Progress Report
Year 16, April 2015
Figure legend: MicroRNA (miRNA) expression in T cells isolated from airway bronchoalveolar lavage from subjects with asthma and healthy control subjects. Expression data were generated using a high throughput microfluidic qPCR platform and analyzed by unsupervised hierarchical clustering using the 23 most variable miRNAs. Expression of miR-19a was consistently increased in T cells from asthmatic subjects. Functional analysis in mouse and human T cells showed that miR-19a promotes IL-13 production through the regulation of a network of gene targets that include key antigen and cytokine receptor signaling inhibitors (PTEN, SOCS1, and A20). T cells lacking miR-19a were poor inducers of allergic inflammation and mucus production in the airways in a mouse model.
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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 by a group of 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 successes and growth, the Center subsequently aligned 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 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 evolved into a productive disease-oriented research enterprise within the greater UCSF scientific community. The past year was marked by maturation and growth as the Center expanded and began to take on a greater presence in the arena of human disease. Notable accomplishments included:

1. Implementation of a Strategic Plan to transform the Center to a more human disease-centric platform over a 3-5 year period. The Plan includes a stepwise reduction in funding to basic animal core technologies while expanding outreach into areas of sample collection, patient recruitment and technology development to provide resources for a cadre of young investigators in training.
2. Dr. Jeoung-Sook Shin, the last of our original young faculty recruits to the SABRE Center, was awarded an NIH R01 grant for her work and was advanced to tenure at UCSF.
3. Dr. Laurence Cheng, an M.D./Ph.D. allergist, was recruited to the SABRE Center to study basophil and mast cell biology in asthma. Recruited as an Assistant Professor in Pediatrics, Dr. Cheng was awarded the Mary E. and Oscar L. Frick Endowed Chair in Pediatric Allergy in the fall of 2014.
4. Dr. Mark Ansel, one of our initial recruits, received accelerated promotion to tenure and was bestowed a state FTE position in the UC system.
5. SABRE Center investigators continued to publish high-impact manuscripts in competitive journals and to compete successfully for extramural funds despite the difficult NIH payline. Increasingly, these studies have begun to work with and focus on human patients and materials.

We look forward to ongoing successes in the coming year as we continue with our mission to conquer asthma.
Overview – 2014
Richard M. Locksley, M.D.

The SABRE Center faculty spent a number of months in 2013 constructing a Strategic Plan to address the maturation of the Center, the academic and research advancements of individual personnel and the need to consider organizational adjustments to enhance our capacity to sustain our trajectory. In many ways, the Strategic Plan was brought about by the success of our investigators, who have been promoted to tenure and recruited into Departments at UCSF or rewarded with endowed Chairs and other resources that facilitated personnel and laboratory moves. This allowed the Center to spread investigators more widely across sites on campus and also offered the capacity for ‘backfill’ at the core site on Parnassus in order to bring in additional faculty dedicated to the mission. The response to these changes brought of success drove the need to reposition our organization and mission, and to focus on how best to bring together strengths to achieve our goal of conquering asthma.

Key Elements of the Strategic Plan

The key elements of the Strategic Plan involve a 3-year process of 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; four core more junior faculty - Drs. Allen, Ansel, Cheng and Shin; and Drs. Fahy and Woodruff, who occupy Cardiovascular Research Center labs on a separate floor in the same building. Dr. Cheng is our newest member and is a pediatrician allergist/immunologist, who will facilitate the move to increase our studies in human patients. Dr. Limin Liu, who had previously been a full-time member, has been phased out of the Center to allow him to pursue his interests in cancer biology. A search has begun in conjunction with the Pulmonary Division in the Department of Medicine to bring an additional M.D./Ph.D. investigator to the Center. Three outstanding candidates have been selected for interview and will visit in the coming months. 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. 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.

Dr. Mark Ansel is working to understand the gene expression networks that mediate immune cell differentiation and effector functions in allergy, particularly asthma. His focus remains on microRNAs, transcription factors and epigenetics as critical executioners of these pathways. 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 several productive collaborations with UCSF Airway Clinical Research center investigators, including Dr. Fahy, Dr. Woodruff, and Dr. Homer Boushey. One of his collaborative projects with Dr. Woodruff and Dr. Fahy was recently reported in *Nature Immunology*. Together, they discovered that miR-19a is specifically upregulated in T cells from the airways of asthmatic subjects. Further work in the Ansel lab showed that miR-19a strongly promotes Th2 cytokine production in mouse and human T cells through coordinate repression of antigen and cytokine receptor signaling inhibitors. An additional submitted manuscript describes the 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. Altogether, Dr. Ansel contributed to 12 published manuscripts in 2013-14. In addition to his high-impact primary research articles, Dr. Ansel was invited to author reviews in *Nature Reviews Immunology* and the *Journal of Clinical Investigation*, and to guest edit the “RNA regulation of the immune system” issue of *Immunological Reviews* and the latest “Allergy and Hypersensitivity” issue in *Current Opinions in Immunology*. Dr. Ansel has established himself as a leader in his field, and has recently delivered invited lectures at national and international scientific conferences in San Francisco, Chicago, Canada, Brazil, Australia, and the Czech Republic.

Dr. Ansel’s work has also been rewarded with substantial extramural grant support. His first R01 funded grant from the National Heart, Lung and Blood Institute of the NIH leverages collaborations formed with Dr. Woodruff, and provides over $1,000,000 over 5 years. Dr. Ansel is also a participating Principal Investigator in the first Program Project Grant among SABRE Investigators from the NIH, now in its second of five years with annual funding of approximately $1,575,000. In recognition of his outstanding accomplishments as a young investigator, Dr. Ansel was awarded a Leukemia & Lymphoma Society Scholar Award, resulting in approximately $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 the next five years.
The Ansel laboratory currently consists of three graduate students, four postdoctoral fellows, and two technicians. One student was supported by a National Science Foundation Predoctoral Research Fellowship and received an HHMI Graduate Education in Medical Science (GEMS) Training Program Award to pursue translational studies in asthma patients in collaboration with Dr. Fahy in the Airway Clinical Research Center. Current postdoctoral fellows competed successfully for fellowship support from the Leukemia & Lymphoma Society, the Immunology Program T32 training grant, and the UCSF Clinical and Translational Science Institute, and another was just awarded an NIH K08 Career Development Award. All of Dr. Ansel’s previous 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. For example, he has worked with Dr. Woodruff, Dr. Fahy, and Dr. Boushey to improve and apply high dimensional flow cytometry and mass cytometry (a.k.a. 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. He is pursuing RNAseq on rare immune cell populations in connection with the Locksley lab.

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 recently named one of 150 recipients of UCSF’s 150th Anniversary Alumni Excellence Awards. He participates in teaching for medical, dental, and graduate students, and directs the immunology course for the doctor of pharmacy program. In addition, he recently became director of the UCSF Biomedical Sciences (BMS) graduate program.

Dr. Jeoung-Sook Shin is investigating the role of dendritic cells in immune homeostasis and disease. Her focus remains on the role of dendritic cells in regulatory T cell development, novel aspects of IgE function, and asthma pathogenesis. Her recent study illustrates an important role of a dendritic cell-derived enzyme, MARCH1, in regulatory T cell development. This study was highlighted in *Nature Reviews Immunology* and in the *Faculty 1000 prime*. More recently, she demonstrated that dendritic cells participate in IgE clearance and IgE-mediated peripheral tolerance. Additionally, she found that dendritic cells infiltrate lungs and airways in association with fibrosis and Th2-associated asthmatic inflammation. These studies resulted in four publications in peer-reviewed journals in 2014. She has been invited to present at a number of scientific conferences including Keystone Symposia and the American Academy of Allergy Asthma and Immunology Annual Meeting. She was also invited to write review articles in *Immunological Reviews, Cellular and Molecular Life Sciences*, and *Immune Network*.

Dr. Shin received her first R01 grant from the National Institute of General Medical Sciences of the National Institute of Health in 2013. This funding of $950,000 in direct research dollars will support her laboratory over the next five years. Dr. Shin has been also supported by the four-year Scientist Development award from the American Heart Association with total $280,000 through July, 2015. Dr. Shin was also awarded a pilot research fund of $30,000 from the UCSF Research Evaluation and Allocation Committee earlier this year. Dr. Shin was invited
to submit a grant proposal to the Department of Defense, which is currently pending; if funded, this grant will provide approximately $1,000,000 in direct costs.

Dr. Shin’s laboratory includes two postdoctoral fellows. One of them was selected as a speaker in a Keystone Symposium to be held in Montreal in March 2015. The other fellow, recently recruited from Stanford University, has applied for a prestigious Jane Coffin Childs Postdoctoral Fellowship. His research will be devoted to further understanding the role of dendritic cells in IgE function and asthma. Dr. Shin continues to collaborate with Drs. Prescott Woodruff in the Airway Clinical Research Center and Paul Wolters in the Department of Medicine to examine human lung tissues and cell lavages from patients with asthma and pulmonary fibrosis. Dr. Shin works closely with the Flow Cytometry Core, Genomics, and Imaging Cores.

In recognition of Dr. Shin’s research and contributions to UCSF, she was promoted to Associate Professor in July, 2014.

Dr. Chris Allen joined the SABRE center seven 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 some of his initial findings in a report in *Immunity* reporting his discovery that IgE heavy chains inherently drive movement of B cells out of germinal centers, a process that may serve to limit somatic hypermutation and thus affinity. This finding will drive new hypotheses regarding mechanisms by which some allergic individuals develop high-affinity IgE, and constitute major efforts of his laboratory. 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. Last year, Dr. Allen published a review on recent advances in IgE biology for *Current Opinion in Immunology*. Dr. Allen was invited to present his work on IgE at the American Academy of Allergy, Asthma, and Immunology (AAAAI) Annual Meeting this February. 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 direct costs to support his lab over the coming year. The Dean of the UCSF School of Medicine selected Dr. Allen as the recipient of the 2013 Weston Havens Foundation Award, which provided an additional $428K in direct costs over two years.

In recognition of these accomplishments, 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 2013. Dr. Allen rapidly recruited a new postdoc, a new technician, and his first graduate student who is fully funded by the Singapore’s Agency for Science, Technology and Research (A*STAR). In the past year, Dr. Allen recruited a second graduate student in the Biomedical Sciences program to his laboratory. Dr. Allen also has had a medical student volunteering in the lab to begin translating his IgE studies into human samples. Dr. Allen moved his laboratory to the Smith Cardiovascular Research Building on the Mission Bay campus, 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. Laurence Cheng is an M.D./Ph.D. pediatric allergist, and is the newest addition to the SABRE Center. His research program is centered on the role of IgE in allergic inflammatory diseases including asthma, and his expertise spans the use of mouse models to patients with allergic diseases and immunodeficiencies associated with allergic diseases. His expertise involves cellular and molecular immunology together with imaging capacity using 2-photon and confocal approaches that have enabled insights regarding spatiotemporal relationships among cells and their microenvironment, with a special emphasis on barriers surfaces like the lung and skin. His imaging expertise was instrumental in his Immunity publication describing the mechanism by which perivascular mast cells become loaded with serum IgE by extending cellular processes between endothelial cells directly into the blood lumen. More recently, he has used these approaches to describe a role for IgE-activated basophils in regulating eosinophil infiltration through activation-dependent interactions with the endothelium. These interactions promote endothelial expression of integrins vital for eosinophilic infiltration. This manuscript has been accepted for publishing in the Journal of Experimental Medicine.

Dr. Cheng is also investing efforts on studies in children with debilitating food allergy (with Drs. Joe DeRisi and Kurt Thorn). Drs. Cheng and DeRisi, along with Chris Allen, are also undertaking an effort to characterize the depth of the IgE repertoire in children afflicted with allergy and asthma. Such studies involving barrier dysfunction in allergic children will be crucial in understanding the frequently observed ‘atopic march’ by which children with allergic diseases have very high risk for progression to full-blown asthma. This emphasis on human disease, particularly children, who can be difficult to study, is in line with the Strategic Plan goals to transition to an emphasis on human disease within an integrated basic science approach.

Dr. Cheng has attracted substantial funding to begin his independent research activities. He was awarded a K08 grant from the National Institutes of Health (five years at $100K direct costs/yr). After several offers from other premier academic institutions, the Department of Pediatrics offered Dr. Cheng a faculty position, and a substantial start-up package was negotiated based on the SABRE Center being able to offer Dr. Cheng laboratory space within the research core at Parnassus, where his clinic is located. Dr. Cheng has also attracted support from the Rogers Family Foundation for investigations of food allergy in collaboration with the DeRisi laboratory at Mission Bay. Drs. Cheng, Thorn, and DeRisi were also recently awarded an R01 from the National Institutes of Health (NIH) to support efforts related to pediatric food allergy with Dr. Cheng serving as a co-investigator. In recognition of his reorganization and streamlining of the Pediatrics Clinic for Diseases of Allergy and Asthma, the Department of
Pediatrics honored Dr. Cheng as recipient of the Mary E. and Oscar L. Frick Endowed Chair in Allergy, which was bestowed in March 2014.

Dr. Cheng continues to organize his laboratory, and works with a Research Assistant and an Allergy/Immunology fellow. He plans to expand the laboratory with an additional postdoctoral fellow this spring and a possible PhD student in the summer. He works closely with a number of SABRE Center investigators, including Drs. Locksley, Ansel, Allen, Fahy, and Shin, and makes extensive use of the Imaging and Flow cores.

Dr. 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 remained on a deeper understanding of the evolutionary 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, which revealed previously unknown links with metabolic homeostasis, have been influential in driving the nascent field of immunometabolism. His laboratory also explores the induction of allergic immune responses by the environmental polysaccharide chitin, a constituent of fungi and insects associated with human allergic sensitivity. He continues to direct an active laboratory effort with 18 peer-reviewed publications since 2013.

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. He is a Professor in the Departments of Medicine and Microbiology & Immunology, and an Investigator in the Howard Hughes Medical Institute. He has presented his research at prominent national and international conferences. His laboratory is supported by HHMI and by grants from the NIH, including directing one of the subprojects for the SABRE Center PPG under the direction of Dr. Fahy. Postdoctoral trainees in his laboratory were recipients of 2 NIH K08 awards and a Damon Runyon Fellowship over the past year. Dr. Locksley has directed the SABRE Center for 10 years and organized the recruitment of all of the current investigators to the Center.

Drs. John Fahy and Prescott Woodward direct the Airway Clinical Research Center and are integral members of the SABRE Center. Both are physician scientists with primary appointments in the Pulmonary Division in the Department of Medicine. The two share overlapping interests in asthma pathogenesis and translational opportunities for research, particularly in the fields of precision medicine and primary intervention trials. Their 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 the IL-4/IL-13 pathway. Dr. Fahy has additional interests in the biology of mucins and in immunologic characterization of patients with severe asthma, who continue to represent a major unmet medical need and who drive large healthcare expenditures. Dr. Woodward has additional interests in chronic diseases characterized by structural lung damage, including not only asthma but also chronic obstructive pulmonary disease (COPD) and sarcoidosis. Both investigators support laboratories pursuing basic bench research relevant to asthma but also translational studies and clinical trials, and both remain very active in the care of asthma patients. Both serve on a number of NIH NHLBI panels dedicated to asthma research and both are involved in the SABRE Center PPG, with Dr. Fahy
being the PI on that grant. Both interact closely with all of the other investigators in the SABRE Center.

Core Activities and Technology Development

An integral component of the SABRE Center during its formative years included 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. In part due to the success of the cores in attracting matching funds from alternative sources and the initiation of a campus payback system that has linked cores with a system-wide reimbursement policy, we are phasing out core support and re-directing these 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. To avoid disruption, the SABRE Center core support was phased out over a 3-year period to allow planning and appropriate adjustments for the individual cores and core personnel. This constitutes the last year of support at a reduced amount for the traditional core support system. We continue to direct leveraged support to the Genomics Core, under the guidance of Dr. Erle, and to the Microscopy Core, under the guidance of Dr. Krummel, for technological innovations of importance to the Center, particularly the increasing use of RNAseq and the development of newer microscopy and lung clarification techniques, respectively. These are discussed more completely in the individual write-ups describing these two Cores. We also continue to support the Genetics Core, under the direction of Dr. Burchard, to expand the repository of human samples from diverse patient groups with asthma. Summaries of the activities of these three Cores, which continue to be supported by the Center, are included in this report.

The re-directed funds previously attributed directly to the Mouse Physiology and Flow Cores was used for technology acquisitions using SABRE Center resources to leverage and match funds from other sources. Examples over the past 18 months include:

1. SABRE Center provided $25K to the Genetics Core (Erle) to facilitate purchase of a $215K robot that supports around-the-clock next generation high-throughput automated sequencing. Funds from two NIH grants and the Chancellor’s Core Initiative Funds matched SABRE Center funds. The machine worked over a long weekend to generate data from over 100 inner-city African American children with asthma in Detroit (study supervised by H. Keoki Williams) that was used to support an NIH R01 application that received a priority score in the 8th percentile and was funded by NIH. The UCSF Genetics Core has a subcontract component in support of the grant. The robot is currently completing an update of a number of sequences from the Burchard database, and has linked with a number of other SABRE projects, including RNA sequencing of cells from the labs of Ansel, Woodruff and Locksley. We are currently considering support for an AAF-funded investigator to pursue single-cell RNAseq in the Genetics Core for a project relevant to the SABRE Mission, attesting to the flexibility of this approach.
2. SABRE Center provided $50K to the Imaging Core (Krummel) that was used for a number of enhancing technologies. A $12K investment was used to leverage $135K from the Chancellor’s Emerging Technologies Initiative and partnered with $50K from two different NIH grants to build a one-of-a-kind scope (‘bleeding edge’) called a super-resolution Bessel beam microscope. This scope images individual cell membrane dynamics and signaling perturbations at 200 nm resolution at frame rates approaching 1 Hz. The scope has been built and is working, and an R21 was just submitted by Dr. Krummel to provide support for personnel to continue to ‘tweak’ the scope in order to improve its capabilities further. Several SABRE labs (Allen, Locksley, Sheppard) are working with harnessing the capabilities of this instrument. An additional $10K investment was used to match $15K from another grant to design and construct a new gradient refractive index that improves imaging from airway tissue explants and intravital tracheal imaging. This is now supporting two asthmarelated projects at UCSF. A $5K investment of SABRE funds was used to leverage $20K from 4 labs to purchase a workstation that manages very large data sets generated by these intravital imaging technologies. Finally, an $8K investment was leveraged using PBBR (internal UCSF funds) funds to build a new prototype microscope capable of counting single RNA molecules and to beta test the scope. A progress report on the scope should be available by late spring. SABRE Center continues to support the salary of the imaging center operator and teacher, Dr. Henry Pinkard, who writes all of the code that enables faster processing rates. The SABRE Center will continue to support technology in the Microscopy Core for the next 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.

3. SABRE Center invested $10K to match $75K from other sources involved in purchasing a Fluidigm instrument for single-cell expression studies. The Ansel, Woodruff, Fahy, Allen and Locksley Laboratories are all participating in studies using the instrument.

4. SABRE Center committed $25K to support acquisition of a CyTof mass spectrometry unit on the Parnassus site through an NIH Technology Grant. This reflects a relatively modest commitment for an expensive (~$450K) instrument that has established new technology on the
Parnassus campus. The grant was awarded and the instrument is being readied for operation. Drs. Ansel and Woodruff are heavily involved in establishing the core reagents and cost structures that will enable efficient operation of the instrument on campus and for SABRE investigators.

5. SABRE Center committed $25K to support a state-of-the-art lipid mass spectrophotometer technology grant that is being spearheaded by Dr. Jason Cyster in the Department of Microbiology & Immunology. This grant is being matched by UCSF technology funds and has been submitted, but not scored. There is no such instrument anywhere on the UCSF campus, but this will push new avenues of investigation in multiple fields of lipid chemistries, many of which are applicable to asthma, where lipid mediators have been implicated in airway smooth muscle reactivity and other aspects of inflammation. These monies will not be donated until the grant is successful. The overall costs of the instrument and operator approach $600K.

6. SABRE Center committed $50K to an innovative grant from Dr. James Fraser, an Assistant Professor in the Department of Bioengineering and Therapeutic Sciences at UCSF. Dr. Fraser is an expert in innovative structural approaches to understanding large molecular machines. To this end, Dr. Fraser proposes to probe the mechanism by which chitin, a widespread environmental polysaccharide derived from fungi and insects, is degraded by chitinase and chi-lectins secreted and resident in airway fluids. This grant will be used to provide ‘proof-of-principle’ by generating the requisite proteins for biochemical and crystallization studies while also evaluating the capacity to analyze ‘in situ’ formed crystals of the chi-lectins, Ch3l3 and Ch3l4, which can self-crystallize in the lung tissues of older mice. These chi-lectins, like the lung epithelial chitinase, Chia, are further induced by IL-13, and thus expressed highly in allergic lung diseases, including asthma. These studies will begin support of structural studies that will open pathways to interventional studies as part of an overall move to transitional research with translational potential in the area of therapeutic intervention. Dr. Fraser is a state-of-the-art young investigator in innovative methods for structural analysis, including cryo-electron microscopy, and this grant will help support a BioPhysics PhD student, Benjamin Barad, who will be devoted entirely to this project at this formative period in his career. The Fraser innovative grant and the biosketches for Dr. Fraser and PhD-candidate Barad are included.

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 four large NIH research programs that involve multicenter network collaborations in asthma and COPD, thus supporting large numbers of patient visits per year:

(i) AsthmaNet - U10 HL098107 (Boushey, Lazarus, Cabana [Pediatrics])

(ii) Severe Asthma Research Program (SARP) - 1U10HL109146-01 (Fahy).

(iii) COPD Clinical Research Network (CCRN) (Lazarus)

(iv) SPIROMICS (Woodruff) - N01-08-08. The goal of this study is to identify sub-populations and intermediate outcome measures in COPD (chronic obstructive pulmonary disease) through a large multi-center longitudinal study.

The Center also supports the clinical components of multiple other NIH awards involved with various aspects of the SABRE Center, including:

(i) 1P01HL107202 (Fahy) 8/1/12 - 6/30/17

(ii) 2U19AI077439-06 (Sheppard) 4/1/13 - 3/31/18
NIH/NIAID. Asthma and Allergic Diseases Cooperative Research Centers (AADCRC). IL-13 and IL-17 dynamics in the asthmatic airway - Sheppard, Woodruff, Krummel, Erle.

(iii) 5R01 HL080414-05 (Fahy) 7/1/5-5/31/15
NIH/NHLBI. Protein carbohydrate interactions in the pathophysiology of acute asthma exacerbations.

(iv) Inner City Asthma Consortium (Boushey) – a part of NIH Asthma-Net.

(v) 1U01HL126493-01 (Woodruff, PG) 8/01/14-04/30/2019
NIH/NHLBI. Defining a Comprehensive Reference Profile of Circulating Human Extracellular RNA.

(vi) Pending PO1: Carbohydrate-based Therapy for Lung Disease (Fahy, JV).
NIH/NHLBI. Dr Fahy and collaborators at UCSF and beyond have submitted an application in response to the RFA for tPPG grants (PAR14-245 - TRANSLATIONAL PROGRAMS IN LUNG DISEASES [P01]). The Fahy grant (pending review in Feb/Mar 2015) specifically 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.

In addition to NIH grants, the 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.

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:

**Human Based Research**

To facilitate our transition to an increased emphasis on human studies, SABRE Center/ACRC has establishing an alliance with Kaiser Permanente Division of Research at the Kaiser Permanente Medical Care Program in Oakland, California. The investigator we are collaborating with is Carlos Iribarren M.D., Ph.D. Carlos has experience using the large Kaiser databases for research in both cardiovascular and lung disease. Carlos was able to use Kaiser clinical databases to build a cohort of 203,595 Northern California adults with asthma. As part of an IRB approved collaboration, UCSF and Kaiser are screening the Kaiser electronic medical record for patients with asthma who meet prescoedicie criteria for severe diseases. These Kaiser patients are then invited to participate in for mechanism-oriented studies at UCSF with an emphasis on the NHLBI supported Severe Asthma Research Program of research. As part of this collaboration, we have recruited 20 Kaiser asthmatics to the SARP ad these recruits have allowed us to meet our recruitment goals for this program. This is important because achieving recruitment goals will help ensure funding in the next cycle of SARP funding.

The SABRE Center is instigating a working relationship with a local surgical practice with experience taking care of a 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 are working through planning meetings, human use forms and other regulatory issues in order to establish formal collaborative investigation 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 undergo exploration prior to a firm establishment, we plan to commit resources to this collaboration in order to strengthen basic and clinical research interactions with this surgical group, who have been very receptive to our overtures. The biosketches of Dr. Goldberg and Pletcher are appended.

**Young Investigator Career Support in Asthma Studies**

In order to capture young investigators early in their careers at a time when they can be trained and excited by research in asthma, the SABRE Center has begun to fund young scientists across the spectrum of training to pull them into the field while also exposing them to the greater asthma research community at UCSF. The first group of young investigators supported through this mechanism include, two junior faculty, one postdoctoral trainee and one graduate student. The postdoc and graduate student are both structural chemists, reflecting a concern raised in the Strategic Plan regarding needs for this type of research in the Center.

**Nirav Bhakta, M.D./Ph.D.,** is a recently appointed Assistant Professor in the Pulmonary Department who is working with Drs. Woodruff and Ansel to investigate the role of extracellular RNAs as biomarkers in body fluids, including sputum, in subsetting patients with asthma. He was recently awarded an NIH/NHLBI Career Development Award (K23 HL116657) to study the role of IL-17 in asthma, and the additional SABRE Center support will be used to facilitate technology development to ensure his progress and maximal productively during this key early period in his academic research career. Dr. Bhakta’s CV is included in the appendix.

**Michael Peters, M.D.,** will be appointed Assistant Professor in the Pulmonary Department on July 1, 2015. He has been a fellow in pulmonary and critical care medicine at UCSF for the past 4 years with Dr. Fahy and exploring the concept of disease endotypes in asthma. He has optimized methods for gene profiling in sputum cells and a methodology to perform molecular characterization of the large cohort of asthmatic patients in the ACRC. He was recently awarded an NIH/NHLBI Career Development Award (K12) to study the role of IL-6 in asthma, and the additional SABRE Center support will be used to support his gene profiling studies in the UCSF asthma cohort and in the SARP cohort. This support will help ensure his success at this critical juncture in his research career. Dr. Peters’ CV is included in the appendix.

**Beomkyu Kim, Ph.D.,** received his Ph.D. at Stanford under Ted Jardetsky investigating structural impediments to dissociating IgE from its high-affinity receptor that was used to identify compounds with activity against the complex. SABRE is facilitating his continued training in asthma biology by supporting his postdoctoral fellowship with Dr. Jeoung-Sook Shin to further characterize IgE interactions with the human high-affinity receptor. It is anticipated that he will apply for extramural fellowship support once he begins to accrue data towards his new project in the Shin lab. Dr. Kims’ CV is appended.

Ben Barad is a Biophysics graduate student in the Fraser lab on the Mission Bay campus who graduated with a strong undergraduate chemistry background from Stanford. SABRE Center is providing resources in the form of an Innovative Award to the Fraser lab to support Ben’s
project, which is to gain structural insights regarding the degradation of large polysaccharides of chitin. Chitin is associated with dust mite and mold allergens inhaled from the environment, and understanding how the lung disposes of these prevalent allergen-associated constituents may yield insights pertinent to airway homeostasis. Ben meets with members of the SABRE Center to increase his exposure to and understanding of the ongoing research programs associated with asthma.

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.

Since the initial recruitment of Dr. Liu and the additions of Drs. Ansel, Cheng, Shin and Allen, we have seen a steady climb in the amounts of external funds accrued 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; Dr. Liu left in 2015.**
In addition, 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 2014-15


A comprehensive discussion of ‘endotypes’ in asthma – subsets linked by the presence or absence of specific types of inflammation, which will presage the use of biomarkers in approaching care of asthma patients. Identifying mechanistic pathways underpinning non-Th2-associated asthma remains a major unmet medical need, and this solicited review highlights the path forward.


Elevations in serum IgE are a hallmark of allergic asthma and pharmacologic targeting of the pathway has efficacy in some patients. Unlike mouse dendritic cells, human dendritic cells and monocytes express the high-affinity IgE receptor, FcεRI. Here, the investigators show that the myeloid cell receptor is important in clearing IgE from serum, and thus competing with the capacity of IgE to load on to potentially pathogenic mast cells and basophils. This study attracted interest because understanding the pathway may suggest new strategies for lowering serum IgE and decreasing the risk for allergic diseases, such as anaphylaxis and asthma.


Human airway-infiltrating T cells from patients with asthma showed upregulation of microRNA-19. Manipulating miR-19a in human and mouse CD4 T cells revealed a role for this microRNA in amplifying Th2 cytokine production by suppressing several anti-inflammatory targets, including PTEN, SOCS1 and A20. Upregulation of miR-19a might be a biomarker and a target for enhanced type 2 cytokines in T cells.


Population studies by the Burchard group have identified subsets of Latino populations that respond poorly to standard bronchodilators prescribed in asthma. Using genome-wide associative data together with clinical data, these investigators were able to implicate rare genomic variants in patients with substandard control, thus pointing the way for mechanistic...
studies to identify the pathways underlying these deficits such that alternative approaches might be prospectively uncovered.


Roles for epithelial cytokines are suspected in asthma based on genetic and mechanistic studies, but evidence associating the presence or absence of these markers in patients with asthma are lacking. Here, plasma IL-25 divided asthma patients into two subsets, with the IL-25-high group characterized by typical Th2-associated asthma as defined by greater airway hyperresponsiveness, eosinophilia, IgE and type 2 signature genes. This group also responded better to corticosteroids, suggesting a potential biomarker in predicting therapeutic responsiveness or the need to seek alternative approaches.


Chitin is a natural polysaccharide widespread in the environment, where is accumulates as an insoluble constituent of fungal and insect cell walls. When instilled into the lung, chitin particulates initiate local injury, followed by accumulation of neutrophils, but also eosinophils and alternatively activated macrophages, cells typically associated with allergic inflammation. Here, the authors identify key mediators of neutrophil and eosinophil recruitment to be distinct populations of lung innate-like lymphoid cells, including IL-17-producing γδ T cells and IL-5 and -13-producing ILC2, respectively. Epithelial cytokines were also demonstrated upstream of these cells, including IL-1β/IL-23 and IL-33/IL-25/TSLP, respectively. This begins to fill in the pathway which IL-17- and IL-13-mediated lung elicits inflammation through activation of an epithelial- innate lymphocyte circuit.


Despite the importance of IgE in mediating manifestations of atopy and asthma, methods for studying the B cells that produce IgE were lacking, thus precluding the examination of this pathway as a potential strategy for intervention. Based on data obtained from IgE knockin reporter mice, including strains established by the Allen lab, a number of investigators have begun to assess the regulation of IgE-expressing B cells and plasma cells that are of importance to the pathogenesis of asthma and other allergic diseases. Here, Chris Allen summarizes these recent data in an authoritative review that updates the field and frames the important questions that remain.
Organization of the body of this Annual Report

We will organize this report by reviewing the SABRE Center activities and updating 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 will 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. Plans for the coming year including addition of two members with expertise in structural science of relevance to asthma targets to reflect projected needs in this arena in the future.

SABRE Center Executive Committee Members

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

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

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

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

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

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

Art Weiss, M.D., Ph.D., Professor
Departments of Medicine and Microbiology/Immunology

Zena Werb, Ph.D., Professor
Department of Anatomy
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 Darmsädter 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
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 focuses on mechanisms by which the immune system becomes organized in stereotyped ways against discrete types of challenges. This involves the differentiation of naïve helper T cells to subsets that produce different kinds of cytokines, key effector molecules of the immune system. In turn, these different T cells subsets work with different kinds of innate cells, including neutrophils, eosinophils, macrophages and others, to mediate immunity. Properly executed, such responses mediate protection against infectious organisms or repair of damaged tissues, but, when dysregulated, these immune responses lead to disease, including asthma.

Dr. Locksley’s laboratory investigates immunity using mice genetically engineered to report cytokines expressed during the different types of immune responses. This approach reveals the shared expression of important cytokines by innate and adaptive immune cells. Using these methods, the laboratory participated in recent discoveries of innate lymphoid type 2 cells, which represent a previously unstudied cell now implicated in allergic immunity. The laboratory also revealed a novel mechanism by which cutaneous mast cells capture IgE from blood. The laboratory continues to study the role of chitin, a structural component of many allergens – including dust mites, cockroaches, shellfish and molds – as well as helminthes, in inducing
infiltration of cells involved in allergy into tissues, and to pursue recent findings connecting the cells of allergic immunity with metabolic pathways involved in vertebrate homeostasis.

Representative Publications

Christopher D. C. Allen, Ph.D.
Assistant Professor
Cardiovascular Research Institute
Departments of Anatomy and Microbiology and Immunology
Sandler Asthma Basic Research Center

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Dr. Allen is an Investigator of the Cardiovascular Research Institute and an Assistant Professor in the Departments of Anatomy and Microbiology and Immunology 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-Newmann 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), 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, iTreg, 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 miRNAs. 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 define the molecular mechanisms that control miRNA homeostasis, and determine how the miRNA repertoire is so dramatically remodeled during T cell activation.
2) To characterize the function of individual miRNAs that regulate T cell differentiation and immune effector functions.
3) To determine how the expression and function of miRNAs contribute to the pathogenic properties of T cells in human asthma.

Selected Publications


Dr. Laurence Cheng is an Assistant Professor in the Department of Pediatrics. He received an A.B. in Molecular and Cell Biology from the University of California, Berkeley. He then joined the MSTP at the University of Washington, where he received his M.D. and a Ph.D. in Immunology. He completed pediatric residency training at UCSF, followed by subspecialty clinical and research training in Allergy & Immunology through a joint UCSF and Stanford program. His laboratory in the Sandler Asthma Basic Research Center focuses on understanding the cellular regulation of allergic disease in both animal models and patients.

Allergic diseases, including asthma, lead to a myriad of symptoms with disparate acuity and chronicity. Despite this clinical heterogeneity, most all patients with allergic disease share two key features: elevated serum IgE and the infiltration of eosinophils into target tissues. The major goal of Dr. Cheng’s studies is to understand the mechanisms by which antigen binding to IgE drives the clinical pathology associated with allergic disease.

Dr. Cheng’s basic research focuses on understanding the interactions between two myeloid cells associated with allergic disease, mast cells and basophils, and IgE. Dr. Cheng utilizes both genetic and imaging approaches to investigate how mast cells and basophils contribute to chronic allergic diseases, such as atopic dermatitis and asthma. Dr. Cheng has utilized dermatologic models of allergic inflammation to tease apart these pathways and will investigate whether similar principles contribute to allergic lung disease.

In conjunction with his clinical work in the Pediatric Allergy clinic at UCSF Benioff Children’s hospital, Dr. Cheng has also initiated translational research associated with identifying the biochemical signatures associated with IgE-mediated diseases. As part of collaboration with Dr. Joseph DeRisi at UCSF, Drs. Cheng and DeRisi seek to apply developing technologies to stratify patients into risk-groups for diseases such as food allergy, asthma, and atopic dermatitis. The second is in conjunction with the UCSF Pediatric Gastroenterology division. The goal of this collaboration is to use both experimental models and human biospecimens to better understand eosinophilic gastrointestinal diseases. Many of these diseases are closely tied to the ingestion of specific food allergens, and the goal of this work will be to investigate the cellular hierarchies governing this response.
Lab Objectives

1. Determine the molecular and cellular interactions required for basophil control of eosinophilic infiltration into the skin and lung in models of atopic dermatitis and asthma.

2. Define the character and significance of mast cell positioning at the endothelium.

3. Define populations of ‘pathologic’ IgE molecules as biomarkers of risk in allergic disease.

Selected Publications


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

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

John Fahy 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.

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. Important collaborators include Drs Stefan Oscarson and Stephen Carrington at University College Dublin.
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


allergy and airway hyperresponsiveness. Clinical and Experimental Allergy 2012; 42:144-55.
27. Fahy JV. Type 2 inflammation in asthma; Present in most, absent in many. Nature Reviews in Immunology. IN PRESS.
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 function 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 FcεRI expressed in dendritic cells. Although the role of FcεRI in the pathogenesis of allergy is well known, its physiologic role remains unclear. Dr. Shin’s laboratory has recently found that FcεRI is constitutively endocytosed and transported to the lysosomes in human dendritic cells and monocytes, and that this FcεRI endolysosomal trafficking mediates cellular entry of circulating IgE contributing to serum IgE clearance. These findings suggest that FcεRI 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 FcεRI 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

17. Greer, AM and Shin, JS. The Role of FceRI expressed by dendritic cells and monocytes. *Cellular and Molecular Life Sciences*. in press
Prescott Woodruff, M.D., M.P.H.
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UCSF

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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 has 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 10th 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


Functional Genomics Core

Director: David J. Erle, M.D.
Associate Director: Andrea Barczak

Objective
To make cutting-edge functional genomics technology readily available for investigators researching questions relevant to basic biology of asthma.

Accomplishments

Supported projects: We continue to support many investigators studying immunology, airway cell biology, lung development, and other relevant areas. This includes faculty members who participate actively in a range of SABRE activities (including Ansel, Erle, Krummel, Sheppard, and Woodruff) and current or former AAF-funded investigators (Alix Ashare and Keoki Williams). Here is a partial listing of relevant projects that have been completed this year or are still in progress:

<table>
<thead>
<tr>
<th>PI</th>
<th>Project (status)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mark Ansel</td>
<td>mRNA protein binding sites in immune cells. <em>In Progress.</em></td>
</tr>
<tr>
<td>Mark Ansel</td>
<td>Regulation of Th17 cells by miR-17~92 mimics. <em>Completed.</em></td>
</tr>
<tr>
<td>Alix Ashare¹*</td>
<td>Mechanisms of Increased Asthma Severity Secondary to Polymorphisms in the ACE Gene. <em>In Progress.</em></td>
</tr>
<tr>
<td>Leland Dobbs</td>
<td>Alveolar Epithelial Cell Fate: A comparison of prenatal day 18 pre-alveolar epithelial cells in mouse line RT22 and line 114 using RNA-Seq. <em>In Progress.</em></td>
</tr>
<tr>
<td>David Erle</td>
<td>Investigating the effects of IL-17A and IL-13 on miRNA expression in cultured bronchial epithelial cells. <em>In Progress.</em></td>
</tr>
<tr>
<td>David Erle/Prescott Woodruff</td>
<td>Defining a Comprehensive Reference Profile of Circulating Human Extracellular RNA</td>
</tr>
<tr>
<td>De’Broski Herbert</td>
<td>Wound repair macrophages. <em>Completed.</em></td>
</tr>
<tr>
<td>Matthew Krummel</td>
<td>UCSF immunoprofiler consortium. <em>In Progress.</em></td>
</tr>
<tr>
<td>Richard Locksley</td>
<td>Expression profiles of innate and Th2 lymphocytes. <em>Completed.</em></td>
</tr>
<tr>
<td>Dean Sheppard</td>
<td>Effects of Itga8 Ab on OVA treated mice. <em>Completed.</em></td>
</tr>
<tr>
<td>Dean Sheppard</td>
<td>Characterizing molecular diversity of renal, hepatic and lung fibroblasts in the setting of tissue fibrosis. <em>In Progress.</em></td>
</tr>
<tr>
<td>Qizhi Tang</td>
<td>Regulatory T cell subsets in the NOD mouse. <em>In Progress.</em></td>
</tr>
<tr>
<td>Keoki Williams²*</td>
<td>Pharmacogenomics of asthma. <em>Ongoing.</em></td>
</tr>
<tr>
<td>Prescott Woodruff</td>
<td>Targeting microRNAs for asthma treatment. <em>Ongoing.</em></td>
</tr>
<tr>
<td>Prescott Woodruff</td>
<td>Gene expression profiling in asthmatics. <em>In Progress.</em></td>
</tr>
</tbody>
</table>
Prescott Woodruff  

Designing a model system to screen for miRNAs, which regulate mucin production. *In Progress.*

1 Dartmouth-Hitchcock Medical Center, 2Henry Ford Health, *AAF awardee

**Personnel**

Andrea Barczak (manager), Rebecca Barbeau (SRA), and Joshua Pollack (biostatistician) continue to provide outstanding service to core users. In aggregate, they have over 25 years of experience as core staff.

**New technologies**

The SABRE Functional Genomics Core is a resource for the UCSF community (and beyond); we collaborate on more than 60 projects per year. SABRE support is critical for development and implementation of new methods. Priority is given to development of methods required for studies requested by SABRE investigators. For the past three years we have offered comprehensive RNA-Seq services (including library preparation, coordination of sequencing runs, and data analysis) and have transitioned our users from arrays to RNA-Seq technologies. In the following sections we highlight two areas of focus during the past year: 1) automation of additional services, and 2) methods for RNA-Seq analysis with limiting amounts of starting material, 3) development of methods for analysis of extracellular RNAs in human body fluids.

1) **Improving sample throughput with automation:** We purchased an automated RNA-Seq library preparation system in 2013 (several SABRE investigators generously contributed funds towards this purchase). The system can generate up to 96 RNA-Seq libraries on one day and has significantly improved our turn around time and lowered our labor cost. Another benefit of this high throughput system is that it allows us to process larger numbers of samples at one time, thus removing technical batch-to-batch variability that can occur when manually processing smaller numbers of samples over sequential experiments. Over the past year we have automated two additional methods; the NuGen Ovation RNA V2 system for preparation of amplified cDNA with low input samples and RNAdvance for RNA purification of tissues and cells. Standard RNA-Seq library construction methods start with a minimum of 100ng of total RNA. Many of our users are working on studies where the RNA is limiting (laser capture microdissection and cell sorting are two common examples). Library construction methods that are used with limiting amounts of material require a cDNA amplification step before library construction. We have implemented automation for the NuGen Ovation V2 method; a whole transcript amplification method works with less than 1 ng of starting material. A highly requested service from core users is RNA purification, which is not currently available at UCSF. We have successfully implemented the Agencourt RNAdvance protocol for RNA extraction from tissues and cells. We optimized this method to generate total (and small RNA if desired) from as little as 1,000 cells or 1mg of tissue in less than 2 hours. We plan to offer this service in the coming months and anticipate that it will be quite desirable for clinical researchers who lack expertise in RNA isolation methods and/or may have limited access to required laboratory equipment.
2) RNA-Seq analysis with limiting amounts of starting material: There is growing interest in performing RNA-Seq on single cells. There are currently two Fluidigm C1 single cell auto prep system at UCSF, including one that was purchased by a consortium that includes several SABRE investigators (Chapman, Woodruff, Rock and Sheppard). The C1 microfluidic technology enables the user to isolate, process, and amplify single cells for genomic analysis. We performed some pilot runs with SABRE investigator Dean Sheppard results and identified distinct subsets of fibroblast-like cells in the lung and kidney. The core will soon offer the downstream library preparation services (Illumina Nextera) of C1 amplified samples that will be used for single cell RNA-Seq. Many users that we work with are interested in small RNA-Seq analysis. Standard library construction for these types of analyses requires 1µg of total RNA, which is unobtainable for the majority of the studies that we work on. The core has successfully adapted a method (Illumina TruSeq small RNA) to work with 100ng of starting material and is currently working to further optimize the protocol to work with amounts as low as 10ng of total RNA. The advances that we have made towards working with lower input amounts will allow us to offer this service for many more sample types.

3) Development of methods for analysis of extracellular RNAs in human body fluids. David Erle and Prescott Woodruff are co-PIs of a new NIH U01 grant that was funded as a part of the NIH Common Fund’s Extracellular RNA Communication (ERC) program, which “aims to discover fundamental biological principles about the mechanisms of extracellular RNA (exRNA) generation, secretion, and transport; to identify and develop a catalogue of exRNA in normal human body fluids; and to investigate the potential for using exRNAs as therapeutic molecules or biomarkers of disease.” Our project focuses on profiling of all classes of exRNAs in 12 different human body fluids, including some of special interest for asthma (sputum and bronchoalveolar lavage fluid). This requires development of methods that are appropriate for analyzing small amounts of small and large RNAs. We have implemented RNA-Seq pipelines for both small and large RNA in human plasma and have been testing the suitability of a new platform (from HTG Molecular) that can measure thousands of RNAs in very limited samples (12.5 µl).

Plans for the coming year

We have begun to work towards automating protocols for additional services, including the following: 1) preparation of small RNA libraries, 2) preparation of ChIP-Seq libraries, and 3) preparation of libraries for single cell sequencing. The core has obtained an automated method for Illumina Nextera library preparation and is currently working on implementing it for use with C1 amplified samples that will be used for single cell RNA-Seq data. Another priority for the coming year is to develop methods to analyze extracellular RNAs. The recent discovery that extracellular biofluids contain miRNAs that are abundant and stable has garnered great interest in their utility as minimally invasive biomarkers. RNA-Seq analysis of extracellular RNAs has several challenges, including the low RNA content of biofluids (low ng/ml range) and library preparation for small RNA analysis is technically challenging. We are continuing to work closely with other NIH ERC program participants to implement and validate appropriate methods. We will also continue to implement state-of-the-art methods for analyzing next-generation sequencing data. Goals for the coming year include the
development of pipelines for the following: 1) analysis of alternative polyadenylation, 2) Chip-Seq analysis, and 3) implementation of visualization tools to display next-generation sequencing data more effectively.

Training and Integration with SABRE and AAF programs

We provide extensive consultation and training for investigators using the Core. We meet with each group (PI and other group members, including students and postdoctoral fellows) to help with project planning. We help with grant preparation, sample size determination, appropriate selection of controls, and RNA extraction protocols. We meet with each group again after the initial data analysis to discuss the results and provide guidance about further analysis. When work is being readied for publication, we assist with preparation of figures and tables and submission of the results to a public database (NCBI’s Gene Expression Omnibus [GEO]). The core director attends the monthly UCSF SABRE Research Conference and the annual AAF meeting. This allows many opportunities for raising awareness about the core services among SABRE and AAF investigators. Although we continue to work with other investigators in order to maintain the high volume needed to operate in an economical manner, SABRE projects receive the highest priority.

David Erle is co-PI of the UCSF Career Development Program in Omics of Lung Diseases K12 grant. One K12 Scholar (Stephanie Christenson, mentored by Prescott Woodruff) is making extensive use of the core for studying endotypes in asthma and COPD, together with Nirav Bhakta, a K23 awardee also in the Woodruff lab. The other K12 scholar, John Greenland, also has plans to perform RNA-Seq experiments.

Grants and Publications

The core is supported by SABRE and by a recharge mechanism, which covers labor and reagent costs for projects performed by the core. Core staff members work closely with investigators as they apply for NIH and other extramural funding. Some grants include partial salary support for core staff. This is a partial list of funded grants with major components that involve the core:

- **R01 HL118267-01A1 (PI Williams, subcontract PI Erle)** 02/01/2014-01/31/2018
  Henry Ford Health System (Subcontract)  $181,184
  **Combined Transcriptomics and Genomics to Find Asthma Genes in Admixed Populations**
  Perform RNA-Seq for transcript profiling of blood cells in asthma

- **U19 AI 077439-06 (PD: Sheppard)** 04/01/2013-03/31/2018
  NIH/NIAID  $1,116,011
  **IL-13 and IL-17 dynamics in the asthmatic airway**
  Overall project goal is to determine how immune cells producing IL-13 and IL-17 specifically modulate contractile responses of airway smooth muscle and the relevance of these pathways to human asthma. The PI (Sheppard) and project and core leaders (Erle, Krummel, and Woodruff) are all making extensive use of our core.

- **P01 HL108794 (PD: Sheppard)** 08/09/2012-07/31/2017
  NIH/NHLBI  $1,580,537
Targeting Epithelial Cells to Treat Pulmonary Fibrosis
This translational program project grant is designed to develop new effective therapies for idiopathic pulmonary fibrosis (IPF). Core director Paul Wolters is using the core to study fibrosis.

1K12 HL119997-01 (Erle/Burchard) 09/01/2013-5/31/2018
NIH/NHLBI $249,640

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. Dr. Erle is the co-PI of this institutional K career development award and

R01 HL124285-01 (Erle) 08/01/2014-06/30/2019
NIH/NHLBI $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.

U01 OD019769-01 (Erle/Woodruff) 08/01/2014-06/30/2019
NIH $449,517

Defining a Comprehensive Reference Profile of Circulating Human Extracellular RNA
The goal is to profile extracellular RNAs in multiple body fluids from healthy individuals.

Bristol-Myers Squibb (Krummel) 01/01/2015-12/31/2016
UCSF Immunoprofiler Genomics core ~$200,000/yr
The core is profiling gene expression in various immune cell subsets isolated from human cancers.

Publications
Core-supported projects led by SABRE-affiliated faculty published or accepted for publication during 2014:


Genetics Core

Director: Esteban González Burchard, M.D., M.P.H.,
Professor of Medicine and Bioengineering & Therapeutic Sciences

Executive Summary

We have built the largest gene-environment study of asthma in minority children in the U.S. (total sample n > 10,000). We have detailed data on social, environmental, and biologic risk factors for asthma, as well as detailed information on medical history and drug response. We have established the Asthma Genetics Core and Asthma Biobank to facilitate asthma genetic research among Sandler/AAF-sponsored investigators. In keeping with the Mission of the original Sandler-sponsored Asthma Research Program, we have made this resource an “open source” by having an extensive range of national and international collaborations. We offer investigators a full service of genetic testing and analyses. Specifically, we analyze promising candidate genes identified by investigators using biologic material (DNA and plasma) from large well phenotyped family-based and case-control asthma studies of racially/ethnically diverse subjects.

Data obtained from the Asthma Biobank have allowed us to build multiple national and international collaborations, as discussed further below. We provide open access to the databank, we provide biological specimens at cost for worthy projects, and we assist investigators with use of the data in the Asthma Biobank, including statistical analysis. This resource has also facilitated research on asthma in minority populations by scores of laboratories around the world, including multiple SABRE and AAF funded investigators, and by national and international consortia. Since funding for the Genetics Core began in 2008 we have collaborated with 70 individual investigators and two national and six international consortia. Moreover, we are using these data in collaboration with Genentech to select asthmatic patients who are most likely to respond to their drug, anti-IL13.

This past year the Genetics Core Facility has focused on three main goals: 1) Recruitment of well-phenotyped children with and without asthma 2) Collaboration and 3) Research.

Accomplishments in 2014

Recruitment

Since 2008 we have been recruiting children with and without asthma. We now have the largest pediatric asthma genetic study of Latino and African American pediatric populations in the U.S. (n > 10,000 children with and without asthma). We continue to recruit and to characterize children with and without asthma.

Collaboration

UCSF Sandler Program and the AAF: In the era of large “team science” the value and importance of collaboration cannot be overstated. We have made the existing cohorts available to more than 30 Sandler-sponsored investigators (UCSF SABRE
The Asthma Genetics Core assists investigators with study design and provides genotyping and expertise with statistical genetic analyses. We also allow our databank to be used for replication of promising results from other investigative groups.

**Other Collaborations:** In 2014 we have collaborated with the following faculty from UCSF and elsewhere: Ryan Hernandez (UCSF), Carol Ober (Chicago), Kathleen Barnes (Johns Hopkins), Evan Eichler (University of Washington), Jim Gauderman (USC), Charles Rotimi (NIH/NHGRI), Noah Zaitlen (UCSF), Mario Castro (Washington University), L. Keoki Williams (Henry Ford Health Systems), Fernando Martinez (University of Arizona), Max Seibold (National Jewish Health), Neil Trivedi (UCSF), Rajesh Kumar (Children’s Memorial Hospital, Chicago), Pedro Avila (Northwestern University), Stephanie London (NIEHS), Scott Weiss (Harvard), Kathy Giacomini (UCSF) Carla Rothin (Yale) and Charles Nichols (LSU). We have contributed our data to national and international consortiums to study asthma, obesity and eczema.

**Large-scale Collaborative Projects:** This past year we participated in the NHLBI-sponsored EVE Asthma Consortium and several other national and international collaborations, including the following:

We are part of the new NHLBI initiative to perform whole genome sequencing in asthma-related traits. This year, we received the largest pharmacogenetic grant of minority children in the U.S.

**Research**

We have generated genome-wide association studies (GWAS) data from our study populations and have provided our results as *in silico* replication to supplement initial findings for several Sandler investigators. In addition, we have worked closely with asthma investigators throughout the country to advance the field by collectively working towards testing and replicating novel genetic associations identified from basic science models (animal and human) to GWAS.

**Obesity & Asthma:** We performed an epidemiologic analysis of asthma control and obesity (defined as BMI percentile) in Latino and African American children (Borrell, et. al., AJRCCM 2013). Children and adolescents ages 8 to 19 years (n=2,174) with asthma were recruited from the Genes-environments & Admixture in Latino Asthmatics Study (GALA II, n=2022) and the Study of African Americans, Asthma, Genes, & Environments (SAGE II, n=769). Ordinal logistic regression was used to estimate odds ratios (OR) and their confidence intervals (95% CI) for worse asthma control. In adjusted analyses, boys who were obese had a 33% greater chance of having worse asthma control than their normal weight counterparts (OR: 1.33; 1.04-1.71). However, for girls, this association varied with race/ethnicity (p-interaction=0.008). When compared to their normal weight counterparts, obese African American girls (OR: 0.65; 95%CI:0. 41-1.05) were more likely to have better...
controlled asthma while Mexican American girls had a 1.91 (95%CI: 1.12-3.28) greater odds of worse asthma control. Worse asthma control is uniformly associated with increased BMI in boys. Among girls, the direction of this association varied with race/ethnicity.

Obesity is associated with poor asthma control, increased asthma morbidity, and decreased response to inhaled corticosteroids. We hypothesized that in children and adolescents with asthma, obesity would be associated with decreased bronchodilator responsiveness. In addition, we hypothesized that subjects who were obese and bronchodilator unresponsive would have worse asthma control and require more asthma controller medications. In SAGE II and GALA II, two identical, parallel, case-control studies of asthma, we examined the association of obesity and bronchodilator response using multivariable logistic regression in 2,879 African American and Latino subjects. We compared asthma symptoms, controller medication usage, and asthma exacerbations between non-obese and obese subjects by bronchodilator responsiveness.

Being obese is associated with a 24% increased odds of being unresponsive to bronchodilators compared to not being obese (aOR 1.24, 95% CI 1.03-1.49) after adjustment for age, race/ethnicity, sex, recruitment site, baseline lung function (FEV1/FVC), and controller medication. Bronchodilator unresponsive obese subjects were more likely to report asthma symptoms and controller medication use, however there was not an association between obesity and asthma exacerbations. Obesity is associated with bronchodilator unresponsiveness among African American and Latino children and adolescents with asthma, after controlling for other factors that affect bronchodilator response. Children and adolescents who are obese and bronchodilator unresponsive represents a unique asthma phenotype that has not yet been previously described. Given the high prevalence of obesity and asthma in children and adolescents, our results will have significant clinical implications in the treatment of the obese asthma phenotype (manuscript in press, CHEST 2014).

Admixture & Asthma: We leveraged the mixed ancestry in 7,008 Latinos and African Americans in the EVE Asthma Genetics Consortium to perform an admixture mapping meta-analysis for asthma. We replicated associations in GALA II, an independent study of 3,774 Latinos. We measured gene expression in the whole blood of 504 African Americans, Mexican Americans, and Puerto Ricans from our replication study to identify potential biomarkers for lung function, bronchodilator drug response, and exacerbations. We identified a genome-wide significant admixture-mapping peak centered on SMAD2 in Latinos (p=6.8 x 10^-6), where Native American ancestry was associated with increased risk of asthma (OR=1.20, 95% CI=1.07-1.34, p=0.002) and European ancestry with decreased risk (OR=0.86, 95% CI=0.77-0.96, p=0.008). Our findings replicated in GALA II (p=5.3x10^-3, overall meta-analysis p=2.6x10^-7). Asthma cases had 13.4% lower whole blood gene expression of SMAD2 compared with controls (95% CI:8–18%, p<0.001), corresponding to a best-fit OR of 3.93 (95% CI=2.12-7.28, p<0.001) for high versus low SMAD2 expression. Lower whole blood SMAD2 gene expression was also
associated with decreased albuterol response and increased numbers of exacerbations, including hospitalizations, ER visits, and oral steroid use. We identified a Latino-specific association between local ancestry at \textit{SMAD2} and asthma, and found that decreased \textit{SMAD2} gene expression in the blood was strongly associated with increased asthma risk and severity. \textit{SMAD2} gene expression associations extend to both European and African American populations. Our findings may help explain differences in asthma prevalence and morbidity between racial/ethnic groups, and identified \textit{SMAD2} gene expression in blood as a potential biomarker for asthma (Gignoux, et. al., manuscript under review).

In addition, we have repeated the admixture mapping scans using our most powerful sample in the discovery phase (GALA II), as genome wide data was recently available in our laboratory for this sample, and we have replicated the findings in GALA I (Galanter, et. al., \textit{JACI} in press). Further, we have incorporated admixture-mapping analyses for BMI with case/control and total IgE. By doing this, we have identified a stronger candidate region that is not only associated with asthma and obesity, but also with total serum IgE levels (Pino Yanes, et. al., \textit{JACI} 2014).

We performed two epidemiologic analyses in Latino and African American children with and without asthma. First, we demonstrated that air pollution causes asthma and that African American children are more susceptible to air pollution than Latino children (Nishimura, \textit{AJRCCM}, 2013). We also demonstrated that socioeconomic status (SES) has opposite affects on asthma risk for Latino and African American children (Thakur et. al., \textit{AJRCCM}, 2013 in press). Using the social, environmental and genetic data described above we sought to determine whether genetic ancestry is associated with the odds of asthma among Latinos, and secondarily whether genetic ancestry is associated with lung function among children with asthma. To address this we analyzed 5,493 Latinos with and without asthma from three independent studies: GALA II, study for discovery, and the Genetics of Asthma in Latino Americans (GALA I) and Children's Health Study (CHS) for replication. In each study we estimated the proportion of African, European, and Native American ancestry for each participant using genome-wide data. We tested whether genetic ancestry was associated with the presence of physician-diagnosed asthma. We then evaluated whether genetic ancestry was associated with measures of lung function among subjects with asthma in the GALA II study. Odds ratios (OR) and effect sizes were assessed for every 20% increase in each ancestry.

We found that Native American ancestry was associated with lower odds of asthma (OR=0.72, 95% confidence interval [CI]: 0.66-0.78, \textit{p}=8.0\times10^{-15}), while European and African ancestry were associated with higher odds of asthma (European ancestry: OR=1.22, 95%CI: 1.14-1.32, \textit{p}=1.1\times10^{-7} and African ancestry: OR=1.40, 95%CI: 1.14-1.72, \textit{p}=0.001). These associations were robust to adjustment for covariates related to early life exposures, air pollution and socioeconomic status. Among children with asthma, African ancestry was associated with lower lung function, including both pre- and post-bronchodilator measures of forced expiratory volume in the first second (-77\pm19 ml, \textit{p}=5.8\times10^{-5} and -83\pm19 ml, \textit{p}=1.1\times10^{-5}, respectively) and forced vital capacity (-100\pm21 ml, \textit{p}=2.7\times10^{-6} and -107\pm22 ml, \textit{p}=1.0\times10^{-6},
respectively). Differences in the proportions of genetic ancestry can partially explain disparities in asthma susceptibility and lung function among Latinos. (Pino Yanes, et. al., *Journal of Allergy and Clinical Immunology* 2014).

**Financial Support**

We have been successful at leveraging Sandler funding with support from UCSF, the NIH, and Genentech. Sandler funding ($125,000) contributes partial salary support for the Asthma Biobank manager, for the clinical data manager, and for the statistical geneticist who will continue to support analyses requested by Sandler-sponsored investigators. Recently, 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 Biobank.

**Active Grants**

1R01 HL104608-01A1 (PI: Barnes) 09/28/2011-6/30/2015  
*Johns Hopkins University-Subcontract*  
Role: Subcontractor  
New Approaches for Empowering Studies of Asthma in Populations of African Descent

1P60 MD006902 (PI: Bibbins-Domingo) 08/27/2012-02/28/17 2.10 CM (17.5%)  
NIH $173,527  
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

1R01HL117004-01 (PI: Burchard) 08/01/2013-06/30/2017  
NIH/NHLBI $478,999  
Pharmacogenomics of Bronchodilator Response in Minority Children with Asthma

1K12 HL119997-01 (PIs: Erle/Burchard) 09/01/2013-5/31/2018  
NIH/NHLBI $115,000  
Role: Co-PI  
UCSF Career Development Program in Omics of Lung Diseases

W81XWH-13-1-044 (PI: Geoffrey Manley) 10/01/2013-09/30/2015  
Source: NIH/DOD $480,512  
Role: Co-investigator  
Transforming Research and Clinical Knowledge in Traumatic Brain Injury
T32 GM007546 (PI: Burchard) 07/01/2008 - 06/30/2015
NIH/NIGMS $253,028
UCSF Clinical Pharmacology and Therapeutics Training Grant

U01 OD019769-01 (Erle/Woodruff) 07/01/2014-06/30/2019
NIH $449,517
Role: Co-investigator
Defining a Comprehensive Reference Profile of Circulating Human Extracellular RNA

R21ES24844-01 (PIs: Burchard/Gauderman) 12/1/2014-11/30/2017
NIH/NIEHS $132,354
Role: Co-PI
Gene-Environment Analyses of Early Life Exposures and Asthma in Ethnically Diverse Children

Publications in 2014


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 unique challenges for imaging and many powerful existing 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 2015, the core will focus on implementation of two new technologies for investigators across the UCSF campuses and three specific goals for the advancement of intravital imaging.

1. To develop and implement a selective plane illumination microscope (SPIM) to enable high resolution, high throughput imaging of whole cleared lungs and other tissues. Not only will this enable cells of interest to be visualized in the full context of the lung, it will also allow more availability on established instruments specialized for in vivo work.
2. To develop and build a two-photon instrument equipped with adaptive optics able to correct optical aberrations that currently limit imaging in the lung to depths <75um.
3. To optimize 3D Bessel microscopy and open instrument access to the UCSF community.
4. To extend the usage of human lung imaging through training, sample-processing capabilities, novel labeling technologies, and through collaboration with asthma researchers with access to primary biopsy material.
5. To extend the usage and utility of mouse lung imaging through continued development of minimally invasive intravital imaging methods and instrumentation.
6. To provide ongoing technical and instrumentation support to the UCSF (and beyond) asthma community in order to put existing and emerging imaging technologies to practical use in the study of asthma.
Organization

The SABRE Microscopy Core is contained within the Biological Imaging Development Center (BIDC). The larger BIDC is an interdisciplinary center configured to assemble, test, and apply emerging light microscopy techniques and technologies. The BIDC is designed to serve as a conduit for new optical imaging technology at UCSF and as a site for new technology development. In its role as a conduit for new optical imaging technology, the BIDC also runs an incubator program, which provides support to investigators to acquire, maintain, and share equipment with other investigators, allowing a broader access to these valuable instruments. The SABRE center is currently one of the major supporters for this campus-wide imaging initiative and now holds major stakes in confocal and 2-photon instruments in addition to driving key development initiatives. SABRE-affiliated labs and investigators enjoy privileged access to both the SABRE microscopy core and the larger BIDC. This center is managed by a managing director (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 240 registered users of the BIDC. These users represent 68 principal investigators or labs. These labs are drawn from 21 departments or organizational units.

In 2014, 63 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:

<table>
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<tr>
<th>Alliston</th>
<th>Krummel</th>
<th>Marcucio</th>
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<td>Bluestone</td>
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<td>Lowell</td>
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Recent Accomplishments

In 2014, scientifically:

1. We developed open source software for the visualization of large data sets (>100GB) that includes a multi-resolution file format, which allows instantaneous visualization of
tissues at multiple scales, essentially generating maps of the sample at the point of acquisition that allow users to easily and quickly navigate large tissues.

2. We are actively developing and optimizing control software as a part of the open-source Micro-Manager project started at UCSF that will be distributed to users around the world free of charge upon its completion. It includes an intuitive user interface for demarcating non-rectangular volumes of tissues to be imaged, allowing users to capture areas of interest (such as space immediately adjacent to airways in the lung) without bloating file size due to conventional rectangular format constraints. This allows users without knowledge of programming to harness the full power of BIDC instruments and ask biological questions at unprecedented scales of space and time.

3. We have developed culture and imaging methods that have allowed imaging of the developing embryonic lung for up to 24 hours, allowing the direct observation of airway branching at 12.5dpf.

4. We have developed minimally invasive surgical methods for accessing the trachea in living mice as well as custom hardware and optics to allow direct long-term observation and imaging of immune involvement in allergic asthma and airway remodeling with intact blood flow, allowing many emerging questions about the recruitment, interactions, and egress of immune cells to be addressed.

5. 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, investigators working with the BIDC obtained funds to purchase build a Selective Plane Illumination Microscope (SPIM) to enable whole organ imaging. Further, we completed construction of a Bessel microscope. Both microscopes will reside under the BIDC umbrella.

Space

We maintain instruments and development tools in three core rooms in Medical Sciences S11 and we also maintain additional microscopes in 6 other sites throughout the campus, including behind the animal barrier.

Funding

The following represent some of the lung-related grants that were funded in 2014, in part through our efforts and support:

1) Krummel, PBBR (SPIM)
2) Krummel, R21
3) Luke Cassereau, NRSA F31

The following were submitted:

1) Corey Miller, PBBR
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:


63

Plans for the Coming Year

1. A major push in the next year will be to build a light sheet microscope and make it available for use by the UCSF community in collaboration with Larry Ackerman who will train researchers in tissue clearing.
2. We also have begun work to overhaul an existing two-photon microscope to keep it at the forefront of new technologies, redesigning the optical train to incorporate high sensitivity detectors and an adaptive optics unit to allow deep, high-resolution imaging in the living lung currently obscured by the lung’s inherent optical properties.
3. We plan to renovate the current BIDC space; this will provide much needed space for new instruments as well as allow currently isolated instruments to be brought into a centralized space where temperature conditions can be more precisely controlled, improving instrument reliability and performance.
4. The completion and optimization of the intravital tracheal imaging methods will culminate in training of researchers interested in investigating immune involvement in asthma and allergy in living mice.

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. This year, we have undertaken the training of Henry Pinkard (imaging specialist) in performing immunology-based assays as well as Kaitlin Corbin in performing lung-based assays so that they may undertake experiments with new users who may not have experience with these assays and imaging preparation. This removes a major barrier to entry for users and is critical for the success of experiments. We have also taught living lung imaging techniques to visitors from Yale University.
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. 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
Evolving Microenvironments in Airway Inflammation

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

Program Project Grant HL024136 is nearing completion of its 35th year, the 5th of a planned 5 years of interdisciplinary study of airway inflammation competitively renewed on May 11, 2010. Each of the component projects focuses on different populations of airway cells and molecules mediating structural changes in the airway accompanying chronic airway inflammation. The Projects are supported by two Cores, one administrative and one scientific (Tools for Analysis of Airway Inflammation).

Summary of Advances this Year

Project 1: Roles of Peptidases in Chronic Airway Inflammation (Project Leader: G.H. Caughey)

A significant advance was discovery of an evolutionary pathway for liberation of type I transmembrane proteases from their membrane anchors, allowing diffusion away from the membrane surface, access to remote targets, and acquisition of new functions over the course of mammalian evolution. This newly identified pathway, which can result from (and has resulted from) a nonsense mutation involving a single nucleotide in a protease gene, identified a general pathway for evolution of mammalian marapsins, prosemins, and soluble tryptases, which have proliferated in number and functions in mammals. This finding helps explain the extant diversity of otherwise closely related human tryptase genes, which our studies in connection with Aim 3 indicated are subject to major inherited variation in humans, with implications for disease susceptibility in asthma and sepsis. Another significant achievement, conducted in connection with Aim 2, was the discovery of previously unknown roles for Cathepsin L (a protease that is particularly abundant in lysosomes and secretory granules of immune cells) as a determinant of immune infrastructure and defense against lung infection. In studies involving mice lacking this protease, we found that it protects against death from mycoplasma pneumonia and bronchitis and that it supports mycoplasma-induced airway remodeling in the form of lymphangiogenesis. Because Cathepsin L is a potential therapeutic target for relief of inflammation, these unanticipated findings of roles in defense against a common respiratory bacterium and in lymph vessel growth suggested that inhibition has a drawback of defective host defense and vascular remodeling.

Project 2: Imaging T cell Airway Responses during Inflammation (Project Leader: M.F. Krummel)

In this year, we completed studies proposed in this grant and broke ground in exciting new areas. Related to our original first Aim, we developed a novel color-reporting system to track differentiation of incoming inflammatory monocytes and their progenitors in allergic lung. This work showed how these cells differentiate in distinct regions of the challenged lung and how antigens are captured by distinct subsets of cells along the monocyte lineage. Additionally, in collaboration with Drs. Caughey (Project 1) and McDonald (Project 3), we succeeded in labeling FcεR1-positive mast cells in the trachea and airway and in demonstrating how injury in the airway and parenchyma affects antigen surveillance at these sites. We further applied our imaging technologies to track eosinophils, mast cells and innate-type 2 cells in model systems. Finally, we developed a system to track interactions between infiltrating immune cells and cells of the lung.
nervous system. Using a novel knockout strategy, we showed the requirement for these cells to generate a profound immune response, which also spawned new studies separate from this renewal.

Project 3: Lymphangiogenesis and Angiogenesis in Airway Inflammation (Project Leader: D.M. McDonald)

The advances during this year built upon earlier findings of lymphangiogenesis in the airways and lung during sustained inflammation. Having previously found that lymphangiogenesis in the lung after *Mycoplasma pulmonis* infection was prevented by inhibition of VEGFR-2 and VEGFR-3 signaling, we addressed the clinically relevant question of whether the process could be reversed by treatment with antibiotics, which reversed most of the lung pathology, but the new lymphatics did not regress. Persistence of the newly grown lymph vessels despite reversal of other aspects of the inflammatory response raised questions of whether the persistent lymphatics influence responses to subsequent infections and whether alternative treatment strategies can promote regression. Expanding our work on lymphangiogenesis beyond *M. pulmonis* infection, we examined a non-infectious mouse model of lymphatic growth, where VEGF-C expression in the respiratory epithelium was induced by doxycycline in CCSP-rtTA/tetO-VEGF-C double-transgenic mice. We found that perinatal overexpression of VEGF-C led to a condition resembling pulmonary lymphangiectasia, a life-threatening disorder characterized by abundant widely dilated lymphatics around major airways and pulmonary vessels and beneath the visceral pleura. Collaboration with Dr. Sara Vargas, a pulmonary pathologist who works on lymphatic abnormalities at Boston Children’s Hospital, confirmed that abnormalities in lungs of the CCSP-VEGF-C double-transgenic mice resembled pulmonary lymphangiectasia in human cases. Mechanistic studies revealed that signaling of VEGFR-2 and VEGFR-3 was required for development of lymphangiectasia in these mice. Abnormal abundance of VEGFR-2 and VEGFR-3 heterodimers on lymphangiectatic vessels was consistent with altered VEGF-C signaling. Further studies revealed that lymphangiectasia in CCSP-VEGF-C mice could be prevented but not reversed by inhibiting VEGF-C signaling, even after suppression of VEGF-C production for 19 months. In this respect, the lack of regression of new lymphatics in CCSP-VEGF-C mice was similar to that in mice infected with *M. pulmonis*. These findings prompted the exploration of novel strategies to promote lymphatic regression.

Scientific Core (Core Leaders M.F. Krummel and P. Baluk)

This Core, with its *Mycoplasma* production, Mouse Genetics, and Imaging components, re-established, titered and validated stocks of *M. pulmonis* and provided PCR-, blotting- and FACS-based genotyping services. The imaging Core provided two-photon intravital microscopy services to personnel associated with individual projects, and generated tools for ongoing advances in intravital live imaging of the lung. Further, as shown in Preliminary Data, it generated a gradient-index (GRIN) “stick” lens system for imaging the trachea and other discrete sites (with minimally invasive surgery), which will serve all projects in the coming cycle. Through personnel associated with all aspects of this Core, it serves to develop, normalize and disseminate tools for the projects.

Training and Integration with the Sandler Program

The SABRE Center continues to provide 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. As in past years of this Program Project, the Sandler-supported 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. It also facilitated sharing of models and advanced imaging technologies.

P01 HL024136-supported Publications in 2014


Sandler Asthma Basic REsearch Center  Asthma Related Research Projects

NIAID Asthma and Allergic Diseases Cooperative Research Center
Principal Investigator, Dean Sheppard

Objective

We were able to successfully renew this Center grant with a new program focused on understanding the dynamic effects of IL-13 and IL-17 in allergic airway disease.

Projects

The new 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, we have developed improved, automated methods for performing RNA-Seq and, after some initial problems with variable responses to cytokines, now have appropriate samples to analyze miRNA and mRNA responses to IL-13 and IL-17 in cultured HBECs. We have also developed techniques that give specific in situ staining for two miRNAs selected based on our prior experiments. We completed a manuscript describing our fast-UTR system and demonstrating how it could be used to identify active cis-regulatory elements in an airway epithelial cell line (BEAS-2B). A revised version of the manuscript is now in review. We have also used mimics and inhibitors of miR-34/449 family members to address the potential roles of these miRNAs in IL-13-induced mucous metaplasia. Our data suggest that these miRNAs are not directly involved in mucous metaplasia.

For Project 2, directed by Dean Sheppard, we are in the process of generating mice to test the hypothesis that Th17 cells enhance airway hyperresponsiveness through direct effects of IL-
17 on airway smooth muscle. We have found that IL-13 and IL-17 synergistically enhance contractility of airway smooth muscle with long term, but not short term, exposure. Synergy does seem to involve enhanced induction of RhoA protein expression and we are in the process of identifying where in the pathways linking STAT6 (downstream of IL-13) and Traf6 (downstream of IL-17) synergy is occurring. We are in the process of developing methods to detect IL-17 activity in human airways. The work on the effects of segmental allergen challenge has not yet begun because we are still awaiting NIAID approval for these human studies.

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 finding of a critical role for IL-17 in directly increasing the contractility of airway smooth muscle suggests the possibility of developing novel therapies for severe asthma that target this cytokine or the upstream steps involved in its induction in Th17 cells (for example the pathway of TGFbeta activation by the integrin avb8). Our finding of the synergistic interaction between IL-17 and IL-13 suggests that even patients with Th2 high asthma might benefit from therapies targeting Th17 cells.

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 15 post-doctoral fellows and 4 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 that supplied preliminary data for projects 1 and 2 were performed in the SABRE mouse physiology and morphology core, the studies supporting miRNA and mRNA expression analysis used to justify project 1 were all generated in the SABRE functional genomics core, and the studies supporting 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. This Center grant would not have been likely to succeed without this extensive support from SABRE, especially the core facilities, and thus represents a clear example of leveraging SABRE funds to further enhance research into both basic and translation biology underlying asthma.
Processivity and Specificity in Chitin-mediated Inflammation

James Fraser, Assistant Professor of Bioengineering and Therapeutic Sciences, UCSF

Objective:

The overall goal is to test the hypothesis that chitin polymers of distinct sizes are signals that are used by the immune system to initiate and terminate inflammation. We will define how chi-lectins and chitinases assemble into processive macromolecular machines to generate these fragments and exploit chitin-binding domains to develop sensors that can be used to determine where these fragments are present in the lung. By determining how the action of chitin degrading enzymes shapes the inflammatory response, we will be able to test how new pathways and targets, that are likely shared by other allergenic materials, impact the environmental contributions to asthma. Currently, these ideas cannot be directly tested due to limitations in the ability to generate and detect chitin fragments of defined sizes. We will build the next-generation of chitin biosensors and create renewable biodegradative processes for generating chitin fragments. Accomplishing these goals will enable precise measurement of chitin levels in mouse and in vitro studies to test the idea that the action of processive chitinase enzymes initiates inflammatory responses to chitin and that the generation of smaller chitin fragments is translated into a terminating signal.

Summary:

Our efforts received a major boost by recruiting an excellent graduate student, Benjamin Barad, to work on the project in mid-2014. Previously, Ben worked on lignin degradation in a Chemical Engineering lab at Stanford and is therefore well positioned to characterize the complex nature of chitin degradation. He has already completed the major molecular biology aims of the work and expanded our chitinase projects to include directions in electron microscopy and X-ray Free Electron Lasers. Currently we are focusing on expression of AMCase for evaluation as a biologic therapy to counteract chitin-irritation in a mouse model.

Progress

1 – Cloning and expression of Chitin binding domains and enzymes

1.1 – Selection of binding domains and creation of catalytically dead chitinases as eukaryotic chitin sensors

The outcome of this sub-aim is to generate constructs for heterologous expression and affinity purification of a panel of LysM domains, chi-lectins, and chitinases that will then be profiled for binding preferences. This aim is completed for all chi-lectins and chitinases.

1.2 – Express and create fluorescent-fusion/dye conjugates of binding domains

The outcome of this sub-aim will be to determine which candidate biosensors that have desirable biophysical properties such that their binding preferences can be characterized. Purified proteins will also be directed to the Antibiode pipeline (Jim Wells and colleagues) to generate renewable affinity and detection reagents. This aim is underway and is focusing first on generating large quantities of human and mouse AMCase for mouse experiments.

1.3 – Characterize the binding preferences of biosensors
The outcome of this sub-aim will be a unique binding profile for each potential biosensor, which will allow us to track the dynamic generation of physiologically relevant chitin fragments. This aim is underway and will begin with catalytically dead AMCase.

1.4 – Distribute biosensors to the asthma research community
To encourage the use of these tools in the wider asthma and allergy research community, we will distribute plasmids and protocols describing their use immediately after they are validated and characterized in our labs. We will deposit plasmids in Addgene, which is a non-profit plasmid repository dedicated to helping scientists around the world share high-quality plasmids. Protocols for protein purification and use will be made publically available on our website. This aim is underway.

2 – Towards visualizing processive chitin degrading machines
A major hypothesis of our work is that chitin degrading enzymes are themselves glycosylated and can use chitin binding domains to assemble into processive chitin degradation machines of >100kDa size. Single particle cryo electron microscopy has emerged as a premier technique for characterizing such assemblies. Now that cryoEM can allow for building de novo atomic models into high-resolution density maps, new challenges must be overcome. While established validation metrics independently assess map quality and model geometry, efforts to assess the precise fitting of an atomic model to the map and to validate high resolution features are less well developed. We developed EMRinger, which reports on model-to-map agreement using side-chain dihedral directed density sampling. Enrichment of weak features around side chains at rotameric angles acts as a sensitive marker of whether the backbone is correctly positioned in stronger density regions. The EMRinger Score improves during model refinement, suggesting its utility as an effective model-to-map validation metric. Additionally, EMRinger sampling identifies differential effects of radiation damage on negatively charged amino acids during data collection. EMRinger will be useful in assessing how computational and experimental advances in CryoEM increase the ability to resolve and model side chain and ligand conformations. We envision using this computational method to validate on chitin degrading machines

3 – XFEL crystallography
The chi-lectin, Ym1, forms in vivo crystals in mouse lungs some genetic backgrounds. The advent of X-ray free-electron lasers (XFELs) has made it possible to obtain atomic resolution macromolecular structures from crystals grown in vivo. The first example, cathepsin B, was grown in Sf9 insect cells and the crystals were extracted before injecting them in the XFEL beam for data collection. Recent studies from the Eisenberg lab injected living bacillus thuringiensis cells into the XFEL beam and determined a Cry3A toxin structure. We extracted Ym1 crystals from motheaten mice (Ptpn6 mutant) and exposed them to X-rays at the advanced light source. Unfortunately, we were unable to observe the powder pattern necessary for proceeding to XFEL screening experiments.

Relevance to Asthma
The goal is to identify how chitin is sensed by the immune system and to understand how the signaling it induces can exacerbate the symptoms of asthma. To accomplish this goal, we will
develop new tools to enable more precise identification of chitin pathways and their biomarkers. Although chitin represents only a single environmental constituent associated with many allergens, we view it as a model for interrogating the environmental factors that contribute to asthma. Our tools will likely implicate pathways and targets that are shared by other environmental agents implicated in asthma. We hope that our mechanistic studies will open new therapeutic opportunities to treat asthma by controlling the extent and timing of how environmental allergens are recognized and degraded in patients. In particular, the potential for AMCase to be delivered as a biologic agent to treat acute chitin-derived inflammation is a promising immediate direction.

**Budget Requested**
We are working on a no-cost extension as we have now recruited a superb graduate student to the project. We anticipate the results obtained from these studies will serve as valuable preliminary data for obtaining external funding. For example, collaborative work on AMCase biologic development will be targeted at two recent NIH Program Announcements (PA-15-028 and PA-15-027) that seek innovative Research on Eosinophil Associated Disorders. Preclinical testing of potential therapeutic interventions (biologics, small molecules or other mechanisms) is of particular interest to the program.
CONTRIBUTIONS TO RELEVANT SCIENTIFIC ACTIVITIES
# SABRE Asthma Research Conference Schedule 2015

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

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<tr>
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<tr>
<td>1/28/15</td>
<td>Jeoung-Sook Shin</td>
<td><em>The role of FceRI expressed by dendritic cells</em></td>
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<tr>
<td>2/25/15</td>
<td>Hal Chapman</td>
<td><em>Targeting Airway Fibrosis in Asthma</em></td>
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<td>3/25/15</td>
<td>Anthony DeFranco</td>
<td><em>Divergent T cell effector responses in the lung following sensitization with antigen with two different TLR ligands as adjuvants</em></td>
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<td>4/22/15</td>
<td>Dean Sheppard</td>
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<td>5/27/15</td>
<td>Chris Allen</td>
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<td>6/24/15</td>
<td>David Erle</td>
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<td>7/22/15</td>
<td>Prescott Woodruff</td>
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<td>John Fahy</td>
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<td>Sam Oh</td>
<td>Donald McCarthy</td>
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<td>Michael Peters</td>
<td>Sarah Utley</td>
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<td>12/01/14</td>
<td>Stephanie Christenson</td>
<td>Joshua Vasquez</td>
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<td>12/08/14</td>
<td>Nirav Bhakta</td>
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<td>Neeta Thakur</td>
<td>Sheena Kerr</td>
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<td>Matthew Donne</td>
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<td>Fellows Feedback (no conference)</td>
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<td>Priya Shete</td>
<td>Andrew Vaughan</td>
</tr>
<tr>
<td>03/09/15</td>
<td>Robert Blount</td>
<td>Erin Gordon</td>
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<td>03/16/15</td>
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<td></td>
<td>Douglas White, Visiting Professor</td>
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<tr>
<td>03/23/15</td>
<td>Eleanor Dunican</td>
<td>Luke Bonser</td>
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<tr>
<td>03/30/15</td>
<td>Farzad Moazed</td>
<td>Mihir Parikh</td>
</tr>
<tr>
<td>04/06/15</td>
<td>Sofya Tokman</td>
<td>John Greenland</td>
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<tr>
<td>04/13/15</td>
<td>Allison Morris, Visiting Professor</td>
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<td>04/20/15</td>
<td>Brett Ley</td>
<td>Marrah Lachowiza-Scroggins</td>
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<td>04/27/15</td>
<td>Dara Torgerson</td>
<td>Jeffrey Gotts</td>
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<td>05/04/15</td>
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<tr>
<td>05/11/15</td>
<td>Noah Zaitlen</td>
<td>Eric Snyder</td>
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<td>05/18/15</td>
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<td>05/25/15</td>
<td>Memorial Day holiday (no conference)</td>
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<tr>
<td>06/01/15</td>
<td>Michael Guarnieri</td>
<td>Birthe Jessen</td>
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<tr>
<td>06/08/15</td>
<td>Patty Lee - Visiting Professor</td>
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<tr>
<td>06/15/15</td>
<td>Fellows feedback (no conference)</td>
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<tr>
<td>06/22/15</td>
<td>Year end party</td>
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</tbody>
</table>
# Immunology Seminar Series
## 2014-2015 Schedule
### Mondays, 9am
### Room: N-225

<table>
<thead>
<tr>
<th>Date</th>
<th>Speaker</th>
<th>Host</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 8</td>
<td>Jane Grogan, <em>Genentech</em></td>
<td>Rich Locksley</td>
</tr>
<tr>
<td>September 15</td>
<td>Erika Pearce, <em>Washington University</em>, <em>St. Louis</em></td>
<td>Jeroen Roose</td>
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<tr>
<td>September 22</td>
<td>Michelle Hermiston, <em>UCSF</em></td>
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<tr>
<td>September 29</td>
<td>Shane Cotty, <em>La Jolla Institute</em></td>
<td>Tony DeFranco</td>
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<tr>
<td>October 6</td>
<td>Alexander Marson, <em>UCSF</em></td>
<td>Jennifer Puck</td>
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<tr>
<td>October 13</td>
<td>Stefan Muljo, <em>Nat’l Cancer Institute-NIH</em></td>
<td>Mark Ansel</td>
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<tr>
<td>October 20</td>
<td>Mitchell Kronenberg, <em>La Jolla Institute</em></td>
<td>Art Weiss</td>
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<tr>
<td>October 27</td>
<td>Bill Robinson, <em>Stanford University</em></td>
<td>Mark Anderson</td>
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<tr>
<td>November 3</td>
<td>Carl June, <em>University of Pennsylvania</em></td>
<td>Michelle Hermiston</td>
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<tr>
<td>November 10</td>
<td>Jennifer Puck, <em>UCSF</em></td>
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<tr>
<td>November 17</td>
<td>Ken Murphy, <em>Washington University</em></td>
<td>Charlie Kim</td>
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<tr>
<td>December 1</td>
<td>Ira Mellman, <em>Genentech</em></td>
<td>Matthew Krummel</td>
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<tr>
<td>December 8</td>
<td>Ryan O’Connell, <em>University of Utah</em></td>
<td>Mark Ansel</td>
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<tr>
<td>December 15</td>
<td>Changchun Xiao, <em>Scripps</em></td>
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<tr>
<td>January 5</td>
<td>Susan Carpenter, <em>UCSF</em></td>
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<tr>
<td>January 16</td>
<td>Carola Vinuesa, <em>Australian Nat'l Univ</em></td>
<td>Jason Cyster</td>
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<tr>
<td>February 2</td>
<td>Mary Ellen Conley, <em>Rockefeller University</em></td>
<td>Jennifer Puck</td>
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<tr>
<td>February 9</td>
<td>Nan Shen, <em>Shanghai Institute of Rheumatology</em></td>
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<tr>
<td>February 23</td>
<td>Anne Sperling, <em>University of Chicago</em></td>
<td>D'Broski Herbert</td>
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<tr>
<td>March 2</td>
<td>David Wiest, <em>Fox Chase Cancer Ctr</em></td>
<td>Jennifer Puck</td>
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<tr>
<td>March 9</td>
<td>Stephen Hedrick, <em>UCSD</em></td>
<td>Tony DeFranco</td>
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<tr>
<td>March 16</td>
<td>Thorsten R. Mempel, <em>Harvard</em></td>
<td>Chris Allen</td>
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<td>March 23</td>
<td>Anjana Rao, <em>La Jolla Institute</em></td>
<td>Averil Ma</td>
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<tr>
<td>April 6</td>
<td>Wendy Garrett, <em>Harvard</em></td>
<td>Averil Ma</td>
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<td>April 13</td>
<td>Mark Schломchik, <em>National Cancer Institute-NIH</em></td>
<td>Clifford Lowell</td>
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<td>April 20</td>
<td>Chris Allen, <em>UCSF</em></td>
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<td>April 27</td>
<td>David Artis, <em>University of Pennsylvania</em></td>
<td>De'Broski Herbert</td>
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<td>May 4</td>
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<td>May 18</td>
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</table>
Immunology Seminar Series

“Roles of Lin28b and microRNAs in (re)programming lineage-specific gene expression for immunity”

Stefan Muljo, Ph.D.
National Institutes of Health (NIH)

Monday, October 13, 2014
9:00am, Parnassus, N-225
Host: Mark Ansel

Livestream | SPONSORS | Gladstone Institute of Virology & Immunology
Rosalind Russell Medical Research Center for Arthritis
Sandler Asthma Basic Research Center, SABRE
INFORMATION (415) 502-1961 http://immunology.ucsf.edu/immunology-seminar-series
Live stream and archive available (UCSF MyAccess login required) at http://tinyurl.com/pw3snsf
RECENT AND NEW PUBLICATIONS
SUPPORTED BY THE SANDLER ASTHMA
BASIC RESEARCH CENTER
(2013-2015)
Christopher C.D. Allen, Ph.D.

K. Mark Ansel, Ph.D.
Baumjohann D, Clingan JM, de Kouchkovsky D, Bannard O, Bluestone JA, Matloubian M, Ansel KM#, Jeker LT#. The microRNA cluster miR-17~92 is essential for follicular helper T cell differentiation. *Nat Immunol.* 14:840-8 (2013) (#co-corresponding authors)
Bronevetsky YB and Ansel KM. Regulation of miRNA biogenesis and turnover in the immune system. *Immunol Rev.* 253:304-16 (2013)

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


**Homer Boushey, M.D.**


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


George Caughey, M.D.

Harold Chapman, M.D.

Laurence E. Cheng, M.D., Ph.D.


Anthony DeFranco, Ph.D.

David Erle, M.D.


**John Fahy, M.D.**


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


Fenwick RB, van den Bedem H, Fraser JS, Wright PE. Integrated description of protein
dynamics from room temperature X-ray crystallography and NMR. *Proceedings of the National Academy of Sciences.* 2014; 28(4): E445-54. PMCID: PMC3910589


Woldeyes RA, Sivas DA, Fraser JS#. E pluribus unum, no more: from one crystal, many conformations. *Current Opinion in Structural Biology.* 2014; 28C: 56-62. PMID: 25113271


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


Xiaozhu Huang, M.D.


Beomkyu Kim, Ph.D


Matthew Krummel, Ph.D.


through T cell-intrinsic meandering motility, mediated by Myo1g. *Cell.* Jul 31; 158(3): 492-505. PMCID: In Progress


**Richard Locksley, M.D.**


Cheng LE, K Hartmann, A Roers, MF Krummel, **RM Locksley**. 2012. Perivascular mast cells dynamically probe cutaneous blood vessels to capture IgE. *Immunity* 38:166-75. PMC3576928


Bando JK, JC Nussbaum, H-E Liang, **RM Locksley**. 2013. Type 2 innate lymphoid cells constitutively express arginase-1 in the naïve and inflamed lung. *J Leukoc Biol* 94:877-884. PMC3800063


**Steven D. Fletcher, M.D.**


**William Seaman, 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 has evolved into a more mature research organization dedicated to its mission to define and interrupt the pathways leading to asthma. The current organization includes 7 full-time faculty working within an extended network of approximately 20 faculty and laboratories whose interests align with those of the Center. The SABRE Center at UCSF participates in all of the major asthma multi-institutional efforts of the NIH, including AsthmaNet (under the leadership of Homer Boushey), the Severe Asthma Research Program (SARP; under the leadership of John Fahy) and the Asthma and Allergic Diseases Cooperative Research Center Network (under the leadership of Dean Sheppard). Members of the SABRE Center were awarded a Program Project Grant from the National Institutes of Allergy and Infectious Diseases at NIH to investigate the role of innate lymphoid cells in human asthma (Fahy, Locksley, Ansel, Woodruff). Extramural funding secured by the core members of the SABRE Center continue to accumulate with an upward trajectory. The conferences and seminars are well attended and publicized across the campus. Thus, by a number of metrics, asthma-centered research is now well established and recognized at UCSF.

As the research focus has matured, we have increasingly moved towards human-based studies, while continuing to sustain the ability to move rapidly through animal models for testing and discovery. We aligned the SABRE Center closely with the Airways Clinical Research Center to improve our ability to study human asthma patients. We recruited a new investigator, Dr. Cheng, who is an MD/PhD pediatrician who brings expertise in childhood atopy and asthma to the Center. We have actively recruiting an additional MD/PhD investigator with expertise in allergy/asthma to join the group. We have re-directed Foundation support previously allocated for animal-based core support to facilitate three major objectives: acquisition of human patients and samples for study; support for young investigators focused on asthma research at early periods in their careers; and technology support in areas of microscopy, sequencing and structural analysis that will facilitate continued advancement in areas of need during this transitional period. Re-allocation of resources has generated a nimble, opportunity-based, ability to move quickly into new areas of discovery, as they are needed, rather than having to wait for annual budgetary requests. Here, input from the Board will be most helpful in establishing priorities and in identifying new areas for opportunity that may have been overlooked, unappreciated or unexplored. Together, these approaches, driven in large part by development of a Strategic Plan, have created a more dynamic and responsive Center that will benefit from wider input and participation of all members.

Strategic planning was fostered by the maturation and growth of the Center and its investigators, but increasingly will serve as a self-evaluative component for continued course corrections required to sustain success. We understand that the SABRE Center will need to move more comprehensively to studies on human patients involving human tissues; will need to capture more individuals like Chris Allen early in science when they can be attracted into the field in a lasting and substantive way; will need to move seamlessly into ‘big science’ technologically-driven fields at low cost, necessitating an interactive and integrated group of scientists; will need to partner with industry in ways to move scientific understanding towards interventional efforts that remain cost-prohibitive for a small Center; and will need to grow an
endowed financial base that will enable nimble re-direction and follow-up using competitive priorities to fund shifting emergent needs for equipment, personnel (including visiting scientists) and short-term needs in response to windows of opportunity. Here, we have elected to support young investigators committed to asthma research across a spectrum of human-based study, basic research and structural chemistry as a mechanism for integrating diverse laboratory efforts through common goals driven by young investigators during formative years of training.

Our goal is to continue the trajectory established over the first 10 years 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.
Benjamin Asher Barad, B.S.
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.
Laurence Cheng, 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.
Beomkyu Kim, PhD.
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>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
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<tr>
<td>Massachusetts Institute of Technology</td>
<td>B.S.</td>
<td>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, Department of Anatomy, Department of Microbiology and Immunology, and Sandler Asthma Basic Research Center, University of California, San Francisco
2012-current  Investigator, Cardiovascular Research Institute, University of California, San Francisco, CA

Honors

1994-1995  National Science Foundation Young Scholars Program Fellowship
1997  National Hispanic Scholar
1998  San Diego Biotech Employee Development Coalition (BEDC) Scholarship
1999, 2000  Academic Excellence Award, Office of Minority Education, Massachusetts Institute of Technology
2001  Phi Beta Kappa
2001 Whitehead Prize in Biomedical Research
2001-2002 University of California Regents Fellowship
2002-2007 Howard Hughes Medical Institute Predoctoral Fellowship
2010 Seminars in Immunology Top Cited Article 2008-2010
2012 NIH Director’s New Innovator Award
2013 Weston Havens Foundation Award

Selected peer-reviewed publications (in chronological order)


**Research Support**

**Ongoing Research Support**

1 DP2 HL117752-01 Allen (PI) 09/30/2012 – 08/31/2017
NIH/NHLBI
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

5 R01 AI103146-03 Allen (PI) 12/01/2012 – 11/30/2017
NIH/NIAID
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

Weston Havens Foundation Allen (PI) 07/01/2013 – 06/30/2015
Characterization of IgE+ B Cell Responses During Allergic Sensitization
The major goals of this project are to determine the location in the respiratory tract where allergic sensitization occurs, and to characterize the early events that lead to tolerance versus sensitization to inhaled allergens.
Role: PI

**Completed Research Support**

None
**BIOGRAPHICAL SKETCH**

<table>
<thead>
<tr>
<th>NAME</th>
<th>POSITION TITLE</th>
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</thead>
<tbody>
<tr>
<td>K. Mark Ansel</td>
<td>Associate Professor of Microbiology and Immunology</td>
</tr>
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</table>

| eRA COMMONS USER NAME | anselm |

**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>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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<td>Immune Disease Institute, Harvard Medical School</td>
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<td>2001-2007</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 -** 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-** Board of Reviewing Editors, Science Signaling
- **2011-** International Predoctoral Fellows Review Cmte., Howard Hughes Medical Institute
- **2012-** NIH peer review committee: Cellular & Molecular Immunology B, ad hoc reviewer
- **2012-** Associate Editor-in-chief, American Journal of Clinical & Experimental Immunology
- **2013-** Associate Editor, Journal of Immunology
- **2013** Guest Editor, Immunological Reviews issue: RNA regulation in the immune system
Awards and Honors

1997 - 2001  Howard Hughes Medical Institute Predoctoral Fellowship
2001 - 2004  Damon Runyon Cancer Research Fund Postdoctoral Fellowship
2005 - 2007  Leukemia and Lymphoma Society Special Fellow
2006   Burroughs Wellcome Career Award in Biomedical Sciences
2007   International Cytokine Society Outstanding Postdoctoral Fellow
2009    Dana Foundation Human Immunology Scholar
2012 American Association of Immunologists Young Investigator Travel Award
2012  Leukemia & Lymphoma Society Scholar

Selected Peer-reviewed Publications


Research Support

Ongoing Research Support

1U19 CA179512 Blelloch (PI) 9/1/13 – 8/31/18
NIH/Common Fund

In Vivo Regulated Release and Function of Extracellular Small RNAs

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.

1P01HL107202 Fahy (PI) 8/15/12 – 5/31/17
NIH/NHLBI
Innate and Adaptive Immune Responses in Th2-high Asthma (PI Dr. John Fahy, co-director UCSF ACRC)

Project 2: Role of miRNAs in Th2-Driven inflammation in Asthma (Project Leader Ansel)
Project 3: Mechanisms of airway Th2 inflammation in asthma (Project Leader Fahy, Co-project Leader Ansel)

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 helper type II cells in human asthma.

Role: Project 2 leader, Project 3 co-project leader

1R01HL109102-01 Ansel (PI) 8/1/11 – 6/30/16
NIH/NHLBI
Role of miRNAs in Th2-driven inflammation in Asthma
The major goal of this project is to identify and characterize the in vivo activity of miRNAs that regulate helper T cell functions relevant to asthma. The project will be conducted in collaboration with co-investigator Dr. Prescott Woodruff, co-director of the UCSF Airway Clinical Reasearch Center.
Role: PI

LLS Scholar Award Ansel (PI) 7/1/12 – 6/30/17
Leukemia & Lymphoma Society
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, immunopathology, and immune malignancies. In particular, we aim to identify and characterize miRNAs that regulate helper T cell growth, survival, and cytokine production.

U10HL098107 Lazarus (PI) 9/30/09 – 9/30/13
NIH/NHLBI (in no-cost extension)
AsthmaNet Clinical Center
The major goal of the Microbiome study is to elucidate the role of the commensal microbiota in determining asthma susceptibility, pathophysiology, and immune cell involvement in disease. My role is to use flow cytometry to characterize circulating and bronchial lavage immune cells and cytokines in ~80 subjects this multicenter study.
Role: Co-investigator

R01 AI106923 Jeker (PI) 8/1/14 – 7/31/19
NIH/NIAID
The Role of miRNAs 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.
BIOGRAPHICAL SKETCH

NAME  
Benjamin Asher Barad

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

POSITION TITLE  
Doctoral Student

EDUCATION/TRAINING

<table>
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<tr>
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<th>DEGREE</th>
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<th>FIELD OF STUDY</th>
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<td>Stanford University</td>
<td>B.S.</td>
<td>06/13</td>
<td>Chemistry</td>
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<tr>
<td>University of California, San Francisco</td>
<td>Ph.D.</td>
<td>TBD</td>
<td>Biophysics</td>
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Positions and Honors

2008    Research Assistant, David Eisenberg Lab, UCLA, Los Angeles, CA
2011-2012 Resident Tutor, Center for Teaching and Learning, Stanford University, Stanford, CA
2011-2013 Research Assistant, Elizabeth Sattely Lab, Stanford University, Stanford, CA
2013-2014 Rotation Student, UCSF, San Francisco, CA
2014-    Doctoral Researcher, James Fraser Lab, UCSF, San Francisco, CA

Professional memberships

2011-2013    Member, American Institute of Chemical Engineers
2013-    Member, Biophysical Society

Honors and Awards

2009    National AP Scholar
2009    National Merit Scholar
2011    Rose Hills Foundation Summer Research Fellowship
2011, 2012 Stanford VPUE Chemical Engineering Department Summer Research Fellowship

Selected Peer-reviewed publications

BIOGRAPHICAL SKETCH

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

POSITION TITLE
Assistant Adjunct Professor of Medicine

eRA COMMONS USER NAME
(Behavioral, physiological, or mental process)
BHANIR

EDUCATION/TRAINING

<table>
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<th>DEGREE</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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<tr>
<td>University of California, San Francisco</td>
<td>Internship</td>
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<td>University of California, San Francisco</td>
<td>Postdoctoral</td>
<td>2011</td>
<td>Asthma</td>
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<td>American Board of Internal Medicine</td>
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<td>Board certification</td>
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<td>Critical Care Medicine</td>
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</table>

Positions

2013 – present Assistant Adjunct 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).

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).

Honors

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, SAPHOP
2001  First place, oral presentation, Stanford Medical Student Research Symposium,

Professional Societies

2007 - present    American College of Physicians, Associate Member,
2008 - present    American Thoracic Society, Trainee Member,
2011- present    American College of Chest Physicians, Affiliate Member,

Teaching Experience

April 2014  Adult Respiratory Failure, part of CODA course for fourth-year UCSF medical students
March 2013 - present  Physiology in the Pulmonary Function Laboratory for first-year pulmonary fellows.
July 2013 - present  Critical Care Rotation Core Curriculum – Lectures on hemodynamic monitoring.
2011  Sepsis small group leader for first-year residents core curriculum.
2010  Central line placement workshop for UCSF Internal Medicine Interns.
2008, 2010, 2011  Pulmonary small group sessions during pulmonary core, 1st year medical students. each year, leading discussion of 3 pulmonary cases, 2 hours each.
2002, 2004  Center for Clinical Immunology at Stanford. Worked one-on-one with two high school students in the laboratory.Introduced them to laboratory science by designing projects for them and helping them complete work leading to poster and oral presentations.

Selected peer-reviewed publications


Reviews


Research Support

Ongoing Research Support

Active, 12/1/12-11/30/14 (Bhakta Co-I)

Targeting the αvβ8 integrin for treatment of severe asthmatics with persistent granulocytic inflammation

Pfizer, UCSF-CTI award, PI: Sheppard, D, No award number

The studies of this proposal aim to develop humanized αvβ8 integrin blocking antibodies with the goal of interfering with the production of Th17 cells, and to develop biomarkers of IL-17 driven inflammation in asthma to guide early stage clinical studies.

Active, 05/01/14-04/01/19

Translational research on the role of IL-17 cytokines in severe asthma

NIH K23, PI: Bhakta
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).

Completed Research Support

Recently removed, 09/01/13-06/30/2014
In vivo regulated release and function of extracellular small RNAs
NIH/NCI U19 CA179512, PI: Bleloch, R
Project 1: Ex-miRNA Release by Immune Cells and its Functional Consequences (Project Leader, Ansel) This proposed 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, Dr. Ansel 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.

Recently removed, 08/21/12-06/30/2014 (Bhakta Co-I) Layering of the Human Immune System, viral infections, and childhood asthma
NIH 1R01AI100082-01, PI: Mccune, JM,
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.

Recently removed, 05/01/12-06/30/2014
Genomic phenotyping and mechanisms in sarcoidosis and AAT NIH/NHLBI
U01HL112696, PI Koth
The major goal of this project is to investigate two understudied conditions that affect the lungs: Sarcoidosis and Alpha-Antitrypsin Deficiency (AAT).
BIOGRAPHICAL SKETCH

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

POSITION TITLE
Professor of Medicine

eRA COMMONS USER NAME
Boushey

EDUCATION/TRAINING

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</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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<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</td>
<td>Residency</td>
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<td>Internal Medicine</td>
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<td>Beth Israel Hospital, Boston, MA</td>
<td>Residency</td>
<td>1971</td>
<td>Internal Medicine</td>
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<td>Oxford University, Oxford, England</td>
<td>Fellowship</td>
<td>1972</td>
<td>Pulmonary Medicine</td>
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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 residency, University of California, San Francisco.
- **1986- Present**: Member, senior staff, Cardiovascular Research Institute, University of California, San Francisco.
- **1987-1989**: Professor of Medicine in residence, University of California, San Francisco.
- **1989-Present**: Professor of Medicine, University of California, San Francisco.
- **1989-1995**: Vice Chair for Clinical Affairs, Department of Medicine, University of California, San Francisco.
- **1996-2009**: Chief, Allergy/Immunology Division, Department of Medicine, University of California, San Francisco.

Honors and Awards

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<td>1964-1968</td>
<td>Regents' Scholar</td>
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<td>1968</td>
<td>Gold-Headed Cane Recipient</td>
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<td>1977</td>
<td>H. J. Kaiser Award for Excellence in Teaching</td>
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<td>1988, '90, '95, 99, 2000</td>
<td>Faculty-Student Teaching Award for &quot;An Outstanding Lecture&quot;</td>
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<td>1993</td>
<td>Clean Air Award (Education/Research), American Lung Association, San Francisco</td>
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Selected peer-reviewed publications (in chronological order)


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

HHS N272200900052C (Boushey, HA) 09/30/09-09/29/14
NIH/NIAID
Inner-City Asthma Consortium II / UCSF ICAC-II Basic Science Site -

The major goal is to serve as a basic science site for the ICAC, enabling examination of relationships of the microbial 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
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

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.

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

COPD Clinical Research Network at UCSF

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

Histoblood Group Antigens, Viruses & Asthma

The major goals are to understand how expression of histo-blood groups antigens by airway epithelial cell and airway mucins influences susceptibility to asthma exacerbations. Role: Co-Investigator
# BIOGRAPHICAL SKETCH

**NAME**

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

**POSITION TITLE**

Professor, Bioengineering & Therapeutic Sciences and Medicine  
Director, Center on Genes, Environments & Health

## EDUCATION/TRAINING

<table>
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<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
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<tbody>
<tr>
<td>San Francisco State University, San Francisco, CA</td>
<td>B.S.</td>
<td>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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<tr>
<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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<tr>
<td>Stanford University, Stanford, CA</td>
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<td>2001-2002</td>
<td>Genetic Epidemiology</td>
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<td>University of California, Berkeley</td>
<td>M.P.H.</td>
<td>2005-2006</td>
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## Positions and Honors

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<tr>
<td>1995 - 1996</td>
<td>Intern in Medicine, Brigham &amp; Women’s Hospital, Harvard Medical School, Boston, MA</td>
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<tr>
<td>1996 - 1998</td>
<td>Junior/Senior Resident in Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston MA</td>
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<tr>
<td>1998 - 2001</td>
<td>Fellow in Pulmonary and Critical Care Medicine, UCSF</td>
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<tr>
<td>2001 - 2010</td>
<td>Director, UCSF DNA Bank and Asthma Genetics Core Facility</td>
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<tr>
<td>2008 -</td>
<td>Director, UCSF Center on Genes, Environments &amp; Health</td>
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<td>2009 -</td>
<td>Director, UCSF Clinical Pharmacology Training Program</td>
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<td>2010 -</td>
<td>Vice Chair, UCSF Department of Bioengineering &amp; Therapeutic Sciences</td>
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<td>2011 -</td>
<td>Professor, UCSF Bioengineering &amp; Therapeutic Sciences Medicine</td>
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<td>2013</td>
<td>American Thoracic Society (ATS) Health Equality Committee</td>
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<td>2005-2010</td>
<td>RWJ Amos Medical Faculty Development Award</td>
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<td>2008</td>
<td>NIH Study Section Member, Genetics of Health and Disease (GHD)</td>
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<td>2009</td>
<td>American Society of Clinical Investigation (ASCI), inducted member</td>
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## Contributions to Science

Gene-environment studies in minority children with asthma. I conceived the Genetics of Asthma in Latino Americans (GALA) Study; I recruited the patients alongside with my collaborators, I built the bio-repository and database to house the biologic and clinical data, my colleagues and I did the analyses and wrote the manuscript. I also created a replication study in Latinos (GALA...
II) and African Americans (SAGE I & II). We demonstrated that Puerto Rican children have lower drug response to albuterol than Mexican children. Our results were the first to demonstrate racial/ethnic-specific differences in drug response to commonly prescribed medications.


Pharmacogenetic studies of minority children. We demonstrated ethnic-specific differences in pharmacogenetic associations of bronchodilator drug responsiveness between Puerto Rican and Mexican children with asthma. I conceived idea to test the beta 2 adrenergic receptor (b2AR) gene as part of the candidate gene list in the original GALA proposal.


c. Drake KA, Torgerson DG, (28 other authors), and Burchard EG. A genome-wide association study of bronchodilator response in Latinos implicates rare variants. *J Allergy Clin Immunol*. 2013; 133(2):370-378.e15. PMID: 23992748, PMCID: PMC3938989

Gene-environment studies. We performed the largest gene-environment of asthma in minority children in the U.S. I conceived the idea, established the collaborations, directed recruitment and ascertainment of the data and analyses.


b. Nishimura KK, Galanter JM, (20 other authors), Burchard EG. Early-life air pollution and asthma risk in minority children. The GALA II and SAGE II studies. *Am J Respir Crit Care Med*. 2013; 188(3): 309-18. PMID: 23750510; PMCID: PMC3778732


**Genome-wide analyses of asthma in minority children.** We performed the largest genome-wide and admixture mapping analyses of asthma and related traits in minority children in the U.S. I conceived the idea, obtained funding and my lab performed all genetic and statistical analyses.


b. Torgerson DG, Gignoux CR, (12 other authors), and Burchard EG. Case-control admixture mapping in Latino populations enriches for known asthma-associated genes. *J Allergy Clin Immunol*. 2012; 130(1): 76-82.e12. PMID: 22502797, PMCID: PMC3593143

c. Galanter JM, Gignoux CR, (30 other authors), and Burchard EG. GWAS and admixture mapping identify different asthma-associated loci in Latinos: The GALA II Study. *J Allergy Clin Immunol*. 2014; pii: S0091-6749(13)01765-X. PMID: 24406073

**Ancestry-environment analyses of lung function.** We identified a significant inverse relationship between African ancestry and forced expiratory volume at one second (FEV$_1$) and forced vital capacity (FVC) in African Americans. In predicting lung function, the ancestry-based model demonstrated a better fit of the observed data compared with standard models. Ancestry-based models reclassified asthma severity (based on percent predicted FEV$_1$) in 4-5% of African American participants. Current predictive equations, which rely on self-identified race alone, may misestimate lung function among African American subjects. We replicated these results in Mexicans from Mexico and Latino American children. Incorporating ancestry into normative equations may improve lung function estimates and more accurately categorize disease severity. I conceived the idea to test genetic ancestry and lung function in African Americans. Students, fellows and staff, from my lab, whom I have hired and trained, performed the analyses. The Mexico and Latino American projects were collaborative with the Bustamante lab. My laboratory performed all of the genetic analyses and estimates of local ancestry. All analyses were jointly performed by both laboratories.


b. Andrés Moreno-Estrada, Christopher R. Gignoux, Juan Carlos Fernández-López (34 other authors), Irma Silva-Zolezzi, *Esteban Gonzalez Burchard, *Carlos D. Bustamante. The genetics of Mexico recapitulates Native American substructure and...


d. Nishimura KK, Galanter JM (20 other authors), and **Burchard EG**. Early-life air pollution and asthma risk in minority children. The GALA II and SAGE II studies. *Am J Respir Crit Care Med*. 2013; 188(3): 309-18. PMID: 23750510; PMCID: PMC3778732

**Research Support**

**Ongoing Research Support**

1R01HL117004-01 Burchard (PI) 08/1/13-06/30/17
Pharmacogenomics of Bronchodilator Response in Minority Children with Asthma
The goals of this project are: (1) Perform “Exome Plus” DNA sequencing on the extremes of bronchodilator drug response among minority children with asthma; (2) Identify genetic variation associated with bronchodilator response; (3) Replication and meta-analysis.
Role: PI

P60 MD006902 Bibbins-Domingo (PI) 08/27/12-02/28/17
Program title: Addressing Disparities in Chronic Disease with a Teen and Young Adult Focus
The Genetics of Asthma and Obesity Using Admixture Mapping in Latinos
The major goal of this proposal is to identify novel genetic variants associated with both asthma and obesity by deep re-sequencing of candidate regions identified through admixture mapping.
Role: Project PI

1R01 HL104608-01A1 Barnes (PI) 09/28/11-6/30/15
New Approaches for Empowering Studies of Asthma in Populations of African Descent
The major goal of this project is to identify genetic variants specific to African populations. We will sequence Latino and African American samples to design a custom GeneChip for populations with African ancestry.
Role: Subcontractor

1K12 HL119997-01 (PI: Erle/Burchard) 09/01/13-5/31/18
UCSF Career Development Program in Omics of Lung Diseases
Overall project goal is to launch the careers of an outstanding group of next generation scientists equipped to use omics approaches to help transform lung research and pulmonary medicine.
Role: Co-PI
# BIOGRAPHICAL SKETCH

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

## EDUCATION/TRAINING

<table>
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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>
<td>Medicine</td>
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<td>Pennsylvania Hospital/UPenn</td>
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<td>1982</td>
<td>Internal Medicine</td>
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<td>University of California, San Francisco</td>
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<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  
- **1995-** Editorial Board, *American Journal of Respiratory Cell and Molecular Biology*  
- **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-** Editorial Board, *Current Respiratory Medicine Reviews*  
- **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** Elected to American Society for Clinical Investigation  
- **2000** Elected to American Association of Physicians  
- **2004-** Julius and Lillian Nadel Endowed Chair of Medicine  
- **2010** Elected to Collegium Internationale Allergologicum
**Contributions to Science**

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 and diffract human pro-chymase, thereby providing the first crystal-derived structure of the pro-form of an inflammatory cell serine protease and revealing a unique mechanism of controlling protease activity prior to activation. The laboratory revealed the single-gene nature of the human chymase locus and the multi-gene nature of the human tryptase locus, discovered alpha-tryptase deficiency and remarkable diversity of tryptase gene inheritance in humans, and was the first to purify, clone and characterize mastins, which the principal tryptase-like enzymes of basophils. We co-discovered a transmembrane version of mast cell tryptase (gamma-tryptase), and revealed its evolutionary and phylogenetic relationship to soluble tryptases and epithelial proteases like prostatin and marapsin (which we also discovered), and discovered that cathepsin C-null mice deficient in active forms of one or more chymases and tryptases. Using innovative methods, including combinatorial approaches, we identified novel, protease-selective substrates and inhibitors of mast cell tryptases, chymases, cathepsin G, and mastin. We made a number of highly cited discoveries concerning the actions of tryptases and chymases on peptides, proteins, cells and airway tissues, including mitogenic and secretagogue activity, non-ACE-mediated generation of angiotensin II, and activation of MMP9 and matrix 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<sup>W<sub>sh</sub></sup>/Kit<sup>W<sub>sh</sub></sup> 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 potent secretagogue activity, proteoglycanase activity, inactivation of surfactant apoproteins, and genetic mutations in primate genes that altered human cathepsin G activity and function. Our discovery that neutrophils are inducible, highly significant sources of histamine in mice with pneumonia received major attention from the lay and scientific press 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.


**Research Support**

Ongoing Research Support

P01 HL024136 Caughey (PI) 05/11/2010-3/30/2015
“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

DVA Shared Equipment (ShEEP) Grant Caughey (Co-PI) 07/01/2014-06/30/2015
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

K23 HL121145 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
# 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>1968</td>
<td>Premedical</td>
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<td>University of Alabama School of Medicine</td>
<td>M.D.</td>
<td>1972</td>
<td>Medicine</td>
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</table>

## Positions and Honors

- 1972-1975 Residency Training in Internal Medicine, University of Utah Affiliated Hospitals, Salt Lake City, UT
- 1975-1977 Associate Investigator, V.A. Medical Center, Salt Lake City, UT
- 1978-1979 Pulmonary Fellow, University of Utah Affiliated Hospitals, Salt Lake City, UT
- 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 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.
Selected Peer-reviewed Publications (Selected from ~140)


Research Support

Ongoing Research Support

5 R01 HL44712 (Chapman, HA) $250,000 per yr direct
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 TGFb1 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.

U01 HL111054-01 (Chapman HA, PI) $250,000 per year direct
NIH/NHLBI
Epithelial Progenitor Cells in Lung Repair and Regeneration 1/1/2012-12/31/2016

The major goals of this project are (1) to define the transcriptional program of heretofore-uncharacterized distal airway and alveolar progenitors and 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) 250,000 per year direct
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.
Completed Research

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.

5 R01 CA125564 (Chapman, HA)   No cost extension   7/1/2007 – 5/31/2013  
NIH/NHLBI  
Urokinase Receptor Integrin Interactions in Lung Cancer

The major goals of this project are to define the physical basis of urokinase 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  
Daiichi Sankyo  
Human Epithelial Progenitor Cells in Idiopathic Pulmonary Fibrosis

Pending Research Support

R01HL128484-01  (Chapman HA, PI)  
Epithelial Stem/Progenitor Cells in Repair of the Injured Lung  7/1/2015-6/30/2020  
The major goals of this project are to define determinants of alveolar stem/progenitor cell differentiation after lung injury and identify the human equivalent of recently identified undifferentiated epithelial cells in the mouse lung parenchyma.
# BIOGRAPHICAL SKETCH

<table>
<thead>
<tr>
<th>NAME</th>
<th>POSITION TITLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheng, Laurence Eng-Chee</td>
<td>Assistant Professor In Residence</td>
</tr>
</tbody>
</table>

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

## 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 California, Berkeley</td>
<td>A.B.</td>
<td>06/96</td>
<td>Molecular and Cell Biology</td>
</tr>
<tr>
<td>University of Washington, Seattle Medical Scientist Training Program</td>
<td>M.D.</td>
<td>06/04</td>
<td>Medicine</td>
</tr>
<tr>
<td>University of Washington, Seattle Medical Scientist Training Program</td>
<td>Ph.D.</td>
<td>06/04</td>
<td>Immunology</td>
</tr>
<tr>
<td>University of California, San Francisco</td>
<td></td>
<td>06/06</td>
<td>Pediatrics Residency</td>
</tr>
<tr>
<td>University of California, San Francisco and Stanford University</td>
<td></td>
<td>06/09</td>
<td>Allergy and Immunology Fellowship</td>
</tr>
</tbody>
</table>

## Positions and Honors

2009 - 2011 Non-ACGME Fellow/Health Sciences Clinical Instructor, Pediatrics, University of California, San Francisco

2011 - 2013 Assistant Adjunct Professor, Department of Pediatrics, University of California, San Francisco

2013 - Present Assistant Professor in Residence, Department of Pediatrics, University of California, San Francisco

1992 Bank of America Science and Mathematics Scholarship Award

1995 Biology Fellow Program, Howard Hughes Medical Institute

1995 ARCS Foundation Scholarship Prize, Achievement Reward for College Scientists

1996 Phi Beta Kappa Lifetime Member, University of California, Berkeley and Phi Beta Kappa

1996 Highest Distinction in General Scholarship, University of California, Berkeley

1996 Honors in the Immunology Emphasis of the Department Molecular and Cell Biology, University of California, Berkeley

1996 Outstanding Scholar Citation, Department of Molecular and Cell Biology, University of California, Berkeley

1999 Cora May Poncin Scholarship Award, Poncin Foundation
2001  Alexandra & Charles Morse Fellow in Immunology, Achievement Reward for College Scientists
2003  Alpha Omega Alpha (AOA), University of Washington
2004  Molecular Medicine Training Program Fellow, University of California, San Francisco
2008  AAAAAAI-GSK Career Development Award, American Association of Allergy, Asthma and Immunology
2009  A.P. Giannini Foundation Medical Research Fellow
2011  Melvin M. Grumbach Excellence in Pediatric Research Award, University of California, San Francisco
2013  415 Top Doctors, Marin Magazine
2014  Mary E. and Oscar L. Frick, MD Endowed Chair in Allergy
2014  Fellow, American Academy of Allergy, Asthma and Immunology

Selected Peer-Reviewed Publications


**Research Support**

On-going Research Support

IK08AI095319-01 Cheng (PI) 09/09/2011 – 08/31/2016
NIH/NIAID
Surveillance of Serum Contents by Mast Cells and Regulation of Allergic Immunity
K08 Career Develop Award
Role: PI

Completed Research Support

N/A Cheng (PI) 07/01/2009 – 08/31/2011
AP Giannini Medical Foundation
Mast Cell Loading of IgE Mechanisms of Uptake, Effects on Survival and Functional Implications Upon Activation
Postdoctoral research award
Role: PI
BIOGRAPHICAL SKETCH

NAME
Anthony L. DeFranco, Ph.D.

POSITION TITLE
Professor,
Department of Microbiology & Immunology

eRA COMMONS USER NAME
DeFranco

EDUCATION/TRAINING

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvard University, Cambridge, MA</td>
<td>A.B.</td>
<td>6/75</td>
<td>Biochem. &amp; Molec.</td>
</tr>
<tr>
<td>University of California, Berkeley, CA</td>
<td>Ph.D.</td>
<td>10/79</td>
<td>Biochemistry</td>
</tr>
<tr>
<td>National Institutes of Health, Bethesda, MD</td>
<td>Postdoctoral</td>
<td>11/79-8/83</td>
<td>Immunology</td>
</tr>
</tbody>
</table>

Positions and Honors

1972-1975 Undergraduate research, laboratory of Dr. Jack Strominger. HLA antigens.
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.

Professional Service (selected list)

Associate Editor (1986-90), Section Editor (1990-1994), Deputy Editor (1999-2001); Annual Review of Immunology, Editorial Committee for Volumes 9,13, 15, 17 (1991, '95, '97, '99);

Selected peer-reviewed publications (in chronological order)

Original Research/Peer-reviewed journals (from total of 75 original research publications)


Research projects ongoing or completed during the last three years

Active

“BCR Regulation of Antibody Responses”
Principal Investigator: Anthony DeFranco
1 R56 AI108684-01A1 (Anthony DeFranco, PI) 8/1/14-7/31/15 Agency: NIAID/NIH
The goals of this project are to determine how quantitative changes in diacylglycerol levels produced in response to BCR signaling affect the production of antibodies that protect against influenza virus infection in mice. In addition, the project aims to assess how quantitative changes in Erk MAP kinases affect the magnitude of antibody responses.
OVERLAP: none

“Sensitized mouse genetic screen for amelioration of murine lupus-like autoimmune disease”
Principal Investigator: Anthony DeFranco
Agency: Program in Breakthrough Biomedical Research (UCSF internal) 7/1/13-6/30/14
This project will generate ENU mutagenized pedigrees from a well-defined mouse strain that spontaneously develops SLE-like autoimmune disease with the goal of obtaining and identifying mutations that ameliorate autoimmune disease while leaving some degree of immunity to infection intact.
OVERLAP: none

“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
The major goals of this project are to determine the mechanism by which Apobec3 enzyme expression in mice affects the marginal zone B cell compartment.
OVERLAP: none
**Completed** (last 3 years)

UCSF SOM Dean’s Bridge Award  
Period:  2/1/12-1/31/13  
This bridge award was to support studies of B cell antigen receptor signaling related to grant R56AI20038.

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
BIOGRAPHICAL SKETCH

NAME
David J. Erle, M.D.

POSITION TITLE
Professor of Medicine

eRA COMMONS USER NAME
DJERLE

EDUCATION/TRAINING

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvard College, Cambridge, MA</td>
<td>A.B.</td>
<td>1980</td>
<td>Biochemistry</td>
</tr>
<tr>
<td>University of California, San Francisco, CA</td>
<td>M.D.</td>
<td>1984</td>
<td>Medicine</td>
</tr>
<tr>
<td>University of California, San Francisco, CA</td>
<td>Resident</td>
<td>1984-87</td>
<td>Internal Medicine</td>
</tr>
<tr>
<td>University of California, San Francisco, CA</td>
<td>Fellow</td>
<td>1987-90</td>
<td>Pulmonary Disease</td>
</tr>
<tr>
<td>University of California, San Francisco, CA</td>
<td>Postdoc</td>
<td>1988-1990</td>
<td>Cell &amp; Molecular Biology</td>
</tr>
</tbody>
</table>

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

Honors

1977 Detur Prize
1984 Alpha Omega Alpha, elected
1990-1993 Edward Livingston Trudeau Award of the American Lung Association
2008-2012 Member, LCMI Study Section (chair 2010-2012)
selected peer-reviewed publications

Fifteen most relevant to my role as director of the SABRE Center Functional Genomics Core (all include microarray studies):


Research Support

Active

P01 HL108794 (Sheppard) 04/01/2013 – 03/31/2018 2.3calendar
NIH/NIAID
Role: Project 1 Leader Program: $1,086,097 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: Co-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 GK118267-01A1 (Williams) 12/01/2013 – 11/30/2018 0.6 calendar
Henry Ford Health System (subcontract) $181,184
Role: Subcontract PI
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) 07/01/2014-06/30/2019 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.

U01 HL126492 (Erle/Woodruff) 07/01/2014-06/30/2019 2.0 calendar
NIH $449,517 Role: Co-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.

R01 GM110251 (Erle/McManus) 09/01/2014-08/31/2019 2.0 calendar
NIH $452,511
Role: Co-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.
BIOGRAPHICAL SKETCH

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

POSITION TITLE
Professor of Medicine in Residence

eRA COMMONS USER NAME
johnfahy

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>University College Dublin</td>
<td>MB BAO</td>
<td>1985</td>
<td>Medicine</td>
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<tr>
<td>University College Dublin</td>
<td>BCH</td>
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</tr>
<tr>
<td>Trinity College Dublin</td>
<td>Intern</td>
<td>1985-1986</td>
<td>Medicine and Surgery</td>
</tr>
<tr>
<td>University College Dublin</td>
<td>Resident</td>
<td>1986-1989</td>
<td>Internal Medicine</td>
</tr>
<tr>
<td>University College Dublin</td>
<td>Registrar</td>
<td>1988-1999</td>
<td>Respiratory Medicine</td>
</tr>
<tr>
<td>University of California, San Francisco</td>
<td>Fellow</td>
<td>1989-1993</td>
<td>Pulmonary/Critical Care Medicine</td>
</tr>
<tr>
<td>University College Dublin</td>
<td>M.D.</td>
<td>1997</td>
<td>Respiratory Medicine</td>
</tr>
<tr>
<td>Trinity College Dublin</td>
<td>M.Sc.</td>
<td>2003</td>
<td>Molecular Medicine</td>
</tr>
<tr>
<td></td>
<td>(doctorate by thesis)</td>
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</tr>
<tr>
<td></td>
<td>(Sabbatical year)</td>
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Positions

Internship and Residencies

1985 - 1986 Medicine Intern, St Vincent’s Hospital, University College Dublin.
1986 - 1988 Senior House Officer, St James’ Hospital, Trinity College Dublin.
1988 - 1989 Medicine Registrar (pulmonary medicine), St Vincent’s Hospital, University College Dublin.
1989 - 1993 Fellow, Pulmonary and Critical Care Medicine, UCSF.

Academic Appointments

1993 - 1998 Assistant Adjunct Professor of Medicine, UCSF.
1999 - 2005 Associate Professor of Medicine in Residence, UCSF.
2005 - Present Professor of Medicine in Residence, UCSF.
2006 - Present Michael S. Stulbarg Endowed Chair in Pulmonary Medicine, UCSF.

Other Experience and Professional Memberships

2006 - Present Director, Airway Clinical Research Center, UCSF.
2010 - Present Member, Scientific Committee, Transatlantic Airway Conference.
2011 - Present Member, UCSF Department of Medicine Research Council.
Selected Peer-reviewed Publications


16. Fahy JV. Type 2 inflammation in asthma - present in most, absent in many. *Nat Rev...

Research Support

1P01HL107202 (Fahy, JV) 8/1/12 - 6/30/17
Innate and Adaptive Immune Responses in Th2-high Asthma
This PPG will comprehensively investigate the molecular underpinnings of the Th2-high molecular subtype of asthma
Role: Overall PPG PI (Project leader for project 3 and Core leader for the Administrative Core and the Human Subjects Core.

1U10HL109146 (Fahy JV) 8/1/2011-7/31/2017
Clinical and Molecular Phenotypes of Severe Asthma
This grant was submitted in response to the RFA for Clinical Centers for the Severe Asthma Research program) – a 6-center national program for research into mechanisms of severe asthma.
Role: PI

1U10HL109146 (Fahy JV) 8/1/2011-7/31/2017
Clinical and Molecular Phenotypes of Severe Asthma
This grant was submitted in response to the RFA for Clinical Centers for the Severe Asthma Research program) – a 6-center national program for research into mechanisms of severe asthma.
Role: PI

5 R01 HL080414 (Fahy, JV) 7/01/05-05/31/15
Protein carbohydrate interactions in the pathophysiology of acute asthma exacerbations
The major goals of this project are to investigate how lectins interact with mucin glycans to cause airway mucus obstruction in acute severe asthma.
Role: PI

1P50HL107191 (Fahy, JV) 5/01/11-04/30/15 (NCE)
Preventing fucose-dependent binding of aspergillus and pseudomonas to lung mucin
This grant was submitted in response to the RFA for “Centers for Advanced Diagnostics and Experimental Therapeutics (CADET-1)”.
Role: PI
BIOGRAPHICAL SKETCH

NAME
James Solomon Fraser, Ph.D.

POSITION TITLE
Assistant Professor

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

EDUCATION/TRAINING

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

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)

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)

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  International Structural Genomics Organization Travel Fellowship
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

Selected Peer-reviewed Publications


Research Support

Ongoing Research Support

1 DP5 OD009180-01 Fraser (PI) 09/01/2011 – 08/31/2016
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.
Role: PI

R21 GM110580 Fraser (PI) 04/01/14-03/31/16
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, which is key to structure-based drug design.

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.
The major goal of this project is to use small molecules or mutations to restore the motion and function of proteins involved in human diseases or to combat pathogens that are resistant to current antibiotics.

The major goal of this project is to create and apply methods to examine low signals in electron density maps and diffraction images to study the importance of conformational dynamics in protein function.

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.

The major goal of this award is to collect preliminary data to test the hypothesis that chitinases assemble into processive machines to generate the signals that initiate and terminate inflammation in the context of allergy and asthma.

Completed Research Support

None
BIOGRAPHICAL SKETCH

NAME
Andrew N. Goldberg

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

POSITION TITLE
Research Investigator

EDUCATION/TRAINING

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

Positions

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

1989  George C. Schein, MD Research Award  
 University of Pittsburgh, School of Medicine
1993  Resident Appreciation Award  
 Washington University of St. Louis, Department of Otolaryngology, 
 Head and Neck Surgery
2002  Distinction in Teaching Award, Honorable Mention  
 UCSF Academic Senate
2002  Roger Boles Resident Teaching Award  
 UCSF Otolaryngology, Head and Neck Surgery
2003  Best Doctors in San Francisco, San Francisco Magazine
2005  Fellow, American Rhinologic Society
2005  Excellence in Direct Teaching Award  
 UCSF Haile T. Debas Academy of Medical Educators
2005  Honor Award, American Academy of Otolaryngology, 
 Head and Neck Surgery
2006  Research Award, 3rd prize, American Society of Ophthalmic 
 Plastic and Reconstructive Surgery
2007  Clinical Research Award, American Rhinological Society
2010  Francis A. Sooy, MD Resident's Award for Clinical Excellence  
 UCSF, Otolaryngology, Head and Neck Surgery

Selected Peer-reviewed Publication and Patent Citations


**Research Support**

**Ongoing Research Support**

Rebecca Susan Buffet Foundation        Goldberg (PI)  1/1/03-12/31/15
Clinical Research in Otolaryngology
Unrestricted grant for clinical research in otolaryngology. These funds are used to support the Center for Clinical Research in Otolaryngology and ongoing research in a multitude of areas, principally smaller projects or pilot studies for larger grants.

Cystic Fibrosis Foundation Goldberg (co-I)
Characterization of upper respiratory microbial communities in Cystic Fibrosis  4/1/13 – 4/1/15

HRI, Incorporated        Goldberg (PI)  7/1/05-6/30/09
Acupuncture and Chronic Rhinosinusitis
The goal of this study is to evaluate the benefits of acupuncture in treating chronic rhinosinusitis.

**Completed Research Support (selected)**

Aspire Medical        Goldberg (PI)  7/1/04-6/30/05
A Cadaver Model of Obstructive Sleep Apnea
The goal of this project was the creation of a cadaver model of obstructive sleep apnea to evaluate changes in airway mechanics associated with specific surgical interventions.

Bristol-Myers Machtay (PI)  7/1/97-6/30/01
A Phase II Trial of Combined Modality Therapy for Oropharyngeal Carcinoma (UPCC 11397)
The goal of this project was to examine multimodality treatment for oropharyngeal cancer. Role: Co-Investigator

5R01 HL57843-04        Schwab (PI)  1997-2001
NIH/NHLBI
Biomechanical Basis for the Treatment of Sleep Apnea
The goal of this study was to compare anatomical structure in obstructive sleep apnea patients versus normals using multiple imaging techniques. Role: Co-Investigator
# BIOGRAPHICAL SKETCH

<table>
<thead>
<tr>
<th>NAME</th>
<th>POSITION TITLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beomkyu Kim</td>
<td>Postdoctoral Scholar</td>
</tr>
</tbody>
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## EDUCATION/TRAINING

<table>
<thead>
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<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
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<tr>
<td>Yonsei University, Seoul, Korea</td>
<td>BS</td>
<td>02/06</td>
<td>Biochemistry</td>
</tr>
<tr>
<td>Northwestern University, Evanston, IL</td>
<td>-</td>
<td>08/07</td>
<td>IBiS Graduate Program</td>
</tr>
<tr>
<td>Stanford University, Stanford, CA</td>
<td>Ph.D.</td>
<td>01/14</td>
<td>Structural Biology</td>
</tr>
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</table>

## Positions and Honors.

2014 - Present  
Associate Researcher, New Drug Discovery Team 1, SK Chemicals, Republic of Korea

## Selected peer-reviewed publications


## BIOGRAPHICAL SKETCH

<table>
<thead>
<tr>
<th>NAME</th>
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<tr>
<td>Matthew Frederick Krummel, Ph.D</td>
<td>Associate Professor</td>
</tr>
<tr>
<td>eRA COMMONS USER NAME</td>
<td>Krummel</td>
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## EDUCATION/TRAINING

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<th>FIELD OF STUDY</th>
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<tbody>
<tr>
<td>University of Illinois at Champaign-Urbana</td>
<td>B.S.</td>
<td>1989</td>
<td>Biology and Chemistry</td>
</tr>
<tr>
<td>University of California at Berkeley</td>
<td>Ph.D.</td>
<td>1995</td>
<td>Immunology</td>
</tr>
<tr>
<td>Walter and Eliza Hall Institute, Melbourne Australia</td>
<td></td>
<td>1996-1997</td>
<td>Immunology</td>
</tr>
<tr>
<td>Stanford University</td>
<td></td>
<td>1997-2001</td>
<td>Immunology</td>
</tr>
</tbody>
</table>

### 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
- **July 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

- **2009-2012**: Fellow of the American Asthma Foundation
- **2005-2010**: Leukemia and Lymphoma Foundation, Career Award
- **1997-2000**: NRSA Postdoctoral Fellowship, National Institutes of Health
- **1996-1997**: Postdoctoral Fellowship, Juvenile Diabetes Foundation International
- **1997-2000**: NRSA Postdoctoral Fellowship, National Institutes of Health

1987 Summer Undergraduate Research Fellowship, Howard Hughes Medical Institute

**Selected Peer-reviewed Publications** (out of 75)


**Research support**

**Ongoing Research Support**

R01 AI52116 (PI: Krummel) 01/15/2008-12/31/2017
NIH/NIAID
Myosin Motors in T cell Synapse Formation and Activation
The major goals of this project are to analyze MyoIIA regulation during T cell motility and synapse formation. This includes mutational analyses as well as generation and analyses of knockout animals.

P01 HL024136 (PI: Caughey) 05/01/2010-03/31/2015
NIH/NHLBI
Evolving Microenvironments in Airway Inflammation
The aims of this proposal are to identify shifts in antigen trafficking into APC, the temporal pairing of specific APC with T cell subsets, and the effects of mycoplasma-mediated inflammation and mast-cell-mediated regulation upon T cell-APC pairing in lung microenvironments.
Role: Co-PI

01 HL024136 (PI: Caughey) 05/01/2010-03/31/2015

U54 CA163123 (Multi-PIs: Coussens, Krummel, Van't Veer) 09/01/2011-08/30/2016
NIH/NCI
Leukocyte Biomarkers for Predicting Human Breast Cancer Outcome
In this proposal, we will identify clinically significant leukocyte biomarkers in breast cancer, reveal correlation of outcomes in human breast cancer with leukocyte transcriptomes and novel leukocyte biomarkers, and drive translation of leukocyte biomarkers into clinically applicable diagnostic and therapeutic probes.
Epithelial Progenitor Cells in Lung Repair and Regeneration

The major objectives are (1) to define the transcriptional program of heretofore uncharacterized distal airway and alveolar progenitors and test the hypothesis that differential expression of adhesion receptors underlies the capacity of epithelial subtypes of self-organize and promote repair, (2) to define the requirement for neuroendocrine cells (PNECS) and alveolar progenitor cells in maintenance and reconstitution of distal airway and alveolar cells following lung injury, and (3) to 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.

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.
# BIOGRAPHICAL SKETCH

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

| eRA COMMONS USER NAME | |
|-----------------------| |
| Locksley              | |

## EDUCATION/TRAINING

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

## Positions and Honors

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

## Editorial Boards

- **1999-03**: Immunity, Journal Clinical Investigation, Immunology & Cell Biology, Annual Review Immunology

## Honors

- **1991**: American Society for Clinical Investigation
- **1994**: Association of American Physicians
1992-97 Burroughs Wellcome Fund Scholar in Molecular Parasitology
1994 Bailey K Ashford Medal, American Society Tropical Medicine and Hygiene
2001-05 Ellison Medical Foundation Senior Scholar in Global Infectious Diseases
2003 Distinguished Service Award, American Association of Immunologists
2003 Sandler Distinguished Professorship
2003 American Academy of Arts and Sciences
2005 R37 Merit Award
2005 American Academy of Arts & Sciences
2006 NIAID/NIH
2006 Inspirational Teacher Award, UCSF

Selected peer-reviewed publications (of >170)


Research Support

Active

Not assigned Locksley (PI) 10/97 – 9/15 (budgeted annually)
Howard Hughes Medical Institute

Activation of Immunity
The goals of this project are to provide new strategies to optimize host defense and vaccines and to treat pathologic immune responses associated with autoimmunity and allergy. 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 control of mucosal inflammation by helminthes.

R37 AI026918 (Locksley) 7/1/88-3/31/16
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 AI119944 (Fahy) 7/1/12 – 6/30/17
NIH/NHLBI

Innate and Adaptive Immune Responses in Th2-High Asthma
The goal of this project is to focus on the role of ILC2 cells as proximal regulators of Th2 inflammation in the airway. This project proposes to characterize markers for these cells, delineate their role in allergic airway responses and collaborate with investigators in Project 3 to advance understanding of ILC2 cells in human asthma.
Role: PI Subproject 1

Completed

U19 AI077439 Sheppard (PI) 4/08-3/13
NIH/NIAID

Mechanisms of initiation and persistence of allergic asthma
The major goals of this grant were to understand mechanisms of allergic lung inflammation induced by fungi in murine models and human studies.
Role: PI Subproject 1

P01 AI078869 DeFranco (PI) 8/08-7/13
NIH/NIAID

Cross-talk between innate and adaptive immune cells in inflammation and autoimmunity
The major goals were to assess the role of innate signaling pathways in the induction of mucosal responses to pathogens.
Role: PI Subproject 4
BIOGRAPHICAL SKETCH

NAME
Steven D. Pletcher

POSITION TITLE
Associate Professor: Otolaryngology – Head and Neck Surgery

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

EDUCATION/TRAINING

<table>
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<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
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<th>FIELD OF STUDY</th>
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<tbody>
<tr>
<td>Yale University</td>
<td>BS</td>
<td>06/95</td>
<td>Molecular Biophysics and Biochemistry</td>
</tr>
<tr>
<td>University of California, Los Angeles</td>
<td>MD</td>
<td>06/00</td>
<td>Medicine</td>
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<tr>
<td>University of California, San Francisco</td>
<td></td>
<td>06/01</td>
<td>Intern: General Surgery</td>
</tr>
<tr>
<td>University of California, San Francisco</td>
<td></td>
<td>06/05</td>
<td>Resident: Otolaryngology, Head and Neck Surgery</td>
</tr>
<tr>
<td>Massachusetts Eye and Ear Infirmary</td>
<td></td>
<td>06/06</td>
<td>Fellow: Rhinology and Paranasal Sinus Disorders</td>
</tr>
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</table>

Positions and Honors

2000-2005  Resident, Department of Otolaryngology, Head and Neck Surgery; University of California, San Francisco
2005-2006  Fellow, Rhinology and Disorders of the Paranasal Sinus, Massachusetts Eye and Ear Infirmary, Boston, MA
2006-2012  Assistant Professor, Department of Otolaryngology, Head and Neck Surgery; University of California, San Francisco
2011-      Associate Residency Program Director, Department of Otolaryngology, Head and Neck Surgery; University of California, San Francisco
2011-      Chief, Otolaryngology Section, San Francisco VA Medical Center San Francisco, CA
7/2012 -    Associate Professor, Department of Otolaryngology, Head and Neck Surgery, University of California, San Francisco

Other Experience and Professional Memberships

2002-      Member, American Academy of Otolaryngology – Head and Neck Surgery
2003-      Member, American Rhinologic Society
2010-2011  Chair, Clinical Affairs Committee, UCSF Academic Senate

Honors

1995       Cum Laude, Distinction in Molecular Biophysics and Biochemistry
           Yale University, New Haven, CT
2000       AOA, University of California, Los Angeles School of Medicine. Los Angeles, CA.
2005       Resident Research Award, Department of Otolaryngology – Head and Neck Surgery
           University of California, San Francisco. San Francisco, CA
2008   Roger Boles, MD Teaching Award. Department of Otolaryngology, Head and Neck Surgery. University of California, San Francisco. San Francisco, CA

2014   1st Place Basic Science Research Award, American Rhinologic Society Fall Meeting

2011-2015   Top Doctor, Otolaryngology, Marin Magazine.

Peer-reviewed Publications and Patent Citations

6. Pletcher SD, Hoxworth JM, Goldberg AN, Murr AH, Glastonbury CM.
17. Patent pending  Sinus diagnostics and therapeutics, 61/624,105
Research Support

Cystic Fibrosis Foundation 07/01/2013 - 07/01/2015
252585 (Co-PI; Cope PI) $40,000 direct/yr
Characterization of upper respiratory microbial communities in CF $40,000 total

Hearing Research Institute, Incorporated (Pletcher PI)
Impact of topical antibiotics on microbial communities in the sinuses 7/1/11-6/30/12
# 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

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

### 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
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 Present   Faculty of 1000

15 Selected Peer-Reviewed Publications (of 94)


**Research Support**

**Ongoing Grants:**

I closed my laboratory in 2014.

**Ongoing Mentored Grant**

**Title:** The role of CCR2 and Macrophages in Traumatic Brain Injury

**Agency/Type:** Department of Veterans Affairs PI: Christine Hsieh 1/1/2011 to 12/31/2013

**Role:** Mentor

**Program:** This is a VA Career Development Award to Christine Hsieh, Ph.D., a postdoctoral fellow in my laboratory for whom I am the mentor on this award. Dr. Hsieh has been
studying traumatic brain injury as part of my DoD grant (below). As part of this work, she showed that TBI results in an influx of macrophage to the brain, and that this influx is primarily dependent on the chemokine receptor, CCR2. This grant has allowed her to study the functional consequences of this response and to develop as an independent investigator. Key persons in addition to Dr. Hsieh and myself include our colleague, Mary Nakamura.

Completed support (last 3 years)

Title: The Role of Microglial Subsets in Regulating Brain Injury
Agency/Type: Department of Defense - PT075679 PI: WE Seaman 7/1/06 to 6/30/2013
Role: Principal Investigator
Program: These studies examine the role of microglial subsets in the response to TBI. They examine the hypothesis that microglia, like macrophages may be divided into pro-inflammatory vs. reparative subsets, and that injury following TBI may be improved by driving microglia from the former to the latter. Key persons in addition to myself were Christine Hsieh, Ph.D., Mary Nakamura, M.D., and Jialing Liu, Ph.D., a colleague in Neurosurgery who is expert in TBI.
BIOGRAPHICAL SKETCH

NAME
Dean Sheppard, M.D.

POSITION TITLE
Professor of Medicine

eRA COMMONS USER NAME
sheppard

EDUCATION/TRAINING

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

Positions

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

Other Experience

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

Elected member, American Society for Clinical Investigation, 1992
Elected member, Association of American Physicians, 1995
Clean Air Award, American Lung Association of California, 1995
Parker B. Francis Lecturer, Aspen Lung Conference, 1996
Lifetime Scientific Achievement Award, American Thoracic Society, 1998
Jerome I. Flance Visiting Professor, Washington University, 2000
Roger Mitchell Lecturer, Aspen Lung Conference, 2001
NIH Merit Award, 2004-2014
Robert Johnston Lecturer, Drexel University, 2005
McClement Lecturer, New York University, 2006
Kass Medal, University of Nebraska, 2007
Amerson Lecturer, American Thoracic Society, 2010

Selected Relevant Publications (from a total 252)


**Research Support**

Ongoing

R01 HL102292 (Sheppard) 12/03/10-11/30/14 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.
NIH
In Vivo Functions of Pulmonary Integrins
The major goals of this project are to determine the roles of TGFβ1 activation in the induction of lung inflammation and protection from pulmonary fibrosis in integrin β6 subunit null mice.

Scleroderma Research Foundation (Sheppard)  5/1/12-4/30/15
Role of αv Integrins in Scleroderma
The goals of this project are to determine whether specific integrins expressed on epithelial cells or myofibroblasts could be effective therapeutic targets for treatment of scleroderma.

P01 HL108794 (Sheppard)  07/01/2012–6/30/17
NIH/NHLBI- Project 2 and Core A
Targeting Epithelial Cells to Treat Pulmonary Fibrosis
Overall project goal: This grant will address 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)  07/01/2012–6/30/17
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

U19 AI077439 (Sheppard)  4/1/13-3/31/18
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  20% (2.4 cal mos)
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.
BIOGRAPHICAL SKETCH

NAME

Jeoung-Sook Shin, Ph.D.

POSITION TITLE

Assistant Professor

eRA COMMONS USER NAME

SHINJS

EDUCATION/TRAINING

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
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<th>FIELD OF STUDY</th>
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<tbody>
<tr>
<td>Seoul National University, Seoul, Korea</td>
<td>BS</td>
<td>1988-1993</td>
<td>Chemistry</td>
</tr>
<tr>
<td>Seoul National University, Seoul, Korea</td>
<td>MS</td>
<td>1993-1995</td>
<td>Biochemistry</td>
</tr>
<tr>
<td>Duke University, Durham, NC</td>
<td>Ph.D.</td>
<td>1997-2002</td>
<td>Pathology</td>
</tr>
<tr>
<td>Duke University, Durham, NC</td>
<td>Postdoc</td>
<td>2002-2003</td>
<td>Pathology</td>
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<tr>
<td>Yale University, New Haven, CT</td>
<td>Postdoc</td>
<td>2003-2008</td>
<td>Cell Biology</td>
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</table>

Professional Positions

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

Honors and Awards

1999  The Best Research Student Award in the Department of Pathology, 9th Graduate Student Symposium, Duke University
2004  The Jane Coffin Childs Memorial Fund Research Fellowship Award
2009  Strategic Innovative Award in Asthma Research
2009  Cancer Research Institute Investigator Award
2010  American Heart Association Scientist Development Award

Professional Memberships

2008-2009  American Thoracic Society, member
2010  American Society of Cell Biology, member
2011-Present  American Association of Immunologists, member
Selected peer-reviewed publications


*Shin JS and Mellman contributed equally to this work.
Research Support

1R01GM105800-01 Shin (PI) 9/5/2013 – 5/31/2018
National Institute of Health, NIGMS

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 Treg differentiation in the thymus.

Schussler Toby Fund (PI)
UCSF School of Medicine REAC (Research Evaluation and Allocation Committee)
1/1/2015 – 12/31/2015
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.

Completed (last 3 years)

10SDG3500062 Shin (PI) 7/1/2010 – 6/31/2014
American Heart Association Scientist Development Award
IgE-mediated Activation of Dendritic Cells in the Lungs
The major goal of this project is to characterize IgE-mediated dendritic cell activation in the lungs using mouse models.

Cancer Research Institute Investigator Award (PI) Shin (PI) 7/1/2009-6/30/2013
Cancer Research Institute

Mechanism and Function of Ubiquitin-mediated Membrane Traffic in Dendritic Cells
The major goal of this project was to identify the specific role of regulated ubiquitination in dendritic cell function and its underlying mechanisms.
BIOGRAPHICAL SKETCH

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

POSITION TITLE
Research Specialist

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

Positions and Honors

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

Selected Peer-reviewed Publications


BIOGRAPHICAL SKETCH

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

eRA COMMONS USER NAME
weissa

POSITION TITLE
Professor of Medicine and of Microbiology and Immunology

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 Chicago</td>
<td>Ph.D.</td>
<td>1978</td>
<td>Immunology</td>
</tr>
<tr>
<td>University of Chicago</td>
<td>M.D.</td>
<td>1979</td>
<td>Medicine</td>
</tr>
</tbody>
</table>

Positions and Employment

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

Other Experience and Professional Memberships

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

Honors

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

Selected Peer-reviewed Publications (from a total of 225)


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 (3 postdocs and 4 technicians) focus on structure of the TCR and the ZAP-70 protein tyrosine kinase.
Role: Principal Investigator

1PO1 AI091580-01 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.

Completed Research

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

1 RC2 AR058947-01 (A.Weiss) 09/25/09-08/31/12 No Cost Extension
NIH/NIAMS
An Allosteric Inhibitor of ZAP-70 as a Novel Therapeutic for Autoimmune Disease
The goals of this project are develop and allosteric inhibitor of ZAP-70 and determine the preclinical utility of a model catalytic inhibitor of ZAP-70 in preclinical models of disease.
Role: Principal Investigator
# BIOGRAPHICAL SKETCH

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

| eRA COMMONS USER NAME | WEISSMAN |

## 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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</thead>
<tbody>
<tr>
<td>Harvard University</td>
<td>A.B.</td>
<td>1984-1988</td>
<td>Physics</td>
</tr>
<tr>
<td>Massachusetts Institute of Technology</td>
<td>Ph.D.</td>
<td>1988-1993</td>
<td>Physics</td>
</tr>
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</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 - 2005**: Professor, University of California San Francisco, Departments of Cellular & Molecular Pharmacology, and Biochemistry & Biophysics
- **2005 - Present**: Investigator, Howard Hughes Medical Institute

## Other Experience and Professional Memberships

- **2005**: External Reviewer, Lawrence Berkeley National Lab Physical Biosciences Division
- **2005 – 2007**: Member, NIH Advisory Board on Amyloid Diseases
- **2005**: Organizer, Mini-symposium of Quality Control for the Annual American Society of Cell Biology (ASCB) Meeting
- **2006 to Present**: Member, Yeast Genetics & Molecular Biology Meeting Program Committee
- **2006 to Present**: Editorial Board, Journal of Molecular Biology
- **2007 to Present**: Board of Reviewing Editors, Science
- **2007 to Present**: Scientific Advisory Board, GlycoFi (Merck & Company, Inc.)
- **2008 to Present**: Scientific Advisor, Merck Research Labs
- **2008 to Present**: Editorial Board, Cell
- **2009**: Program Committee Member, ASCB
- **2009 to Present**: Editorial Board, Current Opinion in Cell Biology
2009  Keynote address speaker at the annual retreat of the Genentech Research Organization
2009  Keynote lecture at the annual International Conference on Systems Biology
2009 to Present  Scientific Advisory Board, Proteostasis Therapeutics
2009  Member, NAKFI Steering Committee on Synthetic Biology
2010  Member, NIH College of CSR Reviewers

Honors and Awards

1987  Phi Beta Kappa, Harvard University
1988  Summa Cum Laude in Physics, Harvard University
1988  Karl Taylor Compton Pre-doctoral Fellowship
1988  National Science Foundation Pre-doctoral Fellowship
1996  David and Lucile Packard Fellowship
1997  Searle Scholars Program Fellowship
2000  Assistant Investigator, Howard Hughes Medical Institute
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

Selected Peer-reviewed Publications (In chronological order; 15 selected of 119 publications)


*corresponding author(s)

**Research Support**

No Project Number (Weissman) 10/01/2000-8/31/2017
Howard Hughes Medical Institute

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. We are also developing experimental and analytical approaches for exploring the organizational principles of biological systems.

Hughes Collaborative Investigator Award - No Project Number (Weissman) 09/18/2012 - 08/17/2017
Howard Hughes Medical Institute
A combined chemical and genetic approach to explore how chaperone and stress networks maintain the integrity of oncogene-addicted cancer cells
P01 AG70770-15 (Prusiner; Weissman Project 2) 04/01/11 - 3/31/16
NIH
Molecular Pathogenesis of Age-Dependent CNS Degeneration
Specific aims of this project are to 1) identify a novel prion domain in the yeast protein New1p; 2) identify novel prion phenomena; and 3) establish a genetic screen in yeast to study propagation of the mammalian prion protein (PrP).

U01 CA168370-01 (McManus) 05/01/12 – 04/30/17
NIH
Bay Area Cancer Target Discovery and Development Network
The overarching goal of the BACTDDN is to discover and characterize new cancer targets and their modulators, placing them into druggable pathways. Specific aims: 1) to develop EXPAND libraries targeting cancer-specific genetic alterations; 2) to identify novel drivers that show transforming potential in immortalized primary cells; and 3) to produce genetic EMAPs to uncover pathway relationships between candidate drivers.

P50 GM073210 (Stroud; Weissman - Key Personnel) 09/01/09 – 08/31/2014
NIH/NIGMS
Centers for Innovation in Membrane Protein Production for Structure Determination
The goals of the project are to develop approaches that will make the solution of simple membrane protein structures routinely achievable and to develop novel methods that can be applied to more complicated membrane proteins containing multiple subunits of the same (homo-oligomers) and different (hetero-oligomers) structure; and to produce and determine structures for complexes that are formed between membrane proteins and their soluble protein partners, small ligands and/or macromolecules.

U01 GM098254 (Agard/Walter) 09/2012 - 08/2017
NIH $85,100 direct (Weissman allocation)
Structural Basis of Protein Homeostasis
The goal is 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.

P50 GM102706-01 (Cate) 09/2012 - 08/2017
NIH
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.

R01 DA036858 (Lim/Qi/Weissman) 09/2013 - 05/2018
NIH/NIDA
Harnessing CRISPR for Targeted and Inducible Epigenomic Reprogramming
Specific aims: 1) development of optimized genome-wide library of dCas9-targeted epigenetic modifiers; 2) using CRISPR to recruit epigenetic modifiers in a temporally controlled manner; 3) using CRISPR epigenetic toolbox to probe temporal and spatial dynamics of chromatin silencing.

Project Number: Not Applicable (Weissman) 10/2013 – 09/2015
Onyx Pharmaceuticals
Identification of genetic vulnerabilities synergizing with the proteasome inhibitor carfilzomib in multiple myeloma cells. We seek to apply 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.
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>
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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

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 & American Association for the Advancement of Science
1979-present
1988-present Society for Developmental Biology
2001-present American Association for Cancer Research
2001-present American Society for Matrix Biology
2004-present International Society for Differentiation

Scientific Leadership

1990-1992 Member, Cell and Molecular Biology Panel, National Cancer Institute of Canada
1991-1995 Member, Board of Scientific Counselors, NIAMS
1992-1995 Council Member, American Society for Cell Biology
1993-1995 Council Delegate, Am. Assoc. for the Advancement of Science
1994-2001 Member, Scientific Advisory Board, Keystone Symposia
2001-2003 Council Member, American Society for Matrix Biology
2001 NIH Oncological SS Boundaries Team
2002 NIH Biochem SS, ad hoc
2003-2005 Council Member, International Society for Matrix Biology
2003-2006 Board of Directors, ACR
2005 President, American Society for Cell Biology
2007-2009 Nominating Committee, ACR
2007 Member, NIH ZRG1ICI–D01
2008 Reviewer, NIH Pioneer Awards
2008 Chair, NIH ZRG1 MOSS-A (02)
2008-2010 Chair, NIH ICI Study Section
2009-2012 Chair, American Academy of Arts and Sciences, Membership Selection Committee Class II, section
2010 Co-organizer, CNIO Cancer Symposium on Frontiers in Invasion and Metastasis, Madrid
2011-Present Member, Steering Committee, AACR Council of Scientific Advisors
2011-2016 Member, Scientific Advisory Board, Max Planck Institute for Biology of Ageing, Cologne, Germany

Honors

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

15 Selected Publications (>450 total full publications)


**Research Support**

Ongoing

NIH/NCI R01 CA057621-22 (Werb, PI) 09/30/13 - 08/31/18
Role of Metalloproteinases in Mammary Gland Remodeling
This competing renewal grant will determine functions of ECM-degrading proteinases and inhibitors in mammary epithelium during development and tumor progression.

NIH/NCI R01CA180039-02 (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?*

NIEHS/NCI 5U01 ES019458-04 (Werb, PI) 09/01/10 - 04/30/15
Environmental Effect on The Mammary Gland Across the Lifespan
The major goal of this multi-investigator program is to determine the susceptible times in breast development and how environmental stressors affect them.

NIEHS/NCI 5U01 ES019458-05 (Werb, PI) 09/01/10-04/30/15
Environmental Effect on The Mammary Gland Across The Lifespan
The major goal of this multi-investigator program is to determine the susceptible times in breast development and how they are affected by environmental stressors.

NIH/NCI R01 CA129523-05 (Werb, PI) 07/01/08 - 04/30/14 (No cost extension)
Transcriptional Regulation of Breast Cancer Metastasis
This study addresses how GATA-3 regulates the differentiated state of breast tumors.
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>6/1989</td>
<td>Letters</td>
</tr>
<tr>
<td>Columbia College of Physicians &amp; Surgeons, NY</td>
<td>M.D.</td>
<td>6/1993</td>
<td>Medicine</td>
</tr>
<tr>
<td>Massachusetts General Hospital</td>
<td>Resident</td>
<td>1993-1996</td>
<td>Internal Medicine</td>
</tr>
<tr>
<td>Harvard School of Public Health</td>
<td>M.P.H.</td>
<td>6/1998</td>
<td>Epidemiology</td>
</tr>
<tr>
<td>Brigham and Women’s Hospital</td>
<td>Fellow</td>
<td>1997-1998</td>
<td>Resp Epidemiology</td>
</tr>
<tr>
<td>University of California, San Francisco</td>
<td>Fellow</td>
<td>1998-2002</td>
<td>Pulmonary/Critical Care</td>
</tr>
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</table>

Positions and Honors

1993-1994  Intern in Internal Medicine; Massachusetts General Hospital, Boston, MA
1994-1996  Resident in Internal Medicine; Massachusetts General Hospital, Boston, MA
1996-1998  Research Fellow, Department of Emergency Medicine; Massachusetts General Hospital, Boston, MA
1997-1998  Clinical and Research Fellow, Channing Laboratory, Department of Medicine Brigham and Women’s Hospital, Boston, MA
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

Other Experience and Professional Memberships

2004-      Steering Committee, NIH NHLBI COPD Clinical Research Network
2009-      Steering Committee, NIH NHLBI Spiromics Network
Honors

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

Selected peer-reviewed publications (Selected from 81 peer-reviewed publications)


Research Support

Active

1U01HL126493-01 (contact PI: Woodruff, Co-PI: Erle) 8/01/14-04/30/2019
NIH/NHLBI 8/01/14-04/30/2019 NIH/Common Fund $449,517 direct/yr
Defining a Comprehensive Reference Profile of Circulating Human Extracellular RNA
The goal is to sequence the full spectrum of extracellular RNAs in 12 different body fluids including respiratory samples.

HHSN268200900014C (Woodruff PG)
NIH/NHLBI 2/1/2009 - 1/31/2016
The Spiromics Project: Clinical Center
The goal of this study is to identify sub-populations and intermediate outcome measures in COPD through a large multi-center longitudinal study.

U19 AI077439 (PI: Sheppard, core director, project Co-I: Woodruff)
NIH/NIAID 04/01/13-03/31/18
IL-13 and IL-17 Dynamics in the Asthmatic Airway
The goal of this study is to study the sources and respective roles of IL-13 and IL-17 in AHR and airway epithelial abnormalities in asthma.

R01 HL114447 (PI: Martinez, subcontract PI: Woodruff)
NIH/NHLBI 4/1/2012 - 3/31/2016
Pulmonary Bacterial Microbiome-Epithelial Cell Interactions in COPD
The goal of this study is to establish the lung microbiome in COPD and to identify epithelial mucin responses associated with selected pathogens.
Innate and Adaptive Immune Responses in Th2 High Asthma
The goal of this study is to identify the roles of iH2 cells, IL-33, and miRNAs in local immune responses in the lung in asthma.

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

Ancillary T-Cell Based Studies in SPIROMICS
The major goals are to determine whether T-cell autoreactivity in COPD is associated with emphysema in cross-sectional and longitudinal human studies (using the Spiromics cohort).

Genomic Phenotyping and Mechanisms in sarcoidosis and AAT
To perform genomic and microbiomic human studies to define disease heterogeneity in sarcoidosis and AAT

Inner City Asthma Consortium (ICAC): Immunologic Approaches to Reduce Asthma’’
To identify immunological approaches to reduction in asthma prevalence and severity in inner city populations.

Targeting the avB8 integrin for treatment of severe asthmatics with persistent granulocytic inflammation
To develop and optimize antibodies targeting avB8 integrin with the goal of blocking Th17 inflammation and treating severe asthma.