Boston University Pharmacology & Experimental Therapeutics – Pfizer Symposium

Emerging Technologies in Therapeutics







BU Pharmacology & Experimental Therapeutics/Pfizer Biotherapeutics Hot Topics Symposia

Dear Colleagues,

Welcome to the symposium "Emerging Technologies in Therapeutics" organized by the NIGMS Training Program in Biomolecular Pharmacology at Boston University in collaboration with Pfizer. This is the sixth symposium in a series that reflects our long-standing collaboration (since 1999) and mutual interests in doctoral education. The object of each symposium is to enhance the research training of doctoral students and their faculty mentors both at BU and Pfizer who participate in our university-wide NIGMS Biomolecular Pharmacology training program. Symposia focus on timely advances in the biomedical sciences that are poised for breakthroughs that lead to therapeutic discovery. We try to 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 Industry-Academia collaboration has provided training opportunities for doctoral students seeking an industry research experience. Importantly, the participation of industry professionals in basic science lecturing and the training of PhD and MD/PhD students has enormously enriched our pharmacological sciences training program.

Five 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 Dysregulations." In December 2010, the symposium focused on "Inflammation Breaking Out: Molecular Mechanisms for Therapeutic Discovery." On 30 April 2012, the program focused on "Therapeutic Innovation: The Next Generation of Discovery." Most recently, on 5 November 2013 the program addressed, "Therapeutic Innovation: Oxidative Stress and the Next Generation of Discovery."

In this year's symposium, the focus is on "Emerging Technologies in 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 new and emerging technological approaches that could be of interest to our broad range of interdisciplinary students and faculty.

We are excited to bring together an eclectic group of thought leaders to share their insights with students, faculty, and guests through exploring the scientific discovery process. It is our hope that sharing the cutting edge science will foster innovation and collaboration that will lead to the discovery of breakthrough therapies for those who suffer from debilitating diseases.

Sincerely,

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

Marion Kasaian, PhD, Inflammation and Immunology, Pfizer

William Gordon, PhD, Senior Principal Scientist and Disease Pathogenesis Lead, Pfizer

Monday, May 1, 2017

- 8:00 8:30 **Registration and Breakfast** *Opening Remarks*
- 8:30 8:40 INTRODUCTION TO THE BU PFIZER DOCTORAL TRAINING PARTNERSHIP David H. Farb, Ph.D., Chair, BU Pharmacology and Director, NIGMS Program in Biomolecular Pharmacology Lori Fitz, Ph.D., Precision Medicine Scientist and Laboratory Head, Pfizer; 2006 Graduate of the Boston University Program in Biomolecular Pharmacology

SESSION 1 CYTOSOLIC DNA SENSORS AND DEATH PATHWAYS

Moderator: Rachel L. Flynn, Ph.D., Assistant Professor of Pharmacology & Experimental Therapeutics, BU

- 8:40 9:00 RIPK1 in Necroptosis and Axonal Degeneration: From Basic Cell Death to Human Clinical Applications Junying Yuan, Ph.D., Elizabeth D. Hay Professor of Cell Biology, Harvard Medical School, Boston, MA
- 9:10 9:30 Receptor Interacting Protein Kinases: Integrating Cell Death and Inflammation Signals Francis Ka-Ming Chan, Ph.D., Professor of Pathology, University of Massachusetts Medical School, Worcester, MA
- 9:40 10:00 To the Edge of Necroptosis and Back Douglas R. Green, Ph.D., Member and Chair, Department of Immunology and the Peter C. Doherty Endowed Chair in Immunology, St. Jude Children's Research Hospital, Memphis, TN
- 10:10 10:30 Morning Break

SESSION 2 THE UNFOLDED PROTEIN RESPONSE

Moderator: Hui Feng, M.D., Ph.D., Assistant Professor of Pharmacology & Experimental Therapeutics, BU

- 10:40 11:00 Protein Misfolding in the Endoplasmic Reticulum and Oxidative Stress Initiate Liver Failure in Non-Alcoholic Steatohepatitis (NASH) Randal J. Kaufman, Ph.D., Director, Degenerative Diseases Program and Endowed Chair in Cell Biology, Sanford Burnham Prebys Medical Discovery Institute La Jolla, CA
- 11:10 11:30 Targeting the Unfolded Protein Response in Pancreatic Neuroendocrine Tumors Scott A. Oakes, M.D., Professor of Pathology, University of California San Francisco School of Medicine, San Francisco, CA
- 11:40 12:00 A Mitochondrial Stress Response and Propagation of Toxic Genomes Cole Haynes, Ph.D., Associate Professor of Molecular, Cell, and Cancer Biology, University of Massachusetts Medical School, Worcester, MA
- 12:00 1:00 Buffet Lunch

Monday, May 1, 2017

SESSION 3 PHARMACOLOGY AS A CENTRAL DISCIPLINE IN DRUG DISCOVERY

Moderator: Camron Bryant, Ph.D., Assistant Professor of Pharmacology & Experimental Therapeutics, BU

- 1:00 1:10 *EDUCATION: Pharmacology in a Changing Therapeutic Landscape* Marion Kasaian, Ph.D., *Inflammation and Immunology, Pfizer*
- 1:20 1:50 DISCOVERY: Learning from Tofacitinib, a JAK Inhibitor for Autoimmune Disease

James D. Clark, Ph.D., Director, Inflammation and Immunology, Pfizer

- 1:50 2:10 PHARMACOLOGY IN CLINICAL TRIALS AND DRUG DISCOVERY Gianluca Nucci, Ph.D., Vice President, Early Clinical Development/Clinical Pharmacology, Pfizer.
- 2:20 2:35 Afternoon Break

SESSION 4 INNOVATION IN CANCER THERAPEUTICS

Moderator: David Peritt, Ph.D., *Research Project Leader, Inflammation and Immunology, Pfizer.*

- 2:40 3:00 Gene and Oncolytics Immunotherapy Clinical Trials for Glioblastoma E. Antonio Chiocca, M.D., Ph.D., Harvey Cushing Professor of Neurosurgery, Harvard Medical School; Chairman, Department of Neurosurgery, Brigham and Women's, Boston, MA
- 3:10 3:30 Replicating Virus Therapeutics for the Treatment of Cancer John C. Bell, Ph.D., Senior Scientist, Centre for Innovative Cancer Research, Ottawa Hospital Research Institute; Professor, Departments of Medicine and Biochemistry, Microbiology & Immunology, University of Ottawa, Ottawa, Ontario, Canada

BUSM ALUMNUS KEYNOTE ADDRESS

- 3:40 4:00 Polymeric Nanoparticles: Tumor Microenvironment Variability and Implications for New Nanoparticle Design and Development Omid C. Farokhzad, M.D. (BUSM '99), Associate Professor, Harvard Medical School; Director, Center for Nanomedicine, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Boston, MA
- **4:10 4:40** *Open Forum Moderator:* William Gordon, Ph.D., Senior Principal Scientist and Disease Pathogenesis Lead, Pfizer
- 4:40 4:45 Closing Remarks David H. Farb, Ph.D.
- 4:45 6:00 Reception

Free and Open to the Public

BU Pharmacology & Experimental Therapeutics – Pfizer Symposium Emerging Technologies in Therapeutics



Junying Yuan, Ph.D., Elizabeth D. Hay Professor of Cell Biology,Harvard Medical School, Boston, MA

RIPK1 in Necroptosis and Axonal Degeneration: From Basic Cell Death to Human Clinical Applications

Junying Yuan received her Ph.D. in Neuroscience from Harvard University in 1989 and her undergraduate degree from Fudan University, Shanghai, China, in 1982. Dr. Yuan carried out her Ph.D. thesis work at the Massachusetts Institute of Technology. She was first appointed as Assistant Professor at Harvard Medical School in 1992, when she became a Principal Investigator of the Cardiovascular Research Center at Massachusetts General Hospital. She joined the Department of Cell Biology in 1996 and was appointed a Professor of Cell Biology at Harvard Medical School in 2000. In 2014, Dr. Yuan was appointed as Elizabeth D. Hay Professor of Cell Biology, a Professorship honors the late Professor Elizabeth D. Hay, the first female full professor in the history of Harvard Medical School.

Dr. Yuan is a pioneer and a leader in the cell death field. Dr. Yuan made transformative discoveries on two distinct forms of cell death, apoptosis and necroptosis in mammalian cells. Her

discovery of mammalian caspases led to a molecular era in apoptosis research. Her development of necrostatins demonstrated the existence and significance of a regulated necrosis mechanism, termed necroptosis, in human degenerative diseases. A lead RIPK1 inhibitor developed by Dr. Yuan has entered a human clinical trial as a first-in-class new drug for the treatment of amyotrophic lateral sclerosis and Alzheimer's disease. Dr. Yuan's accomplishments have been honored by many awards including the Innovator Award for Breast Cancer Research and NIH Director's Pioneer award. She is a fellow of the American Academy of Arts and Sciences and a fellow of the American Association for the Advancement of Sciences.



Francis Ka-Ming Chan, Ph.D.,

Professor of Pathology, University of Massachusetts Medical School, Worcester, MA

Receptor Interacting Protein Kinases: Integrating Cell Death and Inflammation Signals

Dr. Chan's research interest is in the area of cell death, inflammation and immunology. He has a long-standing interest in the biology and signaling mechanism of tumor necrosis factor (TNF), a key cytokine in many inflammatory diseases (e.g. rheumatoid arthritis, inflammatory bowel diseases, etc.) and pathogen infections. He has made seminal discoveries in cell death and inflammation over the years. As a Ph.D. graduate student, he cloned one of the first cell cycle inhibitors, INK4d-p19. As a postdoctoral fellow at the NIH, he discovered that TNF receptors exist and function as pre-assembled trimers that undergo conformational change in response to ligand binding. This discovery changes the long-held paradigm that TNF receptors signal through ligand-induced trimerization mechanism, and explained how non-ligand-binding mutants of the Fas receptor cause an unusual form of autoimmune lymphoproliferative diseases in humans. Since setting up his own research group in 2002, he has focused on elucidating

the molecular mechanism of a novel form of inflammatory cell death termed necroptosis. In 2009, he identified Receptor Interacting Protein Kinase 3 (RIPK3) as a central mediator of necroptosis. This discovery has revolutionized the field of cell death research, leading to an avalanche of recent work on necroptosis and inflammation. In recent years, he has expanded his research beyond necroptosis and identified cell death-independent mechanisms by which RIPK3 stimulates inflammation.

Dr. Chan is currently a Professor of Pathology and Chair of the Immunology and Microbiology Graduate Program at the University of Massachusetts Medical School. He is also a Senior Scholar of the Crohn's and Colitis Foundation of America. He received his B.A. in Biochemistry and Cell Biology Summa Cum Laude in 1991 from the University of California – San Diego and his Ph.D. in Molecular & Cell Biology from the Division of Immunology at the University of California – Berkeley in 1996. From 1997 to 2002 Dr. Chan was a Postdoctoral Research Fellow under the mentorship of Michael Lenardo, M.D., Section Chief of the Laboratory of Immunology at the National Institutes of Health/National Institute of Allergy and Infectious Diseases.





Douglas R. Green, Ph.D.,

Member and Chair, Department of Immunology and the Peter C. Doherty Endowed Chair in Immunology, St. Jude Children's Research Hospital, Memphis, TN

To the Edge of Necroptosis and Back

Doug Green is the Peter C. Doherty Endowed Chair of Immunology at St Jude Children's Research Hospital. Prior to this he was Head of the Division of Cellular Immunology at the La Jolla Institute for Allergy and Immunology. Professor Green received his Ph.D. from Yale University, following which he joined the faculty at the University of Alberta in Edmonton before moving to La Jolla. His research has focused on the process of active cell death and cell survival, extending from the role of cell death in the regulation of cancer and immune responses in the whole organism to the fundamental molecular events directing the death of the cell. This work began with his discovery of activation-induced apoptosis in T lymphocytes, the role of c-Myc in this process, and the finding that Bcl-2 cooperates with Myc in oncogenesis by blocking apoptosis. These are themes that he continues to study. More recently, he discovered the process of LC3-associated phagocytosis, which links the autophagy pathway to phagosome maturation. Other areas of intense interest include regulated necrosis, metabolic reprogramming in T lymphocytes, and the function of the tumor suppressor, p53. He has published over 500 papers,

chapters, and books, and is an ISI "highly cited" investigator. His recent book is "Means to an End: Apoptosis and Other Cell Death Mechanisms," published in 2011 by Cold Spring Harbor Laboratory Press and available at Amazon.



Randal J. Kaufman, Ph.D.,

Director, Degenerative Diseases Program and Endowed Chair in Cell Biology, Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA

Protein Misfolding in the Endoplasmic Reticulum and Oxidative Stress Initiate Liver Failure in Non-Alcoholic Steatohepatitis (NASH)

Dr. Kaufman, a leader in basic biomedical research, has made fundamental contributions to translational medicine in his industrial and academic careers. He received a Ph.D. in Pharmacology at Stanford University and performed postdoctoral work with Dr. Phillip Sharp at the MIT Center for Cancer Research. After post-doctoral work, he was a founding scientist at the biotech Genetics Institute, Inc., where he developed gene cloning and expression strategies in mammalian cells. His team isolated clotting factors, genes, and engineered cells to produce the recombinant proteins for therapeutic use that revolutionized protein replacement for hemophilia A. In 1994, he moved to take positions of Investigator at the HHMI and Warner-Lambert/Park-Davis Professor in Medicine and in the Department of Biological Chemistry at the University of Michigan Medical Center. In Michigan, his pioneering studies to identify rate-limiting steps in protein secretions elucidated the roles of protein chaperones and enzymes that limit protein

folding, processing and trafficking within the early secretory pathway. His ground-breaking studies in this area were paradigm-shifting toward future genetic engineering of mammalian cells to efficiently secrete therapeutic protein and contributed to the discovery of the unfolded protein response (UPR), which has exploded into an entirely new field of investigation. After elucidating the molecular sensors and mechanisms that signal UPR through PERK, IRE1 and ATF6, Dr. Kaufman extended his studies using murine genetic models to show that UPR signaling is essential for normal physiology and also contributes to the progression of diverse pathologies including metabolic syndrome, diabetes, inflammation and cancer. His recent studies identified a molecular mechanism by which protein synthesis causes oxidative stress and dictates whether a cell survives or dies upon accumulation of misfolded proteins in the ER.



Scott A. Oakes, M.D.,

Professor of Pathology, University of California San Francisco School of Medicine, San Francisco, CA

Targeting the Unfolded Protein Response in Pancreatic Neuroendocrine Tumors

Scott André Oakes, M.D., completed medical school at the University of Connecticut during which he spent an additional year doing bench research at the National Institutes of Health (NIH) as a Howard Hughes Medical Institute (HHMI)-NIH Research Scholar. After medical school, he did a residency in anatomic pathology at the Brigham and Women's Hospital and Harvard Medical School in Boston. A board-certified pathologist who supervises the autopsy service at UCSF, Oakes oversees a research laboratory that studies how mammalian cells sense protein-folding crises within the endoplasmic reticulum (ER) and deterministically repair the damage or commit apoptosis. His goal is to understand the precise molecular events that control cell fate in response to ER stress so that they can design small molecules to protect against cell loss in human degenerative diseases such as neurodegeneration and diabetes and promote cell death in highly secretory tumors. He teaches in both the

graduate and medical schools and UCSF, and is also on the Medical Scientist Training Program (MSTP) Council. Dr. Oakes has won numerous awards for his research, including an HHMI Early Career Physician Scientist Award, American Cancer Society Research Scholar Award, Harrington Discovery Institute Scholar-Innovator Award, American Association for Cancer Research Award, and is an Inductee of the American Society for Clinical Investigation (ASCI).



Cole Haynes, Ph.D.,

Associate Professor of Molecular, Cell, and Cancer Biology, University of Massachusetts Medical School, Worcester, MA

A Mitochondrial Stress Response and Propagation of Toxic Genomes

Cole Haynes is an Associate Professor in the Molecular, Cell and Cancer Biology Department at the University of Massachusetts Medical School. He received his Ph.D. in cell biology and biophysics at the University of Missouri-Kansas City and did his post-doctoral fellowship at New York University in David Ron's laboratory. He established his own lab in 2009 at the Memorial Sloan Kettering in Cancer Center focusing on how cells adapt to mitochondrial dysfunction via a mitochondrialto-nuclear signaling pathway known as the mitochondrial unfolded protein response. In 2016, he moved to the University of Massachusetts Medical School. His main interests are in understanding how the UPRmt is regulated and how this stress response pathway is integrated into overall cell biology, organismal physiology and age-associated disease pathology. The lab has found surprising roles for this stress response in innate immunity regulation as well as the propagation of deleterious mitochondrial genomes. For this work he has

received awards including the Ellison Foundation New Scholar in Aging, the Boyer Award, the Glenn Award for Aging Research, the Young Investigator Award from the American Society for Biochemistry and Molecular Biology, a Mallinckrodt Scholar Award and he was recently named a Howard Hughes Medical Institute Faculty Scholar.



E. Antonio Chiocca, M.D., Ph.D.,

Harvey Cushing Professor of Neurosurgery, Harvard Medical School; Chairman, Department of Neurosurgery, Brigham and Women's, Boston, MA

Gene and Oncolytics Immunotherapy Clinical Trials for Glioblastoma

Dr. Chiocca is the Harvey Cushing Professor of Neurosurgery at Harvard Medical School and is the Chairman Neurosurgery at the Brigham and Women's Hospital. He was previously Chairman of the Department of Neurosurgery at the Ohio State University Medical Center. He has been continuously funded by the NIH since 1996. He has more than 250 peer-reviewed publications, in journals such as Nature Medicine, Nature Biotechnology, Molecular Cell, and PNAS. He has elucidated how viruses with specific gene mutations will replicate selectively in tumors with a specific defect in a tumor suppressor pathway. He has also shown how modulation of innate immunity will improve replication of these tumor-selective viruses. More recently, he has elucidated how specific microRNAs (mir128 and mir451) regulate cellular target transcripts to permit tumor cell selfrenewal and invasion into brain. He has been PI of three multiinstitutional clinical trials of gene-, viral-therapies for malignant gliomas, has been permanent member of NIH study sections (NCI DT and NCI P01-D clinical studies), has been a member of the federal recombinant DNA Advisory Committee (RAC/OBA)

and is currently a member of the NINDS Scientific Advisory Council. In 2013, he was elected Vice-President of the Society for Neuro-Oncology (SNO). In 2015, he was elected President of SNO. He is currently Treasurer of the American Academy of Neurological Surgery and is Chair of the Research Committee for the Society of Neurological Surgery. He also serves on the scientific advisory board of several foundations (Sontag, American Brain Tumor Association). He received The Grass Award in 2007, the Farber Award in 2008 and the Bittner Award in 2013. He was elected to the American Society for Clinical Investigation (2005), is an AAAS fellow (2005) and was also elected to the National Academy of Medicine (formerly Institute of Medicine) in 2014. He also has served on multiple editorial boards and is the current Tumor Section Editor for Neurosurgery. He was on the editorial board of Journal of Neurosurgery from 2005 until 2012.



John C. Bell, Ph.D.,

Senior Scientist, Centre for Innovative Cancer Research, Ottawa Hospital Research Institute; Professor, Departments of Medicine and Biochemistry, Microbiology & Immunology, University of Ottawa, Ottawa, Ontario, Canada

Replicating Virus Therapeutics for the Treatment of Cancer

Dr. John Bell received his Ph.D. from McMaster University in 1982. The three years that followed, he trained as a postdoctoral fellow at the University of Ottawa and then at the Medical Research Council in London, England. Dr. Bell began his independent research career at McGill University in 1986 and moved to the University of Ottawa, Department of Medicine, in 1989. He is a member of the Center for Cancer Therapeutics at The Ottawa Hospital Cancer Center, a Senior Scientist with the Ottawa Hospital Research Institute and Professor of Medicine at the University of Ottawa. He heads the Canadian Oncolytic Virus Consortium, a Terry Fox funded group from across Canada that is developing virus based cancer therapeutics and is the Director of the Biotherapeutics Program for the Ontario Institute for Cancer Research. He is the Scientific Director of the recently awarded National Centre of Excellence for the development of Biotherapeutics for Cancer Therapy and is a fellow of the Royal Society of Canada.



Omid C. Farokhzad, M.D.

(BUSM '99), Associate Professor, Harvard Medical School; Director, Center for Nanomedicine, Department of Anesthesiology, Perioperative and Pain Medicine Brigham and Women's Hospital, Boston, MA

Polymeric Nanoparticles: Tumor Microenvironment Variability and Implications for New Nanoparticle Design and Development

Omid Farokhzad is an Associate Professor at Harvard Medical School (HMS) and a physician-scientist in the Department of Anesthesiology at Brigham and Women's Hospital (BWH). Dr. Farokhzad established and directs the Center for Nanomedicine at BWH. He is a faculty member of the Briaham Research Institute Cancer Research Center. He is additionally a member of the Dana Farber/Harvard Cancer Center Programs in Prostate Cancer and Cancer Cell Biology. Dr. Farokhzad's research is focused on the development of therapeutic nanoparticle technologies; most notably, he pioneered the high throughput combinatorial development and screening of multifunctional nanoparticles for medical applications. Dr. Farokhzad has authored approximately 135 papers (>29,000 citations; H-Index 70) and holds more than 146 issued/pending US and International patents. The technologies that Dr. Farokhzad has developed with collaborators at HMS and MIT formed the basis for the launch of five biotechnology companies: BIND Therapeutics (NASDAQ: BIND; acquired by Pfizer), Selecta Biosciences (NASDAQ: SELB), Tarveda Therapeutics (formerly Blend Therapeutics), Placon Therapeutics (formerly Blend Therapeutics), and Koan Biotherapeutics, which are translating

the aforementioned academic innovations toward commercialization and societal impact. Dr. Farokhzad has served in various capacities on the Board of Directors and the Scientific Advisory Board of these companies. He was a recipient of the 2013 RUSNANOPRIZE, one of the largest international nanotechnology prizes, for the development and industrialization of nanoparticle technologies for medical applications. In 2014, he received the Golden Door Award from the International Institute of New England for his societal and economic impact as a naturalized USA citizen. In 2015, he was named as one of The Worldview 100 by Scientific American, which recognized visionaries who shape biotechnology around the world. In 2016, he was among the recipients of the Ellis Island Medal of Honor for his scientific, societal and economic contributions to America as an immigrant. Dr. Farokhzad was elected to the College of the Fellows of the American Institute of Medical and biological Engineering. He was selected by Thomson Reuters among the Highly Cited Researchers in 2014, 2015 and 2016. The Boston Globe selected him among the top innovators in Massachusetts and the Boston Business Journal selected him among the Health Care Champions for his innovations. In 2012, he was among the regional Ernst & Young Entrepreneur of the Year awardees. Dr. Farokhzad completed his post-araduate clinical and postdoctoral research trainings, respectively, at the BWH/HMS and MIT in the laboratory of Institute Professor Robert Langer. He received his M.D. and M.A. from Boston University School of Medicine and his M.B.A. from the MIT Sloan School of Management.

