Frontiers in Health Research

East West Alliance Symposium 2016

UCSF

LI KA SHING FOUNDATION
Welcome Letter

October 15, 2016

Dear Symposium Attendees:

It gives us great pleasure to welcome you to the 2016 East-West Alliance Global Symposium.

The East West Alliance is a global network of universities and medical schools that are supported by the Li Ka Shing Foundation. The Alliance aims to foster knowledge exchange and collaboration among leading biological and biomedical institutions on high-impact research and educational projects. Each year the Li Ka Shing Foundation supports a symposium at one of the participating institutions. This year’s symposium is being held in Berkeley and is co-sponsored by the University of California’s Berkeley and San Francisco campuses.

The theme of this year’s symposium is “Frontiers in Health Research.” A revolutionary approach to biomedical research, health and healthcare, denoted “Precision Medicine”, integrates massive and disparate data across basic, clinical and social/behavioral/population studies, resolving mechanisms of biological and pathological processes at the level of the individual. The revolution is being enabled by powerful new technologies, including high performance computing and targeted learning, cell engineering, genomics and genome editing, molecular imaging, and wearable sensors. These and other strategies and methods are advancing our understanding of many different diseases, and uncovering unexpected connections with therapeutic implications. These topics will be explored at the symposium, as well as exciting new developments in fields such as cancer immunotherapy and regenerative medicine.

We trust that you will find the symposium presentations provocative and enjoyable.

Mike Botchan
Dean of Biological Sciences
UC Berkeley

G. Steven Martin
Symposium convener

Keith Yamamoto
Vice Chancellor for Science Policy and Strategy, UCSF
Program Schedule — Sunday, October 30, 2016

OPENING CEREMONY AND RECEPTION
2nd floor Lobby, Li Ka Shing Center, Berkeley campus

5:00 – 6:15 PM: OPENING CEREMONY & RECEPTION (All symposium attendees welcome)
- 5:30 – 5:35: Welcome: G. Steven Martin (UCB)
- 5:35 – 5:40: Mr. Li and the Li Ka Shing Foundation (Frieda Law, LKSF)
- 5:40 – 5:45: UC Berkeley and the Li Ka Shing Foundation (Robert Tjian, UCB)
- 5:45 – 5:50: Precision Medicine at UCB and UCSF (Keith Yamamoto, UCSF)

Program Schedule — Monday, October 31, 2016

SYMPOSIUM DAY 1: NEW INSIGHTS INTO HEALTH AND DISEASE
Goldman Auditorium, David Brower Center, 2150 Allston Way, Berkeley

8:00 AM: COFFEE AND PASTRIES; REGISTRATION

8:45 – 9:00 AM: WELCOME AND INTRODUCTORY REMARKS (G. STEVEN MARTIN)

9:00 – 10:15 AM: SESSION I – SESSION CHAIR MARIAN JOËLS (GRONINGEN)
- Gregory Barton, University of California, Berkeley: “Mechanisms of Self Versus Non-Self-Discrimination in the Immune System”
- Alexander Marson, University of California, San Francisco: “CRISPR Genome Editing in Primary Immune Cells”
- Jennifer Puck, University of California, San Francisco: “undiagnosed Childhood Diseases”

10:15 – 10:45 AM: BREAK

10:45 – 12:30 PM: SESSION II – SESSION CHAIR JUNHUI BIAN (SHANTOU)
- Richard Gilbertson, University of Cambridge: “Charting the Origins of Cancer”
- Allen Chan, Department of Chemical Pathology, The Chinese University of Hong Kong: “Potential Application of Liquid Biopsy for Cancer Screening”
- Yuval Shaked, Technion – Israel Institute of Technology: “Balancing Host Molecular and Cellular Effects in Response to Anti-Cancer Drugs and their Therapeutic Implications on Cancer”
- Russ B. Altman, Departments of Bioengineering, Genetics, Medicine and Computer Science, Stanford University: “Informatics Methods to Understand Drug Response”
12:30 – 1:30 PM: LUNCH

1:30 – 2:45 PM: SESSION III – SESSION CHAIR MARTIN LANDRAY (OXFORD)
- Janet Smylie, Centre for Research on Inner City Health, St. Michael's Hospital: “Addressing Social Determinants of Indigenous Health in Canada: Emerging Evidence”
- Charles Bernstein, University of Manitoba: “Using Epidemiology to Pursue Etiology in Inflammatory Bowel Disease”
- David Evans, Li Ka Shing Institute of Virology, University of Alberta: “The Li Ka Shing Institute of Virology: Applied Virology”

2:45 – 3:15 PM: BREAK

3:15 – 4:30 PM: SESSION IV – SESSION CHAIR YING-SHING CHAN (HONG KONG UNIVERSITY)
- Cecilia Lindgren, University of Oxford: “Obesity: Using Large-Scale Genetic Data to Dissect Underlying Biology”
- Erik Boddeke, University Medical Center Groningen: “Molecular Mechanisms of Brain Ageing”
- Qiang Shan, Shantou University Medical College (SUMC): “Synaptic Plasticity Underlying Action Control”

Program Schedule — Tuesday, November 1, 2016

SYMPOSIUM DAY 2 – EMERGING THERAPIES AND TECHNOLOGIES
Goldman Auditorium, David Brower Center, 2150 Allston Way, Berkeley

8:30 AM: COFFEE AND PASTRIES

9:00 – 10:15 AM: SESSION I – SESSION CHAIR PETER NICKERSON (MANITOBA)
- Andras Kapus, Keenan Centre for Biomedical Research, St. Michael's Hospital: “Scar Wars: Cellular and Molecular Mechanisms in Fibrosis”
- Patrick Maxwell, University of Cambridge: “Modulating Oxygen Sensing as a Therapeutic Strategy”
- Itamar Kahn, Technion, Israel Institute of Technology: “Novel Translational Imaging Methods to Study Brain Disorders”

10:15 – 10:45 AM: BREAK
10:45 – 12:00 AM: SESSION II – SESSION CHAIR SOFIE KLEPPNER (STANFORD)

- Marion S. Buckwalter, Neurology and Neurological Sciences, Stanford University: “A New Twist On Old Thinking: Immune Surprises in Dementia”
- Christian Beaulieu, Peter S. Allen MR Research Centre, University of Alberta: “Magnetic Resonance Imaging of Human Brain Connectivity”

12:00 – 1:00 PM: LUNCH

1:00 – 2:15 PM: SESSION III – SESSION CHAIR ELIEZER SHALEV (TECHNION)

- Elisabeth de Vries, Department of Medical Oncology, University Medical Center Groningen: “Molecular Imaging Developments in Oncology to Support Drug Development and Immunotherapy Treatment Decisions”
- Daniel Portnoy, University of California, Berkeley: “Listeria Monocytogenes: From Basic Science to Cancer Immunotherapy”
- Aiden Doherty, University of Oxford: “Characterizing the Physical Activity Phenotype Using Wearable Sensors”

2:15 – 2:45 PM: BREAK

2:45 – 4:00 PM: SESSION IV – SESSION CHAIR PAUL MELANÇON (ALBERTA)

- Chengyang Huang, Shantou University Medical College: “Molecular Control of Stem Cell Fate: From Basic Biology to the Clinic”
- Kathy Lui, Department of Chemical Pathology, The Chinese University of Hong Kong, “Driving Cardiovascular Regeneration for Diabetics”
- Nevan Krogan and Anne Hiniker, University of California, San Francisco: “Using Systems Approach to Study Disease: The Case of Global Proteomics and Neurodegenerative Diseases”

4:00—5:00 PM: RECEPTION
Greg Barton received his undergraduate degree from Princeton University. He performed his graduate work in the lab of Alexander Rudensky at the University of Washington and his postdoctoral training with Ruslan Medzhitov at Yale University. He joined the faculty at Berkeley in 2005, where he is now Professor and Head in the Division of Immunology and Pathogenesis within the Department of Molecular and Cell Biology. Barton also holds the Class of 1936 Endowed Chair in the College of Letters and Sciences. Professor Barton’s group studies innate immunity with the goal of understanding strategies of pathogen recognition and self/non-self discrimination, with a focus on the function and regulation of Toll-like receptors (TLRs). His lab investigates mechanisms of recognition of microbial patterns, the functional consequences of innate immune recognition in infections, the role of innate immune recognition in promoting virulence of specific microbes, coevolution of pathogen and host, and regulation of immunity at mucosal sites. He discovered a novel mechanism of processing of the set of TLRs that are specific for nucleic acids, providing new insights into how these receptors are regulated and achieve the capacity for self-nonself discrimination. His group recently discovered a key role for maternal antibodies in limiting T cell-dependent immune responses against the microbiota in newborns. Barton is the recipient of the American Association of Immunologists BD Biosciences Investigator Award, the Burroughs Wellcome Fund Investigators in the Pathogenesis of Infectious Disease Award, and the Lupus Research Institute Distinguished Innovator Award.

**Mechanisms of Self Versus Non-Self-Discrimination in the Immune System**

Receptors of the innate immune system target conserved features of microbes and link this recognition to induction of immune responses. Nucleic acids serve as one such feature, yet this specificity exposes the host to potential self recognition and autoimmunity. Several members of the Toll-like receptor (TLR) family of innate immune receptors recognize forms of nucleic acid, and inappropriate activation of several TLR family members by self nucleic acids has been implicated in the pathology of multiple autoimmune and inflammatory disorders. We now appreciate that tolerance to self nucleic acids requires strict regulation of receptors levels and limited access to self ligands. We are studying the mechanisms that reinforce proper discrimination by these critical innate immune receptors.
Alex Marson completed medical school at Harvard, PhD training at the Whitehead Institute/MIT with Richard Young and Rudolf Jaenisch, Internal Medicine residency at the Brigham and Women’s and clinical training in Infectious Diseases at UCSF. He was a UCSF Sandler Faculty Fellow from 2013-2016. He is now an assistant professor in the UCSF Department of Microbiology and Immunology, with joint appointments in the Department of Medicine and the Diabetes Center. He is also affiliated with the UCSF Helen Diller Cancer Center and the Innovative Genomics Initiative (IGI). His lab integrates systems-scale investigations of human T cell circuitry with functional perturbation studies, including genome editing in primary T cells.

**CRISPR Genome Editing in Primary Immune Cells**

Functional testing of human genome sequences in primary immune cells has been largely impossible until our advances in genome engineering methods that now permit direct DNA editing in human primary T cells. CRISPR/Cas9 has facilitated genome engineering in many cell types, but in human T cells Cas9 efficiency had been limited and Cas9 had not allowed targeted nucleotide replacements. We have now developed a CRISPR/Cas9-based platform that enables both knock-out and knock-in genome editing in primary human T cells by electroporation of Cas9: single-guide RNA ribonucleoproteins (Cas9 RNPs). Cas9 RNPs paired with homology-directed repair (HDR) template oligonucleotides can generate a high frequency of knock-in targeted genome modifications in primary T cells. This Cas9 RNP technology holds great potential for therapeutic genome engineering of human T cells for treatment of cancer, HIV, primary immune deficiencies, and autoimmune diseases. The technology also enables unprecedented explorations of genetic mechanisms that regulate T cell differentiation and function. We aim to understand how sequence variation throughout the human genome affects T cell circuits in health and disease.
Dr. Puck earned her undergraduate and medical degrees at Harvard University and Harvard Medical School, after which she completed clinical and research training in pediatrics, infectious diseases and immunology at Washington University in St. Louis, Missouri, and Baylor College of Medicine in Houston, Texas. After serving on the faculties of the University of Pennsylvania in Philadelphia and the National Human Genome Research Institute, NIH, in Bethesda, Maryland, she joined UCSF in 2006 as Professor of Pediatrics. In addition to caring for patients as an immunologist and teaching biomedical trainees at all levels, Dr. Puck has a basic and translational research program that focuses on human immune disorders as well as mouse models of lymphocyte development. Dr. Puck has used genetic and genomic technology as well as cellular immunology to study the basis of impaired lymphocyte development as well as immune dysregulation. She has published over 165 peer reviewed research papers in addition to over 90 chapters and reviews; she is co-editor of Primary Immunodeficiencies: A Molecular and Genetic Approach, published in its 3rd edition in 2014.

Dr. Puck directs the UCSF Jeffrey Modell Diagnostic Center for Primary Immunodeficiencies. She serves on the Medical Advisory Committee of the Immune Deficiency Foundation, the Committee on Primary Immunodeficiency Disease of the International Union of Immunological Societies, the Board of Scientific Councilors of NIAID, and the Steering Committees of the Primary Immune Deficiency Treatment Consortium (PIDTC) and the US Immunodeficiency Network (USIDNET). She has been elected to the American Society of Clinical Investigation (ASCI), Society for Pediatric Research (SPR), Association of American Physicians (AAP), American Pediatric Society (APS) and Institute of Medicine (IOM). She received the Abbot Award in Clinical and Diagnostic Immunology from the American Society of Microbiology in 2013 and the Colonel Harlan Sanders Award for Lifetime Achievement in Genetics from the March of Dimes in 2014.

Undiagnosed Childhood Diseases

Severe combined immunodeficiency (SCID) is a rare, but life threatening inherited disorder in which infants appear healthy at birth, but lack both T and B cell immunity. SCID can be caused by defects over 15 genes that impair lymphocyte development. In order to survive, infants with SCID require immune-reconstituting treatment, such as a hematopoietic cell transplant (HCT), enzyme replacement or gene therapy. Diagnosing SCID by newborn screening (NBS) avoids infectious complications, thus optimizing treatment and survival with immune reconstitution. Dr. Puck and others developed an effective screening test based on quantitating T cell

JENNIFER PUCK
receptor excision circles (TRECs) in DNA extracted from infant dried blood spots. TRECs are present in newly formed T cells, but are rare or absent in the blood of infants with low T cells, including infants with SCID. In addition to identifying SCID cases of expected genotypes, the population based screening program has revealed the true incidence of SCID and detected infants lacking TRECs who have T cell disorders not previously described. Whole exome sequencing and analysis in such infants has led to new disease gene discoveries.

My research in human primary immunodeficiencies has the combined aims of improving diagnosis and treatment of these rare conditions and also understanding how their underlying gene mutations interrupt non-redundant pathways in lymphocyte development and function. An important focus is on severe combined immunodeficiency (SCID) and other disorders of lymphocyte development from hematopoietic stem cells, including gene identification, genotype/phenotype analysis, early detection and treatment. My translational work began with finding IL2RG, the disease gene for X-linked SCID (XSCID) and has evolved to include preclinical and clinical trials of gene therapy. Beginning with treatment of XSCID patients who had failed standard bone marrow transplantation, this work continues with development of lentiviral gene therapy for SCID due to DCLRE1C (Artemis) gene defects. As a pioneer in SCID newborn screening, I conceived and implemented an assay using DNA from infant dried blood spots to detect T cell receptor excision circles (TRECs). TRECs are a biomarker for new production of a diverse repertoire of T cells in the thymus, and their absence in peripheral blood indicates that T cells have impaired development, poor diversity, or increased destruction. The TREC assay has been widely adopted into newborn screening panels. Serving since 2010 as Immunology Expert for the California Newborn Screening Program (with 500,000 infants per year), I designed this state’s SCID inclusion of lymphocyte enumeration by flow cytometry as an integral second tier test within the program. I interpret and compile screening and lymphocyte data for infants with abnormal TREC screens and refer those with T lymphopenia for definitive diagnosis and treatment. Among infants and children referred to me with immune system defects are many who lack mutations in any previously known gene, and these cases are studied using immunologic and genomic approaches including deep sequencing, allowing discovery and characterization of new immune system defects.
Richard Gilbertson trained as a pediatric oncologist in the UK where he earned his MB.BS. and Ph.D. degrees, becoming a member of the Royal College of Physicians in 1995. He moved to St. Jude Children’s Research Hospital, Memphis, TN, USA in 2000 where he served as the Co-Leader of the Neurobiology and Brain Tumor Program and founding Director of the Molecular Clinical Trials Core before being appointed as the Comprehensive Cancer Center Director, Executive Vice President, and Lillian R. Cannon Endowed Chair in 2011. In 2014 he was appointed as the Scientific Director of St. Jude Children’s Research Hospital. In August 2015, he moved back home to England where he now serves as the Li Ka Shing Chair of Oncology, Head of Department of Oncology and Director of the Cambridge Cancer Centre at Cambridge University. His laboratory research is focused on understanding the link between normal development and the origins of cancer, particularly brain tumors. His lab was the first to describe a cancer stem cell niche; demonstrate that a solid cancer can arise from tissue specific stem cells; use innovative cross-species genomics to trace the developmental origins of pediatric brain tumors; and to use whole genome sequencing to identify novel subgroup-specific mutations in medulloblastoma and ependymoma. His research has been translated into numerous diagnostic tests and innovative clinical trials for children with cancer.

Charting the Origins of Cancer
Cancers are distributed unevenly across the body, but the importance of cell intrinsic factors such as stem cell function in determining organ cancer risk is unknown. This talk describes a study in which Cre-recombination of conditional lineage tracing, oncogene, and tumor suppressor alleles was used to define populations of stem and non-stem cells in mouse organs and test their life-long susceptibility to tumorigenesis. We show that tumour incidence is determined by the life-long generative capacity of mutated cells. This relationship held true in the presence of multiple genotypes and regardless of developmental stage, strongly supporting the notion that stem cells dictate organ cancer risk. Using the liver as a model system, we further show that damage-induced activation of stem cell function markedly increases cancer risk. Therefore, we propose that a combination of stem cell mutagenesis and extrinsic factors that enhance the proliferation of these cell populations, creates a "perfect storm" that ultimately determines organ cancer risk.
Professor Allen Chan is currently appointed as Professor of Chemical Pathology at the Chinese University of Hong Kong. He graduated from the University of Hong Kong in 1996 and obtained his PhD in molecular biology under the supervision of Professor Dennis Lo. Professor Chan’s research interest is on the development of innovative diagnostic approaches based on circulating DNA analysis. He is an inventor of the noninvasive test for Down syndrome using plasma DNA analysis in pregnant women. He has over 40 patents/patent applications on molecular diagnostics. Professor Chan has received several research and teaching awards, including the gold medal for Best Original Research Award from the Hong Kong Academy of Medicine and the Sigi Ziering Award from the American Association of Clinical Chemistry for outstanding contribution to research publications. Professor Chan also received a total of four Teacher of the Year Awards from the Faculty of Medicine, CUHK.

**Potential Application of Liquid Biopsy for Cancer Screening**

Tumor-derived DNA is present in the circulation of cancer patients. Liquid biopsy refers to the detection of cancer-associated molecular changes in the plasma of cancer patients. Using massively parallel sequencing, we were able to detect cancer-associated chromosome copy number aberrations (CNA) and single nucleotide variants (SNVs) in the plasma of cancer patients. As these cancer-associated changes are present in virtually all types of cancers, this method can potentially be used as a generic tumor marker. To explore the potential application of liquid biopsy in cancer screening, we have carried out a 20,000-person prospective trial to screen for early nasopharyngeal cancer in asymptomatic subjects using liquid biopsy. The results of this trial will be presented.
Yuval Shaked (PhD) is an Associate Professor at the Department of Cell Biology and Cancer Science, Rappaport Faculty of Medicine, Technion, Israel. He obtained his PhD from the Department of Neurology at Hebrew University (Israel). Subsequently, he was trained at Sunnybrook Health Sciences Centre, Canada, and studied cancer biology and therapy. In 2008 Prof. Shaked was recruited to the Technion as an Assistant Professor, and within 5 years he received tenure and promoted to a rank of Associate Professor. Prof. Shaked received a number of honors and awards, among those the Igal Allon fellowship for promising young investigators, the Yudim prize for cancer research, and the Krill Prize given by the Wolf foundation to outstanding young Israeli investigators. Prof. Shaked obtained funds from highly competitive grant agencies such as the European Research Council. He also served as a chief editor on a new launching journal, and he is an associate editor in additional cancer related journals. Prof. Shaked is an author of over 85 original publications, some of which were published in highly ranked journals, and he holds 3 patents on new targets for cancer or drug combinations to improve cancer therapy. His research focuses on improving conventional cancer therapies.

**Balancing Host Molecular and Cellular Effects in Response to Anti-Cancer Drugs and their Therapeutic Implications on Cancer**

Anti-cancer treatments including chemotherapy, radiation, surgery and targeted drugs can be curative in patients with early stage disease, but their therapeutic effects in advanced stage metastatic disease are limited. In the latter case innate or acquired resistance are among the factors for upfront reduced or even total non-responsiveness of the tumor to therapy. While most studies of resistance or reduced responsiveness focus on intrinsic changes in the tumor cell population which contribute to their resistance, we have focused on the induction of host molecular and cellular responses in response to the therapy which can lead to tumor outgrowth and relapse despite an initial successful therapy outcome. These include a systemic induction of numerous possible cytokines, and mobilization of various host accessory cells which can invade the treated tumor microenvironment. Thus, the contribution of cancer therapy-induced physiologic changes in host tissues and cells act to reduce or even nullify the desired anti-tumor cell effects of therapy. In my presentation I will discuss these host effects and complementary treatments to overcome the host effects in order to improve therapy outcome.
Russ Biagio Altman is a professor of bioengineering, genetics, & medicine (and of computer science, by courtesy) and past chairman of the Bioengineering Department at Stanford University. His primary research interests are in the application of computing and informatics technologies to problems relevant to medicine. He is particularly interested in methods for understanding drug action at molecular, cellular, organism and population levels. His lab studies how human genetic variation impacts drug response (e.g. http://www.pharmgkb.org/). Other work focuses on the analysis of biological molecules to understand the action, interaction and adverse events of drugs (http://features.stanford.edu/). Dr. Altman holds an A.B. from Harvard College, and M.D. from Stanford Medical School, and a Ph.D. in Medical Information Sciences from Stanford. He received the U.S. Presidential Early Career Award for Scientists and Engineers and a National Science Foundation CAREER Award. He is a fellow of the American College of Physicians (ACP), the American College of Medical Informatics (ACMI), the American Institute of Medical and Biological Engineering (AIMBE), and the American Association for the Advancement of Science (AAAS). He is a member of the Institute of Medicine of the National Academies. He is a past-President, founding board member, and a Fellow of the International Society for Computational Biology (ISCB), and a past-President of the American Society for Clinical Pharmacology & Therapeutics (ASCPT). He has chaired the Science Board advising the FDA Commissioner, and currently serves on the NIH Director’s Advisory Committee. He is an organizer of the annual Pacific Symposium on Biocomputing (http://psb.stanford.edu/), and a founder of Personalis, Inc. Dr. Altman is board certified in Internal Medicine and in Clinical Informatics. He received the Stanford Medical School graduate teaching award in 2000, and mentorship award in 2014.

Informatics Methods to Understand Drug Response

There has been a rapid increase in the amount of data available relevant to drug response at all scales: molecular, cellular, organism and population. This offers an unprecedented opportunity completely to understand the effects (both good and bad) of drugs, and can inform drug discovery and optimal use of drugs in practice. In this talk, I will discuss our work understanding drug response using informatics tools. Our approach is characterized by two features: (1) a “systems” approach in which we focus on the network of genes and small molecules that are perturbed by drug and which respond to drugs in complex ways (moving away from the idea of a single target), and (2) integration of data across scales (for example, integrating clinical side effects with 3D structural interactions to understand them better).
Dr. Janet Smylie is a family physician and public health researcher. She currently works as a research scientist in Indigenous health at St. Michael’s Hospital, Centre for Urban Health Solutions (CUHS), where she directs the Well Living House Applied Research Centre for Indigenous Infant, Child and Family Health. Her primary academic appointment is as an Associate Professor in the Dalla Lana School of Public Health, University of Toronto. She maintains a part-time clinical practice with Inner City Health Associates at Seventh Generation Midwives Toronto. Dr. Smylie has practiced and taught family medicine in a variety of Aboriginal communities both urban and rural. She is a member of the Métis Nation of Ontario, with Métis roots in Saskatchewan. Her research interests are focused in the area of addressing the health inequities that challenge Indigenous infants, children and their families through applied health services research. Dr. Smylie currently leads multiple research projects in partnership with First Nations, Inuit, and Métis communities/organizations. Dr. Smylie holds a CIHR Applied Public Health Research Chair in Indigenous Health Knowledge and Information and was honoured with a National Aboriginal Achievement (Indspire) Award in Health in 2012.

**Addressing Social Determinants of Indigenous Health in Canada: Emerging Evidence**

Indigenous peoples in Canada experience striking and cross-cutting inequities in health status compared to non-Indigenous Canadians. These health inequities have been linked to disparities in the social determinants of health, which in turn are rooted in historical and ongoing colonial policies and social exclusion. Contemporary health system responses to Indigenous health inequities have included an exponential growth in primary and tertiary medical service use Indigenous peoples, including prescription medications and a series of initiatives aimed at improving the “cultural competencies” of health professionals. Despite these responses, health status inequities persist and in some cases are getting worse. In this presentation, Dr. Smylie will introduce emerging evidence from 2 recent studies that aimed to better understand and address barriers to optimal health care for Indigenous peoples at a foundational level. The first study aimed to address systemic barriers for Indigenous peoples in accessing and acquiring non-Indigenous health literacy skills within the context of prescription medications. In this international trial, we tested the effectiveness of a customized, structured educational program addressing CVD medications for Indigenous people with CVD or at high risk CVD and their families. The second study was a systematic review examining the role of racism in the health and well-being of Indigenous peoples in Canada. The presentation of results from this study will focus on evidence regarding the role of implicit health care professional bias in contributing to Indigenous/non-Indigenous health inequities and promising practices regarding the interruption of implicit race bias.
Dr. Charles Bernstein, graduated from the University of Manitoba Faculty of Medicine, and the UCLA Division of Gastroenterology Fellowship Training Program. He is Bingham Chair in Gastroenterology Research and Director, University of Manitoba Inflammatory Bowel Disease Clinical and Research Centre.

He developed among the largest validated population based databases of inflammatory bowel disease (IBD). His main research interests are primarily related to IBD; in terms of optimizing management approaches; exploring predictors of clinical outcomes; and disease etiology. More recently, he has been actively involved in exploring the biological and clinical intersection between different chronic immune mediated inflammatory diseases. He has published 382 peer reviewed articles, 29 book chapters and is a co-editor of one of the seminal gastrointestinal clinical-pathology textbooks (Lewin, Weinstein and Riddell's Gastrointestinal Pathology and its Clinical Implications). He has been elected into the Canadian Academy of Health Sciences (2008) and Royal Society of Canada -Life Sciences Division of the Academy of Science (2012). In 2012, he was awarded the Canadian Association of Gastroenterology Research Excellence Award. In 2014, he was named as Distinguished Professor at the University of Manitoba. It is the highest honor the University can bestow upon a professor.

Using Epidemiology to Pursue Etiology in Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is one of several chronic immune diseases of unknown etiology where the highest incidence rates are evident in western developed nations. However, incidence rates are rising across the developing world which leads to speculation as to what factors may have existed in developed nations that have only recently emerged in developing nations that trigger these diseases. While there are over 200 gene mutations associated with IBD, epidemiological patterns of disease suggest that likely 90% of the disease is environmentally driven. A current favored hypothesis is that changes in the gut microbiome, termed dysbiosis, are the underpinning of IBD development. If this proves to be true then one path toward discerning disease etiology may be in exploring epidemiological trends to understand both the types and timing of various factors that can logically explain how gut dysbiosis may have emerged in the middle of the 20th century in developed nations but only in the past 25 years in developing nations. In Manitoba we have the unique ability to track health on a population-wide basis and have harnessed this to understand trends in IBD and potential etiologic clues over the past 30+ years.
Dr. David Evans is a Professor in the Dept. of Medical Microbiology & Immunology at the University of Alberta and Vice-Dean of Research at the Faculty of Medicine & Dentistry. He is a virologist with diverse interests in poxvirus biology as well as being an accomplished research administrator. His studies are supported by a network of collaborations and have been funded since 1987. Dr. Evans is considered a leader in the study of poxviruses with special expertise in virus recombination and replication. Dr. Evans has also demonstrated a longstanding commitment to research translation. His recombineering technology is licensed as InFusion® kits. More recently his research has focused on developing oncolytic viruses for treating bladder cancer. He holds US patents relating to these technologies and is pursuing a Phase I clinical trial. Dr. Evans is also a builder. In 2006 he was awarded $24.9 million to build and equip new facilities in Alberta. In 2010 the University was gifted with $25 million to support virus research, and Drs. Evans and Tyrrell merged several projects into the new Li Ka-Shing Institute of Virology. Dr. Evans has also accumulated many years service on grant panels, reviews, and consults privately. He is a longstanding member of the WHO smallpox advisory committee. Most recently he conducted site visits for the FAO/OIE, and serves on the Canadian advisory committee on human pathogens and toxins.

The Li Ka Shing Institute of Virology: Applied Virology

The Li Ka Shing Institute of Virology was established at the University of Alberta in 2010. Since that time it has grown to support a community of about 30 laboratories with researchers based in departments across the University. I will provide an overview of the Institute’s activities with a special focus on the Institute’s efforts to translate virus-related discoveries into clinical applications.
Prof. Cecilia Lindgren is currently appointed a Senior Group Leader at the Big Data Institute, Li Ka Shing Centre for Health Information and Discovery at University of Oxford after returning from 3 years as a Scholar in Residence at the Broad Institute of Harvard and MIT. She received a Ph.D. in Molecular Genetics from Lund University and continued her career as a visiting researcher at the Whitehead Institute, MIT, USA where she trained in training in statistical genetics. After post-doctoral work at the Karolinska Institute, she joined the Wellcome Trust Centre for Human Genetics at Oxford University. In this setting, her work has contributed to a substantial furthering of our understanding of the genetic landscape of T2D, obesity and fat distribution. In line with this, she is co-chairing the central adiposity team within the GiANT consortium, the obesity working group within UKBBMC, the quantitative traits team within the GoT2DGenes consortium and the Polycystic Ovary Syndrome (PCOS) consortium. She has been awarded the “Rising Star Award” from European Association for the Study of Diabetes (2010), the “Association for the Study of Obesity’s Obesity and Cardiovascular Health Award” (2011), a Senior Research Fellowship from St. Annes College in Oxford (2011) as well as the inaugural “Leena Peltonen Prize for Excellence in Human Genetics” (2013). In 2014 and 2015 she was listed amongst Thomson Reuters 100 “most highly cited researchers” in Molecular Biology and Genetics. Her research focuses on applying genetics and genomics to dissect the etiology of obesity related traits and their correlation with (female) reproductive health.

**Obesity: Using Large-Scale Genetic Data to Dissect Underlying Biology**

Obesity is an urgent global health challenge with no imminent preventive solutions within reach. In general, obesity results from the interaction of heritable factors with environmental influences. Here, I will focus on different aspects of obesity and explore the extent to which human molecular genetic research has illuminated our understanding of their underlying pathophysiological mechanisms. I will also discuss the challenge in translating genetic associations into functional and pathophysiological mechanisms and ultimately evaluate the clinical relevance of this.
Molecular Mechanisms of Brain Ageing

Microglia are CNS-macrophages and their specific functions and ontogeny distinguish them from other tissue-resident macrophages. A complex variety of activated microglia phenotypes has been described in relation to pathological conditions. Here, we present the gene expression profile of pure mouse and human microglia. In mice we have studied the expression profile of microglia in models for acute microglia activation and microglia priming. In mouse models for aging and neurodegenerative disease a highly conserved gene network was identified representative for primed microglia. This network differed significantly from acutely activated microglia networks and was associated with GO terms for immune response, cell stress, phagosome activity and metabolism.

The transcriptome of human microglia resembles that of mouse microglia and contains most microglia-specific genes that have been described in mouse microglia. Interestingly, a number of immune genes, not identified as mouse microglia signature genes, are abundantly expressed in human microglia. These included TLR3, 5 and 10, Fcε and SIGLEC receptors, NLRC5 and CIITA. In contrast to mouse microglia expression profiles, age-induced changes in human microglia gene expression were not characterized by a primed gene expression network signature, but were enriched for CNS-related biological functions, indicating a change in the neuro-supportive role of human microglia during aging. These data provide the first comprehensive pure human microglia gene expression profile. Human microglia clearly differ from mouse microglia, especially with respect to age-induced changes in gene expression.
Dr. Shan is a professor of Neurobiology at Shantou University Medical College, China. He received his PhD from the University of Queensland, Australia, and held postdoctoral research positions in Australia and the United States. His research focuses on the synaptic plasticity underlying action control in both physiological and pathological conditions, and the structure and function of the glycine and GABAA receptors. In his research, he uses the techniques of patch-clamp electrophysiological recording, animal behaviour, optogenetics, and chemogenetics. His research aims to provide new insights into the etiological mechanism of psychological and psychiatric disorders, such as drug addiction, and into pharmacological therapies for such disorders.

Synaptic Plasticity Underlying Action Control

When performing voluntary actions, maintaining an optimal balance between flexible, goal-directed actions and habitual, stimulus-driven actions is critical to our ability to maintain control in our surrounding environment. The goal-directed and habitual learning processes are encoded by discrete brain regions in the basal ganglia, specifically the caudate nucleus (or dorsomedial striatum in rodents) and the putamen (or dorsolateral striatum in rodents), respectively. Our research has been trying to identify the synaptic plasticity underlying these two intermingled but distinct learning processes. Such research not only helps us to understand the nature of these two basic action strategies, but also provides a new insight into the etiological mechanism of pathological forms of action control, such as drug addiction, potentially contributing a therapeutic strategy to manage this widespread mental and social problem confronting modern society.
Dr. Kapus obtained his MD (1986) and PhD (1990) from cell physiology at the Semmelweis University, Budapest, Hungary. He undertook postdoctoral training at the Division of Cell Biology in the Hospital for Sick Children (1992-1995) in Toronto, and was recruited as a scientist to the Toronto General Research Institute and Dept. Surgery, University of Toronto in 1997. Since 2005 he works at the St. Michael’s Hospital/Li Ka Shing Knowledge Institute/Keenan Research Centre (KRC) for Biomedical Science. He is a full professor (Dept. Surgery and Biochemistry), the Associate Vice Chair of Research (Surgery), Head of the Research Training Centre and Director of the Critical Care/Trauma/Inflammation Research Platform (KRC). His research area is basic (patho)physiology and cell biology, pertaining to cellular stress signaling and adaptation (volume and pH regulation, mechanotransduction, cytoskeleton remodeling). In the past 10 years he has focused on basic mechanisms underlying organ fibrosis, including epithelial-mesenchymal transition and the cytoskeletal regulation of nuclear traffic of mechanosensitive transcription factors, recently recognized determinants of cell fate and phenotype. He has published 137 peer-reviewed papers (H-index: 55, ≈8800 citations), and was the recipient of the Elsie Winifred Crann Memorial Trust Award for Medical Research, the Premier’s Research Excellence Award and two mentorship Dr. Kapus obtained his MD (1986) and PhD (1990) from cell physiology at the Semmelweis University, Budapest, Hungary. He undertook postdoctoral training at the Division of Cell Biology in the Hospital for Sick Children (1992-1995) in Toronto, and was recruited as a scientist to the Toronto General Research Institute and Dept. Surgery, University of Toronto in 1997. Since 2005 he works at the St. Michael’s Hospital/Li Ka Shing Knowledge Institute/Keenan Research Centre (KRC) for Biomedical Science. He is a full professor (Dept. Surgery and Biochemistry), the Associate Vice Chair of Research (Surgery), Head of the Research Training Centre and Director of the Critical Care/Trauma/Inflammation Research Platform (KRC). His research area is basic (patho)physiology and cell biology, pertaining to cellular stress signaling and adaptation (volume and pH regulation, mechanotransduction, cytoskeleton remodeling). In the past 10 years he has focused on basic mechanisms underlying organ fibrosis, including epithelial-mesenchymal transition and the cytoskeletal regulation of nuclear traffic of mechanosensitive transcription factors, recently
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**Scar Wars: Cellular and Molecular Mechanisms in Fibrosis**

Organ fibrosis, a dysregulated form of tissue repair is the final common pathway of a large variety of chronic diseases (e.g. hypertension, diabetes), which accounts for 45% of deaths in the Western World. Different manifestations of fibrosis (e.g. glomerulosclerosis, idiopathic pulmonary fibrosis, cirrhosis) share similar cellular mechanisms, including the central triggering role of epithelial injury. However, the mode whereby epithelial damage facilitates fibrosis is subject to debate. Previously the epithelium was thought to be the source of myofibroblasts (the major cellular culprit of fibrosis) via epithelial-mesenchymal transition (EMT), while recent research suggests that the main mechanism may be the development of a profibrotic epithelial phenotype (PEP) characterized by the release of fibrogenic mediators. Both EMT and PEP require profound phenotypic reprogramming. Recent work, including our own shows that, beside soluble mediators (TGFβ), mechanical factors (tissue stiffness, stretch, contact disruption) play a key role in transcriptional reprogramming. These inputs, acting through the cytoskeleton, alter the nucleocytoplasmic traffic of mechanosensitive transcription factors (TFs), which then provoke phenotype change. Here we highlight new insights about the regulation of nuclear shuttling, activity and interplay of two mechanosensitive TFs, myocardin-related transcription factor and TAZ/YAP. These TFs represent conceptually new potential targets to lessen organ fibrosis.
Professor Patrick Maxwell is currently Regius Professor of Physic at the University of Cambridge. He graduated from Corpus Christi College, Oxford, in 1983 with First Class Honours in Physiological Sciences. Subsequently, his clinical training was at St Thomas’ Hospital where he won the Mead Medal in Medicine and the Cheselden Medal in Surgery. The principal thrust of his research is in transcriptional control of genes by oxygen. He has worked on this for over twenty years, initially in Oxford and then as Professor of Nephrology at Imperial College before moving to UCL in 2008 as Professor of Medicine and then Dean of Medical Sciences. His research programme has received substantial international recognition and has considerable potential for translation into new therapies. In 2003 with three other scientists, he set up ReOx, an Oxford University spin-out company which ultimately aims to develop medicines from these discoveries. Professor Maxwell is a Fellow of the Royal College of Physicians, Fellow of the Academy of Medical Sciences and a Fellow of Trinity College Cambridge. The Regius Professor of Physic is Head of the School of Clinical Medicine at the University of Cambridge and Director of Cambridge University Health Partners, the Academic Health Sciences Centre for Cambridge.

**Modulating Oxygen Sensing as a Therapeutic Strategy**

Oxygen is required for many metabolic processes, including efficient energy generation. Altered oxygen availability results in a very broad range of adaptive changes, many of which are coordinated by the transcriptional regulator Hypoxia-Inducible Factor (HIF). Originally identified from studies of erythropoietin production, HIF is now known to regulate hundreds of genes. HIF activation occurs in many pathological settings, notably in cancers where it promotes angiogenesis and reprograms metabolism. There has been rapid progress in understanding how oxygen concentration alters HIF activity. Central to this are the PHD enzymes, which act as molecular oxygen sensors, hydroxylating specific residues in HIFα. Small molecule inhibitors of the PHD enzymes provide a means of augmenting HIF activation. Modulating HIF activity is likely to be a useful therapeutic approach in a range of settings. Currently several companies are testing PHD inhibitors as treatments for anemia associated with chronic kidney disease. It is now clear that this is an effective approach, and the key remaining question is the effect on morbidity and mortality compared to treatment with recombinant human erythropoietin. Pre-clinical data supports the possibility that increasing HIF activity may also be effective in ischaemic injury, suggesting that HIF activators could be useful in major surgery, myocardial ischaemia and stroke.
Dr. Itamar Kahn of the Technion Ruth and Bruce Rappaport Faculty of Medicine studies brain function and behavior in health and disease, focusing on disease mechanisms related to failures of communication between brain systems. His work has applications for better understanding and treating brain disorders including neurodegenerative conditions such as Alzheimer’s disease and Parkinson’s disease, as well neurodevelopmental disorders, such as neurofibromatosis type 1, autism and attention deficit hyperactivity disorder. To advance these goals, Dr. Kahn uses high-resolution functional magnetic resonance imaging (fMRI) to measure activity in multiple brain systems in humans and mouse models of disease. Dr. Kahn received his bachelor’s degree from Ben-Gurion University of the Negev in Mathematics and Computer Science in 1997. Dr. Kahn received his doctorate at Massachusetts Institute of Technology (MIT) in 2005 in Brain and Cognitive Sciences, and was a visiting scholar at Stanford University in 2004-2005 while completing his PhD. He then went on to become a post-doctoral associate at the Howard Hughes Medical Institute at Harvard University from 2006-2010. Since October 2010, Dr. Kahn is an assistant professor of neuroscience at the Technion.

**Novel Translational Imaging Methods to Study Brain Disorders**

In this talk I will describe our efforts over the past few years to develop fMRI tools to study functional connectivity in the awake mouse. I will focus on a mouse model of a developmental genetic syndrome, neurofibromatosis type 1 (NF1), that is linked to autism and attention deficit hyperactivity disorder (ADHD). Using intrinsic functional connectivity MRI in this mouse model we were able to identify a novel cellular target that can potentially alleviate the cognitive phenotype of NF1 pediatric patients. I will conclude with a discussion of implications to autism and ADHD and will briefly describe behaving mouse fMRI to study brain organization in health and disease.
Marion Buckwalter is a basic scientist and physician who practices neurocritical care at Stanford. She earned a combined MD PhD at the University of Michigan in 1996, and then went on to complete medicine internship, neurology residency and neurocritical care fellowship training at the University of California San Francisco. She co-leads SCAN, the Stroke Collaborative Action Network, a Big Idea in Neuroscience project sponsored by the Stanford Neuroscience Institute. This is a collaborative effort of over 30 Stanford faculty to transform the way we study and treat recovering stroke victims. Her research laboratory focuses on inflammatory responses after brain injury.

A New Twist On Old Thinking: Immune Surprises in Dementia

Dementia is a growing problem as the population ages worldwide, affecting nearly 50 million people now, and projected to affect 75 million people by 2030. There are no effective treatments, however there is a growing awareness that dementia is often multifactorial and that stroke, or brain ischemia, is involved in about half of all people who suffer memory loss. Dr. Buckwalter will discuss evidence from studies in mice and people that stroke triggers a faulty activation of the immune system. This immune activation is long lasting and slowly attacks the brain, causing preventable dementia in mice. There is growing evidence that similar, and potentially treatable, immune responses can happen in people who suffer a stroke.
Magnetic Resonance Imaging of Human Brain Connectivity

Magnetic resonance imaging (MRI) has made major advances for the non-invasive study of human brain structure in unprecedented ways that has led to improvements in the diagnosis of brain disorders as well as insights for fundamental neuroscience research. At a glance, MRI appears to possess only gross anatomical information at coarse resolution, but the contrast generated is due to the interactions of water (the molecule typically being measured in MRI) with its local tissue micro-environment at the level of the cells. The focus here will be on diffusion MRI which is sensitive to the mobility of water in tissue and can yield quantitative metrics indicative of the underlying microstructure, such as axon health and myelination in white matter tracts (i.e. brain “wiring”). Proper connectivity is critical for healthy brain function. This talk will first introduce and highlight technical MRI developments of diffusion MRI with an emphasis on white matter tracts and their connections in the brain, and then discuss their application to provide key insights in stroke, epilepsy, healthy development/aging, and neurodevelopmental disorders.
Dr. Kong received his MD (1983, Luzhou Medical College) and PhD (1994, The First Military Medical University) degrees in China. After postdoctoral trainings at University of Massachusetts Medical Centre and University of Manitoba, he was appointed as an assistant professor in 2002 at the University of Manitoba. He was promoted to associate professor in 2006 and full professor in 2011. His research program examines molecular regulation of neuronal cell death in neurodegenerative diseases. Using in vivo and in vitro models of stroke, amyotrophic lateral sclerosis, Alzheimer’s disease, schizophrenia and depression, his group is interested to examine the role of posttranslational oxidative modification of SOD1 in the development of age-related neurodegenerative diseases, investigate the role of mitochondrial death-inducing proteins in regulating mitophagy and delayed neuronal death in stroke, and test a demyelinating hypothesis of schizophrenia. His research program is continuously supported by international and national grant agencies such as the Muscular Dystrophy Association (USA), National Natural Science Foundation of China, Canadian Institutes of Health Research, Canadian Stroke Network, Canada Foundation for Innovation, and Brain Canada. He has 104 peer-reviewed original publications, a book and 5 book chapters.

Dr. Kong is the Director of the Manitoba-Shantou Joint Laboratory of Biological Psychiatry. He is also the coordinator for Academic Exchange Programs between the University of Manitoba and three Chinese Universities (the Third Military Medical University of China since 2008, the Hebei North University of China since 2011, and the Southern Medical University since 2013).

Functional Restoration of the Brain: White Matter Matters

The brain white matter is composed of bundles of myelinated axons. Myelin acts as an insulator, increasing the speed of transmission of all nerve signals. Disruption of CNS myelin occurs in numerous neurological and psychiatric disorders such as multiple sclerosis, cerebral ischemia, schizophrenia and depression. On the other hand, demyelination alone is often sufficient to cause functional deficits of the nervous system. Remyelination is therefore a key to restore brain functions in such neuropsychiatric disorders.

Myelin in the central nervous system is formed by oligodendrocytes, which arise from oligodendrocyte precursor cells (OPCs). The mature oligodendrocytes in the CNS lose their capability to remyelinate new axons. In response to myelin loss, only OPCs are capable of generating new oligodendrocytes to remyelinate axons. OPCs are widely distributed in the adult CNS, accounting for 5 ~ 8% of the total brain cell population. In
a cerebral ischemic preconditioning model we observed that a sublethal episode of ischemia increased
tolerance of neurons and astrocytes to subsequent strokes but aggravated white matter injury and
significantly increased death of OPCs. OPCs are therefore considered the most vulnerable cells in the brain. To
understand the vulnerability of OPCs, we have examined the expression and redistribution of
monocarboxylate transporters (MCTs) under oxygen/glucose deprivation and found an up-regulation and
trafficking of MCT2, a neuronal-specific MCT. There was no change in glial-specific MCT4, suggesting that
neurons are preferentially advantageous in accessing to monocarboxylates when glucose is in limited supply.
We further obtained evidence to show that ischemic preconditioning primes OPCs to express high levels of
the death gene Bcl-2/E1B-19K-interacting protein 3 (BNIP3) in response to subsequent ischemic insults.
Inhibition of BNIP3 by RNAi or necrostatin-1 and knocking out of the BNIP3 gene robustly reduces death of
OPCs and preserve white matter integrity. Using an in vitro co-culture model of remyelination with neurons
and oligodendrocytes prepared from neural stem cells, we found that pre-myelinating NG2 positive OPCs are
able to make contact with axons and initiate remyelination. This is a short time-course and requires activation
and M2 polarization of microglia.
In conclusion, functional restoration of the brain relies not only on reestablishment of the neural networks,
but also on appropriate remyelination of the axons. Since oligodendrocytes are the most vulnerable cells in
the brain, strategies to protect oligodendrocytes and enhance remyelination shall help restore the brain
functions and reduce demyelination-associated post-injury symptoms such as depression and dementia. The
project was supported by Canadian Institutes of Health Research, Brain Canada and Canadian Stroke Network.
Prof. Dr. E.G. Elisabeth de Vries, MD, PhD is Professor of Medical Oncology at the University Medical Center Groningen, Groningen, the Netherlands. She is involved in patient care, teaching, and research. She actively promoted the view that a multidisciplinary approach with close interactions between the laboratory and clinic is crucial for improving prospects for cancer patients. Her focus is on interdisciplinary, translational research, aiming for personalized medicine. Her research lines are aimed at increasing the sensitivity of tumors to anticancer drugs, and she uses imaging techniques to support this.

Apart from laboratory studies, she performs and coordinates clinical trials. She has received numerous grants, including grants from the Dutch Cancer Society, EU, and is PI of CTMM (Center for Translational and Molecular Medicine) grant MAMMOTH, Alpe d’HuZes grant IMPACT, and ERC advanced grant OnQview. She has supervised over 106 PhD students and published over 800 PubMed listed papers. She is currently chairperson of the committee for the new RECIST 2.0 version on behalf of the EORTC.

In 2002, she was appointed as a member of the Royal Academy of Arts and Sciences (KNAW). She received the European Society of Medical Oncology (ESMO) award in 2009. She is Fellow of the European Academy of Cancer Sciences. She was awarded a Royal Netherlands Academy of Sciences professorship in 2011. In 2014 she received the Professor Muntendam award from the Dutch Cancer Society and De Reinier de Graaf medal 2014 for her work in the field of clinical medicine of the Society of Physics, Medicine and Surgery, Amsterdam.

Molecular Imaging Developments in Oncology to Support Drug Development and Immunotherapy Treatment Decisions

In drug development and treatment decisions, attention is paid not only to pharmacokinetic analysis of the drug, but increasingly to tumor characteristics, using techniques such as immunohistochemistry and genotyping. However often information on whole-body drug biodistribution and potentially on in vivo expression of the tumor characteristic of interest is lacking, leaving a large gap between biopsy-based tumor characterization and what is actually happening in the various tumor lesions in a single patient. Three important issues in this respect are heterogeneity of tumor characteristics, whether the drug reaches the tumor lesions, and whether the optimal dose is administered.

Molecular imaging could become relevant as tool to guide rational drug development and treatment.
Progress in tracer development and imaging platforms will enhance the potential of molecular imaging. Nowadays, multiple radionuclide tracers can be used and several characteristics can be measured as was shown in the ZEPHIR trial evaluating pre-treatment zirconium-89 labelled trastuzumab PET/CT and an early FDG-PET/CT response to identify patients with advanced HER-2 positive breast cancer unlikely to benefit from T-DM1 treatment, as well as in the ongoing IMPACT trial, in which FDG-PET, 89Zr-trastuzumab PET, and 18F-fluoroestradiol-PET are being combined in 200 patients with metastatic breast cancer. Moreover, especially for drug development, when repeat biopsies are performed, it might be interesting to use fluorescent-labeled drug tracers as well. The uptake can be visualized with a number of imaging platforms, and the precise location within the tumor lesions can be verified with fluorescence microscopy. Combining tracers might be even more interesting in designing immunotherapy trials, which is challenging because tumor characteristics do not remain static over time.
Dr. Portnoy received his undergraduate degree in bacteriology from UCLA in 1978 and his Ph.D. in 1983 under the tutelage of Stanley Falkow at the University of Washington and Stanford. In the Falkow Lab, he worked on a conserved virulence plasmid in Yersinia. He did his postdoctoral fellowship in the Zanvil Cohn Laboratory at the Rockefeller University in New York, working with Jay Unkeless and Jeff Ravetch on macrophage Fc receptors and lysosomal proteases. During a two-year stint at Washington University in St. Louis, he began working on Listeria monocytogenes as a model intracellular pathogen. In 1988, he joined the Department of Microbiology at the University of Pennsylvania. In 1997, Portnoy moved to UC Berkeley where he currently holds joint appointments in the Department of Molecular and Cell Biology and in the Division of Infectious Diseases and Vaccinology in the School of Public Health, and he was recently appointed as the Edward E. Penhoet Distinguished Chair in Global Public Health and Infectious Diseases. While his lab continues to examine basic aspects of molecular and cell biology, the lab focus has moved into both innate and acquired immunity. In 2013, Portnoy’s contributions were recognized by his election to the National Academy of Sciences.

**Listeria Monocytogenes: From Basic Mechanisms of Pathogenesis to Cancer Immunotherapy**

Prevention and treatment of diseases caused by intracellular pathogens remains one of the largest challenges facing the international biomedical community. A central problem that we address is how intracellular pathogens are recognized by the host and how the immune system integrates multiple signals to induce an appropriate response, and conversely, how pathogens avoid and/or manipulate the host response to promote their pathogenesis. We have chosen to approach this problem by a detailed analysis of Listeria monocytogenes, an intracellular pathogen that has been studied for many decades as a model system with which to dissect basic aspects of infection & immunity. Infection of mice with L. monocytogenes induces robust and long-lived cell mediated immunity. L. monocytogenes provides a highly tractable model to study many aspects of host-pathogen interactions, ranging from basic microbiology, cell biology of infection, innate immune responses in vitro and in vivo, acquired immunity, and vaccine development. In addition, attenuated strains of L. monocytogenes expressing and secreting foreign antigens have been developed by the private sector as therapeutic vaccines for cancer immunotherapy, and in recent phase 2 studies, have shown remarkable success in the treatment of pancreatic cancer. In this lecture, I will address the cell biological and immunological properties that contribute to the induction of cell-mediated immunity by L. monocytogenes.
Aiden Doherty is a senior research fellow at the University of Oxford. His research interest is in the development of computational methods to extract meaningful health information from complex and noisy sensor data in very large health studies. This builds on experience at Microsoft Research, Dublin City University (both in computing departments) and the University of Oxford (population health and biomedical engineering). Aiden has over 50 peer-reviewed publications and is on the UK Biobank expert working group on processing accelerometer data.

Characterizing the Physical Activity Phenotype Using Wearable Sensors

Current evidence indicates that low levels of physical activity increase the risk of cardiovascular disease. However, this evidence has traditionally relied on subjective self-reported data, meaning that uncertainty exists on the level and type of physical activity people should engage in. In response, large studies such as UK Biobank now aim to provide new insights on objectively measured physical activity through distributing wrist-worn accelerometers to >100,000 participants, with each monitor collecting ~180 million data readings per participant. This affords a unique opportunity to improve understanding of the relationship between physical activity and cardiovascular disease. My team’s research is therefore focused on characterising the physical activity phenotype and its health consequences from such rich streams of complex sensor data. I will show the feasibility of collecting this data at scale (103,712 datasets received at a 44.8% response rate), excellent participant compliance (93.3% of participants provided valid data for final analysis), and face validity of the measure (activity 7.5% lower per decade of age). I will also demonstrate the machine learning methods we are developing to uniquely identify physical activity behaviours (such as walking) from sensor data, their novel validation in free living (rather than laboratory) environments, and preliminary examples of their cross-sectional associations with cardiovascular disease outcomes.
Molecular Regulation of Stem Cell Fate: From Basic Biology to the Clinic

Stem cells are distinguished from other cell types by two important characteristics: self-renewal and differentiation. They are unspecialized cells capable of renewing themselves through cell proliferation. Upon certain physiologic or experimental condition, they can differentiate into tissue- or organ-specific cells with defined functions. The regulation of stem cell fate has become a major area of interest in regenerative medicine. Recent studies including our own have revealed that stem cells balance their self-renewal and differentiation status by epigenetic and transcription mechanisms designed to impose precise control over gene expression of pluripotency-associated factors (PFs, e.g., Oct4 and Nanog), and differentiation-associated factors (DFs, e.g., Fgf4, Sox1 and Nestin). Histone modifications (e.g., methylations and acetylations) are important epigenetic marks that regulate gene activities of PFs/DFs by changing chromatin structure at gene regulatory elements and binding sites for transcription machinery. Here we show that histone-modifying enzyme (KDM7A) and histone-binding protein (Cbx3) can regulate embryonic stem cell fate by affecting the enrichment of transcription factors at the promoters or enhancers of PFs/DFs to regulate their gene expression. These molecular regulators are novel drug targets of precise control of stem cell fate in regenerative medicine.
Dr. Kathy Lui received her Bachelor of Science and Master of Philosophy degrees from the Department of Biochemistry, The Chinese University of Hong Kong. With support from the full scholarship, Dorothy Hodgkin Postgraduate Award, Dr. Lui completed her Ph.D in the field of Stem Cell Immunology at Sir William Dunn School of Pathology, University of Oxford, U.K. Dr. Lui was also the recipient of Senior Scholarship at Lincoln College, Oxford, U.K. and Peter Beaconsfield Prize in Physiological Sciences, Oxford, U.K. which is awarded specifically to young researchers who are ‘capable of escaping from the stereotype of narrow specialization, and who display a wider grasp of the significance and potential applicability of their research.’ Thereafter, Dr. Lui received the Croucher Foundation Fellowship and continued her postdoctoral training in the field of Stem Cells and Vascular Regeneration at Massachusetts General Hospital and Department of Stem Cell and Regenerative Biology, Harvard University, U.S.

Dr. Lui is now an Assistant Professor at Department of Chemical Pathology and a principal investigator at Li Ka Shing Institute of Health Sciences, Prince of Wales Hospital, CUHK. Dr. Lui’s laboratory studies organ regeneration via human pluripotent stem cells and vascular signaling.

**Driving Cardiovascular Regeneration for Diabetics**

Congenital heart disease (CHD) is one of the leading causes of infant mortality. Importantly, maternal diabetes is a significant risk factor for CHD as infants of diabetic mothers have a fivefold increase in the risk of malformation and dysfunction of the heart compared to that of the normoglycemic mothers. To date, pre/postnatal analysis of congenital heart anomalies is mainly restricted to major cardiac structures. Recent studies in chick and mouse embryos reveal that maternal hyperglycemia leads to reduced blood vessel formation during early heart development. In this talk, we will discuss whether hyperglycemia affects development of the early heart progenitors in humans using human pluripotent stem cells. The results of our study will pave the way for a better understanding of CHD with a direct avenue for development of novel therapeutics to prevent or treat CHD associated with maternal diabetes.
Dr. Krogan is a Professor in the School of Medicine at UCSF in the Department of Cellular and Molecular Pharmacology. He is also a Founding-Director of the Quantitative Biosciences Institute (QBI) and the UCSF Director of QB3. Dr. Krogan was born and raised in Regina, Saskatchewan, Canada and obtained his undergraduate degree from the University of Regina. As a graduate student at the University of Toronto, Dr. Krogan led a project that systematically identified protein complexes in the model organism, Saccharomyces cerevisiae, through an affinity tagging-purification/mass spectrometry strategy. This work led to the characterization of 547 complexes, comprising over 4000 proteins, and represents the most comprehensive protein-protein interaction map to date in any organism. To complement this physical interaction data, Dr. Krogan developed an approach, termed E-MAP (or epistatic miniarray profile), which allows for high-throughput generation and quantitative analysis of genetic interaction data. Dr. Krogan’s lab at UCSF focuses on applying these global proteomic and genomic approaches to formulate hypotheses about various biological processes, including transcriptional regulation, DNA repair/repliation and RNA processing. His lab at UCSF is now developing and applying methodologies to create genetic and physical interactions between pathogenic organisms, including HIV, Mtb, and Dengue, and their hosts, which is providing insight into the human pathways and complexes that are being hijacked during the course of infection.

Annie Hiniker is a research neuropathologist who completed her MD/PhD at the University of Michigan and her Anatomic Pathology residency and Neuropathology fellowship at UCSF. She is currently an Adjunct Assistant Professor in the UCSF Department of Pathology, where she is completing her postdoctoral fellowship in Scott Oakes' lab. She is also a faculty member at the UCSF Institute for Neurodegenerative Diseases. Her research program focuses on Parkinson's Disease; particularly, delineating the mechanisms of LRRK2-mediated neurodegeneration in genetic PD and testing the hypothesis that gut enteroendocrine cells serve as a nidus for sporadic PD.
Using Systems Approach to Study Disease: The Case of Global Proteomics and Neurodegenerative Diseases

Point mutations in the multidomain kinase LRRK2 are the most common known genetic cause of Parkinson’s disease (PD), a progressive and fatal neurodegenerative disorder that strikes 1-2% of individuals over 65 years of age. Currently, little is known about LRRK2’s normal functions or how LRRK2 point mutations cause neuronal death. We used mass spectrometry to perform global interactome studies of wild type and PD-driving LRRK2 point mutations. This method allowed us to identify novel LRRK2 interacting partners and to identify binding partners with differential affinities for wild type versus PD-driving LRRK2. Now, we are beginning to adapt the approach to human brain tissue. This technique provides an unbiased starting point from which to delineate pathways of interest in PD. More broadly, the approach is generally applicable to neurodegenerative diseases and may represent a new path to the development of rational diagnostics and therapeutics.