2018 Croucher Symposium

Frontier in Immunometabolism

The University of Hong Kong

18th January, 2018

Lecture Theatre 4, Cheung Kung Hai Conference Centre,
G/F, William M.W. Mong Block,
Li Ka Shing Faculty of Medicine,
The University of Hong Kong

Jointly organized by:

Sponsored by:

Croucher Foundation
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Contents

Croucher Foundation

The Croucher Foundation is an independent private foundation established by the late Noel Croucher (1891-1980) in 1979 to promote the standard of the natural sciences, technology and medicine in Hong Kong. The work of the Foundation is organised into five broad areas:

- scholarships and fellowships for promising young Hong Kong scientists and medical doctors to pursue research overseas;
- research fellowships to enable scientists in Hong Kong to pursue their intellectual inclinations, and to engage in bold new work;
- conferences, workshops and collaborative research to facilitate the exchange of ideas between Hong Kong scientists and their counterparts overseas;
- demonstration lectures to promote a wider understanding of science among Hong Kong school students and undergraduate students; and
- support for any undergraduate student in Hong Kong experiencing sudden financial difficulty.

Noel Croucher entrusted the governance of his Foundation to the discretion of a Board of Trustees. Lord Todd, the Nobel Laureate and Master of Christ's College, Cambridge was the founding President of the Foundation.

To facilitate Hong Kong's relations in science with mainland China and internationally, the Foundation has partnership agreements with several leading academic institutions. The Foundation also provides exploratory occasional grants for exchanges with countries ready to take an interest in working with Hong Kong, including Cambridge Trust, Chinese Academy of Sciences, German Academic Exchange Service (DAAD), INRIA, Pasteur Institute and University of Oxford.

Welcome Message from the Director

2018 Croucher Symposium
Frontier in Immunometabolism

On behalf of the State Key Laboratory of Pharmaceutical Biotechnology, the University of Hong Kong, we would like to extend our warmest welcome to all the speakers and participants of 2018 Croucher Symposium to Hong Kong.

This symposium is the following event of the Croucher Foundation Advanced Study Institute held in April 2016. Here, we continue our fruitful scientific discussion on the forefront of immunology and metabolism research including the topics of cardiometabolic disorders, adipose tissue inflammation, adipokine and hepatokine biology, gut microbiota and immunological and metabolic reprogramming.

We would like to express our gratitude for the generous sponsorship of the Croucher Foundation. We hope that our participants will enjoy this golden opportunity to learn the latest discoveries in immunometabolism.

Aimin Xu

Director, the State Key Laboratory of Pharmaceutical Biotechnology
Professor, Li Ka Shing Faculty of Medicine
The University of Hong Kong

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生物醫藥技術國家重點實驗室
THE STATE KEY LABORATORY OF PHARMACEUTICAL BIOTECHNOLOGY

Organizing Committee

Chairman	Aimin Xu Director, the State Key Laboratory of Pharmaceutical Biotechnology Professor, Departments of Medicine, and Pharmacology & Pharmacy LKS Faculty of Medicine, The University of Hong Kong
Members	Connie Wai Hong Woo Assistant Professor, Department of Pharmacology and Pharmacy, LKS Faculty of Medicine, The University of Hong Kong
	Miss Lily Li Executive Assistant, the State Key Laboratory of Pharmaceutical Biotechnology LKS Faculty of Medicine, The University of Hong Kong

Program at a Glance

Time	*Lecture Title*	*Speaker/Organizer*
8:45 – 9:00	Registration/Opening Ceremony	
9:00 – 9:40	**Special Lecture:** microRNAs in cardiovascular function and disease *(Chairperson: Dr. Liang)*	Prof. Da-Zhi Wang
	Section 1: Immunometabolism in cardiometabolic diseases *(Chairperson: Prof. Jae Bum Kim)*	
9:40 – 10:10	Metabolic Therapies and their Role in Heart Disease	Prof. Jason Dyck
10:10 – 10:40	Adiponectin action in metabolic syndrome	Prof. Gary Sweeney
	Coffee Break	
	Section 2: Adipose tissue inflammation, Adipokines and Hepatokines *(Chairperson: Prof. Weiping Han)*	
11:00 – 11:30	Role of iNKT Cells in Adipose Tissue	Prof. Jae Bum Kim
11:30 – 12:00	Fat distribution and diabetes risk	Prof. Xiaoying Li
12:00 – 12:30	Adipokines and immune environment in the regulation of browning and thermogenesis of adipose tissue	Dr. Zhe Huang
	Lunch	
13:45– 14:00	**Dialogue with Young investigators** Tips for publishing in the American Journal of Physiology: Endocrinology & Metabolism section in 2018	Prof. Andre Marette
	Section 3: Gut microbiota and Immunometabolic diseases *(Chairperson: Dr. Connie Woo)*	
14:00 – 14:30	Reshaping the gut microbiota to alleviate immunometabolic diseases	Prof. Andre Marette
14:30 – 15:00	Impact of diet-gut microbiota interaction on host metabolism	Dr. Petia Kovatcheva-Datchary
	Coffee break	
	Section 4: Immunological and Metabolic Reprogramming in diseases *(Chairperson: Prof. Sookja Chung)*	
15:20 – 15:50	Generation of Human Progenitor T Cells from Stem Cells	Prof. Juan Carlos Zuniga-Pflucker:
15:50 – 16:20	Metabolic reprogramming promotes liver cancer cell proliferation	Prof. Weiping Han
16:20 – 16:50	Prof Congyi Wang: HMGB1, a revived woe from an ancient tale in the modern society during the course of type 1 diabetes	Prof. Congyi Wang
16:50 – 17:20	Browning of perivascular adipose tissues protects against obesity-related vascular diseases independent of thermogenesis	Dr. Xiaoyan Hui

Speakers and Abstracts (Chronological order)

Da-Zhi Wang

Professor, Department of Cardiology,
Boston Children's Hospital, Harvard Medical School

Dr. Da-Zhi Wang received his undergraduate education from Sichuan University and his Master of Science (MS) from Peking University in China. He then received his Ph.D. in 1998 from the Department of Biological Sciences of the University of Iowa in the laboratory of Prof. Jim Lin, where he studied molecular mechanisms of vertebrate development. Dr. Wang conducted his postdoctoral training in the laboratory of Prof. Eric Olson at the University of Texas Southwestern Medical Center at Dallas from 1998 to 2000 and was promoted to an Instructor in 2000. As a postdoctoral fellow and instructor, Dr. Wang identified a novel transcription factor, myocardin, and demonstrated that it is essential for cardiovascular development. Dr. Da-Zhi Wang started his first faculty position in 2002 at The University of North Carolina at Chapel Hill (UNC-CH) as an Assistant Professor of the Department of Cell and Developmental Biology and a member of the Carolina Cardiovascular Biology Center (CCBC). He was promoted to Associate Professor with tenure in 2008 at UNC-CH. Dr. Wang was recruited to the Department of Cardiology of Boston Children's Hospital and Harvard Medical School in July 2009 where he is currently Professor of Pediatrics. Dr. Wang is awarded the AHA Established Investigator award in 2008 and was elected Fellow of American Heart Association (FAHA) in 2013. Dr. Wang has served on the editorial board for many journals and has been an active reviewer for multiple funding agents, including the NIH and AHA. Dr. Wang has been invited to give more than 100 lectures and seminars internationally. Dr. Wang is a recognized leader in the study of heart development, cardiac function and cardiovascular disease. His work has contributed to the understanding of the molecular mechanisms by which non-coding RNAs regulate gene expression and function in the cardiovascular system and skeletal muscle.

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microRNAs in cardiovascular function and disease

It is now recognized that more than 98% of our genome is actively transcribed to produce thousands of non-coding transcripts in many cell types and tissues. However, the molecular nature and functional significance of non-coding transcripts remains largely unknown. The Wang lab is mostly interested in non-coding RNAs, including microRNAs and long non-coding RNAs (lncRNAs) and RNA binding proteins (RBPs) in cardiovascular development, function and disease.

Though genome-wide transcriptome profiling in animal models for human cardiomyopathy, the lab identified candidate miRNAs and lncRNAs that are dysregulated in diseased hearts. Using combination of gain- and loss- of function approaches and molecular dissection, the Wang lab shows that loss-of-miRNAs in the cardiovascular system leads to severe cardiac defects and lethality in mice. The lab has generated and studied multiple lines of knockout and transgenic mice for miRNAs (miR-208a, miR-22, miR-17-92 and miR-155). These investigations demonstrate that miRNAs play a key role in controlling cardio homeostasis in response to pathological and mechanical stress. The lab is currently testing the therapeutic potential of miRNAs in protecting heart from myocardial infarction. The ultimate goal of the Wang lab is to delineate the molecular pathways for the development and function of cardiovascular system and to use this information to design pharmacologic and genetic therapies for human cardiovascular diseases, cardiac hypertrophy and heart failure. In his presentation, Dr. Wang will discuss one of their recent studies focusing on the Trbp-miR-208a-Sox6 pathway in cardiac function and cardiomyopathy.

(Research in the Wang laboratory is supported by National Institutes of Health (NIH), American Heart Association (AHA) and Muscular Dystrophy Association (MDA))

Jason Dyck

Professor, Department of Pediatrics,
Canada Research Chair in Molecular Medicine,
Director, Cardiovascular Research Centre,
University of Alberta, Canada

Dr. Jason Dyck is a Professor in the Department of Pediatrics, a CRC in Molecular Medicine, and the Director of the Cardiovascular Research Centre at the University of Alberta. He is also the co-director of the Alberta HEART, which is a province-wide program aimed at understanding and treating heart failure. Dr. Dyck has a broad area of research that links CVD progression to changes in energy metabolism. He has published over 195 peer-review papers in his career and is currently funded by the Canadian Institutes of Health Research, Diabetes Canada, the Heart and Stroke Foundation and Alberta Innovates Health Solutions.

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Metabolic Therapies and their Role in Heart Disease

In the heart, the production of intracellular energy in the mitochondria is essential for sufficient and sustained contractile function. This energy is derived primarily from mitochondrial oxidation of carbohydrates, fatty acids and ketones. Previous work has shown that alterations in energy metabolism are significant contributors to cardiovascular disease (CVD) and that optimizing cardiac energy metabolism has benefit in some of the most clinically relevant areas in cardiology such as hypertension, ischemia/reperfusion injury, diabetic cardiomyopathy, and chemotherapy-induced cardiotoxicity. While therapies directed at these CVDs have improved cardiac mortality, they have ultimately delayed the onset and increased the overall prevalence of another condition called heart failure. Importantly, a long-standing concept is that the failing heart has defects in metabolic processes that normally allow for proper ATP production and that impaired energetics contributes to a decline in contractile function. Thus, improving cardiac energy metabolism in heart failure may have a significant impact on the treatment of patients with this condition. This talk will focus on emerging new metabolic therapies for heart failure and discuss the mechanisms involved in their beneficial effects.

Gary Sweeney

Professor, Department of Biology,
York University, Toronto, Canada

Dr. Sweeney obtained his BSc and PhD in pharmacology at University of Glasgow, UK. He then moved to the Hospital for Sick Children in Toronto as postdoctoral fellow. Afterwards Dr. Sweeney was appointed as faculty member in the Department of Biology at York University where he is now Professor. Dr. Sweeney has also served as Chief Scientific Officer and Diabetes Group Leader at Institut Pasteur Korea, a world-leading translational research institute. His research has been well funded by Canadian Institutes of Health Research, Canadian Diabetes Association and Heart & Stroke Foundation of Canada and AstraZeneca. Studies have resulted in publications in leading journals including Diabetes, Nature Reviews Cardiology, Proc Natl Acad Sci USA, Journal of Clinical Endocrinology & Metabolism, Journal of Biological Chemistry, Endocrinology and Cell Metabolism. These studies focus mainly on diabetes and cardiovascular disease, in particular the mechanisms linking obesity with diabetes and heart failure. Dr Sweeney has served as Editorial Board Member of top journals such as Diabetes and Am J Physiol. He is recipient of academic awards from Canadian Diabetes Association, the Province of Ontario, Canadian Institutes of Health Research and Heart & Stroke Foundation of Ontario.

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Adiponectin action in metabolic syndrome

This presentation will provide a chronological overview of the contributions from our lab toward understanding the effects and mechanisms of action of adiponectin. Two main areas of focus will be skeletal muscle metabolism as well as remodeling of the myocardium in heart failure. Data spanning metabolism, hypertrophy, fibrosis and cell death will be discussed to bring us up to date and then the remainded of the presentation will focus on current studies. First of all, the ability of adiponectin to stimulate autophagy and it's functional significance will be shown. Biodistribution of adiponectin (viz. movement from circulation to interstitial space) is an important and neglected aspect of adiponectin physiology and in this presentation the change in adiponectin biodistribution in diabetes will be shown. The significance of adiponectin resistance has to date been underappreciated and this presentation will show that iron is likely an important inducer of this phenomenon. Finally, with numerous beneficial effects spanning many disease states adiponectin is a well established therapeutic target and recent advances in this area will be discussed.

Jae-bum Kim

Professor, Department of Biological Sciences,
Director, Center for Adipose Tissue Remodeling,
Institute of Molecular Biology and Genetics,
Seoul National University, Seoul, Korea

Dr. Jae Bum Kim is Professor of Biological Sciences at Seoul National University and Director of Center for Adipose Tissue Remodeling, Creative Research Initiatives in Korea. He obtained his Bachelor and Master of Science at Seoul National University. Then, he earned his Ph. D. at Harvard University under the mentorship of Dr. Bruce Spiegelman, where he cloned and elucidated ADD1/SREBP1c as a key lipogenic transcription factor. After his postdoctoral fellowship training with Dr. Phillip Sharp at MIT, he joined the faculty at School of Biological Sciences, Seoul National University in 2000. His research group has investigated on gene expression regulation and signal transduction pathways of lipid and glucose metabolism, which are crucial to resolve the prevailing health issues such as obesity and diabetes. Recently, his research has focused on the molecular mechanisms of lipid and glucose homeostasis, adipose tissue inflammation, and insulin resistance, which would shed important insights on obesity and its related metabolic diseases.

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Role of iNKT Cells in Adipose Tissue

Systemic low-grade chronic inflammation has been intensively investigated in obese subjects. Recently, various immune cell types, such as macrophages, granulocytes, helper T cells, cytotoxic T cells, and B cells, have been implicated in the pathogenesis of adipose tissue inflammation. However, the roles of invariant natural killer T cells (iNKT cells) and the regulation of iNKT cell activity in adipose tissue are not thoroughly understood. Recently, we have demonstrated that iNKT cells are decreased in number in the adipose tissue of obese subjects. Moreover, iNKT cell-deficient Jα18 knockout mice become more obese and exhibit increased adipose tissue inflammation at the early stage of obesity. Interestingly, CD1d, a molecule involved in lipid antigen presentation to iNKT cells, is highly expressed in adipocytes and CD1d-expressing adipocytes stimulated iNKT cell activity through physical interaction. iNKT cell population and CD1d expression are reduced in the adipose tissue of obese mice and humans compared to those of lean subjects. To investigate the in vivo role of adipocyte CD1d in the regulation of adipose iNKT cell activity and adipose tissue inflammation, we generated adipocyte specific CD1d knockout (adipo-CD1d KO) mice. When adipo-CD1d KO mice were fed with high fat diet, they showed elevated insulin resistance and adipose tissue inflammation. These data suggest that adipocytes regulate iNKT cell activity via CD1d and that the interaction between adipocytes and iNKT cells would modulate adipose tissue inflammation in obesity. In this presentation, I will also present and discuss novel roles of iNKT cells in fat tissue.

Xiaoying Li

Chief and Professor,
Department of Endocrinology and Metabolism,
Zhongshan Hospital, Fudan University, China

Dr. Li obtained MD from Hengyang Medical College (currently Nanhua University) in 1983 and PhD from Shanghai Second Medical University (currently Shanghai Jiao Tong University School of Medicine) in 1996. Dr. Li was trained for Endocrinology and was a postdoctoral fellow in Baylor College of Medicine, USA in 1998-2000 and in McGill University, Canada in 2000-2003. He is an associate editor of Journal of Diabetes and an editor for Chinese Journal of Endocrinology and Metabolism and Chinese Journal of Diabetes. His research interest is focused on obesity, type 2 diabetes and fatty liver disease. He has published 90 scientific papers in peer reviewed international journals, including *Cell Metabolism, JAMA Internal Medicine, JCI, Diabetes, Gut, Gastroenterology, J Hepatology, J Clin Endocrinol Metab* etc.

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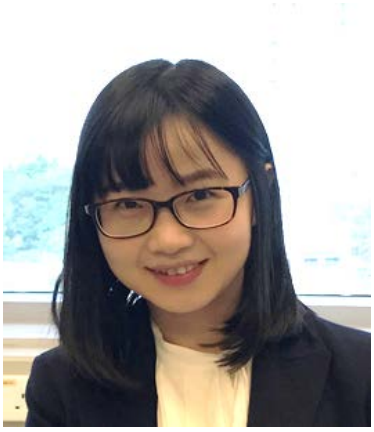
Fat distribution and diabetes risk

Obesity is a pivotal risk factor for type 2 diabetes. In recent years the prevalence of diabetes is promptly increased as the obesity increases. Fat distribution is better associated with diabetes risk rather than body weight. Our epidemiological study showed that subjects with overall obesity had 2.11 (95% CI: 1.05-2.40) folds of risk for diabetes, whereas, subjects with central obesity had 2.37 folds of risk for diabetes as compared with overall obese ones. Moreover, subjects with fatty liver had 3.89 folds of risk for diabetes compared to non-fatty liver subjects.

Fetuin A is produced by hepatocytes, secreted into the blood and promotes insulin resistance and hyperglycemia. Although it has been well established that circulating Fetuin A is significantly elevated in obese individuals, the mechanism for its elevation remains poorly understood. Here we show that Fetuin A protein, but not messenger RNA, levels are up-regulated in the livers of obese mice and humans, pointing to a post-transcriptional regulatory mechanism. We further reveal that Fetuin A protein is recognized and targeted by the SCFFBXW7 ubiquitin ligase. FBXW7 interacts with Fetuin A to induce its ubiquitination and subsequent degradation. Moreover, hepatic FBXW7 expression is markedly reduced in obese livers, and liver-specific knockout of FBXW7 in lean mice leads to diabetic phenotypes through degrading Fetuin A proteins.We also find that overexpression of FBXW7 in the liver not only prevents the development of diet-induced insulin resistance but also reverses the disease signature of obese mice. In addition, we discover a functional FBXW7 coding variant(p.Ala204Thr) in human, which is associated with elevated blood glucose and type 2 diabetes risk. Taken together, our findings implicate that FBXW7 targets Fetuin A for degradation and protects from insulin resistance, and could be a potential target for the treatment of type 2 diabetes.

Zhe Huang

Postdoctoral fellow, Department of Medicine,
The University of Hong Kong, Hong Kong SAR, China



Dr. Zhe Huang is currently a postdoctoral fellow in the Department of Medicine, The University of Hong Kong. She received her M.Sci. (with Hons) from The University of Glasgow, UK in 2009. Subsequently, she joined Prof. Aimin Xu's group at the University of Hong Kong and recently obtained her Ph.D. degree in 2017. Her research focuses on the mechanisms underlying obesity and its related metabolic disorders with a particular interest in browning of white adipose tissues and its immunoregulation. She identifies a novel FGF21-CCL11 axis in adipocytes as a thermogenic circuit that drives the browning reprogramming in white adipose tissues by coupling neuronal and immunological systems with adipose physiology.

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While the main function of white adipocytes is to store energy in the form of triglycerides, brown and beige adipocytes dissipate energy as heat due to the presence of uncoupling protein-1 (UCP1). Although beige adipocytes functionally and morphologically resemble brown adipocytes, they are much less sympathetically innervated, activation of beige adipocytes is therefore heavily dependent on the local microenvironment. Recent studies have identified the involvement of several types of immune cells and type 2 cytokines in the biogenesis of beige adipocytes in response to cold environment, however, the physiological stimulators that trigger the recruitment of immune cells and consequent type 2 immune responses are poorly understood.

We have identified a number of adipocyte-derived factors in the regulation of adaptive thermogenesis. Among them, adiponectin and fibroblast growth factor 21 (FGF21) are found to promote the biogenesis and activation of beige adipocytes by mediating the crosstalk between adipocytes and immune cells in subcutaneous white adipose tissue (scWAT). Chronic cold exposure led to a markedly elevated production of both adiponectin and FGF21 in adipocytes of scWAT. Chronic cold exposure-induced beiging and thermogenic program were markedly impaired in scWAT of adiponectin or FGF21 knockout mice, whereas these impairments were reversed by replenishment with either recombinant adiponectin or FGF21. Mechanistically, adiponectin was bound to M2 macrophages via its binding partner T-cadherin and promoted the cell proliferation by activation of Akt in a paracrine manner, consequently leading to beige cell activation. On the other hand, FGF21 acts on adipocytes in an autocrine manner to promote the production and secretion of CCL11, which drives recruitment of eosinophils into scWAT, leading to increases in accumulation of M2 macrophages, and biogenesis of beige adipocytes.

These findings suggest that adipokines and immune environment cooperatively regulate beiging and thermogenesis of white adipose tissue.

André Marette

Professor, Department of Medicine,
Scientific Director, the Institute of Nutrition and Functional Foods, Université Laval
Chair, CIHR/Pfizer Research Chair in pathogenesis of insulin resistance and cardiovascular diseases

Andre Marette graduated from Laval University in 1990 with a PhD in Physiology and Endocrinology. After post-doctoral training under the supervision of Dr. Amira Klip and Dr. Mladen Vranic at the Hospital for Sick Children, he joined Université Laval where he currently holds a full professor position in the department of Medicine.
Dr. Marette has received constant scholarship and salary awards from MRC/CIHR and Fond de la Recherche en Santé du Québec. He has also received several national and international research grants awards to pursue his research, and has received long-term research and equipment grants from CIHR, CFI and JDRF. In addition, he has received uninterrupted research funding from the Canadian Diabetes Association and MRC/CIHR since 1993. Dr. Marette has also received several industry grants to pursue his diabetes research. He has published over 170 papers and reviews in high-impact journals and received several awards including the Davignon & Lupien Founders Award of the Quebec Society of Lipidology, Nutrition and Metabolism in 2001, Young Scientist Award of the Canadian Diabetes Association in 2005, Simon Pierre Noël Lectureship and Award in Canadian Lipoprotein Conference 2007. Dr. Marette is the holder of Research Chair in Pathogenesis of Insulin Resistance and Cardiovascular Diseases, an international project launched by Canadian Institute of Health Research (CIHR)/Pfizer Canada Inc. aiming at understanding and explaining insulin resistance and the risk of cardiovascular complications in diabetic obese patients. He is also the Editor-in-Chief of American Journal of Physiology–Endocrinology and Metabolism since 2015.

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Reshaping the gut microbiota to alleviate immunometabolic diseases

Type 2 diabetes (T2D) and cardiovascular diseases (CVD) are increasing at an epidemic rate and calls for novel preventive and therapeutic measures. These cardiometabolic diseases are linked to visceral obesity and ectopic fat accumulation in non-adipose tissues such as the liver leading to nonalcohol fatty liver disease (NAFLD). I will present growing evidence that the gut microbiome is a key determinant of diet-induced obesity, T2D and NAFLD. I will show that new polyphenol-rich extracts from various dietary sources protect against obesity-linked inflammation and alleviate T2D and NAFLD in high fat-fed animal models. This is associated with a reshaping of of the gut microbiome and with a major increase in the abundance of specific bacterial species including the mucin-degrading bacterium Akkermansia muciniphila. Increase in the Akkermansia population may therefore contribute to the anti-inflammatory and beneficial effects of dietary polyphenols in obese mice. I will also show that an extract from the amazonian fruit Camu Camu has a remarkable anti-obesity effect that is related to changes in the gut microbiome and in the profile of bile acids, leading to activation of brown fat thermogenesis through a gut-liver axis.

Petia Kovatcheva-Datchary

Postdoctoral Research Fellow, University of Gothenburg, Sweden

Dr. Petia Kovatcheva-Datchary is an expert in gut microbiota. She combines clinical oriented research with gnotobiotic mouse models to study diet microbiota interactions in metabolic disease. She holds PhD from the Wageningen University in the Netherlands, where she studied the microbial metabolism in the human gut. She got a postdoctoral training at the Wallenberg Laboratory at the University of Gothenburg in Sweden. Her work has opened new lines of research related to personalized interventions to prevent metabolic disorders and her first main paper was published in Cell Metabolism in 2015. In October 2017 she moved to China and joined the group of Prof. Dr. Guowang Xu at the Dalian Institute of Chemical Physics, CAS. Her current research focus is to identify the role of infants' nutrition on the microbiome and host metabolism.

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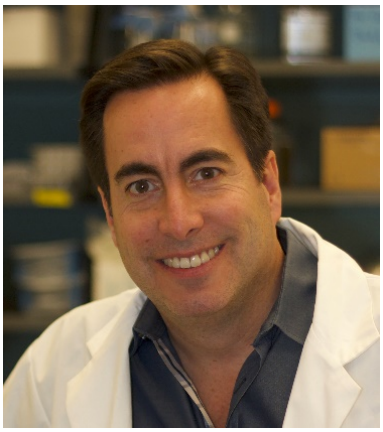
Impact of diet-gut microbiota interaction on host metabolism

The gut microbiota was referred as our "forgotten organ", but the field has developed over the past decade and it has become evident that the microbiota contributes to health and disease of the host. Microbes in the gut can modulate human metabolism through interactions with macronutrients. Diet is a primary determinant in the development of the microbiota colonization pattern from the first stage of life. Increasing evidence indicates that the composition of gut microbiota early in life contributes to host metabolic development and the microbiota has thus been proposed as a potential therapeutic target against metabolic diseases. However we still poorly understand the relationship between diet and gut microbiota structure and operations, and how functional attributes associated with gut microbes influence host metabolism.

We have recently showed that improvement in glucose metabolism following ingestion of barley kernel bread in healthy individuals was linked to a specific bacterial taxa and its fermentative activity in the gut. We used a mouse model to define a mechanism and proposed that Prevotella, a bacterium from the human gut, can improve glucose tolerance by promoting host hepatic glycogen storage. However, it is important to note that an individual's response to dietary interventions, in terms of host metabolism and gut microbiota, is highly variable and poorly predictable. Therefore, we either need novel dietary strategies that consider both an individual's gut microbiota composition and diet, or dietary strategies that shape gut microbiota from early life to prevent the development of metabolic disorders.

Juan Carlos Zúñiga-Pflücker

Chair & Professor, Department of Immunology,
Senior Scientist, Sunnybrook Research Institute (SRI)
University of Toronto, Canada



Juan Carlos Zúñiga-Pflücker graduated with a Ph.D. in 1991 from the George Washington University, Washington DC, USA. He did his graduate studies at the National Cancer Institute, USA, and then a postdoctoral fellowship at the National Institute of Allergy and Infectious Diseases, USA. He has been at the University of Toronto, Canada, since 1994, where he is presently a Professor and Chair of the Department of Immunology, and also since 2001 at the Sunnybrook Research Institute as a Senior Scientist. He is the director of the Flow Cytometry and Microscopy Centre at Sunnybrook. He currently holds a Canada Research Chair in Developmental Immunology. His laboratory developed the OP9-DL system and discovered how to generate T cells from stem cells in vitro. His research centers on hematopoiesis, pre-T cell receptor signaling, and lymphocyte lineage commitment, with a focus on developing model systems for the study of T lymphocyte development from stem cells, and the generation of T cells for immune-regeneration and immune-regulatory therapies.

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Generation of Human Progenitor T Cells from Stem Cells

The thymus provides the necessary environmental cues for the differentiation and generation of T-cells. The thymus is continuously colonized by a rare subset of bone-marrow derived progenitors, which in humans are characterized as CD34+CD45RA+CD7+ cells. Further characterization and directed expansion of this important progenitor subset would represent an important step in developing T-cell and thymus regenerative approaches. We have previously shown the generation of human progenitor T-cells (pro-T) with a thymus-colonizing phenotype from multiple sources of stem cells cocultured on OP9-DL4 stromal cells. To determine whether pro-T cells generated in vitro possess an intrinsic ability to home, engraft and reconstitute a thymus in vivo, sorted CD34+ CD7++ pro-T cells were injected into immunodeficient mouse strains, which can support human multi-lineage differentiation from CD34+ hematopoietic stem cells (HSCs). Our findings showed that T-lineage progenitors generated in vitro exhibit key properties of being able to home to, settle, and effectively reconstitute the thymus of immunodeficient mice. Additionally, in vitro-generated pro-T cells, when transferred together with purified HSCs, were able to dramatically enhance the thymus reconstituting ability of HSC-derived progenitors in vivo. Taken together, the generation of humanized mice reconstituted with in vitro-derived progenitor T-cells offers a new means of therapeutic evaluation and the potential to rapidly restore the T-cell compartment for immune-regenerative approaches.

Weiping Han

Deputy Director, Singapore Bioimaging Consortium
Agency for Science, Technology and Research (A*STAR),
Singapore

Weiping Han obtained his Ph.D. in Physiology from Cornell University in 1996. He did his postdoctoral work at the University of Pittsburgh and HHMI/UT Southwestern Medical Center in Dallas. In 2003, he was promoted to Research Assistant Professor in the Center for Basic Neuroscience at UT Southwestern Medical Center, where he studied molecular mechanisms of hormone secretion and signaling. In 2005, he moved to Singapore to set up a research program in the Laboratory of Metabolic Medicine (LMM) at Singapore Bioimaging Consortium (SBIC). Currently he is Deputy Director of SBIC with concurrent appointment as Head of LMM. He is also Research Director at Institute of Molecular and Cell Biology and Professor in the Program of Cardiovascular and Metabolic Disorders at Duke-NUS Graduate Medical School.

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Metabolic reprogramming promotes liver cancer cell proliferation

Although liver cancer is the second leading cause of cancer-related death worldwide, there is very limited treatment option available. Most of the liver cancer is hepatocellular carcinoma, or HCC. In recent years, accumulating evidence from a renewed interest of onco-metabolism supports metabolic reprogramming as a signature of many cancers including HCC. As such, the cancer phenotype is now viewed as a complex interplay of genetic mutations, epigenetic deregulation, and metabolic reprogram¬ming. It is hoped that understanding the functional integration of the signaling pathways relevant to liver cancer with the altered metabolic network will reveal novel approaches to cancer therapy. Considering that tumors display profound and highly adaptive changes in cellular metabolism, we used a comprehensive 'multi-omics' approach across multiple rodent models of HCC, and identified a novel target and metabolic pathway that may be directed in potential therapeutic development. Here I will provide the latest update on this study.

Cong-Yi Wang

Professor, Tongji Hospital, Tongji Medical College,
Huazhong University of Science & Technology
Director, the Center for Biomedical Research,
Tongji Biobank, Tongji Hospital, China

Dr. Cong-Yi Wang, is the Professor and Director, the Center for Biomedical Research, Vice Director, Department of Sponsored Program Administration, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. Before 2014, he served as a tenured Associate Professor at the Department of Pathology, and the Director of Georgia Esoteric & Molecular Laboratories, LLC, Georgia Regents University, USA. The major focus for his research is to dissect the role of genetic and epigenetic factors in the pathogenesis of diabetes and diabetic complications. Particularly, he employs animal models and human subjects to address how environmental insults interact with genetic factors to modulate disease susceptibility, and through which to develop effective therapeutic approaches for prevention/intervention of these devastating disorders.

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HMGB1, a revived woe from an ancient tale in the modern society during the course of type 1 diabetes

Hmgb1 is an evolutionarily conserved chromosomal protein. It was recently re-discovered to be a potent innate alarmin implicated in both innate and adaptive immune response when it is present extracellularly. Hmgb1 can be either passively released by damaged cells or actively secreted by activated immune cells such as dendritic cells (DCs) and macrophages. Previous studies including ours provided strong evidence indicating a role for Hmgb1 in autoimmune diabetes by regulation of DCs, T effector cells, and regulatory T-cells (Tregs), while the related underlying mechanisms have not been fully addressed. Here we employed NOD mice as a model to dissect the impact of blocking HMGB1 on prevention and treatment of type 1 diabetes. It was interestingly noted that blockade of Hmgb1 passively released during β-mass turnover not only prevents autoimmune progression but also delays diabetes onset. HMGB1 can be served as a therapeutic target to prevent β cell destruction by recurrent autoimmunity after islet transplantation, and to reverse type 1 diabetes in newly diagnosed subjects. Mechanistic studies revealed that extracellular Hmgb1 impairs the stability of Tregs through regulation of PI3K-Akt-mTOR signaling, thereby promoting STAT1 activation. As a result, the activated STAT1 then enhances the transcription of T-bet, a critical transcription factor for T-helper type 1 (Th1) cells, which skews functional Tregs into a Th1-like type of Tregs and eventually loss of Foxp3 expression. Collectively, our data provide pivotal information for understanding of the role of Hmgb1 in type 1 diabetes pathogenesis.

Xiaoyan (Hannah) Hui

Research Assistant Professor, Department of Medicine,
The University of Hong Kong

Dr. Hannah Xiaoyan Hui received her Bachelor Degree from Shanghai Jiao Tong University and her Ph. D degree from Shanghai Institute of Biological Sciences, Chinese Academy of Sciences, majoring in Biotechnology. After that she took the postdoctoral fellow post in the laboratory of Professor. Aimin Xu in University of Hong Kong and has been promoted to research assistant professor in the same department. Her major research interests are the regulation of energy homeostasis and pathological mechanisms of obesity-associated cardio-metabolic diseases, with special reference to adipose tissues. The work conducted by Dr. Hui has contributed to reveal the molecular mechanisms underlying obesity, chronic inflammation, engagement of browning/beiging in adipose tissues, and identified several chemical lead compounds with anti-obese potentials.

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Browning of perivascular adipose tissues protects against obesity-related vascular diseases independent of thermogenesis

There is a close anatomical and functional relationship between adipose tissue and blood vessels. The crosstalk between these two organs is vital to both metabolic and vascular homeostasis. Perivascular adipose tissue (PVAT), the adipose surrounding the blood vessels, is emerging as a critical player in regulating vascular tone. Notably, PVAT exhibits striking similarity to brown adipocytes with abundant expression of uncoupling protein-1 (UCP1), a mitochondrial inner membrane protein which dissipates energy into heat. We found that obesity-induced endothelial dysfunction and vascular inflammation are associated with reduced browning of PVAT, but are reversed by cold exposure-induced conversion of white to brown phenotype of PVAT. Likewise, UCP1 deficiency renders apoE-/- mice more susceptible to diet-induced endothelial damage and atherosclerosis, without obvious effects on glucose, lipid metabolism and adiposity. Mechanistically, UCP1 exerts anti-oxidation and anti-inflammatory activities by reducing mitochondrial membrane potential (MMP) in PVAT. Treatment with a chemical uncoupler is sufficient to reduce reactive oxygen species, inflammation and ameliorate atherosclerosis in UCP1 and apoE double deficient mice. Thus, the brown phenotype of PVAT is protective against vascular disease through a mechanism independent of thermogenesis.

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