



Inflammation Resolution Biology Workshop

Monday, March 25, 2019

1:00 – 5:00 p.m.

Tuesday, March 26, 2019

8:30 a.m. – 4:30 p.m.

**NIEHS Building 101, Rodbell Auditorium
Research Triangle Park, N.C.**

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Agenda



Inflammation Resolution Biology Trans-NIH Workshop

March 25-26, 2019

AGENDA

Monday, March 25, 2019

1:00 p.m. Opening Remarks

Linda Birnbaum, Ph.D., D.A.B.T, A.T.S., Director, National Institute of Environmental Health Sciences and National Toxicology Program

1:10 p.m. Genesis of the Workshop

Sri Nadadur, Ph.D., National Institute of Environmental Health Sciences

Session 1: Introductory Session

Moderator: Houmam Araj, Ph.D., National Eye Institute

1:20 p.m. Turning on and off the Inflammatory Response in Polymicrobial Sepsis

Peter Ward, M.D., University of Michigan

2:00 p.m. Novel Mediators and Mechanisms in the Resolution of Inflammation

Charles Serhan, Ph.D., D.Sc., Brigham and Women's Hospital, Harvard University

2:40 p.m. Break

Moderators: Christina Liu, Ph.D., and Pushpa Tandon, Ph.D., National Cancer Institute

3:00 p.m. Resolution of Endoplasmic Reticulum Stress and Inflammation by Lipid Mediators

Bruce Hammock, Ph.D., University of California, Davis

3:40 p.m. Breast Cancer-Induced Inflammation and its Impact on Tumor Progression and Therapeutics

Xiang Zhang, Ph.D., Baylor College of Medicine

4:20 p.m. Intervention Strategies to Promote Inflammation Resolution

Thomas Van Dyke, D.D.S., Ph.D., Forsyth Institute

5:00 p.m. Adjourn for the Day



Inflammation Resolution Biology Workshop

Tuesday, March 26, 2019

8:30 a.m. Opening Remarks
Gwen Collman, Ph.D., National Institute of Environmental Health Sciences

Session 2: Perturbations and Promotion of Inflammation Resolution in Health and Disease

Moderator: Michael Fessler, M.D., National Institute of Environmental Health Sciences

8:40 a.m. Translational Mechanisms for Inflammation and Defective Resolution in Severe Asthma
Bruce Levy, M.D., Brigham and Women's Hospital, Harvard University

9:10 a.m. Inflammation and Resolution in Chronic Obstructive Lung Disease
Patricia Sime, M.D., University of Rochester Medical Center

9:40 a.m. Resolution of Vascular Injury: Role of Specialized Lipid Mediators
Michael Conte, M.D., University of California, San Francisco Medical Center

10:10 a.m. Break

Moderator: Giovanna Zappala, Ph.D., M.P.H., National Institute on Aging

10:30 a.m. The Peripheral Immune Responses to Brain and Intestinal Immunogens Amplify Stroke Severity
Katrin Andreasson, M.D., Ph.D., Stanford University

11:00 a.m. Inflammaging
Luigi Ferrucci, M.D., Ph.D., National Institute on Aging

11:30 a.m. The Lens: How an Immune Response to Injury and Dysgenesis Occurs in an Avascular Region of the Eye
Sue Menko, Ph.D., Jefferson Medical College

Noon Lunch

Session 3: Exposure-Induced Inflammation in Disease Exacerbation

Moderator: Mike Humble, Ph.D., National Institute of Environmental Health Sciences

1:00 p.m. Accelerating Inflammation Resolution to Counteract Cutaneous and Pulmonary Injury
Sven Jordt, Ph.D., Duke University



Inflammation Resolution Biology Workshop

1:30 p.m. **Irgm1 Links Mitochondrial Quality Control to Autoimmunity**
Michael Fessler, M.D., National Institute of Environmental Health Sciences

2:00 p.m. **Targeting Resolution of Exposure-Induced Lung Inflammation**
Jill Poole, M.D., University of Nebraska, Internal Medicine

2:30 p.m. **Break**

2:50 p.m. **Panel Discussion**

Moderator: Sri Nadadur, Ph.D., National Institute of Environmental Health Sciences

Panelists:

Luigi Ferrucci, M.D., Ph.D., National Institute on Aging

Bruce Hammock, Ph.D., University of California, Davis

Bruce Levy, M.D., Brigham and Women's Hospital, Harvard University

Sue Menko, Ph.D., Jefferson Medical College

Charles Serhan, Ph.D., D.Sc., Brigham and Women's Hospital, Harvard University

Patricia Sime, M.D., University of Rochester Medical Center

Peter Ward, M.D., University of Michigan

4:10 p.m. **Concluding Remarks**
David Balshaw, Ph.D., National Institute of Environmental Health Sciences

4:30 p.m. **Adjourn**

Presentation

Abstracts

Turning on and off the Inflammatory Response in Polymicrobial Sepsis

Peter Ward

University of Michigan

In mice, polymicrobial sepsis triggers a series of proinflammatory responses which often inflict damage on a variety of organs (heart, liver, lungs, kidneys, brain). To determine how these outcomes of sepsis can be attenuated in order to improve survival and protect organs from dysfunction, we have used the polymicrobial model of infectious sepsis in mice. Factors that trigger cell- and organ-damaging outcomes include proinflammatory products of the innate immune system (oxidants, cytokines, chemokines, etc.). The complement system functions as a “driver” of these events which involve the complement anaphylatoxin, C5a, and its receptors (C5aR1 and C5aR2). In addition, the terminal complement activation product, C5b-9 (membrane attack complex), also plays an important role in adverse outcomes of sepsis. Regarding mechanisms, C5a activates phagocytes to form extracellular traps (NETs) in the case of neutrophils. Macrophages also generate extracellular traps (METs). In both cases, extracellular histones are released and are very cell and organ damaging. Generation of C5b-9, the terminal complement pathway product, activates the NLRP3 inflammasome, which releases IL-1 β and IL-18 that are powerful proinflammatory factors. To date, the use of antibodies that neutralize C5a or the use of new small molecule inhibitors of C5aRs markedly attenuate the cell- and organ-damaging effects of C5a. Blockade of C5b-9 can be accomplished with an antibody that reacts with an activation epitope on C9, suppressing buildup of C5b-9. Other strategies to “put the brakes on” proinflammatory products of sepsis include a water-soluble inhibitor of p38 mitogen-activated protein kinase or neutralizing antibodies to histones. The complement system and histones likely play important roles in a variety of other conditions in humans (e.g. ischemia reperfusion injury, trauma and hemorrhagic shock, autoimmune diseases, etc.).

Novel Mediators and Mechanisms in the Resolution of Inflammation

Charles Serhan

Brigham and Women’s Hospital, Harvard University

In recent years, uncontrolled inflammation has entered center stage as an integral component of many widely occurring diseases including arthritis, periodontal disease, metabolic syndrome, asthma, cardiovascular diseases, and neurodegenerative diseases, as well as many others. Using a systems approach with self-limited inflammatory infectious exudates to map tissue events, cell traffic, and identification of protein and chemical mediators, we identified three structurally distinct families of potent essential fatty acid-derived (EPA, DPA, DHA) novel endogenous mediators, named **resolvins**, **protectins**, and **maresins**. The mediators are collectively coined specialized pro-resolving mediators (SPM) together with their newly discovered bioactive peptide-conjugates involved in tissues regeneration (cys-SPM). Complete structural elucidation and total organic synthesis of each of the new molecules and pathway intermediates demonstrated their functions *in vivo* in the resolution of inflammation in experimental animals. Each member of this new super-family is structurally distinct and is a

local acting pro-resolving mediator that controls the duration and magnitude of acute inflammatory responses with actions in pico-nanogram range in animal disease models. Mapping of these resolution circuits provides new avenues to probe the molecular basis of many widely occurring diseases. This presentation focuses on our recent advances in the biosynthesis and functions of SPM and activation of resolution programs. We operationalized LC-MS-MS-based targeted metabololipidomics to identify and profile SPM, cross validating this system with other laboratories using coded samples from human challenges establishing *in vivo* SPM biosynthesis in humans and function in stimulating resolution. These results indicate that resolution pathways and programs in healthy subjects may underlie prevalent diseases associated with uncontrolled inflammation and open the potential for ***resolution-based physiology and pharmacology***.

Resolution of Endoplasmic Reticulum Stress and Inflammation by Lipid Mediators

Bruce Hammock

University of California, Davis

Inflammation is critical for organisms to distinguish self and nonself whether it is protection from pathogens or aberrant tissue leading to cancer. Although essential to life, inflammation not only is energetically expensive, but it presents serious risk to the host in the short term with sepsis and multi-organ failure as examples. Extended inflammation underlies a variety of chronic diseases including diabetes, dementia, arthritis, and others. Thus, both initiation and resolution of inflammation are critical processes which must be tightly regulated for health. Both the initiation and resolution of inflammation can be disrupted by environmental chemicals. In screening for or treating such disruptions in the inflammatory process, we must understand how living systems regulate inflammation.

Lipid mediators are among many chemicals regulating both initiation and resolution of inflammation. Many of these mediators are in the arachidonate cascade including pro-inflammatory mediators such as prostaglandins and thromboxanes, produced by the cyclooxygenase branch, and leukotrienes, produced by the lipogenase branch of the cascade. By weight, over 70 percent of the world's drugs act to block these two pathways both of which stimulate inflammation. Such drugs include aspirin, ketorolac, ibuprofen, celecoxib, and naproxen on the cyclogenase pathway and Singulair in the lipoxygenase pathway.

Most research has been on the largely proinflammatory branch of the arachidonate cascade. More recently a largely anti-inflammatory, anti-hypertensive, and analgesic branch of the cascade has been found where the mediators are epoxides of polyunsaturated fatty acids (EpFA). They are made by both selective and nonselective cytochrome P450 oxidases. The resulting largely anti-inflammatory EpFA are degraded by several pathways but largely by epoxide hydration by the soluble epoxide hydrolase (sEH). This anti-inflammatory pathway can be enhanced by inducing key P450s, using biologically stable mimics of EpFA, or inhibiting epoxide hydration to diols that fail to resolve resolution and may increase inflammation. The inhibitors of the sEH reduce the severity of a variety of diseases. The broad activity of sEH

inhibitors is explained in part by EpFA stabilizing mitochondria to compounds like dinitrophenol, triclosan, and nonsteroidal anti-inflammatory drugs, thus reducing ROS. The EpFA also reduce activation of the endoplasmic reticulum stress response leading to inflammation, autophagy, and apoptotic rather than cell preservation responses. Thus, the sEH inhibitors lead to increased titers of omega 3 and 6 fatty acid epoxides resulting in resolution of inflammation and a reduction in blood pressure and pain. sEH inhibitors are being moved to the clinic to treat chronic pain conditions in man, but they also address a variety of disorders including arthritis and fibrosis in the periphery and neuroinflammation in the central nervous system, possibly influencing Alzheimer's and Parkinson's disease as well as depression, autism, and schizophrenia.

Breast Cancer-induced Inflammation and its Impact on Tumor Progression and Therapeutics

Xiang Zhang

Baylor College of Medicine

Solid tumors can recruit a variety of immune cells and evolve diverse microenvironments. Intertumoral variation of the microenvironment may determine tumor progression and therapeutic responses. However, how this variation arises remains poorly understood. In a group of murine models and multiple human breast cancer datasets, we identified large variation of overall immune cell infiltration, as well as a dichotomous distribution of neutrophil-to-macrophage ratio among the inflamed "hot" tumors, which together define three "myeloid subtypes" of triple negative breast cancer (TNBC), designed as "cold", neutrophil-enriched subtype (NES) and macrophage-enriched subtype (MES), respectively. Mechanistic and comparative studies revealed that the infiltration of immune cells is facilitated by a vessel normalization process, which involves pericyte coverage of endothelium. Furthermore, the infiltrated immune cells not only exhibit variable frequencies of macrophages vs neutrophils, but also distinct functionality, cell-of-origin, and mode of intercellular interactions of these cells, which ultimately contribute to therapeutic responses. Together, these data indicate that the same tumor type may evolve highly diverse immune microenvironments that may involve different biology of inflammation and resolution, which cry for more comprehensive experimental modeling and clinical assessment of the tumor microenvironment.

Intervention Strategies to Promote Inflammation Resolution

Thomas Van Dyke

Forsyth Institute

Periodontitis is an infectious/inflammatory disease associated with dysbiosis of the commensal oral microbiome. Periodontal diseases are the most common inflammatory diseases in humans. Gingivitis is ubiquitous affecting more than 90 percent of people, but periodontitis with irreversible tissue destruction affects more than 47 percent of the U.S. population. Importantly, recent studies demonstrate a relationship between oral infectious and inflammatory conditions, in particular, periodontal disease and risk for the development of cardiovascular

disease and stroke. As our understanding of pathways of inflammation has matured, a better understanding of the molecular basis of *resolution of inflammation*, which is distinct from pharmacologic *anti-inflammation*, has emerged. Resolution of inflammation is an active, receptor agonist-mediated well-orchestrated return of tissue homeostasis, not inhibition of proinflammatory pathways. The isolation and characterization of endogenous lipid mediators of resolution, including analogues under development for human use, has opened new doorways for the management of periodontitis and systemic inflammatory diseases. Preclinical studies have demonstrated that specialized pro-resolving mediators (SPMs) are potent when topically applied in the prevention and treatment of periodontitis. A Phase 1 clinical trial in humans reveals these compounds are safe. Characterization of the molecular basis for regulation of inflammation has changed our understanding of the relationship between infection and inflammation in the oral cavity. Moreover, the inflammatory mechanistic link between systemic conditions, including cardiovascular disease, is revealed to be modifiable with SPMs. This presentation will describe intervention strategies for promoting therapeutic resolution of inflammation in the context of periodontal disease and the role of inflammation and its control in the link between periodontal inflammation and inflammatory cardiovascular disease.

Translational Mechanisms for Inflammation and Defective Resolution in Severe Asthma

Bruce Levy

Brigham and Women's Hospital, Harvard University

Acute lung inflammation is fundamentally important to host defense, but chronic or excessive inflammation can lead to several important diseases, including severe asthma. The resolution of inflammation is an active process that is directed, in part, by specialized pro-resolving mediators that are enzymatically derived from polyunsaturated fatty acids. In health, cell-cell interactions at the onset of acute inflammation establish biosynthetic circuits for these pro-resolving mediators, including the arachidonic acid-derived lipoxins and the omega-3 fatty acid-derived resolvins, protectins, and maresins, which serve as agonists to orchestrate a return of the inflamed tissue to homeostasis. Understanding the cellular and molecular mechanisms for pro-resolving mediators in catabasis is providing new insights into lung tissue responses for resolution of inflammation in health and the pathophysiology of disease, as well as opportunities for therapeutic intervention. E-series and D-series resolvins are enzymatically derived from the essential omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid (DHA), respectively. Protectin D1 and maresin 1 (MaR1) are also derived from DHA. Relevant to lung inflammation, specialized pro-resolving mediators are generated in lung. The ALX/FPR2 receptors for lipoxin A4 (LXA4) and resolvin D1 (RvD1) and the CMKLR1 receptor for resolvin E1 (RvE1) are expressed in the lung and are dynamically regulated with lung inflammation. Evidence will be presented for cellular and molecular mechanisms for representative specialized pro-resolving mediators in their protective actions in the regulation of lung responses and the relationship between specialized pro-resolving mediators and innate immune responses in severe asthma.

Inflammation and Resolution in Chronic Obstructive Lung Disease

Patricia Sime

University of Rochester Medical Center

Inflammation is a protective response to injurious stimuli, but when left unchecked, chronic inflammation can lead to tissue damage and disease. It is now known that resolution of inflammation is an active process mediated by a recently discovered family of specialized pro-resolving lipid mediators (SPMs). Tobacco smoking is a leading preventable cause of respiratory diseases including lung cancer and COPD. It is a profound pro-inflammatory stimulus. Importantly, chronic inflammation persists long after smoking cessation in both humans and animal models, suggesting that tobacco smoke impairs the normal mechanisms of resolution. Data will be presented identifying that smoke inhalation dysregulates resolution mechanisms in animal models and human disease (stable COPD and during COPD exacerbations), and how SPMs can be used therapeutically. Specifically, pro-resolving lipid mediators have anti-inflammatory and pro-resolving effects in primary human cells including structural cells and macrophages when stimulated by cigarette smoke exposure. Resolvin D1 (RvD1) potently inhibits lung inflammation in an acute mouse model of cigarette smoke exposure, accelerates resolution, and inhibits development of emphysema when given concurrently with cigarette smoke over 16 weeks. RvD1 also dampens lung inflammation and enhances clearance of nontypeable *Haemophilus influenzae*, a Gram-negative pathogen that frequently causes exacerbations of COPD.

In summary, our data demonstrate that pro-resolving lipid mediators are dysregulated in patients with COPD and are effective in therapeutically promoting a pro-resolving phenotype in human lung cells and animal models of smoke-induced lung disease. Translational potential is high.

Resolution of Vascular Injury: Role of Specialized Lipid Mediators

Michael Conte

University of California, San Francisco

Unresolved inflammation is central to the pathophysiology of commonly occurring vascular diseases such as atherosclerosis, aneurysm, and deep vein thrombosis—conditions that are responsible for considerable morbidity and mortality. Surgical or catheter-based procedures performed to treat these conditions induce acute on chronic inflammatory responses. The resolution of vascular inflammation is an important driver of tissue remodeling and functional recovery in these clinical settings. Specialized pro-resolving lipid mediators (SPM) derived from omega-3 polyunsaturated fatty acids orchestrate key cellular processes driving resolution and return to homeostasis. Recent studies have demonstrated that SPM are locally synthesized in vascular tissues, have direct effects on vascular cells and their interactions with leukocytes, and play a protective role in the acute injury response. Early translational work has established the potential for SPM as vascular therapeutics, and as candidate biomarkers in vascular disease. Further investigations are needed to understand the molecular and cellular mechanisms of

resolution in the vasculature, improve tools for clinical measurement, and to better define the potential for pro-resolving therapeutics in vascular patients.

**The Peripheral Immune Responses to Brain and Intestinal Immunogens
Amplify Stroke Severity
Katrin Andreasson
Stanford University**

Stroke is a multiphasic process in which initial cerebral ischemia is followed by secondary progression of injury from immune responses to ischemic brain components. We have demonstrated that peripheral CD11b⁺CD45⁺ myeloid cells magnify stroke injury via activation of Triggering Receptor on Myeloid Cells 1 (TREM1), an amplifier of pro-inflammatory innate immune responses. TREM1 was induced within hours after stroke peripherally in myeloid cells trafficking to ischemic brain. TREM1 inhibition genetically or pharmacologically improved outcomes via protective antioxidant and anti-inflammatory mechanisms. Positron electron tomography (PET) imaging revealed elevated TREM1 levels in the spleen and unexpectedly in the intestine. In the intestinal lamina propria, noradrenergic-dependent increases in gut permeability induced TREM1 on inflammatory Ly6C⁺MHCII⁺ macrophages, further enhancing permeability and lipopolysaccharide translocation across the gut barrier. We conclude that peripheral TREM1 induction after cerebral ischemia amplifies pro-inflammatory responses to both brain-derived and intestinal-derived immunogenic components. Critically, selectively targeting this potent innate immune pathway reduces cerebral injury.

**Inflammaging
Luigi Ferrucci
National Institute on Aging**

The aging process is characterized by a progressive pro-inflammatory state, witnessed by high circulating levels of pro-inflammatory cytokines and other inflammatory mediators. This pro-inflammatory signature is even detectable in older persons who are extremely healthy but is overt and rapidly developing in those affected by multiple chronic diseases. Although IL-6 and CRP and by far the most studied biomarkers of inflammation, discovery proteomic studies have found that many inflammatory mediators increase with aging in plasma as well as in other tissues. It is well established that inflammation is associated with several adverse health outcomes, including disability and premature death. The underlying mechanisms that drive inflammaging and the nature of the causal pathway from inflammaging to pathology are still not understood. Epidemiological studies have found that obesity, and especially central obesity, is a strong risk factor for the development of inflammaging. In stressful conditions, adipocytes behave as immune cells and produce pro-inflammatory mediators. In addition, fat that is accumulated in “visceral” compartments, such as abdomen, liver, and pericardium tends to be infiltrated by macrophages contributing to inflammation. Adipose tissue accumulates senescent cells that produce a wide variety of inflammation. Animal models have shown that the

elimination of senescent cells is associated with reduced inflammation, but whether this is true in humans is unknown. There is some evidence that a mechanism that contributes to inflammaging with aging is defective mitophagy, with persistence of unrecycled mitochondrial fragments that activate the NLRP3 inflammasome. Addressing these hypotheses in humans may reveal a new approach to modulate inflammation in older persons and reduce the deleterious consequences of this condition.

The lens: How an Immune Response to Injury and Dysgenesis Occurs in an Avascular Region of the Eye

Sue Menko

Jefferson Medical College

Immune privilege of the eye results from the need to keep vasculature from the central light path where it would impair vision. Therefore, organs and tissues of the eye like the cornea have developed alternative mechanisms of immune surveillance to protect them and to provide a response to tissue injury or pathogenesis. The cornea, which can tolerate foreign antigens, is surveilled by immune cells from its peripheral regions, as well as from the aqueous humor and the tears. The lens has remained an enigma in terms of immune surveillance and protection. We have discovered that, like other tissues, the lens has developed mechanisms of immune surveillance to protect it throughout a lifetime, to respond to stresses and injury, and to maintain its transparency. Since dysregulation of immune surveillance is tightly linked to development of fibrosis, it is possible that the immune cells that associate with the lens are an unexplored cause of cataract and posterior capsule opacification (PCO). We identified that resident immune cells populate the lens during development and provide evidence that they travel to the lens along the ciliary zonules that link the lens to the vascular-rich ciliary body and suspend the lens in the center of the eye. These resident immune cells are activated upon mock cataract surgery, rapidly populate the wound edge, and have essential functions in regenerative repair of the wound area. As leader cells, this immune cell population is susceptible to being induced to acquire a myofibroblast phenotype, the cell type that underlies fibrotic PCO. It was assumed that there were no active sources of immune cells that could surveil and protect the adult lens during homeostasis or in response to stress, injury, or pathogenesis. However, we discovered that lens dysgenesis results in the recruitment of immune cells to the lens, and that immune surveillance is activated in other regions of the eye including the cornea and retina. Similarly, we found that immune surveillance of the lens is induced in response to wounding of the cornea. This protective mechanism involves the migration of immune cells that travel to the lens along the ciliary zonules and then extend on ciliary fibrils along the surface of the lens. This process occurs in the absence of any lens or ciliary zonule-associated vasculature.

Accelerating Inflammation Resolution to Counteract Chemical Cutaneous and Pulmonary Injury

Sven Jordt

Duke University

Inflammation is broadly classified into three temporal phases, such as initiation, amplification and maintenance, and resolution. Resolution of inflammation was thought to be a passive process but recent studies show that resolution is an active process and is mediated by fatty acid-derived mediators (specialized pro-resolving mediators). Chemical exposure to vesicants (sulfur mustard), electrophilic riot control agents (CS tear gas agent), chlorine, and hydrochloric acid cause strong inflammation. Classical anti-inflammatory treatments have focused on interference with target initiation and maintenance of inflammation, with mixed outcomes. Active research on the resolution of inflammation became a widespread interest. We hypothesize that accelerating resolution of inflammation will attenuate the exaggerated inflammatory response following chemical threat exposure, leading to decreased morbidity and improved recovery. In these studies, specialized pro-resolving mediators (SPMs), such as resolvin D1 and resolvin D2, or protectin DX was administered to mice at a dose rate of 2 or 5 $\mu\text{g}/\text{kg}$ body weight i.p post-exposure to cutaneous (2-chloroethyl ethyl sulfide and CS tear gas agent) and pulmonary (chlorine and hydrochloric acid) chemical threat agents. SPMs decreased edema, pro-inflammatory cytokines, and vascular leakage while improving histopathology in cutaneous injury models; bronchoalveolar lavage fluid and serum pro-inflammatory cytokines and pulmonary resistance were decreased with SPM administration in pulmonary injury models. These results support our hypothesis and pave the way for conducting more definitive studies in larger sample size and in higher mammalian species to develop SPMs as potential medical countermeasures under the U.S. Food and Drug Administration Animal Rule.

Irgm1 Links Mitochondrial Quality Control to Autoimmunity

Michael Fessler

National Institute of Environmental Health Sciences

Irgm1 is a GTPase that supports autophagy. Recently, we reported that Irgm1-deficient mice have a spontaneous autoimmune exocrinopathy accompanied by induction of interferon (IFN)-stimulated genes. We hypothesized that IFN induction in Irgm1-deficient cells is driven by cyclic guanosine monophosphate–adenosine monophosphate synthase (cGAS)-dependent sensing of cytosolic mitochondrial (mt)DNA that has failed to be cleared by mitophagy. Here, we show that Irgm1^{-/-} murine embryonic fibroblasts (MEFs) exhibit induction of type I IFN, and that this is associated with decreased mitochondrial membrane potential and increased cytoplasmic mtDNA. Consistent with defective mitophagy as the cause, Irgm1^{-/-} MEFs show no increase in mitochondrial flux to autolysosomes, whereas chemical depletion of cellular mtDNA or chemically-enforced mitophagy both normalize IFN expression. Further, silencing of cGAS, the adaptor stimulator of IFN genes (STING), TANK-binding kinase 1 (TBK1), or IFN-regulatory factor 3 (IRF3) also reduces the IFN response, together suggesting that a mtDNA-cGAS-STING-IRF3 axis to IFN is operative in MEFs. By contrast, we find in Irgm1^{-/-} macrophages that upregulation of

type I IFN is TLR9-dependent and associated with increased localization of mitochondria to autolysosomes, suggesting a defect in terminal mitophagic degradation in this cell type. In vivo, genetic deletion of the type I IFN receptor rescues the in vivo autoimmune tissue pathology of Irgm1^{-/-} animals, whereas STING deletion partially reverses IFN induction and pathology in tissues, suggesting that innate immune receptor(s) in addition to STING induce IFN-driven disease. We provide evidence that one mechanism by which excess type I IFN may drive non-resolving autoinflammation in Irgm1^{-/-} animals is through impairing differentiation of monocytes into efferocytosis-competent tissue macrophages. Taken together, our findings suggest that Irgm1-mediated mitochondrial maintenance plays a critical role in health by repressing inappropriate mtDNA-dependent induction of autoinflammatory IFN.

Intervention Targeting Promotion of Inflammation Resolution

Jill Poole

University of Nebraska

Chronic inhalation of inflammatory environmental bioaerosols causes significant airway inflammatory diseases including asthma, chronic bronchitis, and chronic obstructive pulmonary disease (COPD). No treatments currently exist to significantly reverse exposure-induced respiratory impairment. We know that airway inflammatory consequences following exposures to microbial-enriched organic dust extracts is complex and dependent upon microbial components and proteases with corresponding signaling through Toll-like receptor/Myeloid differentiation primary response 88 (MYD88) and protease-activated receptor pathways. However, there remains a *gap of knowledge* in understanding the mechanisms governing the transition from airway inflammatory disease to repair and recovery. We made several novel discoveries implicating the epidermal growth factor receptor agonist amphiregulin (AREG) as key in promoting lung repair pathways. Employing our three-dimensional human lung scaffold model, we found that epithelial recellularization is reduced with organic dust exposure and can be rescued with AREG treatment. Preliminary studies support that inhibition of AREG impairs the lung repair process in an established model of organic dust-induced inflammatory disease. Experimental studies also demonstrate that epithelial cells, macrophages, and type 2 innate lymphoid cells produce AREG in the context of dust exposure. Finally, AREG can be enhanced with omega-3 fatty acid supplementation resulting in protection against dust-induced lung inflammation. Future work to delineate the functional and mechanistic contribution of AREG with lung repair pathways and to determine whether dietary manipulations to impact AREG lead to beneficial responses following exposure to complex environmental inflammatory insults is necessary. These studies could provide new insights into lung repair regulation as it relates to microbial-enriched, environmental exposures, and ultimately lead to developing new treatment strategies to reduce lung disease burden.

Biographies

Katrin Andreasson
Stanford University

Katrin Andreasson, M.D., Ph.D., is physician-scientist studying mechanisms of immune-mediated neurodegeneration in the Department of Neurology and Neurological Sciences at the Stanford University School of Medicine. She received her medical degree from Columbia University College of Physicians & Surgeons and completed her residency in neurology at Johns Hopkins Hospital. After this, she carried out postdoctoral studies with Paul Worley in the Department of Neuroscience at the Johns Hopkins School of Medicine and identified novel activity-regulated genes in the hippocampus, or neuronal immediate-early genes. Currently, her laboratory is focused on understanding immune mechanisms of brain injury and validating immune pathways as potential therapeutic targets. Initial work in the lab focused on cyclooxygenase-2 (COX-2) and the effects of downstream inflammatory prostaglandin pathways in models of cerebral ischemia and Alzheimer's disease. Approaches included pharmacologic as well as genetic conditional knockout strategies, with identification of immune effector pathways currently under investigation as disease modifying targets. More recent systems approaches targeting brain-immune interactions have identified novel metabolic pathways in immune cells that modify brain injury in models of stroke and Alzheimer's disease.

David Balshaw
National Institute of Environmental Health Sciences

David Balshaw, Ph.D., Chief of the Exposure, Response, and Technology Branch at the National Institute of Environmental Health Sciences (NIEHS). Balshaw oversees a team focused on building research capacity in the environmental health sciences through planning and administration of NIEHS-funded research programs in bioengineering, integrated systems, and computational methods to understand complex systems; development of sensor technologies for environmental exposure assessment; discovery and validation of emerging biomarkers; and application of innovative "omics" research for reducing the risk of exposure and disease including development of databases.

His primary focus is on the development of emerging technologies with particular emphasis on enabling innovative approaches to improving exposure and risk assessment. To this end, Balshaw has been a leading figure in the development of the Exposure Science and the Exposome Program to develop a new generation of tools to characterize the personal environment integrating direct, personal assessment of multiple chemical factors, dietary intake, physical activity and psychosocial stress as well as assessment of the biological response to these factors on major biological pathways.

Balshaw received training in pharmacology and biophysics from the University of Cincinnati and University of North Carolina at Chapel Hill. His interdisciplinary training has enabled him to effectively bridge between disparate communities including engineering, mechanistic toxicology, and both clinical and public health application. These successes have led to

recognition of his leadership as an expert translational scientist at the NIH and leadership roles in the NIH Common Fund, the NIH Genes, Environment, and Health Initiative Exposure Biology Program, and the NIEHS Children's Health Exposure Analysis Resource (CHEAR)

Linda Birnbaum

National Institute of Environmental Health Sciences

Linda Birnbaum, Ph.D., D.A.B.T., A.T.S., is director of the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP) within the National Institutes of Health (NIH). A board-certified toxicologist, Birnbaum has served as a federal scientist for over 37 years. She has received many awards and recognitions, including the North Carolina Award in Science, the Women in Toxicology Elsevier Mentoring Award, the Society of Toxicology Public Communications Award, the U.S. Environmental Protection Agency (EPA) Health Science Achievement Award and Diversity Leadership Award, the National Center for Women's 2012 Health Policy Hero Award, the Breast Cancer Fund Heroes Award, and 14 Science and Technology Achievement Awards, which reflect the recommendations of EPA's external Science Advisory Board, for specific publications. Birnbaum was also elected to the Institute of Medicine of the National Academies and received an honorary degree from Ben-Gurion University in Israel.

Birnbaum is a former president of the Society of Toxicology, the largest professional organization of toxicologists in the world; former chair of the Division of Toxicology at the American Society of Pharmacology and Therapeutics; and former vice president of the American Aging Association. She is the author of more than 800 peer-reviewed publications, book chapters, and reports. She is also an adjunct professor at several universities, including the University of North Carolina at Chapel Hill and Duke University.

A native of New Jersey, Birnbaum received her master's and doctoral degrees in microbiology from the University of Illinois at Urbana-Champaign.

Gwen Collman

National Institute of Environmental Health Sciences

Gwen Collman, Ph.D., is director of the NIEHS Division of Extramural Research and Training where she leads approximately 60 professional staff in areas of scientific program administration, peer review, and the management and administration of about 1,500 active grants each year. She directs scientific activities across the field of environmental health sciences, including basic sciences (i.e., DNA repair, epigenetics, environmental genomics), organ-specific toxicology (i.e., reproductive, neurotoxicology, respiratory), public health-related programs (i.e., environmental epidemiology, environmental public health), and training and career development. She also oversees the implementation of the Superfund Research Program and the Worker Training Program.

Prior to her current role, Collman served in program development and management, beginning in 1992 as a member, then as chief of the Susceptibility and Population Health Branch. During this time, she directed research on the role of genetic and environmental factors on the development of human disease, from animal models of genetic susceptibility to population studies focusing on etiology and intervention. She was responsible for building the NIEHS grant portfolio in environmental and molecular epidemiology and developed several complex multidisciplinary research programs. These include the NIEHS Breast Cancer and the Environment Research Centers Program, the NIEHS/EPA Centers for Children's Environmental Health and Disease Prevention, and the Genes, Environment, and Health Initiative. Also, under her guidance, a team created a vision for the Partnerships for Environmental Public Health program for the next decade.

Michael Conte

University of California, San Francisco

Michael Conte, M.D., received his medical degree from Albert Einstein College of Medicine. He completed surgical residency at New York Hospital-Cornell Medical Center, and a research fellowship at Brigham and Women's Hospital (BWH) and Massachusetts Institute of Technology in Boston. He completed vascular surgery fellowship training at BWH and Harvard Medical School. Conte was an assistant professor of surgery at Yale University from 1994-1997, then returned to BWH as assistant professor (1997-2001) and associate professor (2001-2008) of vascular surgery.

In 2008, Conte assumed the role of Chief of Vascular and Endovascular Surgery at the University of California, San Francisco (UCSF) Medical Center. He is professor of surgery at UCSF and holds the E.J Wylie Chair in Vascular Surgery. He also serves as co-director of the UCSF Heart and Vascular Center, director of the Noninvasive Vascular Laboratory, and co-director of the UCSF Center for Limb Preservation.

Conte's clinical interests include diseases of the aorta, carotid artery disease, and peripheral artery disease (PAD). He is particularly interested in diabetic vascular disease, and in complex revascularization for limb preservation in patients with critical ischemia. He led the largest multicenter clinical trial to date in vein bypass surgery for severe PAD and is nationally and internationally recognized for his leadership in this arena.

As a career surgeon-scientist, Conte's translational research is focused on understanding the biology of vascular injury and improving the healing response of blood vessels following angioplasty and bypass surgery. His work has been continuously funded by the NIH, and he has served as a charter member on the Bioengineering, Technology, and Surgical Sciences NIH study section. He has authored more than 200 publications spanning from basic to clinical science.

Conte is a member of many professional organizations and has served on editorial boards including *Circulation* and the *Journal of Vascular Surgery*. He is a past chair of the American Heart Association Council on Peripheral Vascular Disease. He also serves as Chief Medical Officer of the non-profit foundation Vascular Cures.

Luigi Ferrucci

National Institute on Aging

Luigi Ferrucci, M.D., Ph.D., is a geriatrician and an epidemiologist who conducts research on the biological and phenotypical pathways leading to progressive physical and cognitive decline in older persons. He has made major contributions in the design of many epidemiological studies conducted in the U.S. and Europe, including the European Longitudinal Study on Aging, the AKEA study of Centenarians in Sardinia, the Women's Health and Aging Study and more recently the Genetic and Epigenetic Signatures of Translational Aging Laboratory Testing (GESTALT) study. He was also the principal investigator of the InCHIANTI study, a longitudinal study conducted in the Chianti geographical area (Tuscany, Italy) looking at risk factors for mobility disability in older persons. Ferrucci received his medical degree and board certification in 1980, board certification in geriatrics in 1982, and doctorate in the biology and pathophysiology of aging in 1998 at the University of Florence, Italy. For many years, he was an associate professor of biology, human physiology and statistics at the University of Florence. Between 1985 and 2002 he was the director of the Laboratory of Clinical Epidemiology at the Italian National Institute of Aging (NIA). In September 2002, he became the chief of the Longitudinal Studies Section at NIA and redesigned the Baltimore Longitudinal Study of Aging to create an interface between the rising field of geroscience and study of age-related changes of phenotypes, as well as physical and cognitive function. He is a member of the Association of American Physicians and has received numerous awards including the Enrico Greppi Award, the IPSEN Foundation Longevity Prize and the Cavaliere dell'Ordine della Stella d'Italia. Ferrucci collaborates extensively with many researchers in the U.S. and Europe, has published more than 1,400 peer-reviewed manuscripts on aging and age-related diseases and is considered as the most productive Italian scientist in the area of medical science. Ferrucci is currently the scientific director of NIA, since May 2011.

Michael Fessler

National Institute of Environmental Health Sciences

Michael Fessler, M.D. is a senior investigator and chief of the Immunity, Inflammation and Disease Laboratory in the Intramural Research Division of the NIEHS. A physician scientist, he obtained his doctor of medicine. at Harvard Medical School, internal medicine training at Massachusetts General Hospital and a pulmonary/critical care medicine fellowship at the University of Colorado. In 2006, he moved to the NIEHS, but has also remained clinically active as an adjunct associate professor of medicine at Duke University. Fessler's research program addresses basic and translational aspects of innate immunity with a focus on Toll-like receptor

signaling in macrophages and the lung. Within this area, a longstanding research focus is the role of cholesterol trafficking and metabolism in host defense; more recent areas of interest include mitochondria and cellular metabolism in immunity.

Kym Gowdy

East Carolina University

Kymberly Gowdy, Ph.D. is an assistant professor in the Department of Pharmacology and Toxicology at the Brody School of Medicine at East Carolina University. Gowdy has held this position since 2014. Prior to her faculty position, Gowdy trained at the NIEHS and Duke University. Her current research program focuses on understanding the molecular mechanisms behind the adverse health effects of air pollution. She is currently funded by the NIH and the Health Effects Institute. Additionally, she is the current president of the North Carolina Society of Toxicology and an active member of the Society of Toxicology and American Thoracic Society. In 2015, Gowdy was awarded the Walter A. Rosenblith New Investigator Award by the Health Effects Institute.

Gowdy holds a doctorate in immunology and toxicology (2008), and master's degree in science (2004) from North Carolina State University. She has authored more than 30 peer-reviewed publications investigating how air pollution can alter the pulmonary immune response, increasing susceptibility to infectious and inflammatory lung diseases.

Bruce Hammock

University of California, Davis

Bruce Hammock, Ph.D., is a Distinguished Professor at the University of California Davis (UCD) and the UCD Comprehensive Cancer Center. As a toxicologist he is known for his work on using natural chemical mediators to speed resolution of inflammation and control of intractable pain. He is the founding director of the NIEHS UCD Superfund Research Program now renewed through 35 years and was principal investigator of the NIH Biotechnology Graduate Training Program at UCD for more than 15 years. He has directed a metabolomics laboratory for 22 years. Hammock is a member of the National Academy of Sciences and the National Academy of Inventors and is a past NIH Career and Merit Awardee; a Burroughs Wellcome Fund scholar; and a von Humboldt Foundation, Marcus, and Fulbright Fellow. He recently was selected for the Brodie Award in Xenobiotic Metabolism, the Lands Lecturer in Biochemical Nutrition, and as the first McGiff Memorial Awardee in Lipid Biochemistry. He and colleagues discovered the soluble epoxide hydrolase which degrades endogenous inflammation resolving epoxy fatty acids and many of his over 1200 publications and patents are on this analgesic and anti-inflammatory P450 branch of the arachidonate cascade. He founded several companies, has helped raise over \$50 million in private capital, and currently is CEO of EicOsis developing an orally active non-addictive drug for inflammatory and neuropathic pain in humans and companion animals. EicOsis is supported by several SBIR grants and an NIH NINDS Blueprint Development Grant.

Sven Jordt
Duke University

Sven-Eric Jordt, Ph.D., is associate professor of anesthesiology and pharmacology at Duke University School of Medicine and associate adjunct professor of psychiatry at Yale School of Medicine.

Jordt trained as a biochemist at the Free University of Berlin from 1989-1994, continuing with doctoral studies on ion channel mechanisms in the lung and brain, and receiving his doctorate in 1997. These studies had impacts on respiratory physiological and epilepsy research.

In 1998, Jordt began postdoctoral studies in the laboratory of David Julius, Ph.D., at the University of California, San Francisco, where he contributed to breakthrough discoveries in pain research by identifying receptors for pain-inducing natural products and thermal stimuli.

In 2005, Jordt joined the Department of Pharmacology at Yale School of Medicine. Supported by the NIEHS, he identified TRP ion channels as targets of reactive environmental irritants and endogenous lipid mediators produced in inflammatory states, revealing a key role for these receptors in chemical pulmonary and cutaneous injury, asthma, and environmental contact dermatitis. He relocated his lab to Duke University in 2014, where he continued studying pain and itch mechanisms and exposure health effects, and identified interventions to counteract chemical injury mechanisms.

Jordt received the Presidential Early Career Award for Scientists and Engineers by the President of the United States, and the Outstanding New Environmental Scientist Award by the NIEHS, among other awards. In 2018 he was elected Chair of the Terrorism and Inhalation Disaster Section of the American Thoracic Society (ATS), the professional society of pulmonary physicians and research scientists in the U.S., with >15,000 members.

Debra Laskin
Rutgers Environmental and Occupational Health Sciences Institute

Debra Laskin received a Bachelor of Arts from New York University, a Master of Arts from City University of New York, and a doctorate in pharmacology and toxicology from the Medical College of Virginia, Virginia Commonwealth University. This was followed by postdoctoral training in immunology at the Wistar Institute of the University of Pennsylvania in Philadelphia.

Laskin is currently distinguished professor and chair of the Department of Pharmacology and Toxicology at Rutgers University Ernest Mario School of Pharmacy; she also holds the position of the Roy A. Bowers Endowed Chair of Pharmacy. Laskin serves as deputy director of the Rutgers University NIEHS funded P30 Center for Environmental Exposures and Diseases.

Laskin's research is focused on understanding the role of inflammation in chemically-induced tissue injury. She has made seminal contributions to this field, publishing over 300 journal articles, reviews, and book chapters. Those include numerous influential invited reviews on macrophages, and inflammatory mediators in tissue injury, and repair and disease pathogenesis, which are widely cited. She has been continuously funded for her research by multiple grants from NIH for over 35 years. She has received many awards for her scientific contributions including the Society of Toxicology (SOT) Achievement Award, the Burroughs Wellcome Toxicology Scholar Award, the SOT Inhalation and Respiratory Specialty Section Career Achievement Award, and most recently, the SOT Mechanisms Specialty Section Career Achievement Award. Laskin has served on numerous NIH grant review committees and is currently a permanent member of the Systemic Injury by Environmental Exposure study section. She is also actively involved in various scientific societies. She is a recent past president of the Toxicology Division of the American Society for Experimental Therapeutics and is currently the president of the Society of Toxicology Inhalation and Respiratory Specialty Section.

Laskin is also actively involved in research training and mentoring and was recently honored by the SOT with the Education Award. She has trained 23 doctoral students and 13 postdoctoral fellows. Her trainees have won awards for their work at various national and international meetings and they have also received prestigious fellowships.

Bruce Levy
Harvard University

Bruce Levy, M.D. is the Parker B. Francis Professor of Medicine at Harvard Medical School and chief of the Pulmonary and Critical Care Medicine Division at Brigham and Women's Hospital. Bruce received his doctor of medicine from the University of Pennsylvania School of Medicine. He completed his internship and residency in internal medicine and his fellowship in pulmonary and critical care medicine at Brigham and Women's Hospital. He was a postdoctoral research fellow in the laboratory of Charles Serhan, Ph.D., D.Sc. Levy's laboratory aims to identify new pathways to resolve pulmonary inflammation, infection, or injury through the roles of naturally derived, specialized pro-resolving mediators. His work has helped lead to more than 175 peer-reviewed publications, at least 10 patents awarded or pending, and continuous funding from the NIH since 1993. He is currently a standing member of the Lung Cellular, Molecular and Immunobiology Study Section and associate editor for the New England Journal of Medicine's clinical problem-solving interactive case series. He has been elected into the American Society for Clinical Investigation, the Association of American Physicians, and the Interurban Clinical Club. He has also been active in the American Thoracic Society and currently serves as chair of the Publication Policy Committee and as member of the Board of Directors.

Sue Menko
Jefferson Medical College

Sue Menko, Ph.D. is a professor and vice-chair of the Department of Pathology, Anatomy, and Cell Biology in Sidney Kimmel Medical Center of Thomas Jefferson University (TJU) with a secondary appointment in the Department of Ophthalmology. She is the co-founder of the Wills Vision Research Center at TJU. She also serves as chair of the Jefferson Committee on Research and leads the Programmatic Initiative in Fibrosis at TJU. Menko is a vision researcher whose studies in the visual system are aimed at elucidating mechanisms of wound healing and fibrosis, unique mechanisms of immune surveillance in the eye, and the signaling mechanisms that underlie a cell's decision to embark on its differentiation program.

Srikanth Nadadur
National Institute of Environmental Health Sciences

Srikanth (Sri) Nadadur, Ph.D., is program director at the Division of Extramural Research and Training overseeing research programs in air pollution cardiopulmonary health, Nanotechnology Environmental Health and Safety (Nano-EHS), and Countermeasures Against Chemical Threat agents (a Trans-NIH program). Nadadur has more than 20 years of research experience in molecular biology, chemical carcinogenesis, cardiopulmonary biology and molecular toxicology. His work on cloning and expression of novel tumor necrosis factor induced proteins at Roswell Park Cancer Institute resulted in a patent. Prior to joining NIEHS, Nadadur worked as a principal investigator at the National Center for Environmental Assessment (NCEA), National Health and Environmental Effects Research Laboratories, Office of Research and Development, U.S. Environmental Protection Agency. At NCEA his research efforts were focused on developing ambient air quality criteria documents for the health effects of ozone and lead (Pb) in support of the national ambient air quality standard setting process. Nadadur served as Embassy Science Fellow from NIEHS for a sabbatical at the US Embassy, New Delhi in 2015. He initiated collaborative research efforts between US and India to address air quality and health. Nadadur established and lead a Communities of Researchers workgroup with scientists in the US and India, he developed recommendations on US-India joint efforts to improve air quality and health.

Jill Poole
University of Nebraska

Jill A. Poole, M.D., is a professor of medicine in the Pulmonary, Critical Care, Sleep & Allergy Division, and is the Section Chief and Medical Director of Allergy Services at the University of Nebraska Medical Center in Omaha, Nebraska. She is originally from Grand Island, Nebraska, and completed her medical school training at University of Nebraska. During medical school, she participated in the Clinical Research Training Program at the NIH in the Institute of Allergy and Infectious Disease. She completed an internal medicine residency program at Washington

University Barnes Jewish Hospital in St. Louis, Missouri, and fellowship training in allergy, asthma, and immunology at National Jewish Medical Center that is affiliated with the University of Colorado Health Sciences in Denver, Colorado. She was recruited back to the University of Nebraska Medical Center in the summer of 2005. Poole's primary research work has been focused on agricultural-related respiratory diseases since 2005, and she has published more than 70 peer-reviewed studies. She has had funding through the NIEHS and the National Institute for Occupational Safety and Health since 2007. She is also active in the American Allergy, Asthma, and Immunology Society for which she was recently elected officer in the Environmental and Occupational Respiratory Disease Interest Section. She also serves as the Occupational Airway Disease Section editor of Current Allergy and Asthma Reports. She has also served on NIH study sections. Poole maintains a clinical practice at Nebraska Medicine caring for patients with allergic and asthmatic disorders.

Charles Serhan

Brigham and Women's Hospital, Harvard University

Charles Nicholas Serhan, Ph.D., D.Sc., is the Simon Gelman Professor of Anesthesia (Biochemistry and Molecular Pharmacology) at Harvard Medical School and also professor of oral medicine, infection and immunity at Harvard School of Dental Medicine. He is director of the Center for Experimental Therapeutics and Reperfusion Injury at Brigham and Women's Hospital. Charles received a Bachelor of Science in biochemistry from Stony Brook University followed by a doctorate in experimental pathology and medical sciences from New York University School of Medicine. He was a visiting scientist and post-doctoral fellow at the Karolinska Institutet in Stockholm with Professor Bengt Samuelsson (Nobel Laureate in medicine, 1982). In 1987, he joined the faculty at Harvard Medical School and received an honorary degree from Harvard University (1996).

He has received several awards including an NIH MERIT award and has delivered > 50 keynote and plenary lectures. Among these recent awards: the 2008 William Harvey Outstanding Scientist Medal and AAAS Fellow in 2011. In 2010, he received the Society for Leukocyte Biology Bonazinga Award, the American College of Rheumatology Hench (Nobel Laureate) Award Lecture in 2011 presented by the Mayo Clinic Hench Society, and Mérieux 2013 Laureate.

In 2016, he received the International Union of Biochemistry and Molecular Biology Lecture Metal and the Ross Prize in Molecular Medicine. Recently, he received the International Eicosanoid Research Foundation's 2017 Lifetime Achievement Award, the American Society of Investigative Pathology 2018 Rous Whipple Award, and the 2018 Gaddum International Prize and Award Lecture from the British Pharmacology Society. As a measure of his impact, Serhan's h-index is 144, and he has been cited more than 77,000 times.

Patricia Sime

University of Rochester School of Medicine and Dentistry

Patricia J. Sime, M.D., received her doctor of medicine training at the University of Edinburgh, Scotland where she graduated with honors. She then went on to do her specialist training in pulmonary medicine in Edinburgh. After being awarded a prestigious research fellowship she travelled to McMaster University, Ontario, Canada to train in the science of lung inflammatory and scarring diseases. In 1999, she was recruited to the faculty of the University of Rochester as a physician, educator and researcher. She has an international reputation of her clinical and research work in the area of lung inflammation and scarring where she is developing new therapies for these life threatening diseases.

Sime holds the C. Jane Davis & C. Robert Davis Distinguished Professor in Pulmonary Medicine, and is currently Professor of Medicine, Chief of the Pulmonary and Critical Care Division, and Co-Director of the Mary Parkes Center for Asthma, Allergy and Pulmonary Care at University of Rochester Medical Center. She is director of the Interstitial Lung Disease Clinic at the University of Rochester and co-directs the Pulmonary Fibrosis Foundation Care Center Network Site there.

Sime leads a team of physicians and researchers focused on understanding lung inflammation and resolution in diseases such as Chronic Obstructive Pulmonary Disease and the mechanisms and therapy of fibrotic lung diseases. In her role as vice chair for research in the Department of Medicine she guides strategic research directions and builds multidisciplinary research teams. Sime receives funding from the National Institutes of Health, the Department of Defense, as well as industry, and philanthropy.

On July 1, 2019 she will assume the position of Chair of Medicine at Virginia Commonwealth University, Richmond, VA.

Thomas Van Dyke

Forsyth Institute

Thomas Van Dyke, D.D.S, Ph.D. is Vice President for Clinical and Translational Research and senior staff member at the Forsyth Institute in Cambridge, Massachusetts, and Professor of Oral Medicine, Infection, and Immunity at Harvard University Faculty of Medicine. He obtained his Doctor of Dental Surgery degree from, Case Western Reserve University; his Master of Science degree from, SUNY Buffalo in Oral Sciences; his Periodontics Certificate from the State University of New York (SUNY) Buffalo; his doctorate from SUNY Buffalo in oral biology, and two doctoral degrees honoris causa from Justis Liebig University, Giessen and the University of Copenhagen. He received the Balint Orban Memorial Prize for Research in Periodontology, Diplomate of the American Board of Periodontology award, International Association for Dental Research (IADR) Award for Basic Research in Periodontology, Norton Ross Award for Excellence in Clinical Research, and William J. Gies Periodontology Award. He serves on numerous editorial

boards has edited two volumes of Periodontology 2000. He is president of the International Association of Periodontology (1997-1999). Van Dyke has published 330+ original articles, and numerous abstracts and book chapters. He is a member of the American/International Association of Dental Research; American Academy of Periodontology; International Academy of Periodontology; American Association for the Advancement of Science; American Society of Microbiology; IADR Periodontal Research Group; American Dental Association; and American Association of Immunologists. His research interests are the structural and functional relationship of abnormalities of the inflammatory process in the etiology and pathogenesis of periodontal and other infectious inflammatory diseases with a focus on phagocytic cells and microorganisms. Van Dyke is also involved in clinical research and clinical trials focusing on drug treatment for periodontal disease, local delivery systems, and clinical trials. The remainder of his time is devoted to administration and training of fellows. He is best known for his work on the pathogenesis of juvenile periodontal diseases, resolution of inflammation in periodontitis, and clinical research.

Peter Ward

University of Michigan

Peter Ward, M.D., grew up in upstate New York and obtained both a Bachelor of Science and doctor of medicine degree from the University of Michigan (Ann Arbor, Michigan). In 1961, he completed a first-year residency in medicine at Bellevue Hospital in New York City, followed by a residency in anatomic pathology at the University of Michigan Hospital. From 1963-1965 he was a postdoctoral fellow at Scripps Clinic and Research Foundation (La Jolla, California). In 1965, he became Captain, U.S. Army Medical Corps (Walter Reed Medical Center) in Washington, D.C., and stayed on until 1971 when he joined the University of Connecticut Health Center and School of Medicine in Farmington, Connecticut, where he served as chair of the Department of Pathology until 1980. Then he joined the University of Michigan Medical School as chair of the Department of Pathology (1980-2005). He currently is the Stobbe Professor of Pathology at the University of Michigan Medical School. He has long studied the complement system and its role in inflammation and has over 700 peer-reviewed publications.

Xiang Zhang

Baylor College of Medicine

Xiang “Shawn” Zhang, Ph.D., whose research focuses on breast cancer metastasis, joined Baylor College of Medicine in June 2011. He is a member of the Lester & Sue Smith Breast Center at Baylor. Prior to his appointment at Baylor, he was a research associate in the Cancer Biology and Genetics Program at Memorial Sloan-Kettering Cancer Center, where he conducted research since 2006. He received a bachelor of science degree in genetics and genetic engineering from Fudan University in Shanghai and a doctorate from Columbia University. It was after receiving his doctorate that he decided to focus on breast cancer in his postdoctoral research.

The long-term goal of Zhang's laboratory at Baylor College of Medicine is to elucidate biological mechanisms and therapeutic strategies of metastasis, the major threat to the lives of solid cancer patients. Toward this end, his team has developed a set of unique techniques and models to study the interaction between microscopic metastases and various stromal components in different organs particularly in the bone. Among various components in tumor microenvironment, his lab is particularly interested in immune cells, and have conducted several studies to investigate the mechanisms underlying co-evolution between tumor cells and the immune microenvironment. Their ultimate objective is to understand how tumor develop distinctive and heterogeneous immunosuppressive microenvironment and identify context-specific strategies to unleash anti-tumor immunity. To date, Zhang published over 50 papers including first- and senior-authored papers on Cell, Nature, Cancer Cell, Nature Cell Biology, Nature Communications, Genes and Development, and the Proceedings of the National Academy of Sciences.

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