NHMRC A*STAR
Molecular Mechanisms of Obesity and Metabolic Diseases
Scientific Symposium

17-18 March 2015
Mercure Sydney, 818-820 George Street, Ultimo NSW 2007
# PROGRAM

## DAY 1 - TUESDAY 17 MARCH 2015

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<tr>
<td>9.00 – 9.05</td>
<td>Welcome</td>
<td>5 min</td>
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<td>The Hon. Justice Annabelle Bennett AO, Chair NHMRC Council</td>
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<tr>
<td>9.05 – 9.25</td>
<td>Introduction</td>
<td>20 min</td>
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<td></td>
<td>Prof Caroline MCMILLEN &amp; Prof HONG Wanjin</td>
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<tr>
<td>9.25–10.25</td>
<td>Plenary Speakers</td>
<td>60 min</td>
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<td>9.25 – 9.55</td>
<td>Prof David JAMES</td>
<td>30 min</td>
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<td>1K10Y – Individualised modern medicine</td>
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<td>9.55 – 10.25</td>
<td>Prof HONG Wanjin</td>
<td>30 min</td>
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<td></td>
<td>Regulators of Insulin Secretion and Insulin Action</td>
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<td>10.25 – 10:45</td>
<td>MORNING TEA</td>
<td>20 min</td>
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<tr>
<td>10.45 – 12.05</td>
<td>1. Epigenetic and Developmental Determinants of Metabolic Health and Disease</td>
<td>80 min</td>
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<td>Moderator/s: Prof Robert NORMAN</td>
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<td>10.45 – 11.05</td>
<td>Dr Prof SUN Lei</td>
<td>20 min</td>
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<td>Regulation of brown fat development by non-coding RNAs</td>
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<td>11.05 – 11.25</td>
<td>Dr Craig MCFARLANE</td>
<td>20 min</td>
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<td>Myostatin yostatin signals through miR-34a to regulate Fndc5 expression and browning of white adipose tissue</td>
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<td>11.25 – 11.45</td>
<td>Dr Michelle LANE</td>
<td>20 min</td>
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<td>Paternal Programming: Mechanistic pathways to impaired metabolic health of offspring</td>
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<td>11.45 – 12.05</td>
<td>Dr Lisa NICHOLAS</td>
<td>20 min</td>
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<td>The Early Origins of Obesity and Insulin Resistance: Timing, Programming and Mechanisms</td>
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<td>12.05 – 12:50</td>
<td>LUNCH</td>
<td>45 min</td>
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<td>12.50 – 14.10</td>
<td>2. Molecular and Cellular Basis of Metabolic Health and Disease 1</td>
<td>80 min</td>
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<td>Moderator/s: Prof HONG Wanjin</td>
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<td>12.50 – 13.10</td>
<td>Dr Colin STEWART</td>
<td>20 min</td>
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<td>Characterisation of a novel murine model of Dunnigan-type familial partial lipodystrophy (FPLD2)</td>
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<td>13.10 – 13.30</td>
<td>Dr XU Feng</td>
<td>20 min</td>
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<td>Epigenetic regulation of adipogenesis</td>
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<td>13.30 – 13.50</td>
<td>A/Prof Andrew HOLMES</td>
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<td>Obesity, Insulin resistance, the gut microbiome and the dysbiosis concept.</td>
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<td>13.50 – 14.10</td>
<td>Prof Matthew WATT</td>
<td>20 min</td>
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<td>Do liver secreted factors link over nutrition to diabetes?</td>
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<td>14.10 – 15.30</td>
<td>3. Molecular and Cellular Basis of Metabolic Health and Disease 2</td>
<td>80 min</td>
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<td>Moderator/s: Prof Matthew WATT</td>
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<tr>
<td>14.10 – 14.30</td>
<td>Prof Jon WHITEHEAD</td>
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<td>Manipulating Fabulous Adipose Tissue (FAT) to reduce the negative impact of obesity</td>
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<td>14.30 – 14.50</td>
<td>Dr Paul LEE</td>
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<td>Brown Fat in humans: turning up the heat on metabolism</td>
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<td>14.50 – 15.10</td>
<td>Dr HAN Weiping</td>
<td>20 min</td>
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<td>Molecular regulation of hormone secretion and diabetes</td>
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<td>15.10 – 15.30</td>
<td>Dr Adrian TEO</td>
<td>20 min</td>
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<td>Human induced pluripotent stem cells for understanding diabetes disease mechanisms</td>
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<td>15.30 – 15.50</td>
<td>AFTERNOON TEA</td>
<td>20 min</td>
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NHMRC - A*STAR Molecular Mechanisms of Obesity and Metabolic Diseases Scientific Symposium
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<td>15.50 – 17.10</td>
<td>4. Biomarkers and Intervention Targets – the Need for Novel Approaches</td>
<td>80 min</td>
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<td>Moderator/s: Dr HAN Weiping</td>
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<tr>
<td>15.50 – 16.10</td>
<td>Prof LAM Kong Peng FAS Apoptosis Inhibitory Molecule (FAIM) in the regulation of energy balance</td>
<td>20 min</td>
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<td>16.10 – 16.30</td>
<td>Dr Vinay TERGAONKAR Novel players in energy homeostasis and metabolism</td>
<td>20 min</td>
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<td>16.30 – 14.50</td>
<td>Prof Steve SIMPSON Putting the balance back in diet: the nutritional geometry of ageing, obesity and metabolic health</td>
<td>20 min</td>
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<td>16.50 – 17.10</td>
<td>Prof Michael COWLEY Obesity Therapies: What has failed lately, what is around the corner?</td>
<td>20 min</td>
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<td>17.10 – 17.25</td>
<td>Closing remarks by Co-chairs</td>
<td>15 min</td>
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<td>17.25</td>
<td>CLOSE DAY 1</td>
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<td>17.25 – 18.25</td>
<td>Networking Function - Mercure Sydney</td>
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**DAY 2 - WEDNESDAY 18 MARCH 2015**

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<tr>
<td>8.45 – 8.50</td>
<td>Welcome back - Dr Clive MORRIS</td>
<td>5 min</td>
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<tr>
<td>8.50 – 10.10</td>
<td>5. Biomarkers and Intervention Targets: Where is there hope?</td>
<td>80 min</td>
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<td>Moderator/s: Dr Vinay TERGAONKAR</td>
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<tr>
<td>8.50 – 09.10</td>
<td>Prof Susan CLARK The epigenomes of human subcutaneous and visceral adipocytes reflect differential gene function and change in obesity</td>
<td>20 min</td>
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<td>9.10 – 09.30</td>
<td>Prof Gary WITTERT The Stomach as a target for Obesity Management</td>
<td>20 min</td>
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<td>9.30 – 9.50</td>
<td>A/Prof TAN Nguan Soon Molecular signalling and metabolism</td>
<td>20 min</td>
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<tr>
<td>9.50 – 10.10</td>
<td>Dr Shigeki SUGII Fat depot-specific molecular signatures of adipose-derived stem cells</td>
<td>20 min</td>
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<td>10.10 – 10.30</td>
<td>MORNING TEA</td>
<td>20 min</td>
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<td>10.30 – 11.45</td>
<td>6: Summary and Outcomes: A Facilitated Panel Discussion</td>
<td>75 min</td>
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<td>Moderator/s: Prof Caroline MCMILLEN and Prof HONG Wanjin</td>
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<td>10.30 – 10.50</td>
<td>Key highlights from the Program</td>
<td>20 min</td>
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<td>10.50 – 11.40</td>
<td>Facilitated Panel Discussion Emerging research priorities - where are the opportunities for advances? Panellists: TBA</td>
<td>50 min</td>
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<tr>
<td>11.40 – 11.45</td>
<td>Thanks and End of Symposium</td>
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<tr>
<td>11.45 – 12.30</td>
<td>LUNCH</td>
<td>45 min</td>
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**NHMRC AND A*STAR OFFICIALS DISCUSSION**

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<tr>
<td>13.00</td>
<td>Themes emerging from the Symposium</td>
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<td>Ongoing collaborations between NHMRC and A*STAR</td>
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<td>15.00</td>
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NHMRC AND A*STAR LEADERSHIP

Professor Warwick Anderson AM
CEO, National Health and Medical Research Council

Professor Warwick Anderson is the Chief Executive Officer (CEO) of NHMRC, Australia's major governmental funding body for health and medical research. Previously, he was Head of School of Biomedical Sciences at Monash University and Deputy Director of the Baker Medical Research Institute, following research fellowships at the University of Sydney and Harvard Medical School.

Professor Anderson obtained his PhD from the University of Adelaide. His research has focused on renal causes of hypertension, including the roles of renal vascular remodeling, renal innervation and the renin-angiotensin system. He has published over 170 peer review articles.

Professor Anderson is a Board member of the Global Alliance for Chronic Disease, a member of Heads of International (Biomedical) Research Organizations. He is an Honorary Fellow of the Royal College of Pathologists of Australasia and a Fellow of the Council for High Blood Pressure of the American Heart Foundation. He was made a Member of the Order of Australia in 2005.

Dr Seet Hun Yew Benjamin
Executive Director of the Biomedical Research Council, Agency for Science, Technology and Research (A*STAR)

Dr Benjamin Seet is the Executive Director of the Biomedical Research Council, Agency for Science, Technology and Research (A*STAR), where he oversees 10 research institutes, various research support facilities in the Biopolis, and a scientific workforce of more than 2,000 people.

Prior to joining A*STAR, Dr Seet was the Chief of the Medical Corps in the Singapore Armed Forces; as well as the Chief Medical Officer of the United Nations Department of Peacekeeping Operations in New York. Previous appointments included Visiting Consultant to the Ministry of Health; Board Director of the Agri-food and Veterinary Authority; Chairman Medical and Dental Board of the Health Promotion Board; Chairman of the Executive Committee of the Singapore Bioimaging Consortium; Chairman of InVivos; and Adjunct Research Fellow with the Defence Medical Research Institute. Dr Seet currently serves as a Board Member of the National Medical Research Council, as well as on a number of inter-Ministry steering committees.

Dr Seet graduated with a Bachelor in Medicine and Surgery, and Master of Medicine from the National University of Singapore; is a Fellow of the Royal College of Surgeons in Edinburgh; and holds a Master of Public Health from Johns Hopkins University.
The Hon. Justice Annabelle Bennett AO
Chair, National Health and Medical Research Council

Justice Bennett practised as a barrister, later specialising in intellectual property. She was appointed to the Federal Court of Australia in May 2003 and as Senior Counsel in 1994. Justice Bennett is an additional Judge of the Supreme Court of the Australian Capital Territory, President of the Copyright Tribunal of Australia, and a Presidential Member of the Administrative Appeals Tribunal. Justice Bennett has been involved in a number of committees, including the Genetic Manipulation Advisory Committee, the Biotechnology Task Force and the Gene Patenting Advisory Committee of the Australian Law Reform Commission. She has also served as Pro-Chancellor of the Australian National University, Director of the Sydney Children’s Hospital Foundation, member of the Eastern Sydney Area Health Board, a Director of Neuroscience Research Australia and President of the Australian Academy of Forensic Sciences.

Dr Clive Morris
Head, Policy Group, National Health and Medical Research Council

Clive Morris is Head of the Policy Group at the National Health and Medical Research Council (NHMRC), Australia’s major governmental body for supporting health and medical research funding and the translation of research into policy practice.

The NHMRC Policy Group is responsible for developing and implementing strategies for NHMRC’s health and medical research funding schemes; new approaches to research funding; continuous improvement of peer review processes; international engagement; the responsible conduct of research; clinical trials reform; and developing and implementing NHMRC’s policies on significant research issues such as Open Access, Dual Use Research of Concern, and the measurement of research outcomes and achievements.

Prior to joining the Federal Government, Clive was active in biomedical research work in Australia and Europe. During his time with NHMRC, Clive has undertaken a number of roles, including overseeing research and health ethics, evidence and guideline development and the regulation of stem cell research. Prior to joining NHMRC, Clive also worked with the Australian Therapeutic Goods Administration and Food Standards Australia and New Zealand (FSANZ).
INTRODUCTIONS - CO-CHAIRS

Professor Hong Wanjin (Co-Chair)

After graduating from Xiamen University in 1982, Wanjin Hong was one of a few hundred Chinese students chosen for further graduate training in the United States via the CUSBEA program. He received his PhD from the State University of New York (SUNY Buffalo), and was a postdoctoral fellow there before he joined IMCB as a Principal Investigator in 1989.

In Singapore, his research group has published over 200 papers in international journals including Science, Nature, Nature Medicine, Nature Cell Biology, Nature Commun, Developmental Cell, EMBO J, Genes&Dev, JCB, MBC, JCS and JBC. His work in the early 1990s identified the Golgi-targeting motifs for TGN38 and Golgi sugar transferases and defined the trafficking pathway of KDEL receptor in mammalian cells. Among the 38 SNAREs in mammalian cells involved in vesicle docking and fusion, about half of them were independently identified and functionally characterized by his lab. His lab also showed that endobrevin (VAMP8) is a major v-SNARE responsible for regulated exocytosis in exocrine cells and other secretory cells. His group also discovered that the PX (phox) domain is a novel structural module capable of interacting with phosphoinositides, Arl1 GTPase regulates Golgi targeting of the GRIP domain-containing proteins Golgin-97 and Golgin-245, and Rab7 and Rab34 share a common downstream effector (RILP). He also worked on COPII and COG complex.

His recent work has uncovered that TAZ (WWTR1) is an oncogene and TAZ interacts with TEAD transcriptional factors to drive oncogenic process. Wbp2 and Amot were identified as positive and negative regulator, respectively, of TAZ/YAP. TAZ and YAP are inhibited by the emerging Hippo tumor suppressor pathway and his lab has recently defined that Amot proteins are substrates of the Hippo pathway.

Professor Caroline McMillen (Co-Chair)

Professor Caroline McMillen joined the University of Newcastle as Vice- Chancellor and President in October 2011.

Professor McMillen has dedicated almost 30 years to the higher education sector, holding leadership roles across research, innovation and teaching. She holds a Bachelor of Arts (Hons) and Doctor of Philosophy from Oxford University, and completed her medical training at the University of Cambridge.

In 1983, she moved to Australia to lecture at Monash University. In 1992, she was appointed Professor, Chair and Head of the Department of Physiology at the University of Adelaide. In 2005, she accepted the position of Deputy Vice-Chancellor and Vice President: Research and Innovation at the University of South Australia, a position she held until her move to Newcastle.

As a biomedical researcher, Professor McMillen is internationally recognised for her work into the impact of the nutritional environment before birth on the risk of developing cardiovascular disease and obesity in adult life.

Professor McMillen has published more than 200 publications and been invited to present at more than 70 international and national meetings. She is also currently the Chair of the Endocrinology, Reproduction and Development Commission of the International Union of Physiological Societies.
She has served on government groups focused on: building innovation, climate change, manufacturing and the resources industry. Professor McMillen was a member of the Prime Minister’s Science, Engineering and Innovation Council Working Group on Aboriginal and Torres Strait Islanders focusing on maternal and peri-natal health. She has served as Chair of the Australian Research Council and National Health and Medical Research Council’s grant review panels.

Professor McMillen is committed to building collaborative partnerships between universities, government, industry and communities that directly contribute to the economic, environmental, social and cultural health of Australia.

Dr Han Weiping

Dr Weiping Han graduated from Cornell University and did his postdoctoral training at the University of Pittsburgh and HHMI/UT Southwestern Medical Center. In 2003, he was appointed Research Assistant Professor in Center for Basic Neuroscience and Department of Cell Biology at UT Southwestern Medical Center. Since then, his research has been focused on molecular mechanisms of hormone secretion and its role in metabolic diseases.

In December of 2005, he moved to Singapore to set up a research program at Singapore Bioimaging Consortium (SBIC), where he is now Deputy Director with concurrent appointment as Head of Laboratory of Metabolic Medicine. He also holds joint appointments at Institute of Molecular and Cell Biology, National University of Singapore and Duke-NUS.

Professor Rob Norman

Professor Robert Norman is Professor of Reproductive and Periconceptual Medicine at the Robinson Research Institute, University of Adelaide. He currently serves on the NHMRC Research Committee as well as the NHMRC’s Embryo Licencing Committee. He was the Founding Director of the Robinson Research Institute, which focuses on the early stages of life to improve the health and well being of children and families over the life-course and across generations. It comprises approximately 400 researchers including ten NHMRC Fellows.

Professor Norman is a clinician scientist who has sub-specialised in reproductive medicine and endocrinology and is particularly interested in events around the time of conception. His expertise is in assisted reproduction, infertility management and polycystic ovary syndrome, a condition which is very commonly found in women across the reproductive and post-reproductive lifespan.

He has been Chief Investigator on two NHMRC Program Grants and has had project, development and Centre of Research Excellence funding for the past two decades from NHMRC.

He is currently Medical Director of a fertility clinic (Fertility SA), a Visiting Medical Specialist at the Royal Adelaide Hospital, a co-Director of the NHMRC Centre of Research Excellence for the origins, outcomes and optimal management of polycystic ovary syndrome. He remains a research active member of the Robinson Research Institute. He has recently been President of the Asia Pacific Initiative on Reproduction (ASPIRE) which is the largest society covering reproductive medicine in the Asia Pacific region. He became an Officer in the Order of Australia (AO) in 2013.
Dr Vinay Tergaonkar

Dr Vinay Tergaonkar obtained his Ph.D. (2001), from National Center for Biological Sciences, Bangalore, India, where he studied the molecular pathogenesis of human papillomaviruses.

During his graduate studies he was awarded an international cancer society (UICC) fellowship for collaborative research at Tufts University, Boston, USA. He has been a fellow (2001-2004) and a special fellow (2004-present) of the Leukemia and Lymphoma Society of America and conducted his postdoctoral studies at the Salk Institute for Biological Studies, La Jolla, California. He joined IMCB in late 2005 as an Assistant Professor and currently is an Associate Professor (since 2010).

He holds adjunct appointments at:

1) Department of Biochemistry (NUS)
2) Department of Pathology (NUH) and
3) Singapore Eye Research Institute.

He has been invited to speak at various international venues and meetings such as the Barossa valley meeting in Australia, Genes and Cancer meeting in UK, The Argentine Pharmacological society meeting, Japanese Cancer Society meeting and the Keystone Symposia. He serves on Editorial Boards of 1) Biochemical Journal (Portland Press) 2) Critical Reviews in Oncology/Hematology (Elsevier Press), 3) BMC Research Notes (Biomed Central) and a new journal Telomeres and Telomerase.

Professor Matthew Watt

Professor Matthew Watt is a Senior Research Fellow of the National Health and Medical Research Council of Australia and heads the Biology of Lipid Metabolism laboratory located within the Department of Physiology at Monash University.

His group studies the molecular and cellular regulation of lipid metabolism in fat, muscle, liver and the brain and how defects in lipid metabolism cause insulin resistance, a major feature of obesity and precursor to type 2 diabetes. More recently, Professor Watt’s team has studied the endocrine role of adipose tissue and the liver specifically; they are using “omics” technology to discover novel proteins and lipids that are secreted by these tissues and how this influences metabolism in obesity.
Professor Susan Clark

Professor Susan Clark has a highly acclaimed international reputation for her work in cancer epigenetics. Susan is the inaugural Director of the Genome and Epigenetics Division at the Garvan Institute of Medical Research in Sydney, Australia. She graduated in 1982 with a PhD in Biochemistry, University of Adelaide and then spent ten years in the Recombinant Technology Industry before returning to basic research in gene regulation in 1992.

Her molecular studies over the last twenty years have initiated profound questions about the importance of epigenetics in early development and in disease, especially in cancer. She has made extensive ground-breaking discoveries relating to DNA methylation patterns in normal and cancer genomes, that have led to the commercialization of new methylation-based tests for early cancer detection. The techniques she pioneered in the early 1990s, including bisulphite sequencing, have revolutionised and now underpin a new era in epigen“omic” research. She was founding member of IHEC (International Human Epigenome Consortium) and led the formation of the AEpiA (Australian Epigenetics Alliance).

She has a number of awards including the RPAH Research Medal in 2002, Julian Wells Medal in 2003; “Biochemisch Analytik Preis” for outstanding contribution for Methylation analysis in 2004. In 2006 was elected a Fellow of the World Technology Network for Biotechnology, 2012 was awarded the National Rotary Vocational Award and in 2014 was awarded a NHMRC Senior Principal Research Fellowship.

Abstract

THE EPIGENOMES OF HUMAN SUBCUTANEOUS AND VISCERAL ADIPOCYTES REFLECT DIFFERENTIAL GENE FUNCTION AND CHANGE IN OBESITY

Stephen Bradford, Susan Van Dijk, Shalima Nair, Brodie Sutcliffe, Hilal Varinli, Wenjia Qu, Aaron Statham, Hugh French, Elena Zotenko, Tim Peters, Michael Buckley, Helen Lutgers, Julius Von Martels, Rosanne Arnoldy, Madhavi Maddugoda, Michelle Peranec, Michael Swarbrick, Jason Ross, Reginald Lord, Katherine Samaras, Peter Molloy and Susan Clark

Human development, from a single fertilized egg to adulthood and throughout life, is driven by gene expression programs unique to each cell type. These programs are executed by transcription factors and co-factors binding to regulatory elements within a genome common to all cells. Upon this common genome, the epigenome is essential in enforcing, and sequentially restricting, cell specific expression throughout development, and in then maintaining cells in their appropriate states. To better understand the epigenome’s role in defining different cell types, we performed full methylome sequencing analysis at base pair resolution on two similar, yet functionally distinct, in vivo human cell types – subcutaneous (SA) and visceral adipocytes (VA). We found that while there is a common adipocyte specific DNA methylation profile, there are also profound differences. These differentially methylated regions (DMRs) are enriched around transcription factors important in development, such as the HOX clusters and TBX family. When overlapped with strand specific RNA-seq many are associated with genes differentially expressed between SA and VA and known to be important in adipocyte function. Using our methylation data we computationally identified putative promoters and enhancers elements that exquisitely matched the expected histone profiles for these active elements. Finally, we generated further data from the VA of age and sex matched obese individuals and identified DMRs associated with obesity.

Interestingly, a large proportion of these DMRs overlapped with those identified between SA and VA, suggesting co-ordinate mechanisms are involved between fat depots and that these are modulated during disease.
Professor Michael Cowley

Professor Michael Cowley is the founding director of the Monash Obesity & Diabetes Institute and a physiologist with a focus on obesity, diabetes, and metabolic disorders. He received his science degree from the University of Melbourne, and did his PhD at Prince Henry's Institute of Medical Research at Monash Medical Center, before a post-doctoral fellowship at The Vollum Institute in Oregon. He was later an Assistant then Associate Scientist at Oregon National Primate Research Center in the USA. In 2008 he returned to Australia to Monash University. His work has mapped the neural circuits in the brain that sense nutrients and fat, to control appetite and body weight. He has published more than 75 papers and chapters, is the inventor of 85 patents, and the co-founder of Orexigen Therapeutics, a publically listed (NASDAQ: OREX) San Diego biotech company where he served as the Chief Scientific Officer till December 2008. Michael is a Professor of Physiology at Monash University, and a director of an Australian diabetes drug development company, Verva Inc, and a primate contract research company. Michael has a significant focus on public outreach, the promotion of science in schools, and better metabolic health.

Michael is a fellow of The Australian Academy of Technological Sciences and Engineering, a Veski Innovation Fellow, in 2009 he was awarded The Australian Science Ministers Prize for Australian Life Scientist of the Year and in 2014 the inaugural Jacques Miller Medal for Experimental BioMedicine from the Australian Academy of Science.

Abstract

OBESITY THERAPIES: WHAT HAS FAILED LATELY, WHAT IS AROUND THE CORNER?

Obesity confers significant health risks, and rates of obesity continue to rise within the developed and developing world. The Cowley lab has discovered how the brain detects levels of leptin, which signals adipose stores. This signal allows the brain to regulate food intake and energy expenditure to maintain homeostasis. More recently the lab has discovered how the brain becomes resistant to leptin, and how leptin resistance in a hallmark of obesity. Leptin was ineffective for the treatment of obesity in multiple clinical trials, and many other potential therapies have not lived up to expectations or been removed from the market. The Cowley lab has developed several therapies that bypass leptin resistance and regulate food intake and energy expenditure to reduce adipose stores and cause weight loss. One of these therapies has recently received approval by the FDA and EMEA for the treatment of obesity and will be discussed, as will other newly approved obesity medications.
PRESENTERS

Dr Han Weiping

Dr. Weiping Han graduated from Cornell University and did his postdoctoral training at the University of Pittsburgh and HHMI/UT Southwestern Medical Center. In 2003, he was appointed Research Assistant Professor in Center for Basic Neuroscience and Department of Cell Biology at UT Southwestern Medical Center. Since then, his research has been focused on molecular mechanisms of hormone secretion and its role in metabolic diseases.

In December of 2005, he moved to Singapore to set up a research program at Singapore Bioimaging Consortium (SBIC), where he is now Deputy Director with concurrent appointment as Head of Laboratory of Metabolic Medicine. He also holds joint appointments at Institute of Molecular and Cell Biology, National University of Singapore and Duke-NUS.

Abstract

MOLECULAR REGULATION OF HORMONE SECRETION AND DIABETES

Neurotransmitters, neuropeptides and hormones are released through regulated exocytosis of synaptic vesicles (SVs) and large dense core vesicles (LDCVs), a process that is controlled by Ca2+. Synaptotagmins are a family of membrane proteins that share a common domain structure. Most synaptotagmins are expressed in brain and endocrine cells, and some of these synaptotagmins bind to phospholipids and Ca2+ at the levels that trigger regulated exocytosis of SVs and LDCVs. A major research interest in my lab is to understand the molecular regulation of insulin secretion. The cellular process of insulin secretion is well established, and numerous molecular players involved in insulin granule biogenesis, trafficking and exocytosis have been documented and analyzed. Although it is well known that incretins, such as GLP-1 can potentiate insulin secretion, its underlying molecular mechanisms are poorly defined. We have used mouse genetic and physiology approaches, along with biochemistry and molecular biology to analyze the effects of depleting synaptotagmins on insulin secretion, and whether synaptotagmins are involved in the incretin potentiation of insulin secretion. Depletion of synaptotagmin-7 in mice results in impaired glucose tolerance and reduced insulin secretion, along with defective response to GLP-1 stimulation. Furthermore, synaptotagmin-7 undergoes post-translational modification in response to signaling pathways that potentiate insulin secretion. As synaptotagmin-7 regulates insulin granule exocytosis only in elevated intracellular calcium levels, downstream of high glucose-induced metabolic and membrane events, synaptotagmin-7 may represent an ideal target in enhancing GSIS in diabetes treatment.
Associate Professor Andrew Holmes
School of Molecular Bioscience & Charles Perkins Centre, University of Sydney

Associate Professor Andrew Holmes has general interests in microbial diversity, its evolutionary origins and ecological applications. He did his PhD studies at the University of Queensland (1989-1992) before postdoctoral stints at the University of Warwick, UK (1992-1996) and Macquarie University (1996-2002). In 2002 he commenced his current position at the University of Sydney where he is now Associate Professor in the School of Molecular Bioscience and Microbiome Project node leader in the Charles Perkins Centre.

A deeper understanding of factors that influence the assembly of microbial communities is essential for both human and environmental health. Andrew’s current research encompasses both these with a particular focus on understanding the dynamics of gut microbial community composition, the mechanisms of host-microbe interaction in the gut and development of tools to enable management of the gut microbial ecosystem for health. He has particular interests in the relationship between animal nutrition and the host-microbiome interaction. He is a Senior Editor for Microbiology and The ISME Journal and a member of the Editorial Boards of Applied and Environmental Microbiology, and Environmental Microbiology.

Abstract

OBESITY, INSULIN RESISTANCE, THE GUT MICROBIOME AND THE DYSBIOSIS CONCEPT

Microbes so profoundly influence animal systems that animals can be viewed as “holobionts” comprised of animal and microbial cells. In this concept, microbes are part of us and our health is inextricably linked to function of our microbiome. Diseases in which a breakdown in normal host-microbiome interaction (dysbiosis) is implicated as a major feature have emerged among the most important public health problems facing modern societies. These include diabetes, obesity, and allergic disorders among others. It is widely accepted that change in the nutrient environment of modern societies has been a major driver of this pattern. The complex sensory mechanisms and behaviours of animals have evolved to increase their ability to control their physiological state across a range of environmental conditions, including food availability. This raises the question; Why have these mechanisms failed to prevent the emergence of dysbiosis? An oft-neglected feature of animal biology is the tension between selective processes that operate at the level of the holobiont, and those that operate on either the animal or its many microbial partners. We are exploring how the nutrient environment influences host-microbiome interaction. A systematic exploration of nutrient intake in mice has shown that macronutrient distribution and energy density in the diet interact with host feeding behaviour to alter microbial community composition in multiple ways. Model simulations reveal tradeoffs between microbiome composition and aspects of animal performance that can be driven by its nutrient environment. These insights are informing strategies to prevent, or reverse, dysbiosis.
Professor Hong Wanjin

After graduating from Xiamen University in 1982, Wanjin Hong was one of a few hundred Chinese students chosen for further graduate training in the United States via the CUSBEA program. He received his PhD from the State University of New York (SUNY Buffalo), and was a postdoctoral fellow there before he joined IMCB as a Principal Investigator in 1989.

In Singapore, his research group has published over 200 papers in international journals including *Science*, *Nature*, *Nature Medicine*, *Nature Cell Biology*, *Nature Commun*, *Developmental Cell*, *EMBO J*, *Genes&Dev*, *JCB*, *MBC*, *JCS* and *JBC*. His work in the early 1990s identified the Golgi-targeting motifs for TGN38 and Golgi sugar transferases and defined the trafficking pathway of KDEL receptor in mammalian cells. Among the 38 SNAREs in mammalian cells involved in vesicle docking and fusion, about half of them were independently identified and functionally characterized by his lab. His lab also showed that endobrevin (VAMP8) is a major v-SNARE responsible for regulated exocytosis in exocrine cells and other secretory cells. His group also discovered that the PX (phox) domain is a novel structural module capable of interacting with phosphoinositides, Arl1 GTPase regulates Golgi targeting of the GRIP domain-containing proteins Golgin-97 and Golgin-245, and Rab7 and Rab34 share a common downstream effector (RILP). He also worked on COPII and COG complex.

His recent work has uncovered that TAZ (WWTR1) is an oncogene and TAZ interacts with TEAD transcriptional factors to drive oncogenic process. Wbp2 and Amot were identified as positive and negative regulator, respectively, of TAZ/YAP. TAZ and YAP are inhibited by the emerging Hippo tumor suppressor pathway and his lab has recently defined that Amot proteins are substrates of the Hippo pathway.

Abstract

REGULATORS OF INSULIN SECRETION AND INSULIN ACTION

My lab has been interested in defining the targeting motifs and machineries governing intracellular membrane trafficking. Our efforts have enabled us to uncover many cellular proteins regulating various steps of membrane trafficking including the SNAREs, Sorting nexins, and small GTPases and their effectors. Among the SNAREs, we have studied the physiological function of VAMP8 through knockout mice. Our independent and collaborative works established that VAMP8 is important for regulated secretion of exocrine tissues. Together with VAMP2 and VAMP3, VAMP8 also plays a redundant function in insulin-stimulated surface of GLUT4. VAMP8 is also involved in glucagon-like-peptide-1 (GLP-1) stimulated potentiation of glucose-stimulated insulin secretion. Our study on Arl1 and its regulators enabled us to molecularly identify BIG3 and our functional analysis has established that BIG3 is a negative regulator of insulin secretion.
Professor David James

Professor David James is currently Leonard P Ullmann Chair in Metabolic Systems Biology at the Charles Perkins Centre, and Professor of Systems Biology in the School of Molecular Bioscience and Sydney Medical School, at The University of Sydney.

David received his PhD from the Garvan Institute in 1985 and since then has made major contributions to our understanding of insulin action. In the late 1980s he published a series of *Nature* papers describing the identification and characterization of the insulin responsive glucose transporter GLUT4. He then focused his efforts on unveiling the cellular and molecular control of insulin-stimulated glucose transport. He has also made contributions in the area of SNARE proteins, signal transduction and more recently has established new interests in systems biology.

David has held positions at the Washington University School of Medicine in St Louis, at the University of Queensland, and at the Garvan Institute of Medical Research, where he was Director of the Diabetes & Obesity Research Program from 2002 until early 2014.

David was the winner of the prestigious Glaxo Wellcome research medal in 1999, and was elected as a Fellow of the Australian Academy of Science in 2007.

Abstract

1K10Y – INDIVIDUALISED MODERN MEDICINE

Individuals often have a unique response to disease, drugs or their dietary and physical environment. This is due to a combination of their own personal genetic blueprint and their pre-birth and early life exposure to environmental factors. This unique combination programs individuals for distinct health outcomes later in life and determines how they will interact or respond to their particular environment. The ability to predict individual health outcomes would revolutionise modern medical care providing a major step forward in disease prevention.

To bring individualized medicine to the forefront of modern medical care will require comprehensive and systematic analysis of individuals and their families during key periods of life. 1K10Y will follow 1,000 heterosexual couples in their early 30’s for 10 years. During this period extensive information will be repeatedly collected on these individuals, their parents and their offspring during gestation and thereafter.

This information will include ongoing profiling of genetics, gut bacteria, sleep patterns, food habits, activity patterns and detailed blood analysis. This will provide a comprehensive and progressive health record for each individual. Planned transient interventions will also be performed to determine individual responses to food or activity. By matching these data prospectively with disease progression over the 10-year period we will establish markers that predict future disease risk in individuals long before disease emergence, and more importantly, design optimal environments that prevent or delay disease onset.

This will open up new avenues for preventive medicine creating an entire industry of health that will be unparalleled in the modern health revolution.
Dr Paul Lee

Dr Paul Lee is an endocrinologist and clinician scientist with an interest in adrenal and fat metabolism. He underwent endocrine training in Sydney and completed his doctoral studies on adrenergic metabolism at the Garvan Institute of Medical Research. During 2012-2014, Paul worked as a NHMRC Neil Hamilton Fairley Clinical Fellow in Diabetes, Endocrinology, Obesity Branch in NIDDK at the National Institutes of Health in the United States. He spent the majority of his time pondering over brown fat modulatory strategies, both within and outside the clinic and the laboratory. His goal is to determine the therapeutic potential of brown fat in health and disease.

Abstract

**BROWN FAT IN HUMANS: TURNING UP THE HEAT ON METABOLISM**

White fat was once believed to be the only significant adipose depot in adult humans. Advances in metabolic imaging have led to the rediscovery of brown fat in adults. Brown fat is thermogenic, metabolically active, and greater abundance is associated with leanness, lower glycaemia and enhanced adaptive thermogenesis. Induction of high brown fat states reverse metabolic syndrome in animals. New appreciation of brown fat biology in humans marks a metabolic renaissance, offering a renewed perspective on energy and substrate homeostasis. Knowledge on human brown fat physiology may illuminate novel therapeutic opportunities in the treatment of diabetes, obesity and related metabolic disorders.
Professor Lam Kong Peng

Kong-Peng Lam obtained his BA (summa cum laude) at the University of Minnesota and his M.A., M.Phil and PhD at Columbia University in the USA. Thereafter he joined the Institute for Genetics at the University of Cologne in Germany as a postdoctoral research scientist, where he was awarded both the EMBO and HFSP long-term fellowships to study B cell development using conditional gene knockout approaches. He returned to Singapore in 1998 and assumed the position of Principal Investigator at the Institute of Molecular and Cell Biology (IMCB).

In 2002-3, he attended the Sloan Fellow Program at Stanford University Graduate School of Business where he graduated with an MSc (Mgmt) degree. He was seconded to A*STAR Biomedical Research Council where he served as Director (2003), Deputy Executive Director (2004) and Acting Executive Director (2005-2006) while concurrently heading a research laboratory at the Center for Molecular Medicine (CMM). He returned to full-time research in October 2006 and was the founding Executive Director of the Singapore Immunology Network (SIgN), a post he held from 2006 to 2008. He joined the Bioprocessing Technology Institute (BTI) as Scientific Director in May 1 2008, and is currently its Executive Director.

Kong-Peng also holds tenured Full Professorship at the National University of Singapore and Adjunct Full Professorship at the Nanyang Technological University. He is also the Co-Chair of the Scientific Advisory Panel of the Environmental Health Institute and sits on various BMRC and NMRC grant review committees. He was awarded the Arthur Kornberg Memorial Medal by the Asia-Pacific International Molecular Biology Organisation in November 2010.

Abstract

**FAS APOPTOSIS INHIBITORY MOLECULE (FAIM) IN THE REGULATION OF ENERGY BALANCE**

Jianxin Huo, Yi Ma, Jian-jun Liu, Ying Swan Ho, Shuwen Chen, Shengli Xu, Weiping Han, An Hong, Su Chi Lin

Fas apoptosis inhibitory molecule (FAIM) is an evolutionary-conserved molecule with unknown function. We had previously characterized FAIM in the context of lymphocyte signaling and cell death. Here, we demonstrate that FAIM plays a role in energy balance. We show that FAIM-deficient mice develop an obese phenotype resembling human metabolic syndrome even though they are fed on a normal chow diet. Mutant mice and hepatocytes manifest impaired insulin signaling. In human, FAIM expression is significantly lower in obese individuals than in lean controls and inversely correlated with body mass index (BMI) and fasting plasma insulin level. Our study indicates that FAIM might play a critical role in insulin signaling and the maintenance of energy homeostasis.
Dr Michelle Lane

Dr Michelle Lane is an NHMRC Senior Research Fellow at the Robinson Research Institute at the School of Paediatrics and Reproductive Health at the University of Adelaide where she is the Head of the Gamete and Embryo Biology Laboratory. She has published over 140 peer reviewed papers, >30 book chapters and edited 2 books. She has extensive translation and clinical experience, having >20 products sold worldwide and 8 awarded patents in the field of clinical IVF that have resulted from her research.

Her research interests are focussed on understanding how environmental insults impact gametes to alter the development of the embryo to set the developmental trajectory of the offspring. With an additional focus on how IVF technology intersects with these environmental factors to further influence embryo health.

Abstract

PATERNAL PROGRAMMING: MECHANISTIC PATHWAYS TO IMPAIRED METABOLIC HEALTH OF OFFSPRING

Michelle Lane, Julie A. Owens, Tod Fullston, Nicole O. McPherson

Obesity is a global health problem that is reaching epidemic proportions with 1.6 billion adults classified as overweight and 400 million classified as obese. In Australia, since the 1970s the rates of obesity in reproductive aged men have nearly tripled. Male obesity is implicated in impaired hormone profiles and increased sexual dysfunction. However, recent evidence has also determined that paternal obesity affects the sperm by altering the physical and molecular structure of germ cells in the testes and mature sperm. Furthermore, there is increasing evidence that paternal health cues can be passed to the next generation. Data from animal models suggests that paternal high fat diet induced obesity, with or without overt diabetes, impairs metabolic health of offspring with earlier onset in females. The diminished metabolic health of the offspring is co-morbid with impaired reproductive function. The mechanisms by which paternal exposures and physiological status can impact on offspring long term health are unknown, however, sperm and epigenetic changes are clearly implicated as the mediators of transmission of such paternal exposures. Although as there is evidence that the seminal fluid composition can also influence offspring phenotypes, this mechanism cannot be discounted. Epigenetic alterations either to the DNA or the surrounding histones and protamines have been suggested to be a key mediator of paternal programming effects on the next generation. We have determined that male obesity alters acetylation of the germ cells in the testes, reduces germ cell global methylation and alters the abundance of microRNAs in both testes as well as in mature sperm. Together this provides evidence that the nutritional status of the father directly affects the epigenome of sperm with implications for fertility and beyond.

A key question which requires further investigation, is to what extent interventions such as diet and exercise in the father can reduce the risk of disease in the next generation. Certainly in mouse models of paternal obesity, diet and exercise interventions before conception improve sperm function and embryo development, with small human studies also showing exercise can improve male fertility. There is a continuing need to define this new concept in embryo programming and its mechanistic basis, with a view to improving pregnancy and child health, and to identify effective interventions for the overweight or obese father before pregnancy, as this may represent a new window of intervention in the epidemic of childhood chronic diseases.
Dr Craig McFarlane

Dr Craig McFarlane is currently a principal investigator at Singapore Institute for Clinical Sciences (SICS), a biomedical sciences institute under the Agency for Science, Technology and Research (A*STAR), Singapore. After completing his PhD in 2007, he joined Nanyang Technological University as a post doctoral fellow, primarily focused on defining the role of Myostatin, a negative regulator of skeletal muscle growth, during post natal muscle growth and wasting. He joined SICS as an assistant Principal Investigator in 2009, and in collaborations with clinician scientists, he studied the molecular mechanisms behind insulin resistance in humans. As a principal investigator at SICS, his lab is focused primarily on understanding the role that adipose tissues play during the development of obesity and insulin resistance using genetic and epigenetic approaches.

Abstract

MYOSTATIN SIGNALS THROUGH miR-34a to REGULATE Fndc5 EXPRESSION AND BROWNING OF WHITE ADIPOSE TISSUE

Xiaojia Ge, Durgalakshmi Sathiakumar, Bing Jia Gavian Lua, Sabeera Bonala, Prasanna Kumar Juvvuna, Himani Kukreти, Marcus Lee, Peter D. Gluckman

Myostatin (Mstn), predominantly expressed in skeletal muscle, plays a pivotal role in glucose and lipid metabolism. Mstn deficiency protects mice from developing diet-induced obesity and insulin resistance. Increased browning of white adipose tissue (WAT) was previously described in Mstn-/- mice, which contributed to increased energy expenditure and reduced adiposity. However, the underlying molecular mechanism(s) behind this browning phenotype is poorly understood. Therefore, we investigated the molecular mechanism(s) through which Mstn regulates browning of WAT. Here we show that Mstn negatively regulates expression of Fndc5/Irisin (a potent “browning” factor), to inhibit browning of WAT. Mstn treatment of myoblasts inhibited Fndc5 expression in a dose- and time-dependent manner, while loss of Mstn resulted in increased Fndc5 expression in muscles and in circulation. We further show that Mstn inhibition of Fndc5 is miR-34a-dependent. Mstn treatment of C2C12 myoblasts upregulated miR-34a expression, while reduced miR-34a expression was noted in Mstn-/- muscle and WAT. Reporter analysis demonstrated that miR-34a directly suppresses Fndc5 expression through a miR-34a-specific binding site within the Fndc5 3’UTR. Consistent with this, Fndc5 expression in muscle and adipose tissues are inversely associated with miR-34a expression. Moreover, specific overexpression of miR-34a inhibited Fndc5 expression, while blockade of miR-34a increased Fndc5 expression in myoblasts. Importantly, Mstn-mediated inhibition of Fndc5 was blocked upon miR-34a inhibition. We further show that Mstn deficiency promotes browning of WAT through up-regulating endogenous Fndc5 expression in white adipocytes through an autocrine mechanism. Mstn-/- adipocytes, when compared to wildtype adipocytes, show reduced miR-34a, enhanced Fndc5 expression and an associated increase in thermogenic gene expression, which was reversed upon antibody-mediated neutralization of Fndc5. Consistent with this, Mstn-/- adipocytes have increased mitochondria, improved mitochondrial function and increased heat production. Our data demonstrate that Mstn regulates Fndc5/Irisin expression and secretion through a novel miR-34a-dependent post-transcriptional mechanism. Loss of Mstn in mice leads to increased Fndc5/Irisin expression, which contributes to the browning of WAT. This study provides novel insights into the molecular mechanism through which Mstn regulates browning of WAT and thus energy homeostasis.
Dr Lisa Marie Nicholas is currently a post-doctoral fellow at Lund University Diabetes Centre in Sweden where she is investigating the role of mitochondrial dysfunction in pancreatic beta cells in the development of type 2 diabetes. Dr Nicholas received her PhD from the University of South Australia in 2013 in the field of fetal programming. Her thesis examined the molecular mechanisms that are recruited within the developing embryo exposed to maternal obesity or imposed dietary restriction, which impact on programming of metabolic pathways in postnatal life. Dr Nicholas was recently awarded an NHMRC C J Martin Fellowship to study the transgenerational epigenetic inheritance of parental obesity at the University of Cambridge and the Victor Chang Cardiac Research Institute.

Abstract

THE EARLY ORIGINS OF OBESITY AND INSULIN RESISTANCE: TIMING, PROGRAMMING AND MECHANISMS

L M Nicholas, J L Morrison, L Rattanatray, S Zhang and I C McMillen

Maternal obesity is associated with an increased risk of gestational diabetes and of giving birth to a large baby with increased fat mass. Moreover, offspring of overweight/obese women are also at an increased risk of obesity and insulin resistance in childhood, adolescence and adult life. It has been proposed that exposure to maternal obesity may therefore result in an ‘intergenerational cycle’ of obesity and insulin resistance. In order to develop targeted interventions it is important to determine the separate or interdependent contributions of maternal pre-pregnancy BMI, gestational weight gain and glycemic control on the longer term metabolic outcomes for the offspring. It is, therefore, essential to identify critical periods during development during which exposure to maternal obesity programs specific metabolic changes in the offspring.

Studies in sheep have found that exposure to maternal overnutrition in late gestation resulted in an increase in fetal glucose and insulin concentrations and an up-regulation of the gene expression of key adipogenic, lipogenic and adipokine genes. Furthermore, exposure to maternal overnutrition in late gestation also resulted in a higher relative subcutaneous fat mass in one month old lambs. The periconceptional period has also been identified as a critical window during which exposure to maternal obesity programs an increased risk for obesity and insulin resistance in the offspring. We have found that when sheep embryos were transferred from obese ewes to non-obese ‘recipient’ ewes at one week after conception, that the female offspring had an increased total fat mass at four months after birth as a predominant consequence of an increase in the mass of the visceral fat depots. Furthermore, exposure to maternal obesity confined only to the periconceptional period was sufficient to program changes in abundance of key insulin signalling molecules in the liver and to a more limited extent in skeletal muscle of both male and female offspring. Defects in insulin signalling are among the earliest indicators that an individual is predisposed to the development of insulin resistance and type 2 diabetes (T2D).

Early embryogenesis in mammals is a critical period for the establishment of the epigenome. This period, therefore, represents a critical window in development during which the embryo is vulnerable to environmental and/or nutritional cues that disrupt the establishment of epigenetic marks. Indeed, we found that exposure of the oocyte/early embryo to maternal obesity resulted in up-regulation of the hepatic expression of miR-29b, miR-103 and miR-107 in lambs. Expression of these microRNAs have been shown to be related to decreased insulin signalling in adipocytes and liver in mouse models of obesity and T2D.

As most women who are overweight/obese at conception remain so through their pregnancy, our findings indicate that exposure to maternal obesity in the periconceptional period and in late pregnancy represent ‘two hits’ in the programming of obesity in the offspring. Thus intervention to limit the impact of maternal obesity in the periconceptional period may limit the negative impact of the first and possibly also the second hit of maternal obesity on adiposity and metabolic outcomes in the offspring.
Professor Steve Simpson

Professor Steve Simpson is Academic Director of the Charles Perkins Centre (The University of Sydney’s $500 million initiative to ease the burden of obesity, diabetes, cardiovascular disease and related conditions) and an Australian Research Council (ARC) Laureate Fellow in the School of Biological Sciences at the University of Sydney. Stephen returned to Australia in 2005 as an ARC Federation Fellow after 22 years at Oxford. Before that he undertook his PhD at the University of London, and his undergraduate degree and honours at the University of Queensland.

Steve working with David Raubenheimer has developed an integrative modelling framework for nutrition (the Geometric Framework), which was devised and tested using insects but has since been applied to a wide range of organisms, from slime moulds to humans and real-world problems, from aquaculture and conservation biology to the dietary causes of human obesity and ageing. He has also revolutionised understanding of swarming in locusts, with research spanning neurochemical events within the brains of individual locusts to continental-scale mass migration.

Steve has been Visiting Professor at Oxford, a Fellow of the Institute for Advanced Study (Wissenschaftskolleg) in Berlin, Distinguished Visiting Fellow at the University of Arizona, and Guest Professor at the University of Basel. In 2007 he was elected a Fellow of the Australian Academy of Science, in 2008 he was awarded the Eureka Prize for Scientific Research, in 2009 he was named NSW Scientist of the Year, and in 2013 he was elected to the Royal Society. He was also the presenter of a four-part documentary for ABC TV, Great Southern Land, which was aired to critical and viewer acclaim in September 2012.

Abstract

PUTTING THE BALANCE BACK IN DIET: THE NUTRITIONAL GEOMETRY OF AGEING, OBESITY AND METABOLIC HEALTH

Macronutrients (protein, fats and carbohydrates) are fundamental dietary components, yet the question of what represents a macro-nutritionally balanced diet and how this maintains health and longevity remains unanswered. We have developed a set of state-space models called the Geometric Framework (GF) to capture the multidimensional nature of nutritional requirements, the relative values of foods in relation to these requirements, the behavioural and physiological responses when feeding on diets of varying composition, and the growth and performance consequences of being restricted to particular dietary regimes. We have also derived the necessary theory for defining health and performance in relation to nutrient intake, for describing key nutritional traits and assessing trade-offs between different responses. I begin by introducing these models and then show how they have been used to address problems in life-history theory, appetite, immunity, ageing, obesity, cardio-metabolic health, gut microbial ecology, and foetal development. Along the way I will use examples spanning insects to humans.
Dr Colin Stewart

Dr Colin Stewart received his D.Phil from the University of Oxford where he studied interactions between teratocarcinomas, the forerunners of ES cells, and early mouse embryos. He was the first to show that mouse chimeras can be produced by aggregation of EC and then ES cells with 8-cell stage embryos, a now widely used technique in experimental mouse genetics.

During postdoctoral work with Rudolf Jaenisch he showed EC cells and early embryos had a powerful mechanism, associated with de novo DNA methylation at transcriptionally silencing retroviruses. Subsequently as a staff scientist at the EMBL he was instrumental in discovering the role of the cytokine LIF in maintaining mouse ES cells in an undifferentiated state. There he also initiated an interest in the nuclear lamins and nuclear architecture. Subsequently at the Roche Institute of Molecular Biology in New Jersey, he pursued studies on the lamins, embryonic stem cells and genomic imprinting. There he showed that, paradoxically, LIF was not essential for embryonic development. Rather LIF, produced in the uterus, was essential at regulating embryo implantation. In 1996, he moved to the ABL research program in Frederick, Maryland and in 1999 was appointed Chief of the Laboratory of Cancer and Developmental Biology at the NCI.

Over the last decade he continued his interest in the functional architecture of the cell’s nucleus in stem cells, epigenetics, regeneration and various diseases, particularly with regard to how the nucleus integrates its functions with the cytoskeleton. Since June 2007 he has been Research and Assistant director at the Institute of Medical Biology at the Singapore Biopolis.

Abstract

CHARACTERISATION OF A NOVEL MURINE MODEL OF DUNNIGAN-TYPE FAMILIAL PARTIAL LIPODYSTROPHTY (FPLD2)

Nardev Ramanathan, Nicole Lim

Mutations in the LMNA gene, encoding the nuclear lamins A/C, result in a wide variety of diseases known as laminopathies. One of these conditions, Dunnigan-type familial partial lipodystrophy (FPLD2), (OMIM # 151660) is a rare monogenic disease, which in humans is characterized by loss of subcutaneous fat from the extremities, trunk and gluteal region, usually at the onset of puberty. FPLD2 patients display many of the clinical features associated with the metabolic syndrome, such as insulin resistance, dyslipidemia and type 2 diabetes. Approximately 85% of FPLD2 patients are affected by a heterozygous missense substitution at amino acid 482 of lamin A/C. We generated a R482Q Lmna knock-in mouse model to investigate the role of LMNA in adipose tissue. The phenotype observed in our FPLD2 model resembles some of the clinical features associated with FPLD2, including altered adiposity and metabolism. Stromal vascular fraction (SVF) preadipocytes and mouse embryonic fibroblasts (MEF) harvested from FPLD2 mice fail to differentiate normally into adipocytes in culture. Our data suggests that the R482Q LMNA missense mutation disrupts adipogenesis in a largely cell autonomous manner and that this may contribute to the development of lipodystrophy in affected FPLD2 patients. Currently we are using novel proteomic tools to investigate how the R482Q mutation impairs the adipogenic molecular programme. Overall we propose that the R482Q Lmna mouse provides a novel and valuable model to determine the molecular mechanisms underlying lipodystrophy in patients with this mutation. In addition it may yield valuable new insights regarding the role of the lamins and other nuclear factor(s) in the development of adipose tissue.
Dr Shigeki Sugii graduated from Kyoto University, Japan. He received his Ph.D. in Molecular and Cellular Biology at Geisel School of Medicine at Dartmouth (U.S.A.), where he studied intracellular cholesterol homeostasis and transport. He then moved to the Salk Institute for Biological Studies and Howard Hughes Medical Institute (La Jolla, California) to conduct his postdoctoral research on roles of nuclear receptors in adipocyte biology and metabolism with Professor Ronald Evans. He was a recipient of Kakiuchi Yoshinobu Memorial Award from Japanese Society for Science and Technology Studies in 2009. Since 2011, he has assumed a joint appointment as Group Leader of Fat Metabolism and Stem Cell Group at Singapore Bioimaging Consortium, A*STAR and as Assistant Professor of Cardiovascular and Metabolic Disorders Program at Duke-NUS Graduate Medical School. He also holds a position of Adjunct Assistant Professor at Lee Kong Chian School of Medicine of Nanyang Technological University in Singapore. His current research interests include the characterization and clinical application of adipose-derived stem cells.

Abstract

FAT DEPOT-SPECIFIC MOLECULAR SIGNATURES OF ADIPOSE-DERIVED STEM CELLS

It is becoming evident that subcutaneous (SC) and visceral (VS) fat depots differ in their pathophysiological contributions to metabolic homeostasis, but little is known about molecular differences between the two depots. In vitro, adipose-derived stem cells (ASCs) derived from SC fat differentiate into mature adipocytes well under standard adipogenic stimuli, whereas those from VS fat poorly differentiate. We isolated and cultured subcutaneous (abdominal region) and visceral (omental region) ASCs from human subjects. High content screening assay of over 240 human cell surface markers was performed to identify potential depot-specific cell surface markers of ASCs. Among these, CD10 was found to be SC-specific whereas CD200 was predominant for VS-ASCs. Furthermore, we found that these markers can distinguish different populations by their adipogenic capabilities; CD10hi and CD200lo ASCs differentiate into adipocytes better than CD10lo and CD200hi counterparts that are derived from SC and VS depots, respectively. Identification of such markers would allow us to differentially isolate, visualize and characterize ASCs in the depot-specific manner. I will discuss the potential of using these markers for metabolic reprogramming studies: bioimaging, screening for cellular phenotypic switch and improved adipocyte differentiation, or reprogramming into induced pluripotent stem (iPS) cells.
Dr Sun Lei

Dr Sun Lei is an Investigator in Institute of Molecular and Cell Biology and an assistant professor in the Program in Cardiovascular and Metabolic Disorders, Duke-NUS Graduate Medical School. He received a B.S degree from Beijing University in 2001 followed a Ph.D in Biochemistry from Case Western Reserve University in 2008. From 2008 to 2012, he underwent postdoctoral fellowship training in the lab of Harvey Lodish at the Whitehead Institute in Boston, MA. In 2012 he was awarded an NRF fellowship award in Singapore and joined IMCB and the faculty at Duke-NUS. His research focuses on epigenetic regulation of adipocyte development.

Abstract

REGULATION OF BROWN FAT DEVELOPMENT BY NON-CODING RNAs

Brown adipose tissue (BAT) protects against obesity by promoting energy expenditure via uncoupled respiration. To uncover BAT-specific long non-coding RNAs (lncRNAs), we used RNA-seq to reconstruct de novo transcriptomes of mouse brown, inguinal white, and epididymal white fat and identified ~1500 lncRNAs, including 127 BAT-restricted loci induced during differentiation and often targeted by key regulators PPARγ, C/EBPα and C/EBPβ. One of them, Inc-BATE1, is required for establishment and maintenance of BAT identity and thermogenic capacity. Inc-BATE1 inhibition impairs concurrent activation of brown fat and repression of white fat genes, and is partially rescued by exogenous Inc-BATE1 with mutated siRNA-targeting sites, demonstrating a function in trans. We show that Inc-BATE1 binds heterogeneous nuclear ribonucleoprotein U and that both are required for brown adipogenesis. Our work provides an annotated catalog for the study of fat depot-selective IncRNAs, available online, and establishes Inc-BATE1 as a novel regulator of BAT development and physiology.
Abstract

MOLECULAR SIGNALING AND METABOLISM

Walter Wahl, Sander Kersten

The consumption of saturated and trans fatty acids raises risk for coronary heart disease, the second most important cause of death in Singapore. In the human body, fatty acids are not only an important fuel but also influence many processes in the cell by activating gene expression. One gene that is highly sensitive to regulation by fatty acids is Angiopoietin-like 4 (Angptl4). We showed that Angptl4 functions to protect cells from lipid overload and consequent lipotoxicity. In mice lacking Angptl4, saturated fat but not unsaturated fat, induces a severe and lethal phenotype characterized by fibrinopurulent peritonitis, ascites, intestinal fibrosis, and cachexia. Thus, Angptl4 prevents macrophage activation and foam cell formation, protecting against progressive, uncontrolled saturated fat-induced inflammation. Despite major efforts by the food industry to find replacements for trans-fat, intake of trans-fat in 30% of adults in Singapore exceeds the WHO recommendation. However, little is known about the biological actions of trans fatty acids, particularly via Angptl4. We share our preliminary observations on the (patho)physiological effect of trans-fat. We are also interested to understand the role Peroxisome-Proliferator Activated Receptor (PPAR) alpha in neonatal liver during dietary change. We observed that pup-deficient in PPAR-a exhibited a transient fatty liver phenotype. We will present our preliminary findings on the possible mechanism.
Dr Adrian Teo

Adrian Teo, Ph.D., is currently a junior investigator at the Institute of Molecular and Cell Biology (IMCB), A*STAR, Singapore, an Adjunct Assistant Professor at the School of Biological Sciences, Nanyang Technological University, Singapore, and an Adjunct Assistant Professor at the Department of Biochemistry, NUS Medicine, Singapore. He obtained his B.Sc. (1st Class Honours) from the National University of Singapore in February 2007. He then started to work on human embryonic stem cells (hESCs) with Ray Dunn, Ph.D., and Alan Colman, Ph.D., at ES Cell International Pte. Ltd., before joining the Institute of Medical Biology (IMB), A*STAR, Singapore, for an internship as a Research Officer in the laboratory of Ray Dunn, Ph.D..

In April 2008, he joined the laboratory of Ludovic Vallier, Ph.D., at the University of Cambridge to pursue his Ph.D., under the A*STAR Graduate Scholarship (Overseas). Concurrently, he was also an Honorary Cambridge Commonwealth Trust Scholar. His thesis described how pluripotency factors regulate endoderm specification via key regulator EOMESODERMIN. He completed his Ph.D. in July 2010 and joined the laboratory of Ray Dunn, Ph.D., at IMB as a postdoctoral fellow before heading to the laboratory of Rohit Kulkarni, M.D. Ph.D., at Joslin Diabetes Center, Harvard Medical School (September 2011 to August 2014). During his fellowship at Joslin, he obtained two Harvard Stem Cell Institute seed grants and a Juvenile Diabetes Research Foundation (JDRF) fellowship to pursue his research interests in using human pluripotent stem cells (hPSCs) for in vitro disease modelling of diabetes.

Abstract

HUMAN INDUCED PLURIPOTENT STEM CELLS FOR UNDERSTANDING DIABETES DISEASE MECHANISMS

Diabetes is a debilitating chronic disease which is spirally out of control. In Asia, diabetes is growing at an alarming rate which could worsen work productivity and increase healthcare burden. Despite intensive research, mechanisms underlying human pancreatic beta cell failure which occurs during the course of diabetes remains elusive due to the lack of access to patient material. Presence of species-specific differences between model organisms and humans, in pancreatic development and islet architecture also partly accounts for the knowledge gap and ineffectiveness of numerous drugs in diabetes clinical trials.

The discovery of human induced pluripotent stem cells (hiPSCs) now provide a unique opportunity to potentially produce mature functional pancreatic beta cells and various cell types of interest for 1) in vitro disease modelling to study diabetes-related disease mechanisms, 2) developing small molecules that can enhance human beta cell replication and even 3) transplantation therapy. The generation of diabetic-hiPSCs which retain the genetic make-up of their initial somatic cells certainly provides an inexhaustible source of material for studying tissue formation and disease development in diabetic patients.

Here, I will highlight our efforts in recruiting various types of diabetic patients, obtaining skin biopsies and deriving hiPSCs from these skin fibroblasts. These hiPSCs are characterised by the typical expression of pluripotency markers OCT4, SOX2, NANOG, SSEA-4 and TRA-1-60, and the ability to give rise to derivatives of the three germ layers in a teratoma assay. Importantly, I will then illustrate our efforts in optimising a protocol for the directed differentiation of hiPSCs into pancreatic cells, going through the developmental stages of CXCR4+SOX17+FOXA2+ definitive endoderm, PDX1+ pancreatic progenitors and endocrine progenitors. Last but not least, I will also provide an example of subjecting these diabetic-hiPSCs through the pancreatic differentiation protocol for in vitro disease modelling of diabetes. Overall, it will be evident that disease modelling of human diabetes via the use of diabetic-hiPSCs will provide novel insights into the development of diabetes and its complications.
Dr Vinay Tergaonkar

Dr Vinay Tergaonkar obtained his Ph.D. (2001), from National Center for Biological Sciences, Bangalore, India, where he studied the molecular pathogenesis of human papillomaviruses. During his graduate studies he was awarded an international cancer society (UICC) fellowship for collaborative research at Tufts University, Boston, USA. He has been a fellow (2001-2004) and a special fellow (2004-present) of the Leukemia and Lymphoma Society of America and conducted his postdoctoral studies at the Salk Institute for Biological Studies, La Jolla, California. He joined IMCB in late 2005 as an Assistant Professor and currently is an Associate Professor (since 2010). He holds adjunct appointments at 1) Department of Biochemistry (NUS) 2) Department of Pathology (NUH) and 3) Singapore Eye Research Institute. He has been invited to speak at various international venues and meetings such as the Barossa valley meeting in Australia, Genes and Cancer meeting in UK, The Argentine Pharmacological society meeting, Japanese Cancer Society meeting and the Keystone Symposia. He serves on Editorial Boards of 1) Biochemical Journal (Portland Press) 2) Critical Reviews in Oncology/Hematology (Elsevier Press), 3) BMC Research Notes (Biomed Central) and a new journal Telomeres and Telomerase.

Abstract

NOVEL PLAYERS IN ENERGY HOMEOSTASIS AND METABOLISM

Inflammation involving the innate and adaptive immune systems is a normal response to infection. However, it is now known that when allowed to continue unchecked, chronic inflammation is a key underlying cause for the development of autoimmune disorders, neurodegenerative diseases, metabolic syndromes such as diabetes and cancer. Our lab studies a transcription factor called NFkB which is a master regulator of inflammation. Indeed deregulated activity of NFkB precedes and is causally linked to chronic inflammation and the development of several human ailments including metabolic syndromes and cancers. I will describe our current understanding of the pathway and our efforts to identify novel players in energy homeostasis and metabolism. Understanding the mechanism of action of these targets will help develop drugs for human ailments ranging for metabolic syndromes to cancer.
Professor Matthew Watt

Professor Matthew Watt is a Senior Research Fellow of the National Health and Medical Research Council of Australia and heads the Biology of Lipid Metabolism laboratory located within the Department of Physiology at Monash University.

His group studies the molecular and cellular regulation of lipid metabolism in fat, muscle, liver and the brain and how defects in lipid metabolism cause insulin resistance, a major feature of obesity and precursor to type 2 diabetes. More recently, Professor Watt’s team has studied the endocrine role of adipose tissue and the liver—specifically; they are using “omics” technology to discover novel proteins and lipids that are secreted by these tissues and how this influences metabolism in obesity.

Abstract

Matthew J. Watt, Ruth C.R. Meex

Obesity is a risk factor for the development of secondary complications including dyslipidemia, non-alcoholic fatty liver disease, cardiovascular disease and type 2 diabetes. An accumulation of lipid in the liver, which is clinically known as hepatic steatosis, is a pathologic abnormality that is common in obese and type 2 diabetes patients. Hepatic steatosis occurs when fatty acid supply outweighs fatty acid demand and occurs in a time-course that usually precedes the induction insulin resistance and type 2 diabetes. We hypothesised that the protein and lipid secretome is altered with the development of hepatic steatosis and that this altered secretome contributes to the development of insulin resistance. In this presentation, we describe how ‘omics’ approaches are used to delineate the hepatocyte protein and lipid secretome in health and obesity. Further, we report on the pre-clinical validation of several liver secreted factors that cause insulin resistance and disturbances in systemic metabolic homeostasis.
Professor Jon Whitehead undertook undergraduate and postgraduate training at the University of Liverpool (UK) before moving to the University of Cambridge (UK) where he began work in the area of insulin signalling, insulin resistance and obesity with Prof Steve O’Rahilly. In 1999 he secured an International Travelling Fellowship from the Wellcome Trust, enabling him to relocate to the Institute for Molecular Bioscience at The University of Queensland (UQ) and then the Diabetes & Obesity Research Program at the Garvan Institute of Medical Research in Sydney.

In 2002 he returned to UQ to take up an independent position as a Lions Senior Medical Research Fellow, then NHMRC Senior Research Fellow. He currently heads the Metabolic Medicine Team within the Mater Research Institute – UQ (MRI-UQ), situated on the Princess Alexandra Hospital Campus in the Translational Research Institute (TRI). The overall aim of the Team's research is to identify novel strategies to improve cardiometabolic health using in vitro and in vivo (pre-clinical and clinical) systems and approaches that employ a range of techniques involving molecular and cellular biology combined with biochemistry and ‘omics’ technology to define molecular mechanisms that contribute to cardiometabolic health. Jon regularly serves on NHMRC GRP and is a council member of the Australia and New Zealand Obesity Society (ANZOS).

**Abstract**

**MANIPULATING FABULOUS ADIPOSE TISSUE (FAT) TO REDUCE THE NEGATIVE IMPACT OF OBESITY**

The World Health Organisation recognises obesity as one of the greatest global health problems of the 21st century. Being overweight or obese increases the risk of developing chronic “obesity-related” diseases that include cardiovascular disease, type 2 diabetes and hypertension as well as most cancers. The underlying reasons for these associations are intrinsically linked to the adipocyte. We now know that adipocytes serve as energy stores and dynamic endocrine cells that secrete a plethora of hormones into our bloodstream in a regulated fashion. These adipocyte-derived hormones, or adipokines, coordinate most aspects of our physiology, from behaviour to fertility. In the lean state, small ‘healthy’ adipocytes secrete a cocktail of hormones that help prevent the development of diseases such as type 2 diabetes and hypertension. However, in most obese individuals, adipocytes become enlarged and ‘angry’ causing them to secrete an inflammatory mixture of hormones that promote disease. We are pursuing complementary approaches to ameliorate or prevent this. First, we are identifying ways to prevent adipocyte hypertrophy by defining the processes that govern the generation of new healthy adipocytes, with a view to modulating these processes in people. Second, we are establishing ways to increase the production and or sensitivity of a key hormone, adiponectin, secreted by adipocytes. Adiponectin is a beneficial hormone and paradoxically, although produced by adipocytes, its production goes down in obesity and related diseases. Evidence suggests that reversing the decline in adiponectin will prevent many obesity related complications. In complementary studies we are characterising the molecular details of the adiponectin receptors, which are atypical 7 transmembrane-domain receptors, to identify ways to enhance adiponectin sensitivity. We envisage that these novel approaches will also promote weight loss due to improved metabolism and view them as potential adjuncts to lifestyle education and intervention approaches to combat this 21st century pandemic.
Professor Gary Wittert

Professor Gary Wittert obtained his medical degree from the University of the Witwatersrand in Johannesburg South Africa. He trained as an endocrinologist in Christchurch New Zealand and subsequently received postdoctoral training at Harvard Medical School and Oregon Health Sciences University. He joined the University of Adelaide in 1994, received a Personal Chair in 2004 and is currently Head of the Discipline of Medicine, and Senior Consultant Endocrinologist Royal Adelaide Hospital. He is Director of the Freemasons Foundation Centre for Men’s Health Research, and a founding member of the Centre of Research Excellence in Nutritional Physiology. He Heads the Centre for Nutrition and Gastrointestinal Diseases within the Nutrition Theme at the South Australian Institute for Health and Medical Research.

His research, focused on obesity, involves basic, clinical and population health approaches. He initiated and oversees the Florey Adelaide Male Ageing Study (FAMAS), the Male, Adelaide, Inflammation, Lifestyle and Stress (MAILES) Study, and leads a large multi-center diabetes prevention trial in men (T4DM). His basic research is currently focused on peripheral mechanisms of appetite regulation and intermediary metabolism. Among other appointments Professor Wittert is currently Independent Chair of the Weight Management Council of Australia, and founding Editor in Chief of Obesity Research and Clinical Practice. He has authored over 260 peer reviewed journal articles and book chapters, and is currently funded by the NH&MRC and ARC.

Abstract

THE STOMACH AS A TARGET FOR OBESITY MANAGEMENT

Gary Wittert, Stephen Kentish, Amanda Page

Centre for Nutrition and Gastrointestinal diseases, School of Medicine University of Adelaide and South Australian Health and Medical Research Institute.

The stomach plays an important role in appetite regulation. It is targeted in bariatric surgery and gastric electrical stimulation to treat obesity. An evolving understanding of how the stomach participates in mediating sensations of hunger or satiety, and responds to stimuli (nutrient or distension) is offering peripheral targets for novel pharmacological approaches to the management of obesity.

The cell bodies of gastric vagal afferents express clock genes and gastric vagal mechanosensitivity varies in a circadian manner even in the absence of light and food cues suggesting a gastric component to diurnal regulation of food intake.

Gastric endocrine cells synthesise and secrete leptin and vagal afferent neurones express leptin receptor mRNA. We have established that in mice fed a standard laboratory diet (SLD) leptin increases the mechanosensitivity of gastric mucosal vagal afferents thereby increasing satiety. By contrast in mice with high fat diet (HFD)-induced obesity leptin has no effect on gastric mucosal receptor mechanosensitivity but inhibits gastric vagal afferent tension receptors, an effect that persists after resumption of SLD for 12 weeks. Our further studies have shown that the excitatory effect of leptin on gastric vagal afferents is mediated by phospholipase C (PLC)-dependent activation of transient receptor potential channel 1 (TRPC1) while the inhibitory effect is mediated through phosphatidylinositol 3-kinases (PI3K)-dependent activation of large-conductance, calcium-activated potassium (BKCa) channels.

Ghrelin decreases the sensitivity of tension but not mucosal receptors in normal SLD fed mice. After caloric restriction or following HFD-induced obesity, ghrelin inhibits mucosal receptors, and enhances the inhibition of mechanosensitive tension receptors.
Neuropeptide W (NPW) immunoreactive cells are found in close proximity to traced vagal afferent endings and NPW inhibits responses of gastric vagal tension receptors to stretch in SLD but not HFD or fasted mice.

There is a dynamic inter-regulation between these appetite regulatory peptides and receptors that is disrupted by HFD-induced obesity.

Our data also suggest a role for NADPH oxidase 2 (NOX2) and nitric oxide in the regulation of gastric vagal mucosal and tension receptor mechanosensitivity in fed and fasted states. We are testing the novel hypothesis that NOX induced generation of reactive oxygen species (ROS) may mediate the HFD-obesity induced changes in the regulation of vagal afferent activity, either directly or by altering the effects of gastric appetite regulating peptides.
Dr Xu Feng

Dr. Feng Xu has been a principal investigator at Singapore Institute for Clinical Sciences, A-STAR since 2009. He also holds an adjunct assistant professor position in the Department of Biochemistry, NUS. Prior to his independent position in Singapore, Dr. Xu worked with Dr. Michael Grunstein as a chromatin biologist at UCLA. His current research interest centers on the epigenetic regulation of adipogenesis. His work has been published in Cell, Molecular Cell and Cell Metabolism.

Abstract

EPIGENETIC REGULATION OF ADIPOGENESIS

Reinhard Brunmeir, Sofi Julien, Xu Peng, Qiongyi Zhang, Muhammad Khairul Ramlee, Muhammad Idris, Joanna Sinnakannu, Wei Xie, Weiping Han

The global epidemic of obesity and diabetes has economically and socially burdened many countries worldwide. As such, understanding the molecular mechanism that controls fat cell differentiation would greatly enhance our ability to solve these problems. Epigenetic mechanisms play essential roles in modulating adipogenesis. Our studies revealed that epigenetic analysis could be used to identify novel cis-elements for adipogenic gene regulation and trans-factors necessary for adipogenesis.