2014 JOINT INTERNATIONAL SYMPOSIUM: BIOMEDICAL RESEARCH ACROSS THE CONTINENTS

Time: 10-11 April 2014

Venue: Room 416, Medical Sciences Building,

Tsinghua University, Beijing, China

Sponsors: Tsinghua-Peking Center for Life Sciences

2014 JOINT INTERNATIONAL SYMPOSIUM: BIOMEDICAL RESEARCH ACROSS THE CONTINENTS

10-11 April 2014

Thursday, 10 April

8:00 a.m. Symposium Registration

8:20 a.m. **WELCOME AND INTRODUCTION TO SYMPOSIUM CONCEPT AND PARTNERS**

Host: Linqi Zhang, PhD
Professor and Vice Dean, School of Medicine, Tsinghua University

Qikun Xue, PhD
Vice President for Research, Tsinghua University

Yigong Shi, PhD
Professor and Dean, School of Life Sciences
Director, Institute of Biomedicine, Tsinghua University

Bai Lu, PhD
Senior Vice Dean, School of Medicine, Tsinghua University

Wai-Yee Chan, PhD
Director, School of Biomedical Sciences, The Chinese University of Hong Kong

Nancy Ip, PhD
Dean of Science, Hong Kong University of Science and Technology

Danny Chan, PhD
Assistant Dean (Research Postgraduate Studies)
The University of Hong Kong

Arthur S. Levine, MD
Senior Vice Chancellor for the Health Sciences and Petersen Dean of Medicine University of Pittsburgh

8:45 a.m. **GROUP PHOTO**

9:00 a.m. **CANCER—Session Intro: Arthur S. Levine, MD (Pitt)**

9:15 a.m. GdX/UBL4A Down-Regulates STAT3 Activity and Represses Colon Cancer Cell Proliferation
Zhijie Chang, PhD (Tsinghua)

9:45 a.m. Regulation of DNA Replication in Normal and Cancer Cells
Chun Liang, PhD (HKUST)

10:15 a.m. Identification of Somatic Variants of Hepatocellular Carcinoma by Genome Sequencing Separate line
Nathalie Wong, DPhil (CUHK)

10:45 a.m. Mutational Evolution and Heterogeneity in Cancer
Adrian V. Lee, PhD (Pitt)

11:15 a.m. **REFRESHMENTBREAK**

11:30 a.m. **IMMUNOLOGY—Session Intro: Liwei Lu, PhD (HKU)**

11:45 a.m. Regulation of Germinal Center Formation and Reaction by ICOS
Hai Qi, PhD (Tsinghua)

12:15 noon Regulatory B Cells in Autoimmune Arthritis
Liwei Lu, PhD (HKU)

12:45 p.m. The Ins and Outs of Germinal Centers: Selection, Generation, and Identity
Mark J. Shlomchik, MD, PhD (Pitt)

1:15 p.m. Kill the Cancer by Modulating Its Microenvironments: Role of TGF-ß/Smad3 Separate line
Hui Yao Lan, MD, PhD (CUHK)

1:30 p.m. **LUNCH**

2:45 p.m. **NEUROSCIENCE—Session Intro: Nancy Ip, PhD (HKUST)**

3:00 p.m. Using Mouse Forward Genetics to Study Disease Mechanisms Underlying Neurodegeneration
Yichang Jia, PhD (Tsinghua)

3:30 p.m. Role of PICK1-ICA69 BAR Domain Complexes in Protein Trafficking: Mechanisms and Diseases
Jun Xia, PhD (HKUST)

4:00 p.m. Interaction between Amyloid Plaques and Cerebrovascular Disease—An *in-vivo* Clinical Study using Pittsburgh Compound B PET
Vincent Mok, MD (CUHK)

4:30 p.m. Novel Mitochondrial Mechanisms in Parkinson's disease Pathogenesis
J. Timothy Greenamyre, MD, PhD (Pitt)

5:00 p.m. Cheating on Your Partner: GSK-3ß Is Activated by the Cdk5 Regulatory Protein, P25
Karl Herrup, PhD (HKUST)

5:30 p.m. **ADJOURN FOR THE DAY**

Friday, 11 April 2014

8:00 a.m. Symposium Registration

8:30 a.m. **DRUG DISCOVERY—Session Intro: Jeremy Berg, PhD (Pitt)**

8:45 a.m. Synaptic Repair: Translating BDNF Biology into New Medicines for Neurological and Psychiatric Diseases
Bai Lu, PhD (Tsinghua)

9:15 a.m. From Understanding Synaptic Plasticity to Drug Discovery for Neurodegenerative Diseases
Nancy Ip, PhD (HKUST)

9:45 a.m. A Peptide Targeting Blood Vessels for Cancer Diagnosis and Therapy
Chi Hin Cho, BPharm, PhD (CUHK)

10:15 a.m. Implications of Cellular Heterogeneity in Drug Discovery, Development, and Diagnostics
D. Lansing Taylor, PhD (Pitt)

10:45 a.m. **BREAK**

11:00 a.m. **STRUCTURAL BIOLOGY—Session Intro: Yigong Shi, PhD (Tsinghua)**

11:15 a.m. Mechanistic Study of Human Proteins that Regulate Cell Proliferation and Differentiation
Guang Zhu, PhD (HKUST)

11:45 a.m. DNA Aptamer-Mediated Recognition of Malaria Diagnostic Target *Plasmodium* Lactate Dehydrogenase—Structure, Discrimination, and Application
Julian A. Tanner, PhD (HKU)

12:15 p.m. An Atomistic View on How to Assemble an HIV-1 Capsid
Peijun Zhang, PhD (Pitt)

12:45 p.m. MERS Coronavirus Cell Entry: From Structure to Neutralizing Antibody
Xinquan Wang, PhD (Tsinghua)

1:15 p.m. **LUNCH BREAK**

2:15 p.m. **STEM CELLS AND DEVELOPMENTAL BIOLOGY—Session Intro: Wai-Yee Chan, PhD (CUHK)**

Jiang Xiaohua / Qiaoran Xi

2:30 p.m. A Poised Chromatin Platform for TGF-Beta Access to Master Regulator
Qiaoran Xi, PhD (Tsinghua)

3:00 p.m. Regulation of Mechanical Signals during Tissue Morphogenesis
Yan Yan, PhD (HKUST)

3:30 p.m. Towards an Effective Stell Cell-Based Therapy: Application of Dedifferentiation-Reprogrammed MSCs
Xiaohua Jiang, MD, PhD (CUHK)

4:00 p.m. Progenitor Cells in the Making of a Synovial Joint
Danny Chan, PhD (HKU)

4:30 p.m. Extracellular Component Hyaluronic Acid and Its Receptor Hmmr Are Required for Zebrafish Heart Regeneration
Michael Tsang, PhD (Pitt)

5:00 p.m. The Role of STAT3 in Muscle Stem Cells
Zhenguo Wu, PhD (HKUST)

5:30 p.m. **SYMPOSIUM CONCLUSION AND WRAP-UP: SUSTAINING THE PARTNERSHIP**

Qi-Kun Xue, PhD *(Tsinghua University)*

Vice President for Research, Professor

Qi-Kun Xue, born in 1963, received his BSc in Shan-Dong University in 1984, and PhD degree in condensed matter physics from Institute of Physics, The Chinese Academy of Sciences (CAS) in 1994. From 1994 to 2000, he worked as a Research Associate at IMR, Tohoku University, Japan and a visiting Assistant Professor at Department of Physics, North Carolina State University, USA. He became a professor at Institute of Physics, CAS in 1999. He was elected into The Chinese Academy of Sciences in 2005. Since 2005, he has been a professor in Department of Physics, Tsinghua University. From 2010 to 2013, he was the Chair of Department of Physics and the Dean of School of Sciences. He became the Vice President for Research in May 2013, Tsinghua University. He won the TWAS Prize in Physics in 2010.

His research interests include scanning tunneling microcopy/spectroscopy, molecular beam epitaxy, low-dimensional and interface-related superconductivity, topological insulators, and quantum size effects in various low-dimensional structures. He has authored/coauthored ~360 papers (5 in Science, 9 in Nature associated journals, and 31 in Phys. Rev. Lett.) with a citation of ~7400 times. He has presented more than 100 invited/keynote/plenary talks at international meetings/conferences, such as American Physical Society March Meeting (1996, 2005, 2010, 2012, 2014). Currently, he is the Editors-in-Chief for Nano Research and Surface Review & Letters, and on the Editorial Board of Physical Review B, Applied Physics Letters, Journal of Applied Physics, Surface Science Reports and AIP Advance.

Yigong Shi, PhD *(Tsinghua University)*

Professor and Dean, School of Life Sciences
Director, Institute of Biomedicine

Dr. Shi is a University Professor and dean of the School of Life Sciences at Tsinghua University, Beijing, China. He is a structural biologist recognized for his research into mechanisms of programmed cell death (apoptosis). Dr. Shi received his bachelor's degree with highest honor from Tsinghua University in 1989 and his PhD in biophysics from Johns Hopkins School of Medicine in 1995. He performed his postdoctoral research at Memorial Sloan-Kettering Cancer Center before joining Princeton University as an assistant professor in 1998. Dr. Shi was promoted to the rank of tenured full professor in 2003 and named Warner-Lambert Parke-Davis Professor of Molecular Biology in 2007. He declined an offer to become a Howard Hughes Medical Institute Investigator and returned to Tsinghua University in 2008. He is a recipient of the 2003 Irving Sigal Young Investigator Award, 2010 Sackler Prize in Biophysics, and 2014 GregoriAminoff Prize in crystallography. Dr. Shi is an Academician of the Chinese Academy of Sciences, a Fellow of the American Association for the Advancement of Science, an Honorary Foreign Member of the American Academy of Arts and Sciences, and a Foreign Associate of the European Molecular Biology Organization.

Using X-ray crystallography and a variety of complementary biophysical and biochemical methods, Dr. Shi studies the molecular mechanisms of several key classes of proteins that execute apoptosis, a form of cell death that plays essential roles in the development of multicellular organisms and in the prevention of diseases like cancer and autoimmune diseases. The execution of apoptosis is evolutionarily conserved among metazoans, culminating in activation of a cascade of cell-killing intracellular proteases known as caspases. Over the past 16 years, Dr. Shi has pursued mechanistic understanding of caspase regulation in mammalian as well as fruit fly and worm systems. His laboratory has examined how caspases are activated by upstream activating complexes (apoptosome), how they are inhibited by inhibitor of apoptosis proteins (IAPs), and how the inhibition is derepressed by Smac-like proteins. Dr. Shi is also interested in mechanistic understanding of regulated intramembrane proteolysis (RIP). He has examined the structures of all three known classes of intramembrane proteases: rhomboid-like serine protease, S2P metalloprotease, and a presenilin-like aspartate protease. Finally, as a biophysicist, Dr. Shi is fascinated by adenosine triphosphate (ATP)-powered macromolecular machineries and small molecule transport across the cell membrane.

Bai Lu, PhD *(University of Pittsburgh)*

Professor and Senior Vice Dean School of Medicine

Dr. Lu received his undergraduate training at East China Normal University in Shanghai and did his PhD work at Cornell University Medical College in New York, studying neurotrophin gene expression. After postdoctoral training with Nobel laureate Paul Greengard at Rockefeller University, he became an assistant professor at Roche Institute of Molecular Biology/ Columbia University. He joined the U.S. National Institutes of Health (NIH) in 1996 and became chief of the Neural Development and Plasticity Section in 2001. In 2004, he was named associate director of NIH's Gene, Cognition, and Psychosis Program (GCAP). Dr. Lu worked in GlaxoSmithKline (GSK) R&D-China from July 2009 to September 2013. At GSK R&D China, Dr. Lu was responsible for the overall biology vision and strategy; drug discovery for neurodegenerative disease; innovative clinical research using experimental medicine; GSK's internal discovery engine for exploratory research; and external collaborations with academic institutions, nonprofit foundations, and other business entities. In October 2013, Dr. Lu became executive vice dean of Tsinghua University Medical School.

Dr. Lu pioneered research on the role of neurotrophins in synapse development and plasticity and is credited for several major discoveries: (1) discovery of brain-derived neurotrophic factor (BDNF) regulation of long-term potentiation(LTP), a cellular model for memory; (2) identification of a single-nucleotide polymorphism (SNP) that influences BDNF secretion and short-term memory in humans; (3) elucidation of extracellular cleavage of proBDNF to mature BDNF and its role in long-term synaptic plasticity; (4) demonstration of the opposing roles of proBDNF and mature BDNF in synaptic plasticity, leading to a "Yin-Yang" hypothesis of neurotrophin actions; (5) and elucidation of the functional role of activity-dependent BDNF transcription. Dr. Lu's current research focuses on neural circuits underlying cognitive functions and neurodegenerative and psychiatric diseases, translational medicine, molecular pathways underlying synaptic function, and neural repairs. He has received a number of distinguished awards, including the MathildeSolowey Award in 2003.

Linqi Zhang, PhD *(Tsinghua University)*

Professor and Vice Dean School of Medicine

Dr. Zhang received his doctoral degree in molecular genetics from the University of Edinburgh, UK (1992). He then joined the laboratory of David Ho, MD, as a postdoctoral fellow in 1993 at the Aaron Diamond AIDS Research Center of the Rockefeller University in New York, and subsequently became a staff member as well as assistant and associate professor of the institute until 2007. Dr. Zhang's primary research interest is HIV pathogenesis, focusing on virologic and immunologic changes during disease and treatment with highly active antiretroviral therapy (HAART). His most recent research has focused on the design and development of an effective mucosal vaccine against the most dominant HIV-1 strains in China. Recently, Dr. Zhang has expanded his research into highly pathogenic avian influenza infection (H5N1) and swine flu (H1N1) in China. Dr. Zhang has established a wide local network of scientists and physicians to fight the current upsurge of HIV/AIDS in China. He is the recipient of the National Outstanding Young Scientist Award, privileged Changjiang Professorship, and the principal investigator of the National Basic Research Project (973 Project) on HIV Virology and Immunology supported by the Chinese Ministry of Science and Technology. He is also the recipient of China's 11th 5-year and 12th 5-year Mega project on developing mucosal vaccines against HIV-1, H5N1, and H1N1 infection by the Ministries of Health and Science and Technology.

Arthur S. Levine, MD *(University of Pittsburgh)*

Senior Vice Chancellor for the Health Sciences
John and Gertrude Petersen Dean of Medicine
Professor of Medicine and Molecular Genetics

Since coming to the University of Pittsburgh in 1998, Dr. Levine has focused his priorities on studies that exploit the vast amount of data emerging from the human genome project andon the newly emerging and powerful technologies that enable us to visualize the three-dimensional structures, locations, and interactions of the proteins encoded by genes as they exist at particular times in particular cells. With respect to education, Dr. Levine has initiated new mechanisms designed to enhance the recruitment and retention of talented students and trainees, with the goal of helping to reverse the precipitous decline across the nation in the numbers of young physicians and other health science students embarking upon substantive careers in research and education. The faculty of the University of Pittsburgh ranks fifth nationally in NIH research, and Dr. Levine has been instrumental in fostering the University's remarkable research trajectory. Beyond his University responsibilities, Dr. Levine works closely with UPMC (University of Pittsburgh Medical Center), one of the largest academic medical centers in the U.S., to ensure that health care delivery, biomedical research, and education—the three legs of the "classic academic stool" – remain equally strong and well positioned for future growth.

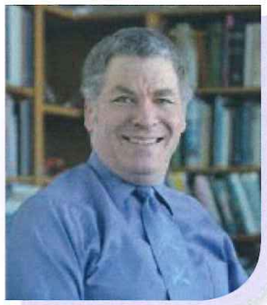
Prior to his appointment to the University of Pittsburgh, Dr. Levine served at the National Institutes of Health for more than three decades, having joined the National Cancer Institute in 1967. From 1982 to 1998, he was the Scientific Director of the National Institute of Child Health and Human Development, widely recognized as one of the world's leading centers in developmental biology. Earlier in his career, Dr. Levine played a leading role in clinical research on childhood malignancies, and he was one of the first to carry out systemic investigations on the prevention and treatment of opportunistic infections in patients with cancer. He has also been engaged in molecular biologic research. He and his colleagues carried out the first physical and genetic mapping of SV40, a mammalian tumor virus. These investigators were also the first to work on naturally occurring viral recombinant DNAs, and the results provided an important source of information in the beginning of the recombinant DNA era. Dr. Levine continues to direct his own laboratory, which is focused on the molecular mechanisms that maintain the fidelity of the genome.

Dr. Levine, who has authored or co-authored more than 250 scientific publications, has been widely recognized for his achievements. He has chaired numerous national and international scientific meetings, been elected to membership in a number of the leading research societies and has held visiting professorships and

distinguished lectureships at many universities here and abroad. Dr. Levine has served on the editorial boards of four scientific journals and was editor-in-chief of The New Biologist, a journal of cellular and molecular biology. He received the Meritorious Service and the Distinguished Service Medals of the United States Public Health Service, The Surgeon General's Exemplary Service Medal, the NIH Director's Award, and the Distinguished Alumnus Award and an Honorary Doctor of Humane Letters degree from the Rosalind Franklin University of Medicine and Science, Chicago, IL. Dr. Levine is a graduate of Columbia College where he majored in comparative literature and edited The Columbia Review. In 1964, he received his M.D. from the Chicago Medical School. After an internship and residency in pediatrics at the University of Minnesota Hospitals, Minneapolis, Dr. Levine served as a fellow in hematology and biochemical genetics at the University of Minnesota prior to joining the NIH.

Jeremy M. Berg, PhD *(University of Pittsburgh)*

Pittsburgh Foundation Professor and Director Institute for Personalized Medicine
Professor of Computational and Systems Biology School of Medicine
Associate Senior Vice Chancellor for Science Strategy and Planning, Health Sciences



Dr. Berg's research focuses the relationships between the structures and functions of biological molecules. He has made major contributions to understanding how zinc-containing proteins bind to the genetic material DNA or RNA and regulate gene activity. His work, and that of others in the field, has led to the design of metal-containing proteins that control the activity of specific genes. These tailored proteins are valuable tools for basic research on gene function, and such proteins could one day have medical applications in regulating genes involved in diseases, as well. Dr. Berg has also made contributions to our understanding of systems that target proteins to specific compartments within cells and to the use of sequence databases for predicting aspects of protein structure and function.

Prior to joining the University of Pittsburgh in June 2011, Dr. Berg was director of the National Institute of General Medical Sciences (NIGMS) at the National Institutes of Health (NIH), where he oversaw a $2 billion budget that funds basic research in the areas of cell biology, biophysics, genetics, developmental biology, pharmacology, physiology, biological chemistry, bioinformatics and computational biology. Prior to his appointment as NIGMS director, Dr. Berg directed the Institute for Basic Biomedical Sciences at the Johns Hopkins University School of Medicine, where he also served as professor and director of the department of biophysics and biophysical chemistry.

Dr. Berg received his BS and MS in chemistry from Stanford University and his PhD in chemistry from Harvard University. His honors include a Presidential Young Investigator Award (1988-1993), the American Chemical Society Award in Pure Chemistry (1993), the Eli Lilly Award for Fundamental Research in Biological Chemistry (1995), the Maryland Outstanding Young Scientist of the Year (1995), election as an American Association for the Advancement of Science Fellow (2007), the Distinguished Service Award from the Biophysical Society (2009), the Howard K. Schachman Public Service Award from the American Society for Biochemistry and Molecular Biology (ASBMB) (2011, presented in 2010), election to the Institute of Medicine of the National Academies (2010), a Public Service Award from the American Chemical Society (2011). He also received teaching awards from both medical students and graduate students and served as an advisor to the Johns Hopkins Postdoctoral Association since its founding.

Nancy Ip, PhD *(Hong Kong University of Science and Technology)*

Dean of Science. The Morningside Professor of Life Science
Chair Professor, Division of Life Sciences

Dr. Ip received her PhD in pharmacology from Harvard Medical School and was senior staff scientist at Regeneron Pharmaceuticals Inc., New York. Since joining HKUST in 1993, she has served as associate dean of science (1998-2005), director of the Biotechnology Research Institute (1996-2008), and head of the Department of Biochemistry (2000-2009).

Dr. Ip is well-known for her seminal discoveries in the biology of neurotrophic factors, which are proteins that promote the survival, development, and maintenance of neurons. She has made important contributions toward understanding the molecular mechanisms underlying brain development and synaptic plasticity and their dysregulation in neurological disorders. She also plays a significant role in the development of biotechnology in Hong Kong. She has helped to establish the expertise and capabilities to drive local drug discovery efforts and launched prominent collaborations with major biopharmaceutical companies, thus placing HKUST on the map for cutting-edge research and development in molecular neuroscience.

As a highly accomplished researcher, Dr. Ip has published more than 230 scientific papers with ~ 16,000 SCI citations and holds 23 patents. She is also senior editor of the Journal of Neuroscience and an elected councillor for two leading organizations in the fields of neuroscience and psychopharmacology: the Society for Neuroscience and the Collegium InternationaleNeuro-Psychopharmacologicum (CINP). In recognition of her excellent achievements in science and biotechnology, Dr. Ip has received numerous awards and honors. These include the Croucher Foundation Senior Research Fellowship; the National Natural Science Award, China's highest honor in the natural sciences; the L'OREAL-UNESCO for Women in Science Award, making her the first honoree in the life sciences from China; the Scientific and Technological Progress Prize of Ho Leung Ho Lee Foundation; and the Chevalier de l'Ordre National du Mérite. As a further testament to her professional achievement, she was elected academician of the Chinese Academy of Sciences and fellow of the Academy of Sciences for the Developing World.

Chan Wai-Yee, PhD *(The Chinese University of Hong Kong)*

Professor of Biomedical Sciences and Director of School of Biomedical Sciences

Dr. Chan obtained his B.Sc. (Hon. 1st Class) from the Chinese University of Hong Kong in 1974 and Ph.D. in Biochemistry from the University of Florida, Gainesville, Florida, USA in 1977. After a two year Genetics fellowship, he joined the Department of Pediatrics at the University of Oklahoma Health Science Center in Oklahoma City, Oklahoma, USA, first as an Assistant Professor and then a tenured Associate Professor. He became Professor, Department of Pediatrics, Georgetown University, Washington, DC, USA in 1989. He remained there as a tenured Professor of Pediatrics and Adjunct Professor of the Department of Biochemistry and Molecular & Cellular Biology till 2009. In 2001, he was seconded to the U.S. National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), to help found the Laboratory of Clinical Genomics. He was later appointed as Head and Principal Investigator of the Section on Developmental Genomics, NICHD. In June 2009 he became Professor of Biomedical Sciences and the Founding Director of the School of Biomedical Sciences, Faculty of Medicine, the Chinese University of Hong Kong. Currently, he is also the Director, CUHK-Beijing Genome Institute Innovation Institute of Transomics.

His expertise is in the developmental functional genomics and epigenomics of male germ cells, and the molecular genetics of human endocrine disorders. He was a recipient of the Merrick Award for Outstanding Biomedical Research from the Oklahoma Medical Research Foundation, Service Award from the Department of Biochemistry and Molecular Biology, University of Oklahoma Health Sciences Center, and the 2008 Presidential Award from the Association of Chinese Geneticists in America. He served as member in a number of research funding agencies including the NIH of USA, Health Research Council of New Zealand, the UK Wellcome Trust and Health Research Board, Science Foundation of Ireland, French National Alliance for Life and Health Sciences and French National Cancer Institute, Diabetes, UK, and Hong Kong Food and Health Bureau Research Fund. He is a member of the editorial board of 15 international scientific journals. He holds 5 patents, has edited 5 books, contributed 25 book chapters, and published over 150 scientific articles in international peer-reviewed scientific journals.

Danny Chan, PhD *(The University of Hong Kong)*

Assistant Dean (Research Postgraduate Studies)

After graduating from the University of Melbourne, with a Bachelor of Science (with honors), MS, and PhD, Dr.Chan continued research at his alma mater on heritable skeletal disorders, with a focus on extracellular matrix proteins. His research contributed significantly to the understanding of the molecular consequences in many forms of the human osteochondrodysplasias. In recognition of his work, Dr. Chan was presented with an award for "Excellence in Medical Research" by the State Premier of Victoria, Australia. He joined the University of Hong Kong in 1998, maintaining his research in skeletal biology using mouse as a model to address disease mechanisms *in vivo*, as well as human genetic studies to define genetic risk factors for common degenerative skeletal conditions like intervertebral disc degeneration. Key findings in his laboratory included the consequence of cellular stress in chondrocytes, allowing matured chondrocytes to be "rejuvenated," and how the capacity and range of a signaling molecule, Indian hedgehog, are regulated in development. His work on the genetics of intervertebral disc ratio has led to the identification of new genetic risk factors, Asporin and CHST3, providing new insights into disease mechanisms and the potential for new therapeutic targets. In translational research, he is interested in defining the progenitor cells in joint and disc development and the molecular controls that regulate the differentiation process of these progenitors.

PROGRAM ABSTRACTS

SESSION 1: CANCER

GdX/UBL4ADown-Regulates STAT3 Activity and Represses Colon Cancer Cell Proliferation

Zhijie Chang, PhD (*Tsinghua University*)
Professor, School of Medicine

Impaired phosphatase activity contributes to the persistent activation of STAT3 (signal transducer and activator of transcription 3) in tumors. Given that STAT family members with various or even opposite functions are often phosphorylated or dephosphorylated by the same enzymes, the mechanism for STAT3-specific dephosphorylation in cells remains largely unknown. Here, we identified that GdX (UBL4A), a house-keeping gene located on the X chromosome, promotes STAT3 dephosphorylation by mediating the interaction between TC45 (the nuclear isoform of T-cell protein tyrosine phosphatase or TC-PTP) and STAT3 specifically. Only in the presence of GdX can STAT3 be efficiently dephosphorylated by TC45; thus, STAT3 dephosphorylation by TC45 becomes inefficient in $GdX^{-/-}$ cells. Moreover, GdX inhibits malignancy by reducing the level of phospho-STAT3 (p-STAT3) in tumor cells while deletion of GdX results in a high level of p-STAT3 and accelerated colorectal tumorigenesis induced by azoxymethane/dextran sodium sulphate (AOM/DSS). GdX expression is inversely correlated with p-STAT3 levels, and low expression of GdX is an independent prognostic factor for overall survival in human colon cancers. We propose that GdX converts TC45, a non-specific phosphatase, into a STAT3-specific phosphatase by bridging an association between TC45 and STAT3.

Dr. Zhijie Chang obtained his PhD from the Northern Western Agricultural University, Shaanxi, P.R.C., in 1989 in animal genetics and breeding. He worked on quantitative genetics between 1989 and 1995. He then went to the Pharmaceutical and Physiological Department at St. Louis University to study molecular biological technology from 1995 to 1996 and transferred to the Medical Center of Washington University at St. Louis as a research fellow to study molecular mechanisms in osteoblast differentiation from 1996 to 1997. He continued his research on osteoblast differentiation as a postdoctoral fellow in the Department of Pathology of the University of Alabama at Birmingham from1997 to 1998. Dr. Chang returned to the Department of Biological Sciences and Biotechnology, Tsinghua University, in 1998 as an associate professor, where he set up a laboratory with Xin Yuan Fu, PhD, working on TGF-beta, STAT, and FGF signal transduction. He was promoted to full professor in the Department of Biological Sciences and Biotechnology and the School of Medicine in 2005. Dr. Chang has published more than 70 papers in major journals including Cancer Cell, Molecular Cell, Journal of Cell Biology, Molecular and Cellular Biology, Journal of Biological Chemistry, Journal of Molecular Biology, Proceedings of the National Academy of Sciences, Journal of Cell Science, Cancer Research, Breast Cancer Research, Journal of Molecular Biology Research, Carcinogenesis, Gene Therapy, Cellular Signaling, Cell Research, Biochemical and Biophysical Research Communications, and FEBS Letters, and has obtained 17 patents including one U.S. patent at Tsinghua University. He is now a tenured full professor in the School of Medicine, Tsinghua University. He serves as an editor of FEBS Letters.

2014 JOINT INTERNATIONAL SYMPOSIUM:
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Regulation of DNA Replication in Normal and Cancer Cells

Chun Liang, PhD *(Hong Kong University of Science and Technology)*
Associate Professor, Division of Life Science

Eukaryotic DNA replication licensing, which is a prerequisite for genome duplication and also helps to ensure that all chromosomal DNA is replicated exactly once per cell cycle, involves the recruitment of many replication-initiation proteins to form pre-replicative complexes (pre-RCs) at replication origins. My lab has been studying the mechanism and regulation of DNA replication in budding yeast and human cells and investigating the regulation of replication-initiation proteins in normal and cancer cells. Here I will present our studies in the following two areas: (1) identification and characterization of DNA replication-initiation proteins in budding yeast and (2) regulation of CDC6 by microRNA-26 in lung cancer.

Dr. Liang obtained his BSc in chemistry from Sun Yat-Sen University in 1982, his MSc in chemistry from Miami University in 1988, and PhD in biology from Brown University in 1993. He then served as a postdoctoral fellow from 1993-1998 at Cold Spring Harbor Laboratory. Dr. Liang studies the mechanisms and regulation of DNA replication in budding yeast and human cells, as well as the potential applications of replication-initiation proteins in cancer. He work has been published in Cell,Genes & Development,and the Proceedings of the National Academy of Sciences (PNAS) (two papers in each), as well as in the Journal of Cell Biology,Molecular and Cellular Biology, Cancer Research, Journal of Biological Chemistry,Journal of Cell Science, Nucleic Acids Research, Journal of Molecular Biology, Cell Cycle, BMC Cancer, Developmental Biology, and others.

Identification of Somatic Variants of Hepatocellular Carcinoma by Genome Sequencing

Nathalie Wong, DPhil ***(The Chinese University of Hong Kong)***

Professor of Anatomical and Cellular Pathology

Hepatocellular carcinoma (HCC) is the fourth-leading cause of cancer-related deaths worldwide, and over half of HCC cases are related to hepatitis B virus (HBV) infection. In most patients, HCC is diagnosed at a late advanced stage. Hence, patient prognosis is generally poor, with a five-year survival rate of less than 5 percent. Earlier genome analyses had provided valuable information on the vital genomic alterations of HCC, but information on the pattern of mutational changes remains largely undefined. Recent advances in next-generation sequencing technology have revolutionized gene discoveries in human cancers and promises to provide novel tumor biomarkers. By next generation sequencing, we sequenced primary HCC tumors and reference tissue from the same individual to explore nucleotide variants and other acquired somatic abnormalities that are tumor-specific. We found nucleotide substitutions of HCC to exhibit a predominance of T>C/A>G and C>T/G>A transitions. In addition, indels and HBV integrations were also distinctive. Among the non-synonymous somatic mutated genes detected, validation study in an independent series of primary HCC tumors further showed recurrent mutations of CTNNB1, TP53, and MLL2. Our findings illustrate the potentials for next-generation sequencing to provide novel insights into the mutational processes of HCC development. The assessment of novel biomarkers discovered for their diagnostic value and research into the biology should provide the basis for future developments of their clinical utilities and therapeutic potentials.

Dr. Wong, obtained her DPhil from the University of Oxford and later received her postdoctoral training at King's College School of Medicine and Dentistry, London. She is now a professor of anatomical and cellular pathology at CUHK.

Dr. Wong's current research focuses on understanding the molecular carcinogenesis of human hepatocellular carcinoma (HCC). Her group has previously defined a number of vital cytogenetic loci of HCC and delineated causal tumor suppressor genes and oncogenes in liver tumorigenesis. Her current research includes whole genome and transcriptome analysis of HCC, functional characterization of somatic variants for cancer-causing effects, and elucidation of signaling pathways in the development of HCC.

Mutational Evolution and Heterogeneity in Cancer

Adrian V. Lee, PhD ***(University of Pittsburgh)***

Professor of Pharmacology and Chemical Biology, School of Medicine

Carcinogenesis generally proceeds over a long period of time, with genetic alterations providing growth and survival advantages. Pathologists have long recognized that tumors show intra-tumor heterogeneity of both cell types and molecular markers. This heterogeneity is thought to evolve either from clonal selection of cancer cells and/or via alterations in cell differentiation. Limited evidence suggests that tumors with increased intra-tumor heterogeneity may have an unfavorable outcome, perhaps due to their ability to evolve and circumvent therapy. Recent studies of metastatic disease have revealed novel mutations that arise during progression and may represent novel therapeutic targets. For example, we identified a mutation in estrogen receptor that arose in a patient with breast cancer undergoing endocrine therapy. There are likely many more of these drug-resistant mutations to be found. Recent advances in the miniaturization and multiplexing of high-throughput analytic platforms have allowed an unprecedented and comprehensive view of molecular changes in breast cancers. However, nearly all studies have been performed on whole crushed tissue and, thus, represent only an average of molecular changes across the tumor. Recent studies on molecular changes in specific regions of tumors, or on single cancer cells, reveal dramatic evolution of tumor heterogeneity. We have measured intra-tumor heterogeneity both in cell lines in culture and in breast tumors and find an evolution of proteomic and genomic change during breast cancer progression. This tumor heterogeneity has important implications for precision medicine, particularly as it relates to measuring prognostic/predictive markers, and the successful delivery of targeted therapies.

Dr. Lee received his BSc in biochemistry from Kent University in England. He performed his graduate studies with Roger J.B. King, PhD, DSC, at the Imperial Cancer Research Fund in London and then at the University of Surrey in Guildford, England. Dr. Lee came to the University of Texas Health Science Center at San Antonio (UTHSCSA) for his postdoctoral studies with Douglas Yee, MD, studying the role of insulin-like growth factors (IGFs) in breast cancer and mechanisms of therapeutic targeting of this pathway. He was promoted to instructor of medicine and subsequently recruited as an assistant professor to Baylor College of Medicine, where he rose to the position of tenured associate professor in the Breast Center and Departments of Medicine and Molecular and Cellular Biology. Dr. Lee is currently professor of pharmacology and chemical biology at the University of Pittsburgh School of Medicine and director of the Women's Cancer Research Center at the University of Pittsburgh Cancer Institute and Magee Womens Research Institute.

The goal of Dr. Lee's laboratory is to translate basic cell and molecular research findings into the understanding and treatment of breast cancer. To this end, Dr. Lee's laboratory studies many aspects of translational breast cancer research using basic biochemistry and molecular biology, cell lines, mouse models, and patient biopsies from clinical trials. The laboratory's main focus is the understanding of how IGFs regulate breast transformation and how this knowledge can be used for successful treatment of patients. Dr. Lee's lab also studies the role of novel nanotechnology agents in the imaging and treatment of early breast cancer and the role of structural genomic rearrangements in breast cancer.

Dr. Lee has published more than 100 peer-reviewed research articles and has funding from the U.S. National Institutes of Health (NIH), Department of Defense, Susan G. Komen Foundation, and other sources. He is a member of the NIH Molecular Oncogenesis (MONC) study section and serves on numerous other national peer-review committees. Dr. Lee has received numerous awards, including a T.T. Chao Scholarship. Dr. Lee is actively involved in teaching both graduate and medical students.

SESSION 2: IMMUNOLOGY

Regulation of Germinal Center Formation and Reaction by ICOS

Hai Qi, PhD ***(Tsinghua University)***
Professor, School of Medicine

During a T-dependent B cell response, germinal center (GC) formation and subsequent generation of high-affinity bone-marrow plasma cells (BMPC) requires proper functions of follicular T-helper (Tfh) cells. ICOS, a classic B7-family costimulatory molecule, has long been known as necessary for Tfh development and GC formation, but the underlying cellular mechanism is not fully clear. I will discuss our published results and ongoing work that indicate a dual role for ICOS in the T-dependent B cell response. First, by promoting persistent T-cell motility in the absence of concomitant antigen recognition, ICOS facilitates helper T cell recruitment into the primary follicle in a bystander B cell-dependent manner. Second, by promoting cognate T-B contact, with extensive surface engagement in the GC, ICOS facilitates delivery of CD40L signals from T to B cells in an intercellular feed forward fashion and, thereby, drives high-affinity variants into the BMPC pathway. Collectively, our work defines how ICOS regulates the GC response.

Dr. Qi received his bachelor of medicine degree from the Beijing Medical University and his PhD in pathology from the University of Texas Medical Branch at Galveston. He went on to conduct postdoctoral research at the U.S. National Institutes of Health (NIH), with Ronald Germain, MD, PhD, examining cell migration and cell-cell interactions during immune responses *in vivo*. He joined the faculty of Tsinghua University in 2009.

Dr. Qi's research aims to understand how dynamic intercellular communication among different cell types underlies a functional immune system.His current focus is the dynamic regulation of the humoral immune response and germinal center (GC) biology. Within this context, his group tries to understand how critical cellular interactions are molecularly orchestrated, how qualitative and quantitative properties of such interactions are translated into cell fate decisions, how lymphoid tissues and GC microdomains are spatiotemporally patterned, and how such patterns facilitate productive yet prevent unwanted immune activation. To pursue these studies, his toolkit includes genetic, biochemical, cell biological, live cell imaging, and intravital 2-photon tissue imaging methods. His recent work demonstrates that B cell activation can be initiated by dendritic cells carrying antigen *in vivo* (Science 2006), that the signaling lymphocytic activation molecule-associated protein (SAP) molecule controls the strength of cognate T-B interactions *in vivo* (Nature 2008), and that inducible costimulator (ICOS) signaling directly controls T cell motility and follicular recruitment (Nature 2013).

Dr. Qi is an ad hoc reviewer for Science andthe Journal of Experimental Medicine and serves on the editorial board ofScientific Reports and Immunity, Inflammation and Disease.

Regulatory B Cells in Autoimmune Arthritis

Liwei Lu, PhD ***(The University of Hong Kong)***
Professor of Pathology, Li KaShing Faculty of Medicine

Extensive studies have demonstrated the prominent functions of B cells in antibody production and antigen presentation. However, certain B cell subsets have been recognized as immune regulators through cytokine production. Accumulated data indicate that IL-10-producing B cells possess a regulatory function in the development of autoimmune diseases, but microenvironmental factors and/or cytokines involved in inducing regulatory B cell differentiation remain largely uncharacterized.

B cell-activating factor (BAFF), a member of the tumor necrosis factor (TNF) family of cytokines, is a key regulator of B cell maturation and function. In this study, we identified a novel function of BAFF in the induction of IL-10-producing regulatory B cells. BAFF-induced IL-10-producing B cells showed a distinct CD1dhiCD5+ phenotype mainly derived from marginal-zone B cells, which possessed a potent function in inhibiting T cell activation and cytokine production. BAFF was found to activate the transcription factor AP-1 for binding to IL-10 promoter. In collagen-immunized mice, adoptive transfer of BAFF-induced IL-10-producing B cells markedly reduced the disease severity and joint damage of autoimmune arthritis via suppression of the Th17 cell response. Taken together, our findings have provided further insight in understanding the roles of BAFF and regulatory B cells in autoimmune pathogenesis, which may facilitate the development of therapeutic strategies for targeting human rheumatoid arthritis.

Upon his graduation in medicine from Jiangsu University, Dr. Lu became a lecturer in anatomy at the same medical school until his PhD studies at McGill University in 1993. After receiving his PhD in 1997, he continued his postdoctoral research at the University of Toronto. He joined the University of Hong Kong as an assistant professor in 2000 and has been a tenured professor of immunology since 2012.

Dr. Lu's research has been focusing on lymphocyte development and its dysregulation in autoimmune diseases. Using an animal model of collagen-induced arthritis for human rheumatoid arthritis, his laboratory is developing novel strategies for the treatment of autoimmune arthritis. Dr. Lu's group was among the first to successfully target autoimmune arthritis in mice by silencing a tumor necrosis factor (TNF) family cytokine BAFF (B-cell activating factor), which has significantly contributed to the validation of BAFF as a therapeutic target for human rheumatoid arthritis. Recently, his group has developed a protocol for in vitro expansion of B cells with regulatory functions and further demonstrated the therapeutic effects of regulatory B cells on autoimmune arthritis.

Dr. Lu has published more than 80 research papers in leading immunology and rheumatology journals including Nature Immunology, Proceedings of the National Academy of Sciences, Blood,Journal of Immunology, and Arthritis & Rheumatism. He has served as chairman of the Hong Kong Society for Immunology. Dr. Lu received the David Rae Memorial Award from the Leukemia Research Fund of Canada in 2000 and the Young Investigator Award from the Hong Kong Society for Immunology in 2003. He was awarded the Medical Faculty Teaching Award at the University of Hong Kong in 2008. In 2012, he received the Croucher Senior Research Fellowship Award.

The Ins and Outs of Germinal Centers: Selection, Generation, and Identity

Mark J. Shlomchik, MD, PhD *(University of Pittsburgh)*
Professor and Chair of Immunology, School of Medicine

Germinal centers (GCs) are structures that develop in B follicles of secondary lymphoid tissue after the initiation of an immune response. Memory B cells (MBCs) are defined as cells that have experienced antigen stimulation, divided, differentiated, and then returned to quiescence. Such MBCs are typically studied after the initial immune response has faded. MBCs can be restimulated by antigen and presumably respond in a different fashion than their naïve counterparts, classically by making a rapid burst of short-lived antibody forming cells. Long-lived plasma cells (LLPC) have ceased division, have an extremely long lifespan, are not restimulatable, and typically reside in the bone marrow. GCs are thought to be the source of long-lived MBCs and LLPCs. GC B cells proliferate rapidly, undergo somatic mutation of V regions, and undergo a poorly understood process of selection for higher affinity for nominal antigen while avoiding autoreactivity. We have been interested in several questions related to these processes. How do GC B cells "decide" whether to divide and maintain identity, die, or differentiate into either MBCs or LLPCs? What is the identity, origin, and nature of MBCs themselves? How does the MBC compartment preserve itself over long periods and avoid being depleted if restimulation causes terminal differentiation into antibody-forming cells (AFCs)? I will present data on MBC heterogeneity, origin, and function. I will also discuss how the GC generates various types of MBCs and LLPCs and discuss concepts of GC function that seek to explain how high affinity long-lived B cell compartments develop following immunization.

Dr. Shlomchik received his medical and doctoral degrees in 1989 from the University of Pennsylvania, where he also completed residency training in pathology and laboratory medicine. After postdoctoral work at Fox Chase Cancer Center in Philadelphia, he joined the faculty of Yale University, rising to the rank of full professor in 2004. He came to the University of Pittsburgh School of Medicine in 2012 to become chair of the Department of Immunology. Dr. Shlomchik's laboratory is interested in B cell development and immunopathogenesis. One set of projects focuses on autoimmunity: how do autoreactive B cells arise and what are their role(s) in mediating autoimmune disease? His research group is using transgenic and knockout mouse models to answer these questions. The group has made intriguing discoveries on the roles of Toll-like receptors in systemic autoimmunity and is following up on these findings. A second project addresses B cell activation and memory. The lab has made several recent insights, including via *in vivo* multiphoton microscopy, into the mechanisms of cellular selection and differentiation in the germinal center, a site of rapid proliferation, mutation, and differentiation into memory cells. The Shlomchik lab has identified novel memory-specific genes and is studying their roles using knock-out mice and in vitro signaling assays. Finally, the lab is investigating why memory T cells fail to cause graft-versus-host disease using a new TCR Tg model.

In the area of lupus, Dr. Shlomchik was among the first to elucidate the roles of B lymphocytes and Toll-like receptors in promoting disease. Both of these are now targets of drugs that are either approved or in development to treat autoimmune disorders in patients. He is the first recipient of the Lupus Insight Prize from the Lupus Research Institute, given in 2012. In October 2012, Dr. Shlomchik's team showed that an enzyme complex called NADPH oxidase, or NOX2, which plays an important role in the body's resistance to bacteria and fungi, is also necessary to curb genetic predisposition to lupus. In addition to autoimmunity, B-cell immune responses and how vaccines elicit protective antibodies, Dr. Shlomchik has worked on bone marrow transplantation, where some of his findings have also resulted in an ongoing clinical trial.

2014 JOINT INTERNATIONAL SYMPOSIUM:
BIOMEDICAL RESEARCH ACROSS THE CONTINENTS

Kill the Cancer by Modulating Its Microenvironments: Role of TGF-ß/Smad3

Hui Yao Lan, MBBS, PhD *(The Chinese University of Hong Kong)*
Professor of Medicine and Therapeutics, Assistant Dean for Research, Faculty of Medicine
Associate Director, Li KaShing Institute of Health Sciences
Director, Inflammatory Diseases Research, Shenzhen Research Institute

It is now well accepted that transforming growth factor β (TGF-β) plays a pivotal role in tumor progression. However, mechanisms underlying this process are extremely complex and intricate. TGF-β is highly produced by cancer cells and promotes cancer progression by concomitantly enhancing tumor growth and metastases while inhibiting the host immunity. We found that increased TGF-β/Smad3 signaling contributes significantly to cancer progression by enhancing angiogenesis and T regulatory cell differentiation while suppressing NK cell differentiation and function. The promoting role of Smad3-dependent microenvironments in cancer progression is demonstrated by the findings that mice lacking Smad3 are protected against tumor growth, invasion, metastasis, and death in two syngeneic mouse models induced by highly invasive lung carcinoma (LLC) and melanoma (B16F10). Furthermore, targeting Smad3 with a Smad3 inhibitor suppresses cancer progression and prevents cancer death. Thus, a Smad3-dependent tumor microenvironment in the host is a key determinant in cancer progression and could be a new therapeutic target for cancer.

Dr. Lan received his MD fromSun Yat-Sen University of Medical Sciences, China, and his PhD from Monash University, Australia. He was previously a senior lecturer at Monash University; tenured professor of medicine at Baylor College of Medicine, US; and a held a full professorship at the University of Hong Kong.

Dr. Lan's major research interest is TGF-β/Smad signaling in chronic cardiovascular and kidney diseases and, more recently, cancer microenvironments. He has published more than 270 articles with h-index 53. Currently, he is an editorial board member of the Journal of the American Society of Nephrology, the International Journal of Biological Sciences, and Frontiers in Renal and Epithelial Physiologyand an associate editor of Nephron Experimental Nephrology and Clinical Experimental Pharmacology and Physiology.

SESSION 3: NEUROSCIENCE

Using Mouse Forward Genetics To Study Disease Mechanisms underlying Neurodegeneration

Yichang Jia, PhD (***Tsinghua University***)
Assistant Professor, School of Medicine

Neurodegenerative diseases afflict millions of people worldwide; but so far no effective cure has been developed for these devastating disorders, partially due to our poor understanding of disease mechanisms. Because the mouse shares over 90 percent gene similarity with humans, the study of chemically induced mutant mice carrying neurodegenerative phenotypes will great enhance our knowledge of disease mechanisms and accelerate the identification of therapeutic interventions. Recently, increasing evidence, including ours, suggests that dysfunction of RNA metabolism may play a key role in the etiology of a range of neurodegenerative disorders. However, how RNA dysfunction causes neurodegeneration is largely unknown. We currently use several available mouse models and develop new mouse models relevant to RNA dysfunction-induced neurodegeneration to understand the disease mechanisms. We hope our disease-oriented research will advance future therapeutic interventions against these devastating disorders.

Dr. YichangJia received his PhD from the Institute of Neuroscience, Chinese Academy of Sciences, Shanghai, China, in 2006. He then moved to the Jackson Laboratory/ Howard Hughes Medical Institute for his postdoctoral training in mouse genetics. In 2012, Dr. Jia obtained the Pathway to Independence Award (K99/R00) from the U.S. National Institutes of Health. In 2013, he was selected into the 1,000 Talented Young Scientists Program, P.R.C. Currently, Dr. Jia's laboratory focuses on: (1) the disease mechanisms underlying neurodegeneration caused by RNA metabolism abnormalities, and (2) the molecular basis of RNA metabolism in specific neuron types and their subcellular compartments during both physiological and pathological conditions. Dr. Jia is an assistant professor in the School of Medicine, Tsinghua University, and also a principal investigator in the Peking-Tsinghua Joint Center for Life Sciences.

Role of PICK1-ICA69 BAR Domain Complexes in Protein Trafficking: Mechanisms and Diseases

Jun Xia, PhD (***Hong Kong University of Science and Technology***)
Associate Professor, Division of Life Science

Mammalian cells are divided by elaborate membrane compartments. Proteins are transported between different compartments via trafficking vesicles. Protein trafficking is tightly regulated to ensure proper function of different proteins. We identified PICK1, a peripheral membrane protein with a PDZ domain and a BAR domain, as an important protein trafficking regulator. The PDZ domain of PICK1 binds to a number of membrane proteins while the BAR domain of PICK1 binds to liposome and couples membrane proteins to trafficking vesicles. In addition, the BAR domain of PICK1 forms a tight heteromeric BAR domain complex with ICA69, another BAR domain-containing protein. The switch from heteromeric PICK1-ICA69 to homomeric PICK1-PICK1 BAR domain complex provides an important mechanism for vesicle sorting and refinement. In brain, PICK1 interacts and regulates the trafficking of AMPA type glutamate receptor, and this regulation is critical to synaptic plasticity, the cellular basis of learning and memory. In pancreatic beta-cells, PICK1 controls the trafficking of insulin granules, and its deficiency leads to glucose intolerance and symptoms related to diabetes.

Dr. Xia received his medical degree in 1993 from Xiangya Medical School of Central South University in China. After obtaining his initial scientific training from the Shanghai Brain Research Institute at the Chinese Academy of Sciences, he completed his PhD in neuroscience at the Johns Hopkins University School of Medicine in the United States. He joined the Division of Life Science, HKUST, as a faculty member in 2002. Dr. Xia is interested in synapse organization and function, with implications in learning, memory, and psychiatric disorders. He also works on molecular mechanisms of protein trafficking and their implication in diseases. His work identified PICK1 as a key regulator of protein trafficking. PICK1 forms heteromeric BAR domain complexes with ICA69 and controls the biogenesis and maturation of dense core vesicles like insulin granules and proacrosomal granules. Deficiency of PICK1 in mice led to glucose intolerance and other features resembling diabetes.

Interaction between Amyloid Plaques and Cerebrovascular Disease—an in-vivo Clinical Study using Pittsburgh Compound B PET

Vincent Mok, MD ***(The Chinese University of Hong Kong)***

Assistant Dean (Clinical), Faculty of Medicine

Although deposition of amyloid plaques is a key pathological hallmark of Alzheimer's disease, autopsy studies show that amyloid plaques are also frequently found in non-demented elderly subjects. Recent autopsy studies suggest that concurrent presence of infarct may significantly enhance the manifestation of dementia. However, given the retrospective nature of autopsy study, firm conclusions cannot be drawn.

In the present study, we used *in-vivo* Pittsburgh compound B positron emission tomography (PET) to evaluate the interaction between various cerebrovascular diseases and subjects harboring amyloid plaques. We found that even a mild cerebrovascular event (e.g., transient ischemic attack) was able to induce rapid cognitive deterioration in subjects harboring amyloid plaques. Findings of this study provide further evidence on the interaction between cerebrovascular disease and amyloid plaques in causing dementia.

Dr. Mok is assistant dean (clinical) of the Faculty of Medicine. He is also director of the Master of Science Program in Stroke and Clinical Neurosciences, associate director of the Institute of Integrative Medicine (Neuroscience), chairman of the Dementia Advisory Board of Otsuka International Asia Arab, a member of the executive Committee of the International Society of Vascular Behavioural and Cognitive Disorders, honorary treasurer of the Asian Society against Dementia, honorary executive member of the Cognitive Disorder and Dementia Group of the National Chinese Medical Association, immediate past president of the Hong Kong Movement Disorder Society, vice-president of the Chinese Dementia Research Association, honorary secretary of the Hong Kong Neurological Society, and Hong Kong Delegate of the World Federation of Neurology. He also serves on the editorial board of several international journals in dementia, stroke, and movement disorders.

Dr. Mok received the Natural Science Prize (First Class, 2012), awarded by the Ministry of Education of the People's Republic of China (自然科學獎 , 1 级). He has authored more than 160 peer-reviewed publications and five book chapters. His research interests include cognitive disorders, Parkinsonism, and neuroimaging.

Novel Mitochondrial Mechanisms in Parkinson's disease Pathogenesis

J. Timothy Greenamyre, MD, PhD (*University of Pittsburgh*)

Love Family Professor and Vice Chair Chief, Division of Movement Disorders Dept of Neurology, Director, Pittsburgh Institute for Neurodegenerative Diseases, School of Medicine

Mitochondrial impairment has been implicated in the pathogenesis of both sporadic and genetic forms of Parkinson's disease (PD). Mutations in the gene encoding alpha-synuclein (AS) are another rare cause of PD, but AS also is thought to play a central role in most forms of the disease. We have shown that mitochondrial impairment leads to accumulation, oligomerization, and aggregation of AS, and other groups have shown that AS overexpression causes mitochondrial impairment and production of reactive oxygen species (ROS). The mechanisms for this bi-directional interaction between mitochondrial impairment and AS have been obscure. Recent work from our laboratory suggests that modified forms of alpha-synuclein (oligomers and fibrils) interact specifically with the TOM20 and TOM70 receptors that control most mitochondrial protein import. The interaction of AS with the mitochondrial protein import machinery leads to decreased import of key proteins and, ultimately, to accumulation of senescent, poorly functioning mitochondria. Genetic and experimental evidence suggests this "vicious cycle" can begin with abnormalities in either mitochondria or AS. In addition to these mechanisms, we have found, using induced pluripotent stem cell (iPSC)-derived neurons, that leucine-rich repeat kinase 2 (LRRK2) mutations (the most common autosomal dominant form of PD) cause mtDNA damage. Zinc finger nuclease (ZFN)-mediated gene editing can prevent this phenotype. We will present data to suggest that this may provide a novel biomarker for PD. Together, our data suggest that mitochondrial impairment may provide both a therapeutic target and a biomarker for target engagement in PD.

Dr. Greenamyre received his BS from Michigan State University and his MD and PhD from the University of Michigan. After his neurology residency at the University of Michigan, he joined the faculty of the University of Rochester in 1990 and was recruited to Emory University in 1995. He moved to the University of Pittsburgh in 2005. Dr. Greenamyre's research team focuses on mechanisms that cause nerve cell death in disorders like Parkinson's, Huntingdon's, and Alzheimer's diseases, with the goal of using them as potential targets for therapeutic intervention. He is particularly interested in how genetic-environmental toxin interactions may affect individual susceptibility to Parkinson's disease. The work focuses on mitochondrial impairment, oxidative damage, and protein aggregation. Regarding Huntington's, investigations focus on mitochondrial calcium handling and proteomics. The lab employs *in vivo* models of neurodegeneration and in vitro culture of cells and brain slices to study mechanisms of degeneration with a variety of biochemical, anatomical, and physiological techniques.

Dr. Greenamyre has received numerous honors, including the Langston Award from the Michael J. Fox Foundation. He delivered a "Decade of the Brain Lecture" at the annual meeting of the American Academy of Neurology and a Presidential Lecture at the annual meeting of the Society for Neuroscience. Dr. Greenamyre is also director of the American Parkinson Disease Association's Advanced Center for Parkinson's disease Research at the University of Pittsburgh. He is a member of the executive advisory board of the Michael J. Fox Foundation and a member of the scientific advisory committee of the Parkinson's disease Foundation. He is editor-in-chief of the journal Neurobiology of Disease and of MedLink Neurology. In addition to research, Dr. Greenamyre maintains an active clinical practice.

Cheating on Your Partner: GSK-3ß Is Activated by the Cdk5 Regulatory Protein, P25

Karl Herrup, PhD ***(Hong Kong University of Science and Technology)***
Head and Chair Professor Division of Life Science

Glycogen synthase kinase 3β (GSK3β) and cyclin-dependent kinase 5 (CDK5) have overlapping substrate targets and influence many of the same functions. Their three-dimensional structures are remarkably similar; both are tau kinases and have been proposed to contribute to the pathogenesis of Alzheimer's disease. This observation led us to hypothesize that both might be capable of binding cyclin proteins—the activating cofactors of all CDKs. CDK5 is normally activated by the cyclin-like proteins, p35 and p39, but can nonetheless bind all major cyclins. By contrast, we show that GSK3ß does not bind to cyclin A or D, but unexpectedly binds to both p35 and its calpain cleavage product, p25. Indeed, over-expressed GSK3β out-competes CDK5 for p25, while Cdk5 is the preferred p35 partner. FRET analysis in primary cortical neurons reveals nanometer apposition of p25:GSK3ß in cell soma as well as in synaptic regions. Interaction with p25 increases GSK3β activity, leading to enhanced hyperphosphorylation of tau. In silico modeling suggests the docking site for p25 on GSK3ß is the Axin-binding domain. Consistent with this idea, p25 inhibits the formation of the GSK3β/Axin/APC destruction complex, resulting in decreased phosphorylation of ß-catenin. Co-expression of GSK3β and p25 in cultured neurons results in a neurodegeneration phenotype that exceeds that observed with CDK5 and p25. When p25 is transfected alone, the resulting neuronal damage is blocked more effectively with a specific GSK3β inhibitor than with CDK5 inhibitor roscovitine. We propose that the effects of p25, though normally attributed to hyperactivated CDK5, may be mediated in part by elevated GSK3ß activity.

Dr. Herrup received his bachelor's degree from Brandeis University in Waltham, MA, and his PhD in neuroscience from Stanford University in 1974. After two postdoctoral fellowships – in neurogenetics at Children's Hospital/Harvard Medical School and in neuropharmacology at the Biozentrum in Basel, Switzerland – he joined the faculty of the Human Genetics Department of Yale Medical School in 1978 as an assistant, then associate, professor. He became director of the Division of Developmental Neurobiology at the E.K. Shriver Center in Waltham, MA, in 1988. In 1992 he moved to the Departments of Neurosciences and Neurology at Case Western Reserve University Medical School and University Hospitals of Cleveland. While there, he directed the University Alzheimer's Center from 1999 through 2005. In 2006 he moved to the Piscataway/New Brunswick campus of Rutgers University to become professor and chair of the Department of Cell Biology and Neuroscience. In addition to this leadership role in a large public university, he helped to found the Brain Health Institute, a unique public/private partnership devoted to basic research with relevance to clinical neuroscience. In July 2012, he moved to Hong Kong to become the head of Life Sciences at HKUST. His laboratory research is focused on the biology of nerve cell death and the paradoxical role that failed cell cycle regulation plays in the process. His work includes a strong translational interest that directs his studies toward a few select human neurodegenerative diseases, including Alzheimer's, a common late-life dementia, and ataxia-telangiectasia, a very rare multisystem disorder of childhood. Dr. Herrup has authored a large number of highly cited papers and, until 2010, served as the founding senior editor of the Neurobiology of Disease section of the Journal of Neuroscience.Dr. Mok received the Natural Science Prize (First Class, 2012), awarded by the Ministry of Education of the People's Republic of China (自然科學獎, 1級). He has authored more than 160 peer-reviewed publications and five book chapters. His research interests include cognitive disorders, Parkinsonism, and neuroimaging.

SESSION 4: DRUG DISCOVERY

Synaptic Repair: Translating BDNF Biology into New Medicines for Neurological and Psychiatric Diseases

Bai Lu, PhD (*Tsinghua University*)
Professor and Senior Vice Dean
School of Medicine

Despite significant progress in identifying novel targets for brain disorders, these efforts have not been translated into superior treatments over existing therapies. Increasing evidence suggests that synapse and circuit dysfunctions underlie the pathophysiology of major brain illnesses. Studies of brain-derived neurotrophic factor (BDNF), the best known "synaptogenic" molecule proven in humans, may pave the way for a paradigm shift in treating psychiatric disorders. Emerging evidence on BDNF regulation of memory and emotion, the impact of the BDNF genotype on psychiatric endophenotypes, and the progress in tools to measure synaptic dysfunction in humans all suggest that the time is ripe to target synaptic repair by the BDNF pathway in the clinic. In this talk, I will highlight evidence for BDNF regulation of synaptic plasticity and synaptogenesis and its role in cognitive functions like memory and extinction. I will then discuss our recent work on translating BDNF biology into the clinic. Specifically, I will talk about (1) efforts in developing measures of synaptic changes in human brain *in vivo*, and (2) possibilities in using BDNF val/met polymorphism for patient stratification in clinical trials. Through experimental medicine in humans, we hope that a paradigm-shifting "synaptic repair" strategy will yield innovative medicines for the treatment of psychiatric diseases.

Dr. Lu received his undergraduate training at East China Normal University in Shanghai and did his PhD work at Cornell University Medical College in New York, studying neurotrophin gene expression. After postdoctoral training with Nobel laureate Paul Greengard at Rockefeller University, he became an assistant professor at Roche Institute of Molecular Biology/Columbia University. He joined the U.S. National Institutes of Health (NIH) in 1996 and became chief of the Neural Development and Plasticity Section in 2001. In 2004, he was named associate director of NIH's Gene, Cognition, and Psychosis Program (GCAP). Dr. Lu worked in GlaxoSmithKline (GSK) R&D-China from July 2009 to September 2013. At GSK R&D China, Dr. Lu was responsible for the overall biology vision and strategy; drug discovery for neurodegenerative disease; innovative clinical research using experimental medicine; GSK's internal discovery engine for exploratory research; and external collaborations with academic institutions, nonprofit foundations, and other business entities. In October 2013, Dr. Lu became executive vice dean of Tsinghua University Medical School.

Dr. Lu pioneered research on the role of neurotrophins in synapse development and plasticity and is credited for several major discoveries: (1) discovery of brain-derived neurotrophic factor (BDNF) regulation of long-term potentiation(LTP), a cellular model for memory; (2) identification of a single-nucleotide polymorphism (SNP) that influences BDNF secretion and short-term memory in humans; (3) elucidation of extracellular cleavage of proBDNF to mature BDNF and its role in long-term synaptic plasticity; (4) demonstration of the opposing roles of proBDNF and mature BDNF in synaptic plasticity, leading to a "Yin-Yang" hypothesis of neurotrophin actions; (5) and elucidation of the functional role of activity-dependent BDNF transcription. Dr. Lu's current research focuses on neural circuits underlying cognitive functions and neurodegenerative and psychiatric diseases, translational medicine, molecular pathways underlying synaptic function, and neural repairs. He has received a number of distinguished awards, including the MathildeSolowey Award in 2003.

From Understanding Synaptic Plasticity to Drug Discovery for Neurodegenerative Diseases

Nancy Ip, PhD ***(Hong Kong University of Science and Technology)***
Dean of Science. The Morningside Professor of Life Science
Chair Professor, Division of Life Sciences

Synaptic remodeling is precisely regulated by the co-ordinated activation of diverse cell surface receptors. My laboratory is interested in understanding how neurons transduce signals from these cell surface receptors to regulate synapse function and plasticity of the adult brain under normal and diseased conditions. We have recently identified distinct receptor-mediated signaling pathways that can positively or negatively regulate neurotransmission, thereby differentially promote the strengthening and weakening of existing synapses. For example, the receptor tyrosine kinase TrkB binds to the growth factor BDNF and modulates structural changes of the synapse during memory formation. On the other hand, another receptor tyrosine kinase, EphA4, is a major negative regulator of neurotransmission. Activation of EphA4 attenuates synaptic transmission by promoting the degradation of neurotransmitter receptors and the loss of synaptic contacts. In our attempt to translate our discoveries from basic research to the development of neurotherapeutic agents, we have leveraged our research strengths in molecular neuroscience and Chinese medicine to establish a focused drug discovery program in search of new drug leads, including those that can regulate synaptic activity. Through discovery of new molecular targets in neurodegenerative diseases, we have screened for potential modulators of these targets using specific bioassay platforms or structure-based molecular docking approach. This drug discovery strategy has proven to be a very effective approach in identifying potential drug candidates, some of which are currently at various stages of pre-clinical development for neurological disorders.

Dr. Ip received her PhD in pharmacology from Harvard Medical School and was senior staff scientist at Regeneron Pharmaceuticals Inc., New York. Since joining HKUST in 1993, she has served as associate dean of science (1998-2005), director of the Biotechnology Research Institute (1996-2008), and head of the Department of Biochemistry (2000-2009).

Dr. Ip is well-known for her seminal discoveries in the biology of neurotrophic factors, which are proteins that promote the survival, development, and maintenance of neurons. She has made important contributions toward understanding the molecular mechanisms underlying brain development and synaptic plasticity and their dysregulation in neurological disorders. She also plays a significant role in the development of biotechnology in Hong Kong. She has helped to establish the expertise and capabilities to drive local drug discovery efforts and launched prominent collaborations with major biopharmaceutical companies, thus placing HKUST on the map for cutting-edge research and development in molecular neuroscience.

As a highly accomplished researcher, Dr. Ip has published more than 230 scientific papers with ~ 16,000 SCI citations and holds 23 patents. She is also senior editor of the Journal of Neuroscience and an elected councillor for two leading organizations in the fields of neuroscience and psychopharmacology: the Society for Neuroscience and the Collegium InternationaleNeuro-Psychopharmacologicum (CINP). In recognition of her excellent achievements in science and biotechnology, Dr. Ip has received numerous awards and honors. These include the Croucher Foundation Senior Research Fellowship; the National Natural Science Award, China's highest honor in the natural sciences; the L'OREAL-UNESCO for Women in Science Award, making her the first honoree in the life sciences from China; the Scientific and Technological Progress Prize of Ho Leung Ho Lee Foundation; and the Chevalier de l'Ordre National du Mérite. As a further testament to her professional achievement, she was elected academician of the Chinese Academy of Sciences and fellow of the Academy of Sciences for the Developing World.

A Peptide Targeting Blood Vessels for Cancer Diagnosis and Therapy

Chi Hin Cho, BPharm, PhD ***(The Chinese University of Hong Kong)***
Professor of Pharmacology, Associate Director,
School of Biomedical Sciences, Faculty of Medicine

Ligand-mediated diagnosis and targeted therapy would have significant clinical applications in cancer treatment. In this study, an orthotopic model of colorectal cancer was established in mice. *In vivo* phage library selection was then utilized to isolate peptides specifically recognizing the vasculature of colorectal cancer tissues. A phage (termed TCP-1 phage) was isolated by this manner, and it homed to the colorectal cancer tissues by 11- to 90-fold more than other organs. Chemical synthetic peptide (termed TCP-1) displayed by TCP-1 phage inhibited the homing ability of the phage to the tumor mass when co-injected intravenously with the TCP-1 phage into mice with colon cancer. Meanwhile, immunostaining analysis indicated that TCP-1 phage and peptide localized in the vasculature of the colorectal cancer tissue, but not in normal tissues. Moreover, TCP-1 peptide bound to blood vessels of surgical tissue samples of human colorectal cancer, in particular in the advanced stages. In addition, TCP-1 conjugated with a proapoptotic peptide specifically induced apoptosis of tumor-associated blood vessels *in vivo*. Similar homing ability was also observed for TCP-1 in orthotopic gastric cancer tissues. These data define a novel peptide TCP-1 as an effective agent for imaging detection and drug delivery for gastrointestinal cancers.

Dr. Cho received his bachelor of pharmacy degree from the National Defense Medical Center in Taiwan and his PhD in pharmacology from the University of Hong Kong. He spent some years at the University of Toronto and Harvard Medical School for his postdoctoral training before he took up faculty positions in the National Yang Ming Medical College and Veterans General Hospital in Taipei.

Dr. Cho returned to the University of Hong Kong in 1984 and became chair professor of pharmacology in 2000. In 2007, he joined CUHK as chairman of the Department of Pharmacology. Currently, he is professor of pharmacology and associate director of the School of Biomedical Sciences in the Faculty of Medicine, CUHK.

Dr. Cho was president of the Gastrointestinal Pharmacology Section of the International Union of Basic and Clinical Pharmacology and is a standing committee member of a number of international societies on gastrointestinal diseases. He has been on the editorial board and is also the associate editor or editor of more than 25 international journals and has published more than 430 peer-reviewed articles and books in the fields of gastrointestinal pharmacology and gastroenterology. His major research interest is the pathogenesis of and drug development for gastrointestinal inflammation and cancers. His recent work in the discovery of novel peptides for drugs targeting both inflammatory and cancerous diseases in the stomach and colon has resulted in two patents and has earned national and government grants from China and Hong Kong, as well as interest from the international pharmaceutical industry.

Implications of Cellular Heterogeneity in Drug Discovery, Development, and Diagnostics

D. Lansing Taylor, PhD (*University of Pittsburgh*)

Allegheny Foundation Professor of Computational and Systems Biology
School of Medicine Director, University of Pittsburgh Drug Discovery Institute

It is now well understood in cancer that tumors exhibit both inter- and intra-tumor heterogeneity that increases the challenge to create optimal diagnostic tests and to discover and develop therapeutic approaches. We have implemented a quantitative systems pharmacology (QSP) approach to the development of therapeutics and diagnostics for multiple diseases that considers heterogeneity as an important element of the systems. We have used a phenotypic discovery platform to identify compounds that modulate key pathways that have been validated in multiple cancers. In one study, we have explored the heterogeneity of cellular responses to cytokines and lead compounds that modulate the activation of STAT3 (signal transducer and activator of transcription 3) in several head and neck and breast cancer cell lines. It is evident from our studies that the standard method of analyzing cell-based assays using cell population averages to characterize the responses of cells to challenges gives incomplete and often misleading information on the dose effects. We have created the Heterogeneity Index (HI) to quantify the level of heterogeneity as a guide to developing lead compounds. It is projected that novel therapeutics will be developed and/or combined to manage cellular sub-populations that respond differently to specific drugs. We have extended the concept to human biomimetic models of toxicity and image-based diagnostics, where cellular heterogeneity also affects interpretations.

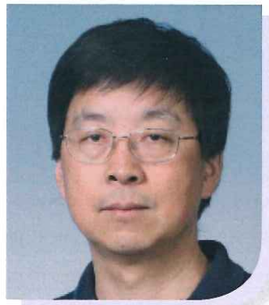
Dr. Taylor received his PhD in cell biology from the State University of New York at Albany and was a postdoctoral fellow in biophysics at the Woods Hole Marine Biological Laboratory. He began his academic career at Harvard University and remained at Harvard until 1982, developing and using novel fluorescence-based reagents and imaging technologies to investigate fundamental cellular processes in living cells. He then moved to Carnegie Mellon University as a professor of biological sciences and director of the Center for Fluorescence Research in the Biomedical Sciences, continuing to develop and to apply novel fluorescence-based technologies to solve fundamental questions in the biomedical sciences. Dr. Taylor left Carnegie Mellon to start a series of companies: Cellomics-high content screening, Cellumen-early safety assessment and Cernostics-cancer diagnostics. Dr. Taylor returned to academia at the end of 2010 to continue his academic interests, which now link large-scale cell and tissue profiling with computational and systems biology to optimize drug discovery and diagnostics. Dr. Taylor holds a substantial number of U.S. patents, including six focused on cell-based screening.

SESSION 5: STRUCTURAL BIOLOGY

Mechanistic Study of Human Proteins that Regulate Cell Proliferation and Differentiation

Guang Zhu, PhD (*Hong Kong University of Science and Technology*)

Professor Division of Life Science



Proper organ development requires the precise regulation of both the total number of cells (cell proliferation) and the types of cells (cell differentiation). During cell proliferation, Cdt1-mediated loading of DNA helicase (Mcm2-7) to replication origins is required for DNA replication, and Hox gene activation is necessary for embryonic cell differentiation. It has been shown that these two processes are linked through the cell cycle-regulator Geminin and the homeodomain-containing transcription factors Hox. To understand the molecular mechanism involved, we determined the solution structures of Geminin-Hox, Cdt1-Mcm6, and Orc6-DNA complexes by nuclear magnetic resonance (NMR) spectroscopy and conducted biochemical studies to delineate the structural basis of this mutual regulation. In addition, we found that histone H4-K20 methyltransferase SET8 is a cell-cycle regulator and plays an important role in the developmental program of metazoans. *(These studies are supported by RGC 663911 and AoE/M-06/08.)*

Dr. Zhu obtained his BSc (Northwest University, Xian, P.R.C.) and MSc (Old Dominion University, Norfolk, VA, U.S.A.) in physics. He studied for his PhD degree and received his postdoctoral training under the supervision of Ad Bax, PhD, at the University of Maryland, College Park, and the National Institutes of Health, Bethesda, MD, U.S.A., specializing in biomolecularnuclear magnetic resonance (NMR) spectroscopy. Subsequently, he was recruited as an assistant professor to HKUST, where he rose to the current position of full professor in the Division of Life Science.

Dr. Zhu's research focuses on (1) the development of biomolecular NMR technology and (2) the structure-functional study of protein and nucleic acid in human and Epstein-Barr virus (EBV) DNA replication. Dr. Zhu has developed many useful biomolecular NMR techniques that are well cited and documented in NMR textbooks. He was awarded the WANG Tianjuan prize in NMR spectroscopy. Currently Dr. Zhu's structure-functional investigations of proteins and nucleic acids in human and EBV DNA replication involve mechanistic studies of human pre-RC, Hox, EBNA1, tRNA, and DNA/RNA G-quadruplex in human cancers. The results of this work will provide a basis for structure-based drug design against cancer.

Dr. Zhu has published more than 75 peer-reviewed research and review articles and has funding from the Hong Kong Research Grants Council, TUYF, and other sources. He is an associate editor of several journals and vice chairmen of the Chinese NMR Society and Hong Kong Biophysics Society. Dr. Zhu is actively involved in teaching both graduate (more than a dozen of Ph.Ds from his lab) and undergraduate students.

DNA Aptamer-Mediated Recognition of Malaria Diagnostic Target Plasmodium Lactate Dehydrogenase—Structure, Discrimination, and Application

Julian A. Tanner, PhD ***(The University of Hong Kong)***

Associate Professor of Biochemistry
Li KaShing Faculty of Medicine

DNA aptamers hold significant promise for molecular recognition in diagnostics, particularly in light of developments of DNA integration within innovative nanotechnology approaches. We are developing DNA aptamers for integration into point-of-care malaria diagnostic devices, an area that the World Health Organization has highlighted as critically needing transformational diagnostic approaches. Major challenges in the aptamer field include structural binding affinities and, in particular, how they can discriminate closely related protein targets. Here, we evolve and characterize a DNA aptamer against the malaria diagnostic target *Plasmodium* lactate dehydrogenase, solve the structure of the aptamer in complex with its target, and discuss approaches we are taking for incorporating the aptamer into a diagnostic device. The 27-base DNA aptamer has a distorted hairpin structure in complex, incorporating seven Watson-Crick base pairs, one noncanonical base pair, and two bases flipped out at critical interaction sites with the target. An extensive hydrogen-bonded network with a loop only present in *Plasmodium* lactate dehydrogenase, but absent in human lactate dehydrogenase, dictates discriminatory recognition by the aptamer. The structure allows a rational approach to extending the structure-blind evolutionary approach of aptamer discovery. Research is ongoing to improve the aptamer using structure-guided approaches and to integrate the DNA aptamer into diagnostic devices for better point-of-care malaria diagnostics.

Dr. Tanner received his BSc in chemistry from Bristol University, UK, followed by a PhD in chemistry from Imperial College, London in 2001. After his PhD, Dr. Tanner moved to the Department of Biochemistry at the University of Hong Kong, where he is now an associate professor. The Tanner lab is presently engaged in three research areas: (1) in vitro evolution of nucleic acid aptamers for diagnostics and therapeutics, (2) polyphosphate biochemistry and function, and (3) biophysical enzymology.

Dr. Tanner co-authored a major chemical biology textbook entitled Essentials of Chemical Biology: Structure and Dynamics of Biological Macromolecules (Wiley, 2008). He has published widely at the biology-chemistry-medicine interface, including recent publications in Proceedings of the National Academy of Sciences, Biochemical Journal, Journal of Biological Chemistry, Chemistry & Biology, and Biochemistry. Dr. Tanner has also been actively involved in undergraduate curriculum reform at the University of Hong Kong, being awarded the Faculty Teaching Medal for developing innovative evidence-based approaches for learning and assessment in undergraduate biochemistry and biomedical sciences education.

An Atomistic View on How to Assemble an HIV-1 Capsid

Peijun Zhang, PhD (*University of Pittsburgh*)

Associate Professor of Computational and Systems Biology
School of Medicine

Mature HIV-1 particles contain a conical-shaped capsid that encloses the viral RNA genome and performs essential functions in the virus life cycle. In mature virion, the assembled capsid structure is best described by a fullerene cone model that is made up from a hexameric lattice containing hexameric and pentameric capsid protein (CA). We obtained a cryo-EM structure of HIV-1 capsid assembly at 8Å resolution. The density map clearly delineates all the α-helical motifs within the structure. The structure allowed unambiguous modeling and refinement by large-scale molecular dynamics simulations, resulting in all-atom models of the HIV-1 capsid comprising 64 million atoms. The models revealed new hydrophobic interactions at the inter-subunit trimer interface. Further, cryoEM structural analysis of immature intermediate capsid-nucleocapsid (CA-NC) assemblies revealed a marked conformational difference at this trimer interface compared to mature CA assemblies. The critical role of the trimer interface in HIV-1 maturation was verified via chemical crosslinking.

Dr. Zhang obtained her PhD in molecular biophysics from the University of Virginia and her MS in solid state physics and BS in electrical engineering from Nanjing University. She carried out postdoctoral work at the National Cancer Institute. In 2006, she joined the faculty of the University Of Pittsburgh School Of Medicine as an assistant professor and was promoted to associate professor with tenure in 2012. Her research focuses on the structural and functional studies of large molecular complexes and assemblies, viruses, and cellular machineries using integrated structural, biochemical, and computational approaches to understand biological complexity.Dr. Zhang has received numerous awards, including the Carnegie Science Center Emerging Female Scientist Award in 2014.

The Zhang lab is interested in structural and functional characterization of macromolecular assemblies using three-dimensional cryo-electron microscopy (cryoEM) as well as biochemical and biophysical methods. Proteins carry out their cellular functions through formation of dynamic multi-protein complexes and macromolecular assemblies. These complexes or machines are usually too large and/or too heterogeneous for structural solution by X-ray crystallography or NMR spectroscopy methods. CryoEM is uniquely poised for structure determination of large complexes and macromolecular assemblies and their conformational changes to provide structural snapshots along dynamic processes. The group's interest is to combine structural information obtained through cryoEM methods with biochemical, physiological analysis to understand molecular mechanisms of protein complexes and machines. The group is currently focused on three research areas: (1) understanding HIV-1 and host cell interactions during the early stages of virus infection; (2) eliciting 3D architectures of the chemotaxis receptor signaling complexes and their assemblies to understand the molecular mechanism of signal transduction in bacterial chemotaxis; and (3) developing technologies to enhance the capability of cryo-electron tomography for 3D architectures of native mammalian cells at different signaling states.

MERS Coronavirus Cell Entry: From Structure to Neutralizing Antibody

Xinquan Wang, PhD (*Tsinghua University*)

Professor
Center for Structural Biology
School of Life Sciences

The recently identified Middle East respiratory syndrome coronavirus (MERS-CoV) causes severe and fatal acute respiratory illness in humans. No prophylactic and therapeutic agents specifically against MERS-CoV are currently available. Entry of MERS-CoV into the target cells depends on binding of the receptor-binding domain (RBD) on the viral envelope spike glycoprotein to the cellular receptor dipeptidyl peptidase 4 (DPP4).We report the 3.0 Å-resolution crystal structure of MERS-CoV RBD bound to the extracellular domain of DPP4. The structure shows that MERS-CoV RBD consists of a core and a receptor binding subdomain. MERS-CoV RBD and related severe acute respiratory syndrome (SARS)-CoV RBD share a high degree of structural similarity in the core subdomain but are notably divergent in the receptor binding subdomain. Structural and mutagenesis analyses identified key residues in the receptor binding subdomain of MERS-CoV RBD that are critical for viral binding to DPP4 and entry into the target cell. Two RBD-specific potent human neutralizing monoclonal antibodies were derived from single-chain variable region fragments (scFvs) from a nonimmune human antibody library. They inhibited infection of both pseudotyped and live MERS-CoV with IC50 at nanomolar concentration. Biochemical analysis indicated that these two antibodies blocked RBD interaction with DPP4 on the cell surface.

Dr. Wang obtained his PhD from the Institute of Biophysics, Chinese Academy of Sciences in 2000. He then remained there as a research assistant professor until 2003, when he went to the Department of Molecular and Cellular Physiology, Stanford University, to conduct postdoctoral research on the structure and mechanism of cell-surface receptor-ligand interactions that play important roles in immune response and human disease. Dr. Wang returned to the School of Life Sciences, Tsinghua University in 2008 as a tenure-track associate professor and set up his laboratory to study structural mechanisms for the recognition and assembly of cytokines with their receptors and viral immune evasion. He was promoted to the rank of tenured full professor in 2013.As corresponding author, Dr. Wang has published nine papers in major journals, including Nature Immunology, Proceedings of the National Academy of Sciences, Genes & Development, Cell Research, PLoS Pathogens, Journal of Immunology, and Journal of Biological Chemistry.

SESSION 6: STEM CELLS AND DEVELOPMENTAL BIOLOGY

A Poised Chromatin Platform for TGF-Beta Access to Master Regulator

Qiaoran Xi, PhD (*Tsinghua University*)

Principal Investigator
School of Life Sciences

Specific chromatin marks keep master regulators of differentiation silent, yet poised for activation by extracellular signals. We report that nodal transforming growth factor (TGF)-beta signals use the poised histone mark H3K9me3 to trigger differentiation of mammalian embryonic stem cells. Nodal receptors induce the formation of companion Smad4-Smad2/3 and TRIM33-Smad2/3 complexes. TRIM33-Smad2/3 binds the histone marks H3K9me3 and K18ac on the promoters of mesendoderm regulators Gsc and Mixl1. Binding is through the PHD-Bromo cassette of TRIM33. In the crystal structure of this cassette bound to histone H3 peptides, PHD recognizes K9me3 and Bromo, an adjacent K18ac. Binding of TRIM33-Smad2/3 to H3K9me3 displaces the chromatin compacting factor HP1g and makes nodal response elements accessible to Smad4-Smad2/3 for Pol II recruitment. In turn, Smad4 increases K18 acetylation to augment TRIM33-Smad2/3 binding. Thus, nodal cues use the H3K9me3 mark as a platform to switch master regulators of stem cell differentiation from the poised to the active state.

Dr. Xi obtained her PhD from New York University Medical Center, U.S.A., after which she went toMemorial Sloan-Kettering Cancer Center in New York for a postdoctoral fellowship with Joan Massagué, PhD, on molecular mechanisms of transforming growth factor (TGF)-β signaling in self-renewal and differentiation of embryonic stem cells. In April 2013, Dr. Xi joined the School of Life Sciences, Tsinghua University as a principal investigator, where she set up a laboratory to investigate how TGF-β signaling regulates stem cell differentiation epigenetically through Smad2/3-TRIM33 complexes. Dr. Xi has published papers in several prestigious journals, including Cell, the Journal of Biological Chemistry, theJournal of Virology, Genes & Development, Structure,and FEBS Letters.

Regulation of Mechanical Signals during Tissue Morphogenesis

Yan Yan, PhD (*Hong Kong University of Science and Technology*)
Assistant Professor
Division of Life Science

The Hippo signaling pathway is an evolutionarily conserved pathway regulating a wide range of developmental and cellular processes, including growth, patterning, and morphogenesis. Importantly, the Hippo signaling pathway is known to respond to regulatory signals from the actin cytoskeleton, consistent with the hypothesis that the Hippo signaling pathway might function to sense and interpret mechanical signals like tissue shape, geometry, and tension to coordinate cell behaviors in a multicellular organism. However, the mechanism of how the actin cytoskeleton regulates the Hippo pathway remains largely elusive.

We identified beta-spectrin as a protein required for Hippo signaling activity in a genetic screen for oocyte polarity defects during *Drosophila* oogenesis. Spectrins are known for linking the actin cytoskeleton to the plasma membrane. In this talk, I will discuss the function of beta-spectrin in regulating cellular tension and Hippo signaling activity. We demonstrated that mutations in *beta-spectrin* cause precocious myosin contraction and oscillation. Moreover, in the *beta-spectrin* mutant cells, the actin filaments lose the planar polarized orientation and frequently form abnormal stress-fiber-like structures on the basal side of the epithelium. Increased cellular tension associated with formation of stress fibers is a critical link between *beta-spectrin* mutations and Hippo signaling defects.

Dr. Yan received her BSc degree from Peking University in 2004. She graduated from Princeton University with a PhD in molecular biology in 2010. As a graduate student in the laboratory of TrudiSchupbach, PhD, she identified and characterized several previously unknown components in the Notch and Hippo signaling pathways. During her postdoctoral training period with Chris Doe, PhD, a Howard Hughes Medical Institute Investigator working at the University of Oregon, she focused on studying the cellular basis of neural stem cell delamination. In 2012 she took a tenure-track assistant professor position at HKUST.

Dr. Yan's laboratory is interested in how cells sense and respond to mechanical signals such as tension and stiffness to regulate tissue development and organogenesis. Currently her lab is combining the powers of Drosophila genetics, quantitative imaging, and computational modeling to explore two main questions: (1) mechanical regulation of the Hippo signaling pathway, and (2) the molecular and cellular basis of cell delamination.

Towards an Effective Stem Cell-Based Therapy: Application of Dedifferentiation-Reprogrammed MSCs

Xiaohua Jiang, PhD *(The Chinese University of Hong Kong)*
Assistant Professor
School of Biomedical Sciences

Dedifferentiation is a cellular process often seen in more basal life forms like worms and amphibians in which a partially or terminally differentiated cell reverts to a more primitive developmental stage, usually as part of a regenerative process. In mammals, the differentiation process was thought to be irreversible. However, recent studies have demonstrated that dedifferentiation may take place during mammalian wound repair *in vivo* or through reprogramming *in vitro*. Our studies show that after *in vitro* induction of neuronal differentiation and dedifferentiation, mesenchymal stem cells (MSCs), which have already committed to neuronal lineage, revert to a primitive cell population (De-neuMSCs) exhibiting a reprogrammed phenotype distinct from their original counterparts. Of therapeutic interest, the De-neuMSCs exhibit enhanced cell survival and higher efficacy in neuronal differentiation compared to unmanipulated MSCs both *in vitro* and *in vivo*. Recently, we have demonstrated that De-neuMSCs express significantly higher levels of chemokines and cytokines, and display enhanced tropism to cancer, indicating their potential application in gene therapy for cancer treatment. Apart from neuronal differentiation, we have revealed that dedifferentiation can happen after osteogenic and chondrogenic differentiation as well. Mechanistically, both histone modification and miRNA –mediated epigenetic mechanisms contribute to the reprogramming of MSCs. Taken together, our findings have the potential to provide a novel and clinically practical method to overcome the major hurdles faced by current MSC-based therapy.

Dr. Jiang graduated from Shanghai Second Medical University (now School of Medicine, Shanghai JiaoTong University) in 1994 and completed her internship and residency at Ruijin Hospital, Shanghai, in 1998. She obtained her PhD in cell biology from the University of Hong Kong in 2003. Dr. Jiang undertook postdoctoral training in the laboratory of Enrique R. Rozengurt, DVM, PhD, Department of Medicine, University of California, Los Angeles, from 2003 to 2006. Her work focused on the role of protein kinase cascades in cancer development. After that, she joined the University of Southern California as a CIRM (California Institute for Regenerative Medicine) fellow, and her research focused on understanding the origin and genetics of Ewing sarcoma by using human embryonic stem cells as an innovative model.

Dr. Jiang was recruited by the CUHK School of Biomedical Sciences as an assistant professor in 2013. There, her research focuses on two interlocking areas of investigation: the basic biology of stem cell programming and reprogramming and the application of the resulting technologies to studies of human development and the diseases that affect it, such as cancer.

Progenitor Cells in the Making of a Synovial Joint

Danny Chan, PhD (*The University of Hong Kong*)
Assistant Dean (Research Postgraduate Studies)

Loss or damage to articular cartilage is the hallmark of arthritic diseases. Synovial joints are encased in a capsule, stabilized by ligaments and tendons on the outside, and lined by a synovial membrane inside. In the synovial joints, articular cartilage provides a smooth, wear-resistant structure that reduces friction and absorbs impact forces. A clear understanding of how a synovial joint develops and the progenitor cells that contribute to its formation and maintenance is essential for the development of therapeutic strategies for degenerative joint diseases. We identified a stem cell marker, Lgr5, expressed specifically in interzone cells at the earliest stage of joint formation. We showed that Lgr5-expressing (Lgr5+) interzone cells are progenitors that contribute to the formation of the supporting tissues such as the ligaments and synovial membrane and, more importantly, to specific regions of the articular cartilage surfaces. We further identified cells that co-express Lgr5+ and an extracellular matrix gene, *Col22a1*, and these cells progressively differentiate to mainly Col22a1+ cells lining the surface of the articular cartilage. We propose that this expression pattern represents the progression of cell fate in joint development, with Lgr5+/Col22a1+ double-positive cells committed to becoming articular chondrocytes. Available mice with molecular tags for *Lgr5* and *Col22a1* expression will allow the isolation of these specific cell pools in a developing joint to gain an understanding of the molecular signature and the signals that regulate this lineage progression and the maintenance of the interzone cells. Understanding the contribution of this pool of committed articular chondrocyte progenitors is highly relevant to the development of cell therapy for the treatment of cartilage diseases like osteoarthritis and in the repair of cartilage trauma.

After graduating from the University of Melbourne, with a Bachelor of Science (with honors), MS, and PhD, Dr.Chan continued research at his alma mater on heritable skeletal disorders, with a focus on extracellular matrix proteins. His research contributed significantly to the understanding of the molecular consequences in many forms of the human osteochondrodysplasias. In recognition of his work, Dr. Chan was presented with an award for "Excellence in Medical Research" by the State Premier of Victoria, Australia. He joined the University of Hong Kong in 1998, maintaining his research in skeletal biology using mouse as a model to address disease mechanisms *in vivo*, as well as human genetic studies to define genetic risk factors for common degenerative skeletal conditions like intervertebral disc degeneration. Key findings in his laboratory included the consequence of cellular stress in chondrocytes, allowing matured chondrocytes to be "rejuvenated," and how the capacity and range of a signaling molecule, Indian hedgehog, are regulated in development. His work on the genetics of intervertebral disc ratio has led to the identification of new genetic risk factors, Asporin and CHST3, providing new insights into disease mechanisms and the potential for new therapeutic targets. In translational research, he is interested in defining the progenitor cells in joint and disc development and the molecular controls that regulate the differentiation process of these progenitors.

Extracellular Component Hyaluronic Acid and Its Receptor Hmmr Are Required for Zebrafish Heart Regeneration

Michael Tsang, PhD *(University of Pittsburgh)*
Associate Professor of Developmental Biology
School of Medicine

Unlike mammals, after cardiac injury zebrafish can effectively regenerate the heart. This process is initiated through the activation of epicardial cells to undergo epithelial to mesenchymal transition (EMT) followed by their migration into the wound to promote angiogenesis. Together with the proliferation of preexisting cardiomyocytes, lost and damaged cardiac tissue is regenerated. Using a proteomic approach, we found Hyaluronan-mediated motility receptor (Hmmr), a hyaluronic acid (HA) receptor, to be increased following injury. In addition, the enzymes that produce HA, hyaluronic acid synthases (has), were also up-regulated after injury, suggesting that this pathway may play a critical role in heart regeneration. Indeed, suppression of HA production, as well as depletion of Hmmr, blocked cardiac regeneration. Mechanistically, HA and Hmmr are required for epicardial cell migration in the regenerating ventricle through the phosphorylation of focal adhesion kinase (FAK). Furthermore, inhibiting Src kinases, a downstream effector of pFAKs, also prevented epicardial cell migration, implicating a HA/Hmmr/FAK/Src pathway in epicardial cell EMT. In rat, HA and Hmmr were detected within the scar tissue in heart following myocardial infarction, suggesting an evolutionary conserved response to cardiac injury. Our studies suggest that HA is an important signaling molecule required to promote epicardial cell EMT. In its absence, this process is suppressed, resulting in the failure of cardiac regeneration in zebrafish.

Dr. Tsang earned a Bsc(Hons) degree in 1992 from the University College Dublin (UCD), Ireland, in pharmacology. From there, he entered a joint PhD program in molecular biology between UCD and the W. Alton Jones Cell Science Center in Lake Placid, New York, USA. There, he cloned the mouse Disheveled 3 and explored its role in Wnt signaling. In 1997, Dr. Tsang joined Dr. Igor Dawid's lab at the U.S. National Institutes of Health, where the research focus was to study zebrafish embryonic development through an RNA expression screen. The group identified a number of novel genes in the fibroblast growth factor (FGF) signaling pathway. Dr. Tsang completed his postdoctoral work in 2004 and started his research program at the University of Pittsburgh to continue studying the role of FGFs in heart development.

Dr. Tsang's lab is primarily interested in the signaling pathways involved in embryonic development. The group uses the zebrafish as a model system to dissect the role of fibroblast growth factors (FGFs) in heart development and in heart regeneration. The group has developed transgenic zebrafish that report on FGF activity in live embryos and has used these animals in a drug discovery screen for molecules that modulate FGF signaling. Using this approach, they have identified a number of agents that hyperactivate the FGF pathway and are now applying these to regenerative therapeutics. More recently, the Tsang lab has taken a proteomic approach to identify key players in zebrafish heart regeneration in order to understand this process at a molecular level and to identify new markers of the regenerative response following injury.

The Role of STAT3 in Muscle Stem Cells

Zhenguo Wu, PhD ***(Hong Kong University of Science and Technology)***

Our laboratory previously demonstrated that the JAK/STAT pathway plays important roles in regulating myogenic differentiation in cell culture models. It remains unclear whether the pathway regulates muscle satellite cells *in vivo*. To address this issue, we generated muscle satellite cell-specific conditional *STAT3* as well as *JAK1* knockout mouse models. Both mutant mice were viable, and skeletal muscle development appeared normal. However, upon repeated injuries, satellite cell-dependent muscle regeneration was defective in the mutant mice. Moreover, when we conditionally deleted *STAT3* in the satellite cells of dystrophin-null mice, a mouse model for human Duchenne muscular dystrophy, the compound mutant mice exhibited more pronounced muscle defects, with smaller muscle size, decreased number of muscle satellite cells, increased fibrosis, and enhanced infiltration of CD68+ macrophages. Our mechanistic studies showed that STAT3 regulates the re-entry into the quiescent state of muscle satellite cells after injury. (*This project was funded by the Hong Kong Research Grant Council.*)

Dr. Wu received his bachelor's degree in 1986 from Nanjing University in China and his PhD in biochemistry in 1995 from the University of Western Ontario, Canada, under the supervision of George Chaconas, PhD. He did his postdoctoral training at the University of California, San Diego from 1996 to 1999, where he studied MAP kinase-mediated cell signaling with Michael Karin, PhD. He set up his own laboratory at HKUST in 1999.

Dr. Wu's laboratory has a longstanding interest in elucidating the roles of different intracellular signaling pathways in regulating muscle stem cells and muscle differentiation using both primary and immortalized mouse myoblasts as well as different mouse models. His group has shown that both the p38 MAP kinase and the PI3K/Akt pathways are indispensable for myogenic differentiation by regulating the transcription of the myogenin gene that encodes a key myogenic regulatory factor required for myogenic differentiation. In recent years, his laboratory has focused on the roles of the JAK/STAT pathway in muscle stem cells, muscle differentiation, and muscle regeneration. Both muscle stem cell-specific JAK1 and STAT3 conditional knockout mice have been generated in Dr. Wu's laboratory to facilitate the *in vivo* studies.

Dr. Wu is currently a co-director in the Center for Stem Cell Research and a member of the Center for Systems Biology and Human Health at HKUST.

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