

# Therapeutic Innovation: Oxidative Stress and the Next Generation of Discovery



BOSTON  
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**BU Pharmacology & Experimental Therapeutics/Pfizer Biotherapeutics  
Hot Topics Symposia**

Dear Colleagues,

Welcome to the symposium, “**Therapeutic Innovation: Oxidative Stress and The Next Generation of Discovery**,” organized by the NIGMS Training Program in Biomolecular Pharmacology at Boston University in collaboration with Pfizer Biotherapeutics. This is the fifth symposium in a series that reflects our long-standing collaboration and mutual interests in doctoral education. The objective of each program is to enhance the research training of doctoral students and their faculty mentors both at BU and Pfizer who participate in this university-wide Biomolecular Pharmacology training program. This series of symposia focus on timely advances in an area of biomedical sciences that are poised for important breakthroughs in research on mechanisms of action through therapeutic implementation. We identify topics to be of interest to a broad range of scholars and industrial scientists who work in multiple disciplines of basic science.

Since its inception with the Genetics Institute in 1999, our collaboration has provided internship opportunities for BU Pharmacology & Experimental Therapeutics and Biomedical Engineering graduate students seeking an industry research experience. The participation of industry professionals in basic science lecturing and the training of new PhDs in Pharmacology & Experimental Therapeutics from Pfizer have enriched our training environment.

Four previous symposia have been held at BU, beginning with, “Degeneration and Regeneration of the Central Nervous System,” convened on 10 November 2005. In October 2008, we addressed the global mechanisms of “Metabolic Dysregulation.” In December 2010, the symposium focused on “Inflammation Breaking Out: Molecular Mechanisms for Therapeutic Discovery.” Most recently, on 30 April 2012, the program focused on “Therapeutic Innovation: The Next Generation of Discovery.”

In this year’s symposium, we intend to focus on several advanced technologies in the area of experimental therapeutics that will likely lead the way toward advances in drug discovery. In planning this program, we wanted to capture the energy surrounding the elucidation of the new and emerging concepts for perturbing underlying disease mechanisms related to oxidative stress. We are excited to bring together an eclectic group of thought leaders to share their insights with students, faculty, and guests with an interest in exploring the scientific discovery process.

On behalf of the entire organizing committee, we hope that the sharing and discussion of cutting edge science during the symposium will foster innovation and collaboration that will lead to the discovery of breakthrough therapies for those who suffer from debilitating diseases.

With best regards,

David H. Farb, PhD, Professor, Director NIGMS Program in Biomolecular Pharmacology and Chair, Department of Pharmacology & Experimental Therapeutics

Cara M.M. Williams, PhD, Adjunct Associate Professor, BU, and Director of Cell Biology and Pharmacology within the Inflammation & Remodeling RU, Pfizer





**Joseph S. Beckman, Ph.D.**

Ava Helen Paul Endowed Chair,  
The Linus Pauling Institute  
University Distinguished Professor  
Director, Environmental Health  
Sciences Center  
Oregon State University,  
Portland, OR

The long-term goal of Dr. Beckman's research is to develop new therapeutic agents using mechanistic insights drawn from understanding how copper, zinc superoxide dismutase (SOD) malfunctions in ALS (also known as Lou Gehrig's disease). We have made substantial progress in understanding how SOD causes motor neurons to die in ALS as well as identifying new mechanisms by which astrocytes and microglia drive the progressive death of motor neurons. Although mutant SODs expressed in mice and rats confer a toxic gain-of-function that recapitulates human ALS better than more recently identified ALS-linked mutations, twenty years of animal testing based on ALS-mutant SOD expression have so far failed to yield an effective therapy for motor neuron disease in mice or men. To understand how SOD malfunctions, a new mass spectrometric method has been developed to characterize copper and zinc binding to partially unfolded intermediates of SOD isolated directly from ventral spinal cord. It is the only method that can simultaneously determine copper and zinc content as well as the presence of the stabilizing sulfhydryl bridge on the same SOD subunit. This method has helped evaluate new copper complexes that are showing remarkable protection in multiple lines of ALS-SOD transgenic mice.

Joe Beckman received a BA degree in Molecular Cellular and Developmental Biology in 1975 and an MA in Environmental, Population and Organism Biology in 1977, both from the University of Colorado. He served as a Second Lieutenant at the 121st Evac Hospital in Seoul Korea (of M\*A\*S\*H fame) in 1978 in US Army Medical Service Corp. He completed his Ph.D. in Botany at Duke University in 1984. He moved to the University of Alabama at Birmingham (UAB) in 1985 as a post-doc. In 1988, Dr. Beckman was promoted to Assistant Professor in the Department of Anesthesiology at UAB and became a Professor in 1994. While in Alabama, he described how the reaction of superoxide with nitric oxide to produce peroxynitrite as a major pathological mechanism and discovered nitrotyrosine to be a major protein modification in many diseases. In 2001, he joined the Linus Pauling Institute at Oregon State University as the Ava Helen Pauling Endowed Chair. In 2002, he also became the Director of the Environmental Health Sciences Center. He was recognized as the University's Distinguished Professor and as Oregon's Medical Research of the Year in 2013. He enjoys skiing and whitewater rafting in northwestern rivers. His research is focused on the biological chemistry of the oxidant peroxynitrite and its reactions with superoxide dismutase. This has led to his current research in understanding how tyrosine nitration drives the degeneration of motor neurons in ALS. He also is interested in developing new types of mass spectrometers, particularly for probing intact proteins isolated directly from tissues.



**Shyam Biswal, Ph.D.**

Professor of Environmental Health  
Sciences  
Associate Chair for Research  
The Johns Hopkins Bloomberg  
School of Public Health.  
Professor of Medicine, Pulmonary  
and Critical Care  
Department of Oncology, the Johns  
Hopkins School of Medicine

Dr. Shyam Biswal's research is focused on discovering the novel mechanisms of host defense that determine immunobiology and pathobiology of COPD and other environmental lung diseases to develop experimental therapeutics for the prevention and intervention. His group has discovered that the transcription factor, Nrf2, protects against pulmonary oxidative stress and inflammation and improves bacterial clearance that determines the pathobiology of COPD progression and exacerbations. His laboratory is developing Nrf2 as a therapeutic target for COPD and other inflammatory lung diseases.

Dr. Biswal has published around 120 papers in peer-reviewed journals and his research has been extensively funded by NIH and other foundations. He serves as a member on the committee of the American Thoracic Society. He also serves on the editorial board of the American Journal of Physiology and American Journal of Respiratory Cell and Molecular Biology.



**Catherine F. Clarke, Ph.D.**

Professor of Biochemistry,  
Department of Chemistry and  
Biochemistry, University of  
California at Los Angeles

Catherine Clarke received her training as a biochemist at the University of California, Los Angeles (UCLA) and Princeton University (Princeton, NJ). Following an appointment as Assistant Professor in the Department of Medicine, UCLA, Clarke moved to the Department of Chemistry and Biochemistry, also at UCLA, where she has been a professor since 2002.

Clarke is a world leader in the area of coenzyme Q (ubiquinone or Q) biosynthesis and function. She has published 93 peer-reviewed papers in top international journals. Clarke has received continuous funding from competitive national agencies (NIH-GMS, NIH-NIA, NSF), from foundations (AHA, AHAF, Ellison Medical Foundation) and from industry. She regularly reviews for international journals, and for national and international granting agencies. From 2005–2008 Clarke was a reviewer for NIA CMAD Study Section and in 2006 was Co-Chair of the FASEB Summer Conference on Biological Methylation. Clarke was an Ellison Medical Foundation Senior Scholar Award from 2001–2005, and in 2009 was awarded

the UCLA Department of Chemistry and Biochemistry Hanson-Dow Award for Teaching Excellence. Clarke has received more than 100 invitations to present seminars at universities and international meetings, including Gordon Research Conferences, FASEB Conferences, and International Coenzyme Q10 Association meetings.

Clarke is recognized internationally for her research on elucidating the gene-enzyme relationships of coenzyme Q biosynthesis, characterizing the polypeptide components responsible for the production of Q, and investigating the functional roles of Q. Her research takes advantage of respiratory defective coq mutants of the yeast *Saccharomyces cerevisiae* auxotrophic for Q. Her laboratory has identified and characterized eight of the ten yeast COQ genes that are required for Q biosynthesis and its function in respiration. The goals of her research are to characterize the Coq polypeptides responsible for production of Q and to determine how their activity can be modulated for optimal health. The findings Clarke made in the yeast model have shed much light on diseases resulting from Q deficiency.

In collaboration with Retrotope, Clarke is using novel isotope-reinforced polyunsaturated fatty acids (PUFAs) that reveal the importance of Q as an essential antioxidant. Polyunsaturated fatty acids (PUFA) undergo autoxidation and generate reactive carbonyl compounds that are toxic to cells and associated with apoptotic cell death, age-related neurodegenerative diseases, and atherosclerosis. PUFA autoxidation is initiated by the abstraction of bis-allylic hydrogen atoms. Replacement of the bis-allylic hydrogen atoms with deuterium atoms (termed site-specific isotope-reinforcement) arrests PUFA autoxidation due to the isotope effect. Clarke's findings show that inclusion of only a small fraction of PUFA deuterated at the bis-allylic sites is sufficient to profoundly inhibit the chain reaction of standard PUFAs.



**Yves Gorin, Ph.D.**

Associate Professor of Medicine  
Department of Medicine/Division  
of Nephrology  
University of Texas Health Science  
Center at San Antonio

During his Ph.D. graduate training at the University of Paris XI in France, Dr. Yves Gorin received extensive training in the field of the reactive oxygen species (ROS) biochemistry, particularly the generation of oxidants by the NADPH oxidases of the Nox family. He was actively involved in the identification of the thyroid NADPH oxidase, a member of the Nox family called Duox, which provides the hydrogen peroxide required for the thyroid hormone synthesis.

Dr. Gorin received his Ph.D. in 1998 and trained as a Postdoctoral Fellow in the Department of Medicine/Division of Nephrology at the University of Texas Health Science Center at San Antonio (UTHSCSA), where he applied his expertise related to NADPH oxidase biology to renal pathologies. His work explored the role of oxidative stress in kidney diseases with emphasis on the redox mechanisms involved in the hypertrophic and fibrotic responses of glomerular mesangial cells to angiotensin II and hyperglycemic conditions. Dr. Gorin has demonstrated that ROS generated by a member of the Nox family, Nox4, play a key role in the effects of angiotensin II or high glucose on

mesangial cell hypertrophy and extracellular matrix expansion. Using animal models of diabetes, Dr. Gorin identified Nox4 as mediator of oxidative stress, renal hypertrophy and extracellular matrix accumulation in early diabetic nephropathy. After becoming a faculty at UTHSCSA and establishing his own laboratory, Dr. Gorin further explored the biological function of Nox4 and reported for the first time its localization to mitochondria. These studies have revealed and defined the role of Nox4-derived ROS in the pathogenesis of diabetic kidney disease.

Much of Dr. Gorin's present activity focuses on the characterization of Nox4 downstream effectors and upstream regulators. Dr. Gorin's research group made the recent observation that ROS generated by Nox oxidases and specifically Nox4 play a pivotal role in endothelial nitric oxide synthase (eNOS) dysfunction in the glomerular endothelium and mesangium, thereby resulting not only in the elimination of the protective effect of eNOS, but also converting the enzyme to a phlogistic mediator that further enhances ROS generation. He has also identified the novel Sestrin family of stress-inducible protein as upstream modulators of Nox4 and demonstrated that Sestrin 2/AMP-activated protein kinase (AMPK) pathway attenuates Nox4-mediated eNOS dysfunction and renal cell injury in the diabetic environment. This research provided insight into new therapeutic targets for the treatment or prevention of diabetic kidney disease. In order to translate these findings to clinical application, Dr. Gorin is currently testing the bioefficacy of new small molecules inhibitors of Nox4 to protect against diabetic nephropathy in experimental animal models in collaboration with the biotech company GenKyoTex. Finally, Dr. Gorin has recently embarked on the investigation of the role of Duox1 and Duox2 NADPH oxidases in the complications of diabetes in the kidney.

Dr. Gorin is currently Principal Investigator on a NIH RO1 Grant and Co-Investigator on two others. He has received scientific awards from the Juvenile Diabetes Research Foundation, American Heart Association and National Kidney Foundation.





**Leonard P. Guarente, Ph.D.**

Novartis Professor of Biology  
Director, The Glenn Laboratory for  
the Science of Aging  
Massachusetts Institute of  
Technology, Cambridge, MA

Leonard Guarente is the Novartis Professor in the Department of Biology and Director of the Paul F. Glenn Laboratory at MIT. He is an editor of *Cell*, *Genes and Development*, *Cell Metabolism*, *TIG*, *EMBO Reports*, author of *Ageless Quest* (CSH Press), and editor of *Molecular Biology of Aging* (CSH Press). He discovered the central role of sirtuins in slowing aging, and found the biochemical function of this class of proteins—NAD-dependent protein deacetylation, which links metabolism, protein acetylation and aging. His recent research has focused on mammalian SIRT1, which deacetylates and regulates scores of transcription factors and cofactors in the nucleus. SIRT1 can be activated by calorie restriction (CR) to alter many physiological pathways that govern cell metabolism and stress resistance. SIRT1 can also mitigate diseases of aging, such as diabetes, neurodegenerative diseases, cardiovascular diseases, cancer, inflammatory diseases and osteoporosis, in a manner similar to CR. SIRT3 has emerged as another very exciting sirtuin, because it is activated by CR in mitochondria and functions to suppress reactive oxygen species (ROS). Recent data from many labs shows that SIRT3 links sirtuins, aging, CR, ROS and

mitochondria, and also plays an important role in tumor suppression. Sirtuin based therapies may therefore offer new approaches to human diseases.



**Dean P. Jones, Ph.D.**

Professor, Department of Medicine,  
Division of Pulmonary, Allergy,  
and Medicine and Department of  
Biochemistry  
Director, Emory Clinical Biomarkers  
Laboratory, Emory University,  
Atlanta, GA

Dr. Dean P. Jones received a B.S. in Chemistry from the University of Illinois, Urbana, in 1971 and a Ph.D in Biochemistry from Oregon Health Sciences University, Portland, in 1976. He was a National Sciences Foundation Postdoctoral Fellow in Nutritional Biochemistry at Cornell University, Ithaca, New York, and a Visiting Scientist in Molecular Toxicology at the Karolinska Institute, Stockholm, Sweden, prior to moving to Emory University in Atlanta, Georgia, as Assistant Professor of Biochemistry in 1979. He was promoted to Associate Professor of Biochemistry in 1985 and Professor of Biochemistry in 1991. In 1997-98, he was a Nobel Fellow at the Karolinska Institute, Stockholm. He has served in several leadership roles at Emory University, including Program Director of the Ph.D. program in Nutrition Health Sciences, Core Laboratory Director of the Emory University General Clinical Research Center, Executive Committee of the Emory-Georgia Tech Predictive Health Institute, and has chaired several committees of Emory University and Emory School of Medicine.

Dr. Jones studies redox biology and medicine and currently has research programs in the areas of redox systems biology and clinical metabolomics. The purpose of the former is to define redox control and signaling mechanisms and sites of disruption due to oxidative stress. This research uses a range of molecular and cell biology approaches, mass spectrometry-based proteomics and transgenic mouse models designed to understand oxidative stress in mitochondria and cell nuclei. The clinical metabolomics program uses high-resolution mass spectrometry to understand nutritional, environmental, genetic and therapeutic aspects of disease.

Recognized for his research in oxidative stress, environmental health and toxicology, mitochondrial mechanisms of cell death and thiol antioxidants glutathione and thioredoxin, Dr. Jones has over 270 peer-reviewed publications and over 140 invited reviews and book chapters. He has edited volumes on mitochondrial toxicity and microcompartmentation of metabolism. He recently received the R. Wayne Alexander Research Career Achievement Award from Emory University, and earlier received the Albert E. Levy Research Award, the most prestigious research award of Emory University, the Science and Humanity Award of the Oxygen Club of California, and is a member of the Emory Millipub Club, recognizing authors of manuscripts cited more than 1000 times. He has been a visiting professor at multiple institutions, sponsored by Medical Research Council of Canada, Burroughs Wellcome Trust, and Glaxo and others. His research has been supported by the National Institutes of Environmental Health Sciences, National Heart Lung and Blood Institute, National Institute of Aging, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute on Alcohol Abuse and Alcoholism, National Cancer Institute, National Eye Institute, National Institute for Allergy and Infectious Disease, Office of Naval Research, American Heart Association, American Institute for Cancer Research and other sources. He has served on multiple editorial boards and grant review panels, including Chair of the Alcohol and Toxicology Study Section for NIH, and a member of the Basic Mechanisms of Cancer Therapeutics Study Section for NCI.



**Manisha Patel, Ph.D.**  
Professor, Department of  
Pharmaceutical Sciences  
Skaggs School of Pharmacy and  
Pharmaceutical Sciences  
University of Colorado Anschutz  
Medical Campus, Aurora, CO

Dr. Manisha Patel received her Ph.D. in Pharmacology and Toxicology at Purdue University and post-doctoral training in Neuroscience at Duke University. She is currently a tenured Professor in the Department of Pharmaceutical Sciences at the University of Colorado Anschutz Medical Campus.

Her early work demonstrated a role for superoxide radicals in excitotoxic cell death and its amelioration by a metalloporphyrin antioxidant. The overarching theme of her research is to understand the role of reactive species and mitochondria in neuronal disorders. Epilepsy is a recent addition to the diverse array of acute and chronic neurological disorders in which the role of oxidative stress and mitochondria is rapidly emerging. Dr. Patel's laboratory has identified distinct subcellular sources and mechanisms of seizure-induced free radical production and impaired mitochondrial redox status. Ongoing efforts are aimed at determining the role of mitochondrial dysfunction and oxidative mechanisms in epileptogenesis.

Another focus of her laboratory is to identify the mechanisms by which mitochondrial reactive oxygen species mediate the death of dopaminergic neurons in Parkinson's disease.

Dr. Patel's laboratory is engaged in developing neuroprotective therapeutic entities such as metalloporphyrins designed to catalytically eliminate reactive oxygen species. Ongoing preclinical studies are aimed at testing their efficacy in animal models of neurological diseases.

She has authored more than seventy scientific publications including articles in the journals *Neuron*, *Journal of Neuroscience*, *Journal of Biological Chemistry* and *Proceedings in the National Academy of Sciences*. Dr. Patel serves on the editorial board of *Free Radical in Biology and Medicine*, *Epilepsy Currents* and *Redox Biology*. She has been the recipient of numerous grants from the National Institutes of Health, Michael J. Fox Foundation, Parkinson's disease foundation and CURE.



**George Perry, Ph.D.**  
Dean, College of Sciences,  
Semmes Foundation Endowed  
Chair in Neurobiology  
Professor of Biology, University of  
Texas at San Antonio

Dr. Perry received his bachelor's of arts degree in zoology with high honors from University of California, Santa Barbara. After graduation, he headed to Scripps Institution of Oceanography and obtained his Ph.D. in marine biology under David Epel in 1979. He then received a postdoctoral fellowship in the Department of Cell Biology in the laboratories of Drs. Bill Brinkley and Joseph Bryan at Baylor College of Medicine where he laid the foundation for his observations of abnormalities in cell structures.

In 1982, Perry joined the faculty of Case Western Reserve University, where he currently holds an adjunct appointment. He is distinguished as one of the top Alzheimer's disease researchers with over 1,000 publications, one of the top 100 most-cited scientists in neuroscience and behavior and one of the top 25 scientists in free radical research ([http://en.wikipedia.org/wiki/George\\_Perry\\_\(neuroscientist\)](http://en.wikipedia.org/wiki/George_Perry_(neuroscientist))) #Research\_focus.

Perry has been cited over 48,000 times and is recognized as a Thompson-Reuters highly cited researcher. Perry is editor for numerous journals and is editor-in-chief for the *Journal of Alzheimer's Disease*. He is a fellow of the American Association for the Advancement of Sciences, the Microscopy Society of America, past-president of the American Association of Neuropathologists, a member of the Dana Alliance for Brain Initiatives, and a Fulbright Senior Specialist.

Perry is recognized internationally for his work. He is a Foreign Correspondent Member of the Spanish Royal Academy of Sciences, the Academy of Science Lisbon, and a Foreign Member of the Mexican National Academy of Sciences. He is also a recent recipient of the National Plaque of Honor from the Republic of Panama Ministry of Science and Technology.

Perry's research is primarily focused on how Alzheimer disease develops and the physiological consequences of the disease at a cellular level. He is currently working to determine the sequence of events leading to damage caused by and the source of increased oxygen radicals along with mechanisms to provide more effective treatment.





**Ned A. Porter, Ph.D.**

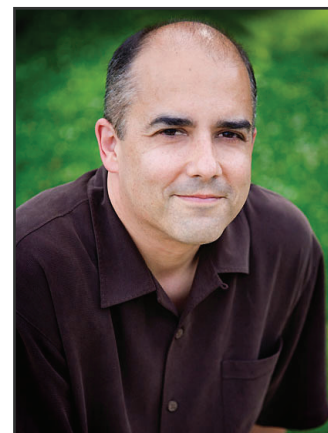
Professor, Department of Chemistry  
Associate Director, Vanderbilt  
Institute of Chemical Biology  
Vanderbilt University College of the  
Arts, Nashville, TN

Ned A. Porter. B.S. Che. E. (Summa cum laude) 1965, Princeton University; Ph.D. 1969, Harvard University (P. D. Bartlett); Duke University; Assistant Professor (1969-1974), Associate Professor (1974-1980), Professor (1980-1984), James B. Duke Professor (1984-1998); Vanderbilt University; Stevenson Professor (1998-Present), Professor of Biochemistry (2003-Present), Chairman, Department of Chemistry (2003-2009) Associate Director, Vanderbilt Institute of Chemical Biology (2003-Present); Phi Beta Kappa (1965, Princeton University), NIH Research Career Development Award (1977-1982); NC Distinguished Chemist Award (1984); NIH Merit Awardee (1996-2006); Cope Scholar of the American Chemical Society (2000); C. K. Ingold Prize of the Royal Society of Chemistry (2005); Board of Editors, Journal of Organic Chemistry (1980-1985, 1996-2001); Board of Editors, Journal of the American Chemical Society (1986-1991); NIH Study Section Member (1984-1989); Humboldt Senior Prize Winner (Institute of Organic Chemistry, Darmstadt, 1998; Institute of Organic Chemistry, Freiburg, 1994); Merck-Frosst Lectureship (1991); AAAS Fellow (2003); James Flack Norris Award from the Northeast Section of the ACS (2013). His research interests are primarily focused on free radical chemistry,

oxidation reactions, and antioxidants. He has published more than 250 papers, articles, reviews and a book on "Control of Stereochemistry in Free Radical Reactions; Concepts, Guidelines, and Synthetic Applications", coauthored with Dennis Curran and Bernd Giese. He has also presented over 350 plenary and invited lectures at international conferences, symposia, universities, research institutes and companies.

Ned Porter's research over the past thirty-five years has dealt with the fundamental questions of structure and reactivity as they are manifested in free radical reactions in solution or in molecular aggregates. In choosing targets for research, he has emphasized fundamental questions in free radical chemistry and has led the way in many important areas. His work has consistently emphasized reaction mechanism in the Ingold tradition although the application of his discoveries spans much of organic chemistry from synthesis to bioorganic chemistry.

Mechanistic work by Porter's group provides a rational basis for understanding the free radical reactions of molecular oxygen with compounds of biological importance such as polyunsaturated fats and other lipids. This work was initiated in 1975 and continues today and it has emphasized fundamental aspects in this field which today has come to be known as free radical biology. The biochemical literature is today full of papers that report on lipid peroxidation in membranes and other biological materials containing poly-unsaturated fats and it was Porter who provided the fundamental studies on which much of this work is based. His systematic study of peroxy radical abstraction, fragmentation, and cyclization in the period of time 1975-1985 led to a mechanistic framework for these three competing reactions which are involved in every peroxidation chain and his discovery that inhibitors of autoxidation influence products as well as the dynamics of the chain process are fundamental contributions to this field. Today, he continues his active publication in this field and much of his recent work in this field has a focus on the mechanism of oxidation in biologically relevant particles such as low density lipoproteins (LDL).



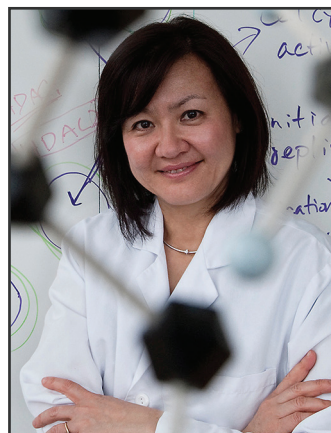
**Kenneth J. Rhodes, Ph.D.**

Vice President, Neurology  
Discovery, Biogen Idec

Ken leads the Neurology Research group at Biogen Idec. The mission of this group is to drive the discovery and validation of novel drug targets and translational biomarkers that will be used in the treatment of MS and other neurodegenerative diseases.

Ken joined Biogen Idec in 2007, after nearly 5 years as a Research Fellow and CNS Team Leader at Johnson & Johnson Pharmaceutical Research and Development, LLC. Prior to J&J, Ken spent 10 years in Neuroscience Discovery Research at Wyeth, where he lead drug discovery activities in neurodegenerative disease, with a focus on ion channels and epilepsy. Over his twenty year career in biopharmaceutical R&D, Ken has lead drug discovery programs in the areas of Alzheimer's disease, MS, Parkinson's disease, epilepsy and stroke, among other CNS disorders.

Ken has published over 50 original research articles in peer-reviewed journals. He earned his Ph.D. in Anatomy and Neurobiology at Boston University, and completed postdoctoral training at the National Eye Institute, National Institutes of Health, and the Department of Pharmacology, Boston University School of Medicine.



**Li-Huei Tsai, Ph.D., D.V.M.**

Picower Professor of Neuroscience  
Director, The Picower Center for  
Learning and Memory  
Investigator, Howard Hughes  
Medical Institute  
Massachusetts Institute of  
Technology, Cambridge, MA

Dr. Li-Huei Tsai was born in Taipei, Taiwan. In 1986, she began her Ph.D. at the University of Texas Southwestern. Under the direction of Bradford Ozanne, she graduated in 1990 and joined Ed Harlow's laboratory at Cold Spring Harbor Laboratory and Massachusetts General Hospital for postdoctoral training. She was appointed Assistant Professor of Pathology at Harvard Medical School in 1994, and promoted to Professor of Pathology in 2002. In 2006, she relocated her lab to MIT and became the Picower Professor of Neuroscience and was named Director of the Picower Institute for Learning & Memory in 2009. Dr. Tsai was elected Fellow of the American Association for the Advancement of Science in 2008 and Member of the Institute of Medicine in 2011. Her research focuses on the elucidation of the cellular, molecular and circuit mechanisms contributing to the development and manifestation of the pathology and symptoms of Alzheimer's disease (AD).



**Neal L. Weintraub, M.D.**

Herbert S. Kupperman Endowed  
Chair in Cardiovascular Science;  
Associate Director, Medical College  
of Georgia Vascular Biology Center  
Georgia Regents University,  
Augusta, GA

Neal L. Weintraub, M.D., graduated from Tulane University School of Medicine in 1984. He completed clinical training in Internal Medicine at Emory University and the University of Illinois and undertook a combined research/clinical Cardiovascular Fellowship at St. Louis University from 1991-1995. He joined the faculty at the University of Iowa College of Medicine in 1995, rising to the rank of Professor of Medicine in 2005 and serving as Interim Division Director of Cardiovascular Diseases from 2003-2005. In 2006, he was recruited to the University of Cincinnati College of Medicine as the Stonehill Professor of Medicine and Director, Division of Cardiovascular Diseases. In June of 2013, Dr. Weintraub was recruited to Georgia Regents University/Medical College of Georgia, where he holds the title of GRA Kupperman Eminent Scholar in Cardiovascular Medicine and serves as Professor of Medicine and Associate Director of the Vascular Biology Center.

Dr. Weintraub's laboratory is focused on vascular biology research with emphasis on oxidative stress, inflammation, and obesity. In particular, his work has advanced the understanding of the role of oxidative stress in the pathogenesis of abdominal aortic aneurysm (AAA) disease. He has been NIH funded since 1997 and currently is a principal investigator on two R01 grants. Dr. Weintraub served on the NIH AICS study section from 2008-2013 and was Chairman from 2011-2013. He has served on the editorial board of the journal *Arteriosclerosis, Thrombosis and Vascular Biology* since 2000.

As a clinical cardiovascular physician, Dr. Weintraub treats patients with a variety of cardiovascular disorders and has been ranked among the Best Doctors in America for six consecutive years. He also conducts clinical research in stem cell therapy, heart failure, and remote cardioprotection. Dr. Weintraub is Co-Founder and Chief Medical Officer of Cardioception, LLC, a biotech company established in 2010 that is utilizing the skin's natural protective functions to develop innovative therapies for limiting heart damage in the setting of a heart attack. He chaired an American Heart Association Writing Committee that developed a scientific statement on acute treatment of heart failure in 2010. Also, he served as President of the Central Society for Clinical Research, an academic medical society in the Midwest, during 2013.





**Donna D. Zhang, Ph.D.**  
Professor, Department of  
Pharmacology and Toxicology  
College of Pharmacy, University of  
Arizona, Tucson, AZ

Donna D. Zhang received her Ph.D. from New York University in 1997. After a brief postdoctoral fellowship at the DuPont-Haskell Laboratory, she took a Research Assistant Professor position in the Biochemistry Department at the University of Missouri-Columbia. She joined the University of Arizona as an Assistant Professor in 2005 and is currently a Professor in the Department of Pharmacology and Toxicology, College of Pharmacy, University of Arizona (UA).

Dr. Zhang's research program focuses the key physiological and pathological roles of the Nrf2-Keap1-ARE pathway. She has published over 70 well-received papers as evidenced by the total number of citations (2829) and h-index (25) [Web of Science database as of August 29, 2013]. Dr. Zhang has made seminal contributions to both the mechanistic understanding of Nrf2 regulation, the protective role of Nrf2, and the positive and negative relationship between Nrf2 and cancer. Her work has been continuously supported by the NIH and American Cancer Society. In 2012, She got the Society of Toxicology Achievement Award.

In the area of physiologic Nrf2 regulation, Dr. Zhang identified that three cysteine residues of Keap1 (C151, C277 and C288) are critical in sensing cellular redox conditions and electrophilic xenobiotics to regulate the activity of Nrf2. Dr. Zhang also determined that Keap1 is part of an E3-ubiquitin ligase complex that constantly ubiquitylates Nrf2, targeting it for degradation, which has been proven to be the primary mode of regulating Nrf2 activity. In addition, Dr. Zhang's group has published many influential papers reporting the functional significance of crosstalk between the Nrf2 pathway and other important pathways/proteins including p53-p21, p62-autophagy, and the deubiquitylating enzyme USP15.

Dr. Zhang has discovered many chemopreventive small-molecules that activate Nrf2 and are effective for disease prevention. However, in 2008, Dr. Zhang presented the unprecedented concept of "the dark side of Nrf2", demonstrated that Nrf2 also contributes to chemoresistance and she provided strong evidence that inhibiting expression of Nrf2 renders cancer cells more susceptible to chemotherapeutic drugs. Building on this idea, her team has identified the first rationally discovered compound, brusatol, to inhibit the Nrf2 pathway. Brusatol was able to overcome both intrinsic and acquired chemoresistance both in vitro and in vivo. Dr. Zhang is also examining the effects of Nrf2 signaling on arsenic toxicity/carcinogenicity. Her team found that arsenic leads to constitutive Nrf2 activation through autophagy deregulation, which represents a previously unrecognized connection between prolonged Nrf2 activation and arsenic carcinogenicity in humans. Her group has leveraged these data to show that Nrf2 activation by chemopreventive small-molecules is a strategy to alleviate arsenic-mediated damage. This work should have broad impact on diseases caused by arsenic exposure that still affects millions of people worldwide.

Tuesday, November 5, 2013

8:00 – 8:30 **Opening Remarks**

8:30 – 8:40 **Welcome**

David H. Farb, Ph.D., Chair, *Department of Pharmacology & Experimental Therapeutics, Boston University School of Medicine*

**SESSION 1: SMALL MOLECULES: POTENTIATORS OF NRF2 ANTIOXIDANT RESPONSE**

Moderator: Neil J. Ganem, Ph.D., *Assistant Professor, Departments of Pharmacology & Experimental Therapeutics and Medicine, Division of Hematology and Medical Oncology, and Member, The Cancer Center, Boston University School of Medicine*

8:40 – 9:10 **The Nrf2-Keap1-ARE Pathway and its Dual Role in Cancer**

Donna D. Zhang, Ph.D., Professor, Department of Pharmacology and Toxicology College of Pharmacy, University of Arizona, Tucson, AZ

9:10 – 9:40 **Sirtuins and NAD—Approaches to Diseases of Aging**

Leonard P. Guarente, Ph.D., Novartis Professor of Biology and Director, The Glenn Laboratory for the Science of Aging, Massachusetts Institute of Technology, Cambridge, MA

9:40 – 10:10 **Nrf2 as a Therapeutic Target for COPD**

Shyam S. Biswal, Ph.D., M.S., Professor and Associate Chair for Research, Department of Environmental Health Sciences, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD

10:10 – 10:30 **Morning Break**

**SESSION 2: INHIBITORS/MODULATORS OF REDOX SENSITIVE ENZYMES**

Moderator: Richard D. Wainford, Ph.D., F.A.H.A., *Assistant Professor, Departments of Pharmacology & Experimental Therapeutics and Medicine, Division of Cardiovascular Medicine, and The Whitaker Cardiovascular Institute, Boston University School of Medicine*

10:30 – 11:10 **Inhibitors/Modulators of Nox4 NADPH Oxidase as Novel Therapeutic Tools for the Treatment of Diabetic Kidney Disease**

Yves Gorin, Ph.D., Associate Professor, Department of Medicine, Division of Nephrology, University of Texas Health Science Center, San Antonio, TX

11:10 – 11:40 **Modulating Histone Deacetylases to Treat Neurodegenerative Disorders**

Li-Huei Tsai, Ph.D., D.V.M., *Picower Professor of Neuroscience and Director, The Picower Center for Learning and Memory; Investigator, Howard Hughes Medical Institute, Massachusetts Institute of Technology, Cambridge, MA*

11:40 – 12:30 **Buffet Lunch**

12:30 – 12:40 **Educational Lecture/Introduction of Keynote Speaker**

Cara M.M. Williams, Ph.D., *Pfizer Biotherapeutics & BU Pharmacology*

12:40 – 1:30 **Deconstructing DMF: Lessons Learned in the Development of Tecfidera**

Kenneth J. Rhodes, Ph.D., *Vice President, Neurology Discovery Biogen Idec*

**Tuesday, November 5, 2013**

**SESSION 3: FROM CHEMICAL BIOLOGY TO MIMETICS**

- Moderator: Shelley J. Russek, Ph.D.  
*Professor, Department of Pharmacology & Experimental Therapeutics, Boston University School of Medicine, Director, Graduate Program for Neuroscience, Boston University*
- 1:30 – 2:00** **New Insights and Therapeutics for Superoxide Dismutase Toxicity in ALS**  
Joseph S. Beckman, Ph.D., *Ava Helen Paul Endowed Chair, The Linus Pauling Institute, University Distinguished Professor; and Director, Environmental Health Sciences Center, Oregon State University, Portland, OR*
- 2:00 – 2:30** **Targeting Oxidative Stress in Neuronal Disorders with Metalloporphyrins**  
Manisha Patel, Ph.D., *Professor, Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora, CO*
- 2:30 – 2:50** **Afternoon Break**
- 2:50 – 3:20** **Oxidative Stress as a Target for Pharmacotherapy in Abdominal Aortic Aneurysms**  
Neal L. Weintraub, M.D., *Herbert S. Kupperman Endowed Chair in Cardiovascular Science and Associate Director, Medical College of Georgia Vascular Biology Center, Georgia Regents University, Augusta, GA*
- 3:20 – 3:50** **Isotope-Reinforced Polyunsaturated Fatty Acids Suppress Lipid Autoxidation**  
Catherine F. Clarke, Ph.D., *Professor of Biochemistry, Department of Chemistry and Biochemistry, University of California at Los Angeles, CA*

**SESSION 4: NOVEL TECHNOLOGIES TO ASSESS OXIDATIVE STRESS**

- Moderator: Rachel L. Flynn, Ph.D., *Assistant Professor, Departments of Pharmacology & Experimental Therapeutics and Medicine, Division of Hematology and Medical Oncology, and The Cancer Center, Boston University School of Medicine*
- 3:50 – 4:20** **Role of Mitochondria in the Oxidative Stress of Alzheimer's Disease**  
George Perry, Ph.D., *Dean, College of Sciences, Semmes Foundation Endowed Chair in Neurobiology, Professor of Biology, University of Texas at San Antonio, TX*
- 4:20 – 4:50** **Free Radical Oxidation of Sterols and Sterol Esters *in vitro* and *in vivo***  
Ned A. Porter, Ph.D., *Professor, Department of Chemistry and Associate Director, Vanderbilt Institute of Chemical Biology, Vanderbilt University College of the Arts, Nashville, TN*
- 4:50 – 5:20** **Oxidative Stress and Redox Proteomics: Targeting Complex Networks**  
Dean P. Jones, Ph.D., *Professor, Department of Medicine, Division of Pulmonary, Allergy, and Medicine and Department of Biochemistry; Director, Emory Clinical Biomarkers Laboratory, Emory University, Atlanta, GA*
- 5:20 – 5:50** **Open Forum**
- 6:00 – 7:00** **Reception**



