Sandler Asthma Basic REsearch Center
University of California San Francisco

Progress Report
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Figure Legend: Dendritic cells in human airway epithelium. The number of dendritic cells significantly increases in asthma associated with high production of IL-13 and IgE, and eosinophilia. Blue = cell nuclei; red = dendritic cells; green = extracellular matrix. Magnification 1000X. Photo by Alexandra Greer.
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Mission Statement

The Sandler Asthma Basic Research Center (SABRE Center) at UCSF is an investigative unit dedicated to basic research discovery in asthma. Founded in 1999, the SABRE Center was nucleated originally by five basic scientists supported by advanced technology cores and linked with the larger scientific community through Center Grants and Program Project Grants focused around asthma research. With maturation, the Center aligned in 2014 with the Airway Clinical Research Center at UCSF to facilitate an increased focus on human studies. Our mission remains to be a progressive, nimble, transformative scientific group that will pioneer basic discovery in asthma research to accomplish our vision of a world free of asthma. The SABRE Center is made possible through the generous support of the Sandler Foundation.

Summary of Accomplishments over the Past Year

The SABRE Center has become a productive asthma research enterprise within the greater UCSF scientific community. With a current core of four basic scientists, a population geneticist and two translational scientists, the Center has networked into the greater UCSF research and the national asthma research organizations, including the NIH, to establish increasing recognition for contributions to asthma research.

Notable accomplishments for SABRE Center members over the past 12 months covered in this report include:

(1) Jeoung-Sook Shin was awarded a UCSF Catalyst Grant to develop small molecule inhibitors of MARCH1 in an effort to target the ubiquitination pathway in asthma.
(2) Mark Ansel continues to contribute groundbreaking insights into the role of microRNAs in modulating allergic immune cells. He is Director of the Biomedical Sciences Graduate Program and was a recipient of a UCSF 150th Anniversary Alumni Award in recognition of his outstanding contributions.
(3) John Fahy has gained widespread recognition for defining asthma endotypes, was elected to the American Association of Physicians in 2016, and received a Research Recognition Award from the American Thoracic Society in 2017.
(4) Chris Allen was named a national Pew Scholar in the Biomedical Sciences in 2016 in recognition of his exceptional scholarship and potential for scientific discovery related to asthma.
(5) Esteban Burchard has built the Asthma Collaboratory at UCSF, which represents the largest annotated collection of genomes from ethnically underrepresented populations with asthma.
(6) Richard Locksley was elected to the National Academy of Sciences, one of the highest honors in the scientific field, honoring distinguished and continuing achievements in original research.
(7) Prescott Woodruff has gained national recognition for his research in inflammatory lung diseases. He was elected to the American Society for Clinical Investigation in 2016.
Overview – 2017
Richard M. Locksley, M.D.

The SABRE Center continues to move forward in implementing the 2014 Strategic Plan with an emphasis on re-directing resources from animal-related cores toward technology resources and human-based research. With the loss of Drs. Liu (2014) and Cheng (2015), a substantial effort has been directed at recruitment efforts, focusing on those who bring patient-oriented basic research interests to the SABRE Center. The Search Committee made an offer to an outstanding candidate in 2015, and courted two additional outstanding candidates in 2016-17, but for various reasons these young scientists elected to remain at their current Universities, where they were highly recruited. We continue to pursue exceptional scientists for the position, although realize the challenges of recruitment to the Bay area.

Additional events that will affect the SABRE Center include the plans for development of the Parnassus site to coincide with the new hospital scheduled for build-out in 2025 and the discontinuation of the American Asthma Foundation over the next 2 years. The former involves a number of plans for shuffling and relocation of various research entities across the Parnassus – Mission Bay landscape both to promote strategic re-alliances of programs that have become increasingly isolated at one site or another and to enable free-up of space while re-designing the Parnassus site for the next century. Each of these has the potential to affect location of the SABRE Center, and events over the next 24 months are likely to more clearly define the best among several scenarios. The phase-out of the American Asthma Foundation will end a leadership role that has developed for SABRE Center investigators in interacting with AAF investigators, supporting their studies through training and core technology efforts, and participating in the annual meeting in substantial ways. Despite this, the many interactions and collaborations that have been established through this mechanism will enable continuing scientific cooperation among these various groups across the country for many years.

Key Elements of the Strategic Plan

The key elements of the Strategic Plan involve a 3-year period focused 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 towards the goals of better diagnostics, prognostics and treatments. This involves strengthening studies in human research, re-directing resources from animal-centric core facilities to a human-centric acquisition of samples and specimen banks, supporting young investigators by re-investing in targeted innovative grants in areas of need, and speeding the capacity to leverage technology investments that will enhance the ability to move nimbly into new areas. The process involves a phased re-allocation of resources over 3 years, re-investment in young investigators working in emerging areas of importance to asthma discovery, and adding internal and external Advisory Board members who bring expertise in areas of human disease, molecular structure and target drug development.
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 Mission Bay. 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 fully 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 regular lab and research meetings. The fruits of this collaborative effort resulted in the first 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 important research addition on the UCSF campus with the role of generating new understanding and therapeutic approaches to asthma. We will review the individual investigators and their progress, followed by an overview of the constituents 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.

Mark Ansel 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. Recently, 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 motivates productive collaborations with UCSF Airway Clinical Research center investigators, including Dr. John Fahy, Dr. Prescott Woodruff, Dr. Laura Koth, and Dr. Homer Boushey. One of his collaborative projects with Dr. Fahy and Dr. Erin Gordon was recently reported in *Proceedings of the National Academy of Science*. Together, they analyzed inflammatory cells captured in the sputum from human subjects and made the surprising discovery that basophils are increased in asthma and appear to be the major source of the type 2 cytokines that mediate allergic inflammation. Another publication in *Immunity* described microRNA-directed discovery of novel regulators of Th2 cytokine production through the analysis of two co-expressed miRNAs (miR-24 and miR-27) that repress Th2 differentiation and allergic airway inflammation. Dr. Ansel’s group also collaborated with Dr. Locksley to extend their prior work on a miRNA, miR-19a, which is specifically upregulated in T cells from the airways of asthmatic subjects and which strongly promotes cytokine production by Th2 cells. Recent work in the Ansel lab showed that miR-19 also promotes allergic inflammation mediated by innate lymphocytes (ILC2s) through an overlapping but non-identical downstream gene regulatory network. Altogether, Dr. Ansel contributed to 3 published manuscripts in 2016-17, 4 others are in revision for publication, and several others are in preparation for submission. Dr. Ansel is an established leader in his field, and has recently delivered
invited lectures at national and international scientific conferences in New York, Germany, Switzerland, Seattle, San Francisco, and Stanford.

Dr. Ansel’s work has also been rewarded with substantial extramural grant support. In 2016, his funded R01 grant from the National Heart, Lung and Blood Institute was renewed with a score in the 2nd percentile, providing over $800,000 over the next 4 years. Dr. Ansel participates as a Principal Investigator in the first Program Project Grant among SABRE Investigators from the NIH, now in its 4th of 5 years with annual funding of approximately $1,575,000. Dr. Ansel is a Leukemia & Lymphoma Society Scholar, recognition that provided $525,000 in direct costs from 2012-2017. In addition, he is a Principal Investigator in a U19 project grant led by Dr. Robert Blelloch that is 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 U19 was funded in September of 2013 and provides approximately $1,100,000 of direct support to Dr. Ansel’s laboratory over five years.

The Ansel laboratory is currently populated by four graduate students, four postdoctoral fellows, and two technicians. One student is supported by a National Science Foundation Graduate Research Fellowship, and a second by an NIH F31 award to support her research and training. Two students are completing their current postdoctoral fellowship support from the Leukemia & Lymphoma Society, the Immunology Program T32 training grant, the Dermatology Foundation and the prestigious Cancer Research Institute Fellowship. Dr. Heather Pua is supported by an NIH K08 Career Development Award and is currently weighing offers at several institutions to start her own laboratory focused on RNA regulation of allergy and airway disease. 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 two cases, as principal investigators of independent laboratories in the US and Germany. 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, 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 Dr. David Erle to push the boundaries of genomic analyses of RNA regulation and collaborates actively with multiple other investigators in the SABRE Center and throughout UCSF.

In recognition of his success to date, Dr. Ansel was promoted to a ladder rank position as Associate Professor of Microbiology & Immunology. 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 on a large NIH-funded training grant to support graduate student training. In addition, he participates in teaching for medical, dental and graduate students, and directs the immunology course for the Doctor of Pharmacy program at UCSF.
Jeoung-Sook Shin is working to identify the molecular mechanisms underlying antigen-presenting function of dendritic cells with the ultimate goal of exploiting the mechanisms for the development of novel therapeutics. One of the major research projects is to understand the role of the ubiquitin ligase MARCH1. MARCH1 mediates ubiquitination and turnover of MHCII and CD86, the key molecules that execute antigen-presenting function of dendritic cells. Using genetically modified mouse strains, Dr. Shin has found that MARCH1 plays an important role in dendritic cell function of developing regulatory T cells in the thymus. She has also discovered that MARCH1 is crucial for dendritic cells to develop allergic immunity in the airways. Most strikingly, MARCH1-deficient mice were resistant to developing airway inflammation and IgE production after challenge with house dust mite allergens, implicating the important role of MARCH1 in allergic asthma. Dr. Shin is investigating the molecular mechanisms underlying this resistance and assessing the candidacy of MARCH1 as a therapeutic target for prevention or treatment of asthma. Another research project is to understand the role of the high affinity IgE receptor FεRI in dendritic cell function. Dr. Shin has found that this receptor mediates internalization and degradation of extracellular IgE, thus contributing to serum IgE clearance. More recent studies suggest that this receptor enhances dendritic cell function of activating Th2 immunity possibly contributing to the exacerbation of allergic inflammation in asthma. The specific mechanisms are under active investigation.

Dr. Shin has published 5 peer-reviewed research papers and 3 invited reviews over the last three years. Two new research papers are under current review or revision. Dr. Shin was invited to serve as a member in the NIH study section on Mucosal Immunology, Allergy, and Asthma. Dr. Shin received her first R01 grant from NIH in 2013. This funding will support her study on the role of MARCH1 in dendritic cell function in health and asthma through May 2018. Dr. Shin was recently awarded a UCSF Catalyst grant that will support her studies attempting to develop MARCH1 small molecule inhibitors for the treatment of asthma. Two NIH R21 grants are currently also under review.

Dr. Shin’s laboratory consists of a postdoctoral fellow and a graduate student. The postdoctoral fellow was selected to give an oral presentation at the American Association of Immunologists 2016 annual meeting. The graduate student was awarded the National Institute for General Medical Sciences (NIGMS), Initiative for Maximizing Student Development (IMSD) fellowship.

Dr. Shin is in active collaboration with a number of investigators in and outside UCSF. Most recently, she is working with Dr. William DeGrado in the Department of Pharmaceutical Chemistry at UCSF, who will assist in solving the structure of MARCH1. Collaborations with pharmaceutical industry such as GSK and MedImmune are also under discussion in hopes of developing small molecule inhibitors of MARCH1 for treatment of asthma. Dr. Shin continues to actively participate in SABRE monthly seminars and interacts with multiple SABRE core facilities, including BIDC and the Genomics core.

Chris Allen joined the SABRE center nine years ago as a UCSF Fellow and 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* last year. 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 on the specificity of IgE plasma cells in mouse models of asthma and how cytokine signals regulate IgE responses that he is currently writing up for submission. 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 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 attracted substantial extramural funding to support his studies. This includes two five-year grants from the NIH: an R01 focusing on imaging of basophils in tissues *in situ* and an NIH Director’s New Innovator Award, fewer than 9% of which were funded. Together, these awards provide $550K in annual direct costs to support his lab.

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 in late 2012. Dr. Allen then 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 continues to participate in monthly and quarterly meetings with SABRE investigators on the Parnassus site. Dr. Allen rapidly recruited a new postdoc, a new technician, and his first graduate student who is funded by the Singapore’s Agency for Science, Technology and Research (A*STAR). In 2014, Dr. Allen recruited a second graduate student in the Biomedical Sciences program to his laboratory. A UCSF medical student also volunteered to work part-time in Dr. Allen’s lab to begin translating his IgE studies into human samples and was then awarded a UCSF Resource Allocation Program, Pathways to Explore fellowship to spend a summer working full time in the lab, during which he developed and optimized techniques for human IgE studies. Based on his initial success, this student was recognized with a 2016-
17 HHMI Medical Research Fellows award, which is allowing him to currently spend a full year working with Dr. Allen on these studies, between his third and fourth years of medical school.

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 homeostatic role for allergic immunity, 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 induction 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 15 peer-reviewed publications and 3 additional reviews and/or commentaries since 2015.

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, new cells that contribute to allergic inflammation, in 2010. In 2016, his laboratory was the first 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 in crosstalk between epithelia and ILC2s associated with allergic immune responses. He is a Professor in the Departments of Medicine and Microbiology & Immunology, and an Investigator in the Howard Hughes Medical Institute, where he completed a successful review and renewal in 2015. 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 was elected to the American Academy of Arts & Sciences and is a Fellow in the American Academy of Microbiology. He received the first annual William Paul Award for contributions in cytokine research from the International Cytokine & Interferon Society. This year he was elected to the National Academy of Sciences. 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. His past UCSF MSTP graduate will be a medical intern at UCSF this year, and his most recent BMS graduate student was awarded an F30 Award from the NIH with a perfect score on his grant investigating the development of ILC2s.
John Fahy is a longstanding supporter of SABRE research and a formal faculty member in the SABRE Center for the past 3 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 airway 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 also the PI of the UCSF center in the NHLBI Severe Asthma Research Program (SARP), and he has a pending application to 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 is Associate Director of the Airway Clinical Research Center, has been an integral member of the SABRE Center for the past 3 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 fields 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 the development of novel biomarkers such as extracellular RNAs (exRNA). 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 also co-investigator and/or core director 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. Sheppard, and in the American Lung Association Asthma and COPD Clinical Research Network. 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 that 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 recent honors include election to membership in the American Society for Clinical Investigation.

Esteban Burchard directs the Asthma Genetics Core Facility, now designated the Asthma Collaboratory, which has become the largest annotated gene biorepository from minority populations with asthma in the world. The Asthma Biobank is open to reputable scientists seeking to assess genetic risk for variants in populations of interest or to extend findings made in animal models to 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 and more recently 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 whole genome sequence (WGS) 15,580 minority children with asthma and drug response (valued at $45 million). These efforts will facilitate numerous collaborators and bolster the careers of trainees, and underpin additional successful competition for extramural funding.

Core Activities and Technology Development

An integral component of the SABRE Center includes support and guidance for advanced technology cores. These included cores in Mouse Physiology (which provides both 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. Erle, to the Microscopy Core, under the guidance of Dr. Krummel, and to the Genetics Core, under the guidance of Dr. Burchard. The Genomics Core has led a number of technological innovations of importance to the Center, particularly in facilitating deep-sequencing efforts, single-cell RNAseq and cutting-edge epigenetic analyses, such as ATACseq methods. The Microscopy Core continues to lead applications in in situ microscopy of the lung and more powerful approaches for visualizing chemistry in single cells using lattice-sheet microscopy 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 database 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 match 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 rollout 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 alone. 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 a campus-wide resource that is 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, for enhanced imaging capacity using SPIM (selective plane illumination microscopy) imaging of whole lung, and for continued training of SABRE investigators.

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 have 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.

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, 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.

The SABRE Center will also re-invigorate the Innovative Grants program by supporting 3 grants at $65K/yr with a competitive second year. These grants will be available to non-SABRE, non-Pulmonary faculty for the purposes of bringing novel approaches and technologies to bear on the basic investigation of asthma. In the past, this mechanism proved an extremely fruitful way to pull top scientists into the field, and we look forward to assessing what are sure to be highly innovative, creative and bold proposals from the UCSF community.

**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 Airway Center 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 activity in this space. The Airway Clinical Research Center 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 following instruments are currently on site.

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

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

Sputum Induction: Devilbiss UltraNeb 99 ultrasonic nebulizer (2), Nouvag UltraNeb ultrasonic nebulizer (2), NuAire NU-810-SPEC Biohood sputum induction booths (2).


Other: 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.

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 Airway Research Center 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:

1. Grants funded in last year:
   (i) R01 HL080414-05 Mechanisms of mucus pathology in acute severe asthma (Fahy). The competitive renewal of this Fahy R01 grant received a positive funding decision in 2016 and will now be active through 2020.
(ii) PO1 HL128191: Carbohydrate-based Therapy for Lung Disease (Fahy). This Fahy-led translational PPG (tPPG) received a positive funding decision in 2016 and will now be funded through 2021. The tPPG proposes to develop 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.

2. Active grants with ongoing funding:
   (i) U10- HL109146: Severe Asthma Research Program (SARP)(Fahy and Woodruff). Clinical and Molecular Phenotypes of Severe Asthma.
   (ii) P01- HL107202: Program Project Grant. Innate and Adaptive Immune Responses in Th2-high Asthma (Fahy, Ansel, Woodruff, Locksley).
   (iii) U19 - AI077439-06 Asthma and Allergic Diseases Cooperative Research Centers (AADCRC). IL-13 and IL-17 dynamics in the asthmatic airway Sheppard, Woodruff, Krummel, Erle.
   (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 newly awarded 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 will serve as an important integrative unit for translational interests of the SABRE
Center. There is also a monthly research conference for SABRE/ACRC investigators at the Parnassus site to promote interactions and collaborations.

Funding from the SABRE center is promoting human based research and junior faculty careers in clinical and translational asthma studies, as follows:

(i) **Senior faculty support**: NIH salary caps means that the salaries of Drs Fahy and Woodruff are not met by the salary support received from their multiple grants. The gap between their salary and NIH grant support is met in part by their clinical activities, but SABRE support helps minimize the extend of these clinical activities so that time for research is maximized.

(ii) **Junior faculty support**: Flexible funding provided by SABRE to Drs Fahy and Woodruff allows them to support junior faculty by providing funding for pilot studies, exploratory analyses, and enabling equipment and technology for their research.

**Human Upper Respiratory Tract Analysis**

The SABRE Center has established a scientific relationship with a UCSF surgical practice located at Mt. Zion campus with experience taking care of large number of patients with allergic nasal polyposis. These investigators, Drs. Andrew Goldberg and Steven Pletcher, faculty in the Department of Otolaryngology and Head and Neck Surgery at UCSF, have been examining the interactions of the nasal microbiome and allergy-associated immune cells in excised nasal polyps. We have worked through planning meetings, human use forms and other regulatory issues in order to establish formal collaborative relationships with these investigators and their research group. These nasal polyps provide a rich source of human epithelia, macrophages, eosinophils and ILC2s that collect in these tissues. A substantial number of these recurrent allergic nasal polyposis patients have severe asthma, thus establishing a patient base for further study, including in clinical intervention trials. While the working relationship continues to evolve, we continue to strengthen basic and clinical research interactions with this surgical group, which remains enthusiastic and receptive to our overtures. A postdoc, Benjamin Terrier, in the Locksley lab, is working regularly with this group investigating nasal upper airway epithelial cells involved in sensory perception to allergens. The biosketches of Dr. Goldberg and Pletcher 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. As demonstrated by our ability to obtain a Program Project last year by capitalizing on the access and expertise of colleagues in the Airway Clinical Research Center, 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 2016-17


Interleukin-33, IL-33, is an ‘alarmin’, a nucleus compartmentalized member of the IL-1 family of cytokines that can induce allergic cytokine release from other immune cells. How IL-33 gets out of the nucleus by mechanisms other than cell death has remained mysterious. Here, alternative splicing of the IL-33 was demonstrated in human airway epithelial cells, and such splicing could delete nuclear-localizing signals, allowing
cytosolic localization of IL-33. Increased numbers of IL-33-responsive cells, including mast cells and basophils, were present in sputum of patients with chronic asthma, raising a therapeutic opportunity for blocking IL-33 in these patients in order to block the production of downstream cytokines implicated in mediating airway reactivity and mucus hypersecretion.


TYRO3 is one of 3 receptor kinases in the TAM family and is expressed on immune cells, including dendritic cells. Population studies using GWAS performed in the Burchard lab at SABRE Center identified intronic variants of TYRO3 associated with asthma in three independent studies. In these studies done primarily at Yale, mice deficient in TYRO3 has unrestrained allergic pathology in the lungs when challenged with house dust mite. Further, deletion of TYRO3 only from dendritic cells led to enhanced Th2 differentiation, which was associated with expression of cell surface Pros1, a ligand for TYRO3, which serves to feedback and dampen Th2 cytokine expression. These studies carried out in mouse and human cells and in human populations, have identified a new circuit of feedback regulation of Th2 differentiation that might be targeted for control of allergic inflammation.


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. How microRNAs regulate the function of Th2 cells, which are central to the pathogenesis of allergic pathology, including most forms of asthma, remains unstudied. Here, the authors used a functional screen of all the microRNAs expressed in primary T cells to uncover unsuspected roles for miR-24 and miR-27 in repressing the expression of IL-4 during in vitro T cell differentiation to Th2 cells. Next, the clusters containing these microRNAs were deleted in mice to show that these animals developed increased Th2 responses and tissue allergic findings in response to allergic airway challenges in vivo. Finally, gene expression and pathway analysis was used to identify the re-enforcing network of transcripts regulated by these microRNAs in restricting elaboration of type 2 cytokines in T cells. The analysis revealed both previously implicated but also unsuspected components of these pathways, thus creating novel targets for intervention in efforts to impede Th2 differentiation and/or function.

In this comprehensive review, the authors explore the expanding functions for ubiquitination in regulating MHCII antigens and new areas of dendritic cell biology. Dendritic cells are key activators of immunity, and this activation is transduced to helper T cells by presentation of discrete peptides on surface MHCII molecules. Ubiquitinylating ligases, particularly MARCH1 and sometimes MARCH8, regulate enzymatic decrease in membrane-associated MHCII complexes, thus regulating the duration of immune activation. Unexpectedly, studies in various cell lines and in genetically manipulated mice have demonstrated roles for MARCH1/8 in affecting Toll-like receptor cytokine production by dendritic cells and in influencing thymic regulatory T cell production. These antigen-independent effects of ubiquination suggests unknown pathways that could provide new mechanisms for controlling allergic immunity.


Epithelial cytokines, such as TSLP, IL-33 and IL-25, are associated with allergic immunity, but how and where these signals are generated is not well understood. Here, a novel genetic reagent was created to enable 'marking' of IL-25 in vivo and revealed this cytokine was produced by tuft cells, rare, enigmatic epithelial cells in mucosa of all vertebrates, including humans. After intestinal helminth infection, tuft cell IL-25 was 'sensed' by lamina propria ILC2s, which released IL-13. In turn, IL-13 altered the cell fate of intestinal crypt progenitors to increase the output of epithelial tuft cells and goblet cells, mucin-secreting cells associated with allergic immunity in the mucosa of the lung and intestines. This study, followed shortly by two corroborative manuscripts in Nature and Science, have implicated this unusual epithelial cell as an early 'sensor' that initiates activation of innate lymphoid cells in order to reorganize the epithelium to a highly secretory state associated with increased smooth muscle contractility. Tuft cells were readily identified in the lung mucosa, where they are likely to also function as key initiating cells in asthma, where IL-25 has been identified as a potentially important upstream target for therapeutic intervention.


The authors review the history of biomarkers that evolved from studies targeting specific inflammatory pathways, like IL-4 and IL-13, in patients with asthma. The importance of biomarkers was revealed by the ability to identify responsive and non-responsive individuals in the treatment cohorts. Increasing emphasis has been created on identification of markers in the non-responsive asthma patient populations, particularly older patients, who often present with steroid resistance, additional underlying conditions, like obesity, and poor response to therapies targeting type 2 cytokines. This review succinctly summarizes the need for further study in order to pivot to new approaches for intervening in this increasingly recognized group of poorly served patients.

IgE is at the center of human allergic immunity, yet mechanisms that regulate the production of IgE from B cells remain incompletely understood. Unexpectedly, the IgE receptor, when expressed on appropriately isotype-switched B cells, promoted antigen-independent signaling that drove terminal differentiation of cells to plasma cells. Coupled with prior discoveries from the Allen lab, it appears that special properties intrinsic to the IgE molecule promote autonomous signals that may serve to limit continued somatic hypermutation by curtailing residence in the germinal center. These novel findings open up completely new understanding regarding mechanisms underlying selection of IgE-secreting cells, and suggest new hypotheses concerning how persons with allergy and asthma are able to circumvent these cell-intrinsic properties and develop high-avidity mutated IgE molecules that can drive devastating anaphylactic reactions.

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, by integrating their accomplishments across the greater UCSF campus, 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 major role in overseeing the progress of SABRE Center faculty and provides oversight in sustaining progress towards the overall goals of the Center.

SABRE Center Executive Committee Members

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

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

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

John V. Fahy, M.D., Professor
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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
SCIENTIFIC ADVISORY BOARD
Mitchell Kronenberg, Ph.D.
President and Scientific Director
LIAI - La Jolla Institute for Allergy & Immunology

Mitchell Kronenberg was appointed President of the La Jolla Institute for Allergy and Immunology in September 2003. He is responsible for the overall administration of physical resources, finances and space at the Institute; and works with the Institute’s board of directors, faculty, and executive management to develop and implement strategic plans for shaping the Institute’s future. In addition to his duties as LIAI’s chief executive officer, Dr. Kronenberg serves as Scientific Director of the Institute and Head of the Division of Developmental Immunology. He conducts an active research program on the development of the immune system and the pathogenesis of autoimmune disease, and is a world-renowned expert in the fields of mucosal and innate immunity.

Dr. Kronenberg graduated with a bachelor’s degree in biochemistry from Columbia University, and earned his Ph.D. from the California Institute of Technology (Caltech) in 1983. He stayed on at Caltech as a postdoctoral fellow, and joined the faculty of the UCLA School of Medicine in 1986, serving first as Assistant, and later as Associate and full Professor. In 1997, he moved to LIAI to head the Division of Developmental Immunology. He also is an Adjunct Professor of Biology at the University of California, San Diego.

Dr. Kronenberg is the co-author of more than 215 scientific publications and holds six research grants from the U.S. National Institutes of Health (NIH). He has served on a number of grant review panels for NIH and other private medical research agencies, and is on the editorial board of four scientific journals. He is the winner of the Richard Dwyer award for cancer research (UCLA) and has been the Kroc Professor of Medicine at the University of California, Davis, and the Wellcome Foundation visiting Professor at Harvard University.
Philippa (Pippa) Marrack, Ph.D.
Professor of Molecular Biology and Immunology
Vice Chair, Department of Immunology
National Jewish Medical and Research Center, Denver
Professor at the Health Sciences Center, University of Colorado
Research Investigator at the Howard Hughes Medical Institute, USA

As one of the world’s leading research scientists investigating T cells, the family of cells that help the body fight off disease, Dr. Marrack’s work has led to a greater understanding of their role in the immune system.

Born in the United Kingdom, Philippa Marrack earned her undergraduate and doctoral degrees in biological sciences from the University of Cambridge. She left the UK in 1971 to do postdoctoral work in the USA, where she has lived and worked ever since, initially at the University of California, and then at the University of Rochester. Since 1979, she has been based in Denver, Colorado, where she is now a research investigator at the Howard Hughes Medical Institute, Vice Chair of the Department of Immunology and Professor at National Jewish Medical and Research Center, and Professor at the University of Colorado’s Health Sciences Center.

During her career, Philippa Marrack has published more than 300 peer-reviewed journal articles and she has served on the editorial boards of numerous journals, including Cell, Science, and the Journal of Immunology. Amongst her many honors are the Royal Society’s Wellcome Foundation Prize (1990), the Paul Ehrlich and Ludwig Darmtsädter Prize (1993) and the Louisa Gross Horwitz Prize (1995). She has served on various panels and boards for the American Cancer Society, the U.S. National Institutes of Health, and the Burroughs Wellcome Fund. She was the President of the American Association of Immunologists in 2000-2001, and is currently the President of the International Union of Immunological Societies.
Christopher Wilson, M.D.
Director, Global Health Discovery Program, Gates Foundation

Dr. Chris Wilson, Director of the Global Health Discovery program, leads a team that targets fundamental scientific and technological advances in global health that could lead to new ways to prevent, treat, and diagnose disease.

Wilson joined the foundation in 2009 as Deputy Director, Vaccine Discovery and Human Biology, Global Health Discovery.

Wilson is a pediatrician and immunologist. He joined the faculty at the University of Washington in 1979 in the Infectious Diseases Division of the Department of Pediatrics and later served as head of the Division of Infectious Diseases, Immunology and Rheumatology. In 1989, he became one of the founding faculty members in the new Department of Immunology, and served as Chairman of the Department of Immunology and head of the graduate program in immunology from 1999-2009.

He has also served on a number of national advisory panels, including the Institute of Medicine Vaccine Safety Review Committee (2001-2004) and the National Advisory Council on Child Health and Human Development, NICHD, NIH, and he co-chaired the NIAID US Immunodeficiency Network Pilot Grant Review Committee. He is an elected fellow of the American Association for the Advancement of Science.

Wilson received a bachelor’s degree from the University of California, Irvine and a medical degree from UCLA. He trained in pediatrics at Boston Children’s Hospital /Harvard Medical School, served in the US Public Health Service, and then was a post-doctoral fellow in infectious diseases while performing immunology research at Stanford University.
SABRE CENTER INVESTIGATORS
Richard M. Locksley, M.D.
Professor, Departments of Medicine and Microbiology & Immunology
Investigator, Howard Hughes Medical Institute

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Dr. Locksley is the Director of the Sandler Asthma Basic Research Center (SABRE) and a Howard Hughes Medical Institute Investigator. He is a Professor in the Departments of Medicine and Microbiology & Immunology. He received his undergraduate degree in biochemistry from Harvard and his M.D. from the University of Rochester. After completing his residency at UCSF, he trained in infectious diseases at the University of Washington. Prior to his position as director of the SABRE Center, Dr. Locksley served 18 years as the Chief of the Division of Infectious Diseases at UCSF Medical Center. Dr. Locksley is a fellow of the American Academy of Arts and 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, which represent a previously unknown cell now implicated in allergic immunity. The ability to study the activation and organization of innate ILC2s uncovered a role for cells associated with allergy and asthma, such as eosinophils, in processes involved with basal metabolism and tissue homeostasis. Activation of ILC2s in the small intestine was implicated in alteration of the mucosa to a secretory phenotype characterized...
by high numbers of goblet cells and tuft cells. The latter, a previously mysterious epithelial cell of unknown function, was shown to be the source of IL-25, a cytokine capable of activating ILC2s and other immune cells associated with allergy and asthma, thus opening up entirely new avenues for discovery.

Representative Publications

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

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

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

Publications


Mark Ansel is 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. However, 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 (e.g. Th1, Th2, Th17, Treg, Tfh, etc.). These lineages are defined by their characteristic gene expression programs and mediate distinct immune functions. These gene expression 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. Naive CD4+ T cells that cannot produce any miRNAs exhibit reduced cell division and survival in response to immune stimuli. Surprisingly, they also undergo rapid unrestrained differentiation into effector cells. We have developed a screening technology that allows us to rapidly determine which specific miRNAs regulate each of these T cell behaviors, and a high throughput nanoscaled pipeline for determining miRNA expression patterns in small clinical samples (such as sorted T cell subsets from the airways of human asthmatic subjects, serum, sputum, and other sources of extracellular miRNAs, etc.). In addition, we discovered that T cells rapidly reset their miRNA repertoire upon activation. This process that involves ubiquitination and degradation of Argonaute proteins, but the signaling mechanisms and the fate of associated miRNAs remains unknown. This rapid change in miRNA expression may be important 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**


Esteban González Burchard, M.D., M.P.H., is a physician-scientist with formal training and expertise in pulmonary medicine, epidemiology, molecular genetics, genetic and clinical research. He has led a large research program focusing on minority children and gene-environment interactions since 2001. Dr. Burchard serves as an advisor to the National Academy of Sciences of the U.S. Congress on gene-environment interactions. Dr. Burchard has expertise in the field of precision medicine and served on the Expert Panel for President Obama’s Precision Medicine Initiative. He initiated and now directs four independent asthma studies in minority children. He has assembled a collaborative team of co-investigators on several projects with specific expertise in genetics, social and environmental epidemiology.

Dr. Esteban Burchard directs the Asthma Genetics Core Facility, now named the Asthma Collaboratory, which is now the largest annotated gene biorepository from minority populations with asthma in the world. The Asthma Biobank is open to reputable scientists seeking to assess genetic risk for variants in populations of interest or to extend findings made in animal models to suggest potential mechanistic involvement in human asthma. The Asthma Collaboratory has met continued goals to expand the numbers of patient samples; to extend the numbers of collaborators both nationally and internationally who use the database; and to continue to spearhead genetic studies in minority populations with asthma. The Burchard lab has led efforts to identify genetic modifiers of drugs used in asthma that might contribute to the poorer response in a number of ethnic populations and more recently is leading efforts to find biomarkers for different subsets of asthma as defined by presentation or response to therapy. These efforts have contributed to over 20 publications in the past 2 years with numerous collaborators and trainees, and successful competition for extramural funding. Dr. Burchard served on President Obama’s Precision Medicine Initiative and has begun efforts to prepare a US-wide Asthma Genetics Consortium grant funded by the NIH.

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

**Lab Objectives**

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

**Selected Publications**

6. Andrés Moreno-Estrada, Christopher R. Gignoux, (35 authors), Irma Silva-Zolezzi,*


11. 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

12. 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

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

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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 the regulation of gene expression in the immune system.

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
21. Fahy JV. Chair's summary: Mechanisms of relevance to clinical heterogeneity of asthma


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

The Shin laboratory is interested in understanding the molecular mechanism and functional role of dendritic cell-mediated antigen presentation. Dr. Shin has previously found that the antigen-presenting molecule MHCII is ubiquitinated by MARCH1 ubiquitin ligase in dendritic cells, and this ubiquitination mediates MHCII endocytosis and lysosomal degradation. Her laboratory has recently found that the costimulatory molecule CD86 is also ubiquitinated by MARCH1 and that this ubiquitination also mediates endocytosis and degradation of CD86. More recently, Dr. Shin’s laboratory has studied the functional role of this ubiquitination. This study indicates that MHCII ubiquitination is required for proper production of regulatory T cells (Tregs) in the thymus. Currently, Dr. Shin is investigating how MHCII ubiquitination contributes to Treg development and whether Tregs generated in MHCII ubiquitination-dependent manner are distinct in their repertoire and function.

The Shin laboratory is also interested in understanding the role of the high affinity IgE receptor FceRI expressed in dendritic cells. Although the role of FceRI in the pathogenesis of allergy is well known, its physiologic role remains unclear. Dr. Shin’s laboratory has recently found that FceRI is constitutively endocytosed and transported to the lysosomes in human dendritic cells and monocytes, and that this FceRI endolysosomal trafficking mediates cellular entry of circulating IgE contributing to serum IgE clearance. These findings suggest that FceRI expressed by dendritic cells and monocytes may play an important role in regulating serum IgE concentration in humans. Her laboratory is currently investigating whether unusually high blood IgE levels found in some human diseases is attributed to the alteration in FceRI endolysosomal trafficking that results circulating IgE not efficiently entering cells but accumulating in the blood.

Dr. Shin’s research programs are greatly benefited by many of the excellent core facilities supported by SABRE. Flow cytometry core is being used in a daily basis for most of the projects. Microscopy facility is helping in situ analysis of dendritic cells in human tissues and also the analysis of protein distribution inside dendritic cells. Mouse physiology core is being used to test the therapeutic potential of human IgE derivative that Dr. Shin has recently found to be capable of regulating immune stimulation.
Selected Publications


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


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

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

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

These studies fall into three specific categories:

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

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

3) Clinical trials of novel therapeutic approaches.

Selected Publications


Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function. 


inflammation and intercellular communication in asthmatic airways. *J Immunol.* 2011 Feb 1; 186(3): 1861-9


Executive Summary

I direct the UCSF Asthma Collaboration, which represents the largest gene-environment study (bio-repository) of minority children in the world. We have recruited more than 10,000 study participants. In addition to DNA samples, we have collected detailed data on social, environmental, and biologic risk factors for asthma, as well as detailed information on medical history and drug response.

We are using this biorepository to make new discoveries in asthma and to educate the next generation of scientists. We also use this bio-repository to support the Sandler Asthma Genetics Core Facility, which serves as a core laboratory for investigators sponsored by either the internal UCSF Sandler Center for Basic Research in Asthma or the National Sandler Program for Asthma Research. We provide consultation, genetic testing, biological assays and statistical analysis for multiple UCSF and non-UCSF investigators sponsored through the Sandler programs. We have facilitated research on asthma in minority populations for scores of laboratories around the world, including multiple SABRE and AAF funded investigators, as well as for national and international consortia. Since funding for the Genetics Core began in 2008, we have collaborated with 80 individual investigators and two national and seven international consortia. Moreover, we are using these data in collaboration with Genentech and MedImmune to select patients with asthma who are most likely to respond to their proprietary drug, anti-IL13 and anti-IL-5, respectively.

I recently became the lead Principal Investigator (PI) of the newly formed Asthma Translational Genomics Collaborative (ATGC). We will perform WGS on 16,000 minority children with asthma to assess drug response. This is in addition, to the 2,500 samples already sequenced (total n ~ 18,500). This nationwide effort represents 33% of the NHLBI’s budget for whole genome sequencing (WGS) and is the largest study of its kind in the world. However, this was an XO1 mechanism and only provided funds for sequencing. Therefore, we are currently writing an RO1 to perform the analyses. No other groups are working on the type and scale of science that we are conducting. These data will be invaluable to Sandler-sponsored investigators.

Accomplishments in 2016-2017

This past year the Genetics Core Facility has focused on three main goals: Expansion, Collaboration and Research.

Expansion

1) Recruitment
This past year we have reinitiated recruitment of well-characterized children with and without asthma. Although bronchial tissue is ideal for measuring gene expression patterns, research bronchoscopies are unethical in children. Therefore, we developed and pioneered techniques sample tissue from the posterior nasal turbinate of children with and without asthma (Poole, *JACI* 2014). We recruited more than 1000 children in the last two years. These children include nasal brushing for RNA Seq analyses and detailed lung function measures and bronchodilator testing. We are trying to partition asthma endotypes using gene expression signatures. We have previously demonstrated that there is ~90% overlap in gene expression from bronchial biopsies compared to nasal brushings (Poole, *JACI* 2014). We will now compare nasal brushing gene expression to peripheral blood from children with and without asthma.

2) Expansion of data

We joined the new NHLBI initiative to perform whole genome sequencing in African American and Latino children with asthma-related traits. We have completed the sequencing work for about 1500 children. We are pleased to have recently submitted our manuscript entitled, “Whole genome sequencing of pharmacogenetic drug response in racially and ethnically diverse children with asthma” to be considered for publication. This manuscript presents the first results of the National Heart, Lung, and Blood Institute’s Trans-Omics for Precision Medicine (TOPMed) whole genome sequencing program.

Bronchodilators, such as albuterol, are the first line treatment for asthma worldwide. Bronchodilator response (BDR) varies significantly between racial/ethnic groups and this variation may be a contributing factor to the disparity in asthma morbidity and mortality observed between populations. Our study is the largest pharmacogenomic study of BDR using whole genome sequencing (WGS) data from three populations of minority children with asthma, including African Americans and Puerto Ricans, the populations with the highest risk of asthma morbidity and mortality. We identified novel BDR-associated loci that are highly relevant to albuterol drug response and verified their functional relevance using ChIP-seq, RNA-seq, and enhancer assays.

In addition to the unprecedentedly large WGS dataset generated for pharmacogenomic study in three racially/ethnically diverse populations, our study also made use of an extreme phenotype study design to increase the power to identify BDR associations that would be relevant to the most vulnerable patients.

Our study integrated genetic with functional studies to investigate a complex phenotype. We believe that it fits well within the scope of Journal and would be of great interest to your audience. Furthermore, the findings of our study would help to guide future development of asthma-related therapeutics or other interventions to improve patient care. Finally, the current underrepresentation of racial and ethnically diverse populations in clinical and biomedical research is a missed scientific opportunity, and this manuscript is therefore of great importance to future genetic studies of the changing demographics in the U.S. and worldwide.
In collaboration with Noah Zaitlen, Ph.D. (UCSF), we measured DNA methylation for almost 600 individuals using Illumina’s Infinium Methylation 450K platform. Methylation is thought to have genetic, social and environmental contributors. We used our rich dataset from the GALA study to ask what proportion of the variance in methylation is explained by genetic ancestry vs. self-identified race ethnicity. We demonstrated that 75% of the variance in methylation is explained by genetic ancestry. Whereas, 25% is explained by social and environmental measures which co-vary with self-identified race/ethnicity. This publication (Galanter, Elife 2017) significantly advanced our understanding of the role of race/ethnicity in clinical and biomedical research.

**Collaboration**

**UCSF Sandler Program and the AAF:** In the era of large “team science” the value and importance of collaboration cannot be overstated. In the spirit of collaboration we have renamed our lab the UCSF Asthma Collaboratory. We have made the existing cohorts available to more than 35 Sandler-sponsored investigators (UCSF SABRE and the AAF). Below we describe three recent collaborations.

Marsha Wills-Karp, Ph.D., Johns Hopkins University:
In order to support their findings in a mouse model, we studied associations of 143 SNPs in CLEC7A with asthma, baseline lung function (FEV1), and skin prick test in Latino (n = 2,861) and African American (n = 1,414) children with and without asthma. GALA II and SAGE. We identified a genetic variant that is significantly associated with baseline lung function (FEV1) after Bonferroni correction. We did not see significant association results of CLEC7A SNPs with asthma or skin prick test.

Russel Bowler, M.D., Ph.D., National Jewish Health System:
They have found a SNP in SOD3 (rs1799895) that changes ECM binding of the protein in mouse. We evaluated whether we would find similar association of the same SNP with asthma exacerbation in human samples. The SNP was not typed in GWAS data but we have it in WGS data. In 997 children with asthma (263 Mexican, 342 Puerto Rican, and 392 African American), we did not find association of the SNP with asthma exacerbation.

To help AAF investigator Carla Rothlin (Yale) study the importance of TAM (TYRO3, AXL and MERTK) Receptor Tyrosine Kinase Signaling Pathway in the pathogenesis of asthma, we have run association tests between asthma and genetic variants in TYRO3, a member of TAM. In a meta-analysis across three independent genetic studies, GALA I, GALA II and SAGE, we identified multiple intronic variants in TYRO3 to be significantly associated with asthma in Latinos and African Americans. The most significant association was at a SNP located within several putative transcription factor-binding sites (rs1200341, p=3.3 x 10^-7, OR=0.77), suggesting it may play a role in regulating the expression of TYRO3. Our association test results have complemented and strengthened findings in functional studies that Dr. Rothlin’s group designed in a mouse model. A manuscript based on the collaborative work has been published in Science, 2016.
Other Collaborations: In 2016 we have collaborated with the following faculty from UCSF and elsewhere: Ryan Hernandez (UCSF), Carol Ober (Chicago), Kathleen Barnes (Johns Hopkins), Jim Gauderman (USC), Noah Zaitlen (UCSF), Mario Castro (Washington University), L. Keoki Williams (Henry Ford Health Systems), Fernando Martinez (University of Arizona), Max Seibold (National Jewish Health), Rajesh Kumar (Children’s Memorial Hospital, Chicago), Scott Weiss (Harvard), Carla Rothin (Yale), Christopher Hunter (U Penn), Chris Allen (UCSF), John Balmes, UCSF, and Ellen Eisen (UCB). We have contributed our genotype data to national and international consortiums to study asthma, obesity, eczema, skin color and anthropometry. We have also contributed our genome-wide methylation data to the Pregnancy And Childhood Epigenetics (PACE) consortium to study how DNA methylation pattern responds to maternal smoking in pregnancy. All our published data have been submitted to the database of Genotypes and Phenotypes (dbGaP).

New Investigators to the field: One of the stated goals of the Sandler program is to recruit new investigators with exceptional talent to focus their attention on asthma. We have done this in two ways: (1) Scientific Collaboration with young investigators and (2) Education of high school, college graduate and professional students.

(1) Scientific Collaboration: We recruited top young talent to focus on asthma in minority children. We have published with colleagues at UC Berkeley (Ellen Eisen, ScD. And John Balmes, M.D.) to address the issue of air pollution in children with asthma. Together we have shared a talented postdoctoral fellow and Fulbright scholar, Andreas Neophytou, Sc.D. and Eunice Lee. Dr. Neophytou’s work and recent publication on ethnic-specific effects of air pollution are described below (Neophytou, et al., AJRCCM 2016). Dr. Neophytotou is currently applying for an NIH K99R00 for April 2017.

Marquitta White, Ph.D. is a new postdoctoral fellow. She is one of the only U.S. born African American geneticist in the U.S. She was ranked highly and considered to be Vanderbilt’s top genetic graduate student in 2015. Dr. White is leading the gene-environment initiative in the UCSF Asthma Collaboratory. In addition to being an outstanding scientist she is a tremendous teacher and she has taken on six students including one high school student from Lowell High School in SF. All six will have first author publications submitted in 2016. She has a K-award under review as of March 2016.

Angel Mak, Ph.D. is the new Director of Genetics Research for the Asthma Collaboratory. Dr. Mak is new to the field of asthma but she is not new to genetics and bioinformatics. Dr. Mak spent four years as a postdoctoral fellow in the laboratory of Dr. Pui-Yan Kwok. She is currently leading the NHLBI sponsored Whole Genome Sequencing (WGS) project described above and her manuscript was submitted to Nature Genetics on March 21, 2017.

Walter Eckalbar, Ph.D. is a postdoctoral fellow in Nadav Ahituv’s lab. He is studying the pharmacologic basis of ethnic-specific differences in bronchodilator drug response in children with asthma. He is using a variety of approaches including RNA Seq, CHiP Seq and whole genome sequencing to investigate high and low drug responders to albuterol. Dr. Eckalbar is currently applying for an NIH K99R00 for April 2017.
Dexter Hadley, M.D., Ph.D. is a new faculty recruit from Stanford University. He is using the asthma biorepository to identify asthma endophenotypes. His K-award used our data and was funded in 2016.

Marina Sirota, Ph.D., a new faculty recruit from Stanford University, is using the asthma biorepository to identify early biologic predictors of preterm birth and asthma. He first manuscript is under review. Her K-award used our data and was funded in 2016.

Max Seibold, Ph.D. is an Associate Professor at National Jewish Health. He recently received two RO1’s using the asthma biorepository. His first RO1 focuses on the nasal transcriptome and using gene signatures to differentiate type 2 asthma endophenotypes. His second RO1 focuses on genetic determinants of ethnic-specific ancestry differences in pulmonary function measures and their impact on asthma. He was recently promoted to Director of Stem Cell Research at National Jewish Health.

**Large-scale Collaborative Projects:** This past year we participated in the NHLBI-sponsored EVE Asthma Consortium, Trans-Omics for Precision Medicine (TOPMed) Program, and several other national and international collaborations, including the new NHLBI initiative to perform whole genome sequencing for asthma-related traits and the Hispanic Anthropometry Consortium.

**Research**

Many Sandler/AAF-sponsored investigators study asthma using animal models and have found interesting results. Their findings would be more significant if confirmed in human genetic studies. We have generated genome-wide association studies (GWAS), WGS, methylation, microbiome, and biomarker data from our study populations. We have worked closely with asthma investigators throughout the country to advance the field of asthma research. We provide our data and results to Sandler/AAF investigators as in silico replication to supplement initial findings from basic science models.

**DNA Methylation and asthma:**

Methylation is known to vary by cell type and the proportion of cell types can vary by asthma status. We have collaborated with Eran Halperin’s group at UC Berkeley to estimate cell type proportions from methylation data. Based on our collaboration, a new method, Reference-Free Adjustment for Cell Type composition (ReFACTor), has been developed for the estimation of cell type composition of each individual in an unsupervised manner, without the need for a reference dataset. This method is based on an unsupervised feature selection step followed by a sparse principal component analysis, and thus it is highly efficient and scalable for large studies. Our results show that estimates of the cell type composition using ReFACTor are better compared to both principal component analysis and reference-based estimates, resulting in an improved power and a better control for false positives in epigenome-wide association studies (EWAS) (Elior, et. al., Nature Methods).
GWAS of asthma in African Americans: Asthma displays a significant racial/ethnic disparity in both prevalence and mortality, with African Americans bearing a much larger disease burden than European Americans. We have run GWAS for asthma in 1227 African Americans in SAGE. Genotypes were measured on the Affymetrix Axiom array. Logistic regression was used to identify significant associations between genetic variants and asthma susceptibility. The analysis was adjusted for age, sex, body mass index (BMI), and global African ancestry. We identified five SNPs putatively associated with asthma susceptibility, after adjusting for BMI, in the SAGE cohort. One SNP is a replication of a known association discovered in a recent meta-analysis for asthma susceptibility among multiple racial/ethnic groups. Interestingly, several of our most significant SNPs were associated with both asthma and BMI/obesity quantitative trait loci (QTL). This may indicate that these markers may be important in the recently emergent “obese-asthma” phenotype. This manuscript was published in Immunogenetics, 2016 and was co-authored by a 16 year old highschool female student from Lowell High School in San Francisco.

Air pollution and lung function GALA II & SAGE II studies: Air pollution has been associated with adverse respiratory health effects including reduced lung function. Few studies, however, have examined possible effects in minority populations, which may be more susceptible to adverse health outcomes, due to genetic susceptibility and/or increased social vulnerability. In 1449 Latino and 519 African American children with asthma from five different geographical regions in the mainland U.S. and Puerto Rico, we examined associations between pollutant exposures and lung function parameters, and tested for interaction terms between exposures and genetic ancestry. We found associations between exposures to particulate matter and reduced lung function in Latino and African American children with asthma. Our results suggest geographical heterogeneity of short-term effects of exposures to particulate matter and potential differences in early lifetime exposure effects in children from different racial and ethnic backgrounds. Our work has been published in the American Journal of Respiratory and Critical Care Medicine (Neophytou et al. AJRCCM 2016).

New Initiatives in 2016

Early life infections in children and their relationship to asthma: We hypothesize that Respiratory Sycntial Virus (RSV) and Human Rhinovirus (RV) infection in early life substantially predispose children to asthma later in life. To test this hypothesis we are initiating a new collaboration with Sam Oh, Ph.D (epidemiologist), Max Seibold, Ph.D. (molecular biologist) and Jose Rodriguez, M.D. We are launching a new pilot study with the hopes of an RO1 submission in June 2016. We will sample all children less than one year of age who are admitted for any respiratory condition to the Pediatric ICU. We will also sample their peers from the child daycares from which they came. We will perform nasal lavage and blood collection on all children (ICU and daycares) and their mothers. We will measure the nasal lavage. We will then prospectively follow children for five years to determine who develops asthma and who does not.
Financial Support

We have been successful at leveraging Sandler funding with support from UCSF, the NIH, MedImmune and Genentech. Sandler funding ($125,000) contributes partial salary support for the *Asthma Collaboratory* manager (Celeste Eng), for the clinical data manager (Sandra Salazar), and for the statistical geneticist (Donglei Hu, Ph.D.) and epidemiologist (Sam Oh, Ph.D.) who will continue to support analyses requested by Sandler-sponsored investigators. UCSF and the Harry Hind Family Foundation have agreed to provide $225K of matching funds on a yearly basis to support my lab and me. Of this, I am using $100K to fund members of my lab and $125K of this to support the *Asthma Collaboratory*.

Active Grants

Current

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<th>End Date</th>
<th>Funding</th>
<th>Role</th>
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<td>Role: Project PI&lt;br&gt;Project title: UCSF Clinical Pharmacology and Therapeutics Training Grant&lt;br&gt;Goal: To train physician, pharmacist and Ph.D. scientists in clinical and therapeutic actions of drugs in humans.</td>
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<td>CM</td>
<td>$779,767</td>
<td>Role: Project PI&lt;br&gt;Program title: Addressing Disparities in Chronic Disease with a Teen and Young Adult Focus&lt;br&gt;Project title: The Genetics of Asthma and Obesity Using Admixture Mapping in Latinos&lt;br&gt;Goal: To identify novel genetic variants associated with both asthma and obesity by deep re-sequencing of candidate regions identified through admixture mapping</td>
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<td>Role: Project PI&lt;br&gt;Project title: Pharmacogenomics of Bronchodilator Response in Minority Children with Asthma&lt;br&gt;Goal: 1) To perform “Exome Plus” DNA sequencing on the extremes of bronchodilator response among minority children with asthma. 2) To identify genetic variation associated with bronchodilator response. 3) To determine whether promoter variants associated with bronchodilator response modulate gene expression in primary airway smooth muscle cells</td>
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**Sandler Asthma Basic Research Center**

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<td>CM</td>
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<td>Project title: “SF State BUILD: Enabling Students to Represent in Science”</td>
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<td>Project title: Gene-Environment Analyses of Early Life Exposures and Asthma in Ethnically Diverse Children</td>
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<td>TRDRP</td>
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<td>Project title: Air Pollution, Tobacco Smoke, and Asthma in Minority Children</td>
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Sandler Asthma Basic Research Center

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<td>R01Hl128439 (Seibold) 08/15/15-05/30/20 0.47 NIH-NHLBI $52,462 (sub only) 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.</td>
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<td>R01HD085993 - 01 (Wu) 09/01/15-08/31/20 0.60 NIH-UCSF Subcontract $76,551 (sub only) 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 β2-agonists. This research employs existing genetic, genomic, and metabolomics data from clinical trial and real-life populations. Linking genetic variants to the therapeutic responses with additional information from genomics and metabolomics will provide insight into the biologic pathways that may be activated. Knowledge gained from this research will advance the field of personalized medicine for pediatric asthma through the creation of a prediction model.</td>
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<td>1R01MD010443 (Burchard/Seibold) 04/22/16-12/31/20 1.36 NIH-NIMHD $589,510 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.</td>
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<td>UM1HG008901 (Darnell) 01/14/16-11/30/17 0.57 NIH/NHGRI $12,216 (sub only) Role: Subcontract PI 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.</td>
</tr>
</tbody>
</table>
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.

Pending

R01HL135156 (Seibold) 09/01/16-08/31/21 1.80
CM
NIH/NHLBI $232,433
Role: Co-PI
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.

(Ahituv, Burchard & Seibold) 9/1/16 – 08/31/21 1.09
CM
NIH/LCMI $499,999
Role: Co-PI
Goal: This project plans to use several genomic technologies on cells treated with these drugs from asthmatic patients with detailed clinical response and genetic data, to identify the genetic factors that lead to differences in asthma response.

Publications
Core-supported projects led by SABRE-affiliated faculty published or accepted for publication during 2016-2017:


associated with higher lung function in African American youths with asthma. *J Asthma*. 2016 Dec 8:0. PubMed PMID: 27929698


Microscopy Core

Managing Director: Kaitlin Corbin
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 existing powerful imaging 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, 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 2017, the core will focus on expanding use of two new technologies, and continue to develop and elaborate custom built tools for image acquisition and analysis.

1. To further automate the analysis of 3D lattice light sheet imaging data, and expand the use of 3D Bessel microscopy through guided pilots and collaborations with new users.
2. To update and reconfigure two outdated, and thus little used multiphoton microscopes into a single, cutting edge instrument which will exceed current capabilities and drive further development of custom software and hardware tools.
3. To refine and expand the use of the Lattice Light-Sheet microscope (LLSM), and elaborate its capabilities to meet the needs of a growing user base.
4. To extend the usage and utility of mouse lung imaging through continued development of minimally invasive intravital imaging methods and instrumentation.
5. 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 (Kaitlin Corbin) 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 228 registered users of the BIDC. These users represent 51 principal investigators or labs. These labs are drawn from 19 departments or organizational units.

In 2016, 53 new users were trained. All users received comprehensive training on Center instruments or image processing stations. Many users are trained on multiple instruments. 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. Users are encouraged to ask questions and request assistance as needed. We do not charge for our time through recharges, and many projects are essentially ‘collaborations’. We have specifically trained users from the following labs:

- Anderson
- Baskin
- Bluestone
- Debnath
- Gould
- Fong
- Hebrok
- Huang
- Klein
- Krummel
- Laird
- Lanier
- Locksley
- Looney
- Lue
- Molofsky
- Muschen
- Nystul
- Oakes
- Park
- Roose
- Rosenblum
- Rubenstein
- Schneider
- Sheppard
- Shin
- Sneddon
- Solomon
- Steward
- Verkman
- Weaver
- Weiss
- Werb
Recent Accomplishments

In 2016, scientifically:

1. We completed implementation of the Lattice Light-Sheet Microscope (LLSM), and opened the instrument to the BIDC and UCSF community. There are currently two major users, and five recent pilot users from UCSF labs. The data collected from this microscope resulted in a Science publication titled, “Visualizing Dynamic Microvilar Search and Stabilization during Ligand Detection by T cells” In Press. The data from this microscope represents its own processing and analysis challenges due to its size (a typical afternoon of imaging routinely results in 1TB of data). We have implemented a data processing pipeline that is available to users to speed the process from collection to visualization in Imaris. We have also written microscope specific executable programs to improve the “quality of life” for the users of the microscope that both shorten time from microscope alignment to data collection and allow a “preview” of user’s collected data to ensure imaging quality is maximized.

2. As we have begun to use upwards of six channels of spectral data, and to multiplex fluorophores to identify cell populations, current analysis techniques have proven computationally inefficient and have become inadequate. In order to deal with these issues, we have developed robust and efficient image analysis software, capable of handling multidimensional data based on machine learning. Utilizing dimensionality reduction, with just a training data set, we are able to automatically identify cell populations that previously required manual classification. This analysis tool nearly exponentially decreases time required to analyze complex image data and distinguish between single, and multi-labeled cells with fluorophores of overlapping emission spectra.

3. We extended the utility of Micro-Magellan microscope control software (a part of the Micro-Manager project started at UCSF, and now distributed globally free of charge) to both laser scanning and camera-based instruments. Included in this extension is a number of new features, designed to decrease imaging time through more granular control over device operations, including dual Z—drive control for extended imaging range and ability to autofocus even over large areas. We have adapted a previously published technique for eight color fixed cell imaging in cleared lungs in order to determine the physiological location and source of cytokines important in lung injury and asthma. Using this technique, we are identifying and tracking both the cell types that specifically produce cytokines of interest during asthma (IL17, IL-13, etc) during asthma and the cells with which they interact. To follow up on this work in fixed histocytometry, we have also set up live slice imaging systems using transgenic cytokine reporter mice; by utilizing correlative markers we can track differences in the behavior of cytokine producing cells in different tissue compartments of the lung in real time in the context of both lung injury and asthma.

4. We continue to provide ongoing technical and instrumentation support to the asthma community at UCSF and beyond, in order to put existing and emerging imaging technologies to practical use in the study of asthma.
Introduction of new equipment, and training

This year the BIDC has overseen the installation of a Nikon C2 MacroConfocal microscope for fast confocal imaging of whole organ or organism imaging, and training of new users. We have overseen the migration of scheduling of all resources to MyCores to reduce the amount of time dedicated to yearly billing. Jordan Briscoe has undergone extensive training in multi-tissue preparation and staining, including protocol optimization. The LLSM has been opened to a range of pilot users for data collection, prompting continuing development.

Space
In 2016, the BIDC recently took possession of three new rooms in Medical Sciences S11. We have created an office area next to data analysis work stations, which fosters collaboration on analysis projects. We have also outfitted a wet lab space for sample preparation, including a vibratome, compressitome, incubator and fume hood that has allowed comprehensive training of new and inexperienced users from start to finish. We have also moved three microscopes into a new imaging room, where the overall performance and reliability of the instruments has improved due to better temperature stability. We maintain instruments and development tools in three core rooms in Medical Sciences S11 and also maintain additional microscopes at six other sites throughout the campus, including behind the animal barrier.

Funding
The following represent some of the lung-related grants that were funded in 2016, in part through our efforts and support:

1) Schneider S10

The following were submitted:

1) Matthew Krummel, RAP award

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:


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


Plans for the Coming Year

1. As we continue to develop state of the art machine learning algorithms to automate high-dimensional data, building on the open source software previously developed in the BIDC for the visualization of large data sets, 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.

2. In the next year, Kyle Marchuk (BIDC Specialist) will work to expand the user base for the LLSM microscope, and with that elaborate it to accommodate various users specific needs. Within the complexity of the microscope a lot of variation can be found to expand and optimize what can be imaged at the highest spatial and temporal resolution available. We will also work to further refine and automate the microscope itself. On the LLSM in multi-color acquisition there are currently two sources of image registration mismatch that arise; mechanical (from the raising and lowering of the objective configuration) and fundamental (light at different wavelengths pass through the collection optics slightly differently). Currently, channel registration is a manual process that is part of the data processing pipeline. We will write a stand-alone program that will make use of multi-color fiducial markers to perform a non-biased channel correction with minimal user input.

3. In the last year, the BIDC created custom software that stitched multiple fields of view, subsampled, filtered, and packaged data for further analysis in one step, streamlining the process from microscope to data. In the next year, we will expand this tool box, allowing users to access the full suite of FIJI plugins and tools during this pre-processing phase.

4. In the next year, Jordan Briscoe (BIDC specialist) will 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.

5. A major push in the next year will be to open and extend access to our light sheet microscope, and develop a library of known fluorophores which can be used with different clearing agents to minimize optimization time.

6. Kaitlin Corbin will continue to develop and validate standard practices for imaging live biopsies that retain relevant physiological behavior, as defined through intravital imaging. A major component of this project will be to define “zones” of behavior and characterize immune behaviors and their regulation. To match zones between intravital and slice models, we will establish maximal tissue processing time, optimal storage and imaging conditions including media, oxygenation, temperature, and time of sectioning, to ensure that immune behavior and motility are reflective of physiological affects rather than culture and imaging conditions. These conditions will then be validated using human tumor and lung biopsies to elucidate immune cell behavior in the tumor microenvironment and in the asthmatic lung.
7. We plan to renovate the newly acquired BIDC space; this will provide much needed space for new instruments and vendor demonstrations, which allow us to stay at the cutting edge of imaging technology. Renovations will also allow currently isolated instruments to be brought into a centralized space where temperature conditions can be more precisely controlled, improving instrument reliability and performance.

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 founded an image analysis working group that meets bimonthly, each meeting three researchers discuss the issues they are facing in analysis so that the group can share knowledge, code, and encourage collaboration. We have also begun hosting 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 Kyle Marchuk will take on lung imaging pilots, with a focus on improving and expanding Micro-Magellan and analysis capabilities to address the specific needs of these users.

Current Equipment

Permanent Equipment:
1. Gen1 custom built 2-photon: 4 color
2. Gen2 custom built 2-photon: 5 color
3. *Gen3 custom built 2-photon: 6 color/2 laser
4. *Spectral laser scanning confocal microscope (C1Si)
5. Spinning-disk confocal microscope (Yokogawa 4-laser on a Zeiss 200M base)
6. IVIS live animal imager (animal colony)
7. Nikon spinning-disk confocal with TIRF and photo-ablation (Wittman)
8. Zeiss Cell Observer with Apotome (Nystul)
9. *Alaris 3D printer
10. Nikon A1R Multiphoton microscope
11. Nikon-based RNA Counting Microscope (Roose)
12. Zeiss large field of view spinning disk microscope (Yokogawa CSU-X1)
13. 3D Bessel Microscope

* Indicates SABRE is a partial owner of this instrument.
Analysis Computers and Software Platforms:
We continue to maintain three IMARIS licenses and associated Matlab licenses. As previously, MDS/Molecular Devices supplies upgraded keys for PC-based analysis stations for image processing. We have partnered with and will support the following commercial partners who supply working copies of their software as part of the sponsorship program:

- MDS/Molecular Devices 'Metamorph' supplies the three offline computers/keys as well as online keys
- Bitplane 'Imaris' has subsidized the purchase of software used in the facility.
- Solidworks has supplied 2 software keys for our prototyping and manufacturing purposes.
- Nikon has supplied a software key for a full image analysis version of NIS-Elements.
ASTHMA RELATED RESEARCH PROJECTS
Objective

This Center grant is focused on understanding the dynamic effects of IL-13 and IL-17 in allergic airway disease.

Projects

The center is composed of 3 projects and 1 human subjects core that supports each of the 3 projects.

A. Specific Aims (corresponding to aims of each of the 3 projects)

1. To identify critical miRNAs that are differentially expressed in the airway epithelium of patients with asthma at baseline and in response to allergen challenge or corticosteroid treatment, to determine the roles of IL-13 and IL-17 in regulating these miRNAs and to identify miRNAs that mediate cytokine-induced mucous metaplasia.
2. To determine the relative importance of responses of airway smooth muscle and epithelium to IL-17 in the induction of airway hyperresponsiveness and to determine the individual and combined effects of IL-13 and IL-17 on airway smooth muscle contractility and on clinical responses of patients with severe and mild-to-moderate asthma and in response to allergen challenge or treatment with corticosteroids.
3. To determine the temporal and spatial dynamics of the interactions of IL-13 and IL-17 producing cells with antigen-presenting cells and with airway epithelium and airway smooth muscle in lung slices from allergen-challenged mice and in human airway biopsies from patients with severe and mild-to-moderate asthma and in response to allergen challenge or treatment with corticosteroids.

B. Studies and Results

For Project 1, directed by David Erle and Prescott Woodruff, in addition to ongoing studies of miRNAs, we completed studies showing that 1) mucus plugs in fatal asthma contain distinct MUC5AC- and MUC5B- rich domains, 2) IL-13 stimulation of human bronchial epithelial cells mimics this pathological mucus gel, 3) IL-13 stimulation also causes near complete arrest of mucociliary transport, 4) this arrest is due to tethering of MUC5AC-rich domains to the airway epithelium. These experiments identify a novel mechanism that is likely to be a major contributor to airway obstruction and mucus plugging in asthma.

For Project 2, directed by Dean Sheppard, during the past year we have we have extended our work using the exaggerated responses of airway smooth muscle induced by IL13 and IL17 to validate a completely new way to treat the exaggerated airway narrowing that characterizes asthma – weakening the tethering of contracting muscle to the underlying airway extracellular matrix. We showed that blocking the alpha5beta1 integrin with small molecule inhibitors decreases force generation by airway smooth muscle and improves in vivo airway hyperresponsiveness and validated this approach with mice lacking this integrin only in smooth muscle. We have also extended this approach to
targeting another integrin, alpha2beta1 and a cadherin critical for cell cell adhesion of airway smooth muscle, cadherin 11.

For Project 3, directed by Max Krummel, we have generated the combined reporter mice and staining protocols required to track cytokine-expressing ab T cells in real time and have been working to develop a ‘clearing’ protocol for lungs so that we can map extremely large volumes of lung tissue to characterize the branch-by-branch distribution of these cells. We are in the process of completing the constructs and lines required to track cellular polarization and cytokine release in vivo. We have also screened phage-display antibody libraries to isolate novel antibodies with desirable properties directed against seven first round targets. These are to be used for imaging and improved immune profiling of immune cells within lung specimens. These include CD1c, CD4, CD161, CrTh2, Sigelec 8, CCR4, CCR6 and. Selections have been completed for five of these and antibodies have begun to be further profiled for the first two.

C. Significance

We have found that airway epithelial miRNA expression is altered in most subjects with mild-moderate stable asthma as compared with healthy control subjects. A more complete understanding of the causes and consequences of these alterations in miRNAs could be useful in identifying subsets of asthmatics with distinct pathophysiology and may lead to novel therapeutic approaches based on modulating miRNAs or their targets. Our recent studies of the effects of IL-13 on mucins and mucociliary transport identified a novel mechanism likely to be a major contributor to the 250,000 worldwide asthma deaths that are estimated to occur each year. This focuses attention further on therapies that might reduce mucus production, secretion, or tethering.

Our identification that airway smooth muscle tethering is critical for airway narrowing in response to airway smooth muscle contraction has identified a novel therapeutic approach to asthma. We have already identified three new promising targets and obtained additional funding specifically designed to commercialize this new approach and lay the groundwork for clinical trials.

Human asthmatics are heterogeneous and treatments for some are ineffective for others. The source of this variation almost certainly maps to differences in the cells that are recruited to the afflicted lungs as well as the spatial distribution. Our study will define the critical interactions that underlie IL13- and IL17- driven asthma and will propose key sites of therapeutic cellular (e.g. antibody-blocking) interventions for each.

Training and Integration with Sandler Program

This Center grant provides training in basic and applied biology of asthma for approximately 14 post-doctoral fellows and 5 graduate 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 each of the Projects and Cores are already actively involved in SABRE. Most of the preliminary data that served as the basis for this successful application was generated at least in part through support from SABRE, especially by utilizing the SABRE core facilities, which were absolutely indispensable for the long-term success of this program and will be sorely missed. The studies using murine models of asthma in projects 1 and 2 were performed in the SABRE mouse physiology and morphology core, the studies supporting miRNA and mRNA expression analysis in project 1 were all generated in the SABRE functional genomics core, and the studies in project 3 were performed in the SABRE in vivo imaging core (directed by the project leader, Max Krummel). All of the project and core leaders have greatly benefited from SABRE funding and in particular from core utilization that contributed to generation of the preliminary data supporting their projects. Supplementary grants provided through this center grant have already supported 4 junior faculty members, Nirav Bhakta, Aparna Sundaram, Erin Gordon and Stephanie Cristenson, who are just launching careers focused on translational and basic research in asthma.
Evolving Microenvironments in Airway Inflammation

Program Director: George H. Caughey, M.D.

Program Project Grant HL024136 is no longer active but studies published over the past year previously were supported by it. This grant funded interdisciplinary studies of lung and airway inflammation. Newer areas of involvement in research for the Caughey laboratory now include investigating the significance of human tryptase variants and copy number variations in susceptibility to allergic disorders, including asthma, and as determinants of the amount of tryptase present in and released from human mast cells, and of responsiveness to anti-asthma therapeutic agents.

Asthma-related publications in the past year from the Caughey laboratory:


Training and Integration with the Sandler Program

The SABRE Center provided a focus to bring together all of the groups studying fundamental questions relevant to asthma at UCSF. This focus includes a monthly research meeting of investigators with asthma-focused basic research. The Center’s Core also provided advice and training in sensitization and challenge protocols for creating mouse models of chronic allergic inflammation and for monitoring changes in airway resistance, and facilitated sharing of models and advanced imaging technologies.
A global map of mRNA regulatory elements in primary human T cells and airway epithelium

Mark Ansel, David Erle, Noah Zaitlen, and Hani Goodarzi

We proposed to combine high-throughput functional and biochemical approaches developed in our laboratories to develop a global map of cis-regulatory elements.

Progress Report

We developed new techniques to interrogate post-transcriptional regulatory processes on a transcriptome-wide scale. Global cross-linking protein purification and sequencing (GCLiPP) produces detailed maps of RNA binding protein occupancy. It does for post-transcriptional regulation what DNase hypersensitivity and ATAC-seq do for transcriptional regulation. GCLiPP analysis of resting and activated mouse T cells revealed 27000 high confidence protein occupied “peaks”. By starting with this unbiased biochemical method to identify RBP occupied sequences in mRNAs, we discovered that RBP occupied sites in 3′ UTRs tend to have a higher GC content (~48%) than the 3′ UTRs themselves (~43.5%). These GC rich RBP binding sites tend to be less strictly conserved across vertebrates than less bound, GC poor regions of 3′ UTRs.

To directly test whether bound sequences regulate mRNA stability, we adapted the Erle lab’s massively parallel functional annotation of sequences from 3′ UTRs (FAST-UTR) system for primary T cells. We generated and tested retroviral FAST-UTR libraries containing all 27000 “peaks” identified by GCLiPP and thousands of control regions. Across multiple experiments in primary mouse cells and human cell lines, GC rich 3′ UTR sequences were associated with lower gene expression as measured by the steady state mRNA level, amount of protein and half-life of transcripts. Furthermore, it appears that the protein bound sequences that are GC rich are more likely to be folded, as demonstrated both by theoretical local folding energies for the bound and unbound sequences as well as in vivo measurements of RNA conformation. Across vertebrate 3′ UTRs, there is a tendency towards purifying selection of GC poor UTRs, whereas GC rich UTRs tend to exhibit evidence of rapid selection in specific lineages. We conclude that RBP occupied sequences act as a rapidly evolving substrate for gene regulatory interactions.

Our data also provide a rich resource globally correlating protein bound mRNA sites and their concomitant effect on transcript stability and translation. We are mining these data for regions that control expression of genes linked to asthma susceptibility and pathogenesis. Asthma and allergy-associated SNPs lie within regions of RBP occupancy that display post-transcriptional regulatory activity. In addition, the Goodarzi lab’s TEISER algorithm identified structural motifs overrepresented in highly destabilizing protein-occupied peaks. These may represent targets of trans-acting factors that post-transcriptionally regulate gene expression.

These studies have opened entirely avenues for uncovering the genetic basis of allergy and asthma. Current results are under review for publication in the journal eLife, and an NIH R21 proposal to extend this work received a priority score of 27. We successfully profiled Jurkat T cells, and immediately realized the advantage of cross-mapping protein occupancy, disease-associated SNPs and quantitative trait loci. We intend to extend our analysis to human airway epithelial cells and cell lines, an airway smooth muscle cell
line, and primary human Th2 cells, and other cells whose gene expression impacts asthma. We are also leveraging our recently established ability to rapidly mutate endogenous genomic sequences with CRISPR/Cas9 RNP transfection to directly test the function of putative cis-regulatory elements in asthma susceptibility loci.

**RBP occupied sequences are GC rich, rapidly evolving and destabilize reporter mRNAs.**

a) Representative GCLiPP data, including matched RNAseq data and computation calling for GCLiPP peaks and conserved voids in Ccf. PhyloP measures conservation across placental mammals. Schematic indicates that these regions were used for the construction of FAST-UTR libraries for functional analysis. (b) GC content of GCLiPP peaks and conserved voids. (c) Relationship between GC content and conservation for GCLiPP peaks. ρ represents Pearson correlation. (d) Relationship between GC content and steady state mRNA level in FAST-UTR reporter assay for GCLiPP peaks.

**TEISER identifies in vivo folded 3′ UTR structural motifs that inhibit gene expression** (A) TEISER analysis identifies structural motifs enriched in destabilizing sequences. Columns show enrichment of motifs in deciles of GCLiPP peaks arranged by FAST-UTR steady-state mRNA level, rows represent individual motifs. (B) Generic motif structures and (C) a predicted structure for an example of each motif is depicted with icSHAPE signal indicated by color.
CONTRIBUTIONS TO RELEVANT SCIENTIFIC ACTIVITIES
### UCSF PULMONARY RESEARCH CONFERENCE  2016-2017

**Mondays, 4:30 pm - Parnassus**

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<th><strong>Talk 1 (Clinical)</strong></th>
<th><strong>Talk 2 (Basic)</strong></th>
<th><strong>Moderator</strong></th>
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<td>Mark Looney</td>
<td>Luke Bonser</td>
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<td>Laura Koth</td>
<td>David Erle</td>
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<td>Christopher Allen</td>
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<td>Sam Oh</td>
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<td>Neeta Thakur</td>
<td>Ram Naikawadi</td>
<td>Meshell Johnson</td>
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<tr>
<td>11/21/16</td>
<td>Priya Shete</td>
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<td>Bill Parks, Visiting Professor Speaker</td>
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<td>12/05/16</td>
<td>Mehrdad Arjomandi</td>
<td>Selena De Maio (cancelled)</td>
<td>Dean Sheppard</td>
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<tr>
<td>04/24/17</td>
<td>Brett Ley</td>
<td>Ajay Dharia</td>
<td>Kamran Atabai</td>
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<td>Chaz Langelier</td>
<td>Michael Podolsky</td>
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<td>05/08/17</td>
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<td>Andy Tager, Visiting Professor Speaker</td>
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<tr>
<td>05/15/17</td>
<td>Nicholas Arger</td>
<td>Jonathan Budzik</td>
<td>Meshell Johnson</td>
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<tr>
<td>05/22/17</td>
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<td>ATS - (no conference)</td>
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<td>05/29/17</td>
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<td>Memorial Day holiday (no conference)</td>
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<tr>
<td>06/05/17</td>
<td>Nina Sung</td>
<td>Marrah Lachowicz-Scrooggins</td>
<td>Prescott Woodruff</td>
<td>HSW-303</td>
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<tr>
<td>06/12/17</td>
<td>Robert Brownell</td>
<td>Jessica Tsui</td>
<td>Meshell Johnson</td>
<td>TBA</td>
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<tr>
<td>06/19/17</td>
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<td></td>
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<tr>
<td>06/26/17</td>
<td></td>
<td></td>
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<td>CVRI Retreat</td>
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</table>

**Conference Speakers:**

- Bill Parks, Visiting Professor Speaker
- Avrum Spira, Visiting Professor Speaker
- Marsha Wills-Karp, Visiting Professor Speaker
- Nadia Hansel, Visiting Professor Speaker
- Andy Tager, Visiting Professor Speaker

**Holiday Dates:**

- MLK Day Holiday (no conference)
- Memorial Day holiday (no conference)
- President’s Day Holiday (no conference)
- ATS - (no conference)
<table>
<thead>
<tr>
<th>Date</th>
<th>Speaker</th>
<th>Host</th>
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<tr>
<td>September 12</td>
<td>Hao Wu, <em>Boston Children’s Hospital</em></td>
<td>Averil Ma</td>
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<tr>
<td>September 29</td>
<td>Marion Pepper, <em>University of Washington</em></td>
<td>Ari Molofsky</td>
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<tr>
<td>September 26</td>
<td>Immunology Retreat – no seminar</td>
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<tr>
<td>October 3</td>
<td>Daniel Cua, <em>Merck Research Laboratory</em></td>
<td>Richard Locksley</td>
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<tr>
<td>October 10</td>
<td>Morgan Huse, <em>Memorial Sloan Kettering Cancer Center</em></td>
<td>Oren Rosenberg</td>
</tr>
<tr>
<td>October 17</td>
<td>Hilde Cheroutre, <em>La Jolla Institute for Allergy and Immunology</em></td>
<td>Anthony DeFranco</td>
</tr>
<tr>
<td>October 31</td>
<td>Axel Kallies, <em>University of Melbourne</em></td>
<td>Anita Sil</td>
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<tr>
<td>November 7</td>
<td>Sing Sing Way, <em>Cincinnati Children’s Hospital Medical Center</em></td>
<td>Trevor Burt</td>
</tr>
<tr>
<td>November 14</td>
<td>Michael Sixt, <em>IST Austria Institute of Science &amp; Technology</em></td>
<td>Jason Cyster &amp; Max Krummel</td>
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<tr>
<td>November 28</td>
<td>Michael Kenardo, <em>NIH</em></td>
<td>Jennifer Puck</td>
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<tr>
<td>December 5</td>
<td>David Masopust, <em>University of Minnesota</em></td>
<td>Adrian Erlebacher</td>
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<tr>
<td>December 12</td>
<td>Frederic Geissman, <em>Memorial Sloan Kettering Cancer Center</em></td>
<td>Jody Baron</td>
</tr>
<tr>
<td>December 19</td>
<td>Sarah Gaffen, <em>University of Pittsburgh</em></td>
<td>Judith Hellman</td>
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<tr>
<td>January 9</td>
<td>Crystal MacKall, <em>Stanford University</em></td>
<td>Lewis Lanier</td>
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<tr>
<td>January 23</td>
<td>Adolfo Ferrando, <em>Columbia University</em></td>
<td>Michael McManus</td>
</tr>
<tr>
<td>February 1*</td>
<td>Zhijian ‘James’ Chen, <em>UT Southwestern Medical Center</em></td>
<td>Averil Ma</td>
</tr>
<tr>
<td>February 6</td>
<td>Gabriel Victoria, <em>Whitehead Institute for Biomedical Research</em></td>
<td>Julie Zikherman</td>
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<tr>
<td>February 13</td>
<td>Alexander Hoffmann, <em>UCLA</em></td>
<td>Marcus Muschen</td>
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<tr>
<td>February 27</td>
<td>Dorian McGavern, <em>National Institute of Neurological Disorders &amp; Stroke</em></td>
<td>Katerina Akassoglou</td>
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<tr>
<td>March 6</td>
<td>Shiv Pillai, <em>Massachusetts General Hospital</em></td>
<td>Anthony DeFranco</td>
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<tr>
<td>March 13</td>
<td>Donna Farber, <em>Columbia University</em></td>
<td>Trevor Burt</td>
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<tr>
<td>March 20</td>
<td>Catherine Lynn Hedrick, <em>La Jolla Institute for Allergy &amp; Immunology</em></td>
<td>Julie Zikherman</td>
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<tr>
<td>March 27</td>
<td>Chris Garcia, <em>Stanford University</em></td>
<td>Art Weiss</td>
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<tr>
<td>April 3</td>
<td>Susan Kawch, <em>Yale University</em></td>
<td>Jeroen Roose</td>
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<tr>
<td>April 10</td>
<td>Chyi Hsieh, <em>Washington University, St. Louis</em></td>
<td>Mark Anderson</td>
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<tr>
<td>April 17</td>
<td>Louis Picker, <em>Oregon Health &amp; Science University</em></td>
<td>Lewis Lanier</td>
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<tr>
<td>April 24</td>
<td>Melody Swarz, <em>University of Chicago</em></td>
<td>Mellanie Ott</td>
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<tr>
<td>May 1</td>
<td>Yang Xin Fu, <em>University of Texas Southwestern Medical Center</em></td>
<td>Oizhi Tang</td>
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<tr>
<td>May 8</td>
<td>Alex Marson, <em>UCSF</em></td>
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<tr>
<td>May 15</td>
<td>Carla Rothlin, <em>Yale University</em></td>
<td>Richard Locksley</td>
</tr>
<tr>
<td>May 22</td>
<td>Ian Wilson, <em>Scripps Research Institute</em></td>
<td>Jeff Bluestone</td>
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SEMINAR
Department of Microbiology and Immunology

Immunology Seminar Series

“Resolution of Inflammation”

Carla Rothlin, PhD
Associate Professor of Immunobiology and Pharmacology
Yale University

Monday, May 15, 2017
9:00 am, Parnassus, N-225
Host: Richard Locksley

Livestream | SPONSORS | Gladstone Institute of Virology & Immunology
Rosalind Russell Medical Research Center for Arthritis
Sandler Asthma Basic Research Center, SABRE
Live stream and archive available (UCSF My Access login required)

University of California, San Francisco
# SABRE Asthma Research Conference Schedule 2017

**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*)

<table>
<thead>
<tr>
<th>Date</th>
<th>Presenter</th>
<th>Title</th>
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<tbody>
<tr>
<td>1/27/17</td>
<td>Prescott Woodruff</td>
<td><em>Type 2 and Interferon Pathways in Asthma</em></td>
</tr>
<tr>
<td>2/22/17</td>
<td>Richard Locksley</td>
<td><em>Chitinases and lung homeostasis</em></td>
</tr>
<tr>
<td>3/22/17</td>
<td>John Fahy</td>
<td><em>Links Between Airway Eosinophilia, Mucus Plugs and Airflow Obstruction in Asthma</em></td>
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<tr>
<td>4/27/17</td>
<td>Esteban Burchard</td>
<td><em>Leveraging the Genetics of Racially Mixed Children to Advance Precision Medicine</em></td>
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<tr>
<td>5/24/17</td>
<td>Jeoung-Sook Shin</td>
<td><em>Cancelled - rescheduled for August</em></td>
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<tr>
<td>6/22/17</td>
<td>David Erle</td>
<td><em>Airway Epithelial Reprogramming in Asthma</em></td>
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<td>7/27/17</td>
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<td><em>Summer Break</em></td>
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<tr>
<td>8/23/17</td>
<td>Jeoung-Sook Shin</td>
<td><em>The Role of MARCH1 Ubiquitin Ligase in Dendritic Cell Function in Allergic Asthma</em></td>
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<tr>
<td>9/28/17</td>
<td>Dean Sheppard</td>
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<tr>
<td>10/26/17</td>
<td>Jason Cyster</td>
<td></td>
</tr>
</tbody>
</table>
8:00-8:30 am [SC-159]: Coffee and pastries

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

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

10:00-11:00 am [SC-159]: Ten-Minute Talks (+5 minutes for Q&A) Part 2
10:00-10:10  Luke Bonser (Erle Lab), “Investigating airway epithelial reprogramming in asthma”
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 [Spark Social SF]: Lunch

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

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

1:30-2:30 pm [SC-159]: Trainee Roundtable Discussions
  1 Group Leader from each lab to lead discussions
  Burchard Lab: Sam Oh
  Woodruff Lab: Sana Saddiqui
  Erle Lab: Luke Bonser
  Ansel Lab: Heather Pua
  Fahy Lab: Marrah Lachowicz-Scroggins
  Locksley Lab: Steve Van Dyken

2:30-3:00pm [SC-159]: Present Round Table Findings / Closing Remarks
RECENT AND NEW PUBLICATIONS
SUPPORTED BY THE SANDLER ASTHMA
BASIC RESEARCH CENTER
Christopher D.C. Allen, Ph.D.


CD Allen. Germinal center quality control: death by Fas. 19; 42(5): 783-5. doi: 10.1016/j.immuni.2015.05.005. PMID: 25992852


K. Mark Ansel, Ph.D.


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


**Homer Boushey, M.D.**


Denlinger LC, King TS, Cardet JC, Craig T, Holguin F, Jackson DJ, Kraft M, Peters SP, Ross K, Sumino K, **Boushey HA**, Jarjour NN, Wechsler ME, Wenzel SE, Castro M, Avila PC; NHLBI AsthmaNet Investigators. Vitamin D supplementation and the risk of colds in


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


PMID: 27920091


Anthony DeFranco, Ph.D.


David Erle, M.D.


**John Fahy, M.D.**


James S. Fraser, Ph.D.


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


Xiaozhu Huang, M.D.

Matthew Krummel, Ph.D.


Richard M. Locksley, M.D.


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


**Dean Sheppard, M.D.**


**Jeoung-Sook Shin**


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


Jonathan Weissman, Ph.D.


Zena Werb, M.D.


**Prescott Woodruff**


Looking to the Future

Richard M. Locksley, M.D.

The SABRE Center continues to evolve as an integral component of the research community at UCSF. Challenges have emerged in maintaining interactions among established members at both Parnassus and Mission Bay campuses, but opportunities have also become clear in the increased capacities for genomics, genetics, tissue engineering and precision medicine. We continue to participate in major multi-institutional and multi-investigator initiatives supported by the National Institutes of Health, including the Severe Asthma Research Program (SARP), the Asthma and Allergic Diseases Cooperative Research Center, and a Program Project Grant oriented around patients recruited through the UCSF Airways Clinical Research Center. Dr. Burchard has become a national leader in deconvoluting genomes from minority populations that suffer disproportionately from asthma while establishing the Asthma Collaboratory. SABRE Center members continue to push innovative areas in allergy basic research involving new cells, like innate lymphoid cells, and new pathways in old cells, including IgE-producing B cells and IgE receptor-bearing dendritic cells. 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 of research agendas relevant to asthma.

The SABRE Center is playing a role in shaping opportunities as the new Parnassus campus planning efforts 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, remains a model that generates much excitement. 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 outlines a goal, which would coincide with the buildout of a new hospital on the Parnassus site by 2026. This remains a key initiative for the future of the UCSF campus, and incorporation of the SABRE Center into these efforts will remain imperative for the next several years.

Beyond interdigitating across campus sites, the SABRE Center is continuing efforts for outreach and integration. After much discussion, we have 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 reporting next year on the novel and unexpected discoveries made by laboratories at UCSF new to asthma-related research.
Continued implementation of the Strategic Plan with re-direction of efforts to human-based asthma studies will need input from individuals with relevant areas of profession expertise. To this end, we have transitioned the outside Review Board to get insight from experts in human and population studies while retaining rigorous scientific insights. This transition is ongoing but we hope to have completed identification of new external review board members shortly. 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. Our internal Review Board is being altered by the addition of a structural biologist and chemist to complement efforts to enhance technology development. Finally, the SABRE Center members will complete a strategic planning retreat at the end of the summer in order to more thoughtfully prepare for transitions of the Center during this period of growth and re-direction.

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.
David Erle, M.D.
John Fahy, M.D., M.Sc.
James S. Fraser Ph.D.
Andrew N. Goldberg, M.D., M.S.
Xiaozhu Huang, M.D., M.S.
Matthew Krummel, Ph.D.
Richard Locksley, M.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
Christopher David Caballero Allen, Ph.D.

POSITION TITLE
Assistant Professor of Anatomy
Investigator, Cardiovascular Research Institute

EDUCATION/TRAINING

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

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


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


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

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.


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

Ongoing Research Support

DP2 HL117752-01  Allen, Christopher David Caballero (PI)  09/30/2012 – 06/30/2017
Cellular interactions in asthma
This project is focused on the dynamic communication among inflammatory cells in asthmatic lungs. The major goals of this project are 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 AI103146-05  Allen, Christopher David Caballero (PI)  12/01/2012 – 11/30/2017
Analysis of basophil function in secondary immune responses
The major goal of this project is to determine the functional role of basophils that have captured antigen via IgE antibodies in secondary immune responses. Specifically, this project will determine whether basophils contribute to antigen transport, to the enhancement of adaptive immunity, and to tissue damage and repair.
Role: PI

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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
BIOGRAPHICAL SKETCH

NAME
K. Mark Ansel

eRA COMMONS USER NAME
anselm

EDUCATION/TRAINING

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
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<tr>
<td>Virginia Tech, Blacksburg, VA</td>
<td>B.S.</td>
<td>1992-1996</td>
<td>Biochemistry</td>
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<tr>
<td>University of California, San Francisco</td>
<td>Ph.D.</td>
<td>1996-2001</td>
<td>Biomedical Sciences</td>
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<tr>
<td>Immune Disease Institute, Harvard Medical School</td>
<td></td>
<td>12/2007</td>
<td>Immunology</td>
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</table>

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
2016 Standing member, NIH CMIB study section
2012- Associate Editor-in-chief, American Journal of Clinical & Experimental Immunology
2013-2017 Associate Editor, Journal of Immunology
2017 Section 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
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.


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 Eomesoderm. This same miRNA and several others that we have studied also regulate the differentiation of Th17 and T regulatory (Treg) cells. Recently, we have extended this approach to leverage our ability to assign biological functions to miRNAs and identify their direct target mRNAs as a means of directed pathway discovery. For example, we found that miRNAs miR-24 and miR-27 potently inhibit Th2 responses in vitro and in vivo, and combined empirical and bioinformatics methods identified a network of functionally relevant target mRNAs including some that encode well-known regulators of Th2 cell differentiation, such as GATA-3 and Ikaros, and others that represent novel players in Th2 biology.
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.


To support the studies described above, we have developed sophisticated capabilities in single cell analysis in mouse and human biospecimens using flow cytometry (FACS) and more recently, 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. As described in the progress report, the studies proposed in this renewal application will extend unpublished observations of airway Treg cell subsets associated with decreased allergic inflammation and improved lung function in human asthma.


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

Research Support

Ongoing Research Support
2011/08/01-2020/03/31
5R01HL109102-06, National Heart, Lung, and Blood Institute
K Mark Ansel (PI)
MicroRNA-Directed Pathway Discovery In Helper T Cell Driven Airway Inflammation
The major goals of this project are to identify and characterize the in vivo activity and molecular targets of miRNAs that regulate helper T cell functions relevant to asthma. Overlap with P01HL107202 was resolved in year 2 by removing the clinical study.

Role: PI

2012/08/15-2017/05/31
SPO1HL107202-02, 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

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

2012/07/01-2017/06/30
CDP-1593-13, The Leukemia & Lymphoma Society
K Mark Ansel (PI)
Microrna Regulation of Lymphocyte Growth And Effector Functions

This career development program award would support our research program focus on miRNAs that regulate essential helper T cell functions that contribute to immunity, immuopathology, and immune malignancies. In particular, we aim to identify and characterize miRNAs that regulate helper T cell growth, survival, and cytokine production.

Role: PI

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

2015/07/01-2017/06/30
1R21AI117378-01, National Institute of Allergy and Infectious Diseases
DeFranco (PI)
B cell TLRs and Germinal Centers
The major goals of this project are to determine the molecular mechanism by which TLR9 stimulation of germinal center B cells enhances affinity maturation in a cell-intrinsic fashion. Changes in mRNA and microRNA levels will be determined at the population level and at the single cell level.
Role: Co-investigator
BIOGRAPHICAL SKETCH

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

POSITION TITLE
Assistant Professor of Medicine

eRA COMMONS USER NAME
BHANIR

EDUCATION/TRAINING

<table>
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<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
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<th>FIELD OF STUDY</th>
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<tr>
<td>Massachusetts Institute of Technology</td>
<td>SB</td>
<td>1998</td>
<td>Electrical Engineering</td>
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<tr>
<td>Stanford University School of Medicine</td>
<td>MD</td>
<td>2006</td>
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<tr>
<td>Stanford University School of Medicine</td>
<td>PhD</td>
<td>2006</td>
<td>Mol. and Cell Physiology</td>
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<td>University of California, San Francisco</td>
<td>Internship</td>
<td>2007</td>
<td>Internal Medicine</td>
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<td>University of California, San Francisco</td>
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<td>University of California, San Francisco</td>
<td>Fellowship</td>
<td>2011</td>
<td>Pulmonary, Critical Care</td>
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<tr>
<td>University of California, San Francisco</td>
<td>Postdoctoral</td>
<td>2011</td>
<td>Asthma</td>
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Positions and Employment

2011-2013  Instructor of Medicine, Department of Medicine, Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, University of California, San Francisco. >80% of my time was devoted to research.

2013 to Present  Assistant Professor of Medicine, Department of Medicine, Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, University of California, San Francisco. >80% of my time is devoted to research; 20% of my time is spent on clinical attending in the intensive care units and pulmonary function laboratory.

Honors

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 Member
- **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**

In this work, I developed and used a metric to reproducibly quantify Th2 inflammation in human airway epithelial brushings. Given the importance of Th2 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 Th2 inflammation. For the first publication listed: I played an equal role in conceiving the idea of the study and collecting the data with the senior author Dr. Woodruff. I primarily conceived the experimental designs. I supervised the performance of the experiments. I conceived and performed all data analyses, and primarily wrote the manuscript.


Expression profiling of cellular and extracellular miRNA by microarrays and qPCR to study their role as biomarkers and regulators of airway epithelial and T cell function. Designed and performed expression profiling experiments and/or analysis in each of these studies.


These studies show the potential biomarker value of studying blood cell gene expression for inflammatory diseases of the lung, specifically sarcoidosis. In these studies, I designed and performed expression profiling experiments and/or analysis.


This work was performed in my PhD thesis laboratory. Assisted Dr. Lewis in building the two-photon microscope: 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. I co-wrote the manuscript with Dr. Lewis. The techniques presented in this publication continue to be used by immunologists to study signaling and motility of immune cells in their native environments.


In the course of my own projects and ongoing collaborations, I have become a local UCSF expert on the unique analysis challenges of high-throughput microfluidic qPCR data: large datasets, issues of normalization, missing data, outliers, and extracting signatures that are statistically significant. I have primarily performed the data analysis in a number of collaborations at UCSF, with the most significant publication to date being a single-cell gene expression profiling study in breast cancer:

Complete List of Published Work in MyBibliography:

**Research Support**

**Ongoing Research Support**

**K23 HL116657 Bhakta (PI) 05/01/14-04/01/19**  
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).  
Role: PI

**Sandler Asthma Basic Research Fund 06/01/2014**  
The purpose of this fund is to provide support for my work as an investigator in the UCSF Airway Research Center, where I see study subjects and perform research bronchoscopies.  
Role: PI

**R01 HL131560 Bhattacharya (PI) 06/01/2016-**  
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 the grant.  
Role: Co-Investigator

**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) 04/01/2013-03/31/2014**  
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)  08/21/12-06/30/2014
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)  01/01-01/01/16
SPIROMICS (Subpopulations and intermediate outcome measures in COPD study)
mRNA and miRNA profiling in epithelial brushings, sputum cell pellets, BAL fluid, bronchial wash, serum, plasma, and sputum supernatant on network-wide samples.
Role: Subcontract PI
## BIOGRAPHICAL SKETCH

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

### EDUCATION/TRAINING

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

### Positions and Honors

- **1974-1981** Assistant Professor of Medicine in residence, University of California, San Francisco.
- **1981-1987** Associate Professor of Medicine in residence, 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, 1999, 2000** Faculty-Student Teaching Award for "An Outstanding Lecture"
- **1993** Clean Air Award (Education/Research), American Lung Association, San Francisco
Contribution to Science

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


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


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


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


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


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


**Research Support**

Ongoing Research Support

U10 HL098107 (Boushey, HA) 09/30/09-06/30/16

NIH/NHLBI

UCSF AsthmaNet Clinical Center

The major goals are to serve as a clinical center participating in the conduct of NHLBI-supported multi-center clinical trials of asthma therapies in children and adults with asthma, and to conduct smaller, focused studies of mechanisms of action of asthma therapies, of novel treatments for severe asthma, and of concepts of asthma pathophysiology that could lead to the development of new asthma treatments. Role: Co-Investigator
The major goal is to serve as a basic science site for the ICAC, enabling examination of relationships of the microbiological environment of inner city households, the development of immune function in infancy, and the development of allergic disease, especially asthma, in childhood. Role: Principal Investigator

P01 HL070831-06A1  (Lemanske, R)  05/01/08-04/30/13
NIH
Rhinovirus Infection and Childhood Asthma
The major goals of this study are to apply the Virochip microarray to search for novel viruses in respiratory secretions obtained from children with severe clinical illnesses with the features of a respiratory infection but in whom standard PCR tests have not detected a virus, and further to expand the ViroChip to detect regions of the rhinovirus genome associated with virulence. Role: Co-Investigator

1R43HL120427-01  (Gonda, I and Boushey, H)  08/05/2013 – 07/31/2014
NIH/NHLBI
Development and Validation of a test for Gastro-esophageal Reflux with Aspiration
The goals of this SBIR-funded study are to develop and validate a test for the occurrence of nocturnal or “silent” gastroesophageal reflux and aspiration. This small proof of concept study will examine 5 healthy control subjects and 12 adults with idiopathic pulmonary fibrosis, lung transplantation, or other signs or symptoms of GER with aspiration and also with abnormal findings from esophageal manometry and pH monitoring consistent with the condition.

Completed

5 U10 HL074204-05  (Boushey, HA)  09/15/03-07/31/11
NIH/NHLBI
Asthma Clinical Research Network Center at UCSF
To link the established clinical research group at the University of California, San Francisco with other clinical research groups in an interactive network conducting collaborative studies of novel therapeutic approaches for asthma and disseminating the findings on optimal management of asthmatic patients to practitioners and other health care professionals. Role: Principal Investigator

5 U10 HL074431-05  (Lazarus, SC)  08/15/03-07/31/11
NIH/NHLBI
COPD Clinical Research Network at UCSF
HL-03-002 COPD Clinical Research Network
The purpose of the NIH-sponsored COPD Clinical Research Network is to evaluate new and existing approaches for the management of COPD and to disseminate the findings of this network to the medical community. Role: Co-Investigator
BIOGRAPHICAL SKETCH

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

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

EDUCATION/TRAINING

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<th>YEAR(s)</th>
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<tr>
<td>San Francisco State University, San Francisco, CA</td>
<td>B.S.</td>
<td>1984-1990</td>
<td>Cellular &amp; Molecular Biology</td>
</tr>
<tr>
<td>Stanford University School of Medicine, Stanford, CA</td>
<td>M.D.</td>
<td>1990-1995</td>
<td>Medicine</td>
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<tr>
<td>Harvard School of Public Health, Boston, MA</td>
<td>Certificate</td>
<td>1997</td>
<td>Program in Clinical Effectiveness</td>
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<td>Brigham and Women's Hospital, Boston, MA</td>
<td>Resident</td>
<td>1995-1998</td>
<td>Internal Medicine</td>
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<tr>
<td>University of California, San Francisco, SF, CA</td>
<td>Fellow</td>
<td>1998-2001</td>
<td>Pulmonary &amp; Critical Care Medicine</td>
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<td>Stanford University, Stanford, CA</td>
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<tr>
<td>University of California, Berkeley</td>
<td>M.P.H.</td>
<td>2001-2002</td>
<td>Genetic Epidemiology</td>
</tr>
</tbody>
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Positions and Honors

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

Selected Honors

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

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

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

Contributions to Science

1. I conceived the GALA studies; I recruited patients alongside with my collaborators, I built the biorepository and database to house the biologic and clinical data, my colleagues and I did the analyses and wrote more than 160 manuscripts from this study. We demonstrated that Puerto Rican children have lower drug response to albuterol than Mexican children.

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

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

4. We identified a significant inverse relationship between African ancestry and forced expiratory volume at one second (FEV₁) 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 FEV₁) 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.


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

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

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

Complete List of Published Work in MyBibliography:
Research Support

Ongoing Research Support

24RT-0025 (PI: Burchard) 07/01/15-06/30/18
TDRP
Role: PI
Project title: Air Pollution, Tobacco Smoke, and Asthma in Minority Children
Goal: To identify genetic variation that contributes to differences in bronchodilator drug response using whole genome sequencing of extreme traits.

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.

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.

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.

U54MD009523 (PI: Marquez-Magnana/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.

U01OD019769-01 (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.

1K12HL119997-01 (PI: Erle/Burchard) 09/01/13-05/31/18
NIH/NHLBI
Role: Co-PI
Project title: UCSF Career Development Program in Omics of Lung Diseases
Goal: To launch the careers of an outstanding group of next generation scientists equipped to use omics approaches to help transform lung research and pulmonary medicine.

P60MD006902 (PI: Bibbins-Domingo) 08/27/12-02/28/17
NIH/NIMHD
Role: Project PI
Program title: Addressing Disparities in Chronic Disease with a Teen and Young Adult Focus
Project title: The Genetics of Asthma and Obesity Using Admixture Mapping in Latinos
Goal: To identify novel genetic variants associated with both asthma and obesity by deep re-sequencing of candidate regions identified through admixture mapping

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.

UM1 HG008901 (Darnell) 01/14/16-11/30/17
NIH/NHGRI (Subcontract from New York Genome Center (NYGC)
Role: Subcontractor
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.

(Bustamante) 05/02/16-03/31/20
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 β2-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.

(Ahituv, Burchard & Seibold) 09/01/16 – 08/31/21

NIH/LCMI
Genomic characterization of asthma drug response in multi-ethnic children
This project plans to use several genomic technologies on cells treated with these drugs from asthmatic patients with detailed clinical response and genetic data, to identify the genetic factors that lead to differences in asthma response.

Completed Research Support

R01 HL088133 (PI: Burchard) 03/01/08-02/28/14
NIH/NHLBI
Project title: Whole Genome Analyses for Asthma in Latino Populations

R01 ES015794 (PI: Burchard) 09/01/08-05/31/14
NIH/NIEHS
Project title: Genes-environments & Admixture in Latino Asthmatics (GALA 2)
**BIOGRAPHICAL SKETCH**

**NAME**

George H. Caughey

eRA COMMONS USER NAME
gcaughey

**POSITION TITLE**

Professor of Medicine

**EDUCATION/TRAINING**

<table>
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<tr>
<th>INSTITUTION AND LOCATION</th>
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<tr>
<td>Arizona State University</td>
<td>BS</td>
<td>1975</td>
<td>Chemistry</td>
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<td>Stanford University School of Medicine</td>
<td>MD</td>
<td>1979</td>
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<td>Pennsylvania Hospital/UPenn</td>
<td></td>
<td>1982</td>
<td>Internal Medicine</td>
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<td>University of California, San Francisco</td>
<td></td>
<td>1986</td>
<td>Pulmonary Medicine</td>
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**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 Chief of Pulmonary and Critical Care and Sleep Medicine, San Francisco VA Medical Center
- 2012- Associate Chief of Research and Academic Affairs, Medical Service, San Francisco VA Medical Center

**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. My laboratory used cDNA cloning to obtain the first complete primary structure of a mast cell tryptase, the tryptic enzyme that is the most abundant protein product of human mast cells. My laboratory 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 basophils. We co-discovered a transmembrane version of mast cell tryptase (γ-tryptase), and revealed its evolutionary relationship to soluble tryptases and 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 innovative combinatorial methods, we identified novel, selective 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.


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\textsuperscript{W-sh/Kit\textsuperscript{W-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.


Neutrophil proteases and histamine. My laboratory made highly cited observations concerning the 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.


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.


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.


Complete List of PubMed-indexed Published Work:
Research Support

Ongoing Research Support

Nina Ireland Program in Lung Health  Caughey (PI)  07/01/2013-
Funds SFVA-based studies on lung and airway immunology and remodeling.
Role: PI

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

Diamond Family Fund  Caughey (PI)  07/01/2000-
“Cystic Fibrosis studies”
Funds studies of roles of airway proteases in cystic fibrosis.
Role: 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)  07/01/2014-06/30/2017
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 four
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

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

Positions and Honors

1979-1985  Assistant Professor of Medicine, University of Utah, Department of Medicine, Salt Lake City, UT
1985      Associate Professor of Medicine, University of Utah, Department of Medicine, Salt Lake City UT
1985-1999 Associate Professor of Medicine, Harvard Medical School, Department of Medicine, Boston, MA
1992-1999 Physician, Brigham and Women's Hospital, Boston, MA
1992-1999 Associate Professor of Environmental Health, Harvard School of Public Health, Boston, MA
2000-2008 Chief, Division of Pulmonary and Critical Care Medicine, University of California, San Francisco
2000      Attending Physician, Moffitt-Long Hospital, University of California San Francisco
2000      Professor of Medicine, University of California, San Francisco
2000      Senior Member, Cardiovascular Research Institute, University of California San Francisco
1985-1990  Career Investigator Award, American Lung Association
1987    American Society for Clinical Investigation
1998    American Association of Physicians
2001-2011 MERIT Award, NIH/NHLBI
Ad hoc member of various NIH study sections
Editorial Board of Journal of Clinical Investigation and Associate Editor, American Journal of Respiratory, Cell, and Molecular Biology

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 lipofuscin degradation. Cathepsin S, the first enzyme characterized, proved to be a potent elastase and a critical enzyme in MHC class II maturation. Collaborating with geneticists, we were able to link two of the enzymes to human genetic disorders and inhibitors of one of these, cathepsin K, has recently proven effective in a phase III clinical trial for post-menopausal osteoporosis (Merck).

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


Although epithelial mesenchymal interactions are well known to influence extracellular matrix remodeling, the role of epithelial plasticity in this biology in the lung had been largely undefined. I asked the question of whether epithelial to mesenchymal transition (EMT) occurs in vivo in the lung in the context of injury and, if so, does this contribute importantly to pulmonary fibrosis. Using lineage labeling in vivo we discovered that epithelial cells express mesenchymal genes during fibrogenesis and activation of this pathway required extracellular matrix-induced TGFb1 activation. These results inspired a series of studies examining the influence of integrin receptors on TGFb1 signaling ultimately linking b-catenin-rich cell:cell contacts, integrin a3b1, and Smad signaling. Disruption of this signaling pathway in vivo attenuated epithelial transition and fibrogenesis. The implication that epithelial transition is important to fibrogenesis was subsequently confirmed by Kevin Kim, independent in his own lab, using an epithelial-specific knockout of collagen 1.


A logical extension of studies directed at elucidating mechanisms of fibrosis is the development of new drug targets to block fibrosis. I initiated a small molecule screen through the UCSF Discovery Center for inhibitors of EMT in vitro that did not block Smad signaling directly but blocked fibrosis in vivo. We identified several promising candidates, one of which methacycline has been reported, that proved the screening methodology could be successful. We are using this methodology to further explore promising drug leads for fibrosis.


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

**Research Support**

**Ongoing Research Support**

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

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.

Completed Research

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.

R37 HL67204 (Chapman, HA)  6/1/2001 – 5/31/2012
NIH/NHLBI MERIT AWARD
Role of Elastolytic Cathepsins in Emphysema
The major goal of this project is define the role of cysteine proteases in smoking-related emphysema. The project focuses on pathways of elastase expression in lung mesenchymal cells and on the genetics of emphysema in human subjects with early-onset emphysema and normal alpha-1-antitrypsin.

R01 CA125564 (Chapman, HA)  7/1/2007 – 5/31/2012
NIH/NHLBI
Urokinase Receptor Integrin Interactions in Lung Cancer
The major goals of this project are to define the physical basis of urokiinase receptor beta1 interactions and the influence of these interactions on tumor cell signaling and lung tumor progression. Primary tumor cells from human tumors will be examined for their expression and dependence on urokinase receptors for adhesion and migration.

Sponsored Research Agreement (Chapman, HA)  6/14/2012 – 6/13/2014
Daichii Sankyo
Human Epithelial Progenitor Cells in Idiopathic Pulmonary Fibrosis
BIOGRAPHICAL SKETCH

NAME
Anthony L. DeFranco, Ph.D.

POSITION TITLE
Professor,
Department of Microbiology & Immunology

eRA COMMONS USER NAME
DeFranco

EDUCATION/TRAINING

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<td>University of California, Berkeley, CA</td>
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<td>National Institutes of Health, Bethesda, MD</td>
<td>Postdoctoral</td>
<td>8/83</td>
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Positions

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

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

Honors

1974 Dreyfuss Foundation Fellow
1975 Phi Beta Kappa, Harvard University
1975-1978 NSF Predoctoral Fellow
1979-1982 Helen Hay Whitney Postdoctoral Fellow
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-g2 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 DGKz, which showed that Erk signaling is an important determinant of expansion of B cell numbers, especially at the plasmablast stage. In addition, the data strongly suggested that BCR affinity for antigen is primarily sensed by the B cell via the magnitude of Erk signaling (d).


2. Role of Lyn in inhibitory signaling in B cells - In a long-standing collaboration with Dr. Clifford Lowell (UCSF), we have studied the function of the protein tyrosine kinase Lyn in B cells in vitro and in vivo. Lyn is a member of the Src-family of tyrosine kinases, which at the time were implicated in the initiation of antigen receptor signaling in T cells and B cells. We found that Lyn did indeed participate in the initiation of BCR signaling, but that it was redundant with the other Src family kinases expressed in B cells (primarily Fyn and Blk), a conclusion later confirmed by Tarakhovsky, who made the Lyn-/-Fyn-/-Blk-/- triple KO. Importantly, we found that Lyn is uniquely responsible for enabling the function of the inhibitory receptors CD22 and FcγRIIb, and therefore in its absence BCR signaling was of much greater magnitude after the first few minutes (2a, 2b). We subsequently found that the inhibitory function of the Lyn-CD22-Shp1 pathway is much greater in mature B cells than in immature B cells (2c). This finding is likely relevant to the striking breakdown in B cell tolerance in Lyn-deficient mice, which spontaneously develop a strong lupus-like autoimmunity (see next category). Indeed, selective deletion of Lyn in B cells was shown to be sufficient for lupus-like autoantibody production and lupus nephritis, indicating that B cell tolerance defects contribute importantly to the lupus-like autoimmunity of Lyn-deficient mice (3d).
3). Analysis of Lyn-deficient mice as a murine model of lupus - Also in collaboration with Dr. Lowell, we have studied the autoimmunity that develops in Lyn-deficient mice. We have found that mice deficient in Lyn and Fyn have stronger lupus nephritis than do Lyn-/- mice, which probably reflects a role for 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-g production from T cells (b) and that DCs require MyD88-dependent signaling to promote inflammatory disease in this model (c). Selective deletion of Lyn in B cells also leads to lupus-like autoantibody production and lupus nephritis, indicating that B cell tolerance defects contribute to the lupus-like autoimmunity of Lyn-deficient mice (d). In studies nearing publication, we have found that combination of Lyn-deficiency with a hypomorphic allele of Aire, which is important for thymic expression of organ-specific autoantigens, results in spontaneous autoimmune uveitis, providing a model for multigenic autoimmune susceptibility. This project is the subject of the current application.

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


5). 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 (5b).


Research Support
Active

“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
The major goals of this project are to determine the molecular mechanism by which TLR9 stimulation of germinal center B cells enhances affinity maturation in a cell-intrinsic fashion. Changes in mRNA and microRNA levels will be determined at the population level and at the single cell level.

Completed (last three years)

“Cell Type-Specific Roles of TLR Signaling in Immune Responses”
Principal Investigator: Anthony DeFranco
Agency: NIAID
Type: R01 (R01AI072058-5). Period: 1/1/08-12/31/2012 (no cost extension to 12/31/2013)

“Regulation of B lymphocyte proliferation by antigen”
Principal Investigator: Anthony DeFranco
Agency: NIAID
Type: R56AI20038-27-A1. Period: 7/1/13-6/30/14

“Innate Immune Regulation of Inflammation and Adaptive Immunity”
Program Director: Anthony L. DeFranco. Project #1 “Cellular Basis of TLR Signaling for Mucosal Immune Responses” (A.L. DeFranco, PI)
Agency: NIAID
Type: P01 (AI078869-05). Period: 7/1/08-6/30/14. (no cost extension from 7/1/13-6/30/14)

Toll-like receptors and IgA response to gut microbiota
Principal Investigator: Anthony DeFranco
Agency: Resource Allocation Program (UCSF internal) 7/1/13-6/20/14

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

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

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

NAME
David J. Erle, M.D.

POSITION TITLE
Professor of Medicine

eRA COMMONS USER NAME
DJERLE

EDUCATION/TRAINING

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<td>Pulmonary Disease</td>
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<td>Postdoc</td>
<td>6/1990</td>
<td>Cell &amp; Molecular Biology</td>
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Positions

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

Other Experience and Professional Memberships

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

Honors

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

Contributions to Science

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


2. I have a strong interest in 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.


3. The Functional Genomics Core facility that I direct has been involved in >600 genomics projects and currently handles approximately 60 RNASeq projects annually. I have extensive experience with next generation sequencing methods. I serve as PI, project leader, or subcontract PI for 5 NIH funded projects that make extensive use of Illumina next-generation sequencing. Examples include an Extracellular RNA Communication Program U01 grant (from the NIH Common Fund) that involves sequencing of 3000 extracellular biofluid samples and a subcontract to an NHLBI R01 grant that involves sequencing of >1000 human blood samples.


4. There are 19 members of the protein disulfide isomerase (PDI) family of ER-resident proteins in humans but the roles of most of these remain poorly understood. Our discovery that the PDI family member AGR2 is induced in asthma led us to study the roles of AGR2 and its homolog AGR3. We produced *Agr2−/−* mice and used these to show that AGR2 is essential for mucus production in the intestine and is also important for allergen-induced mucus overproduction in a mouse model of asthma. Surprisingly, we found that the close AGR2 homolog AGR3 has a very different role in airway epithelium: it is expressed in ciliated cells rather than mucus cells and helps regulate ciliary beat frequency.
5. 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.


Complete list of publications in MyBibliography:

Research Support

ACTIVE

U19 AI 077439-06 (Sheppard) 04/01/2013-03/31/2018 2.3 calendar
NIH/NIAID Program: $1,086,097
Role: Project 1 Leader Project 1: $274,962
Program: IL-13 and IL-17 Dynamics in the Asthmatic Airway
Project 1: IL-13/17-regulated Airway Epithelial miRNAs in Asthma
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.

1K12 HL119997-01 (Erle/Burchard) 09/01/2013-5/31/2018 0.6 calendar
NIH/NHLBI $250,000
Role: PI
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.

R01 HL118267-01A1 (Williams) 12/01/2013-11/30/2018 0.6 calendar
Henry Ford Health System $181,184
(Subcontract)
Combined Transcriptomics and Genomics to Find Asthma Genes in Admixed Populations Perform RNA-Seq for transcript profiling of blood cells in asthma.

R01 HL124285-01 (Erle) 07/01/2014-06/30/2018 2.4 calendar
NIH $350,936
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.

R01 GM110251 (Erle/McManus) 09/01/2014-08/31/2018 2.0 calendar
NIH $452,511
Role: PI
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.

U01 HL126492 (Erle/Woodruff) 07/01/2014-06/30/2019 2.0 calendar
NIH $449,517
Role: PI
Defining a Comprehensive Reference Profile of Circulating Human Extracellular RNA
The goal is to profile extracellular RNAs in multiple body fluids from healthy individuals.

Pending

R01 HL138424 (Erle) 07/01/2017-06/30/2022 1.80 calendar
NIH/NHLBI $399,402
Role: PI
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.
**BIOGRAPHICAL SKETCH**

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

**POSITION TITLE**
Professor

**eRA COMMONS USER NAME**
johnfahy

### EDUCATION/TRAINING

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**Positions**

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

**Other Experience and Professional Memberships**

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

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

Contribution to Science

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

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

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

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


(II) Airway Mucus Pathology

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

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

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

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


(III) Novel Drugs for Airway Disease

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

**Central findings:** Although inhibition of NK-1, selectins, or EGFR did not have beneficial effects in clinical trials (publications A-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.


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 - 6/30/17
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 - 7/31/2017
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
Recently Completed

University of California Center for Accelerated Innovation (CAI)(Fahy JV) 7/1/2015-6/30/2016

*Thiol-saccharides as Novel Mucolytics for Lung Disease*

This technology development award provided initial funding for development of novel mucolytic treatment approaches for asthma and other lung diseases. Role: PI.

**1P50HL107191 (Fahy JV)**


Preventing fucose-dependent binding of aspergillus and pseudomonas to lung mucin. Role: P.I.
### BIOGRAPHICAL SKETCH

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<tr>
<td>James Solomon Fraser, Ph.D.</td>
<td>Assistant Professor</td>
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**eRA COMMONS USER NAME (credential, e.g., agency login)**

FRASERJA

### EDUCATION/TRAINING

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<td>University of California, Berkeley, CA</td>
<td>Ph.D.</td>
<td>12/2010</td>
<td>Molecular and Cell Biology</td>
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### 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)

### Other Experience

- **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-** Chair: Linac Coherent Light Source (XFEL) Proposal Review Panel (BIO-C)

### Honors and Awards

- **2001-2005** Canadian Millennium Excellence Undergraduate Scholarship

- **2004** NSERC Undergraduate Summer Research Award (Mentor: Alan Davidson)

- **2006-2007** Natural Sciences and Engineering Research Council (Canada) Postgraduate Fellowship

- **2007-2010** Natural Sciences and Engineering Research Council (Canada) Doctoral Fellowship

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

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 through integrative approaches to discover new, potentially druggable cryptic sites.
   Website: http://ucxray.berkeley.edu/ringer
   Distributed with Phenix (mmtbx.ringer): http://www.phenix-online.org
   Website: https://simtk.org/home/qfit
   Webserver: http://smb.slac.stanford.edu/qFitServer/qFit.jsp
   Website: https://github.com/fraser-lab/EMRinger
   Distributed with Phenix (phenix.emringer): http://www.phenix-online.org
   Website: https://modbase.compbio.ucsf.edu/ cryptosite/

2. 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 allergy and asthma, and the hijacking of the proline isomerase CypA in lentiviral evolution.


3. Creating multi-temperature X-ray data collection methods to inform mechanistic studies. We recognized that the standard practice of cryocooling crystals could distort protein conformations. In both larger surveys and isolated mechanistic studies, we have demonstrated the value of room temperature data collection for revealing the structural basis of protein conformational dynamics, leading to new insights into the enzymes 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. We are now exploiting the capabilities of X-ray free electron lasers to image native state dynamics free from conventional radiation damage effects.


4. 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.


5. Identifying unifying concepts between systems and structural biology. With Nevan Krogan, we have articulated the similarities in genetic epistasis and thermodynamic measurements and applied these insights to large-scale studies of point mutants and posttranslational modifications. This framework forms the basis for the UCSF graduate course that I direct, PUBS (Physical Underpinnings of Biological Systems), which uses deep sequencing to determine the context dependence of fitness effects of mutations. The class is taught through project-based learning where incoming students perform all library preparations, load samples directly on the MiSeq, and write all their own code to process sequencing data.


Research Support

Ongoing Research Support

DP5 OD009180    Fraser (PI)  09/01/11 – 08/31/17 (NCE)
NIH/OSC
The Impact of Mutation on the Conformations and Recognition of Ubiquitin
The major goals of this project are to address how changes in the populations of alternative conformations affect the protein-protein interactions and the generation of distinct poly-ubiquitin linkages. This award is not renewable and under no-cost extension.

R21 GM110580    Fraser (PI)  04/01/14-03/31/17 (NCE)
NIH/NIGMS
Model Comparison in Structural Biology
This project describes new methods for optimizing model selection in structural biology. We aim to create new metrics for determining the precision and accuracy of protein conformations. This award is not renewable and under no-cost extension.

14-SSP-198    Fraser (PI)  07/01/14-06/30/17
Kinship Foundation Searle Scholar Program
New light sources to illuminate protein conformational dynamics
The major goal of this project is to exploit time resolved approaches on X-FEL and synchrotron light sources.

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)  09/01/13-09/01/18
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). The UCSF component (including James Fraser, James Holton, and Bob Stroud) participates by generating samples for X-FEL diffraction and comparing the resulting data to room temperature synchrotron datasets.
Role: Collaborator

Completed Research Support    None
**BIOGRAPHICAL SKETCH**

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<td>Boston University, Boston, MA</td>
<td>MD</td>
<td>1985</td>
<td>Medicine</td>
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<tr>
<td>Los Angeles County-Harbor/UCLA Medical Center, Torrance, CA</td>
<td>Intern</td>
<td>1986</td>
<td>General Medicine</td>
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<tr>
<td>University of Pittsburgh, School of Medicine Eye &amp; Ear Hospital, Pittsburgh, PA</td>
<td>Residency</td>
<td>1990</td>
<td>Otolaryngology, Head and Neck Surgery</td>
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<tr>
<td>National Cancer Institute, Center for Epidemiology and Biostatistics, Philadelphia, PA</td>
<td>Fellow</td>
<td>1996</td>
<td>Clinical Epidemiology of Cancer</td>
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<tr>
<td>University of Pennsylvania, Philadelphia, PA</td>
<td>MS</td>
<td>2003</td>
<td>Clinical Epidemiology</td>
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**Positions**

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

**Honors**

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


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


Research Support

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

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

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

175
NAME
Xiaozhu Huang, M.D.

POSITION TITLE
Adjunct Professor of Medicine

EDUCATION

<table>
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<td>Tongji Medical University, Wuhan, People's Republic of China</td>
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<td>M.S.</td>
<td>1988</td>
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Positions

1987-1992  Associate Professor of Medicine  
University of California, San Francisco

1999-2014  Assistant Professor of Medicine  
University of California, San Francisco

2013-Present  Professor of Medicine  
University of California, San Francisco

1999-Present  Director, Sandler Animal Physiology and Morphology Core  
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,

Contribution to Science

Before joining UCSF, I focused on the etiology and pathogenesis for a common lung disease (Farmer’s lung) in China rural area. My work suggested that Streptomyces thermohygroscopicus (STHs) was possibly one of the pathogens responsible for FL in China's countryside and our data also confirmed that extracellular enzymatic material of streptomyces thermohygroscopicus may directly damage the alveolar type I cells in the lung. Our work provided better understanding for the mechanisms of Farmer’s Lung and helped with the development of potential therapeutic reagents for this un-curable disease.

In 1992, I joined Dr. Sheppard’s lab to study the in vivo relevance of members of the integrin family, identified by the lab. I 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 effect on different responding cells, in experimental models of pulmonary fibrosis, emphysema, acute lung injury and allergic asthma. These studies have stimulated substantial interest in potential anti-integrin therapeutics, including one humanized monoclonal antibody generated based on work in the lab that is now in phase 2 clinical trials for potential treatment of idiopathic pulmonary fibrosis.


I was also involved in studying the role of integrin α9β1 in mediating rapid cell migration, neutrophil differentiation and smooth muscle contraction. Using yeast two hybrid screening and standard biochemical approaches, we found that the short cytoplasmic domain of the α9 subunit can recruit at least 3 different direct binding partners (paxillin, the GCSF receptor and the polyamine-catabolizing enzyme, SSAT, to mediate these diverse effects on cell behavior. These studies provided important insights into the broad diversity of signaling strategies available to integrins and identified several potential novel targets for pharmacologic intervention. Additionally, I have been involved in studying important role of integrin αvβ6 in activating TGFβ in close proximity to contracting epithelial cells; we sought to determine whether there were other integrins that could also activate this growth factor in other contexts. We found that the αvβ8 integrin is an important activator of TGFβ in the context of antigen presentation by dendritic cells and that this process is essential for the generation of Th17 cells. Using mice we generated specifically lacking this integrin in dendritic cells, we identified important roles for this process in models of multiple sclerosis.
and allergic asthma. We have subsequently found that there is another αv integrin on activated fibroblasts 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.


Since 1999, I am the director of the Animal Physiology and Morphology Core Lab within the Lung Biology Center at UCSF. During last 16 years, the core lab has provided high quality service for investigators who are interested in studying airway physiology, immunology, cell and molecular biology and other related areas. We assist 15 investigators from UCSF and other institutions for over 20 different animal related projects in average each year. Many of these studies have helped investigators in the past in initiating studies, making optimal decisions in determining the study focus, obtaining preliminary data for grant applications and publishing high quality scientific observations in the field.


H. Eric Xu, Yuanzheng He, Jingjing Shi, Wei Yi, Xin Ren, Xiang Gao, Jianshuang Li, Nanyan Wu, Kevin Weaver, Qian Xie, Sok Kean Khoo, Tao Yang, Xiao Zhu Huang, and Karsten Melcher. Discovery of a highly potent glucocorticoid for asthma treatment. *Cell Discovery* Epub 2015 Dec. doi: 10.1038/celldisc.2015.35

**Research Support**

Current: none

Past: U19 AI077439 (Core B PI) 04/01/2008 - 03/31/2013

NIH/NIAID

Mechanisms of Initiation and Persistence of Allergic Asthma
**BIOGRAPHICAL SKETCH**

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<tr>
<td>Matthew Frederick Krummel, Ph.D</td>
<td>Professor</td>
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| eRA COMMONS USER NAME | Krummel |

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<td>University of Illinois at Champaign-Urbana</td>
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<td>University of California at Berkeley</td>
<td>Ph.D.</td>
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<tr>
<td>Walter and Eliza Hall Institute, Melbourne Australia</td>
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<td>Stanford University</td>
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**Positions**

- **Summer 1987**: Summer Undergraduate Research Fellow, UTHSCD
- **Summer 1988**: Stagiare (Technician) Institut Pasteur, Paris, Unite de Genie Micro-Biologique.
- **1989-1996**: Graduate Student and Postdoctoral Fellow, University of California at Berkeley, Department of Molecular and Cell Biology
- **1996-1997**: Postdoctoral Fellow, Walter and Eliza Hall Institute, Melbourne Australia
- **1997-2001**: Postdoctoral Fellow, Beckman Institute, Stanford University, Stanford, CA
- **2001-2006**: Assistant Professor, Department of Pathology, UCSF
- **2006-Present**: Associate Professor, Department of Pathology, UCSF
- **2006-Present**: Faculty Director, Biological Imaging Development Center, UCSF
- **2012-Present**: Professor, Department of Pathology, University of California, San Francisco

**Honors**

- **1985**: Illinois State Scholar, National Merit scholar, Westinghouse Science Award
- **1986**: James Scholar, University of Illinois
- **1987**: Summer Undergraduate Research Fellowship, Howard Hughes Medical Institute
- **1989**: Luce Scholar’s competition finalist, Henry Luce Foundation
- **1996-1997**: Postdoctoral Fellowship, Juvenile Diabetes Foundation International
- **1997-2000**: NRSA Postdoctoral Fellowship, National Institutes of Health

2004-2007 Cancer Research Institute, Investigator Award
2005-2010 Leukemia and Lymphoma Foundation, Career Award
2009-2012 Fellow of the American Asthma Foundation

Contributions 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.


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


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


4. Identification of Key Cytoskeletal Regulators of T cell motility and arrest. My laboratory defined the key roles for Myosin 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.


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


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


Complete List of PubMed-indexed Published Work:

**Research support**

Ongoing Research Support

R01 AI52116 (PI: Krummel) 01/15/2008-12/31/2017

NIH/NIAID
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.
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

Krummel (PI) 07/01/2015 - 06/30/2020

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

Krummel (PI) 8/01/2015 - 07/31/2018

The goal of this project is to develop and standardize methodologies for the live-imaging of tumor biopsies, directly after excision from human patients.
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

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


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

3. 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.


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.


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.


**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 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.

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 cytokine-producing cells, including Th2 cells, basophils and eosinophils, in mediating the immune response to parasitic helminths.

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.

R01 HL128903 (Locksley) 7/1/15 – 6/30/19
NIH/NHLBI
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.
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

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

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

Other Experience and Professional Memberships

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

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Honors

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

Contribution to Science

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

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

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

Research Support

On-going Research Support

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

Completed Research Support

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

NAME
William E. Seaman, M.D.

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

eRA COMMONS USER NAME
BSEAMAN

EDUCATION/TRAINING

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

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 - Present Associate Chair of Medicine for Research, UCSF

Other Recent 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
2011 - Present  Associate Chair of Medicine for Research, UCSF
2002 - 2005  President, Society for Natural Immunity

Honors

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

Medical and Research Society Memberships and Board Certifications

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

Editorships

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

15 Selected Peer-Reviewed Publications (of 94)


**Research Support**

I closed my laboratory in 2014 and no longer have grant support.
NAME  Dean Sheppard
POSITION TITLE  Professor of Medicine
eRA COMMONS USER NAME  sheppard

EDUCATION/TRAINING

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

Positions

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

Other Experience

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

Honors and Awards

Elected member, American Society for Clinical Investigation, 1992
Elected member, Association of American Physicians, 1995
Clean Air Award, American Lung Association of California, 1995
Parker B. Francis Lecturer, Aspen Lung Conference, 1996
Lifetime Scientific Achievement Award, American Thoracic Society, 1998
Jerome I. Flance Visiting Professor, Washington University, 2000
Roger Mitchell Lecturer, Aspen Lung Conference, 2001
NIH Merit Award, 2004-2014
Robert Johnston Lecturer, Drexel University, 2005
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

**Contribution to Science**

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


2. When I was appointed to build a center at UCSF focused on applying cell and molecular approaches to the study of lung diseases, I spent a sabbatical year with Robert Pytela, one of the faculty members I recruited to this center. During this sabbatical Robert, David Erle and I developed a method (homology-based PCR) to identify sequences encoding new members of the integrin family, a family of heterodimeric transmembrane receptors known 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 heterodimeric 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 \( \beta \) subunit (\( \beta_6 \)) identified from epithelial cells using the polymerase chain reaction. J Biol Chem 1990; 265:11502-11507. PMID: 2365683


c) Palmer EL, Rüegg C, Ferrando R, Pytela R, Sheppard D. Sequence and tissue distribution of the integrin \( \alpha 9 \) subunit, a novel partner of \( \beta 1 \) that is widely distributed in epithelia and muscle. J Cell Biol 1993; 123(5):1289-97. PMCID: PMC2119880

d) Yokosaki Y, Palmer EL, Prieto AL, Crossin KL, Bourdon MA, Pytela R, Sheppard D. The integrin \( \alpha 9 \beta 1 \) mediates cell attachment to a non-RGD site in the third fibronectin type III repeat of tenascin. J Biol Chem 1994; 269:26691-26696. PMID: 7523411

3. To better understand the in vivo relevance of members of the integrin family we had identified, my lab generated integrin subunit knockout mice and used the phenotypes we identified 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 TGF\( \beta \) and showed that this pathway is important, though distinct effects on different responding cells, in experimental models of pulmonary fibrosis, emphysema, acute lung injury, allergic asthma and in modulating immune responses to tumors. These studies have stimulated substantial interest in potential anti-integrin therapeutics, including one humanized monoclonal antibody generated based on work in my lab that is now in phase 2 clinical trials for potential treatment of idiopathic pulmonary fibrosis and antibodies and small molecule inhibitors we have developed targeting the \( \alpha v \beta 8 \), \( \alpha v \beta 5 \), \( \alpha v \beta 1 \) and \( \alpha 5 \beta 1 \) integrins that are in various stages of clinical development for treatment of severe asthma, fibrotic diseases, acute lung injury and for tumor immunotherapy.


4. Because the integrin $\alpha_9\beta_1$ had no known function, we put considerable effort into understanding how this integrin could modulate cell behavior. By studying the effects of this integrin in multiple different types of cells, we identified critical roles for $\alpha_9\beta_1$ in mediating rapid cell migration, neutrophil differentiation and smooth muscle contraction. Using yeast two hybrid screening and standard biochemical approaches, we found that the short cytoplasmic domain of the $\alpha_9$ subunit can recruit at least 3 different direct binding partners (paxillin, the GCSF receptor and the polyamine catabolizing enzyme, SSAT), to mediate these diverse effects on cell behavior. These studies provided important insights into the broad diversity of signaling strategies available to integrins and identified several potential novel targets for pharmacologic intervention.

a) Chen C, Young BA, Coleman CS, Pegg AE, Sheppard D. Spermidine/Spermine N$^1$-Acetyltransferase specifically binds to the integrin $\alpha_9$ subunit cytoplasmic domain and enhances cell migration J Cell Biol 2004 167:161-170. PMCID: PMC2172529


c) Dehart GW, McCloskey DE, Pegg AE, Sheppard D. $\alpha_9\beta_1$ integrin enhances cell migration by polyamine-mediated modulation of an inward rectifier potassium channel. Proc Natl Acad Sci USA 2008 105:7188-93. PMCID: PMC2386075


5. Having identified an integrin ($\alpha_v\beta_6$) that played an important role in activating TGF$\beta$ 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 $\alpha_v\beta_8$ integrin is an important activator of TGF$\beta$ 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 $\alpha_v$ integrin on activated fibroblasts ($\alpha_v\beta_1$) that is critical to pathologic fibrosis in the lungs, liver and kidney. This work has led us to appreciation of the importance of multiple $\alpha_v$-containing integrins as potential therapeutic targets in a variety of immune-mediated and fibrotic diseases.


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

Research Support

Ongoing Research Support

P01 HL108794 (Sheppard) 07/01/2012–06/30/2017
NIH/NHLBI- Project 2 and Core A
Targeting Epithelial Cells to Treat Pulmonary Fibrosis
Overall project goal: This grant addresses two critical needs - developing effective treatments for pulmonary fibrosis and better ways to determine if drugs are actually hitting their targets. By targeting specific well-defined pathways, modifying drugs for delivery into the airways, and identifying markers of drug efficacy from readily available sites, we hope to dramatically improve current approaches to treatment of pulmonary fibrosis.

T32 HL007185 (Sheppard) 07/01/2012–06/30/2017
NIH/NHLBI
Multidisciplinary training program in lung disease
Role: Program Co-PI
Overall project goal: This is a training grant to train future leaders in basic, clinical and translational pulmonary science. There are 13 annual training slots on this grant.

U19 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.
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.

Completed Research Support

R01 HL102292 (Sheppard) 12/03/2010-11/30/2015 (NCE)
NIH
Integrin-mediated Regulation of Airway Smooth Muscle
The major goals of this project are to determine the mechanisms by which the alpha9beta1 integrin inhibits the sensitivity of airway smooth muscle to contraction induced by agonists of G protein coupled receptors.
Jeoung-Sook Shin, Ph.D.

Associate Professor

SHINJS

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 Fellow 8/2003 Pathology
Yale University, New Haven, CT
Postdoctoral Fellow 1/2008 Cell Biology

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

American Thoracic Society, member
American Association of Immunologists, member
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
NIH study section ZRG1 IMM-T90

The Best Research Student Award in the Department of Pathology, 9th Graduate Student Symposium, Duke University
The Jane Coffin Childs Memorial Fund Research Fellowship Award
Sandler Innovative Award in Asthma Research, Sandler Asthma Basic Research Center
Cancer Research Institute Investigator Award

2008-2009
2010-Present
2008-Present
2017

USA
Contribution to Science

1. **Identification of a novel mechanism by microbes enter and dwell in mast cells.**

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


2. **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.


**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 therapeutically targeted to develop tolerance to disease-causing allergens or auto-antigens. I served as the principle investigator in all these studies.


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


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 General Medical Sciences (NIGMS)
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.

01/01/2016 - 06/30/2017
Nina Ireland Program for Lung Health
Shin, Jeoung-Sook (PI)
The role of FceRI expressed by dendritic cells in allergic asthma
The major goal of this project is to identify the specific role that FceRI expressed by dendritic cells play in asthma.

02/01/2017 – 05/31/2018
Catalyst award, UCSF CTSI (Clinical and Translational Science Institute)
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 allergic asthma is improved by inhibiting MARCH1.

**Completed Research Support During Last Three Years**

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.

07/01/2010 - 06/30/2014
10SDG3500062, American Heart Association
Shin, Jeoung-Sook (PI)
FceRI trafficking in dendritic cells
The major goals of this project are to characterize intracellular trafficking of human high affinity IgE receptor (FceRI) and identify its role in dendritic cell function.
BIOGRAPHICAL SKETCH

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

POSITION TITLE
Research Specialist

eRA COMMONS USER NAME

EDUCATION/TRAINING

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
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<tr>
<td>Xian Medical University, Xian, China</td>
<td>M.D.</td>
<td>12/82</td>
<td>Medicine</td>
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<tr>
<td>Xian Medical University, Xian, China</td>
<td>M.S.</td>
<td>12/85</td>
<td>Immunology</td>
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</table>

Positions and Honors

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

Selected Peer-reviewed Publications


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
1991-1992 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 Integrative Medical Sciences
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

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

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

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


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


Complete List of Published Work in My Bibliography:

Research Support

Ongoing Research Support
Howard Hughes Medical Institute, Weiss (PI) 07/01/85-08/31/17
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
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

<table>
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</tr>
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<tbody>
<tr>
<td>Harvard University</td>
<td>A.B.</td>
<td>06/1988</td>
<td>Physics</td>
</tr>
<tr>
<td>Massachusetts Institute of Technology</td>
<td>Ph.D.</td>
<td>05/1993</td>
<td>Physics</td>
</tr>
</tbody>
</table>

Positions and Honors

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


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

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.


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


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


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


Full List of Published Work:

Research Support

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
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.

Human Gene Knockdowns that May Extend Lifespan

The goal of this project is to screen for genes important in human aging.

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.

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.

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.

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

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

Positions

1973-1975  Research Scientist, Strangeways Res. Lab., Cambridge, United Kingdom
1975-1976  Visiting Assistant Professor of Medicine, Dartmouth Medical School, Hanover, NH
1976-1980  Assistant Professor Radiobiology, Radiology University of California, San Francisco
1979-1980  Assistant Professor Anatomy, University of California San Francisco
1980-1983  Associate Professor of Anatomy and Radiology University of California, San Francisco
1983-Present Professor Anatomy, UCSF
1985-1986  Visiting Professor, Sir William Dunn School of Pathology University of Oxford, United Kingdom
1998  Visiting Professor, Institut Curie, Paris
1999-Present Vice-chair, Dept. of Anatomy, University of California, San Francisco
2006-2008  Visiting Professor, Max-Planck Institute for Biochemistry Martinsried, Germany
2011-present Co-leader, Cancer, Immunity and Microenvironment Program, UCSF Helen Diller Family Comprehensive Cancer Center
2016-present hhhhhAssociate 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
2001-2006   Board of Directors, AACR
2003-2005   Council Member, International Society for Matrix Biology
2003-2006   President, American Society for Cell Biology
2007-2009   Nominating Committee, AACR
2007       Member, NIH ZRG1 ICI–D01
2008       Reviewer, NIH Pioneer Awards
2008       Chair, NIH ZRG1 MOSS-A (02)
2008-2010  Chair, NIH ICI Study Section
2009-2012  Chair, American Academy of Arts and Sciences, Membership Selection Committee Class II, section
2010       Co-organizer, CNIO Cancer Symposium on Frontiers in Invasion and Metastasis, Madrid
2011-Present  Member, Steering Committee, AACR Council of Scientific Advisors
2011-2016   Member, Scientific Advisory Board, Max Planck Institute for Biology of Ageing, Cologne, Germany

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


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 growth context and the concept that regulation of cell adhesion and cytoskeleton altered signaling cascades, gene transcription and apoptosis. These papers show that extracellular proteases are key and substantial targets of integrin and actin cytoskeletal based signaling cascades, and were the first to link Rho GTPases to integrin signaling and point out that the mitochondrion is a key signaling center downstream of this pathway. These pathways are fundamentally involved in the tumor microenvironment and tumor cell behavior.


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


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


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


Complete List of My Published Work in PubMed:

**Research Support**

On Going

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?”

NIH/NCI R01 CA057621-24 (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-8011-02 (Werb, PI) 03/01/15-02/28/18
Testing Chemicals For Likely Contribution To Breast Cancer
This collaborative proposal evaluates the effects of environmental agents on mammary epithelium by mass spectrometry.

NIH/NCI R01 CA190851-02 (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.
Role: PI

NIH/NCI U01 CA199315-01A1 (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.

Completed

NIH/NCI R01 CA129523 (Werb, PI) 07/01/08 - 04/30/14
Transcriptional Regulation of Breast Cancer Metastasis
This study addressed how GATA-3 regulates the differentiated state of breast tumors.
Role: PI

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 they are affected by environmental stressors.
Role: PI
BIOGRAPHICAL SKETCH

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

POSITION TITLE
Associate Professor of Medicine in Residence

eRA COMMONS USER NAME
woodruffp

EDUCATION/TRAINING

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
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<tbody>
<tr>
<td>Wesleyan University, Middletown, CT</td>
<td>B.A.</td>
<td>5/1989</td>
<td>Letters</td>
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<tr>
<td>Columbia College of Physicians &amp; Surgeons, NY</td>
<td>M.D.</td>
<td>5/1993</td>
<td>Medicine</td>
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<tr>
<td>Massachusetts General Hospital</td>
<td>Resident</td>
<td>7/93-1996</td>
<td>Internal Medicine</td>
</tr>
<tr>
<td>Harvard School of Public Health</td>
<td>M.P.H.</td>
<td>6/98</td>
<td>Epidemiology</td>
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<tr>
<td>Brigham and Women’s Hospital</td>
<td>Fellow</td>
<td>07/97-98</td>
<td>Respiratory Epidemiology</td>
</tr>
<tr>
<td>University of California, San Francisco</td>
<td>Fellow</td>
<td>07/98-02</td>
<td>Pulmonary/Critical Care</td>
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</table>

Positions and Honors

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

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

Contribution to Science

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


2. Subphenotyping COPD in the SPIROMICS study. I have been a Site PI in and the director of the bronchoscopy substudy in the SPIROMICS study of COPD, which is the longitudinal COPD cohort in which this study is embedded. SPRIMMICS will provide the airway samples and the detailed clinical and immunological phenotyping required by this grant application.


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


4. Clinical Trials of novel therapeutic approaches in asthma and COPD. These studies include a large multi-center trial, which established the efficacy of a novel therapeutic approach in COPD (azithromycin).


Complete List of Published Work in MyBibliography:

Research Support
Active

COPD Foundation, Inc (PI Woodruff) 8/01/16-7/31/18
Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS)
The goal is to identify subtypes of and biomarkers of intermediate outcomes in COPD.

U01HL128952-01 (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.

U01HL126493-01 (contact PI: Woodruff, Co-PI: Erle) 8/1/14-4/30/19
NIH/Common Fund
Defining a Comprehensive Reference Profile of Circulating Human Extracellular RNA
The goal of this study is to use RNA sequencing to establish the reference range of exRNAs as biomarkers in 12 different body fluids.

U19 AI077439 (PI: Sheppard, core director, 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 respective roles of IL-13 and IL-17 in AHR and airway epithelial abnormalities in asthma.
P01 HL107202 (Fahy JV, Woodruff Core leader) 7/1/12-6/30/17
NIH/NHLBI
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 7/1/11-6/30/17
Severe Asthma Research Program
The goal of this project is to investigate molecular phenotypes and lectins that regulate mucus viscosity in severe asthma.
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 HL095372 (Woodruff PI) 9/30/08-09/29/12
Molecular Phenotyping of Asthma (no cost extension)
To classify asthma based on distinct pathways of inflammation.

R01 HL097591 (Woodruff PI) 8/01/09-7/31/13
NIH/NHLBI
Role of Th2 and non-Th2 Inflammation in Airway Smooth Muscle Remodeling in Asthma
To dissect the Th2 and non-Th2 associated causes of airway smooth muscle dysfunction in asthma

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.

U01 HL112696 (Woodruff Co-I, PI Koth) 4/01/12-3/31/15
NIH/NHLBI
Genomic Phenotyping and Mechanisms in sarcoidosis and AAT
To identify molecular sub-phenotypes of Sarcoïdosis.