymond WW, Lachowicz-Scroggins ME, Di Maio S, Hoffman EA, Castro M, Fain SB, Jarjour NN, Israel E, Levy BD, Erzurum SC, Wenzel SE, Meyers DA, Bleecker ER, Phillips BR, Mauger DT, Gordon ED, Woodruff PG, Peters MC, **Fahy JV**. Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. *J Clin Invest.* 2018; 128:997-1009. PMCID:PMC5824874.

(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. Woodruff PG, Wolff M, Hohlfeld JM, Krug N, Dransfield MT, Sutherland ER, Criner GJ, Kim V, Prasse A, Nivens MC, Tetzlaff K, Heilker R, **Fahy JV**. Safety and efficacy of an inhaled epidermal growth factor receptor inhibitor in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2010; 181:438-45.
B. **Fahy JV**, Fleming HE, Wong HH, Liu JT, Su JQ, Reimann J, Fick RB, Boushey HA. The effect of an anti-IgE monoclonal antibody-E25 on the early and late phase

responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med* 1997; 155:1828-1834.

C. Avila PC, Boushey HA, Wong HH, Grundland H, Liu J, **Fahy JV**. Effect of a single dose of the selectin inhibitor TBC1269 on early and late asthmatic responses. *Clin Exp Allergy* 2004; 34: 77-84.

D. Yuan S, Hollinger M, Lachowicz-Scroggins ME, Kerr SC, Daniel BM, Ghosh S, Erzurum SC, Willard B, Hazen SL, Huang X, Carrington SD, Oscarson S, **Fahy JV**. Oxidation Increases Mucin Polymer Cross-links to Stiffen Airway Mucus Gels. Science Translational Med. *Sci Transl Med*. 2015;7(276) 276ra27

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

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

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

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

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

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

U19 AI 077439 (Erle, D) 4/01/2018 - 3/31/2023
*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: Co-I.

BIOGRAPHICAL SKETCH

NAME **James Solomon Fraser, Ph.D.**	POSITION TITLE Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login) FRASERJA	

EDUCATION/TRAINING

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

Positions and Honors

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)
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	Panel Member: Advanced Light Source Proposal Review (Structural Biology)
2014-2015	Panel Member: Linac Coherent Light Source (XFEL) Proposal Review (BIO-C)
2015-2018	Chair: Linac Coherent Light Source (XFEL) Proposal Review Panel (BIO-C)
2016-	Head of Participating Research Team for Beamline 8.3.1. at the Advanced Light Source
2017-	Associate Director Quantitative Biosciences Institute of UCSF
2017-	Deputy Director of ALS-ENABLE Resource
2017-	Project Director Collaboration for Structural Simulations and Scattering
2018	Co-organizer Protein Society Annual Symposium

Honors and Awards

2001-2005	Canadian Millennium Excellence Undergraduate Scholarship
2004	NSERC Undergraduate Summer Research Award (Mentor: Alan Davidson)
2006-2007	Natural Sciences and Engineering Research Council (Canada) Postgraduate Fellowship
2007-2010	Natural Sciences and Engineering Research Council (Canada) Doctoral Fellowship

2007-2010	National Science Foundation Graduate Research Fellowship
2010	EMBO Short Term Fellowship (Host: Dan Tawfik, Weizmann Institute, Israel)
2010	Warren DeLano Award, Structural Bioinformatics and Computational B
2011	Nicholas Cozzarelli Prize for Best Dissertation in Molecular and Cell Biology (UCB)
2011	Forbes 30 under 30 Science
2014	Searle Scholar, Kinship Foundation
2014	Pew Scholar, Pew Charitable Trusts
2014	Packard Fellow, The David and Lucille Packard Foundation
2017-2018	Raymond and Beverly Sackler UCSF/Berkeley Sabbatical Exchange (Host: Eva Nogales)

Contributions to Science

1. Identifying hidden alternative conformations of proteins in biophysical data. We study proteins as conformational ensembles. Although X-ray crystallography is an ensemble experiment, the results are typically summarized with a single static structure. As a graduate student, and now in my own lab, we have developed software to discover the structural ensembles present in the crystal. The ensemble nature of proteins highlighted by this work feeds into all of our mechanistic studies that interpret the functional effects of mutations, that characterize designed and artificially-evolved proteins, or that seek to modulate protein function with small molecules. We are expanding this direction to include modeling and validating protein structural data generated by cryoelectron microscopy, through EMRinger and collaborations with Gabe Lander's lab on ensemble modeling, and through integrative approaches to discover cryptic sites.
    a. Barad BA, Echols N, Wang RY, Cheng Y, DiMaio F, Adams PD, **Fraser JS**. EMRinger: Side-chain-directed model and map validation for 3D Electron Cryomicroscopy. *Nature Methods*. 2015. PMCID: PMC4589481.
    b. Keedy DA, **Fraser JS**, van den Bedem H. Exposing Hidden Alternative Backbone Conformations in X-ray Crystallography Using qFit. *PLOS Computational Biology*. 2015. PMCID: PMC4624436.
    c. Cimermancic P, Weinkam P, Rettenmaier TJ, Bichmann L, Keedy DA, Woldeyes RA, Schneidman-Duhovny D, Demerdash ON, Mitchell JC, Wells JA, **Fraser JS**, Sali A. CryptoSite: Expanding the Druggable Proteome by Characterization and Prediction of Cryptic Binding Sites. *J Mol Biol*. 2016. PMCID: PMC4794384.
    d. Herzik Jr. MA, **Fraser JS**, Lander GC. A multi-model approach to assessing local and global cryo-EM map quality. Preprint on BioRxiv. 2017. http://dx.doi.org/10.1101/128561
2. Creating multi-temperature X-ray data collection methods to inform mechanistic studies**.** We recognized that the standard practice of cryocooling crystals could distort protein conformations. In both larger surveys and isolated mechanistic studies, we have demonstrated the value of room temperature data collection for revealing the structural basis of protein conformational dynamics, leading to new insights into the enzymes PTP1B, CypA, H-Ras, and DHFR, and increasing connections to dynamics studies from NMR and simulations. Additionally, we have identified how temperature can bias small molecule discovery, leading some fragment sites inaccessible at cryogenic temperatures, and the positioning of crucial water molecules in the flu ion channel M2.
    a. **Fraser JS**, van den Bedem H, Samelson AJ, Lang PT, Holton JM, Echols N, Alber T. Accessing protein conformational ensembles by room-temperature X-ray crystallography. *Proceedings of the National Academy of Sciences*. 2011. PMCID: PMC3182744.
    b. Fischer M, Shoichet BK, **Fraser JS**[#]. One Crystal, Two Temperatures: Cryocooling Penalties Alter Ligand Binding to Transient Protein Sites. *Chembiochem*. 2015. PMCID: PMC4539595.
    c. Thomaston JL, Alfonso-Prieto M, Woldeyes RA**, Fraser JS**, Klein ML, Fiorin G, DeGrado WF. High-resolution structures of the M2 channel from influenza A virus reveal dynamic

pathways for proton stabilization and transduction. *Proceedings of the National Academy of Sciences*. 2015. PMCID: PMC4655559.

d. Keedy DA*, Hill ZB*, Biel JT, Kang E, Rettenmaier TJ, Brandao-Neto J, Pearce NM, von Delft F, Wells JA, **Fraser JS**[#]. New routes for PTP1B allosteric inhibition by multitemperature crystallography, fragment screening and covalent tethering. Preprint on BioRxiv. 2017. http://dx.doi.org/10.1101/218966

3. Developing new X-ray diffuse scattering and X-FEL experiments to probe correlated motions in proteins**.** A major limitation of most biophysical techniques is the inability to directly reveal correlations in motions between distinct regions of macromolecules. Diffuse scattering has the potential to reveal these motions; however, we currently lack the ability to collect, integrate, and refine diffuse scattering data. We are tackling each of these problems directly with collaborators: Michael Wall, Nicholas Sauter, Tom Terwilliger, and Paul Adams. Our long-term goal is to increase the information content of every X-ray diffraction experiment to reveal atomic level coupling at high resolution and improved models of grouped flexibility at low resolution. We are also taking advantage of the new capabilities of next-generation X-ray free electron laser (X-FEL) light sources to perform radiation damage-free imaging of proteins. Our long term goal is to watch how protein conformational ensembles respond when perturbed by rapid temperature jumps using the X-FEL.
    a. Van Benschoten AH, Liu L, Gonzalez A, Brewster AS, Sauter NK, **Fraser JS**[#], Wall ME. Measuring and modeling diffuse scattering in protein X-ray crystallography. *Proceedings of the National Academy of Sciences*. 2016. PMCID: PMC4839442.
    b. Wall ME, Van Benschoten AH, Sauter NK, Adams PD, **Fraser JS**, Terwilliger TC. Conformational dynamics of a crystalline protein from microsecond-scale molecular dynamics simulations and diffuse X-ray scattering. *Proceedings of the National Academy of Sciences*. 2014. PMCID: PMC4273327.
    c. Van Benschoten AH, Afonine PV, Terwilliger TC, Wall ME, Jackson CJ, Sauter NK, Adams PD, Urzhumtsev A, **Fraser JS**[#]. Predicting X-ray Diffuse Scattering from Translation Libration Screw Structural Ensembles. *Acta Crystallographica D*. 2015.
    d. Thomaston JL, Woldeyes RA, Nakane T, Yamashita A, Tanaka T, Koiwai K, Brewster AS, Barad BA, Chen Y, Lemmin T, Uervirojnangkoorn M, Arima T, Kobayashi J, Masuda T, Suzuki M, Sugahara M, Sauter NK, Tanaka R, Nureki O, Tono K, Joti Y, Nango E, Iwata S, Yumoto F, **Fraser JS**, DeGrado WF. XFEL structures of the influenza M2 proton channel: Room temperature water networks and insights into proton conduction. *Proceedings of the National Academy of Sciences*. 2017. PMCID: in progress
4. Identifying unifying concepts between systems and structural biology**.** With Nevan Krogan, we have articulated the similarities in genetic epistasis and thermodynamic measurements and applied these insights to large-scale studies of point mutants and posttranslational modifications. This framework forms the basis for the UCSF graduate course that I direct, PUBS (Physical Underpinnings of Biological Systems), which uses deep sequencing to determine the context dependence of fitness effects of mutations. The class is taught through project-based learning where incoming students perform all library preparations, load samples directly on the MiSeq, and write all their own code to process sequencing data.
    a. Beltrao P, Albanèse V, Kenner LR, Swaney DL, Burlingame A, Villén J, Lim WA, **Fraser JS**, Frydman J, Krogan NJ. Systematic functional prioritization of protein posttranslational modifications. *Cell*. 2012. PMCID: PMC3404735
    b. Braberg H, Jin H, Moehle EA, Chan YA, Wang S, Shales M, Benschop JJ, Morris JH, Qiu C, Hu F, Tang LK, **Fraser JS**, Holstege FC, Hieter P, Guthrie C, Kaplan CD, Krogan NJ. From structure to systems: high-resolution, quantitative genetic analysis of RNA polymerase II. *Cell*. 2013. PMCID: PMC3932829

c. **Fraser JS**[#], Gross JD, Krogan NJ. From systems to structure: bridging networks and mechanism. *Mol Cell*. 2013. PMCID: PMC3558917

d. Mavor D, Barlow KA, Thompson S, Barad BA, Bonny AR, Cario CL, Gaskins G, Liu Z, Deming L, Axen SD, Caceres E, Chen W, Cuesta A, Gate R, Green EM, Hulce KR, Ji W, Kenner LR, Mensa B, Morinishi LS, Moss SM, Mravic M, Muir RK, Niekamp S, Nnadi CI, Palovcak E, Poss EM, Ross TD, Salcedo E, See S, Subramaniam M, Wong AW, Li J, Thorn KS, Conchúir SÓ, Roscoe BP, Chow ED, DeRisi JL, Kortemme T, Bolon DN, **Fraser JS**[#]. Determination of Ubiquitin Fitness Landscapes Under Different Chemical Stresses in a Classroom Setting. *eLife*. 2016. PMCID: PMC4862753

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.

   a. **Fraser JS**, Yu Z, Maxwell KL, Davidson AR. Ig-like domains on bacteriophages: a tale of promiscuity and deceit. *J Mol Biol.* 2006. PMID: 16631788.

   b. Williams BB, Van Benschoten AH, Cimermancic P, Donia MS, Zimmermann M, Taketani M, Ishihara A, Kashyap PC, **Fraser JS**, Fischbach MA. Discovery and characterization of gut microbiota decarboxylases that can produce the neurotransmitter tryptamine. *Cell Host Microbe*. 2014. PMCID: PMC4260654

   c. Kane JR, Stanley DJ, Hultquist JF, Johnson JR, Mietrach N, Binning JM, Jónsson SR, Barelier S, Newton BW, Johnson TL, Franks-Skiba KE, Li M, Brown WL, Gunnarsson HI, Adalbjornsdóttir A, **Fraser JS**, Harris RS, Andrésdóttir V, Gross JD, Krogan NJ. Lineage-Specific Viral Hijacking of Non-canonical E3 Ubiquitin Ligase Cofactors in the Evolution of Vif Anti-APOBEC3 Activity. *Cell Reports*. 2015. PMCID: PMC4613747.

   d. Dellus-Gur E, Elias M, Caselli E, Prati F, Salverda ML, de Visser JA, **Fraser JS**[#], Tawfik DS. Negative epistasis and evolvability in TEM-1 β-lactamase - The thin line between an enzyme's conformational freedom and disorder. *J Mol Biol*. 2015. PMCID: PMC4718737.

Complete List of 46 Publications in MyBibliography:

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

Research Support

Ongoing Research Support

00027331 Fraser (PI) 08/01/14 – 07/31/18
Pew Charitable Trusts Pew Fellows Program
Engineering Enzymes in Action
The major goal of this project is to use small molecules or mutations restore the motion and function of proteins involved in human diseases or to combat pathogens that are resistant to current antibiotics.

Packard Fellowship for Science and Engineering Fraser (PI) 11/01/14 – 10/31/19
The David and Lucile Packard Foundation
Mining the Dark Matter of Crystallography

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 Lattman (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.

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

Completed Research Support

R21 GM110580 Fraser (PI) 04/01/14-03/31/17
NIH/NIGMS
Model Comparison in Structural Biology
This project created new metrics for determining the precision and accuracy of protein conformations.

DP5 OD009180 Fraser (PI) 09/01/11 – 08/31/17
NIH/OSC
The Impact of Mutation on the Conformations and Recognition of Ubiquitin
This project used deep mutational scanning and biophysical characterization to study variants of Ubiquitin.

BIOGRAPHICAL SKETCH

NAME **Andrew N. Goldberg**	POSITION TITLE Research Investigator
eRA COMMONS USER NAME (credential, e.g., agency login) ANGOLDBERG	

EDUCATION/TRAINING

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

Positions

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

Honors

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

2003 Best Doctors in San Francisco, San Francisco Magazine
2005 Fellow, American Rhinologic Society
2005 Excellence in Direct Teaching Award
UCSF Haile T. Debas Academy of Medical Educators
2005 Honor Award, American Academy of Otolaryngology,
Head and Neck Surgery
2006 Research Award, 3rd prize, American Society of Ophthalmic
Plastic and Reconstructive Surgery
2007 Clinical Research Award, American Rhinological Society
2010 Francis A. Sooy, MD Resident's Award for Clinical Excellence
UCSF, Otolaryngology, Head and Neck Surgery

C. Contribution to Science

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

a. Roediger FC, Slusher NA, Allgaier S, Cox MJ, Pletcher SD, **Goldberg AN**, Lynch SV. Nucleic acid extration efficiency and baterial recovery from maxillary sinus mucosal samples obtained by brushing or biopsy. *Am J Rhinol Allergy* 2010 Jul-Aug; 24(4): 263-5.
b. Abreu NA, Nagalingam NA, Song Y, Roediger FC, Pletcher SD, **Goldberg AN**, Lynch SV. Sinus microbiome diversity depletion and Corynebacterium tuberculostearicum enrichment mediates rhinosinusitis. Sci Transl Med. 2012 Sep 12; 4(151):151ra124
c. Cope EK, **Goldberg AN,** Pletcher SD, Lynch SV. A chronic rhinosinusitis-derived isolate of Pseudomonas aeruginosa induces acute and pervasive effects on the murine upper airway microbiome and host immune response. *Int Forum Allergy Rhinol*. 2016 Sep 6.
d. Gelber JT, Cope EK, **Goldberg AN,** Pletcher SD. Evaluation of Malassezia and Common Fungal Pathogens in Subtypes of Chronic Rhinosinusitis. *Int Forum Allergy Rhinol*. 2016 Sep; 6(9): 950-5
e. Cope E, **Goldberg AN**, Pletcher SD, Lynch S. Compositionally and Functionally Distinct Sinus Microbiota in Chronic Rhinosinusitis have Immunological and Clinically Divergent Consequences. *Microbiome.* 2017 May 12; 5(1):53.

When at the University of Pennsylvania, I began a course of study to increase my knowledge and skills in clinical research and outcomes by becoming a fellow in the Clinical Epidemiology of Cancer through the Center for Clinical Epidemiology and Biostatistics and the National Cancer Institute. I continued this study with formal classroom study and earned a Master of Science in Clinical Epidemiology with my thesis being "A Chemosensory Questionnaire for Patients Treated for Cancer of the Head and Neck." This involved over 200 patients who had been treated for cancer of the head and neck investigating the chemosensory changes that occurred as a result of this disease and its treatment. I have used my advanced training in research methods to teach research methods and have used this training to mentor residents and junior faculty in their research. In a significant number of my publications, my role has been in study design, methodology, and analysis for research initiated by other investigators.

a. **Goldberg AN,** Shea JA, Deems DA, Doty RL. A ChemoSensory questionnaire for patients treated for cancer of the head and neck. *Laryngoscope*. 2005 Dec; 115(12): 2077-86.

Research Support

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

5R01 HL57843-04 Schwab (PI) 1997-2001
NIH/NHLBI
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**	POSITION TITLE Assistant Professor
eRA COMMONS USER NAME egordon1	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of California, Berkeley	B.A.	05/01	Molecular & Cell Biology
University of Southern California	M.D.	05/05	Medicine
University of California, San Diego	Board Cert. in Medicine 2009	07/05-06/07	Internal Medicine
University of California, San Francisco	Board Cert. Pulmonary 2010 Critical Care 2011	07/07-06/10	Pulmonary & Critical Care

Positions

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

Honors

Ruth L. Kirschstein National Research Service Award, 01/11.
American Medical Association Student Achievement Award – first ranked student, Class of 2005 USC SOM (05/05).
American Medical Women's Association Janet M. Glasgow Memorial Award – first ranked female student, Class of 2005 USC SOM (05/05).
Summa cum Laude, Keck School of Medicine, USC (05/2005).

Merck Manual Award – awarded to the four highest ranking students in the basic sciences at USC SOM (05/05).
Alpha Omega Alpha, Gamma Chapter, Keck School of Medicine, USC – elected as a junior (05/04).
Dean's Scholar – awarded to top 10% of students each year of medical school (May 2002, 2003, 2004, 2005).
Recipient of merit-based full tuition scholarship at Keck School of Medicine, USC (05/01-05/05).
Grace Fimognari Memorial Award – awarded to the highest achieving graduate in Molecular & Cell Biology, Biochemistry, University of California, Berkeley (05/01).
Phi Beta Kappa, University of California, Berkeley (05/01).
Graduate with Honors, University of California, Berkeley – awarded for undergraduate research thesis (05/01).

Professional Societies
American Thoracic Society.

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

Contributions to Science

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

   a. **Gordon ED**, Simpson LJ, Rios CL, Ringel L, Lachowicz-Scroggins ME, Peters MC, Wesolowska-Andersen A, Gonzalez JR, MacLeod HJ, Christian LS, Yuan S, Barry

L, Woodruff PG, Ansel KM, Nocka K, Seibold MA, Fahy JV. Alternative splicing of IL-33 and type 2 inflammation in asthma. *PNAS*, 2016; 113(31):8765-70. PMCID: PMC4978244

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

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

a. **Gordon ED**, Palandra J, Wesolowska-Andersen A, Ringel L, Rios CL, Lachowicz-Scroggins ME, Sharp LZ, Everman JL, MacLeod HJ, Lee JW, Mason RJ, Matthay MA, Sheldon RT, Peters MC, Nocka KH, Fahy JV, Seibold MA. *IL1RL1* Asthma Risk Variants Regulate Airway Type 2 Inflammation. *JCI Insight*. 2016;1(14):287871. PMCID: PMC5033813

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

3. Asthma is a heterogeneous disease, which is variably heritable within families. While genome wide association studies have been successful in discovering common risk alleles for asthma, only a small portion of the heritability is accounted for by these variants. This has been termed “missing heritability,” and many possible explanations have been proposed to account for it including rare variants, structural variants such as copy number variation, and genetic risk due to interaction effects. Interaction effects encompass both gene-gene

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

a. **Gordon ED**, Palandra J, Wesolowska-Andersen A, Ringel L, Rios CL, Lachowicz-Scroggins ME, Sharp LZ, Everman JL, MacLeod HJ, Lee JW, Mason RJ, Matthay MA, Sheldon RT, Peters MC, Nocka KH, Fahy JV, Seibold MA. *IL1RL1* Asthma Risk Variants Regulate Airway Type 2 Inflammation. *JCI Insight*. 2016;1(14):287871. PMCID: PMC5033813

b. **Gordon ED**, Simpson LJ, Rios CL, Ringel L, Lachowicz-Scroggins ME, Peters MC, Wesolowska-Andersen A, Gonzalez JR, MacLeod HJ, Christian LS, Yuan S, Barry L, Woodruff PG, Ansel KM, Nocka K, Seibold MA, Fahy JV. Alternative splicing of IL-33 and type 2 inflammation in asthma. *PNAS*, 2016; 113(31):8765-70. PMCID: PMC4978244

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

d. **Gordon ED,** Sidhu SS, Wang ZE, Woodruff PG, Yuan S, Solon MC, Conway SJ, Huang X, Locksley RM, Fahy JV. A protective role of periostin and TGF-β in IgE-mediated allergy and airway hyperresponsiveness. *Clinical and Experimental Allergy*, 2012. PMCID: PMC3271792

Research Support

Ongoing Research Support

R01AI136962	Gordon (PI)	01/15/2018-12/31/2022

NIH/NIAID
Understanding the Molecular Genetic Mechanisms of Asthma Risk Loci: IL33, IL1RL1, and GSDMB. The goal of this study is to explore novel genetic mechanisms that influence the development of type 2 inflammation, the most common disease pathology, in asthma.

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

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

Recently Completed Research Support

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 **Xiaozhu Huang, M.D.**	POSITION TITLE Associate Professor

EDUCATION

INSTITUTION AND LOCATION	DEGREE	YEAR	FIELD OF STUDY
Tongji Medical University, Wuhan, People's Republic of China	M.D.	1983	Medicine
Tongji Medical University, Wuhan, People's Republic of China	M.S.	1988	Pathology

Positions

6/83 to 7/84	Teaching Assistant, Dept. of Pathology, Tongji Medical University, China
8/84 to 8/85	Pathology Residence, The First Attached Hospital, Tongji Medical University, China
9/88 to 1/92	Research Assistant, Dept. of Pathology, Tongji Medical University, China
1/92 to 12/95	Postdoctoral Fellow, Dept. of Medicine, Lung Biology Center University of California, San Francisco
1/96 to 6/97	Postgraduate Researcher, Dept. of Medicine, Lung Biology Center University of California, San Francisco
7/97 to 11/99	Assistant Research Molecular Biologist, Dept. of Medicine, Lung Biology Center University of California, San Francisco
12/99 to 6/05	Assistant Professor, Dept. of Medicine, Lung Biology Center University of California, San Francisco
07/2005 to 12/17	Associate Professor, Dept. of Medicine, Lung Biology Center University of California, San Francisco

Honors

1989	*"Outstanding Teacher"* honor, Department of Pathology, Tongji Medical University
1/1992 to 12/1993	Cheng Research Scholar Award,

Selected peer-reviewed publications

1. **Huang XZ**, Wu JF, Cass D, Erle DJ, Corry D, Young SG, Farese RV, Jr., Sheppard D. Inactivation of the integrin 6 subunit gene reveals a role of epithelial integrins in regulating inflammation in the lungs and skin. *J. Cell Biol.* 1996; 133:921-928.
2. **Huang XZ**, Wu JF, Zhu W, Pytela R, Sheppard D. Expression of the human integrin b6 subunit in alveolar type II cells and bronchiolar epithelial cells reverses lung inflammation in b6 knockout mice. *Am. J. Respir. Cell Mol. Biol*. 1998; 19:636-642.
3. **Huang XZ**, Wu JF, Spong S, Sheppard D. The integrin avb6 is critical for keratinocyte migration on both its known ligand, fibronectin, and on vitronectin. *J. Cell Sci*. 1998; 111:2189-2195.
4. JS Munger, **XZ Huang**, H Kawakatsu, MJD Griffiths, SL Dalton, JF Wu, JF Pittet, N Kaminiski, C Garat, MA Matthay, DB Rifkin, D Sheppard. The integrin avb6 binds and activates latent TGFb1: a mechanism for regulating pulmonary inflammation and fibrosis. *Cell* 1999; 96:319-328.
5. Milner R, **Huang XZ**, Wu J, Nishimura S, Pytela R, Sheppard D, ffrench-Constant C. Distinct roles for astrocyte avb5 and avb8 integrins in adhesion and migration. *J. Cell Sci*. 1999; 112: 4271-4279.
6. **Huang XZ**, Griffiths M, Wu JF, Farese RV, Sheppard D. Normal development, wound healing, and adenovirus susceptibility in b5-deficient mice. *Mol. Cell Biol*. 2000; 20:755-759.
7. Kaminski N, Allard J, Pittet J-F, Zuo F, Griffiths MJD, Morris D, **Huang XZ**, Sheppard D, Heller RA. Global analysis of gene expression in pulmonary fibrosis reveals distinct programs regulating lung inflammation and remodeling. *Proc. Nat. Acad. Sci.* 2000; 97:1778-1783.
8. **Huang XZ**, Wu JF, Ferrando R, Wang YL, Lee JH, Farese RV, Sheppard D. Fatal Bilateral Chylothorax in Mice Lacking the Integrin a9b1. *Mol. Cell Biol*. 2000; 20:5208-5215.
9. Pittet JF, Griffiths MJ, Geiser T, Kaminski N, Dalton SL, **Huang XZ**, Brown LA, Gotwals PJ, Koteliansky VE, Matthay MA, Sheppard D. TGF-beta is a critical mediator of acute lung injury. *J Clin Invest.* 2001, 107:1537-44.
10. Reynolds LE, Wyder L, Lively JC, Taverna D, Robinson SD, **Huang XZ**, Sheppard D, Hynes RO, Hodivala-Dilke KM. Enhanced pathological angiogenesis in mice lacking beta3 integrin or beta3 and beta5 integrins. *Nat Med*. 2002, 8:27-34.
11. Eliceiri BP, Puente XS, Hood JD, Stupack DG, Schlaepfer DD, **Huang XZ**, Sheppard D, Cheresh DA. Src-mediated coupling of focal adhesion kinase to integrin alpha(v)beta5 in vascular endothelial growth factor signaling. *J Cell Biol*. 2002, 157:149-60.
12. Kuperman DA, **Huang XZ**, Koth LL, Chang GH, Dolganov GM, Zhu Z, Elias JA, Sheppard D, Erle DJ. Direct effects of interleukin-13 on epithelial cells cause airway hyperreactivity and mucus overproduction in asthma. *Nat Med*. 2002, 8:885-9.
13. Knight PA, Wright SH, Brown JK, **Huang XZ**, Sheppard D, Miller HR. Enteric expression of the integrin alpha(v)beta (6) is essential for nematode-induced mucosal mast cell hyperplasia and expression of the granule chymase, mouse mast cell protease-1. *Am J Pathol*. 2002, 161:771-9.
14. Morris DG, **Huang XZ**, Kaminski N, Wang Y, Shapiro SD, Dolganov G, Glick A, Sheppard D. Loss of integrin-mediated TGF-b activation causes Mmp12-dependent pulmonary emphysema. *Nature* 2003, 422:169-73.
15. Nandrot EF, Kim Y, Brodie SE, **Huang XZ,** Sheppard D, Finnemann SC. Loss of

synchronized RPE phagocytosis and age-related blindness in mice lacking avb5 integrin. *J Exp Med*. 2004, 200:1539-45.
16. Lane NE, Yao W, Nakamura MC, Humphrey MB, Kimmel D, **Huang XZ**, Sheppard, Ross FP, Teitelbaum SL. Mice lacking the integrin beta5 subunit have accelerated osteoclast maturation and increased activity in the estrogen-deficient state. *J Bone Miner Res*. 2005, 20:58-66.
17. Kuperman DA, **Huang XZ**, Nguyenvu L, Hölscher C, Brombacher F, Erle DJ. IL-4 receptor signaling in Clara cells is required for allergen-induced mucus production. *J. Immunol*. 2005, 175:3746-3752.
18. Atabai K, Fernandez R, **Huang X**, Ueki I, Kline A, Li Y, Sadatmansoori S, Smith-Steinhart C, Zhu W, Pytela R, Werb Z, Sheppard D. Mfge8 Is Critical for Mammary Gland Remodeling during Involution. *Mol Biol Cell.* 2005, 16:5528-37.
19. Voehringer D, Reese TA, **Huang X**, Shinkai K, Locksley RM. Type 2 immunity is controlled by IL-4/IL-13 expression in hematopoietic non-eosinophil cells of the innate immune system. *J Exp Med*. 2006, 203:1435-46.
20. Wang B, **Huang X***, Wolters PJ, Sun J, Kitamoto S, Yang M, Riese R, Leng L, Chapman H A., Finn P W., David J R., Bucala R, and Shi GP. Deficiency of Macrophage Migration Inhibitory Factor Impairs Murine Airway Allergic Responses. *J Immunol* 2006, 177:5779-5784 (* Co-first author)
21. Chen C, **Huang X**, Sheppard D. ADAM33 is not essential for growth and development and does not modulate allergic asthma in mice. *Mol Cell Biol*. 2006, 26:6950-6.
22. Chen C, **Huang X,** Atakilit A, Zhu QS, Corey SJ, Sheppard D. The Integrin alpha9beta1 Contributes to Granulopoiesis by Enhancing Granulocyte Colony-Stimulating Factor Receptor Signaling. *Immunity*. 2006, 25:895-906.
23. Su G, Hodnett M, Wu N, Atakilit A, Kosinski C, Godzich M, **Huang XZ**, Kim JK, Frank JA, Matthay MA, Sheppard D, Pittet JF. Integrin {alpha} v {beta} 5 Regulates Lung Vascular Permeability and Pulmonary Endothelial Barrier Function. *Am J Respir Cell Mol Biol*. 2007, 36:377-86.
24. Travis MA, Reizis B, Melton AC Masteller E, Tang Q, Proctor J, Wang Y, Bernstein X, **Huang X**, Riechardt L, Bluestone J, Sheppard D. Loss of integrin avb8 on dendritic cells causes autoimmunity and colitis in mice. *Nature* 2007; 449:361-365.
25. Horan GS, Wood S, Ona V, Li DJ, Lukashev ME, Weinreb PH, Simon KJ, Hahm K, Allaire NE, Rinaldi NJ, Goyal J, Feghali-Bostwick CA, Matteson EL, O'hara C, Lafyatis R, Davis GS, **Huang X**, Sheppard D, Violette SM. Partial Inhibition of Integrin {alpha} v {beta} 6 Prevents Pulmonary Fibrosis Without Exacerbating Inflammation. *Am J Respir Crit Care Med* 2008; 177:56-65.
26. Nakagami Y, Favoreto S Jr, Zhen G, Park SW, Nguyenvu LT, Kuperman DA, Dolganov GM, **Huang X**, Boushey HA, Avila PC, Erle DJ. The epithelial anion transporter pendrin is induced by allergy and rhinovirus infection, regulates airway surface liquid, and increases airway reactivity and inflammation in an asthma model. *J Immunol.* 2008 Aug 1; 181(3): 2203-10.
27. Song Y, Pittet JF, **Huang X**, He H, Lynch SV, Violette SM, Weinreb PH, Horan GS, Carmago A, Sawa Y, Bernstein XL, Wiener-Kronish JP. Role of integrin alphav beta6 in acute lung injury induced by Pseudomonas aeruginosa. *Infect Immun*. 2008 Jun; 76(6): 2325-32
28. Caceres AI, Brackmann M, Elia MD, Bessac BF, del Camino D, D'Amours M, Witek JS, Fanger CM, Chong JA, Hayward NJ, Homer RJ, Cohn L, **Huang X**, Moran MM, Jordt SE. A sensory neuronal ion channel essential for airway inflammation and hyperreactivity in asthma.*Proc Natl Acad Sci U S A.* 2009 Jun 2;106(22):9099-104.
29. Park SW, Verhaeghe C, Nguyenvu LT, Barbeau R, Eisley CJ, Nakagami Y,

Huang X, Woodruff PG, Fahy JV, Erle DJ. Distinct Roles of FOXA2 and FOXA3 in Allergic Airway Disease and Asthma. *Am J Respir Crit Care Med*. 2009 Jul 23.
30. Huang F, Rock JR, Harfe BD, Cheng T, **Huang X**, Jan YN, Jan LY. Studies on expression and function of the TMEM16A calcium-activated chloride channel. *Proc Natl Acad Sci U S A*. 2009 Dec 15; 106(50): 21413-8
31. Frank Kirstein, Horsnell G William, Douglas A Kuperman, **Xiaozhu Huang**, David J Erle, Andreas L Lopata, Frank Brombacher, Expression of IL-4 Receptor alpha on smooth muscle cells is not necessary for development of experimental allergic asthma. *J Allergy Clin Immunol*. 2010 Aug; 126(2): 347-354
32. Li, S., Chen, Y., Zhang, S. , More, S.S. , **Huang, X**. , Giacomini, K.M. Role of Organic Cation Transporter 1, OCT1 in the Pharmacokinetics and Toxicity of cis Diammine(pyridine)chloroplatinum(II) and Oxaliplatin in Mice. *Pharm Res*. 2010 Nov 23
33. Yu Hua Chow, Xiao Dong Zhu, Li Liu, Barbara Schwartz, **Xiaozhu Huang**, John Harlan, Lynn M Schnapp. Role of Cdk4 in lymphocyte function and allergen response. *Cell Cycle*. 2010 Dec 15; 9(24):4922-30
34. Masuno K, Haldar SM, Jeyaraj D, Mailloux C, **Huang X**, Panettieri Jr RA, Jain MK, Gerber AN. Expression Profiling Identifies Klf15 as a Glucocorticoid Target that Regulates Airway Hyperresponsiveness. *Am J Respir Cell Mol Biol*. 2011 Jan 21
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36. Vijayanand P, Seumois G, Simpson LJ, Abdul-Wajid S, Baumjohann D, Panduro M, **Huang X**, Interlandi J, Djuretic IM, Brown DR, Sharpe AH, Rao A, Ansel KM. Interleukin-4 production by follicular helper T cells requires the conserved Il4 enhancer hypersensitivity site V. *Immunity*. 2012 Feb 24; 36(2): 175-87
37. Thornton E, Looney M, Sheppard D, Locksley R, **Huang X**, Krummel M. Dynamics of antigen capture and presentation revealed by two-photon live imaging in the lung. *J Exp Med.* 2012 Jun 4; 209(6): 1183-99
38. Schroeder BW, Verhaeghe C, Park SW, Nguyenvu LT, **Huang X**, Zhen G, Erle DJ. AGR2 is Induced in Asthma and Promotes Allergen-Induced Mucin Overproduction. *Am J Respir Cell Mol Biol*. 2012 Aug; 47(2): 178-85
39. Bhattacharya M, Su G, Su X, Oses-Prieto JA, Li JT, **Huang X**, Hernandez H, Atakilit A, Burlingame AL, Matthay MA, Sheppard D. IQGAP1 is necessary for pulmonary vascular barrier protection in murine acute lung injury and pneumonia. *Am J Physiol Lung Cell Mol Physiol*. 2012 Jul 1; 303(1): L12-9
40. Chun Chen, Makoto Kudo, Florentine Rutaganira, Hiromi Takano, Candace Lee, Amha Atakilit, Toshimitsu Uede, Paul Wolters, Stephen Liggett, Kevan M. Shokat, **Xiaozhu Huang** and Dean Sheppard. Integrin α9β1 in airway smooth muscle regulates a novel brake on exaggerated murine and human airway narrowing. *JCI* 2012 Aug 1; 122(8): 2916-27
41. Huang F, Zhang H, Wu M, Yang H, Kudo M, Peters CJ, Woodruff PG, Solberg OD, Donne ML, **Huang X**, Sheppard, Fahy JV, Wolters PJ, Hogan BL, Finkbeiner WE, Li M, Jan YN, Jan LY, Rock JR. Calcium-activated chloride channel TMEM16A modulates mucin secretion and airway smooth muscle contraction. *Proc Natl Acad Sci USA*. 2012 Oct 2; 109(40): 16354-9.
42. Julia Freimuth, Frederic F. Clermont, Xiaozhu **Huang**, Angela De Sapio, Taku Tokuyasu, Dean Sheppard, Rosemary J. Akhurst. Epistatic interactions between Tgfb1 and genetic loci, Tgfbm2 and Tgfbm3, determine susceptibility to an asthmatic stimulus. *Proc Natl Acad Sci U S A*. 2012 Oct 30; 109(44): 18042-7

43. Kudo M, Khalifeh Soltani SM, Sakuma SA, McKleroy W, Lee TH, Woodruff PG, Lee JW, Huang K, Chen C, Arjomandi M, **Huang X**, Atabai K. Mfge8 suppresses airway hyperresponsiveness in asthma by regulating smooth muscle contraction. *Proc Natl Acad Sci USA*. 2013 Jan 8; 110(2): 660
44. Simpson LJ, S Patel, NR Bhakta, DF Choy, HD Brightbill, X Ren, Y Wang, HH Pua, D Baumjohann, MM Montoya, M Panduro, KA Remedios, **X Huang**, JV Fahy, JR Arron, PG Woodruff, KM Ansel. 2014. A microRNA upregulated in asthma airway T cells promotes Th2 cytokine production. *Nature Immunol* 15:1162-70.

*Equal contribution

BIOGRAPHICAL SKETCH

NAME **Matthew Frederick Krummel, Ph.D**	POSITION TITLE Professor
eRA COMMONS USER NAME Krummel	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of Illinois at Champaign-Urbana	B.S.	05/1989	Biology and Chemistry
University of California at Berkeley	Ph.D.	05/1995	Immunology
University College, London England		06/1988	Dept of Chemistry

Positions

2015-2016	Visiting Sabbatical Scholar, Mediterranean Institute for Advanced Studies, Aix-Marseille University, France
2012-Present	Professor, Department of Pathology, University of California at San Francisco
2008-2009	Visiting Sabbatical Scholar, Cancer, Institut Curie. Paris, France
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
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 Cells. *Cancer Cell* 21, March 20; 402-417. PMC3311997.

b. Broz M, Binnewies M, Boldajipour B, Nelson A, Pollock J, Erle DJ, Barczak A, Rosenblum M, Daud A, Barber DL, Amigorena S, van't Veer LJ, Sperling A, Wolf DM, **Krummel MF**: Dissecting the Tumor Myeloid Compartment Reveals A Rare Antigen Presenting Critical for T cell Immunity. *Cancer Cell*, 2014 26(5):638-52. PMC4254577

c.) Headley, M.R., Bins A., Nip A., Roberts E.W., Looney M., Gerard, A., **Krummel,M.F**. Visualization of Immediate Immune Responses to Pioneer Metastatic Cells in the Lung. *Nature*. March 24, 2016.

d.) Roberts, E.W., Broz, M.L., Binnewies, M., Headley, M.B., Nelson, A.E., Wolf, D.M., Kaisho, T., Bogunovic, D., Bhardwaj, N., and **Krummel, M.F**. 2016. Critical Role for CD103+/CD141+ Dendritic Cells bearing CCR7 for Tumor Antigen Trafficking and Priming of T cell Immunity in Melanoma. *Cancer Cell*. PMC in progress.

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

and recently adapted this to track mast cell probing of vessels in the trachea. We've also applied this method to understand nematode interactions with the immune system in the lung.

a.) Thornton, E.E., Looney M.R., Bose, O., Sen, D., Sheppard, D., Locksley, R., Huang, X., **Krummel, M.F.** 2012. Spatiotemporally Separated Antigen Uptake by Alveolar Dendritic Cells and Airway Presentation to T Cells in the Lung. *J Exp Med.*, 209(6): 1183-99. PMC3371730

b.) Looney, M.R., Thornton, E.E., Sen, D., Lamm, W.J., Glenny, R.W., **Krummel, M.F**. 2010. Stabilized imaging of immune surveillance in the mouse lung. *Nat Methods*. 8(1): 91-6. PMC3076005

c.) Patnode,M.L., Bando, J.K., **Krummel, M.F**., Locksley, R.M., Rosen, S.D. Leukotriene B4 Amplifies Eosinophil Accumulation in Response to Nematodes. *J. Exp.Med.* 2014 Jun 30; 211(7): 1281-8. PMC4076593

d.) Nussbaum, J.C., Van Dyken, S.J., von Moltke, J., Cheng, L.E., Mohapatra, A., Molofsky, A.B., Thornton, E.E., **Krummel, M.F.,** Chawla, A., Liang, H.E., Locksley, R.M. 2013. Type 2 innate lymphoid cells control eosinophil homeostasis. *Nature*. 2013 Oct 10; 502(7470): 245-248. PMC3795960

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

a) Cai, E., Marchuk, K., Beemiller, P., Beppler, C., Rubashkin, M.G., Weaver, V.M., Chen,B-C., Betzig,E., Bartumeus, F., **Krummel, M.F**.,Visualizing Dynamic Microvillar Search and Stabilization during Ligand Detection by T cells. *Science* 2017. In press.

b) Friedman, R.S., Beemiller, P., Sorensen, C.M., Jacobelli, J., **Krummel, M.F**. 2010 Nov 1. Real-time analysis of T cell receptors in naive cells in vitro and in vivo reveals flexibility in synapse and signaling dynamics. J Exp Med. 11(10): 953-61. PMC2989766.

c) Beemiller, P., Jacobelli, J., **Krummel, M.F**., 2012. Integration of Signaling Microclusters Movement with Cellular Motility in Immunological Synapses. *Nat Immunol.* Jul 1. doi: 10.1038/ni.2364. PMC3902181.

d) Gérard, A., Khan, O., Beemiller, P., Oswald, E., Hu, J., Matloubian, M., **Krummel, M.F**. 2013. Secondary T cell-T cell synaptic interactions drive the differentiation of protective CD8+ T cells. *Nat Immunol*. 2013 14(4): 356-63. PMC3962671

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

a) Jacobelli, J. Chmura, S.A., Buxton,D.B., Davis , M.M. and **Krummel, M. F**. 2004. Class II Myosin Heavy Chain 2A/MyH9 Is Involved in the T Cell Stop Signal but is not Required for Synapse Formation. *Nature Immunology*.5 (5): 531-8.

b) Jacobelli, J., Friedman, R.S., Conti, M.A., Lennon-Dumenil, A. -M., Piel, M., Sorensen, C.M., Adelstein, R.S., **Krummel, M.F**. 2010. Confinement-optimized three-dimensional T

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

c) Gilden, J.K., Peck, S., Chen, Y.C.M., **Krummel, M.F**. 2012. The septin cytoskeleton facilitates membrane retraction during motility and blebbing. *J Cell Biol.* Jan 9; 196(1): 103-14. PMC3255977

d) Gérard, A., Patino-Lopez, G., Beemiller, P., Nambiar, R., Ben-Aissa, K., Liu, Y., Totah, F.J., Tyska, M.J., Shaw, S., **Krummel, M.F.** Detection of Rare Antigen-Presenting Cells through T Cell-Intrinsic Meandering Motility, Mediated by Myo1g. *Cell.* 2014 Jul 31; 158(3): 492-505 PMC4119593

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

a) **Krummel, M.F**. and Allison, J.P. 1995. CD28 and CTLA-4 deliver opposing signals, which regulate the response of T cells to stimulation. *Journal of Experimental Medicine.* 182, 459-465.

b) Allison, J.P. and **Krummel, M.F**. 1995. The yin and yang of T cell costimulation. *Science.* 270,932-933.

c) Leach, D.R., **Krummel, M.F**. and Allison, J.P. 1996. Enhancement of antitumor immunity by CTLA-4 blockade. *Science.* 271, 1734-1736.

d) **Krummel, M.F.** and Allison, J.P. 1996. CTLA-4 engagement inhibits IL-2 accumulation and cell cycle progression upon activation of resting T cells. *Journal of Experimental Medicine.* 183, 2533-2540. PMC2192613.

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

Research support

Ongoing Research Support

R01 AI52116 Krummel (PI) 01/15/08-12/31/17
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

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)

1U01HL111054-01 (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

2U19A1077439-06 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

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

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

R21 CA196468 01 Krummel (PI) 09/01/15-08/31/18
NCI LIVING TUMOR BIOPSIES TO INTERROGATE IMMUNE FUNCTION AND RESPONSE TO THERAPY
Here we seek to develop methodology to track immune populations in living biopsies.
Role: PI

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

U01CA217864 Balmain, Krummel, Weiss (PI) 08/17/17-07/31/22
NIH/NCI Integrating targeted and immunotherapy to treat genetically heterogeneous cancers
The goal of this project is to perform crispr screens in monocytes and T cells to identify genes associated with tumor entry and function in two distinct tumor types. Will use genetic or pharmacological perturbation of newly generated candidate genes involved in metabolic stress and ros-induced DNA damage to increase mutation load and antigen abundance in a tumor-specific manner, leading to improved responses to IMT. Will also exploit gene expression networks to identify druggable targets and pathways that augment immune responses. Role: co PI

BIOGRAPHICAL SKETCH

NAME **Richard M. Locksley, M.D.**	POSITION TITLE Sandler Distinguished Professor, Department of Medicine, University of California, San Francisco
eRA COMMONS USER NAME Locksley	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Harvard College, Cambridge, MA	B.A.	1970	Biochemistry
University of Rochester, Rochester, NY	M.D.	1976	Medicine
University of California, San Francisco, CA		1976-80	Resident, Chief Resident
University of Washington, Seattle, WA		1980-83	Infectious Diseases Fellow

Positions and Honors

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

Editorial Boards

1999-03	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, 2016

Contributions to Science

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

a. Locksley RM, FP Heinzel, MD Sadick, BJ Holaday, KD Gardner. 1987. Murine cutaneous leishmaniasis. Susceptibility correlates with differential expansion of helper T-cell subsets. *Ann Inst Pasteur/Immunol* 138:744-49.
b. Heinzel FP, MD Sadick, BJ Holaday, RL Coffman, RM Locksley. 1989. Reciprocal expression of gamma-interferon or interleukin-4 during the resolution or progression of murine leishmaniasis. Evidence for expansion of distinct helper T-cell subsets. *J Exp Med* 169:59-72.
c. Sadick MD, FP Heinzel, BJ Holaday, RT Pu, RS Dawkins, RM Locksley. 1990. Cure of murine leishmaniasis with anti-IL-4 monoclonal antibody. Evidence for a T cell-dependent, IFN-g- independent mechanism. *J Exp Med* 171:115-27.
d. Reiner SL, ZE Wang, F Hatam, P Scott, RM Locksley. 1993. Th1 and Th2 cell antigen receptors in experimental leishmaniasis. *Science* 259:1457-60.

2. Having established critical roles for cytokines in mediating the business of immunity, my laboratory turned to studies of cytokine expression, reasoning that such study might reveal key pathways by which cytokine expression is turned on, off and regulated. We collaborated with the Rubin laboratory at UC Berkeley to further understanding of what are now called CNSs, or conserved noncoding sequences, which could be identified by sequence comparisons among many species, and which are now known to identify major enhancer, promoter and boundary elements that regulate cell-specific gene expression. These studies

have been extrapolated to understanding major organizational aspects of genetic expression in a variety of cell types, as well as in cancer. I was the PI for all of these studies except for the collaboration with the Rubin laboratory, where I coordinated the immunologic aspects of that study to complement the genetics expertise of the Rubin lab.

a. Bix M, **RM Locksley.** 1998. Independent and epigenetic regulation of the interleukin-4 alleles in CD4+ T cells. *Science* 281:1352-54.
b. Loots GG, **RM Locksley,** CM Blankespoor, Z-E Wang, W Miller, EM Rubin, KA Frazer. 2000. Identification of a coordinate regulator of interleukins 4, 13 and 5 by cross-species sequence comparisons. *Science* 288:136-40.
c. Grogan JL, M Mohrs, B Harmon, DA Lacy, JW Sedat, **RM Locksley.** 2001. Early transcriptions and silencing of cytokine genes underlie polarization of T helper cell subsets. *Immunity* 14:205-15.
d. Mohrs M, CM Blankespoor, ZE Wang, GG Loots, V Afzal, H Hadeiba, K Shinkai, EM Rubin, **RM Locksley.** 2001. Deletion of a coordinate regulator of type 2-cytokine expression in mice. *Nature Immunol* 2:842-47.

3. Although the regulation of cytokine expression was clearly a key determinant of the immune response, the field lacked tools to study cytokine expression in situ that would push research into the complexities of multiple cell types, multiple tissues and multiple cytokines. To this end, we developed cytokine 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; the ability to screen complex challenges, such as chitin, to reveal coordinated cytokine responses in multiple cell types; and the identification of innate lymphoid cells that produce these cytokines (see area 4, below). Jackson Laboratories distributes Mouse strains generated in my laboratory to the scientific community for use freely, where they have been utilized in many publications. The strategy we introduced is now widely used in the scientific community. I was the PI for all of these contributions.

a. Mohrs M, K Shinkai, K Mohrs, **RM Locksley**. 2001. Analysis of type 2 immunity in vivo with a biscistronic IL-4 reporter. *Immunity* 15:303-11.
b. Reese TA, H-E Liang, AM Tager, AD Luster, N van Rooijen, D Voehringer, **RM Locksley**. 2007. Chitin induces accumulation in tissue of innate immune cells associated with allergy. *Nature* 447:92-96. PMCID: PMC2527589
c. Reinhardt RL, H-E Liang, **RM Locksley**. 2009. Cytokine-secreting follicular T cells shape the antibody repertoire. *Nature Immunol* 10:385-93. PMCID: PMC2714053
d. Liang H-E, RL Reinhardt, JK Bando, BM Sullivan, I-C Ho, **RM Locksley**. 2011. Divergent expression patterns of IL-4 and IL-13 define unique functions in allergic immunity. *Nat Immunol* 13:58-66. PMCID: PMC3242938

4. The ability to identify cell types that make various cytokines directly in vivo allowed us to identify innate lymphoid group 2, or ILC2, cells as important innate lymphocytes that are located in tissues,

where they contribute to early cytokine responses. Mine was 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 during chitin challenge. My laboratory has recently investigated the development of these cells during embryogenesis, and identified a fetal liver precursor of the ILC lineages. This continues to be a rapidly advancing field with clear implications for the understanding of tissue homeostasis and allergic immunopathology, including in human disease. I was the PI for all of the primary studies and took part in the nomenclature meetings chaired by Dr. Spits for the scientific community.

a. Voehringer D, TA Reese, X Huang, K Shinkai, **RM Locksley**. 2006. Type 2 immunity is controlled by IL-4/IL-13 expression in hematopoietic non-eosinophil cells of the innate immune system. *J Exp Med* 203:1435-46. PMCID: PMC2118302
b. Price AE, H-E Liang, BM Sullivan, RL Reinhardt, CJ Eisley, DJ Erle, **RM Locksley**. 2010. Systemically dispersed innate IL-13-expressing cells in type 2 immunity. *Proc Natl Acad Sci USA* 107:11489-94. PMCID: PMC2895098
c. Van Dyken SJ, A Mohapatra, JC Nussbaum, AB Molofsky, EE Thornton, SF Ziegler, ANJ McKenzie, MF Krummel, H-E Liang, **RM Locksley**. 2014. Chitin activates parallel immune modules that direct distinct inflammatory responses via innate lymphoid type 2 (ILC2) and gd T cells. *Immunity* 40:414-24. PMCID: PMC4019510
d. Bando JK, H-E Liang, **RM Locksley**. 2015. Identification and distribution of developing innate lymphoid cells in the fetal mouse intestine. *Nat Immunol* 16:153-60. PMCID: PMC4297560

5. The ability to recognize cells that coordinately expressed the type 2 cytokines in situ revealed an organizational paradigm by which the laboratory could begin to address how this modular group of cytokines and related cell types were expressed under homeostatic conditions. Based on observations that alternatively activated macrophages (AAMs) were present in lean fat, we reasoned that the cytokines involved in maintaining these cells, such as IL-4 and IL-13, would be expressed in lean adipose. Using our reporter strains and other strategies, we made a number of fundamental contributions, including uncovering the association and relationships between eosinophils and AAMs in healthy adipose; revealing the role for ILC2s in controlling eosinophilopoiesis and eosinophil tissue entry; demonstrating that intestinal ILC2s are responsive to nutrient intake, in part via response to the neuropeptide VIP; showing residence of ILC2s in healthy lean adipose; using cell-specific genetic deletion to demonstrate the key role of cytokines from these cells to sustain the architecture of healthy adipose; and revealing unsuspected interactions between ILC2s and tuft cells, rare mucosal epithelial cells of unclear biology until our discovery of these cells as the producers of IL-25. Our studies helped to propel the field of immunometabolism into previously unrecognized areas characterized by type 2 cytokines and ILC2s, with implications for understanding of inflammation-associated obesity and metabolic syndrome. These studies have served to focus further study of these cytokines, previously associated with allergic immunopathology, on more fundamental roles related to their evolutionary biology. I have benefited from collaborations with the Chawla laboratory at UCSF in metabolic aspects of these studies, and was PI for each of these studies.

a. Wu D, AB Molofsky, H-E Liang, RR Ricardo-Gonzalez, HA Jouihan, JK Bando, A Chawla, **RM Locksley**. 2011. Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. *Science* 332:243-247. PMCID: PMC3144160
b. Nussbaum JC, SJ Van Dyken, J von Moltke, LE Cheng, A Mohapatra, AB Molofsky, EE Thornton, MF Krummel, A Chawla, H-E Liang, **RM Locksley**. 2013. Type 2 innate lymphoid cells control eosinophil homeostasis. *Nature* 502:245-248. PMCID: PMC3795960

c. von Moltke J, M Ji, H-E Liang, **RM Locksley**. 2016. Tuft cell-derived IL-25 regulates an intestinal ILC2-epithelial response circuit. *Nature* 529:221-225. PMC is progress
d. Van Dyken SJ, JC Nussbaum, J Lee, AB Molofsky, H-E Liang, JL Pollack, RE Gate, GE Haliburton, CJ Ye, A Marson, DJ Erle, **RM Locksley**. 2016. A tissue checkpoint regulates type 2 immunity. Nat Immunol 17:1381-1387. PMCID: PMC5275767

PubMed: http://www.ncbi.nlm.nih.gov/pubmed; search 'locksley rm'
My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/richard.locksley.1/bibliograpahy/40681139/public/?sort=date&direction=descending

Research Support

Active

Not assigned Locksley (PI) 10/97 – 9/20 (budgeted annually)
Howard Hughes Medical Institute
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.

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

R01 AI030663 (Locksley) 6/15/08 – 5/31/17
NIH/NIAID
Initiation of allergic immunity by parasites
The major goals of this grant are to understand the innate and adaptive mechanisms for initiation and control of mucosal inflammation by helminthes.

P01 HL107202 (Fahy) 7/1/12 – 6/30/17
NIH/NHLBI (Locksley, PI Subproject 1)
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.

R37 AI026918 (Locksley) 7/1/88-10/31/17
NIH/NIAID
Parasite immunity orchestrated by Th2 cells
The major goal of this project is to identify the role of cyotokine-producing cells, including Th2 cells, basophils and eosinophils, in mediating the immune response to parasitic helminths.

BIOGRAPHICAL SKETCH

NAME **Ari Benjamin Molofsky, M.D., Ph.D.**	POSITION TITLE Assistant Professor, Department of Laboratory Medicine, University of California, San Francisco
eRA COMMONS USER NAME ARIBMOLOSKY	

EDUCATION/TRAINING

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

Positions and Employment

1997-1999	Undergrad Research Fellow, Lab of Janice Fischer, PhD, Developmental Genetics, U. of Texas
1999-2007	Medical Scientist Training Program (MSTP), director Ron Koenig MD PhD, U. of Michigan
2001-2005	Graduate Student, Lab of Michele S. Swanson, PhD, U. of Michigan Micro/Immunology
2007-2009	Laboratory Medicine Resident/Chief Resident, Dept. chair Clifford Lowell MD PhD, UCSF
2009-2010	Clinical Fellow, Hematopathology, 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

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

Contributions to Science

1. My graduate work in the laboratory of Michele S. Swanson focused on the molecular mechanisms regulating *Legionella pneumophila*, a gram-negative bacterium and causative agent of Legionnaire's disease. *L. pneumophila* is a model intracellular bacterium that alternates between an intracellular replicating phase and a transmissible 'virulent' phase. I demonstrated the precise temporal requirements for the master regulator CsrA to promote replication and inhibit transmission-phase virulence genes, including a functional flagellum, during macrophage infection. I characterized the regulation of the flagellum, demonstrating coordinate control of *L. pneumophila* motility with other virulence-associated traits. 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.

a. **Molofsky, A.B.,** & Swanson, M.S. (2003). Legionella pneumophila CsrA is a pivotal repressor of transmission traits and activator of replication. *Mol Microbiol*, *50*(2), 445–461.
b. **Molofsky, A.B.,** and Swanson, M.S. (2004). Differentiate to thrive: lessons from the Legionella pneumophila life cycle. *Mol Microbiol 53*, 29–40.
c. **Molofsky, A.B.,** Shetron-Rama, L.M., & Swanson, M.S. (2005). Components of the Legionella pneumophila flagellar regulon contribute to multiple virulence traits, including lysosome avoidance and macrophage death. *Infection and immunity*, *73*(9), 5720–5734. PMCID: PMC1231111
d. **Molofsky, A. B.,** Byrne, B. G., Whitfield, N. N., Madigan, C. A., Fuse, E. T., Tateda, K., & Swanson, M. S. (2006). Cytosolic recognition of flagellin by mouse macrophages restricts Legionella pneumophila infection. *The Journal of experimental medicine*, *203*(4), 1093–1104. PMCID: PMC1584282

2. As a postdoctoral fellow, I worked in the laboratory of Richard Locksley, an immunologist and Howard Hughes Investigator with extensive expertise in allergic, type 2 immunity and *in vivo* cytokine tracking. I focused on the control and function of allergic and regulatory immune responses in multiple systems, including models of diet-induced obesity and type 2 diabetes, helminth or bacterial infection, and aging. While pursuing broad training in immunology, flow cytometry, and metabolism, I helped to characterize 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 ILC2 by the cytokines IL-33 and IFN and the relationship of ILC2 with regulatory T cells (Treg).

a. Wu, D., **Molofsky, A. B**., Liang, H.-E., Ricardo-Gonzalez, R. R., Jouihan, H. A., Bando, J. K., Chawla, A., Locksley, R.M. (2011). Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. *Science*, *332*(6026), 243–247. PMCID: PMC3144160
b. **Molofsky, A. B**., Nussbaum, J. C., Liang, H.-E., Van Dyken, S. J., Cheng, L. E., Mohapatra, A., Chawla, A., Locksley R.M. (2013). Innate lymphoid type 2 cells sustain visceral adipose tissue eosinophils and alternatively activated macrophages. *Journal of Experimental Medicine*, *210*(3), 535–549. PMCID: PMC3600903
c. Van Gool, F.*, **Molofsky, A.B**.*, Morar, M.M., Rosenzwajg, M., Liang, H.-E., Klatzmann, D., Locksley, R.M., and Bluestone, J.A. (2014). Interleukin-5-producing group 2 innate lymphoid cells control eosinophilia induced by interleukin-2 therapy. *Blood 124*, 3572–3576. PMCID: PMC4256909 **equal contribution*
d. **Molofsky, A.B.**, Van Gool, F., Liang, H.-E., Van Dyken, S.J., Nussbaum, J.C., Lee, J., Bluestone, J.A., and Locksley, R.M. (2015). Interleukin-33 and Interferon-γ Counter-Regulate Group 2 Innate Lymphoid Cell Activation during Immune Perturbation. *Immunity* 43, 1-14. PMCID: PMC4512852

3. As experience in the field of immunometabolism and group 2 innate lymphoid cells has grown, I have undertaken several collaborations. Working with Ajay Chawla's group, 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 demonstrate 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. These collaborations have advanced our knowledge of the regulation and function of ILC2 in diverse homeostatic, therapeutic, and pathologic settings.

a. Lee, M.-W., Odegaard, J.I., Mukundan, L., Qiu, Y., **Molofsky, A.B**., Nussbaum, J.C., Yun, K., Locksley, R.M., and Chawla, A. (2015). Activated type 2 innate lymphoid cells regulate beige fat biogenesis. Cell *160*, 74–87. PMCID: PMC4297518
b. Nussbaum JC, Van Dyken SJ, von Moltke J, Cheng LE, Mohapatra A, **Molofsky AB**, Thornton EE, Krummel MF, Chawla A, Liang HE, Locksley RM. (2013) Type 2 innate lymphoid cells control eosinophil homeostasis. *Nature* 502**,** 245–248. PMCID: PMC3795960
c. **Molofsky, A.B.,** Savage, A.K., and Locksley, R.M. (2015). Interleukin-33 in Tissue Homeostasis, Injury, and Inflammation. *Immunity 42*, 1005–1019. PMCID: PMC4471869
d. Guigas, B., and **Molofsky, A.B**. 2015. "A Worm of One's Own: How Helminths Modulate Host Adipose Tissue Function and Metabolism." *Trends in Parasitology* 31 (9): 435–41. PMCID: PMC4567404

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

a. **Molofsky A.B.** and Lu C.M. (2009). Anaplastic Large Cell Lymphoma, Anaplastic Lymphoma Kinase-Positive (ALCL, ALK+). Check Sample, Hematology, American Society of Clinical Pathology.
b. **Molofsky, A.B.** and Siddiqi, I.N. (2011). Case studies in hematology and coagulation: a new ASCP case set. Book chapter contributors for "Chronic myelogenous leukemia" and "Chronic neutrophilic leukemia", Gulati, G., Flicko-O'Hara, J., and Krause, J.R. eds, American Society of Clinical Pathology.
c. Rollins, M.D., **Molofsky, A.B**., Nambiar, A., Pandey, S., Weiskopf, R.B., & Toy, P. (2012). Two septic transfusion reactions presenting as transfusion-related acute lung injury from a split plateletpheresis unit. *Critical care medicine*, *40*(8), 2488–2491. PMCID: PMC3733455
d. Dawson, A.L., LeBoit, P.E., **Molofsky, A.B**., Ai, W.Z., Pincus, L.B. (2014) Peripheral T-Cell Lymphoma, Not Otherwise Specified Presenting as Erythroderma. *Pathology Case Reviews*, 19(4) 221-226.

A full list of my publications is available at: My Bibliography: http://www.ncbi.nlm.nih.gov/sites/myncbi/14AY37wr6bCAj/bibliography/43618536/public/?sort=date&direction=ascending

Research Support

Active

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.

UCSF PBBR New Frontiers in Research (Molofsky, co-PI) 7/1/2017 – 6/20/2018
Exploring innate lymphocytes at the brain-immune interface.
The major goal of this one-year pilot grant is to begin to explore the lymphocyte composition and cytokine production at the brain meninges and the impact on developing neuronal circuits.

UCSF Department of Laboratory Medicine (Molofsky) ongoing
Departmental Startup Funds.
Tissue type 2 immunity in development, damage, and infection.

Completed

UCSF Nutrition and Obesity Research Center Pilot Grant (Molofsky, PI) 7/1/2016 – 6/30/2017
Impact of infections on adipose tissue composition and metabolic function.
The major goal of this one-year pilot grant is to develop preliminary data on the adipose tissue immune and metabolic alterations induced by gastrointestinal helminth infection.

BIOGRAPHICAL SKETCH

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

EDUCATION/TRAINING

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

Positions and Honors

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

Other Experience and Professional Memberships

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

Honors

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

Contribution to Science

1. The majority of my current research effort focuses on the role of the sinus microbiome in chronic rhinosinusitis. Our research group produced one of the first major papers in this area with a variety of critical findings:
   1) Diverse microbial communities are present in the sinuses of healthy patients,
   2) CRS is associated with a loss of microbial diversity, but not an increased microbial burden
   3) A newly identified microbial pathogen (C. tuberculostearicum) produces inflammation consistent with sinusitis when introduced into the murine nasal cavity
   4) Development of murine sinonasal inflammation is accelerated when the native microbiome is perturbed through antibiotic treatment
   5) Co-instillation of a commensal microbe (L sakeii) prevents C. tuberculostearicum induced inflammatory changes
   Since publication of this 2012 paper, we have investigated the biogeography of microbial communities, fungal contributions to the sinus microbiome, dominant pathogenic species within the sinus microbiome of CRS patients, and continued to develop our mouse model for evaluation of microbial communities in sinusitis. These investigations have resulted in 2 publications currently under review and are multiple manuscripts in preparation.
   Prior to and concomitant with this line of research I have led studies related to rheologic properties of sinonasal mucus and novel steroid deposition methods for treatment of CRS with nasal polyposis.
   a. Abreu NA, Nagalingam NA, Song Y, Roediger FC, Pletcher SD, Goldberg AN, Lynch SV. Sinus microbiome diversity depletion and Corynebacterium tuberculostearicum enrichment mediates rhinosinusitis. Sci Transl Med. 2012 Sep 12; 4(151): 151ra124. PMID: 22972842
   b. Roediger FC, Slusher NA, Allgaier S, Cox ML, Pletcher SD, Goldberg AN, Lynch SV. Nucleic acid extraction efficiency and bacterial recovery from maxillary sinus mucosal samples obtained by brushing or biopsy. Am J Rhinol Allergy. 2010 Jul-Aug; 24(4): 263-5.
   c. Pletcher SD, Goldberg AN. Treatment of recurrent sinonasal polyposis with steroid infused carboxymethylcellulose foam. Am J Rhinol Allergy 2010 Nov-Dec; 24(6): 451-3
   d. Saito D, Innes A, Pletcher SD. Rheologic properties of sinonasal mucus in patients with chronic sinusitis. Am J Rhinol Allergy. 2010 Jan-Feb;24(1):1-5.

Research Support

On-going Research Support

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

Completed Research Support

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

BIOGRAPHICAL SKETCH

NAME **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

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Princeton University, Princeton, NJ	A.B.	1964	English
Harvard Medical School, Boston, MA	M.D.	1969	Medicine
Massachusetts General Hospital, Boston, MA	Resident	1969-1971	Internal Medicine
Arthritis and Rheumatism Branch, NIAMDD, NIH Bethesda, MD	Fellow	1971-1974	Immunology and Rheumatology
Massachusetts General Hospital, Boston, MA	Chief Resident	1974-1975	Medicine
Massachusetts General Hospital, Boston, MA	Fellow	1976	Rheumatology

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
1992-1997	Consulting Editor, Journal of Clinical Investigation
2005 to 2016	Faculty of 1000

15 Selected Peer-Reviewed Publications (of 94)

1. Wofsy D, **Seaman WE**: Successful treatment of autoimmunity in NZB/NZW mice with monoclonal antibody to L3T4. *J Exp Med* 161:378-391, 1985
2. **Seaman WE**, Eriksson E, Dobrow R, Imboden JB: Inositol trisphosphate is generated by a rat natural killer cell tumor in response to target cells or to cross-linked monoclonal antibody OX-34: possible signaling role for the OX-34 determinant during activation by target cells. *Proc Natl Acad Sci USA* 84:4239-4243, 1987.
3. **Seaman WE**, Niemi EC, Stark MR, Goldfien RD, Pollock AS, Imboden JB: Molecular cloning of gp42, a cell-surface molecule that is selectively induced on rat natural killer cells by interleukin-2: Glycolipid membrane anchoring and capacity for transmembrane signaling*, J Exp Med.* 173: 251-260, 1991
4. Yokoyama WM, Ryan JC, Hunter JJ, Smith HMC, Stark M, **Seaman W**E: cDNA cloning of mouse NKR-P1 and genetic linkage with Ly-49: Identification of a natural killer gene complex on mouse chromosome VI. *J Immunol* 147:3229, 1991
5. Ryan JC, Niemi EC, Nakamura MC, and **Seaman WE**: NKR-P1A is a target-specific receptor that activates natural killer cell cytotoxicity. *J Exp Med* 181:1911-1915, 1995

6. Nakamura, MC, Linnemeyer, PA, Niemi EC, Mason L, Ortaldo JR, Ryan JC, **Seaman WE**: Mouse Ly-49D recognizes H-2Dd and activates natural killer cell cytotoxicity. *J Exp Med, 1*89:493-500, 1999.
7. Nakamura MC, Hayashi S, Niemi EC, Ryan JC, **Seaman, WE**: Activating Ly-49D and inhibitory Ly-49A NK cell receptors demonstrate distinct requirements for interaction with H2-Dd. *J Exp Med* 7:192:447-54, 2000.
8. Daws MR, Sullam PM, Niemi EC, Chen TT, **Seaman WE**. Pattern recognition by TREM-2: binding of anionic ligands. *J Immunol.* 171:594-9, 2003.
9. Chen TT, Li L, Chung D-H, Allen CDC, Torti SV, Torti FM, Cyster JG, Chen C, Brodsky, FM, Niemi EC, Nakamura MC, **Seaman WE**, Daws MR. TIM-2 is expressed on B cells and in liver and kidney and it is a receptor for H ferritin endocytosis. *J Exp Med.* 202:955-65, 2005
10. Roach TI, Rebres RA, Fraser ID, Decamp DL, Lin KM, Sternweis PC, Simon MI, **Seaman WE**. Signaling and cross talk by C5a and UDP in macrophages selectively use PLCbeta3 to regulate intracellular free calcium. *J Biol Chem* 283(25): 17351-61, 2008.
11. N'Diaye EN, Branda CS, Branda SS, Nevarez L, Colonna M, Lowell C, Hamerman JA, **Seaman WE**. TREM-2 (triggering receptor expressed on myeloid cells 2) is a phagocytic receptor for bacteria. *J Cell Biol* 184(2): 215-23, 2009
12. Hsieh CL, Koike M, Spusta SC, Niemi E, Yenari M, Nakamura MC, and **Seaman WE**. A role for TREM2 ligands in the phagocytosis of apoptotic neuronal cells by microglia *J Neurochem* 109(4): 1144-1156, 2009.
13. Li L, Fang CJ, Ryan JC, Niemi EC, Lebrón JA, Björkman PJ, Arase H, Torti FM, Torti SV, Nakamura MC, **Seaman WE**. Binding and uptake of H-ferritin is mediated by human transferrin receptor-1. *Proc Natl Acad Sci USA*. 107(8): 3505-10, 2010
14. Rebres, RA, Roach TIA, Fraser IDC, Philip F, Moon C, Lin KM, Liu J, Santat L, Cheadle L, Ross EM, Simon MI, **Seaman WE**: Synergistic Ca^{2+} responses by G_i- and Ga(q)-coupled G-protein-coupled receptors require a single PLC β3 isoform that is sensitive to both Gα(i)- and Gα(q)- Gβγ and Ga(q). *J Biol Chem* 286:1-10, 2011
15. Hsieh CL, Kim CC, Ryba BE, Niemi EC, Bando JK, Locksley RM, Liu J, Nakamura MC, **Seaman WE.** Traumatic brain injury induces macrophage subsets in the brain. *Eur J Immunol* 43:2010-22, 2013

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

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

Positions

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

Other Experience

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

Honors and Awards

Elected member, American Society for Clinical Investigation, 1992
Elected member, Association of American Physicians, 1995
Clean Air Award, American Lung Association of California, 1995

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

Contribution to Science

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

a) **Sheppard D**, Wong SC, Uehara CF, Nadel JA, Boushey HA. Lower threshold and greater bronchomotor responsiveness of asthmatic subjects to sulfur dioxide. *Am Rev Respir Dis* 1980; 122:873-878. PMID: 7458061

b) **Sheppard D,** Saisho A, Nadel JA, Boushey HA. Exercise increases sulfur dioxide-induced bronchoconstriction in asthmatic subjects. *Am Rev Respir Dis* 1981; 123:486-491. PMID: 7235370

c) **Sheppard D**, Thompson JE, Scypinski L, Dusser D, Nadel JA, Borson DB. Toluene diisocyanate increases airway responsiveness to substance P and decreases airway neutral endopeptidase. *J Clin Invest* 1988; 81:1111-1115. PMCID: PMC329638

d) **Sheppard D,** Scypinski L. A tachykinin receptor antagonist inhibits and an inhibitor of tachykinin metabolism potentiates toluene diisocyanate induced airway hyperresponsiveness. *Am Rev Respir Dis* 1988, 138:547-551. PMID: 2462379

2. When I was appointed to build a center at UCSF focused on applying cell and molecular approaches to the study of lung diseases, I spent a sabbatical year with Robert Pytela, one of the faculty members I recruited to this center. During this sabbatical Robert, David Erle and I developed a method (homology-based PCR) to identify sequences encoding new members of the integrin family, a family of heterodimeric transmembrane receptors know at that time as receptors for components of the extracellular matrix. I used this method to identify several new integrins subunits expressed on cells obtained from the lungs, screened expression

libraries to complete the full length sequences of these subunits and used biochemical approaches to identify heterodimer partners for each and to begin to identify relevant ligands for these new integrins These studies helped to substantially expand the known scope of the integrin family and stimulated my lab and a number of other labs around the world to pursue studies to understand the relevance of each to cell behavior and in vivo biology

a) **Sheppard D**, Rozzo C, Starr L, Quaranta V, Erle DJ, Pytela R. Complete amino acid sequence of a novel integrin β subunit (β6) identified from epithelial cells using the polymerase chain reaction. *J Biol Chem* 1990; 265:11502-11507. PMID: 2365683
b) Busk M, Pytela R, **Sheppard D**. Characterization of the integrin αvβ6 as a fibronectin-binding protein. *J Biol Chem* 1992; 267:5790-96. PMID: 1532572
c) Palmer EL, Rüegg C, Ferrando R, Pytela R, **Sheppard D**. Sequence and tissue distribution of the integrin α9 subunit, a novel partner of β1 that is widely distributed in epithelia and muscle. *J Cell Biol* 1993; 123(5):1289-97. PMCID: PMC2119880
d) Yokosaki Y, Palmer EL, Prieto AL, Crossin KL, Bourdon MA, Pytela R, **Sheppard D**. The integrin α9β1 mediates cell attachment to a non-RGD site in the third fibronectin type III repeat of tenascin. *J Biol Chem* 1994; 269:26691-26696. PMID: 7523411

3. To better understand the in vivo relevance of members of the integrin family we had identified, my lab generated integrin subunit knockout mice and used the phenotypes we identified in those mice to identify novel integrin ligands and molecular pathways upstream and downstream of these integrins that contribute to development and disease. Through these studies we identified a completely unexpected role for integrins in activating latent TGFβ and showed that this pathway is important, though distinct effects on different responding cells, in experimental models of pulmonary fibrosis, emphysema, acute lung injury, allergic asthma and in modulating immune responses to tunors. These studies have stimulated substantial interest in potential anti-integrin therapeutics, including one humanized monoclonal antibody generated based on work in my lab that is now in phase 2 clinical trials for potential treatment of idiopathic pulmonary fibrosis and antibodies and small molecule inhibitors we have developed targeting the αvβ8, αϖβ5, αvβ1 and α5β1 integrins that are in various stages of clinical development for treatment of severe asthma, fibrotic diseases, acute lung injury and for tunor immunotherapy

a. Munger JS, Huang XZ , Kawakatsu H , Griffiths MJD, Dalton SL, Wu JF, Pittet JF, Kaminiski N, Garat C, Matthay MA, Rifkin DB, **Sheppard D**. The integrin αvβ6 binds and activates latent TGFβ1: a mechanism for regulating pulmonary inflammation and fibrosis. *Cell* 1999; 96:319-328. PMID: 10025398
b. Morris DG, Huang X, Kaminski N, Wang Y, Shapiro SD, Dolganov G, Glick, A, **Sheppard D**. Loss of integrin αvβ6-mediated TGFβ activation causes Mmp12-dependent emphysema. *Nature* 2003 422:169-173. PMID: 12634787
c. Sugimoto K, Kudo M, Sundaram A, Ren X, Huang K, Bernstein X, Wang Y, Raymond WW, Erle D, Abrink M, Caughey GH, Huang X, **Sheppard D**. The αvβ6 integrin modulates airway hyperresponsiveness by regulating intra-epithelial mast cells. *J Clin Invest* 2012 122:748-758, PMCID: PMC3266785
d. Sundaram A, Chen C, Khalifeh-Soltani A, Atakilit A, Qiu W, Jo H, DeGrado W, Huang X, **Sheppard D**. Integrin alpha5beta1 as a novel target for airway

hyperresponsiveness in asthma *J. Clin Invest* 2017 127:365-374 PMID: 27918306

Having identified an integrin (αvβ6) that played an important role in activating TGFβ only in close proximity to contracting epithelial cells, we sought to determine whether there were other integrins that could also activate this growth factor in other contexts. We found that the αvβ8 integirn is an important activator of TGFβ in the context of antigen presentation by dendritic cells and that this process is essential for the generation of Th17 cells. Using mice we generated specifically lacking this integrin in dendritic cells we identified important roles for this process in models of multiple sclerosis and allergic asthma. We have subsequently found that there is another αv integrin on activated fibroblasts (αvβ1) that is critical to pathologic fibrosis in the lungs, liver and kidney. This work has led us to appreciation of the importance of multiple αv -containing integrins as potential therapeutic targets in a variety of immune-mediated and fibrotic diseases. We also recently showed that αSMA is not an effective marker of collagen producing cells in the lung or kidney and does not identify the fibroblasts that utilize αv integrins to activate TGFβ.

a. Travis MA, Reizis B, Melton AC Masteller E, Tang Q, Proctor J, Wang Y, Bernstein X, Huang X, Riechardt L, Bluestone J, **Sheppard D.** Loss of integrin αvβ8 on dendritic cells causes autoimmunity and colitis in mice. *Nature* 2007 449:361-365. PMCID: PMC2670239
b. Henderson NC, Arnold TD, Katamura Y, Giacomini MM, Rodriguez JD, McCarty JH, Ruminski PG, Griggs DW, Maher JJ, Iredale JP, Lacy-Hulbert A, Adams RH, **Sheppard D**. Selective αv integrin deletion identifies a core, targetable molecular pathway that regulates fibrosis across solid organs. *Nature Medicine* 2013 19:1617-1624 NIHMS495176, PMCID: PMC3855865.
c. Reed NI, Jo H, Chen C, Tsujino K, Arnold TD, DeGrado WF, **Sheppard D**. The αvβ1 integrin plays a critical in vivo role in tissue fibrosis. *Science Translational Medicine* 2015 7:288-294. PMCID: PMC4461057
d. Sun K-H, Chang Y, Reed NI, **Sheppard D.** α-Smooth muscle actin is an inconsistent marker of fibroblasts responsible for force-dependent TGFβ activation or collagen production across multiple models of organ fibrosis. *Am J Physiology Lung Cell Mol Physiol* 2016 310: L824-36. PMC4867351

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

Research Support

Ongoing Research Support

U!9 AI077439 (Sheppard) 04/01/2013- 03/31/2018
NIH/NIAID
IL-13 and IL-17 dynamics in the asthmatic airway
Role: PI, Project Leader, Project 1

Overall project goal: To determine how IL-13 and IL-17 released by T cells and iLCs exert spatially restricted effects on airway epithelium and airway smooth muscle and the relevance of these effects to human asthma.

UH2 HL123423 (Sheppard) 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) 12/07/2012-11/30/2017
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

T32 HL007185 (Sheppard) 07/01/2012–06/30/2022
NIH/NHLBI
Multidisciplinary training program in lung disease

Role: Program Co-PI
Overall project goal: This is a training grant to train future leaders in basic, clinical and translational pulmonary science. There are 13 annual training slots

BIOGRAPHICAL SKETCH

NAME **Jeoung-Sook Shin, Ph.D.**	POSITION TITLE Associate Professor
eRA COMMONS USER NAME SHINJS	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Seoul National University, Seoul, Korea	BS	2/1993	Chemistry
Seoul National University, Seoul, Korea	MS	2/1995	Biochemistry
Duke University, Durham, NC	Ph.D.	5/2002	Pathology
Duke University, Durham, NC	Postdoctoral	8/2003	Pathology
Yale University, New Haven, CT	Postdoctoral	1/2008	Cell Biology

Professional Positions

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

Professional Memberships

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

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

Contribution to Science

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

a. **Shin JS**, Gao Z, Abraham SN. Involvement of cellular caveolae in bacterial entry into mast cells. *Science*. 2000 Aug 4; 289(5480): 785-8. *PubMed PMID*: 10926542.
b. **Shin JS,** Abraham SN. Cell biology. Caveolae--not just craters in the cellular landscape. *Science*. 293:1447-8, 2001. PubMed PMID: 11520975
c. **Shin JS**, Abraham SN. Glycosylphosphatidylinositol-anchored receptor-mediated bacterial endocytosis. *FEMS Microbiol Lett*. 2001 Apr 13; 197(2): 131-8. *PubMed PMID*: 11313125.
d. Duncan MJ, Li G, **Shin JS**, Carson JL, Abraham SN. Bacterial penetration of bladder epithelium through lipid rafts. *J Biol Chem*. 2004 Apr 30; 279(18): 18944-51. *PubMed PMID*: 14976212.

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

a. **Shin JS**, Ebersold M, Pypaert M, Delamarre L, Hartley A, Mellman I. Surface expression of MHC class II in dendritic cells is controlled by regulated ubiquitination. *Nature*. 2006 Nov 2; 444(7115): 115-8. *PubMed PMID*: 17051151.

b. Oh J, Wu N, Baravalle G, Cohn B, Ma J, Lo B, Mellman I, Ishido S, Anderson M, **Shin JS**. MARCH1-mediated MHCII ubiquitination promotes dendritic cell selection of natural regulatory T cells. *J Exp Med*. 2013 Jun 3; 210(6): 1069-77. *PubMed PMID*: 23712430; *PubMed Central PMCID*: PMC3674695.

c. Oh J, **Shin JS**. Molecular mechanism and cellular function of MHCII ubiquitination. *Immunological Reviews*. 2015 July; 266(1): 134-44. *PubMed PMID* 26085212.

d. Oh. J, Perry, JSA, Pua, H, Irgens-Moller, N, Ishido, S, Hsieh, CS, and **Shin, JS**. MARCH1 protects the lipid raft and tetraspanin web from MHCII proteotoxicity in dendritic cells. *J Cell Biol*, Jan 25, 2018

Distinct behavior and role of the high affinity IgE receptor (FceRI) expressed 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 theraperutically targeted to develop tolerance to disease-causing allergens or auto-antigens. I served as the principle investigator in all these studies.

a. Greer AM, Wu N, Putnam AL, Woodruff PG, Wolters P, Kinet JP, **Shin JS**. Serum IgE clearance is facilitated by human FcεRI internalization. *J Clin Invest*. 2014 Mar; 124(3): 1187-98. *PubMed PMID*: 24569373; *PubMed Central PMCID*: PMC3938266.

b. Baravalle G, Greer AM, LaFlam TN, **Shin JS**. Antigen-conjugated human IgE induces antigen-specific T cell tolerance in a humanized mouse model. *J Immunol*. 2014 Apr 1; 192(7): 3280-8. *PubMed PMID*: 24610015; *PubMed Central PMCID* [in process]

c. **Shin JS**, Greer AM. The role of FcεRI expressed in dendritic cells and monocytes. *Cell Mol Life Sci*. 2015 Jun; 72(12): 2349-60. *PubMed PMID*: 25715742; *PubMed Central PMCID* [in process]

The role of mast cells, dendritic cells, and FceRI in asthma.

d. **Shin, JS,** Shelburne, CP, Jin, C, LeFurgey, EA, Abraham, SN. Harboring of particulate allergens within secretory compartments by mast cells following IgE/FceRI-lipid raft mediated phagocytosis, *J Immunol*. 177:5791-5800, 2006. PubMed PMID: 17056503

e. Eggel, A, Baravalle, G, Hobi, G, Kim, B, Buschor, P, Forrer, P, **Shin, JS**, Vogel, M, Stadler, BM, Dahinden, CA, and Jardetzky, TS. Accelerated dissociation of IgE:FceRI complexes by disruptive inhibitors actively desensitzes allergic effector cells, *J of Allergy and Clinical Immunol*, 133:1709, 2014. PubMed PMID: 24642143; PubMed Central PMCID: PMC4083100

f. Greer, AM, Matthay, MA, Kukreja, J, Bhakta, NR, Nguyen, CP, Wolters, PJ, Woodruff, PG, Fahy, JV, and **Shin, JS**. Accumulation of BDCA1+ dendritic cells in interstitial fibrotic lung diseases and Th2-high asthma. *PLoS ONE*, Jun 10;9(6):e99084, 2014. PubMed PMID: 24915147; PubMed Central PMCID: PMC4051692

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

Research Support

Ongoing Research Support

09/05/2013 - 05/31/2018
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.

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

Completed Research Support During Last Three Years
02/01/2016-01/31/2017
Nina Ireland Program for Lung Health
Shin, Jeoung-Sook (PI)
The role of FceRI expressed by dendritic cells in allergic asthma
The goal of this project is to determine the contribution of FceRI expressed by dendritic cells in the progression of allergic asthma.

01/01/2015 - 12/31/2015
Schussler Toby Fund, University of California San Francisco
Shin, Jeoung-Sook (PI)
Mechanistic study of FceRI-mediated intracellular degradation of IgE
The goal of this project is to identify the molecular mechanism by which FceRI traffics to endolysosomes in dendritic cells.

BIOGRAPHICAL SKETCH

NAME **Zhi-En Wang, M.D., M.S.**	POSITION TITLE Research Specialist
eRA COMMONS USER NAME	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Xian Medical University, Xian, China	M.D.	12/82	Medicine
Xian Medical University, Xian, China	M.S.	12/85	Immunology

Positions and Honors

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

Selected Peer-reviewed Publications

1. Sadick, M.D., Holaday, B.J., Heinzel, F.P., **Wang, Z**. and Locksley, R.M.: Leishmania major-specific CD4+ T cells transferred protective immunity to severe-combine immunodeficient (scid) mice." *The Journal of FASEB*, 1990 4(7):1953.
2. Holaday, B.J., Saidck, M.D. Henizel, F.P., **Wang, Z**. and Locksley, R.M.: Establishment of Th1 and Th2-like cell lines from mice infected with Leishmania major. *The Journal of FASEB*, 1990 4(7): 3046.
3. Holaday, B.J., Saidck, M.D. Henizel, F.P., **Wang, Z**. and Locksley, R.M.: Reconstitution of Leishmania major scid mice using Th1 and Th2 cell lines. *Journal of Immunology*, 1991 147(5): 1653.

4. Locksley, R.M., Reiner, S.J., Sadick, M.D., **Wang, Z**., Heinzel, H.P. and Holaday, B.J.: Evidence for restricted V-D-Jß T cell receptor usage in the Th2 response to Leishmania major. 1991 *FASEB J*. 5:A1369.
5. Reiner SL, S Zheng, **Z Wang**, L Stowring, RM Locksley. 1994. Leishmania promastigotes evade IL-12 induction by macrophages and stimulate a broad range of cytokines from CD4 cells during initiation of infection. *J Exp Med* 179:447-56.
6. Loh, E., Wang, M., **Wang, Z**., Hyjek, E., and Kozbor, D.: Expression functional g/d T cell receptor recognize tetanus toxin. *J of Cellular Biochemistry*. 1992 165(D): 67.
7. Kozbor, D., Hyjek, E., Wiaderkiewicz, R., **Wang, Z**., Wang, M. and Loh, E.: Competitor mRNA fragments for quantitation of cytokine specific transcripts in cell lysates. *Molecular Immunology*, 1993. 30(1): 1.
8. Reiner SL**, Z Wang**, F Hatam, P Scott, RM Locksley. 1993. Th1 and Th2 cell antigen receptors in experimental leishmaniasis. *Science* 259:1457-60.
9. **Wang Z,** SL Reiner, F Hatam, FP Heinzel, J Bouvier, CW Turck, RM Locksley. 1993. Targeted activation of CD8 cells and infection of ß2-microglobulin-deficient mice fail to confirm a primary protective role for CD8 cells in experimental leishmaniasis . *J Immunol* 151:2077-86.
10. Reiner SL, S Zheng, **Z Wang**, L Stowring, RM Locksley. 1994. Leishmania promastigotes evade IL-12 induction by macrophages and stimulate a broad range of cytokines from CD4 cells during initiation of infection. *J Exp Med* 179:447-56.
11. Mougneau E, F Altare, AE Wakil, S Zheng, T Coppola, **ZE Wang**, R Waldmann, RM Locksley, N Glaichenhaus, N. 1995. Expression cloning of a protective *Leishmania* antigen. *Science* 268:563-6.
12. Wakil AE, **ZE Wang**, RM Locksley. 1996. Leishmania major: targeting IL-4 in successful immunomodulation of murine infection. *Exp Parasitol* 84:214-22.
13. Pingel S, **ZE Wang**, RM Locksley. 1998. Distribution of protein kinase C isoforms after infection of macrophages with Leishmania major. *Infect Immun* 66:1795-9.
14. Wakil AE, **ZE Wang**, JC Ryan, DJ Fowell, RM Locksley. 1998. Interferon gamma derived from CD4 (+) T cells is sufficient to mediate helper cell type 1 development. *J Exp Med* 188:1651-6.
15. Bix, M, **ZE Wang**, B Thiel, NJ Schork, RM Locksley. 1998. Genetic regulation of commitment to interleukin 4 production by a CD4 (+) T cell-intrinsic mechanism. *J Exp Med* 188:2289-99.
16. Symula DJ, KA Frazer, Y Ueda, P Denefle, ME Stevens, **ZE Wang**, RM Locksley, EM Rubin. 1999. Functional screening of asthma QTL in YAC transgenic mice. *Nat Genet* 23:241-4.
17. Cretu G, RM Locksley, **ZE Wang**, EM Rubin, KA Frazer. 2000. Functional analysis of CNS-1 in YAC transgenic mice. *Science* 288:136-9.
18. Lacy DA, **ZE Wang**, DJ Symola, C McArthur, EM Rubin, KA Frazer, RM Locksley. 2000. Faithful expression of the human 5q31 cytokine cluster in transgenic mice. *J Immunol* 164:4569-75.

19. Loots GG, RM Locksley, CM Blankespoor, **ZE Wang**, W Miller, [EM] Rubin, KA Frazer. 2000. Identification of a coordinate regulator of interleukins 4, 13, and 5 by cross-species sequence comparisons. *Science* 288:136-140.
20. Mohrs M, CM Blankespoor, **Z Wang**, GG Loots, V Afzal, H Hadeiba, K Shinkai, EM Rubin, RM Locksley. 2001. Deletion of a coordinate regulator of type 2 cytokine expression in mice. *Nat Immunol* 2, 842-7.
21. Grogan JL, **ZE Wang**, S Stanley, B Harmon, GG Loots, EM Rubin, RM Locksley. 2003. Basal chromatin modification at the IL-4 gene in helper T cells. *J Immunol* 171:6672-9.
22. Xu M, **ZE Wang**, RM Locksley. 2004. Innate immune responses in peptidoglycan recognition protein L-deficient mice. *Mol Cell Biol* 24:7949-57.
23. Reinhardt RL, S Hong, SJ Kang**, ZE Wang**, RM Locksley. 2006. Visualization of IL-12/23p40 in vivo reveals immunostimulatory dendritic cell migrants that promote Th1 differentiation. *J Immunol* 177:1618-27.
24. Cheng LE**, ZE Wang**, RM Locksley. 2010. Murine B cells regulate serum IgE levels in a CD23-dependent manner. *J Immunol* 185:5040-7.
25. Yang Z, **ZE Wang**, PT Doulias, W Wei, H Ischiropoulos, RM Locksley, L Liu. 2010. Lymphocyte development requires S-nitrosoglutathione reductase. *J Immunol* 185:6664-9.
26. Gordon E, S Sidhu, **Z-E Wang**, P Woodruff, S Yuan, M Solonm S Conway, X Huang, RM Locksley, J Fahy. 2012. A protective role for periostin and TGF-β in IgE-mediated allergy and airway hyperresponsiveness. *Clin Exp Allergy* 42: 144-155. PMC3271792

BIOGRAPHICAL SKETCH

NAME **Arthur Weiss, M.D., Ph.D.**	POSITION TITLE Professor of Medicine and of Microbiology and Immunology
eRA COMMONS USER NAME weissa	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
John Hopkins University, Baltimore	B.A.	05/1973	Biology
University of Chicago	Ph.D.	05/1978	Immunology
University of Chicago	M.D.	05/1979	Medicine

Positions and Employment

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

Other Experience and Professional Memberships

1986-1991	Councilor, American Federation for Clinical Research
1991	President, Western Region of the American College of Rheumatology
1998-2002	Member, Allergy and Immunology Study Section (NIH)
1999-2011	Chair, Scientific Advisory Board, American Asthma Foundation
2000-2002	Chair, Allergy and Immunology Study Section (NIH)
2003-2010	Council, American Association of Immunologists

2008-2009	President, American Association of Immunologists
2005-2012	Advisory Council, RIKEN Research Center for Allergy & Immunology Yokohama, Japan
2013-	Chair, Section 43 (Immunology and Inflammation), National Academy of Sciences

Honors

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

Contribution to Science

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

capability of the TCR. The latter experiment was the inspiration for chimeric antigen receptors that are currently used in cell-based tumor immunotherapy.

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

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

a. Weiss A, Wiskocil R, Stobo JD. The role of T3 surface molecules in the activation of human T cells: A two-stimulus requirement for IL-2 production reflects events occurring at a pre-translational level. *J. Immunol*. 1984 133:123-128.
b. Weiss A, Imboden J, Shoback D, Stobo J. Role of T3 surface molecules in human T cell activation: T3 dependent activation results in a rise in cytoplasmic free calcium. *Proc. Natl. Acad. Sci. USA* 1984 81:4169-4173.
c. Weiss A, Manger B, Imboden J. Synergy between the T3/antigen receptor complex and Tp44 in the activation of human T cells. *J. Immunol.* 1986 137:819-825.
d. Fraser JD, Irving BA, Crabtree GR, Weiss A. Regulation of interleukin-2 gene enhancer activity by the T cell accessory molecule CD28. *Science* 1991 251:313-316.

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

a. Straus DB, Weiss A. Genetic evidence for the involvement of the lck tyrosine kinase in signal transduction through the T cell antigen receptor. *Cell* 1992 70:585-593.
b. Chan AC, Iwashima M, Turck CW, Weiss A. ZAP-70: A 70kD protein tyrosine kinase that associates with the TCR ζ chain. *Cell* 1992 71:649-662.
c. Chan AC, Kadlecek T, Elder ME, Filipovich AH, Kuo W-L, Iwashima M, Parslow TG, Weiss A. ZAP-70 deficiency in an autosomal recessive form of severe combined immunodeficiency. *Science* 1994 264:1599-1601.

d. Iwashima M, Irving BA, van Oers NSC, Chan AC, Weiss A. Sequential interactions of the TCR with two distinct cytoplasmic tyrosine kinases. *Science* 1994. 263:1136-1139.

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

a. Weiss A, Koretzky G, Kadlecek, T. Stimulation of the T cell antigen receptor induces tyrosine phosphorylation of phospholipase Cγ1. *Proc. Natl. Acad. Sci. USA* 1991 88:5484-5488.
b. Yablonski D, Kuhne MR, Kadlecek. T, Weiss A. Uncoupling of non-receptor tyrosine kinases from PLC-γ1 in a SLP-76-deficient T cell. *Science* 1998 281:413-416.
c. Finco TS, Kadlecek T, Zhang W, Samelson LE, Weiss A. LAT is required for TCR-mediated activation of PLCγ1 and the Ras pathway. *Immunity* 1998 9:617-626.
d. Au-Yeung BB, Levin SE, Zhang C, Hsu L-Y, Cheng D, Killeen N, Shokat KM, Weiss A. A genetically selective ZAP-70 kinase inhibitor reveals requirements for catalytic function in Treg cells. *Nature Immunol*. 2010 11:1085-1093. PMCID: PMC3711183

5. The Regulation of Src Family Kinases. Src family kinases (SFKs), such as Lck and Fyn in TCR signaling, are the most proximal kinase required for signaling by ITAM-coupled receptors in the hematopoietic lineage. Their proper regulation is also critical. We established the positive regulatory function of CD45 in TCR proximal signaling events by isolating CD45 deficient T cell lines from Jurkat and HPB-ALL. We showed their signaling defects were the result of CD45's ability to dephosphorylate the negative regulatory tyrosine phosphorylation sites in Lck and Fyn. We have subsequently used an allelic series of mice, expressing different levels of CD45, to show that CD45 quantitatively regulates the phosphorylation status of the negative regulatory sites of SFKs in T cells, controls the magnitude of TCR signaling abilities, and influences T cell development. Similar findings were made with this allelic series in B cells. However, we found that in B cells and in macrophages another transmembrane phosphatase, CD148, plays a partially redundant role with CD45 to control the negative regulatory site of SFKs. In a recent series of studies, we have established that the Csk cytoplasmic tyrosine kinase that phosphorylates the negative regulatory tyrosine phosphorylation site in SFKs is the principle negative regulator of signaling in the basal state by TCRs, BCRs and macrophage FcRs. Our studies suggest that the opposing actions of Csk and CD45 control basal signaling in T cells, B cells and macrophages as well as establishing a threshold for antigen receptor signaling.

a. Koretzky GA, Picus, J, Thomas ML, Weiss, A.: Tyrosine phosphatase CD45 is essential for coupling of the T cell antigen receptor to the phosphatidylinositol second messenger pathway. *Nature* 1990 346:66-68.
b. Zikherman J, Jenne C, Watson S, Doan K, Raschke W, Goodnow CC, Weiss A. CD45-Csk phosphatase-kinase titration uncouples basal and inducible T cell receptor signaling during thymic development. *Immunity*. 2010 32:342-54. PMCID: PMC2865198.
c. Zhu JW, Brdicka T, Katsumoto TR, Lin J, Weiss A. Structurally distinct phosphatases CD45 and CD148 both regulate B cell and macrophage immunoreceptor signaling. *Immunity*. 2008 28:183-96. PMCID: PMC2265106.
d. Tan Y-X, Manz BN, Freedman TS, Zhang C, Shokat KM, Weiss A. Inhibition of the kinase Csk in thymocytes reveals a requirement for actin remodeling in the initiation of full TCR signaling. *Nature Immunol*. 2014 15:186-94 PMC3946925.

Complete List of Published Work in My Bibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/arthur.weiss.1/collections/48006977/public/

Research Support

Ongoing Research Support

Howard Hughes Medical Institute, Weiss (PI) 07/01/85-08/31/18
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

Completed Research Support

1P01AI091580-01 07/15/11-06/30/16
NIH/NIAID (Program Leader A. Weiss)
Deconstructing and Reconstructing the T Cell Signaling Network
The goals of this project are to understand the molecular mechanisms that operate at the plasma membrane to control the specificity, activity and regulation of the TCR signaling mechanisms that lead to protein tyrosine phosphorylation and Ras activity.
Role: Principal Investigator (Project #1)

A119632, Weiss (PI) 07/01/12-06/30/14
American College of Rheumatology
Identifying antigen-specific T cells in mouse and human arthritis
The goals of this grant are to understand how antigen specific T cells are stimulated and to identify and characterize the T cell antigen receptors in mouse and human arthritis.
Role: Principal Investigator

1RC2AR058947-01 (A.Weiss) 09/25/09-08/31/12
NIH/NIAMS
An allosteric inhibitor of ZAP-70 as a novel therapeutic for autoimmune disease
The goals of this project are to develop and allosteric inhibitor of ZAP-70 and determine the preclinical utility of a model catalytic inhibitor of ZAP-70 in preclinical models of disease.
Role: Principal Investigator

BIOGRAPHICAL SKETCH

NAME **Jonathan S. Weissman, Ph.D.**	POSITION TITLE Professor, University of California San Francisco Investigator, Howard Hughes Medical Institute
eRA COMMONS USER NAME WEISSMAN	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Harvard University	A.B.	06/1988	Physics
Massachusetts Institute of Technology	Ph.D.	05/1993	Physics

Positions and Honors

1993 - 1996	Postdoctoral Fellow, Yale University, Structural and Biochemical Studies of GroEL
1996 - 2000	Assistant Professor, University of California San Francisco, Departments of Cellular & Molecular Pharmacology, and Biochemistry & Biophysics
2000 - 2005	Assistant Investigator, Howard Hughes Medical Institute
2000 - 2003	Associate Professor, University of California San Francisco, Departments of Cellular & Molecular Pharmacology, and Biochemistry & Biophysics
2003 - Present	Professor, University of California San Francisco, Departments of Cellular & Molecular Pharmacology, and Biochemistry & Biophysics
2010-present	Vice-chair of Department of Cellular and Molecular Pharmacology, UCSF
2014-present	Co-Director of Innovative Genomics Initiative of Berkeley and UCSF
2016-present	Presidents Advisory Committee of the Chan-Zuckerberg Biohub

Other Experience and Professional Memberships

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

Editorial Boards: Molecular Cell (2001-present); BMC Cell Biology (2003-present); PLoS Biology (2003-present); Molecular Biology of the Cell (2005-2008); Journal of Molecular Biology (2006-present); Cell (2008-present); Current Opinion in Cell Biology (2009-present); Journal of Biology (2009-present); Board of Reviewing Editors, Science (2007-present).

Scientific Advisory Board: NIH, Amyloid Diseases (2005-2007); Proteostasis Therapeutics (2009-2013); Merck Research Labs (2010-2013), Helen Hay Whitney Foundation (2013-present); Stowers Institute for Medical Research (2016-present) Amgen (2016-present), Princeton Department of Molecular Biology (2015-present)

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

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Contribution to Science

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

a. Adamson B, Norman TM, Jost M, Cho MY, Nuñez JK, Chen Y, Villalta JE, Gilbert LA, Horlbeck MA, Hein MY, Pak RA, Gray AN, Gross CA, Dixit A, Parnas O, Regev A, **Weissman JS** (2016) A Multiplexed Single-Cell CRISPR Screening Platform Enables Systematic Dissection of the Unfolded Protein Response. Cell. 167(7): 1867-1882.

b. Liu SJ, Horlbeck MA, Cho SW, Birk HS, Malatesta M, He D, Attenello FJ, Villalta JE, Cho MY, Chen Y, Mandegar MA, Olvera MP, Gilbert LA, Conklin BR, Chang HY, **Weissman JS**, Lim DA. (2016) CRISPRi-based genome-scale identification of functional long noncoding RNA loci in human cells. Science. Dec 15. pii: aah7111. [Epub ahead of print]
c. Gilbert LA, Horlbeck MA, Adamson B, Villalta JE, Chen Y, Whitehead EH, Guimaraes C, Panning B, Ploegh HL, Bassik MC, Qi LS, Kampmann M, **Weissman JS**. (2014) Genome-Scale CRISPR-Mediated Control of Gene Repression and Activation. Cell, 159: 647-61. PMC4253859
d. Horlbeck MA, Gilbert LA, Villalta JE, Adamson B, Pak RA, Chen Y, Fields AP, Park CY, Corn JE, Kampmann M, **Weissman JS**. (2016) Compact and highly active next-generation libraries for CRISPR-mediated gene repression and activation. Elife. Sep 23; 5. pii: e19760.

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

a. Ingolia NT, Ghaemmaghami S, Newman JRS, **Weissman JS**. (2009) Genome-wide analysis in vivo of translation with nucleotide resolution using ribosome profiling. Science, 324(5924) 218-23. PMC2746483
b. Ingolia NT, Lareau LF, **Weissman JS.** (2011) Ribosome profiling of mouse embryonic stem cells reveals the complexity and dynamics of Mammalian proteomes. Cell, 147: 789-802. PMC3225288
c. Li GW, Oh E, **Weissman JS**. (2012) The anti-Shine-Dalgamo sequence drives translational pausing and codon choice in bacteria. Nature, 484: 538-41. PMC3338875
d. Jan CH, Williams CC, **Weissman JS**. (2014) Principles of ER cotranslational translocation revealed by proximity-specific ribosome profiling. Science, 346: 1257521. PMC4285348

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

a. Hollien J, **Weissman JS**. (2006) Decay of endoplasmic reticulum-localized mRNAs during the unfolded protein response. Science, 313:104-7. PMID 16825573
b. Denic V, **Weissman JS**. (2007) A molecular caliper mechanism for determining the length of very long-chain fatty acids. Cell, 130:663-67. PMID 17719544

c. Schuldiner M, Metz J, Schmid V, Denic V, Schmitt HD, Schwappach B, **Weissman JS**. (2008) The GET complex mediates the intersection of tail-anchored proteins into the ER membrane. Cell, 134:634-45. PMC2572727
d. Breslow DK, Collins SR, Bodenmiller B, Aebersold R, Simons K, Shevchenko A, Ejsing CS, **Weissman JS**. (2010) ORM family proteins mediate sphingolipid homeostasis. Nature, 463:1048-53. PMC2877384

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

a. DePace AH, Santoso A, Hillner P, **Weissman JS**. (1998) A critical role for amino-terminal glutamine/asparagine repeats in the formation and propagation of a yeast prion. Cell, 93:1241-52. PMID 9657156
b. Tanaka M, Chien P, Naber N, Cooke R, **Weissman JS**. (2004) Conformational variations in an infectious protein determine prion strain differences. Nature, 428:323-8. PMID 15029196
c. Toyama B, Kelly MOS, Gross JD, **Weissman JS**. (2007) The structural basis of yeast prion strain variants. Nature, 449:233-7. PMID 17767153

Full List of Published Work:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/45844241/?sort=date&direction=ascending

Research Support
Ongoing Research Support

Howard Hughes Medical Institute (Weissman) 10/01/00 - 08/31/17
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.

Howard Hughes Medical Institute Collaborative Investigator Award (Weissman) 09/15/12 - 08/14/17

A Chemical and Genetic Approach to Delineate Stress Networks in Oncogene-Addicted Cancer Cells
A combined chemical and genetic approach to explore how chaperone and stress networks maintain the integrity of oncogene-addicted cancer cells.

NIH/NCI U01 CA168370 (McCormick/McManus/Weissman) 05/01/12 - 04/30/17
Bay Area Cancer Target Discovery and Development Network
Specific aims: 1) develop EXPAND libraries targeting cancer-specific genetic alterations; 2) identify novel drivers that show transforming potential in immortalized primary cells; and 3) produce genetic EMAPs to uncover pathway relationships between candidate drivers.

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

NIH/NIDA R01 DA036858 (Lim/Qi/Weissman) 09/30/13 - 05/31/18
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/NIA 5R01AG041826-04 REVISED (Weissman) 05/01/12 – 04/30/17
Human Gene Knockdowns that May Extend Lifespan
The goal of this project is to screen for genes important in human aging.
Completed Research Support

NIH/NIDA 3R01DA036858-03S1 (Weissman) 06/01/15 – 05/31/16
Harnessing CRISPR for Targeted and Inducible Epigenomic Reprogramming-Supplement
The goals are to develop approaches that will make the solution of simple membrane protein structures routinely achievable and develop novel methods that can be applied to more complicated membrane proteins containing multiple subunits of the same (homo-oligomers) and different (hetero-oligomers) structure; and to produce and determine structures for complexes that are formed between membrane proteins and their soluble protein partners, small ligands and/or macromolecules.

NIH/NIGMS U01 GM098254 (Agard/Frydman/Walter/Weissman) 09/01/12 - 07/31/15
Structural Basis of Protein Homeostasis
The goal of the project was to obtain structural insights into the mechanism by which unfolded and non-native states are recognized by the cytosolic (Hsp70, TRiC chaperones) and ER (UPR and ERAD pathways) protein homeostasis machineries.
Role: Co-Investigator

NIH/NIGMS P50 GM073210 (Stroud) 09/24/04 - 08/31/15
Centers for Innovation in Membrane Protein Production for Structure Determination
The goals of the project were to develop approaches that will make the solution of simple membrane protein structures routinely achievable and to develop novel methods that can be applied to more complicated membrane proteins containing multiple subunits of the same (homo-oligomers) and different (hetero-oligomers) structure; and to produce and determine structures for complexes that are formed between membrane proteins and their soluble protein partners, small ligands and/or macromolecules.
Role: Key Personnel
Onyx Pharmaceuticals (Weissman) 10/01/13 – 09/30/15
Identification of Genetic Vulnerabilities Synergizing with the Proteasome Inhibitor Carfilzomib in Multiple Myeloma Cells
We applied a shRNA screening platform to the identification of genetic vulnerabilities in multiple myeloma cells treated with carfilzomib to establish differences in its mode of action when compared to bortezomib, and to discover synthetic lethal combinations applicable in combination therapy with carfilzomib.

Rogers Foundation Bridging the Gap Award (Bivona) 02/01/12 - 1/30/2014
California Institute for Quantitative Bioscience
Discovery of Rational Companion Targets in Human Lung Cancer
The goal was to define rational polytherapies for lung cancer patients through genome-wide RNAi screening by: 1) determining which genes act together to make cancer tumor cells more vulnerable; 2) testing drug combinations against these targets; 3) identifying additional drug combinations to tackle other subtypes of lung cancers, and expanding studies to include different categories of cancer.
Role: Co-Investigator

BIOGRAPHICAL SKETCH

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

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of Toronto, Toronto, Canada	B.Sc.	06/1966	Biochemistry
Rockefeller University, New York	Ph.D.	06/1971	Cell Biology
Strangeways Research Laboratory, Cambridge, UK	Postdoc.	1971-73	Protein Chemistry

Positions

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

Other Experience and Professional Memberships

Editorial Board Memberships

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

2009-Present	Current Opinion in Cell Biology
2010-Present	Guest Editor, Proc. National Academy Science, USA
2010-Present	Member, Editorial Board, Disease Models and Mechanisms

Professional Memberships

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

Scientific Leadership *(selected)*

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

Honors

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

Contributions to Science

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

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

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

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

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

a. Sympson, C.J., R.S. Talhouk, C.M. Alexander, J.R. Chin, S.M. Clift, M.J. Bissell & Z. Werb (1994). Targeted expression of stromelysin-1 in mammary gland provides

evidence for a role of proteinases in branching morphogenesis and the requirement for an intact basement membrane for tissue-specific gene expression. *J. Cell Biol*. 125: 681-693. PMCID: PMC2119999.

b. Sternlicht, M. D., A. Lochter, C. J. Sympson, B. Huey, J. P. Rougier, J. W. Gray, D. Pinkel, M. J. Bissell & Z. Werb (1999). The stromal proteinase MMP-3/stromelysin-1 promotes mammary carcinogenesis. *Cell*. 98: 137-146. PMCID: PMC2853255.

c. Wiseman, B.S., M. D. Sternlicht, L. R. Lund, C. M. Alexander, J. Mott, M. J. Bissell, P. Soloway, S. Itohara & Z. Werb (2003). Site-specific positive and negative activities of MMP-2 and MMP-3 orchestrate mammary gland branching morphogenesis. *J. Cell Biol*. 162: 1123-1133. PMCID: PMC2172848.

d. (d) Casbon, A.-J., D. Reynaud, C. Park, E. Khuc, D. D. Gan, K. Schepers, E. Passegué & Z. Werb (2015). Tumors reprogram early myeloid differentiation in the bone marrow to generate immunosuppressive neutrophils. *Proc. Natl. Acad. Sci. U.S.A*. 112:E566-E575. [Epub Jan. 26]. PMID: 25624500; PMCID: PMC4330753.

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

a. Nakasone, E., H. A. Askautrud, T. Kees, V. Plaks, A. J. Ewald, M. G. Rasch, Y. X. Tan, J. Qin, M. Fein, J. Park, P. Sinha, M. J. Bissell, E. Frengen, Z. Werb & M. Egeblad (2012). Imaging tumor-stroma interactions during chemotherapy reveals microenvironmental contributions to chemoresistance. *Cancer Cell*. 21:488-503. PMCID: PMC3332002.

b. Kouros-Mehr, H., S. K. Bechis, E.M. Slorach, L. E. Littlepage, M. Egeblad, A. J. Ewald, S.-Y. Pai, I-C. Ho & Z. Werb (2008). GATA-3 links tumor differentiation and dissemination in a luminal breast cancer model. *Cancer Cell*. 13:141-152. PMCID: PMC2262951.

c. Plaks, V., A. Brenot, D. A. Lawson, J. Linneman, E. Van Kappel, K. Wong, F. de Sauvage, O. D. Klein & Z. Werb (2013). Lgr5 expressing cells are sufficient and necessary for postnatal mammary gland organogenesis. *Cell Rep*. 3:70-78. PMCID: PMC3563842.

d. Devignes, C.-S., Y. Aslan, A. Brenot, A. Devillers, K. Schepers, S. Fabre, J. Chou, A.-J. Casbon, Z. Werb* & S. Provot* (2018). HIF signalling in osteoprogenitor cells promotes breast cancer growth and metastasis. *Proc. Natl. Acad. Sci. USA*. In press.

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

a. Chou, J., J.H. Lin, A. Brenot, J.-w. Kim, S. Provot & Z. Werb (2013). GATA3 suppresses metastasis and modulates the tumor microenvironment by regulating miR-29 expression. *Nat. Cell Biol.* 15: 201-213. PMCID: PMC3660859.

b. Lawson, D. A., N. Bhakta, K. Kessenbrock, K. Prummel, Y. Yu, K. Takai, A. Zhou, H. Eyob, S. Balakrishnan, C.-Y. Wang, P. Yaswen, A. Goga & Z. Werb (2015). Single-cell analysis reveals a distinct stem cell program in human metastatic breast cancer cells. *Nature*. 526, 131–135. PMCID: PMC4648562.

c. Horiuchi, D., A. Y. Zhou, A. N. Corella, C. Yau, S. Balakrishnan, K. Kessenbrock, D. A. Lawson, B. N. Anderton, A. V. Bazarov, H. Eyob, P. Yaswen, M. T. McManus, H. S. Rugo, Z. Werb & A. Goga (2016). PIM kinase inhibition presents a novel targeted therapy against triple-negative breast tumors with elevated MYC expression. *Nat. Med.* 22:1321-1329. PMCID: PMC5341692.

d. Shahi, P., C.-Y. Wang, D A. Lawson, E. M. Slorach, A. Lu, Y. Yu, M.-D. Lai, H. Gonzalez Velozo & Z. Werb (2017). ZNF503/Zpo2 drives aggressive breast cancer

progression by downregulation of GATA3 expression. *Proc. Natl. Acad. Sci. USA*. 114: 3169-74. PMCID: PMC5373372.

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

Research Support

NIH/NCI R01 CA057621-25 (Werb, PI) 09/30/13-08/31/18
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.

California Breast Cancer Research Program 21UB-8011-03 (Werb, PI) 03/01/15-02/28/18
Testing Chemicals For Likely Contribution To Breast Cancer This collaborative grant evaluates the effects of environmental agents on mammary epithelium by mass spectrometry.

NIH/NCI R01 CA190851-03 (Werb, PI) 07/01/2015-06/30/20
Role of GATA3 in Transcriptional Pathways Suppressing Breast Cancer Metastasis
This proposal determines how GATA3 regulates metastasis.

NIH/NCI U01 CA199315-02 (Werb, PI) 06/01/16-05/31/21
Integrative Approach to Heterogeneity in Breast Cancer Metastasis
This proposal uses single cell multi-parametric, analytic techniques to probe heterogeneity during metastasis of human breast cancer.

NIH/NCI 5P30 CA082103-18 **(**Ashworth, PI) 5/08/99 - 05/31/18
(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. The Cancer, Immunity, and the Microenvironment Program supports research programs revealing insights into the interactions between evolving neoplastic cells and activated non-neoplastic host cells, and with soluble or insoluble components of extracellular matrix, as well as studies based on these interactions that foster development of novel cellular or molecular-based strategies to combat cancer.

COMPLETED

NIEHS/NCI U01 ES019458 (Werb, PI) 09/01/10-07/31/15
Environmental Effect on the Mammary Gland Across the Lifespan
The major goal of this multi-investigator program was to determine the susceptible times in breast development and how environmental stressors affect them.

NIH/NCI R01CA180039-04 (Werb, PI) 08/01/13-06/30/17
(PQC-4) Fate of Cells Disseminating from Human Breast Cancer Xenografts
This proposal addresses the provocative question of "How do we determine the significance of finding cells from a primary tumor at another site and what methods can be developed to make this diagnosis clinically useful?"

BIOGRAPHICAL SKETCH

NAME **Prescott Gurney Woodruff, M.D., M.P.H.**	POSITION TITLE Associate Professor of Medicine in Residence
eRA COMMONS USER NAME woodruffp	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Wesleyan University, Middletown, CT	B.A.	5/1989	Letters
Columbia College of Physicians & Surgeons, NY	M.D.	5/1993	Medicine
Massachusetts General Hospital	Resident	7/93-1996	Internal Medicine
Harvard School of Public Health	M.P.H.	06/98	Epidemiology
Brigham and Women's Hospital	Fellow	07/97-98	Respiratory Epidemiology
University of California, San Francisco	Fellow	07/98-02	Pulmonary/Critical Care

Positions and Honors

1998-2002	Clinical and Research Fellow, Pulmonary/Critical Care Medicine & Cardiovascular Research Institute, Department of Medicine, University of California San Francisco, San Francisco, CA
2002-2005	Assistant Adjunct Professor; University of California San Francisco
2005- 2010	Assistant Professor in Residence, Pulmonary/Critical Care Medicine, Department of Medicine and CVRI, University of California San Francisco
2010-2014	Associate Professor in Residence, Division of Pulmonary and Critical Care Medicine, Department of Medicine and CVRI, University of California San Francisco
2014-present	Professor in Residence, Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of California San Francisco

Honors

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

Contribution to Science

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

Woodruff PG, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, Koth LL, Arron JR, and Fahy JV. Th2-driven inflammation defines major sub-phenotypes of asthma. *Am J Respir Crit Care Med* 2009 Sep 1;180(5):388-95. (PMCID: PMC2742757)

Woodruff PG, Boushey HA, Dolganov GM, Barker CS, Yang YH, Donnelly S, Ellwanger A, Sidhu SS, Dao-Pick TP, Pantoja C, Erle DJ, Yamamoto KR, Fahy JV. Genome-Wide Profiling Identifies Epithelial Cell Genes Associated with Asthma and with Treatment Response to Corticosteroids. *Proc Natl Acad Sci USA*. 2007 Oct 2;104(40):15858-63. (PMCID: PMC2000427)

Choy DF, Modrek B, Abbas AR, Kummerfeld S, Clark HF, Wu LC, Fedorowicz G, Modrusan Z, Fahy JV, **Woodruff PG**, Arron JR. Gene expression patterns of th2 inflammation and intercellular communication in asthmatic airways. *J Immunol.* 2011 Feb 1;186(3):1861-9.

Christenson SA, Steiling K, van den Berge M, Hijazi K, Hiemstra PS, Postma DS, Lenberg ME, Spira A, **Woodruff PG**. Asthma-COPD Overlap: Clinical Relevance of Genomic Signatures of Type 2 Inflammation in COPD. *Am J Respir Crit Care Med*. 2015 Jan 22. (PubMed PMID: 25611785)

2. Studies of epithelial cell biology and airway remodeling in asthma. In this work I established design-based stereological methods for the measurement of airway epithelial mucin stores, epithelial MUC5AC and MUC5B, and measure the effect of novel therapeutics on aspects of epithelial remodeling and mucin stores.

Woodruff PG, Dolganov GM, Ferrando RE, Donnelly S, Hays SR, Solberg OD, Carter R, Wong HH, Cadbury PS, Fahy JV. Hyperplasia of smooth muscle in mild/moderate asthma without changes in cell size or gene expression. *Am J Respir Crit Care Med.* 2004 May 1; 169(9):1001-6.

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. *denotes authors contributed equally

Woodruff PG, Wolff M, Hohlfeld JM, Krug N, Dransfield MT, Sutherland ER, Criner GJ, Kim V, Prasse A, Nivens MC, Tetzlaff K, Heilker R, Fahy JV. Safety and Efficacy of an Inhaled Epidermal Growth Factor Receptor Inhibitor (BIBW 2948 BS) in COPD. *Am J Respir Crit Care Med.* 2010 Mar 1; 181(5):438-45.

Roy MG, Livraghi-Butrico A, Fletcher AA, McElwee MM, Evans SE, Boerner RM, Alexander SN, Bellinghausen LK, Song AS, Petrova YM, Tuvim MJ, Adachi R, Romo I, Bordt AS, Bowden MG, Sisson JH, **Woodruff PG**, Thornton DJ, Rousseau K, De la Garza MM, Moghaddam SJ, Karmouty-Quintana H, Blackburn MR, Drouin SM, Davis CW, Terrell KA, Grubb BR, O'Neal WK, Flores SC, Cota-Gomez A, Lozupone CA, Donnelly JM, Watson AM, Hennessy CE, Keith RC, Yang IV, Barthel L, Henson PM, Janssen WJ, Schwartz DA, Boucher RC, Dickey BF, Evans CM. Muc5b is required for airway defence. *Nature.* 2014 Jan 16; 505(7483):412-6. PubMed PMC4001806.

3. Studies of the role of microRNAs in asthma pathogenesis. These studies have focused on the role or miRNAs in epithelial cells differentiation and in T-cell differentiation and effector function.

Thomas MF, Abdul-Wajid S, Panduro M, Babiarz JE, Rajaram M, **Woodruff P**, Lanier LL, Heissmeyer V, Ansel KM. Eri1 regulates microRNA homeostasis and mouse lymphocyte development and antiviral function. *Blood*. 2012 Jul 5; 120(1):130-42. Epub 2012 May 21.

Solberg OD, Ostrin EJ, Love MI, Peng JC, Bhakta NR, Hou L, Nguyen C, Solon M, Nguyen C, Barczak AJ, Zlock LT, Blagev DP, Finkbeiner WE, Ansel KM, Arron JR, Erle DJ, **Woodruff PG**. Airway Epithelial miRNA Expression is Altered in Asthma. *Am J Respir Crit Care Med*. 2012 Sep 6

Seumois G, Vijayanand P, Eisley CJ, Omran N, Kalinke L, North M, Ganesan AP, Simpson LJ, Hunkapiller N, Moltzahn F, **Woodruff PG**, Fahy JV, Erle DJ, Djukanovic R, Blelloch R, Ansel KM. An integrated nano-scale approach to profile miRNAs in limited clinical samples. *Am J Clin Exp Immunol*. 2012 Nov 30;1(2):70-89.

Simpson LJ, Patel S, Bhakta NR, Choy DF, Brightbill HD, Ren X, Wang Y, Pua HH, Baumjohann D, Montoya MM, Panduro M, Remedios KA, Huang X, Fahy JV, Arron JR, **Woodruff PG**, Ansel KM. A microRNA upregulated in asthma airway T cells promotes TH2 cytokine production. *Nat Immunol*. 2014 Dec;15(12):1162-70. doi: 10.1038/ni.3026. Epub 2014 Nov 2. PubMed PMID: 25362490; PubMed Central PMCID: PMC4233009.

4. Studies of the origins of airway disease in COPD. I am currently the PI and Steering Committee Chair of the SPIROMICS II study of COPD, which is an NIH-funded longitudinal COPD cohort designed to identify biological subgroups of COPD and factors associated with disease progression. My main contributions to this study have been to define a population of smokers with early disease (Woodruff NEJM 2016). This group appears to have predominantly and airway disease with airway wall thickening and mucin abnormalities (Kesimer NEJM 2017), suggesting an airway epithelial origin.

Woodruff PG, Barr RG, Bleecker E, Christenson SA, Couper D, Curtis JL, Gouskova NA, Hansel NN, Hoffman EA, Kanner RE, Kleerup E, Lazarus SC, Martinez FJ, Paine R 3rd, Rennard S, Tashkin DP, Han MK; SPIROMICS Research Group. Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function. *N Engl J Med.* 2016 May 12; 374(19):1811-21. doi: 10.1056/NEJMoa1505971. PubMed PMID: 27168432; PubMed Central PMCID: PMC4968204.

Kesimer M, Ford AA, Ceppe A, Radicioni G, Cao R, Davis CW, Doerschuk CM, Alexis NE, Anderson WH, Henderson AG, Barr RG, Bleecker ER, Christenson SA, Cooper CB, Han MK, Hansel NN, Hastie AT, Hoffman EA, Kanner RE, Martinez F, Paine R 3rd, **Woodruff PG**, O'Neal WK, Boucher RC. Airway Mucin Concentration as a Marker of Chronic Bronchitis. *N Engl J Med*. 2017 Sep 7; 377(10):911-922. PMCID: PMC5706541.

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Complete List of Published Work in MyBibliography:
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Research Support

ACTIVE

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.

K24 HL137013 (PI Woodruff) NIH/NHLBI 4/28/17-3/31/22
Mentoring Research in Precision Medicine for Lung Disease
To mentor students, fellows and junior faculty in patient oriented precision medicine related research in asthma and COPD.

U01 HL126493-01 (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.

U01 HL128952-01 (Co-PI Woodruff, contact PI: Han) 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.

R01 HL138424 (Erle DJ, Woodruff Co-I) 08/01/2017-06/30/2021
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.

R01 HL121774 (Huffnagle G, Woodruff Co-I) 1/1/17-8/31/20
NIH/NHLBI
Functional Analysis of the Pulmonary Microbiome during COPD
This study investigates a pathway that links inflammation, Gram negative bacterial overgrowth, mucus production and chronic bacterial colonization in COPD.

U19 AI077439 (Overall PI: Sheppard, Core director: Woodruff, project Co-I: Woodruff)4/01/13-3/31/18
NIH/NIAID IL-13 and IL-17 dynamics in the asthmatic airway
To study the sources and roles of IL-13 and IL-17 in AHR and airway epithelial abnormalities in asthma.

P01 HL107202 (Fahy JV, Woodruff Core director, project Co-I) 7/1/12-6/30/17
NIH/NHLBI in no cost extension
Innate and Adaptive Immune Responses in Th2 High Asthma
To identify the roles of iH2 cells, IL-33 and miRNAs in local immune responses in the lung in asthma.

U10 HL109146 (Fahy JV, Woodruff Co-I) NIH/NHLBI 7/1/12-6/30/17
Severe Asthma Research Program in no cost extension
The goal of this project is to investigate molecular phenotypes and lectins that regulate mucus viscosity in severe asthma.

Seeding Bold Ideas Award (PI Christenson, Co-I Langelier and Woodruff) 5/1/17-4/31/18
Marcus Program in Precision Medicine Innovation
Host/Pathogen Metagenomic Deep Sequencing for Precision Diagnosis of Acute Exacerbations of COPD

Seeding Bold Ideas Award (PI Peng, Co-I Christenson and Woodruff) 5/1/17-4/31/18
Marcus Program in Precision Medicine Innovation
Single-cell Discovery Approach for Targeted Regenerative Therapy in Emphysema

COMPLETED

N01 HHSN268200900014C (Woodruff PI) 2/01/09-7/31/16
NIH/NHLBI
The Spiromics Project: Clinical Center
To identify subpopulations and intermediate outcome measures in COPD.

R01 HL114447 (Woodruff Subcontract PI, PI Huffnagle) 4/01/12-3/31/16
NIH/NHLBI
Pulmonary bacterial microbiome-epithelial cell interactions in COPD
To determine the relationships between the airway microbiome and airway mucin and EGFR-pathway abnormalities in COPD.

R01 HL110883 (Woodruff Co-I, PI Kheradmand) 2/15/12-1/31/16 NIH/NHLBI
Ancillary T-Cell Based Studies in SPIROMICS
To identify T-cell effector pathways that are present in COPD and correlate with progression of emphysema.