DUKE / DUKE-NUS

GASTRONAUTS SINGAPORE

A GLOBAL SYMPOSIUM ON GUT-BRAIN MATTERS

3 - 4 MAY 2018

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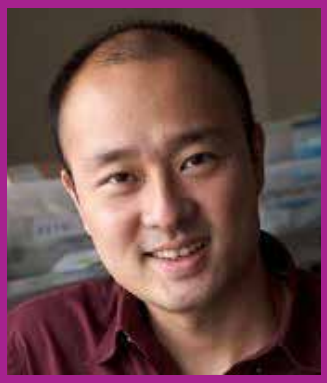
MESSAGE FROM CO-CHAIRS

Diego Bohórquez
Assistant Professor of Medicine and Neurobiology
Duke University



Xiling Shen
Associate Professor
Department of Biomedical Engineering
Duke University

Paul M Yen
Professor
Cardiovascular and Metabolic Disorders Programme
Duke-NUS Medical School

Dear Gastronauts,

On behalf of the organising committee, we are thrilled to welcome you to Singapore: A place known for its cultural tapestry and where people from around the globe come to imagine new possibilities. That's why we are here - to imagine the future of gut-brain biology. Between 3rd May and 4th May, numerous ideas will be born, connections will be made, and change will emerge. Food, microbes, and the gut are the ingredients that contain some of the healing secrets to the brain. And, all of us are here to move this field forward in a one-of-a-kind corner of the world.

Thank you for being a part of Gastronauts - a global network of knowledge entrepreneurs unveiling the secrets of gut-brain biology.

Special thanks to the Office of Naval Research Global, Duke University and Duke-NUS Medical School for their generous support of this symposium.

THURSDAY, 3RD MAY 2018

Symposium HIGHLIGHTS

08:15am-08:30am Opening Remarks
ANDREW MUIR
Duke University

SESSION ONE | MICROBES THAT MATTER

08:30am-10:30am ***Chair:*** DIEGO BOHÓRQUEZ

RAPHAEL H. VALDIVIA, Duke University

JONATHAN KOTULA, Caribou Biosciences

XIUQIN ZHANG, Peking University

MATTHEW CHANG, National University of Singapore

10:30am-11:00am Coffee Break
Refuel and expand your thinking with speakers

SESSION TWO | NUTRIENTS AND METABOLISM

11:00am-12:30pm ***Chair:*** IRENE MIGUEL-ALIAGA

FEIFAN GUO, Shanghai Institute for Biological Sciences

WALTER WAHLI, Nanyang Technological University

PAUL M YEN, Duke-NUS Medical School

GREG S. B. SUH, New York University

12:30pm-02:00pm Lunch Break
Refuel and expand your thinking with speakers

DISCUSSION | FUNDING FUTURE GUT BRAIN RESEARCH

02:00pm-03:00pm ***Chair:*** PAE WU
IAIN DICKSON
JERMONT CHEN
JUSTIN GALLIVAN
ROBERT KOKOSKA
How to think from the perspective of a funding officer

THURSDAY, 3RD MAY 2018

Symposium HIGHLIGHTS

03:00pm-03:30pm Tea Break

Refuel and expand your thinking with speakers

SESSION THREE | THE SECOND BRAIN

03:30pm-05:30pm ***Chair:*** XILING SHEN

JOHN FURNESS, University of Melbourne

ARTHUR BEYDER, Mayo Clinic

NICHOLAS SPENCER, Flinders University

SVEN PETTERSSON, Nanyang Technological University

05:30pm-06:30pm Wine & Cheese

Poster Sessions

Brew your next big idea with your new collaborators

FRIDAY, 4TH MAY 2018

Symposium HIGHLIGHTS

SESSION FOUR | ENGINEERING THE GUT

08:30am-10:30am ***Chair:*** RAPHAEL H. VALDIVIA

NICK BARKER, Singapore A*STAR Insititute of Medical Biology

XILING SHEN, Duke University

HYUNSOO SHAWN JE, Duke-NUS Medical School

MAXIME M. MAHE, University of Nantes

10:30am-11:00am Coffee Break

Refuel and expand your thinking with speakers

SESSION FIVE | NEUROENGINEERING

11:00am-12:30pm ***Chair:*** NICHOLAS SPENCER

LAWRENCE CARIN, Duke University

JOHN DOYLE, California Institute of Technology

WARREN GRILL, Duke University

12:30pm-01:30pm Lunch Break

Explore Singapore's gastronomy with your new colleagues

SESSION SIX | GUT, BRAIN, AND DISEASE

01:30pm-03:00pm ***Chair:*** ARTHUR BEYDER

KARL HERRUP, Hong Kong University of Science and Technology

DAVID L. SILVER, Duke-NUS Medical School

RODGER LIDDLE, Duke University

FRIDAY, 4TH MAY 2018

Symposium HIGHLIGHTS

03:00pm-03:30pm **Tea Break**

Refuel and expand your thinking with speakers

SESSION SEVEN | THE NEUROBIOLOGY OF GUT FEELINGS

03:30pm-05:30pm ***Chair:*** JOHN FURNESS

DIEGO BOHÓRQUEZ, Duke University

LUIS R. SARAIVA, Sidra Medicine, Qatar

IRENE MIGUEL-ALIAGA, Imperial College London

IVAN DE ARAUJO, Yale University

05:30pm-06:00pm **Closing Remarks**

THOMAS COFFMAN
Duke-NUS Medical School

SESSION ONE • MICROBES THAT MATTER

Session Chair:

DIEGO BOHÓRQUEZ
Assistant Professor of Medicine and Neurobiology
Duke University

Speaker 1.1

RAPHAEL H. VALDIVIA
Professor of Molecular Genetics and Microbiology

Vice Dean for Basic Science
Duke School of Medicine

Speaker 1.2

JONATHAN KOTULA
Senior Scientist

Microbial Engineering Group Leader
Caribou Biosciences

Speaker 1.3

XIUQIN ZHANG
Principal Investigator

Director of Pathology Core
Institute of Molecular Medicine
Peking University

Speaker 1.4

MATTHEW CHANG
Associate Professor

Director

NUS Synthetic Biology for Clinical and Technological Innovation

National University of Singapore

SESSION ONE

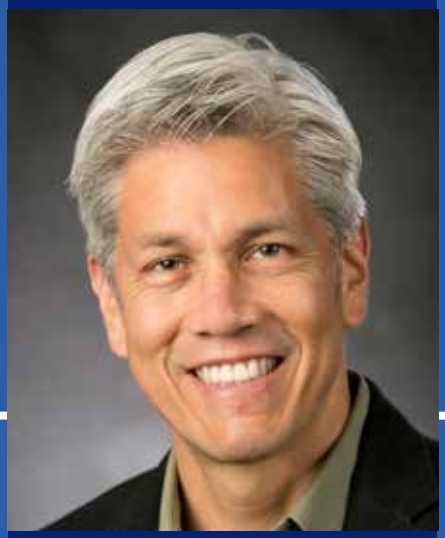
CHAIR:

DIEGO BOHÓRQUEZ

Assistant Professor of Medicine and Neurobiology

Duke University

Dr. Bohórquez is an Assistant Professor of Medicine at Duke University. His expertise is in gut-brain sensory neural circuits. Dr. Bohórquez's training is unique from a scientific and an academic perspective. He has a Ph.D. in Nutrition and Gastrointestinal Physiology, and postdoctoral training in the Neurosciences. Dr. Bohórquez's research focuses on how sensory stimuli from food and bacteria in the gut are transduced to the brain via vagus nerve. This is the neural circuitry basis for gut stimuli to modulate brain function and behaviour. It is also an area of research at the core of treating behavioural disorders such as obesity, anorexia, or autism. Dr. Bohórquez is known for his discovery of a sensory neuroepithelial circuit in the gut-analogous to that transducing the sense of taste in the tongue (J Clin Invest. 2015;125(2):782). His work has been featured in Nature, NeuroPod, ScienceDaily, Wired magazine, TED ideas blog and The New Yorker.



RAPHAEL H. VALDIVIA

Professor of Molecular Genetics and Microbiology

Vice Dean for Basic Science
Duke School of Medicine

Bacterial genetics in the age of the microbiome

BIOGRAPHY

Raphael Valdivia, obtained his PhD in microbial pathogenesis with Stanley Falkow at Stanford University in 1997. Dr. Valdivia became a Damon Runyon Cancer Research Fellow in the laboratory of Randy Schekman at the University of California, Berkeley to study endosome dynamics and biogenesis. He joined the faculty at Duke University in 2002 and developed new methods and technologies to tackle understudied microbial pathogens and symbionts. Dr. Valdivia earned national recognition as a Pew Scholar in the Biomedical Sciences and a Burroughs Wellcome Fund Investigator in the Pathogenesis of Infectious Diseases. Dr. Valdivia serves as an editor in multiple journals, NIH review panels, and is an elected Fellow of the American Association for the Advancement of Science and American Academy of Microbiology. Dr. Valdivia is the founding Director of what is now the Duke Microbiome Center and is the Vice for Basic Science at the Duke School of Medicine.

ABSTRACT

There's a growing appreciation that the complex microbial communities that associate with the human body contribute significantly to the metabolic and immunological health of their hosts. Recent advances in the study of the ecology of these microbial communities have identified key bacterial phyla and even species whose presence is causally associated with dysbiotic disease states or have beneficial effects. Unfortunately, little is known as to the molecular basis of how these microbes contribute to health and disease either because they can't be grown in isolation or few tools exist for their genetic manipulation. In this presentation, I will provide two examples of genetic approaches to characterise novel microbes that have emerged as important contributors to vertebrate health and the new lessons we have learned about mechanisms of host colonisation and the use of host-derived glycans. The methods are of broad applicability and can be used to target a range of non conventional microbes.

JONATHAN KOTULA

Senior Scientist

Microbial Engineering Group Leader
Caribou Biosciences

Synthetic Biology and the tools for engineering the gut microbiota

BIOGRAPHY

Jonathan is an entrepreneurial scientist with 15 years experience performing translational molecular biology research in the fields of synthetic biology, bacterial engineering, microbiome studies, and cancer biology. He currently leads the microbial engineering team at Caribou Biosciences with the goal of using CRISPR-based tools to simplify the process of working with diverse bacterial species. Previously he led the R&D efforts that developed the first engineered microbe tested in human clinical trials. He has been the co-founder of a medical device company, a non-profit organization, and is the inventor on several patents. He earned a PhD in molecular genetics and microbiology at Duke University, and completed a postdoc at Harvard Medical School.

ABSTRACT

Synthetic Biology and the tools for engineering the gut microbiota.

XIUQIN ZHANG

Principal Investigator

Director of Pathology Core
Institute of Molecular Medicine
Peking University

Deficiency of PRKD2 Triggers Hyperinsu-linemia and Metabolic Disorders

BIOGRAPHY

2002, Ph.D., Medical Science, Kumamoto University Medical School, Japan; 1995, M.S., Clinical Pathology, China Medical University, Shenyang; 1995-1996, resident, Department of Pathology, China Academy of Medical Science, Fuwai Hospital, Beijing; 1996-1997, Research fellow, Department of Tumor Biology, Kumamoto University Medical School, Japan;. 1997-1998, stuff scientist, Department of Cell Differentiation, Kumamoto University Medical School, Japan; 2002-2006 Research Associate, Department of Molecular Biology and Pharmacology, Washington University School of Medicine, USA; 2006,3-2013.8, Associate Investigator; 2013.9-present, Principle Investigator, Institute of Molecular Medicine, Peking University.

Research Interests: Mechanistic study of cardiovascular disease and metabolic syndrome; Pre-clinical study of novel drugs using nonhuman primate models; Intestine in metabolic diseases pathogenesis.

ABSTRACT

Hyperinsulinemia is the earliest symptom of insulin resistance (IR), but a causal relationship between hyperinsulinemia and IR remains to be established. Using extreme phenotype sampling and deep sequencing analysis, we identified a protein kinase D2 (PRKD2) nonsense mutation (K410X) in two rhesus monkeys with extreme hyperinsulinemia along with IR and metabolic defects. This mutation reduces PRKD2 at both the mRNA and the protein levels. Taking advantage of a PRKD2-KO mouse model, we demonstrated that PRKD2 deletion triggers hyperinsulinemia which precedes to IR and metabolic disorders in the PRKD2 ablation mice. Mechanistically, PRKD2 deficiency promotes ß-cell insulin secretion by increasing the expression and activity of L-type Ca2+ channels and subsequently augmenting high glucose- and membrane depolarization-induced Ca2+ influx. Altogether, these results indicate that downregulation of PRKD2 is essentially involved in the pathogenesis of hyperinsulinemia which, in turn, results in IR and metabolic disorders.

MATTHEW CHANG

Associate Professor

Director

NUS Synthetic Biology for Clinical and Technological Innovation

National University of Singapore

Engineering microbes to rewire host-microbiome interactions

BIOGRAPHY

Matthew Chang's research interests lie in the development of biological systems that perform programmable functions. His scientific contributions have been recognized with international honours and awards, including the Scientific and Technological Achievement Award from U.S. Environmental Protection Agency, and featured in leading media outlets worldwide. He serves as an editor and an editorial board member for a number of journals including Cell Systems, ACS Synthetic Biology, Biotechnology for Biofuels, Metabolic Engineering, and Critical Reviews in Microbiology. He serves on the advisory committee of key international research programs such as the Synthetic Biology Open Language (SBOL), EU's Future and Emerging Technologies and CSIRO Future Science Platform. He leads the Singapore Consortium for Synthetic Biology (SINERGY) of the National Research Foundation. http://SynCTI.org/

ABSTRACT

Advances in sequencing technologies have greatly increased our knowledge of the composition of the human intestinal microbiota and its importance in health and disease. Various omics and molecular studies have also revealed further insights in host-microbiome interactions at the cellular and molecular level. In order to leverage the close associations between microbes and their host, the development of therapeutics targeting the microbiota has surged in recent years. Many advanced microbiota-targeting intervention strategies are being explored, ranging from the selection of novel probiotic strains and synthetic stool substitutes to maintaining the dynamics of metabolism by prebiotics and dietary interventions. Applying engineering biology to reprogramme gut-resident microbes provides new avenues to investigate microbe-host interactions, perform diagnostics and deliver therapeutics. Herein, we present our work in exploiting commensal microbes to develop therapeutic microbes with programmable functionalities to prevent pathogenesis of various diseases. In particular, we have established and tested in vivo a combination of clinically relevant functionalities to effectively exert specific activities against opportunistic pathogens and chronic metabolic diseases such as cancer. This work provides a strong foundation for the use of engineered functional microbes that modulate microbiota-host metabolism and interactions as a viable clinical intervention.

SESSION TWO

NUTRIENTS AND METABOLISM

Session Chair:

IRENE MIGUEL-ALIAGA
Professor

Genetics and Physiology
Imperial College London

Section Chair
MRC London Institute of Medical Sciences

Speaker 2.1

FEIFAN GUO
Professor

Programme Director of the Key Lab of Nutrition Metabolism and Food safety

Shanghai Institutes for Biological Sciences, CAS

Speaker 2.2

WALTER WAHLI
Professor

Metabolic Disease
Lee Kong Chian School of Medicine
Nanyang Technological University, Singapore

Speaker 2.3

PAUL M YEN
Professor

Cardiovascular and Metabolic Disorders Programme
Duke-NUS Medical School

Speaker 2.4

GREG S. B. SUH
Associate Professor

Department of Cell Biology
NYU School of Medicine
New York University

SESSION TWO

CHAIR:

IRENE MIGUEL-ALIAGA

Professor

Genetics and Physiology
Imperial College London

Section Chair
MRC London Institute of Medical Sciences

Irene obtained her DPhil in Genetics from the University of Oxford, and explored how neurons acquire their identity during postdoctoral work at Harvard, Linkoping University and NIMR (now Crick Institute), London. First at Cambridge and now in London, her research group is investigating the plasticity of internal organs, with a major focus on the gastrointestinal tract and its neurons. She was elected to the EMBO YIP programme in 2012 and became a full EMBO member in 2017. She is the recipient of an ERC Starting Grant and she has recently been awarded an ERC Advanced Grant.

FEIFAN GUO

Professor

Programme Director of the Key Lab of Nutrition Metabolism and Food safety

Shanghai Institutes for Biological Sciences, CAS

Amino acid regulation of metabolism

BIOGRAPHY

Dr. Guo works as a Professor and Principal Investigator of Shanghai Institute for Biological Sciences (Sibs), Chinese Academy of Science (CAS). She is also a director of the Key Lab of Nutrition, metabolism and food safety of CAS. Dr. Guo obtained her Ph.D. in Neuroscience from the University of Tokyo in 2001. After that, she did postdoc training at Department of Psychiatry, University of Minnesota (2001 - 2002), and Division of Endocrinology, Beth Israel Deaconess Medical Center at Harvard Medical School (2002 - 2005). She worked as a Research Assistant Professor at Department of Biology, the Pennsylvania State University before joining Institute for Nutritional Sciences, Sibs, CAS in September 2007. Dr. Guo's research interest focuses on investigating molecular mechanisms underlying the development of metabolic diseases including obesity, diabetes and fatty liver, particularly in the role of amino acid in metabolic diseases.

ABSTRACT

A disorder in nutrient sensing and metabolism regulation is one of the most important reasons leading to the development of metabolic diseases. Recently, increasing evidence has indicated a role for amino acid in insulin sensitivity and lipid metabolism, however, underlying mechanisms are poorly understood. Her lab has focused on studying molecular mechanisms underlying amino acid sensing and metabolism regulation, by using animal and cell culture models maintained on a diet or medium deficient for an essential amino acid leucine, respectively. For the past few years, her work has demonstrated that leucine deprivation rapidly decreases fat loss via stimulating lipolysis in white adipose tissue and thermogenesis in brown adipose tissue, which is controlled by the hypothalamus and found that leucine deprivation also increases insulin sensitivity, which is mediated by mTOR and AMPK signaling pathways as well as demonstrated novel functions for several amino acid sensing proteins in the regulation of lipid metabolism and insulin sensitivity. She continues to investigate signaling pathways involved amino acid sensing and metabolism regulation in animal and humans.

WALTER WAHLI

Professor

Metabolic Disease

Lee Kong Chian School of Medicine
Nanyang Technological University, Singapore

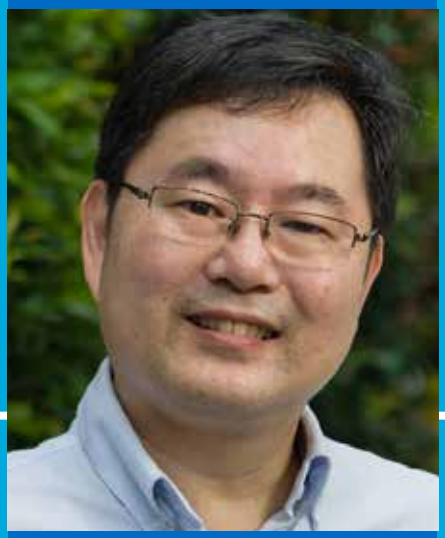
Nuclear receptors integrate microbiome-derived signals in the liver

BIOGRAPHY

Walter Wahli received his PhD in 1977 from the University of Bern. He was a postdoc at the Carnegie Institution of Washington in Baltimore, and a visiting associate at the National Cancer Institute, NIH, Bethesda. He became Professor and Director of the Institute of Animal Biology of the University of Lausanne in 1980, and was Vice-rector for Research and Continuing Education. He founded the Center for Integrative Genomics, which he directed until 2005. He is currently in Lee Kong Chian School of Medicine, NTU in Singapore and the President of the Nestlé Foundation for the Study of Problems of Nutrition in the World. He is an elected member of the EMBO and the Swiss National Academy of Medical Sciences. Walter Wahli is recognized for his contributions to the area of energy metabolism. He is the co-discoverer of the transcription factors PPARs. He has provided insights into their functions, which advanced our understanding of the molecular signalling of lipids in biological processes.

ABSTRACT

The liver is a key organ of metabolic homeostasis with functions that oscillate in response to food intake. The microbiome-mediated effects on peripheral circadian clocks and their output genes are not well known. Our results indicate that the microbiome is required for integration of liver clock oscillations that tune output activators and their effectors, thereby regulating metabolic gene expression for optimal liver function. In germ free mice, liver gene expression networks regulated by nuclear receptors including PPARα are profoundly changed. Morever, at the systemic level, daily changes in the abundance of biomarkers, such as FGF21, depend on the microbiome. FGF21 is a hepatokine with beneficial metabolic effects, including control of sucrose preference. We demonstrated that Fgf21 is a unique hepatic gene inducible by both fasting and glucose signals and that the transcription factors PPARα and ChREBP both regulate the endocrine control of sugar intake by hepatic FGF21.



PAUL M YEN

Professor

Cardiovascular and Metabolic Disorders Programme
Duke-NUS Medical School

Hormonal regulation of autophagy

BIOGRAPHY

Dr. Yen currently is Professor at Duke-NUS Medical School in Singapore and Duke University School of Medicine in Durham, NC. He obtained his M.D. from Johns Hopkins, completed residency in internal medicine at University of Chicago and fellowship in endocrinology at NIH. He was formerly Assistant Professor at Harvard Medical School, Chief of the Neuro-endocrinology and Molecular Regulation Section of the Clinical Endocrinology Branch at NIDDK (National Institutes of Health, Bethesda, MD), and Associate Professor of Medicine and Pharmacology at Johns Hopkins University School of Medicine. He has served on the editorial boards of Endocrinology, Molecular Endocrinology, and Thyroid. He also is a U.S. board-certified physician in internal medicine and endocrinology. He is a member of the Asia Oceanic Thyroid Association Advisory Council, a delegate to the World Thyroid Foundation. and Singapore Representative to the Global Thyroid Network.

ABSTRACT

Thyroid hormone (TH) has long been known to stimulate mitochondrial function, but its role in mitochondrial turnover remains unclear. Mitochondria play an essential role in oxidative phosphorylation and fatty acid oxidation. We previously showed that TH played important roles in these processes via autophagy of lipids and mitochondria in hepatic cells (lipophagy and mitophagy, respectively) Additionally, we showed that T3 is a potent inducer of mitochondrial biosynthesis and utilizes activation of another nuclear hormone receptor ERRa to mediate many of its mitochondrial actions. Our results describe a novel co-ordinated mechanism of TH-induced mitochondrial turnover through mitophagy and mitochondrial biogenesis. This co-ordinated turnover, which is dependent upon ROS generation and the induction of PGC1a, enables TH to maintain oxidative phosphorylation and fatty acid β-oxidation induced by TH. We performed a pilot clinical study that showed TH supplementation was able to decrease hepatosteatosis in diabetic patients after 4 months therapy. We also have examined TH induction of autophagy in many tissues, including the heart, and it is likely to play a key role of metabolism, fuel switching, and cellular differentiation. It is possible that TH and other autophagy-inducing drugs may have beneficial metabolic effects by stimulating mitophagy and mitochondrial biogenesis.

GREG S. B. SUH

Associate Professor

Skirball Institute of Biomolecular Medicine
Neuroscience Institute, Department of Cell Biology

NYU School of Medicine
New York University

Feeding, Nutrient Sensing in Flies and Mice

BIOGRAPHY

Dr. Suh was born in Busan, South Korea. He grew up in Busan and Seoul, and had spent formative years in Hawaii taking summer schools and playing in junior tennis circuits. These were possible because his family had a place in Honolulu, right next to an apartment building where Barak Obama grew up. Dr. Suh went to UC Berkeley for college where he worked for Dr. Hiroshi Nikaido to understand the antibiotic resistance mechanism in bacteria. In a graduate school at UCLA, Dr. Suh switched the field and started working on the genetic basis of neuronal connectivity in Drosophila under the guidance of Dr. Larry Zipursky. He changed the field again during his postdoctoral fellowship to study innate behaviours and neural circuits in the laboratories of David Anderson and Seymour Benzer at Caltech. In 2008, Dr. Suh moved to New York and started his independent career at Skirball Institute and NYU School of Medicine.

ABSTRACT

Sugars in the natural environment can be detected through taste-dependent and taste-independent modalities. Taste-dependent modalities consist mainly of peripheral chemosensory neurons such as sweet taste receptors, which primarily detect the orosensory value of sugar (i.e. sweetness). Evidence of a taste-independent modality - a post-ingestive sugar sensor - that detects the nutritional value of sugar has been shown in insects and mammals. However, the identity of the post-ingestive sugar sensor and the mechanism by which animals respond to the nutritional content of sugar independently of orosensory value is unknown. My laboratory identified six neurosecretory cells in the Drosophila brain that produce Diuretic hormone 44 (Dh44), a homologue of the mammalian CRH, were activated by nutritive sugars and not by nonnutritive sugars. Flies in which the activity of these neurons or the expression of the Dh44 gene was disrupted failed to select nutritive sugars over nonnutritive ones after periods of starvation. Notably, artificial activation of Dh44 receptor-1 neurons dramatically increased the rate of proboscis extension reflex (PER) responses, promoting food intake. This manipulation also resulted in frequent episodes of gut contraction and excretion. Given its strong sequence homology, CRH and CRH expressing neurons in the hypothalamus would offer similar functions in mammals. I will discuss the findings from our recent studies with mice.

DISCUSSION

Chair:

PAE WU
Science Director
Office of Naval Research Global

IAIN DICKSON
Senior Editor
Nature Reviews Gastroenterology & Hepatology
Nature Research

JERMONT CHEN
International Programme Officer
Air Force Office of Scientific Research

JUSTIN GALLIVAN
Programme Manager
DARPA BTO

ROBERT KOKOSKA
US Army Research Office Programme Manager
US Army Research Laboratory, Microbiology

SESSION THREE • THE SECOND BRAIN

Session Chair:

XILING SHEN
Associate Professor

Department of Biomedical Engineering
Duke University

Speaker 3.1

JOHN FURNESS
Professor

Head of Digestive Physiology and Nutrition Laboratories
Florey Institute and University of Melbourne

Speaker 3.2

ARTHUR BEYDER
Consultant, Gastroenterology & Hepatology

Assistant Professor, Medicine and Physiology & Biomedical Engineering

Mayo Clinic

Speaker 3.3

NICHOLAS SPENCER
Professor

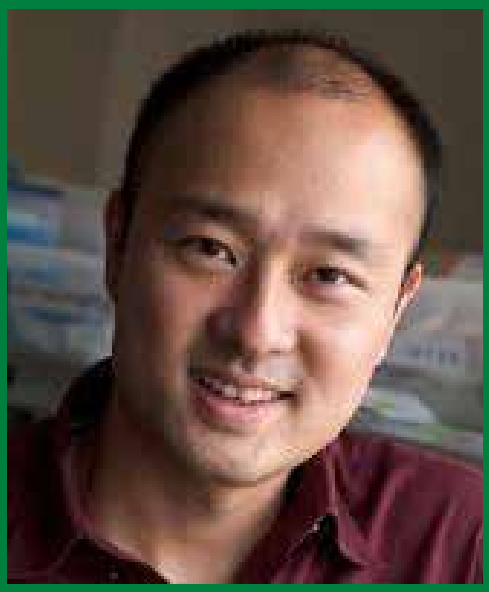
Flinders University

Speaker 3.4

SVEN PETTERSSON
Professor
Lee Kong Chian School of Medicine
Nanyang Technological University

SESSION THREE

CHAIR:



XILING SHEN

Associate Professor

Department of Biomedical Engineering

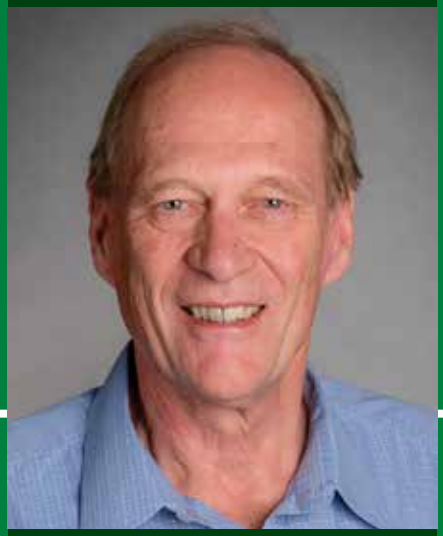
Duke University

Dr. Shen received his BS, MS, and PhD degrees from Stanford University. He was an assistant professor at Cornell University from 2009 to 2015 and won the NSF career award before joining the Biomedical Engineering Department and Center for Genomics and Computational Biology at Duke University as an associate professor. The Shen lab studies cancer, stem cells, and the nervous system in the gut. Ongoing projects include metastasis-induced metabolic and epigenetic reprogramming, normal and cancer stem cells, non-coding RNA, in vivo imaging, and peripheral neuromodulation.

JOHN FURNESS

Professor

Head of Digestive Physiology and Nutrition Laboratories
Florey Institute and University of Melbourne



Evolving concepts of enteric hormone storage and enteroendocrine cell (EEC) classification

BIOGRAPHY

John Furness leads the Digestive Physiology and Nutrition Laboratories at the Florey Institute of Neuroscience and Mental Health and the University of Melbourne.

His laboratory has worked for many years on the physiology of digestion, particularly its neuronal and endocrine control. The current emphasis of his work is:

- The relationships between diet, environment and gut health, and their implications for animal production and for human well-being.
- Anti-inflammatory nerve stimulation for the treatment of inflammatory bowel disease.
- The gastrointestinal manifestations of Parkinson's Disease.
- The cell biology of enteroendocrine cells.
- Identification of targets and development of drugs for the treatment of gastrointestinal motility disorders.
- The roles of ghrelin and its receptors and the exploration of ghrelin receptor ligands as therapeutic tools.

ABSTRACT

The first gut hormones were discovered >100 years ago and now 20-30 are recognised; about 14 can be termed major hormones. Conventional classification places each peptide hormone in a single cell, designated by a letter code, except for the L cell, that contains GLP-1 and PYY. A specific cell, the enterochromaffin cell, was concluded to contain only the amine hormone, 5-HT. This concept is rapidly becoming obsolete. Transcripts for multiple hormones have been found in single EEC. Localisation studies at a cellular and subcellular level in human, mouse, pig and rat also reveals hormone co-expression. At a cell level, for all EEC hormones colocalization with other hormones occurs. At a sub-cellular level, super-resolution microscopy reveals that many hormones combinations found in the same cell are contained in separate storage vesicles. This includes 5-HT and secretin being in separate storage vesicles, and GLP-1 and PYY are also separately stored. At the subcellular level the numbers of some vesicle types can be so low that a cell may not be recognised to contain two hormones by conventional microscopy.

Recent studies also reveal substantial differences between species. In pig, PYY, in combination with other hormones, is common in duodenal and jejunal EEC but is rare or absent in this region of human and mouse. Another example is that CCK is present in the mouse but not the human colon. Functional implications of the newly discovered colocalization patterns are unknown.

ARTHUR BEYDER

Consultant, Gastroenterology & Hepatology

Assistant Professor, Medicine and Physiology & Biomedical Engineering

Mayo Clinic

The touching story of gut epithelial mechano-sensitivity

BIOGRAPHY

Arthur Beyder attended SUNY Buffalo's Medical Scientist Training Programme (MSTP), receiving MD, PhD in 2007. His thesis work with Dr. Frederick Sachs focused on nanoscale electro-mechanical movements during ion channel gating. Dr. Beyder continued his training in the Clinician-Investigator (CI) programme at the Mayo Clinic, where between 2007 and 2014 he completed an internal medicine residency, gastroenterology and hepatology fellowship and post-doctoral research training. For his post-doctoral training, Dr. Beyder worked with Dr. Gianrico Farrugia on ion channel biophysics, exploring mechano-electrical coupling in gastrointestinal smooth muscle cells, and diseases related to ion channel mutations, also called ion channelopathies. Since 2014, Dr. Beyder has practiced as a physician-scientist at the Mayo Clinic. He leads a NIH-funded laboratory, the mission of which is to advance the understanding of gastrointestinal mechanobiology in health & disease.

ABSTRACT

Sensation of mechanical forces, or mechanosensitivity, is critical for normal gastrointestinal (GI) function. Disruptions in mechanosensitivity lead to common functional GI diseases, such as irritable bowel syndrome (IBS). Given the importance of mechanosensitivity, the GI tract has developed several dedicated circuits to sense mechanical forces and generate physiologic responses. However, while the anatomy and physiology of these circuits has received its' due attention, the cellular and molecular mechanisms of GI mechanosensitivity have been elusive. In this work, we focus on an epithelial enterochromaffin (EC) cell, which was proposed to be the primary epithelial mechanosensor nearly 60 years ago by Edith Bulbring. The EC cell is proposed to release serotonin in response to mechanical forces, but direct evidence of this process and the mechanism are lacking. The EC cell is similar in development and function to the Merkel cell, which serves as the skin's light touch sensor. The Merkel cell relies on Piezo2 mechanosensitive ion channels to sense force and convert it to physiologic response. Similarly, we discovered that the human and mouse EC cell expresses Piezo2, but whether the EC cell is mechanosensitive remains unclear. In this talk, I will present our recent findings in exploring EC cell mechanosensitivity, specifically focusing on potential role of Piezo2 channels in EC cell mechanotransduction.

NICHOLAS SPENCER

Professor

Flinders University

How to identify and control the activity of sensory nerve endings that transmit between the gut-brain axis

BIOGRAPHY

Nick Spencer completed his BSc(Hons) in 1995 and then his PhD in Neurophysiology in 1998 at the Department of Physiology, Monash University, Australia. In 1998, Nick then took up a postdoctoral position at The University of Nevada School of Medicine, where he spent 10 years, the first 2 years of which were postdoc. In 2002, Nick obtained a 5 year grant with the National Institutes of Health, where he studied the intrinsic neural reflex circuitry in the wall of the gastrointestinal (GI) tract. Current research in his laboratory is primarily directed to understanding the neurophysiological basis of sensory transduction from visceral organs (particularly the GI tract), including activation of pain pathways from internal organs. His laboratory also carries out a number of projects related to the intrinsic neural control of the enteric nervous system and mechanisms underlying propulsion of content. He has published more than 100 peer reviewed research articles on the gastrointestinal tract.

ABSTRACT

Understanding the gut-brain axis requires an understanding of the sensory nerves that communicate between these organs. Whilst vagal afferent nerve endings in the gut have been well characterized, the vagus nerve provides little, or no innervation of the terminal regions of the gastrointestinal tract, where spinal afferents provide the major, or sole extrinsic sensory innervation. It may seem hard to believe, but the location, morphology and neurochemical coding of all types of spinal afferent nerve endings to all internal organs of all species has remained elusive, until recently. The reason why identifying spinal afferent endings has been so challenging is because of a lack of techniques to distinguish them from the nerve endings of other extrinsic and intrinsic neurons (sympathetic, parasympathetic and enteric that express the same neurochemical markers). We recently developed a surgical approach in live mice to expose dorsal root ganglia (DRG). This allows us, for the first time, to selectively and unambiguously label all the different types of nerve endings of spinal afferents to all visceral organs. We will describe major advances in our understanding of spinal afferent innervation to the gut and how spinal afferents are activated. The new technique we will describe can also be used to perform the first wireless optogenetic control of spinal afferents to internal organs. Understanding spinal afferents is critical to our understanding of the gut-brain axis.

SVEN PETTERSSON

Professor
Lee Kong Chian School of Medicine
Nanyang Technological University

The Gut Microbiome & Ageing; Friend or Foe?

BIOGRAPHY

Professor Sven Pettersson is a cell biologist focusing on microbiome mediated mechanisms regulating mammalian host physiology. Ongoing projects seek to decipher microbiome-mediated signaling pathways and metabolites that support cell metabolism relevant to neurons and muscle cells. He joined the Lee Kong Chian School of Medicine in 2014 as a Professor of Metabolic Disease and was concurrently appointed as Scientific Director of the School's Germ-Free facility in Singapore. In 2015, he was appointed as Deputy Director of Cluster 2 at the Centre of Microbial Excellence, SCELSE. The same year, he was also appointed Senior Research Fellow at the Canadian Institute for Advance Science. (CIFAR)

ABSTRACT

Efficient control of energy homeostasis is a hallmark to support healthy ageing in humans. While gut microbes significantly influence host physiology across life, the precise signaling pathways and metabolites are largely unknown. By transplanting microbiota from old (OM) or young (YM) mice into germ free recipients, we assessed the effect of OM on the process of ageing in the host. Surprisingly, OM transplanted recipients showed normal weight gain and similar skeletal muscle mass. Moreover, OM-microbes appear to promote metabolic efficiency and growth-promoting effects as judged by increased adult neurogenesis and intestinal morphogenesis. Of note, OM transplanted mice show increased activation of AMPK, a key regulator of metabolism, energy homeostasis and lifespan in mice. Metagenomic analysis of OM transplanted recipients' microbiome revealed enrichment of microbe derived metabolites that may explain these findings. In my lecture, I will elaborate on our findings and provide experimental evidence of a possible microbiome-mediated signaling pathway that may explain our beneficial effects observed in the OM transplanted recipients. Our results support the notion that the gut microbiome evolves with host age to promote fitness amongst its eukaryotic guests in the prokaryotic kingdom.

SESSION FOUR • ENGINEERING THE GUT

Session Chair:

RAPHAEL H. VALDIVIA
Professor

Molecular Genetics and Microbiology

Vice Dean for Basic Science
Duke School of Medicine

Speaker 4.1

NICK BARKER
Professor

Research Director, A-STAR Institute of Medical Biology

Professor (Visiting), CRM, University of Edinburgh, UK

Research Professor, Kanazawa University, Japan

Speaker 4.2

XILING SHEN
Associate Professor

Department of Biomedical Engineering
Duke University

Speaker 4.3

HYUNSOO SHAWN JE
Associate Professor

Principal Investigator
Molecular Neurophysiology Laboratory

Duke-NUS Medical School

Speaker 4.4

MAXIME M. MAHE
Assistant Professor
University of Nantes

Institute of Digestive Diseases
University Hospital of Nantes France

SESSION FOUR

CHAIR:

RAPHAEL H. VALDIVIA

Professor

Molecular Genetics and Microbiology

Vice Dean for Basic Science

Duke School of Medicine

Raphael Valdivia obtained his PhD in microbial pathogenesis with Stanley Falkow at Stanford University in 1997. Dr. Valdivia became a Damon Runyon Cancer Research Fellow in the laboratory of Randy Schekman at the University of California, Berkeley to study endosome dynamics and biogenesis. He joined the faculty at Duke University in 2002 and developed new methods and technologies to tackle understudied microbial pathogens and symbionts. Dr. Valdivia earned national recognition as a Pew Scholar in the Biomedical Sciences and a Burroughs Wellcome Fund Investigator in the Pathogenesis of Infectious Diseases. Dr. Valdivia serves as an editor in multiple journals, NIH review panels, and is an elected Fellow of the American Association for the Advancement of Science and American Academy of Microbiology. Dr. Valdivia is the founding Director of what is now the Duke Microbiome Center and is the Vice for Basic Science at the Duke School of Medicine.

NICK BARKER

Professor

Research Director, A-STAR Institute of Medical Biology

Professor (Visiting), CRM, University of Edinburgh, UK

Research Professor, Kanazawa University, Japan

LGR5+ Stem Cells in Epithelial Maintenance, Repair and Cancer of The Stomach

BIOGRAPHY

I was awarded a PhD in 1995 from the Berkshire University of Reading, followed by a postdoc at the University Medical Centre Utrecht in Hans Clevers Laboratory investigating the role of Tcf transcription factors in controlling expression of target genes regulated by the Wnt signal transduction pathway during development and carcinogenesis. This work led to the publication of a seminal paper in Science, which has now become one of the most cited papers in this field (currently > 2700 citations). In 2001 I joined Semaia Pharmaceuticals, to develop colon cancer therapeutics targeted within the Tcf/β-catenin signalling pathway. In 2006 I returned to the Clevers laboratory as staff scientist. This work led to the discovery that Lgr5 marks adult stem cells, which was reported in Nature (currently > 2100 citations). In 2010 I was appointed as a senior principal investigator at the Institute of Medical Biology, Singapore and promoted to Research Director in 2015.

ABSTRACT

We have identified Lgr5 as a facultative component of the Wnt receptor complex specifically expressed on cycling stem cells in the intestine, colon, pyloric stomach, hair-follicles, ovary and embryonic kidney. Long-term ablation of the Lgr5+ cell compartment in vivo severely impairs epithelial homeostasis in both the pyloric antrum and the corpus, establishing the Lgr5+ populations as being critical for daily maintenance of the gastric mucosa. Employing new, non-variegated Lgr5-2A-CreERT2/EGFP/DTR mouse models, we now identify a subset of Lgr5-expressing chief cells responsible for epithelial repair in the corpus stomach following parietal cell atrophy. These Lgr5+ chief cells drive gastric metaplasia in vivo following K-RAS mutation. We additionally characterize the transcriptomes Lgr5+ stem cells in mouse intestine, colon and stomach, revealing new gastric stem cell-specific markers that can be used to isolate human gastric stem cells for regenerative medicine applications and for use in selectively targeting cancer-causing mutations to the Lgr5+ stem cell compartment in mice as a means of evaluating their contribution to gastric cancer initiation and progression.

XILING SHEN

Associate Professor

Department of Biomedical Engineering
Duke University

In vivo imaging and recording of the enteric nervous system

BIOGRAPHY

Dr. Shen received his BS, MS, and PhD degrees from Stanford University. He was an assistant professor at Cornell University from 2009 to 2015 and won the NSF career award before joining the Biomedical Engineering Department and Center for Genomics and Computational Biology at Duke University as an associate professor. The Shen lab studies cancer, stem cells, and the nervous system in the gut. Ongoing projects include metastasis-induced metabolic and epigenetic reprogramming, normal and cancer stem cells, non-coding RNA, in vivo imaging, and peripheral neuromodulation.

ABSTRACT

The enteric nervous system (ENS) is a major division of the nervous system and vital to the gastrointestinal (GI) tract and its communication with the rest of the body. Unlike the brain and spinal cord, relatively little is known about the ENS in part because of the inability to directly monitor its activity in live animals. I will talk about the new imaging and electrical recording tools we have been developing to record the ENS in real-time in live and even awaken animals. We have also been developing analytical tools to analyse such in vivo data.

HYUNSOO SHAWN JE

Associate Professor

Principal Investigator, Molecular Neurophysiology Laboratory

Duke-NUS Medical School

Brain, Gut, and Anxiety

BIOGRAPHY

Dr. Shawn Je is currently an Associate Professor in the Neuroscience and Behavioural Disorders Programme at Duke-NUS Medical School in Singapore. He received his B.S. from KAIST, M.S. from the University of Michigan, Ann Arbor, and his PhD in Neuroscience and Genetics from Graduate Partnership Programme at the National Institutes of Health (NIH) through the George Washington University Medical School. Then, he pursued postdoctoral training at the Howard Hughes Medical Institute (HHMI)/ Duke University Medical School. He joined Duke-NUS Medical School in late 2010 and the focus of his research is on the molecular and cellular mechanisms underlying neuropsychiatric and neurodegenerative disorders.

ABSTRACT

There is growing evidence that the gut microbiota may act as a key regulator of the brain and behaviour. Previously, microbial disturbances triggered by antibiotic exposure or germ-free (GF) animals elicit augmented anxiety-related behaviours in animals. However, the underlying neural circuit mechanism of these behavioural changes in animals has not been elucidated yet. In this seminar, I will present our latest finding that GF male mice exhibit elevated anxiety-related behaviours due to the hyperactivity of basolateral amygdala pyramidal neurons. This study reveals a novel neural mechanism by which gut microbiota control animal behaviour.

MAXIME M. MAHE

Assistant Professor
University of Nantes

Institute of Digestive Diseases
University Hospital of Nantes

Engineering human innervated intestinal tissue from pluripotent stem cells

BIOGRAPHY

For the past 5 years, I have developed model systems of the human intestine with the endeavor to study gastrointestinal physiopathology. Using human pluripotent stem cells, we were able to generate a human intestine reassembling human intestinal features including and enteric nervous system. In addition, we were able to model GI diseases including Hirschsprung's disease. I have been recently recruited by INSERM to join the group of Dr. Michel Neunlist in Nantes, France to develop a basic program to study the enteric nervous system and intestinal development in physiopathology using organoid technologies.

ABSTRACT

The use of human pluripotent stem cells offers great avenues to generate human tissues. The understanding of intestinal development and its translation to human pluripotent stem cells, allowed the field to move forward in understanding intestinal development and gastrointestinal diseases. In this talk, I will highlight our previous work which had focused on generating functional human intestinal organoids (HIOs) from embryonic stem cells and induced pluripotent stem cells. Building on this model, I will highlight the additional complexity we were able to engineer in order to gain insights into intestinal physiology and diseases. In this context, the development of human intestine with an enteric nervous system (ENS) represents a real opportunity to expand our knowledge into the effect of ENS on intestinal development and toward the understanding of pathophysiological processes leading to functional gastrointestinal neuropathies. Finally, I will delinate the forthecoming strategies that could be used to create a fully functional intestine that could pave the way for intestinal regenerative medicine.

SESSION FIVE

MICROBES THAT MATTER

Session Chair: NICHOLAS SPENCER
Professor
Flinders University

Speaker 5.1 LAWRENCE CARIN
Professor
Vice Provost for Research
Duke University

Speaker 5.2 JOHN DOYLE
Jean Lou Chameau Professor of Control and Dynamical Systems
California Institute of Technology

Speaker 5.3 WARREN GRILL
Professor
Edmund T. Pratt, Jr. School Professor of Biomedical Engineering
Duke University

SESSION FIVE

CHAIR:

NICHOLAS SPENCER

Professor

Flinders University

Nick Spencer completed his BSc(Hons) in 1995 and then his PhD in Neurophysiology in 1998 at the Department of Physiology, Monash University, Australia. In 1998, Nick then took up a postdoctoral position at The University of Nevada School of Medicine, where he spent 10 years, the first 2 years of which were postdoc. In 2002, Nick obtained a 5 year grant with the National Institutes of Health, where he studied the intrinsic neural reflex circuitry in the wall of the gastrointestinal (GI) tract. Current research in his laboratory is primarily directed to understanding the neurophysiological basis of sensory transduction from visceral organs (particularly the GI tract), including activation of pain pathways from internal organs. His laboratory also carries out a number of projects related to the intrinsic neural control of the enteric nervous system and mechanisms underlying propulsion of content. He has published more than 100 peer reviewed research articles on the gastrointestinal tract.

LAWRENCE CARIN

Professor

Vice Provost for Research
Duke University

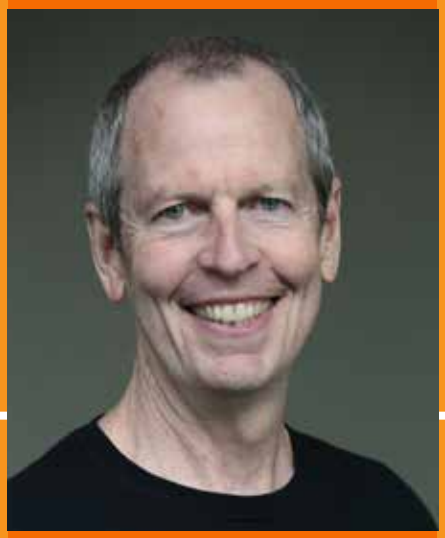
Joint Analysis of Local-Field-Potential Neural Recordings from Multiple Brain Regions

BIOGRAPHY

Lawrence Carin earned the BS, MS and PhD degrees from the University of Maryland, College Park, in 1985, 1986 and 1989, respectively. From 1989 to 1995 he was on the faculty of Brooklyn Polytechnic Institute (now part of NYU), and in 1995 he joined Duke University, where he is now the James L. Meriam Professor of Electrical and Computer Engineering (ECE). He has served as the chairman of Duke's ECE department (2011-2014) and as Duke's Vice Provost for Research (2014-present). His research interests are in statistical machine learning, with an emphasis on applications to medicine. He has published over 370 peer-reviewed publications, and he is an IEEE Fellow. He has also transitioned his research to practical application, having co-founded Signal Innovations Group in 2004, which was acquired by BAE Systems in 2014. In 2017 he founded the AI startup Infinia ML.

ABSTRACT

In neuropsychiatric disorders such as schizophrenia or depression, there is often a disruption in the way that regions of the brain communicate with one another. To facilitate understanding of network-level communication between brain regions, we introduce a novel model of multisite low-frequency neural recordings, such as local field potentials (LFPs) and electroencephalograms (EEGs). The proposed model, named Cross-Spectral Factor Analysis (CSFA), breaks the observed signal into factors defined by unique spatio-spectral properties. These properties are granted to the factors via a Gaussian process formulation in a multiple kernel learning framework. In this way, the LFP signals can be mapped to a lower dimensional space in a way that retains information of relevance to neuroscientists. Critically, the factors are interpretable. In addition, the proposed approach was empirically more or as predictive of genotype and behavioural context for data collected in a rodent model when compared to commonly used approaches that lack the interpretability of CSFA. CSFA provides a useful tool for understanding neural dynamics, particularly by aiding in the design of causal follow-up experiments.



JOHN DOYLE

Jean Lou Chameau Professor of Control and Dynamical Systems

California Institute of Technology

Universal laws and architectures in complex bio, neuro, and tech networks

BIOGRAPHY

BS&MS EE, MIT (1977), PhD Math, UC Berkeley (1984). Mathematical foundations for complex networks. Applications in bio, tech, med, eco, and neuro systems, and multiscale physics, integrating theory from control, computation, communication, optimization, statistics. Universal laws and architectures, robustness/efficiency and speed/accuracy tradeoffs, adaptability, evolvability, large scale systems with sparse, saturating, delayed, quantized, uncertain sensing, communications, computing, and actuation. Robust control with aerospace and industrial applications. Software such as Matlab Robust Control Toolbox and Systems Biology Markup Language (SBML). Prizes: IEEE Baker, Auto Control (2x), world top 10 papers in mathematics 1981-1993, AACC Schuck, ACM Sigcomm and "test of time", and Best Writing on Mathematics 2010. Individual awards: IEEE Hickernell, Centennial, and Control Systems Field Award, AACC Eckman, and UC Berkeley Friedman, world records and championships in various sports.

ABSTRACT

Effective layered architectures such as the brain seamlessly integrate high level goal and decision making and planning with fast lower level sensing, reflex, and action and facilitate learning, adaptation, augmentation (tools), and teamwork, while maintaining internal homeostasis. This is all despite the severe demands such actions can put on the whole body's physiology, and despite being implemented in highly energy efficient hardware that has distributed, sparse, quantized, noisy, delayed, and saturating sensing, communications, computing, and actuation. Similar layering extends downward into the cellular level, out into ecological and social systems, and many aspects of this convergent evolution will increasingly dominate our most advanced technologies. Simple demos using audience's brains can highlight universal laws and architectures and their relevance to future network technologies. Subject to time limits we'll do some live and have others available online in videos. We'll briefly give pointers to a new unified mathematical framework that we hope will facilitate reverse engineering cells, brains, and societies and forward engineering future network architectures. This framework is currently being applied in a Caltech-UCLA MURI collaboration to study the gut microbiome's impact on cognition.

WARREN M. GRILL

Professor

Edmund T. Pratt, Jr. School Professor of
Biomedical Engineering
Duke University

Engineering Bioelectronic Modulation of Gut Function

BIOGRAPHY

Warren M Grill is Professor of Biomedical Engineering at Duke University. He received the BS from Boston University and the PhD from Case Western Reserve University. He teaches courses on circuits and instrumentation, bioelectricity, and fundamentals and applications of electrical stimulation, and in 2014 received the Duke University Scholar/Teacher of the Year. His research is in neural engineering and neuromodulation with applications to restoration of bladder function, deep brain stimulation, autonomic modulation and treatment of pain. He has published over 170 articles and awarded 36 US patents. Dr. Grill serves on the editorial boards of Brain Stimulation, Journal of Neural Engineering, and Current Opinion in Biomedical Engineering. He is Fellow of American Institute of Medical and Biological Engineering and Biomedical Engineering Society, and was awarded an NIH Javits Neuroscience Investigator Award in 2015.

ABSTRACT

The autonomic regulation of organ function, particularly through innervation by the vagus nerve, provides an opportunity to use electrical stimulation and block of neural activity to treat disorders of the gut. Applications range from treatment of obesity to restoration of colonic motility. Although meeting with varying degrees of clinical success, it remains unclear what nerve fibers mediate the desired therapeutic effects or what stimulation parameters are required to activate or block different fibers. First, I will present quantitative biophysically-based modeling analysis of electrical block of the vagus nerve to treat obesity. The results reveal that it is highly unlikely that clinically-used parameters do indeed block vagal nerve fibers and highlight opportunities for other approaches to treat obesity. Second, I will present a quantitative neurobiomechanical model of pacing to increase colonic motility. The model enabled identification of stimulation parameters that were more effective at increasing intrinsic peristalsis, and these predictions were confirmed with in vivo experiments in rats. Collectively, these studies demonstrate the utility of quantitative modeling to analyze and design bioelectronic therapies for treatment of gut disorders. I will close with current work developing species- and patient-specific models intended to facilitate successful translation of novel bioelectronics therapies.

SESSION SIX

GUT, BRAIN AND DISEASE

Session Chair:

ARTHUR BEYDER
Consultant, Gastroenterology & Hepatology

Assistant Professor, Medicine and Physiology & Biomedical Engineering

Mayo Clinic

Speaker 6.1

KARL HERRUP
Professor

Professor of Life Science
Hong Kong University of Science and Technology

Speaker 6.2

DAVID L. SILVER
Professor

Duke-NUS Medical School

Speaker 6.3

RODGER A. LIDDLE
Professor of Medicine
Duke University

SESSION SIX

CHAIR:

ARTHUR BEYDER

Consultant
Gastroenterology & Hepatology

Assistant Professor
Medicine and Physiology &
Biomedical Engineering

Mayo Clinic

Arthur Beyder attended SUNY Buffalo's Medical Scientist Training Programme (MSTP), receiving MD, PhD in 2007. His thesis work with Dr. Frederick Sachs focused on nanoscale electro-mechanical movements during ion channel gating. Dr. Beyder continued his training in the Clinician-Investigator (CI) programme at the Mayo Clinic, where between 2007 and 2014 he completed an internal medicine residency, gastroenterology and hepatology fellowship and post-doctoral research training. For his post-doctoral training, Dr. Beyder worked with Dr. Gianrico Farrugia on ion channel biophysics, exploring mechano-electrical coupling in gastrointestinal smooth muscle cells, and diseases related to ion channel mutations, also called ion channelopathies. Since 2014, Dr. Beyder has practiced as a physician-scientist at the Mayo Clinic. He leads a NIH-funded laboratory, the mission of which is to advance the understanding of gastrointestinal mechanobiology in health & disease.

KARL HERRUP

Professor

Professor of Life Science
Hong Kong University of Science and Technology

The metabolic functions of A T M - the Swiss army knife of Kinases

BIOGRAPHY

Karl Herrup received his Bachelor's degree from Brandeis University and his Ph.D. in Neuroscience from Stanford. After two postdoctoral fellowships – in Neurogenetics at Harvard Medical School, and in Neuropharmacology at the Biozentrum in Basel Switzerland – he joined the faculty of the Human Genetics Department of Yale Medical School. He became Director of the Division of Developmental Neurobiology at the E. K. Shriver Center in 1988. In 1992 he moved to the Department of Neurosciences at Case Western Reserve University Medical School. While there, he directed the University Alzheimer's Center from 1999 through 2005. In 2006 he moved to Rutgers University to become Chair of the Department of Cell Biology and Neuroscience. In July 2012, he moved to Hong Kong to become the Head of Life Science at The Hong Kong University of Science and Technology. His work includes a strong translational interest that directs his studies towards a few select human neurodegenerative diseases.

ABSTRACT

ATM is a PI3K family member. Its deficiency in humans leads to ataxia-telangiectasia (A-T), a complex phenotype involving many organ systems, most prominently the nervous system. ATM is best known for its role in DNA double strand break repair, but it is increasingly appreciated that ATM performs other cellular responses. For example, ATM activity adjusts the epigenome – histone modifications and DNA methylation – in coordination the DNA damage response. A newly emerging area where ATM's multifaceted functionality is further illustrated is in regulating the metabolic status of the cell. Symptoms of human A-T map to genes related to the TCA cycle and mitochondrial oxidative phosphorylation. Experimentally, cultured Atm-/- neurons have an impaired capacity to increase ATP production in response to sustained neuronal activity due to a failure to activate NRF1, a master regulator of nuclear-encoded mitochondrial genes. Modeling data suggests that the unusual sensitivity of large, metabolically demanding neurons to deficiencies in this ATM-dependent pathway helps explain the regionally specific pattern of neurodegeneration in A-T. One final message expands this idea still further: ATM protein is also involved in synaptic vesicle recycling and lysosome trafficking. These are likely total separate functions from its DNA damage response activities. ATM is thus truly a molecular Swiss army knife.

DAVID L. SILVER

Professor

Duke-NUS Medical School

Brain Lipid Transport

BIOGRAPHY

David is a professor in the Programme in Cardiovascular & Metabolic Disorders and serves as the Deputy Director of the program and as Director of Graduate Studies in Integrated Biology and Medicine, Duke-NUS Singapore. David obtained a Ph.D. in Genetics from Michigan State University, and postdoctoral training with Alan Tall at Columbia University specializing in lipid biochemistry and lipid metabolism. David held faculty positions at Columbia University and Albert Einstein College of Medicine before joining Duke-NUS Medical School in 2012. His research interests are in the areas of lipid storage, lipid transporters and blood-brain barrier function and brain growth.

ABSTRACT

Membrane phospholipids in brain and eye are highly enriched in the omega-3 fatty acid docosahexaenoic acid (DHA). DHA is an essential fatty acid associated with cognitive function, but the mechanisms explaining this association and function of DHA in brain and eye is incompletely understood. DHA is not de novo synthesized by neuronal tissues, but must be transported across the blood-brain (BBB) and blood-eye barriers. However, DHA as an unesterified fatty acid is not quantitatively transported across the BBB, but rather is transported by the Major Facilitator Superfamily Domain-containing 2a (Mfsd2a) transporter in a phospholipid form called lysophosphatidylcholine (LPC) (Nguyen et al. Nature 2014). LPCs are produced by the liver and circulate in plasma on albumin and lipoproteins. We previously have demonstrated that Mfsd2a is essential for DHA accretion by brain and eye (Nguyen et al. Nature 2014;Wong et al. JBC 2016), and mice deficient in Mfsd2a and humans with inactivating mutations present with severe microcephaly, indicating that Mfsd2a transport of LPCs (containing essential fatty acids) is essential for normal brain development (Guemez-Gamboa et al. Nat Gen 2015; Alakbarzade et al. 2015). Importantly, the biochemical function of DHA during brain development is not understood. In this seminar, I plan to discuss our latest findings on the biochemical function of DHA and LPC-DHA transport by Mfsd2a.

RODGER A. LIDDLE

Professor of Medicine

Duke University

Parkinson's disease from the gut

BIOGRAPHY

Dr. Liddle is currently Professor of Medicine at Duke University Medical Center. Dr. Liddle received his medical degree from Vanderbilt University and performed his internship and residency in Medicine at the University of California, San Francisco. He was a fellow in Gastroenterology at UCSF where he also perfomed his postdoctoral research training. Dr. Liddle has served on the faculties of UCSF and Duke University. At Duke, Dr. Liddle has held numerous leadership positions, including Chief of the Gastroenterology Division. Dr. Liddle is an internationally recognised investigator in the physiology of the gastrointestinal tract and has had continuous NIH funding for his research for over 30 years.

Dr. Liddle's research focuses on the biology of enteroendocrine cells and pancreatic physiology. He is a member of Alpha Omega Alpha, the American Society for Clinical Investigation and the Association of American Physicians.

ABSTRACT

Parkinson's disease (PD) is a debilitating neurodegenerative condition associated with tremor, rigidity, dementia, and gastrointestinal symptoms such as constipation. The pathological hallmarks of PD are Lewy bodies in the brain and peripheral nerves. The major constituent of Lewy bodies is the neuronal protein α-synuclein. Misfolding of α-synuclein confers prion-like properties enabling its spread from cell to cell. Misfolded α-synuclein also serves as a template and induces misfolding of endogenous α-synuclein in recipient cells leading to the formation of fibrils and eventually Lewy bodies. Evidence suggests that PD may arise in the gut. Clinically, gastrointestinal symptoms often appear in patients before other neurological signs. Aggregates of α-synuclein have been found in enteric nerves of PD patients. And importantly, patients undergoing vagotomy have a reduced risk of developing PD. Experimentally, abnormal forms of α-synuclein appear in enteric nerves before they appear in the brain and injection of abnormal α-synuclein into the wall of the intestine spreads to the vagus nerve. Ingested toxins and alterations in gut microbiota can induce α-synuclein aggregation and PD, however, it is not known how PD starts. We show that enteroendocrine cells (EECs) contain α-synuclein and synapse with enteric nerves, thus providing a connection from the gut to the brain. It is possible that abnormal α-synuclein develops in EECs and spreads to the nervous system.

SESSION SEVEN • THE NEUROBIOLOGY OF GUT FEELINGS

Session Chair: JOHN FURNESS
Professor

Head of Digestive Physiology and Nutrition Laboratories,
Florey Institute and University of Melbourne

Speaker 7.1 DIEGO BOHÓRQUEZ
Assistant Professor of Medicine and Neurobiology

Duke Universtiy

Speaker 7.2 LUIS R. SARAIVA
Principal Investigator
Sidra Medicine, Qatar

Speaker 7.3 IRENE MIGUEL-ALIAGA
Professor

Genetics and Physiology,
Imperial College London

Section Chair
MRC London Institute of Medical Sciences

Speaker 7.4 IVAN DE ARAUJO
Associate Professor of Psychiatry

Associate Professor of Molecular and Cellular Physiology

Yale University School of Medicine

SESSION SEVEN

CHAIR:

JOHN FURNESS

Professor

Head of Digestive Physiology and Nutrition Laboratories, Florey Institute and University of Melbourne

John Furness leads the Digestive Physiology and Nutrition Laboratories at the Florey Institute of Neuroscience and Mental Health and the University of Melbourne.

His laboratory has worked for many years on the physiology of digestion, particularly its neuronal and endocrine control. The current emphasis of his work is:

- The relationships between diet, environment and gut health, and their implications for animal production and for human well-being.
- Anti-inflammatory nerve stimulation for the treatment of inflammatory bowel disease.
- The gastrointestinal manifestations of Parkinson's Disease.
- The cell biology of enteroendocrine cells.
- Identification of targets and development of drugs for the treatment of gastrointestinal motility disorders.
- The roles of ghrelin and its receptors and the exploration of ghrelin receptor ligands as therapeutic tools.

DIEGO BOHÓRQUEZ

Assistant Professor of Medicine and Neurobiology
Duke University

Transduction of a sense from gut to brain

BIOGRAPHY

Dr. Bohórquez is an Assistant Professor of Medicine at Duke University. His expertise is in gut-brain sensory neural circuits. Dr. Bohórquez's training is unique from a scientific and an academic perspective. He has a Ph.D. in Nutrition and Gastrointestinal Physiology, and postdoctoral training in the Neurosciences. Dr. Bohórquez's research focuses on how sensory stimuli from food and bacteria in the gut are transduced to the brain via vagus nerve. This is the neural circuitry basis for gut stimuli to modulate brain function and behaviour. It is also an area of research at the core of treating behavioural disorders such as obesity, anorexia, or autism. Dr. Bohórquez is known for his discovery of a sensory neuroepithelial circuit in the gut- analogous to that transducing the sense of taste in the tongue (J Clin Invest. 2015;125(2):782). His work has been featured in Nature, NeuroPod, ScienceDaily, Wired magazine, TED ideas blog and The New Yorker.

ABSTRACT

The brain perceives the environment through specialized sensory neuroepithelial circuits. In the tongue, for instance, taste receptor cells transduce chemical signals by synapsing with the glossopharyngeal nerve. In the gut, however, the putative sensory epithelial cell known as the enteroendocrine cell is thought to convey signals to the nerves only through endocrine mechanisms-hence its name. Here, we unveil a monosynaptic link between gut sensory epithelial cells and vagal nodose neurons. This neuroepithelial circuit is capable of transducing signals from nutrients, such as glucose, within milliseconds, opening a physical path from gut lumen to brain.

LUIS R. SARAIVA

Principal Investigator

Sidra Medicine, Qatar

Olfactory effects on food detection and intake

BIOGRAPHY

Luis Saraiva graduated in Biology from the University of Evora (Portugal). He then became a Fellow of the International Graduate School in Genetics and Functional Genomics at the University of Cologne (Germany), where he received his PhD in Genetics (summa cum laude) in 2008. After a brief period as a visiting scientist at Harvard Medical School, he did his first postdoc with Nobel Laureate Linda Buck at the Fred Hutch (USA). In 2013, he became an EBI-Sanger Postdoctoral (ESPOD) Fellow, in Cambridge (UK), where he specialized in the application of RNA-sequencing technologies to complex questions.Since October 2015 he is a Principal Investigator at Sidra Medicine (Qatar), and in June 2016 he also became an Adjunct Assistant Member at the Monell Chemical Senses Center (USA).

ABSTRACT

Smell is a major component of food cues and flavor, and it has been long known that olfaction and appetite are closely linked. The importance of sensing the molecular environment is reflected in the genetic investment in encoding olfactory receptors (ORs), which constitute the largest mammalian gene family. The OR gene repertoire is largely species-specific, and shaped by the nature and necessity of chemosensory information (e.g. food sources) for survival in each species' niche. Moreover, the gender, health (e.g. obese vs lean) and internal homeostatic states (e.g. hungry vs satiated) of an individual can modulate olfactory performance and sensitivity, which can severely affect food retrieval and consumption.

But, is detection of key food odours a selective pressure acting on the olfactory system? How can the simple presence of an odour ultimately result in complex behaviours such as appetite enhancement or suppression? How can diet or the internal state of the animal affect such behaviours?

We employ a multidisciplinary strategy aimed at tackling these and other relevant questions. We believe this integrated approach will contribute to a better understanding of the molecular logic underlying environmental and homeostatic effects in appetite, food intake and metabolism. Importantly, these studies could provide clues to potential approaches for controlling appetite and ultimately obesity, which is of serious medical concern in our modern society.

IRENE MIGUEL-ALIAGA

Professor

Genetics and Physiology
Imperial College London

Section Chair
MRC London Institute of Medical Sciences

Sex differences in intestinal plasticity

BIOGRAPHY

Irene obtained her DPhil in Genetics from the University of Oxford, and explored how neurons acquire their identity during postdoctoral work at Harvard, Linkoping University and NIMR (now Crick Institute), London. First at Cambridge and now in London, her research group is investigating the plasticity of internal organs, with a major focus on the gastrointestinal tract and its neurons. She was elected to the EMBO YIP programme in 2012 and became a full EMBO member in 2017. She is the recipient of an ERC Starting Grant and she has recently been awarded an ERC Advanced Grant.

ABSTRACT

Internal organs constantly exchange signals, and can respond with profound anatomical and functional transformations, even in fully developed organisms. Such organ plasticity results from a need to integrate and respond to both environmental information and internal state, and is key to maintaining homeostasis and driving adaptive changes. We are interested in understanding the mechanisms by which organs sense change and respond to it: the molecules, cellular events and physiological adaptations involved. The intestine and its neurons are a fantastic system with which to tackle these questions. Our investigations in Drosophila have uncovered functional similarities between the invertebrate and vertebrate enteric nervous systems. They have also characterized an adaptive mechanism, reminiscent of neurovascular interactions in mammals, which points to a key role for the intestinal vasculature in adaptations to malnutrition. More recently, we have begun to explore the physiological plasticity of the intestinal epithelium: an obvious cellular target of the enteric neurons. I will present some of this work, which has revealed unexpected sexual dimorphisms, as well as intestinal contributions to reproductive success. I will also discuss some of our ongoing work in mammalian systems, aimed at exploring the nature of sex differences beyond the fly intestine.

IVAN DE ARAUJO

Associate Professor of Psychiatry
Associate Professor of Molecular and Cellular Physiology
Yale University School of Medicine

Reward neurons of the gut

BIOGRAPHY

Dr. Ivan de Araujo has been on the faculty at Yale University School of Medicine since 2007 and a Fellow at the John B. Pierce Laboratory, affiliated with Yale Medical School. Starting on September 2018, Ivan will become a Full Professor in the Department of Neuroscience, Member of the Friedman Brain Institute (FBI) and Diabetes, Obesity & Metabolism Institute (DOMI) at the Icahn School of Medicine at Mount Sinai. He received his B.A. in Philosophy from the University of Brasilia in 1995, an M.A. in Applied Mathematics from the University of Brasilia in 1998, a M.Sc. in Artificial Intelligence from the University of Edinburgh in 1999, and his DPhil in Neurophysiology (Experimental Psychology) from the University of Oxford in 2003. The focus of his research is the identification and characterization of the neuronal pathways through which peripheral, especially gastrointestinal, organs influence brain reward circuits.

ABSTRACT

The gut is now recognized as a major regulator of motivational and emotional states. However, the relevant gut-brain neuronal circuitry remains unknown. The talk will describe how optical activation of gut-innervating vagal sensory neurons recapitulates the hallmark effects of stimulating brain reward neurons. It will also describe the brainstem region that links vagal sensory ganglia to brain reward circuits. Unlike previous models of the vagus nerve, our findings establish its gut afferents as components of the reward neuronal circuitry. They also suggest novel vagal stimulation approaches to affective disorders.

OPENING REMARKS:

Dr. Muir's research activities are focused on developing innovative treatments for a variety of liver diseases. He has particular interests including viral hepatitis, primary sclerosing cholangitis, liver transplantation and a longstanding interest in healthcare disparities. He attended Trinity University in San Antonio, TX for his undergraduate education, followed by medical school at Duke University. He completed his internal medicine residency and GI fellowship at Duke where he also served as chief resident at the Durham VA Medical Center. He joined the faculty in the Division of Gastroenterology at Duke in 2000. He joined the faculty at DCRI and worked closely with his mentor, Dr. John McHutchison, to establish the GI and Hepatology Research programme at the DCRI. Through his work at the DCRI, he has participated in the development programmes of many of the direct acting antiviral agents that have revolutionized hepatitis C care. He assumed the leadership of the GI/ Hepatology Research programme at DCRI in 2010 and has expanded the research portfolio to include other liver disorders and GI outcomes. He has authored or co-authored more than 100 peer-reviewed publications.

ANDREW MUIR

Professor

Chief of Gastroenterology
Department of Medicine

Division of Gastroenterology
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Duke University Medical Center

CLOSING REMARKS:

COFFMAN, THOMAS M

Dean & Professor
Cardiovascular & Metabolic Disorders Programme
Duke-NUS Medical School

James R. Clapp
Professor of Medicine
Duke University Medical Center

Director
Cardiovascular Research Center
Duke School of Medicine

Dr Thomas Coffman is Dean of Duke-NUS Medical School and Professor in its Cardiovascular and Metabolic Disorders Signature Research Programme (SRP). He is also the James R. Clapp Professor of Medicine at Duke University Medical Center where he spent almost 18 years as Chief of the Division of Nephrology and served as Senior Vice-Chair in the Department of Medicine.

Dr Coffman graduated from the University of Pennsylvania and obtained his MD from the Ohio State University School of Medicine. He moved to Duke for medicine residency and nephrology fellowship, joining the faculty in 1985 to pursue his career as a clinician and researcher. Along with his leadership of the Division of Nephrology, Dr. Coffman was the founding director of the Duke Cardiovascular Research Center and the Duke O'Brien Center for Kidney Research. He joined Duke-NUS in 2010 as Director of the Cardiovascular and Metabolic Disorders SRP. Dr Coffman was appointed Dean at Duke-NUS on 1 July 2015. He is also a member of the SingHealth Board of Directors.

An international leader in the field of nephrology, Dr Coffman is a Past-President of the American Society of Nephrology. He is also a member of the American Society for Clinical Investigation and the Association of American Physicians, and served on the Nephrology Subspecialty Board of the American Board of Internal Medicine. Dr Coffman has served on a number of editorial boards including Physiological Reviews and Cell Metabolism, and currently serves as Associate Editor of the Journal of Clinical Investigation. He is a Fellow of the Councils for High Blood Pressure Research and the Kidney in Cardiovascular Disease of the American Heart Association (AHA), and serves on the Leadership Committee for the AHA Council for High Blood Pressure Research. Dr Coffman also served as Chair of the Steering Committee for the National Institutes of Health (NIH)-funded Animal Models of Diabetes Complications Consortium. His laboratory work has been supported by grants from the NIH and the Department of Veterans' Affairs. Dr Coffman's research interests include the renin-angiotensin and prostanoid systems, and diabetic nephropathy.

Dr Coffman was conferred the 2014 Excellence Award for Hypertension Research from the AHA Council on Hypertension recognising researchers who have made a major impact in the field of hypertension and whose research has contributed to the improved treatment and greater understanding of high blood pressure. He also received the 2014 Distinguished Faculty Award from the Duke Medical Alumni Association.


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