SYMPOSIUM ORGANIZERS

ZHI-MIN YUAN, M.D., PH.D.
Morningside Professor of Radiobiology
Director of John B. Little Center for Radiation Sciences

ZACHARY NAGEL, PH.D.
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Harvard T.H. Chan School of Public Health

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WE THANK THE FOLLOWING FOR THEIR SUPPORT

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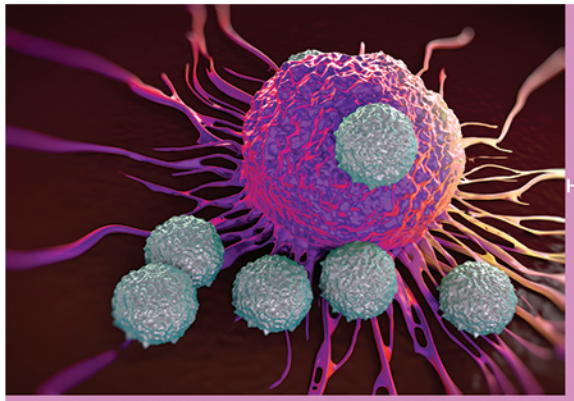


OCTOBER 20, 2017
1:00PM-4:30PM

OCTOBER 21, 2017
900AM-5:00PM

Harvard T.H. Chan School of Public Health
Kresge
Snyder Auditorium G1
677 Huntington Ave.
Boston, Massachusetts

20TH ANNUAL

JOHN B. LITTLE SYMPOSIUM

"The Interface Between Stress Responses and the Immune System in Health and Diseases"

JOHN B. LITTLE
CENTER FOR RADIATION SCIENCES
HARVARD T.H. CHAN
SCHOOL OF PUBLIC HEALTH

John B. Little Center for Radiation Sciences

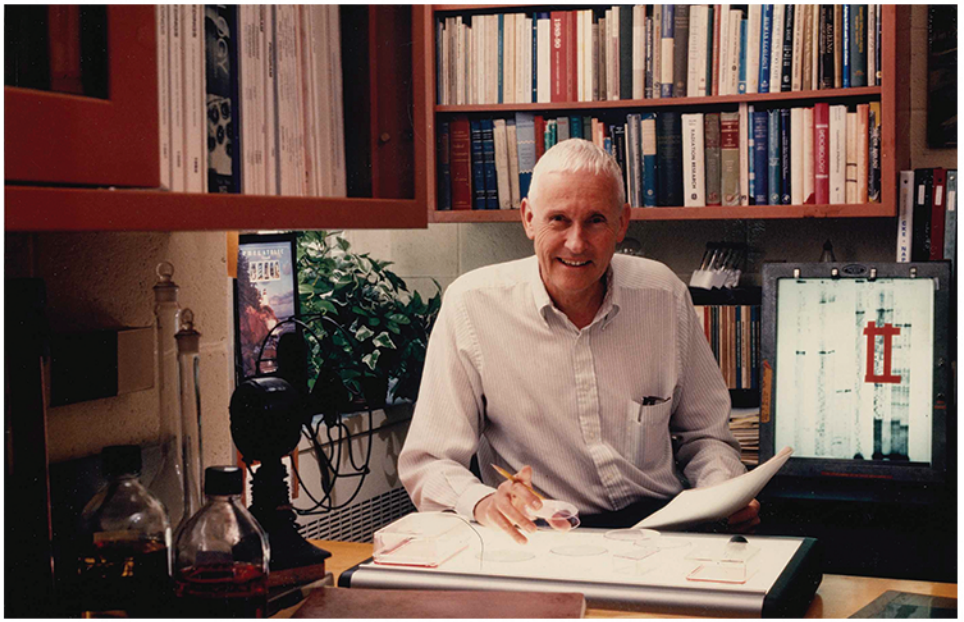
The John B. Little Center for Radiation Sciences [JBLC] has been a pioneer in the field of low-dose radiation research since its establishment at the Harvard T.H. Chan School of Public Health as a result of the philanthropy of Dr. Gerald Chan. The Center is named for John Bertram Little, M.D., James Stevens Simmons Emeritus Professor of Radiobiology, Dr. Chan's mentor. He was the founder of the Radiation Biology Program at Harvard and the visionary leader for the Radiation Biology Training Grant which began in 1975 and continued for thirty-five years. An international figure in the field of radiobiology, Dr. Little, a Board Certified Radiologist, has served on the editorial boards of many scientific journals, been the recipient of multiple scientific awards, and is widely respected and cited for his intellectual accomplishments [including as author or co-author of more than 525 scientific papers], mentoring skill and collegial leadership.

A recent additional anonymous gift of $10 million has placed the JBLC in an unprecedented position to spearhead the effort of developing unbiased and comprehensive scientific evidence necessary to understand the biological impact of low-dose radiation, explore the adaptive and maladaptive responses, and address the health outcomes and public concerns, while also supporting the development of evidence-based public health policy. This generous gift has enabled the JBLC to broaden its reach and scope, becoming a school wide center, involving multiple departments within the HSPH as well as other Harvard University schools and the many hospitals in the larger Harvard community. In addition, the JBLC is establishing additional international partnerships to build upon existing collaborative agreements such as the one it already has with the Hiroshima University. By providing the critical resources for research and training, the JBLC will function as an intellectual home for investigators interested in basic and translational radiation research. It is our hope and conviction that the JBLC will lead a collective effort to strengthen radiation science in the United States and become a global center of excellence for radiation research.

HARVARD T.H. CHAN | SCHOOL OF PUBLIC HEALTH

John Bertram Little, M.D.

James Stevens Simmons Professor of Radiobiology, Emeritus



FRIDAY, OCTOBER 20, 2017

1:00-1:15 PM — WELCOME
John B. Little, M.D.
James Stevens Simmons Professor of Radiobiology, Emeritus
Department of Environmental Health
Harvard T.H. Chan School of Public Health

OPENING REMARKS
Michelle A. Williams, Sc.D.
Dean of the Faculty
Harvard T.H. Chan School of Public Health

1:15-4:30 PM — SESSION I: **Discussion Leader: Kristopher Sarosiek, Ph.D.**
Assistant Professor of Radiation Biology, Department of Environmental Health
Harvard T.H. Chan School of Public Health

1:15-2:00 PM — **Kai Wucherpfennig, M.D., Ph.D.** - Chair
Department of Cancer Immunology and Virology
Dana-Farber Cancer Institute
"Therapeutic reactivation of NKG2D-driven tumor immunity"

2:00-2:45 PM — **Catherine Wu, M.D.** - Associate Professor of Medicine
Dana-Farber Cancer Institute and Harvard Medical School
"Building personal cancer vaccines"

2:45-3:00 PM — BREAK - Outside G1

3:00-3:45 PM — **Harvey Cantor, M.D.. -** Chairman
Department of Cancer Immunology & AIDS
Baruj Benacerraf Professor of Microbiology & Immunobiology
Harvard Medical School
"The Treg Response and Tumor Immunity"

3:45-4:30 PM — **Beth Stevens, Ph.D.**- Associate Professor, Neurology
Harvard Medical School, Boston Children's Hospital
"Immune Mechanisms of Synapse Loss in Health & Disease"

4:30-6:30 PM — RECEPTION - Kresge Cafeteria

Saturday, October 21

8:00-9:00 AM — BREAKFAST - Kresge Cafeteria

9:00 AM-12:15 PM — SESSION II: **Discussion Leader: Zachary Nagel, Ph.D.**
Assistant Professor of Radiation Biology, Department of Environmental Health
Harvard T.H. Chan School of Public Health

SATURDAY, OCTOBER 21, 2017

9:00-9:45 AM — **John MacMicking, Ph.D.**- Investigator, Howard Hughes Medical Institute
Associate Professor of Microbial Pathogenesis and of Immunobiology
Yale Systems Biology Institute
"Cell-autonomous immunity to infection: the art of self-defense"

9:45-10:30 AM — **Xiaole Shirley Liu, Ph.D.-** Professor of Biostatistics
Harvard T.H. Chan School Of Public Health
Co-director, Center for Functional Cancer Epigenetics
Dana-Farber Cancer Institute
"Inference of gene signatures associated with response and resistance to targeted and immunotherapies"

10:30-10:45 AM — BREAK - Outside G1

10:45-11:30 AM — **Ramnik Xavier, M.D., Ph.D.**- Chief, Gastrointestinal Unit & Director & Kurt Isselbacher Professor of Medicine
Center for the Study of Inflammatory Bowel Disease, Massachusetts General Hospital
Harvard Medical School
"Genetics, Microbes & Mucosal Immunity"

11:30 AM-12:15 PM — **Chih-Hao Lee, Ph.D.** - Professor
Department of Genetics and Complex Diseases
Harvard T.H. Chan School of Public Health
"Bioenergetic regulation in inflammatory macrophages by Bmal1-Hif-1a crosstalk"

12:15-1:30 PM — LUNCH - Kresge Cafeteria

1:30-4:45 PM — SESSION III: **Discussion Leader: James R. Mitchell, Ph.D.**
Associate Professor of Genetics and Complex Diseases
Harvard T.H. Chan School of Public Health

1:30-2:15 PM — **K. Dane Wittrup, Ph.D.** - C.P. Dubbs Professor of Biological and Chemical Engineering
Koch Institute at Massachusetts Institute of Technology
"Synergistic Innate and Adaptive Immunotherapy of Cancer"

2:15-3:00 PM — **Lieping Chen, M.D., Ph.D.** - United Technologies Corporation Professor in Cancer Research and Professor of Immunobiology of Dermatology and of Medicine (Medical Oncology)
Co-Director, Cancer Immunology Program
Yale Cancer Center
"Anti-PD Immunotherapy for human cancer"

3:00-3:15 PM — BREAK - Outside G1

3:15-4:00 PM — **Silvia Formenti, M.D.** - Chairman of the Department of Radiation Oncology
Associate Director- Meyer Cancer Center
Radiation Oncologist in Chief- NewYork-Presbyterian Hospital
Weill Cornell
"DNA Damage Response and Immune Rejection of Cancer"

4:00-4:45 PM — **Wafik El-Deiry, M.D., Ph.D., FACP**- American Cancer Society Research Professor
Professor of Medical Oncology, Deputy Cancer Center Director for Translational Research
William Wikoff Smith Endowed Chair in Cancer Research
co-Leader, Molecular Therapeutics Program
Fox Chase Cancer Center
"Imipridone ONC201, a first-in-class clinical stage cancer therapeutic triggers an integrated stress response and potent immune effects"

HARVEY CANTOR, M.D.

The Cantor lab studies the development and function of T-cell subsets. Early studies indicated that the thymus gave rise to two major subsets of T cells that recognized the MHC class II and class I molecules and were equipped to mediate distinct immunological functions before overt encounter with antigen. These experiments were based on the idea that the pattern of proteins expressed on the cell-surface could be used to separate and define the developmental and functional components of the immune system. This approach was also used to dissect cell-mediated immunity into its cellular components, to isolate natural killer cells and, more recently, to define effector and regulatory sublineages belonging to the CD4+ and CD8+ T-cell subsets. Recent studies have further defined the contribution of CD8+ regulatory T cells (Treg) to maintenance of self-tolerance and regulation of anti-tumor immunity. Current studies have also begun to delineate the genetic and epigenetic elements of Helios-dependent control of the differentiation and function of regulatory T-cells belonging to each lineage.

Cantor received a BA from Columbia University and MD from the New York University School of Medicine followed by fellowship training at NIH in Bethesda, Maryland, two years as an NIH Special Fellow at the National Institute for Medical Research in Mill Hill, London, and a residency in medicine at the Stanford University Hospital before joining the faculty at DFCI-Harvard. He is the Baruj Benacerraf Professor of Microbiology & Immunobiology, Division of Immunology at Harvard Medical School and Department of Cancer Immunology & Virology at the Dana-Farber Cancer Institute. Cantor is a member of the US National Academy of Sciences and the American Academy of Arts & Sciences, and a fellow of the American Association for the Advancement of Science.

"The Treg Response and Tumor Immunity "

The Helios transcription factor ensures stable expression of the CD4+ Treg phenotype. We have used ChIP-Seq, pathway analysis and gene profiling to define Helios target genes that include a core pathway formed by an IL-2Rα–STAT5b axis. Inhibition of Helios expression by intratumoral CD4+ Treg induces reprogramming of Treg into T-effector cells that can destroy tumor cells. Analysis of this pathway at the single cell level has provided insight into the genetic basis of this Helios-dependent pathway. Since Treg conversion is restricted to intratumoral CD4 Treg, potential systemic toxicity and IRAEs may be avoided. Strategies that utilize large and small molecules to induce Helios downregulation and Treg reprogramming will be discussed.

Helios is also the canonical transcription factor that controls the differentiation of CD8 Treg. These CD8 Treg recognize self-peptides, including tumor-associated peptides, associated with the Qa-1 (HLA-E) class Ib MHC protein. We have recently identified clonal T cell receptors (TCRs) from CD8 Treg that are specific for Qa-1 and stress-induced peptides. These ligands are expressed by activated and stress-induced effector T cells, as well as many types of tumors. We find that CD8 Treg that express high-affinity TCR for peptide/Qa-1 ligands on tumor cells exert potent anti-tumor activity. These studies open the possibility that CD8 Treg specific for stress-induced Qa-1/HLA-E self-peptide ligands that serve to regulate CD4 responses may also recognize and eliminate transformed cells that express this stress-induced Qa-1–peptide complex.

LIEPING CHEN, M.D., P.H.D.

Dr. Lieping Chen obtained his medical degree in 1982 from Fujian Medical School, China. After completion of his training in hematology and oncology at Fujian Union Hospital and Beijing Union Medical College, Dr. Chen earned a Ph. D. in experimental pathology from Drexel University College of Medicine in Philadelphia. After a postdoctoral fellowship at the University of Washington, in 1990, Dr. Chen began his work at the Bristol-Myers Squib Company as a research scientist. In 1997, he became an immunology professor at the Mayo Clinic, Rochester, Minnesota, where he discovered the B7-H1 (PD-L1) molecule and the role of the B7-H1/PD-1 pathway in the evasion of tumor immunity. In 2004, he joined the faculty at the Johns Hopkins School of Medicine, where he helped initiate the first-in-man clinical trial using antibodies to block the B7-H1/PD-1 pathway for the treatment of human cancer. Dr. Chen has authored more than 300 scientific publications and has served on several committees and advisory boards for state, federal, and international research organizations and pharmaceutical companies. His honors include the William B. Coley Award (2014), the AAI-Steinman Award (2016), and the Warren Alpert Foundation Prize (2017).

Dr. Lieping Chen currently serves as the United Technologies Corporation Professor in Cancer Research, Professor of Immunobiology, Dermatology and Medical Oncology at the Yale School of Medicine and co-Director of the Cancer Immunology Program at the Yale Cancer Center in New Haven, CT.

"Anti-PD Immunotherapy for human cancer"

WAFIK EL-DEIRY, M.D., PH.D., FACP

Wafik El-Deiry, MD, PhD, FACP is the Deputy Cancer Center Director for Translational Research, co-Leader of the Molecular Therapeutics Program, Professor of Oncology, and the William Wikoff Smith Endowed Chair in Cancer Research at Fox Chase Cancer Center in Philadelphia. Until September 2014 he was the Rose Dunlap Professor of Medicine and Chief of Hematology-Oncology at Penn State University. In 2009, El-Deiry became one of 40 active American Cancer Society Research Professors. He earned MD/PhD degrees from University of Miami School of Medicine and completed internal medicine residency and medical oncology fellowship at Johns Hopkins. He discovered cyclin-dependent kinase (CDK) inhibitor p21(WAF1) as a p53 target gene and cell cycle inhibitor that explained the mammalian cell stress response. This work published in 1993 is the most highly cited original work published in Cell. El-Deiry joined University of Pennsylvania School of Medicine in 1994 rising to Professor of Medicine, Pharmacology and Genetics in 2005 and was a Howard Hughes Medical Institute Investigator from 1995-2004. He served as co-Leader of the Radiobiology & Imaging Program at the Abramson Cancer Center from 2004-2010. El-Deiry made important contributions in cell death signaling including discovery of TRAIL receptor DR5 as a p53 target and mediator of extrinsic cell death after DNA damage. He discovered and brought first-in-class TRAIL-pathway activating small-molecule ONC201/TIC10 into clinical trials for patients with cancer. El-Deiry is a well-funded and productive physician-investigator who has >350 peer-reviewed publications and 5 edited books. In 2017 his H-index is 108 and he has nearly 60,000 citations in Google Scholar. He is a member of the Interurban Clinical Club (President 2013-2014), American Society for Clinical Investigation (1999-) and Association of American Physicians (2008-). He won the Michael Brown Award from University of Pennsylvania (1998), the Elizabeth and John Cox Award from Georgetown (2005), the 2009 Kuwait Prize for "Cancer Diseases." El-Deiry is an elected member of the Johns Hopkins University Society of Scholars (2014-). He specializes in the care of patients with colorectal cancer at Fox Chase where he conducts his preclinical and clinical research. In 2017, he serves as the Chair of an NIH Study Section on molecular targets and basic mechanisms of cancer therapeutics (BMCT-C), as the Track Leader for Tumor Biology (ASCO), as a member of the American Cancer Society (ACS) Council for Extramural Grants and as a Member of the Conquer Cancer Foundation Review Board (ASCO).

"Imipridone ONC201, a first-in-class clinical stage cancer therapeutic triggers an integrated stress response and potent immune effects"

We discovered TRAIL death receptor 5 (DR5) as a p53 target gene (Wu et al., Nature Genetics, 1997) and pursued mechanistic studies of cell death and therapeutic opportunities with TRAIL (Kim et al., Clin. Cancer Res., 2000; Burns et al., J. Biol. Chem., 2001; Ricci et al., Mol. Cell. Biol., 2004; Ricci et al., Cancer Cell, 2007). DR5 linked extrinsic cell death to the DNA damage response. The initial findings were presented in October, 2000 at the JBL Symposium. Our subsequent work on DR5 knockout mice showed defects in apoptotic death in multiple organs after exposure to radiation and tumor susceptibility after low dose radiation exposure, c-Myc driven models, or carcinogen exposure (Finnberg et al., Mol. Cell. Biol., 2005; Finnberg et al., J. Clin. Invest., 2008). By 2008 we recognized that TRAIL is a p53 target gene (Kuribyashi et al., Cancer Biol. Ther., 2008). We discovered first-in-class TRAIL-Inducing Compound #10 (TIC10) that stimulates TRAIL gene expression, independent of p53, in a manner that acts through dual inhibition of Akt and ERK resulting in dephosphorylation of Foxo3a and transcriptional activation of TRAIL (Allen et al., Sci. Trans. Med., 2013). TIC10/ONC201 has anti-tumor activity against multiple preclinical in vivo models including GBM, lymphoma, colorectal cancer, breast cancer, prostate cancer, among others. We found that ONC201 stimulates an early PERK-independent integrated stress response involving eIF-2α, ATF4, CHOP and DR5 induction (Kline et al., Sci. Sig, 2016) and has activity against cancer stem cells (Prabhu et al., Cancer Res., 2015). Both the ligand TRAIL and receptor DR5 are induced on tumor cells, and there is a bystander effect with ONC201. ONC201, under clinical development by Oncoceutics, Inc., appears safe and has preliminary clinical efficacy against several tumor types including in patients with GBM, prostate cancer, uterine cancer, colorectal cancer, lymphoma and leukemia (Stein et al., Clin. Cancer Res., 2017; Arrillaga-Romany et al., Oncotarget, 2017). ONC201 has been found to bind dopamine receptors DRD2 and DRD3 and its effects can be antagonized by DRD5 (Prabhu et al., submitted; Kline et al., submitted). ONC201 stimulates NK and T cell infiltration of tumors in vivo and has combinatorial efficacy in vivo with anti-PD1 checkpoint therapy (Wagner et al., submitted) as well as targeted agents such as ABT199, sorafenib, anti-c-MET or anti-IGF1R small molecules. We have additional data on ONC201 combinatorial therapeutics including radiation and characterization of potent analogues such as ONC206, ONC212 and ONC213. The imipridones, exemplified by ONC201, represent an exciting class of novel cancer therapeutics accessible to patients through clinical trials.

SILVIA FORMENTI, M.D.

Dr. Formenti is the Chair of Radiation Oncology at Weill Cornell Medical College and the Associate Director of the Cancer Center.
Trained as a medical and radiation oncologist she devoted her career to translate novel preclinical information to the clinic. Key to her formation was a year spent in Malcolm Mitchell's laboratory at USC, in cancer immunology. Her initial research on how to best combine radiation and systemic therapy, both pre-clinically and clinically evolved on focusing on the systemic effects of radiotherapy, particularly on the immune system. Her lab's original demonstration that the abscopal effect of radiotherapy is immune-mediated has opened a fertile field of research to understand the immune-stimulatory and immune-suppressive effects of ionizing radiation, and to develop strategies directed at harnessing anti-tumor immunity in irradiated subjects. This work has introduced a paradigm shift in radiation and cancer biology. In this novel application, radiotherapy contributes at recovering an immunological equilibrium in the setting of metastatic cancer, by converting an irradiated metastasis into an in situ, individualized vaccine in the presence of immune checkpoint blockade (anti-CTLA4, anti-PDL-1). Once successfully immunized against the irradiated site, the host can develop an anti-tumor immune response capable to reject the other metastases. In some patients with metastatic disease the combination of radiation and immune checkpoint blockade has resulted in complete remissions, sustained for years after treatment (without any other additional interventions). Dr. Formenti's work has been funded by grants from NIH, DOD, ACS and Breast Cancer Research Foundation and is currently leading four investigator-initiated clinical trials of immunotherapy and radiotherapy.

"DNA Damage Response and Immune Rejection of Cancer"

Radiotherapy has revealed an ideal adjuvant to cancer immunotherapy, because of it's ability to convert the irradiated tumor into an individualized, in situ vaccine. Radiation-induced DNA damage response (DDR) is sensed by the innate immune system and can contribute to immune rejection of tumors. When successful at immunizing, radiotherapy evokes T cell memory, and induces effects outside the treated field, defined as abscopal effects (responses at a distant, synchronous, un-irradiated established tumor or metastasis). In the setting of clinical cancer, however, abscopal effects are extremely rare, because of immune-suppressive characteristic of established solid tumors. Thus, strategies to exploit the pro-immunogenic effects of radiotherapy require combination with immunotherapy: preclinical metastatic cancer models successfully testing the combination of local radiotherapy and immune checkpoint blockade (ICB) have matured to clinical translation. Recently, preclinical and clinical evidence has emerged to define optimal radiation protocols to be used during immunotherapy. Specifically, the issue of radiation dose and fractionation seems to be particularly relevant to the success of abscopal responses (responses at a distant, synchronous, un-irradiated established tumor or metastasis). For instance, the role of Trex-1 in he dose-dependence of abscopal response was recently elucidated (Nature Communications 2017; Jun 9;8: 15618). The cross talk between cellular and tissue responses to ionizing radiation and the host's immune system deserves more investigation, in view of the high therapeutic potential of combining radiotherapy with immunotherapy.

CHIH-HAO LEE, PH.D.

Dr. Lee obtained his PhD degree in Pharmacology at University of Minnesota. He then joined the laboratory of Dr. Ronald Evans at the Salk Institute for his post-doctoral training on nuclear receptors and lipid metabolism. During this time, he studied mechanisms that couple lipid sensing signaling and inflammatory responses in immune cells critical for vasculature inflammation in atherosclerosis. In 2004, Dr. Lee was recruited to Harvard T.H. Chan School of Public Health as a faculty member of the Department of Genetics and Complex Diseases and continued his research in the area of metabolic biology. The ongoing work in Dr. Lee's laboratory focuses on mechanisms underlying adaptive responses to metabolic stresses, such as endurance exercise, inflammation and feeding/fasting.

"Bioenergetic regulation in inflammatory macrophages by Bmal1-Hif-1α crosstalk"

Immune signaling plays an important role in initiation of inflammatory responses, resolution of acute tissue damage, and adaptation to chronic stress. Although inflammatory pathways responding to pathogens are well characterized, mechanisms mediating metabolic adaptation to cope with energy demands of various immune functions have just been realized in recent years. Upon activation by inflammatory stimuli, macrophages display a shift in energy utilization in favor of aerobic glycolysis with a diversion of pyruvate toward lactate production and away from further oxidation by mitochondria. While the adaptation in energy metabolism, in part regulated by Hif-1α, is essential to mount an effective pro-inflammatory response, this process also rapidly dampens mitochondrial respiration, which may lead to a progressive energy deficit. Consequently, increased macrophage dysfunction and death has been associated with severe sepsis and poor disease outcome in rodent models and humans. Currently, little is known concerning mechanisms that restore mitochondrial metabolic function in inflammatory macrophages and whether this is necessary to limit inflammatory dysfunction. Our results show that in the macrophage pro-inflammatory stimuli, such as acute LPS treatment or Ifnγ-primed, chronic LPS challenge, induce the expression of Bmal1, a master regulator of circadian rhythm. Using myeloid-specific Bmal1 knockout mice, our results suggest that this "resetting" of the molecular clock following inflammatory stimulation facilitates the restoration of mitochondrial oxidative metabolism and cellular function. At the molecular level, Hif-1α controls the expression of Bmal1, which in turn regulates TCA cycle metabolites to modulate Hif-1α protein stability. As such, the crosstalk between Hif1α and Bmal1 serves as a molecular switch that controls energy utilization from glycolytic to oxidative metabolism to restore energy homeostasis in inflammatory macrophages.

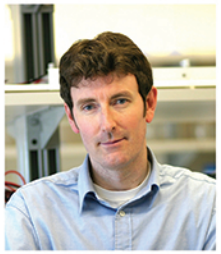
XIAOLE SHIRLEY LIU, P.H.D.

Dr. Liu is a computational cancer biologist, with expertise in algorithm development, data integration, cancer gene regulation, and precision medicine. She is a member of the mod/ENCODE consortia (NHGRI) and Information Technology for Cancer Research initiative (NCI), and the director of the Center for Functional Cancer Epigenetics at the Dana-Farber Cancer Institute. Her group developed many widely used and cited algorithms for transcription factor motif finding (over 2K citations), ChIP-chip/seq (over 4K citations and 10K users), CRISPR screen (over 10K downloads), and recently cancer immunology data analysis. Through integrating genome-wide transcription factor binding, chromatin dynamics, and gene expression profiles, her group discovered the specificity and function of many transcription factors, chromatin regulators and lncRNAs in tumor development and progression. Recently her group is transitioning into translational cancer genomics, by integrating large-scale public data to understand the mechanism of action and predict response to targeted and immunotherapies. She has published over 180 papers, including over 50 in Nature, Science, and Cell series, and has an H-index of 73.

"Inference of gene signatures associated with response and resistance to targeted and immunotherapies"

Predicting clinical response and identifying genes involved in response and resistance to targeted and immunotherapies are critically important in precision cancer medicine. We present Comprehensive Analysis of Resistance (CARE) model which tests the interactions between drug target and other genes on drug response to infer gene signatures of response to targeted therapies from CCLE, CGP and CTRP cell line compound screens. CARE showed superior performance than the signatures from experimental approaches such as shRNA and CRISPR screens or from other computational methods. When finding genes associated with Lapatinib resistance, CARE identified PRKD3 as the top candidate which was experimentally validated. We also present Tumor Immune Dysfunction and Exclusion (TIDE) model which tests gene for their interaction with tumour infiltrating CD8 T cells across large tumour cohorts to influence patient survival. The TIDE signatures, computed from clinical data without immunotherapies, can reliably predict the clinical response of melanoma patients for both anti-PD1 and anti-CTLA4 therapies, with higher accuracy than mutation load and other biomarkers. In summary, CARE and TIDE models not only infer better response biomarkers, but also review novel targets to improve the efficacy of targeted and immunotherapies.

JOHN MACMICKING, PH.D.



Dr. MacMicking studied organic chemistry and biochemistry (B.Sc, Hons 1) at the John Curtin School of Medical Research, Australian National University, in Canberra. He then undertook Ph.D studies with Carl Nathan in the combined Immunology program at Sloan-Kettering Institute-Cornell University in New York City before joining Rockefeller University as a Howard Hughes Medical Institute LSRF Fellow and Adjunct Assistant Professor. In 2004, he moved to Yale University where he is currently an HHMI Investigator, Member of the Yale Systems Biology Institute and tenured Associate Professor within the Departments of Microbial Pathogenesis and Immunobiology at Yale University School of Medicine.

"Cell-autonomous immunity to infection: the art of self-defense"

Cell-autonomous immunity operates across all three domains of life to defend the host from infection. This talk will highlight some of guiding principles of cell-autonomous immunity and the role played by new host defense proteins in orchestrating immunity to distinct pathogen classes. Many of these pathways are mobilized in response to signals from the interferon (IFN) family of cytokines as an evolutionary adaptation in higher species such as vertebrates. In particular, a new group of IFN-inducible GTPases will serve as an example of how cells defend their interior by tailoring antimicrobial activities according to the replicative niche that different pathogens occupy or the damage and stress signals they induce.

BETH STEVENS, P.H.D.

Beth Stevens is an associate professor at Harvard Medical School in the FM Kirby Neurobiology Research Center at Boston Children's Hospital, and an institute member of the Broad Institute, Stanley Center Cambridge MA.

Her research seeks to understand the mechanisms that regulate the development and elimination of synapses by focusing on how microglia and immune-related molecules mediate this process.

Beth received her Ph.D. in Neuroscience in 2003 at the University of Maryland, College Park. She performed her dissertation research at the National Institutes of Health (NICHD) in the area of neuron-glia interactions. In her postdoctoral work with Ben Barres at Stanford University, she discovered that the classical complement cascade, part of the innate immune system, helps to mediate developmental CNS synapse elimination. Their findings have raised many questions about how the complement cascade normally works to eliminate synapses and especially whether it becomes abnormally reactivated in brain diseases such as AD that impair synaptic connectivity.

In 2008, Dr. Stevens established her independent laboratory in the FM Kirby Neurobiology Center at Children's Hospital where she is currently using a combination of molecular, physiological and high resolution imaging techniques to dissect the mechanisms by which microglial cells and immune –related molecules (ie.complement, cytokines) regulate synapse function during health and disease. She is investigating the mechanisms that drive synapse loss and dysfunction in AD, Huntington's disease, as well as neurodevelopmental disorders, such as autism and schizophrenia.

Beth is a recipient of several young investigator awards, including: Ellison Medical Foundation New Scholar in Aging, John Merck Scholar (2011), Presidential Early Career Award for Scientists and Engineers (PECASE), and a 2015 MacArthur Fellow Award.

"Immune Mechanisms of Synapse Loss in Health and Disease"

One of the major unsolved mysteries in neuroscience is how synapses are eliminated in the healthy and diseased brain. During development, neural circuitry undergoes a remodeling process in which excess synapses are eliminated and the remaining synapses are strengthened. This pruning process is required for precise brain wiring; however the mechanisms that drive the elimination of specific synapses in the brain remain unclear. Emerging evidence from several model systems implicate molecules traditionally associated with the adaptive and innate immune system. For example, recent work from our laboratory revealed a key role for microglia and molecules traditionally associated the classical complement cascade in developmental synaptic pruning. Our recent studies support a model in which 'weaker' or less active synapses in the developing brain are targeted by complement proteins (C1q, C3) and then eliminated by phagocytic microglia that express receptors for complement and other immune molecules. These findings raise the question of how microglia differentiate the synapses or axons to prune from those to leave intact. Microglia-mediated synaptic refinement appears to depend on a careful balance of "eat me" (ie. complement) and a group of novel immune- related protective (ie. 'don't eat me' signals). Moreover, our recent work suggest that aberrant activation of these normal immune –related pruning pathways contribute to synapse loss in neurodegenerative diseases (NDDs), including Alzheimer's Disease (AD) and Huntington's disease (HD). Thus, understanding how these immune mechanisms drive developmental pruning may provide novel insight into how to protect synapses in NDDS and other disorders of synaptic dysfunction, including autism and schizophrenia.

K.DANE WITTRUP, PH.D.

Professor K. Dane Wittrup is the Carbon P. Dubbs Professor of Chemical Engineering and Biological Engineering at the Massachusetts Institute of Technology, and the Associate Director of the Koch Institute for Integrative Cancer Research. His research program is focused on design principles and tools for protein engineering of biopharmaceutical proteins.

"Synergistic Innate and Adaptive Immunotherapy of Cancer"

Anti-tumor antibodies can contribute to cancer immunotherapy in ways other than their originally intended functions of signal blocking or direct cytotoxicity from natural killer cells and complement. Antibodies against tumor associated antigens can amplify self-vaccination against tumor antigens, and help reprogram the tumor microenvironment to a more inflammatory state. Examples will be presented of synergies between anti-tumor antibodies and immunotherapies centered on T cell responses.

CATHERINE J. WU, M.D.

Catherine J. Wu, MD is an Associate Professor in Medicine at the Dana-Farber Cancer Institute, Boston. She received her M.D. from Stanford University School of Medicine and completed her clinical training in Internal Medicine and Hematology-Oncology at the Brigham and Women's Hospital and Dana-Farber Cancer Institute in Boston, MA. She joined the staff at the Dana-Farber Cancer Institute in 2000. At DFCI, she has initiated an integrated program of research and clinical activities that focuses on dissecting the underlying mechanisms of pathobiology of chronic lymphocytic leukemia (CLL) as a means to more rationally generate effective therapies, including immune-based treatments, for this common adult leukemia. She has been Principal Investigator of several center-initiated clinical trials. A major priority of her studies is the identification of tumor-specific antigens that would allow effective tumor targeting without collateral toxicity. She has been using exome and transcriptome sequencing technologies to identify unique mutated tumor antigens that arise from individual-specific genetic alterations within a tumor and that could be potentially targeted immunologically, thus paving the way for developing personalized tumor vaccines.

"Building personal cancer vaccines"

With the recent availability of novel immunologic agents, priority has shifted to understanding the mechanisms of and predicting responses to each treatment. At the heart of cancer and host immune cell interactions is the tumor antigen and host antigen-specific T cell interaction, with the cytotoxic T cell-cognate antigen interaction forming the mechanistic basis for immune-mediated recognition and the killing of malignant cells. While the search for immunogenic tumor antigens has been the subject of decades-long studies, multiple lines of evidence have convincingly demonstrated tumor neoantigens as an important class of immunogenic tumor antigens. Neoantigens arise from amino acid changes encoded by somatic mutations in the tumor cell and have the potential to bind to and be presented by personal HLA molecules. Using next-generation sequencing approaches, we can now systematically identify mutations leading to amino acid changes that can be potentially recognized immunologically through the implementation of neoantigen discovery pipelines. In recent studies, we have demonstrated that neoantigen load is associated with clinical outcome to immune-based therapies, and neoantigens can be safely and feasibly targeted to generate customized cancer vaccines. Within this therapeutic landscape, the identification of HLA-bound peptides by liquid chromatography-tandem mass spectrometry (LC-MS/MS) is poised to transform our understanding of rules underlying antigen presentation, through the generation of data to reveal subdominant binding motifs and to understand the factors critical to epitope presentation, such as protein cleavage and gene expression. A MS-based approach to directly identify antigen targets from tumor cells also promises to impact strategies to develop and implement personal cancer vaccines and other immunotherapies.

KAI W. WUCHERPFENNIG, M.D., PH.D.

Kai W. Wucherpfennig is Chair of the Department of Cancer Immunology and Virology at the Dana-Farber Cancer Institute and Professor of Microbiology and Immunobiology as well as Professor of Neurology at Harvard Medical School. He serves as the Co-leader of the Cancer Immunology Program at Dana-Farber/Harvard Cancer Center. His research focuses on the mechanism of T cell mediated immune surveillance, with particular focus on cancer immunology.
He has been elected as a member of the American Society for Clinical Investigation (2006), the Henry Kunkel Society at Rockefeller University (2007) and as Fellow of the American Society for the Advancement of Science (2009). Dr. Wucherpfennig received a MD from the University of Göttingen in Germany, and did his postdoctoral training at the Brigham & Women's Hospital and at Harvard College. He has been a faculty member at the Dana-Farber since 1995.

"Therapeutic reactivation of NKG2D-driven tumor immunity"

Genomic damage and aberrant signaling result in expression of stress molecules by tumor cells that are recognized by the NKG2D receptor on cytotoxic lymphocytes. However, many human cancers evade this immune pathway by proteolytic shedding of these molecules (MICA and MICB). I will present a novel therapeutic strategy that targets this immune evasion pathway.

RAMNIK XAVIER, M.D., PH.D.

Dr. Ramnik Xavier is Chief of Gastroenterology at Massachusetts General Hospital (MGH), Kurt Isselbacher Professor of Medicine at Harvard Medical School, and an Institute Member at the Broad Institute of Harvard and MIT.
In addition to his roles as director of the Center for the Study of Inflammatory Bowel Disease at MGH and co-director of Center for Microbiome Informatics and Therapeutics at MIT, he is also a founding member of the Center for Computational and Integrative Biology.

"Genetics, Microbes & Mucosal Immunity"

Recent advances have provided substantial insight into the maintenance of mucosal immunity and the pathogenesis of inflammatory bowel disease. Cellular programs responsible for intestinal homeostasis use diverse intracellular and intercellular networks to promote immune tolerance, inflammation or epithelial restitution. Complex interfaces integrate local host and microbial signals to activate appropriate effector programs selectively and even drive plasticity between these programs. In addition, genetic studies and mouse models have emphasized the role of genetic predispositions and how they affect interactions with microbial and environmental factors, leading to pro-colitogenic perturbations of the host-commensal relationship.