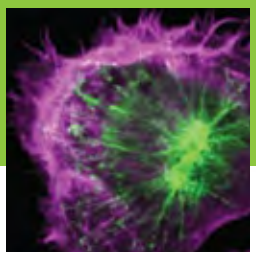
8th Annual CHIS

Center for Human Immunology Symposium

September 25, 2014

Blood Research Institute
Milwaukee, WI

BloodCenter of Wisconsin™



BloodCenter and Blood Research Institute: Discovery, Diagnosis, Treatment and Cure

A Brief History

BloodCenter of Wisconsin (BCW) is a private, not-for-profit organization that provides blood, blood products, and specialized transfusion medicine services to hospitals in Wisconsin. In partnering with Michigan Blood and Heartland Blood Centers, BCW also serves Michigan, northern Illinois, and parts of Indiana. A commitment to pursue research and advance the understanding of blood and blood transfusions was written into the articles of incorporation by visionary members of the board of directors when BCW was founded in 1947. The current mission statement calls for BCW to "advance patient care by providing life-saving solutions grounded in unparalleled medical and scientific expertise."

The Junior League of Milwaukee founded the Junior League Blood Center in 1947 as a community blood bank with five paid staff and 70 regular volunteers. By 1952, the center was serving 30 regional hospitals. The name was changed to Milwaukee Blood Center in 1954 and an active research focus was initiated in the early 1950s. The first federal grant was received by the Milwaukee Blood Center in 1957. The name of the center was changed to the Blood Center of Southeastern Wisconsin in 1979 and again to BloodCenter of Wisconsin in 2005 to more accurately reflect the geographically growing area of its service. With the success of life-saving discoveries, increased research funding and committed scientific staff, BCW built the Blood Research Institute (BRI) on the grounds of the Milwaukee Regional Medical Center in 1991.

Over the years, the contributions of BloodCenter investigators have made a lasting impact on the fields of Transfusion Medicine, Immunology and Vascular Biology. We are proud of the fact that, despite the national lack of NIH funded physician-researchers, nine of our 22 investigators are physicians. Research at BCW extends from basic cellular, molecular and genetic studies, to participation in NIH clinical trial networks such as the Retroviral Epidemiology Donor Study (REDS) II, the Transfusion Medicine-Hemostasis (TMH) Clinical Trials Network and the Center for Human Immunology. Research activities are also strengthened by physical proximity of the BRI to the immediately adjacent Medical College of Wisconsin (MCW) and Children's Hospital of Wisconsin (CHW). BRI investigators hold faculty appointments at MCW and participate actively in the teaching, mentoring and research activities.

Center for Human Immunology: Advancing, Accelerating and Promoting

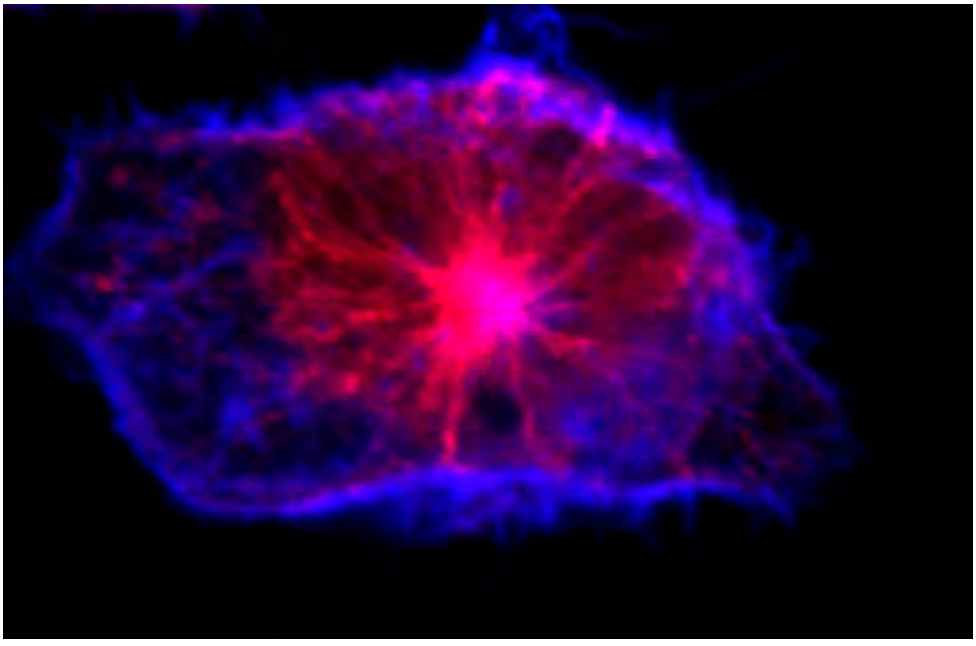
The Center for Human Immunology (CHI) at the Blood Research Institute (BRI) was formed in 2006 under the leadership of Dr. Jack Gorski, Senior Investigator at BRI. Its mission is to improve human health by advancing the basic understanding of the human immune system by accelerating the transition of discoveries from murine studies to clinical practice, and by promoting interactions between regional immunologists and leading experts.

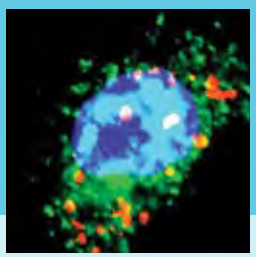
The formation of the CHI also embodies the goal of BloodCenter of Wisconsin to leverage its important resource of blood donor/volunteers to help advance human immunology. With the increasing emphasis by the National Institute of Health on translation of basic mouse immunology into human health-related areas, the CHI plays a prominent role in supporting the regional immunologists at the BRI, Medical College of Wisconsin and Children's Hospital of Wisconsin.

To promote the interaction between regional immunologists and the leading experts, the CHI has been sponsoring an Annual Symposium on Human Immunology. The first of these was held in 2007. The topics of the symposia are either directly related to analysis of the human immune system or cover important areas of study with direct ramifications for human health and disease.

This year's CHI Symposium is organized with the generous financial support from the BloodCenter Research Foundation and the Joan and Fred Brengel Family Foundation and other sponsors.

Dr. Jack Gorski, Senior Investigator at BRI and founder of the Center for Human Immunology.





Center for Human Immunology Annual Symposium

Schedule

7:00 – 8:00 am Registration

8:00 – 8:10 am Handover – Jack Gorski PhD, Senior Investigator, BRI
Demin Wang, PhD, CHIS Co-Chair, Senior Investigator, BRI
Subra Malarkannan, PhD, CHIS Co-Chair, Senior Investigator, BRI

8:10 – 8:20 am Opening Remarks – Jackie Fredrick
President and CEO , BloodCenter of Wisconsin

8:20 – 8:30 am Welcome Address – Gilbert C. White II, MD
Director and Executive Vice President, BRI

8:30 – 9:30 am *Speaker Introduction by Gilbert C. White, II, MD, Director and Executive Vice President, BRI*

Ellen Robey, PhD
Professor, Immunology and Pathogenesis
Department of Molecular and Cell Biology, University of California Berkeley

Title: 'Visualizing T cell selection in the thymus'

9:30 – 10:00 am Coffee Break – Visit our Sponsors

10:00 – 11:00 am *Speaker Introduction by Ming You, MD, PhD, Director, Cancer Center, MCW*

David Rawlings, MD
Director, Center for Immunity and Immunotherapies
Seattle Children's Research Institute
Professor of Pediatrics, University of Washington

Title: 'Altered B cell signaling orchestrates loss of tolerance and systemic autoimmunity'

11:00 am – 12:00 pm *Speaker Introduction by John Crispino, PhD, Professor and Associate Director, Robert H. Lurie Comprehensive Cancer Center, Northwestern University*

Harvey Lodish, PhD
Member, Whitehead Institute for Biomedical Research
Professor, Biology and Biological Engineering
Massachusetts Institute of Technology

Title: 'Self-renewal of human hematopoietic progenitor cells: new drugs to treat bone marrow failure disorders and other erythropoietin-resistant anemias'

Immune Cell: Genome, Transcriptome & Signalsome

12:00 – 1:25 pm	Lunch – Visit our Sponsors
1:25 – 1:30 pm	Reassemble – Behind the Scenes – to Photo Finish
1:30 – 2:30 pm	*Speaker Introduction by Zachary Gerbec, Graduate student, IDP, MCW* **Anjana Rao, PhD** Professor, Division of Signaling and Gene Expression La Jolla Institute for Allergy and Immunology **Title: 'TET proteins, 5-methylcytosine oxidation and cancer'**
2:30 – 3:00 pm	Break – Visit our Sponsors
3:00 – 4:00 pm	*Speaker Introduction by Emery Bresnick, PhD, Professor and Director, UW-Madison Blood Research Program* **Cornelis Murre, PhD** Distinguished Professor , Molecular Biology University of California San Diego **Title: '3D-Trajectories adopted by coding and regulatory DNA elements in developing lymphocytes'**
4:00 – 4:15 pm	Wrap Up – Subra Malarkannan, PhD
4:15 – 7:30 pm	Reception and social

Ellen Robey, PhD

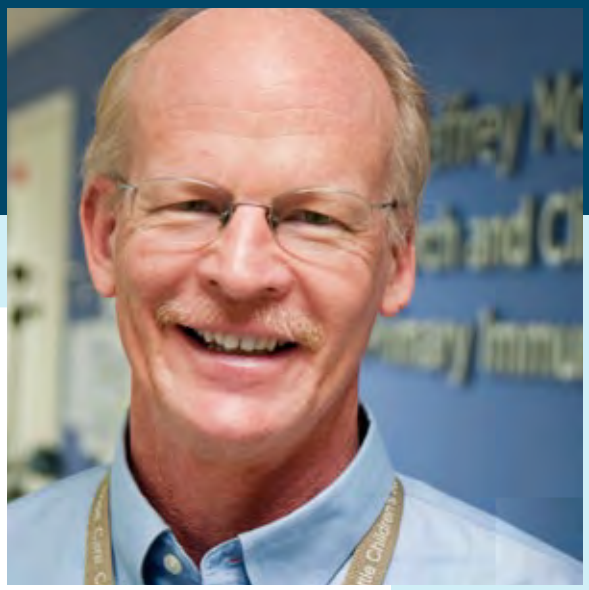
Professor of Immunology and Pathogenesis,
Department of Molecular and Cell Biology,
University of California, Berkeley

Dr. Robey is an expert in how T cells develop and mature in the body. In particular, her laboratory is in the forefront of defining how signaling pathways control developing T cell fate decisions. She uses state of the art 2-photon imaging approaches to peer into organs in live bodies in real-time. In addition, her laboratory investigates host-pathogen interactions using the intracellular parasite, *Toxoplasma gondii* in murine models.

Dr. Robey obtained her bachelor degree from the University of Virginia at Charlottesville, her graduate degree from the University of California at Berkeley and postdoctoral training from Columbia University. She is currently a Professor of Immunology and Pathogenesis and has been at the Department of Molecular and Cell Biology, University of California at Berkeley since 1992. Dr. Robey is an F1000 faculty member and has served on numerous national and international committees.

Her laboratory works on the cellular and molecular mechanisms of the selection process in the thymus that result in eliminating self-reactive T cells. More importantly, how this stringent process fails resulting in a pathological outcome. Autoimmune diseases are one of the major sources of mortality and morbidity among people. In addition, discoveries made in the Robey lab have significantly impacted the basic understanding and translational utilization of thymic education in two major classes of human diseases – cancer and autoimmunity. Using two-photon laser scanning microscopy, the Robey lab has demonstrated that T cell development is a dynamic process and thymocytes are in constant motion, searching for microenvironments supportive of the next step of their differentiation. They found that the earliest T cell progenitors enter at the border between cortex and medulla and migrate towards the thymic capsule, where they rearrange their T cell receptor β (TCRβ) chain and proliferate extensively to become CD^{4+} CD^{8+} double-positive (DP) thymocytes. The Robey lab also showed that the DP cells occupy the majority of the cortex and move at low speeds via random walk trying to rearrange their TCRα chain. The Robey lab is also investigating host-pathogen interactions using a mouse infection model of the intracellular parasite, *Toxoplasma gondii*. Using murine models that enable in vivo quantification of immune responses to the parasites, they visualize the mobilization of T cells in real-time. Their ongoing efforts in this area are focused on examining CD^{8+} T cell during priming and effector phases of the immune response, and examining immune protection during chronic infection. These studies will help to produce an effective vaccine to induce CD^{8+} T cell-mediated induction of immune protection against oral pathogens.

David Rawlings, MD

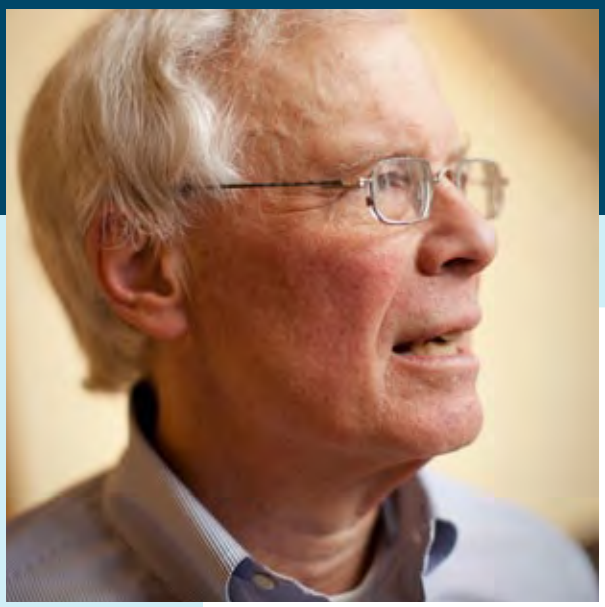


Director, Center for Immunity and Immunotherapies
Seattle Children's Research Institute
Professor of Pediatrics, University of Washington

Dr. Rawlings is an expert in how immune cells respond to infections or cancer. In particular, his work is internationally recognized for providing a better understanding of signaling events that occur inside the immune cells once they recognize a cancer cell. His discoveries have transformed the way we formulate therapies for cancer, autoimmune disorders, and inflammation. The Rawlings laboratory's primary research interests include dysregulated B cell development and signaling leading to immunodeficiency, autoimmunity or lymphoid malignancies, and the development of gene therapy for primary immune deficiency diseases.

Dr. Rawlings graduated Magna Cum Laude in Biological Sciences from Davidson College, and received his M.D. from the University of North Carolina. He completed his residency and chief residency in pediatrics at UCSF, and Pediatric Rheumatology/Immunology subspecialty training at Children's Hospital Los Angeles. He pursued post-doctoral research as an intramural fellow at the NIH and in the HHMI, UCLA. Formerly a member of the UCLA faculty, Dr. Rawlings joined the University of Washington in 2001. He directs the Center for Immunity and Immunotherapies at Seattle Children's Research Institute, and is also Chief of the Division of Immunology overseeing the immunodeficiency clinic at Seattle Children's Hospital. Dr. Rawlings has received numerous awards and was elected to the American Society for Clinical Investigation in 2001 and the Association of American Physicians in 2007. He is currently Professor of Pediatrics, Director for Center for Immunity and Immunotherapies at Seattle Children's Research Institute and Chief of the Division of Immunology at Seattle Children's Hospital. Dr. Rawlings is the Chairman for the USIDNET XLA patient registry and co-directs the Northwest Genome Engineering Consortium, a research program funded as part of the NIH Roadmap for Medical Research.

The Rawlings laboratory studies how B cell antigen receptor (BCR) engagement generates a multi- signaling component complex called signalosome. Their studies seek to understand the protein interactions that constitute the signalosome using genetic and biochemical analysis of tyrosine kinases, adapter proteins, and lipid enzymes. A major focus of this current work is the multi-adapter protein CARMA1, which plays a crucial role in development of human B cell lymphomas. These studies are done to understand how B cell lineage develop and why B lymphoid malignancies arise. Their current studies include analyses of signaling via TSLP-receptor, Toll, Notch, and BAFF-receptor in the generation of peripheral B cell subsets and the PKCθ/NFκB pathways in the development or progression of lymphoma. Another major focus of the Rawlings laboratory is to study how to use gene therapy approaches to correct primary immunodeficiency disorders such as X-linked agammaglobulinemia and Wiskott-Aldrich Syndrome. In addition to the use of cell lineage-specific viral vectors systems, they have begun to evaluate the potential of employing homing endonucleases to facilitate genetic repair of the mutant loci in animal models.



Harvey Lodish, PhD

Member, Whitehead Institute for Biomedical Research
Professor of Biology and Biological Engineering, Massachusetts Institute of Technology

Dr. Lodish is a leader in the fields of cellular and developmental biology. Harvey F. Lodish has isolated, cloned, and characterized numerous proteins and noncoding RNAs that play key roles in formation of blood and fat cells, and that regulate metabolism of glucose and fatty acids. His results have important implications for the treatment of anemias, cancer, diabetes, heart disease, and obesity.

In 1988, the Lodish laboratory accomplished pioneering work on erythropoietin (Epo), a hormone that controls the production of red blood cells. The lab identified and cloned the Epo receptor, leading to a lengthy set of ongoing projects on the activation of, and signal transduction by, the erythropoietin receptor in erythroid progenitor cells and the regulation of transcription, apoptosis, and cell division. The lab is currently characterizing many novel genes that are important for terminal stages of erythropoiesis, including chromatin condensation and enucleation. Other work focuses on the regulation of self-renewal, proliferation, and differentiation of early (BFU-E) erythroid progenitor cells by extracellular signals, including glucocorticoids and oxygen. One goal is the development of novel therapies for erythropoietin-resistant anemias.

The Lodish laboratory has recently discovered several microRNAs and Long Non-coding RNAs that are specifically expressed in developing red blood cells, and that regulate important aspects of development including cell death. One microRNA causes leukemias when overexpressed in human or mouse stem cells. Additionally, the Lodish lab studies hormones controlling fatty acid and glucose metabolism, broadening understanding of obesity and type 2 diabetes. In 1995, the lab cloned adiponectin, a hormone made exclusively by fat cells. A long and ongoing series of studies showed that adiponectin causes muscle to burn fatty acids faster—so they are not stored as fat—and increases the metabolism of the sugar glucose. More recently the laboratory has been focused on identifying and characterizing microRNAs and Long Non-coding RNAs that are specifically expressed in adipose cells. One miRNA unique to brown fat, which burns rather than stores fatty acids as triglycerides, triggers other progenitor cells to become brown fat.

A Founding Member of Whitehead Institute, Lodish joined the MIT faculty in 1968. He has been a professor of biology since 1976 and professor of bioengineering since 1999. He earned his Ph.D. at Rockefeller University in 1966. He was elected a fellow of the American Association for the Advancement of Science in 1986, a member of the National Academy of Sciences in 1987, and a fellow of the American Academy of Arts and Sciences in 1999. He is a member of the Board of Trustees of Boston Children's Hospital, and is Chair of the Scientific Advisory Board of the Massachusetts Life Sciences Center, charged with oversight of the state's 10-year, $1 billion investment in the life sciences. He is also the lead author of the textbook *Molecular Cell Biology*.

Anjana Rao, PhD

Professor, Division of Signaling and Gene Expression
La Jolla Institute for Allergy and Immunology

Dr. Rao is a pioneering leader in the field of molecular regulations of gene expression and her work is directly connected to stem cell biology and genetic dysregulations associated with cancer cell transformations. Her discoveries have helped to formulate better stem cell therapies and cancer treatments.

A member of the National Academy of Sciences (2008), Dr. Rao received her undergraduate and master's degrees from Osmania University in India and her Ph.D. from Harvard University. She was elected fellow of AAAS (2009), American Society for Microbiology (2009), American Academy of Arts and Sciences (2009). After many years as a faculty member at the Harvard Medical School and the Immune Disease Institute in Boston, she joined the La Jolla Institute for Allergy and Immunology in 2010. She is also a faculty member at Sanford Consortium for Regenerative Medicine, UCSD Moores Cancer Center, UCSD Institute of Genomic Medicine, and UCSD Biomedical Sciences Graduate Program.

The Rao laboratory focuses on understanding how signaling pathways that control gene expression using T and other immune cells as models. They are particularly interested in a pathway of gene expression that is regulated by calcium influx in many different cell types. This includes immune cells, neurons, and cells in heart, muscle, bone and skin. The studies involve a calcium sensor in the endoplasmic reticulum, STIM, which couples to a calcium channel in the plasma membrane, ORAI. The increased calcium concentration in the cytoplasm activates a phosphatase, calcineurin, which dephosphorylates and sends a transcription factor, NFAT, to the nucleus. NFAT turns on a large number of genes, in a manner appropriate to the cell type and mode of stimulation. The Rao laboratory has also used T cells to study how gene expression programs are modulated by stress pathways and during cell differentiation. Another exciting area of their investigation revolves around how the TET family of 5-methylcytosine hydroxylases affects DNA methylation patterns and gene expression in embryonic and haematopoietic stem cells. TET proteins appear to be essential regulators of ES cell pluripotency, and their dysegulation is frequently associated with cancer. Using RNA interference screens, mice with targeted alterations of genes, and high-throughput sequencing they are actively investigating how genes are regulated and how loss of function of certain proteins leads to diseases such as autoimmunity, immune deficiencies, developmental defects, and cancer.

Cornelis Murre, PhD

Distinguished Professor, Molecular Biology
University of California San Diego

Dr. Murre is an internationally recognized expert on gene regulation in adult stem cells and developing immune cells. His basic molecular studies also have revealed the changes that occur at the genetic level during aging. He uses chromatin (chromosome) structure and long-range genomic interactions to control gene expressions. His discoveries have formed the basis for better understanding aging-related disorders and how to treat them. The Murre laboratory utilizes both global and single cell strategies with the aim to describe normal development as well as aged and diseased states in molecular terms.

Dr. Murre obtained his graduate degree from Harvard Medical School and his postdoctoral training at MIT. He is currently a distinguished Professor of Biological Sciences at the University of California, San Diego. He was recognized for his contributions through a Searle Scholar Award and a Merit Award from the NIH.

The Murre laboratory has a long-standing interest in deciphering the role and regulation of helix-loop-helix proteins in lymphocyte development. This class of factors plays key roles in hematopoiesis. Currently, their main interests are in the role of these factors in the control of hematopoietic stem cell homeostasis, B- and T-lineage specification and commitment, aging, inflammatory disease and their roles in the periphery in response to invading pathogens. Using cutting edge technologies they have identified a subset of lineage-specific and developmental-stage specific non-coding RNAs. Their interests are to determine the function of these non-coding RNAs, and to study their potential roles in modulating long-range chromatin structure and genomic interactions. They aim to resolve these questions using genome-wide chromosome-conformation capture studies (HiC) in conjunction with computational approaches to describe the topologies of lymphoid and myeloid genomes in molecular terms. They have recently indentified that in eukaryotic cells coding and regulatory genomic elements bounce back and forth within the chromatin network until specific genomic interactions are established, and that spatial confinement of topological domains largely controls the times for such encounters. Their future studies aim to examine how epigenetic and structural determinants affect the trajectories adopted by the chromatin fiber in living cells, and how this relates to genomic encounters involving enhancers and promoters. They have recently demonstrated that genes encoding for key developmental regulators reposition during developmental progression. They aim to address the question as to why and how genomic regions encoding for developmental regulator reposition during developmental progression, how their release from the lamina is regulated and how they associate with active transcription factories.

A Success in the Making: Topics and Speakers of our Past Symposia

2007 – Human Immunology
Bill Kwok, PhD, Benaroya Research Institute at Virginia Mason
Martin Hessner, PhD, Medical College of Wisconsin
Karolina Palucka, MD, PhD, Baylor University
Jorg Goronzy, MD, PhD, Emory University School of Medicine
Elena Naumova, PhD, Tufts University School of Medicine
David D. Eckels, PhD, University of Utah School of Medicine

2008 – Integrating Hemostasis and Immunity
Charles Esmon, PhD, University of Oklahoma Health Sciences Center
May Han, MD, Stanford University
Jay L. Degen, PhD, University of Cincinnati College of Medicine
Hartmut Weiler, PhD, Blood Research Institute

2009 – Immune Memory
Rafi Ahmed, PhD, Emory University
Ignacio Sanz, MD, University of Rochester
Jack Gorski, PhD, Blood Research Institute
Anne West, MD, PhD, Duke University Medical Center

2010 – Systems and Computational Immunology
Tim R. Mosmann, PhD, University of Rochester
Greg E. Lemke, PhD, Salk Institute
Steven H. Kleinstein, PhD, Yale University School of Medicine
Elena Naumova, PhD, Tufts University School of Medicine

2011 – Innate Immunity
David Raulet, PhD, University of California-Berkeley
Alejandro Aballay, PhD, Duke University
Thirumala-Devi Kanneganti, PhD, St. Jude Children's Research Hospital
Subramaniam Malarkannan, PhD, Blood Research Institute
Dan Wu, PhD, Yale University, School of Medicine
Wendy Havran, PhD, The Scripps Research Institute

2012 – Interactions Between the Immune and Nervous Systems
Keith Kelley, PhD, University of Illinois
Alan Lomax, PhD, Queen's University
Katherine Held, PhD, Allergan
Bonnie Dittel, PhD, Blood Research Institute
Jeannette Marketon, PhD, The Wexner Medical Center
Cecelia Hillard, PhD, Medical College of Wisconsin

2013 – Cellular Immunotherapy & Hematopoietic Stem Cells
Stuart Orkin, PhD, Harvard Medical School
Stanley Riddell, MD, University of Washington School of Medicine
Crystal Mackall, MD, National Cancer Institute
Linheng Li, PhD, University of Kansas School of Medicine
Pramod Srivastava, PhD, University of Connecticut

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