

15TH MODELS OF PHYSIOLOGY AND DISEASE SYMPOSIUM

in conjunction with

CALCIUM CHANNEL AND DISEASE SYMPOSIUM

and

EDWARD KOO MEMORIAL SYMPOSIUM IN NEUROSCIENCE



23 TO 24 SEPTEMBER 2026



CENTRE OF LIFE SCIENCE, AUDITORIUM

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WELCOME NOTE

Good morning everyone, distinguished guests, colleagues, students and friends.

It is my great pleasure to welcome all of you to the 15th Models of Physiology and Disease Symposium, one of the signature annual events of the Department of Physiology at the NUS Yong Loo Lin School of Medicine.

This symposium was first initiated in 2009 with the aim of bringing scientists together to exchange ideas, stimulate meaningful discussions and foster new collaborations in physiology, human health and disease. Over the years, it has grown into an important platform for showcasing the breadth of research within our department, while connecting us with leading researchers and collaborators from Singapore and around the world.

We are very fortunate to have an outstanding line-up of international and local speakers joining us this year. This year's symposium is particularly special, as it is being held in conjunction with the Calcium Channels & Disease Symposium and the Edward Koo Memorial Neuroscience Session. The Edward Koo Memorial Neuroscience Session is held in honour and remembrance of Professor Edward Koo, and celebrates his remarkable contributions to neuroscience, particularly his seminal work in understanding the molecular and cellular mechanisms underlying Alzheimer's disease and neurodegeneration, as well as his contributions to dementia research and care.

Together, this year's programme spans a broad range of exciting research areas, including cancer therapeutics, RNA biology, ion channels and disease, and neuroscience. We hope that bringing these diverse fields together will stimulate interactions across disciplines, spark new ideas and create opportunities for new collaborations.

We would also like to express our heartfelt appreciation to our sponsors — Deanery Yong Loo Lin School of Medicine, Healthy Longevity Translational Research Programme, Life Sciences Institutes, NUS Centre for Cancer Research, Lee Foundation, Genomax, Singlabs, Axil Scientific, abcam, cyagen, MDPI, Global Cold Chain Solutions, Vazyme, NovogeneAIT, Nikon, Cancer Science Institute of Singapore, Nikon, Singleron, Probioscience and Bio.etc — for their generous support, without which this symposium would not have been possible.

Finally, on behalf of the Organising Committee, we would like to extend a very warm welcome to all of you. We wish everyone a stimulating, enjoyable and productive symposium, and we look forward to your participation in making this year's meeting a great success. Thank you, and once again, welcome to the 15th Models of Physiology and Disease Symposium.

With Warmest Regards,



Associate Professor
Department of Physiology
National University of Singapore



Assistant Professor
Department of Physiology
National University of Singapore



Professor
Department of Physiology
National University of Singapore



Associate Professor
Department of Physiology
National University of Singapore

ORGANISING COMMITTEE

CO-CHAIRPERSONS:



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WEE WEI



DR ANTHONY
KHONG



PROF SOONG
TUCK WAH



ASSOC. PROF LING
SHUO-CHIEN

COMMITTEE MEMBERS:



KOH SHU WEN



UNIS YEO YONGXIN



LAU EN LIN



SEE HUIMIN

SPECIAL THANKS TO TRP CENTRAL ADMIN EVENTS TEAM:

KALISTA BONG

SITI BADARIAH

LIAW ZI TING

HELEN LEE

SCIENTIFIC PROGRAMME

DAY 1 : 23 SEPTEMBER

8:20 - 8:45 AM	Registration
8:45 - 8:50 AM	Safety Briefing
8:50 - 9:00 AM	Opening Remarks
Session 1: Cancer Therapeutics <i>Session Chairs: Tee Wee Wei & Anthony Khong</i>	
9:00 - 9:40 AM	<i>(Keynote Speaker)</i> Ricky Johnstone <i>Targeting transcriptional CDKs in Cancer</i> University of Melbourne, Australia
9:40 - 10:10 AM	Patrick Tan <i>Molecular Signatures and Clonal Hematopoiesis in Gastric Intestinal Metaplasia</i> Duke-NUS Medical School, Singapore
10:10 - 10:40 AM	Tea Break
10:40 - 11:10 AM	Greg Wang <i>Chromatin Dysregulation, a Cancer Driver</i> Duke Cancer Institute, USA
11:10 - 11:40 AM	Wee Wei Tee <i>Exploiting embryonic vulnerabilities in cancer</i> NUS Medicine, National University of Singapore Institute of Molecular and Cell Biology, A*STAR, Singapore
11:40 - 12:10 PM	Reshma Taneja <i>Metabolic and signaling dependencies of tumor initiating cells in rhabdomyosarcoma</i> NUS Medicine, National University of Singapore
12:10 - 12:20 PM	Short Talk 1
12:20 - 12:30 PM	Sponsor Talk 1 Caroline Chan <i>NULISA™: Next-Generation Ultra-Sensitive Proteomics for Biomarker Research</i> Genomax
12:30 - 1:30 PM	Lunch and Poster Session

Session 2: Cancer and RNA Biology

Session Chairs: Tee Wee Wei & Anthony Khong

1:30 - 2:10 PM	(Keynote Speaker) Shu-Bing Qian <i>Ribosome decoding memory in translational control</i> Cornell University, USA
2:10 - 2:40 PM	Martin Bushell <i>DDX6 is required to regulate ribosome traffic to control co-translational assembly of protein complexes</i> Cancer Research UK Scotland Institute, Scotland
2:40 - 3:10 PM	Anthony Khong <i>Hypoxia-Induced Stress Granules Assemble with Minimal Translational Repression and Selectively Stabilize RNAs</i> NUS Medicine, National University of Singapore
3:10 - 3:40 PM	Tea Break
3:40 - 4:20 PM	(Keynote Speaker) Wan Yue <i>RNA single-strandedness and remodeling promotes stress granule condensation</i> Genome Institute of Singapore, A*STAR
4:20 - 4:50 PM	Eleonora Leucci <i>Contribution of lncRNAs to the generation of drug-tolerant persister cells</i> KU Leuven, Belgium
4:50 - 5:20 PM	Pedro Batista <i>ZNFX1 acts as a negative regulator of Natural Killer cell mediated cytotoxicity in HLRCC</i> National Cancer Institute, USA
5:20 - 5:50 PM	Jiangbo Wei <i>Persistent mRNA m⁶A sustains BET inhibitor resistance in pancreatic cancer</i> Faculty of Science, National University of Singapore
6:00 PM	Conference Dinner
End of Day 1	

SCIENTIFIC PROGRAMME

DAY 2 : 24 SEPTEMBER

8:30 - 8:55 AM	Registration
8:55 - 9:00 AM	Safety Briefing
Session 3: Calcium Channel and Disease <i>Session Chair: Huang Hua</i>	
9:00 - 9:40 AM	<i>(Keynote Speaker)</i> Terrance P. Snutch <i>Targeting Voltage-gated Calcium Channels for the Treatment of Neurological Disorders</i> University of British Columbia, Canada
9:40 - 10:10 AM	Gerald Zamponi <i>Targeting T-type calcium channel de-ubiquitination to treat chronic pain</i> University of Calgary, Canada
10:10 - 10:40 AM	Tea break
10:40 - 11:10 AM	Emmanuel Bourinet - Institut de Genomique Fonctionnelle, Montpellier, France
11:10 - 11:40 AM	Tuck Wah Soong <i>Loss of Cav2.1EFa-dependent Ca²⁺-dependent Facilitation resulted in ataxia and neurological disorders</i> NUS Medicine, National University of Singapore
11:40 - 12:00 PM	Zhenyu Hu <i>A Galectin-3-targeting peptide modulates Cav1.2 channel function in hypertension</i> National Neuroscience Institute, Singapore
12:00 - 12:20 PM	Zhai Jing <i>RNA editing of CaV1.3 modulates circadian rhythm through sex-dependent regulation by brain-derived estradiol : implications in metabolic health</i> NUS Medicine, National University of Singapore
12:20 - 12:40 PM	Yousra El Ghaleb <i>Using Cross-Isoform Homology of Disease-Associated Voltage-Gated Ca²⁺ Channel Variants to Improve Pathogenicity Predictions</i> Medical University of Innsbruck, Austria
12:40 - 1:40 PM	Lunch and Poster Session

SCIENTIFIC PROGRAMME

DAY 2 : 24 SEPTEMBER

Session 4: Edward Koo Memorial Neuroscience Session

Session Chairs: John Wong Eu Li & Ling Shuo-Chien

1:40 - 1:50 PM	Opening Address
1:50 - 2:30 PM	<i>(Keynote Speaker)</i> Rickie Patani <i>Reformulating Neurodegeneration: The emerging role of SFPQ</i> NUS Medicine, National University of Singapore
2:30 - 2:40 PM	Short Talk 2
2:40 - 3:10 PM	Marina Chekulaeva <i>RNA localization in neurons and neurodegeneration</i> Max Delbrück Center for Molecular Medicine, Germany
3:10 - 3:20 PM	Sponsor Talk 2 Suruchi Arora <i>Blood-Based Neurodegenerative Biomarker Detection Using Simple Plex Ultra-Sensitive Assays.</i> Singlab
3:20 - 3:50 PM	Tea Break
3:50 - 4:20 PM	Christopher Chen Li-Hsian <i>Multidomain Interventions for Brain Health to support Healthy Longevity</i> NUS Medicine, National University of Singapore
4:20 - 4:35 PM	Eddie Koo Awardee Prize Presentation
4:35 - 5:15 PM	<i>(Keynote Speaker)</i> <i>Memorial Lecture</i> Takeshi Iwatsubo <i>The path toward disease-modifying therapies of Alzheimer's disease</i> University of Tokyo, Japan
5:15 - 5:30 PM	Closing of Conference
6:00 PM	Conference Dinner
End of Day 2	

KEYNOTE SPEAKERS



Ricky Johnstone

Executive Director Cancer Research

Peter MacCallum Cancer Centre, Australia

BIOGRAPHY

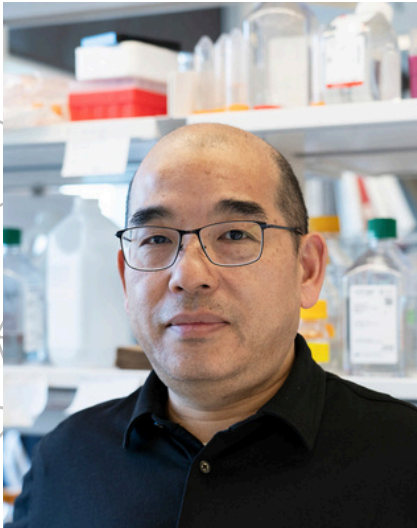
Professor Ricky Johnstone is the Head of the Gene Regulation Laboratory at the Peter MacCallum Cancer Centre and the Head, The Sir Peter MacCallum Department of Oncology, The University of Melbourne. Professor Ricky Johnstone received his PhD from the University of Melbourne in 1993 and after a postdoc at Harvard Medical School returned to Melbourne to establish the Gene Regulation Laboratory at the Peter MacCallum Cancer Centre in 2000. Professor Johnstone is the Executive Director Cancer Research at the Peter MacCallum Cancer Centre overseeing ~700 staff and students and plays a key role in strategic decision making across the organisation. Prof Johnstone is an internationally renowned cancer researcher who has directed his research along a translational pathway that fully integrates fundamental cancer and immunological research, pre-clinical development and testing of novel therapeutic regimes and the initiation of new clinical trials using agents under investigation in his laboratory. He has published more than 270 peer-reviewed papers, was elected as a Fellow of the Australian Academy of Health and Medical Sciences (2015) and was listed by Thomson Reuters/Clarivate as one of the world's most highly-cited scientists (High Cite) in 2014 and 2023. In 2023 he was awarded an L3 NHMRC Investigator Grant in 2023.

Title: Targeting transcriptional CDKs in Cancer

ABSTRACT

Accurate control of gene-expression is essential for normal development and deregulation of transcription invariably results in human pathologies, including cancer. The dependency of tumour cells on aberrant gene-expression programs and the reliance on core-transcriptional machinery in these cells has been coined "transcriptional addiction". Similar to cell cycle regulation, RNA Polymerase II (POLII)-driven transcription should be considered as a unidirectional multistep cycle, consisting of initiation, pausing, elongation, termination and recycling steps, which are tightly controlled by the concerted action of cyclin-dependent kinases (CDKs) and their cognate cyclins, analogous to the cyclin/CDK control of the cell cycle. This talk will focus on transcriptional CDKs (eg CDK7,8,9,11,12,13) and discuss how dysregulation of the transcription cycle plays an important role in cancer. I will discuss the development of small molecules targeting transcriptional CDKs as anti-cancer agents and provide a framework for the rational therapeutic application of these agents in oncology.

KEYNOTE SPEAKERS



Shu-Bing Qian

Professor

Cornell University, USA

BIOGRAPHY

Dr. Shu-Bing Qian is currently the James Jamison Professor at Cornell University. Most of the research work in Dr. Qian's laboratory is broadly interdisciplinary, with a primary emphasis on mRNA translation, nutrient signaling pathway, and stress response. Using biochemical, genetic, and cell biological approach, the Qian laboratory investigates translational control of gene expression, molecular mechanisms of adaptive stress response, dynamic mRNA modifications, and the implications in human health and diseases. Dr. Qian's group pioneered profiling of initiating and terminating ribosomes. In addition to mechanistic understanding of alternative translation, Dr. Qian lab recently developed trans-RNA technology to achieve programmable translation initiation. Dr. Qian is a recipient of NIH Director's New Innovator Award (2009), a faculty scholar at Howard Hughes Medical Institute, and NIH Director's Pioneer Award (2020).

Title: Ribosome decoding memory in translational control

ABSTRACT

During mRNA translation, ribosome dynamics at individual codons critically determine both the quality and quantity of protein products. Codon repeats are widely represented in human genes, and pathological expansions of trinucleotide repeats, particularly CAG repeats, underlies several neurodegenerative disorders, including Huntington's disease and spinocerebellar ataxia. Long stretches of consecutive codons are generally thought to impede elongation by depleting cognate tRNAs. However, in Huntington's disease, ribosomes translate hundreds of consecutive CAG codons without catastrophic stalling. Here, we systematically profiled ribosome behavior across repeats of all 20 amino acids encoded in the human genome. Unexpectedly, for proline and lysine repeats – commonly considered difficult to decode – we found that ribosomes accelerate after an initial phase of slow decoding, a phenomenon we term adaptive decoding. Upon translation of consecutive CAG codons, we found that ribosomes acquired a form of decoding inertia that favors continued decoding of the same codon type. Contrary to prevailing assumptions, the ribosome decoding memory acquired from translation of codon repeats constrains frameshifting. Interrupting this decoding memory with proline codon tracts reduces polyglutamine synthesis and suppresses protein aggregation. These findings uncover an adaptive dimension of ribosome decoding that actively shapes the translation of physiological and pathological amino acid repeats.

KEYNOTE SPEAKERS



Wan Yue

Executive Director

Genome Institute of Singapore, A*STAR

BIOGRAPHY

Yue Wan is the Executive Director of A*STAR Genome Institute of Singapore (GIS). She received her B.Sc. in Cell Biology and Biochemistry from the University of California, San Diego, and her Ph.D. in Cancer Biology from Stanford University, under the mentorship of Dr. Howard Y. Chang. During her Ph.D., she developed the first high-throughput method for genome-wide RNA structure probing.

Yue is a recipient of the A*STAR National Science Scholarship (NSS-PhD) and has received numerous national and international awards and honours in recognition of her research excellence. These include the Branco Weiss Fellowship (Society in Science), EMBO Young Investigator Award, and CIFAR-Azrieli Global Scholar. She was recently elected as an EMBO Associate Member and is also a recipient of the prestigious HUGO Chen Award of Excellence, in recognition of her outstanding achievements and contributions to human genomics and RNA biology. Her other honours include the Young Scientist Award, L'Oréal-UNESCO For Women in Science Award, and Singapore National Research Foundation Fellowship.

Most recently, Yue participated in the international Wellcome Leap RNA Readiness and Response programme. Her research focuses on understanding the functions of RNA structures and advancing novel RNA-based vaccines and therapeutics.

Title: RNA single-strandedness and remodeling promotes stress granule condensation

ABSTRACT

Cells have evolved mechanisms to respond to and recover from environmental stress. During stress, mRNAs are transiently condensed into stress granules (SGs) and subsequently released upon stress resolution. Recent studies suggest that nonspecific trans RNA-RNA interactions drive SG assembly, however, the RNA structural landscape and RNA-RNA interactions within SGs have remained largely unexplored. Here, we employed complementary RNA structure probing approaches to directly characterize RNA conformation within SGs. Surprisingly, although cellular RNAs become globally more structured during stress, RNAs enriched in SGs are more single-stranded both intra- and intermolecularly. We further demonstrate that increased RNA single-strandedness play a role in promoting SG condensation, a process potentially mediated by RNA binding proteins, such as SRSF1. Moreover, we observed active RNA unwinding within SGs by helicases and found that depletion of the RNA helicase, DDX3X, enhances RNA pairing and reduces SG assembly. Together, our findings reveal multiple mechanisms that preserve RNA single-strandedness within SGs, and establish RNA structure regulation as a fundamental determinant of cellular plasticity during stress response.

KEYNOTE SPEAKERS



Terrance P. Snutch

Professor

University of British Columbia, Canada

BIOGRAPHY

Prof. Snutch is considered a pioneer in molecular neurobiology, most well-known for his cloning and characterization of the voltage-gated calcium channel family linked to dozens of serious brain disorders ranging from ataxias, congenital migraine, mood disorders autism and epilepsies. As an innovator and inventor establishing translational research from lab to patients, Prof. Snutch designed and advanced multiple calcium channel blocking drugs into the clinic, as well as taking a long-lasting opioid for severe pain through phase 3 trials, FDA approval and onto the market. Most recently, Z944, a first-in-class T-type calcium channel blocker designed and developed by Prof. Snutch passed Phase 3 clinical trials and has been designated “Breakthrough Therapy” status by the FDA for the treatment of essential tremor, the largest movement disorder worldwide. The work to date has resulted in Prof. Snutch being coauthor on 230 research publications and inventor on 116 issued patents (29 U.S.; 87 international).

In rapid response to the SARS-CoV-2 pandemic, Prof. Snutch founded the Canadian COVID-19 Genomics Network (VirusSeq), a transnational effort assembly of Canada’s provincial, territorial and federal health labs, hospitals and academic centres. During the pandemic VirusSeq sequenced ~433,000 SARS-CoV-2 genomes from Canadian patients, sharing genomic and variant data nationally and internationally in real time to inform health authorities regarding decision making as to best protect Canadians during the pandemic.

In acknowledgement of his many accomplishments, Prof. Snutch has been recognized through prestigious scientific awards and accolades, including Canada’s Margolese National Brain Disorders Prize, the International Albrecht Fleckenstein Award, the Steacie Prize, the Canada Research Chair in Neurobiology and Genomics, and induction as Fellow of the Royal Society of Canada, the Canadian Academy of Health Sciences, and the National Academy of Inventors (USA).

Title: Targeting Voltage-gated Calcium Channels for the Treatment of Neurological Disorders

ABSTRACT

Across the human voltage-gated calcium channel pore-forming α_1 subunit gene family, Cav1.1 to Cav3.3, approximately 30 distinct disorders (channelopathies) have been classified in clinical genetics databases. Of these, 22 primarily affect the central and peripheral nervous systems and include absence and idiopathic epilepsies, spinocerebellar ataxias, neurodevelopmental disorders, bipolar, schizophrenia, and congenital migraine/deafness/night blindness. Beyond monogenic calcium channelopathies, calcium ion dysregulation mediated by voltage-gated calcium channel activity is a central driver in numerous acquired human disorders. Of note, these include major neurological pathophysiologies linked to movement disorders such as sporadic Parkinson’s and essential tremor, various pain syndromes, and neurodegenerative disorders including Alzheimer’s disease. Taken together, there is a strong need to develop subtype-selective calcium channel therapeutics aimed at the multitude of associated neurological disorders. The talk here will describe the bench-to-bedside development of Z944 (Ulixacaltamide), a first-in-class T-type channel blocker currently before the FDA for approval as the first targeted therapeutic for the treatment of essential tremor, the largest movement disorder worldwide. Also to be presented are data supporting the notion of targeting of T-type channel activity relevant to certain pain and neurodegenerative conditions.

KEYNOTE SPEAKERS



Rickie Patani

Professor

NUS Medicine, National University of Singapore

BIOGRAPHY

Rickie Patani is a Neurologist and Cell Biologist. He trained in Neurology in UK institutions including in Queen Square and Addenbrooke's, Cambridge. He was a Co-Director of the MND service at Queen Square from 2017-2025. He obtained a PhD and Post-doctoral experience in Cambridge University and set up his lab at UCL Queen Square Institute of Neurology in 2013. He moved to the Francis Crick Institute in 2017. In 2018, Rickie was elected Fellow of the Royal College of Physicians (FRCP). He was appointed full Professor at UCL in 2019. Rickie recently left his role as a Senior Group Leader at the Francis Crick Institute as he was appointed Director of the Neurobiology Programme at NUS Life Sciences Institute and Professor of Neuroscience at NUS in the Departments of Medicine and Anatomy. Rickie was elected Fellow of the Academy of Medical Sciences (FMedSci) in 2025. He has been awarded international and national prizes for his research including the Paulo Gontijo Prize in Medicine, the Lister Prize, the International 3Rs Prize, the Graham Bull Prize and the Goulstonian Lectureship from the Royal College of Physicians. Rickie's Lab is passionately committed to understanding neurodegenerative disorders to uncover new therapies. His team works primarily on the themes of RNA metabolism and cellular autonomy in ALS/FTD using human induced pluripotent stem cell models as a primary discovery platform.

Title: Reformulating Neurodegeneration: The emerging role of SFPQ

ABSTRACT

As a physician-scientist, I am passionately committed to understanding and ultimately curing devastating diseases. In particular, my laboratory studies age-related diseases of the nervous system, focusing on motor neuron disease (ALS) and different forms of Dementia. In ALS, patients lose the ability to move, eat, speak and ultimately breathe. Such age-related neurodegenerative diseases are largely untreatable because we do not understand the underlying mechanisms. In order to address this critical void, my lab uses human stem cells generated from real patients. With over 15 years of experience using this technology, we can now transform stem cells from patients into human neurons and, separately, glia in a petri dish. This approach allows us to molecularly interrogate the sequence of disease-related events within particular cell types.

This talk will showcase what our laboratory has contributed to this field. Our overarching goal is to identify precisely what goes wrong, when this begins and in which cell type. Broadly, I will cover how the following phenomena contribute to motor neuron degeneration in ALS: i) deregulated RNA metabolism; ii) reactive transformation of astrocytes. More specifically, I will focus how on a form of alternative splicing called intron retention is deregulated in ALS and may drive pathogenesis in different cell types. I will also summarise our contributions to other archetypal age-related neurodegenerative disorders. Through these advances, we hope to precisely target salient underlying disease mechanisms for ultimate patient benefit.

KEYNOTE SPEAKERS



Takeshi Iwatsubo

Professor

University of Tokyo, Japan

BIOGRAPHY

Takeshi Iwatsubo is director of the National Institute of Neuroscience, National Center of Neurology and Psychiatry, Project Professor of the University of Tokyo, and chairman of the Japan Society for Dementia Research. Trained as a neurologist and neuropathologist, Iwatsubo has contributed to the study of human neurodegenerative diseases, particularly Alzheimer's and Parkinson's, using multidisciplinary approaches. He demonstrated that A β ₄₂ is the initial species deposited in senile plaque amyloid, elucidated the process of γ -secretase complex formation, and identified phosphorylated τ -synuclein as a component of Lewy bodies. He was the Principal Investigator of the Japanese AD Neuroimaging Initiative (J-ADNI) and the Japanese Trial Ready Cohort for Prevention of Alzheimer's Disease (J-TRC), and currently is the PI of the Japanese Registry for AD-DMT. He is the recipient of the MetLife Award for Medical Research (2008), AAIC Lifetime Achievement Award (2010), the Potamkin Prize (2012), and the Medal with Purple Ribbon from the Japanese government (2024), and CTAD Lifetime Achievement Award (2025).

Title: The path toward disease-modifying therapies of Alzheimer's disease

ABSTRACT

Disease-modifying therapies (DMT) targeting early Alzheimer's disease (AD), especially those for anti-amyloid β (A β) antibody drugs lecanemab and donanemab, have been successfully implemented in clinical practice, opening up a new era for AD therapies. Notably, these positive outcomes of AD DMT trials have largely depended on molecular imaging and fluid biomarkers, underscoring the needs of markers that surrogate the clinical and pathophysiological progression of AD, as well as the efficacy of DMTs. We have demonstrated that the clinical and biomarker profiles of prodromal AD in J-ADNI were remarkably similar to those in North American ADNI, supporting the harmonization in global clinical trials. Furthermore, DMT trials in the asymptomatic stage of AD (preclinical AD) are underway, including AHEAD study using lecanemab and TRAILBLAZER ALZ-3 using donanemab, are underway. To make these preclinical AD trials successful, trial ready cohorts (TRC) of preclinical and prodromal AD, are being established in the US and Japan. J-TRC launched in 2019 is comprised of a webstudy followed by an on-site study, so far having recruited ~15600 and ~870 participants, respectively, and ~40-50 amyloid-elevated volunteers have been screened in DMT trials. Biomarker studies in J-TRC have shown that combinations of plasma A β ₄₂-related biomarkers and p-tau₂₁₇ are potent in the prediction of A β -PET positivity and may be instrumental in the prescreening for clinical trials of DMTs for preclinical and prodromal AD. These clinical activities will pave the way toward the development of AD therapies targeting its very early stages.



Patrick Tan

Professor

Duke -NUS Medical School, Singapore

BIOGRAPHY

Prof. Patrick Tan is Dean of Duke-NUS Medical School, Singapore and Provost's Chair in Cancer and Stem Cell Biology. He is also Executive Director of PRECISE (Precision Health Research Singapore) coordinating Singapore's National Precision Medicine program, and Professor (adjunct) at Duke University, USA. He received his B.A. (summa cum laude) from Harvard University and MD PhD degree from Stanford University, where he received the Charles Yanofsky prize. Other awards include the President's Scholarship, Loke Cheng Kim scholarship, Young Scientist Award (A-STAR), Singapore Youth Award, Chen New Investigator Award (Human Genome Organization), President's Science Award, Japanese Cancer Association International Award, Public Administration Medal (Silver), Exemplary Public Service Award, and NUS University Research Recognition Award. He has received the American Association for Cancer Research (AACR) Team Science Award as Team Leader, and Genome Valley Excellence Award by the Government of Telangana (India). He is a member of the American Society for Clinical Investigation (ASCI), Association of American Physicians (AAP), the Singapore Bioethics Advisory Committee (BAC), a Board Member of the International Gastric Cancer Association, Global Alliance for Genomics and Health (GA4GH), Board of Editors for Science and Cancer Discovery, and an advisory member for Qatar Precision Health Institute.

Title: Molecular Signatures and Clonal Hematopoiesis in Gastric Intestinal Metaplasia

ABSTRACT

Intestinal metaplasia (IM) is a pre-cancerous condition of the stomach where IM patients are at risk for progressing to gastric malignancy (gastric cancer; GC). However, not all IM patients will develop GC, motivating the need to identify molecular factors defining those 'high-risk' IM patients that may benefit from enhanced surveillance. In this talk, I will describe our attempts to delineate factors contributing to IM-to-GC progression, across distinct environmental, somatic, and germline axes.



Greg Wang

Professor

Duke Cancer Institute, USA

BIOGRAPHY

Greg Wang received his PHD from University of California San Diego and his postdoctoral training with David Allis at Rockefeller University. He started his independent career as a tenure-track assistant professor at University of North Carolina (UNC) at Chapel Hill in 2012 where he was promoted to associate professor with tenure and then full professor by 2022. In 2023, Dr. Wang joined the Department of Pharmacology and Cancer Biology and Duke Cancer Institute, Duke University as a tenured full professor, and in 2026, is named as James B Duke Distinguished Professor in Pharmacology and Cancer Biology. Dr. Wang has received a number of career-related awards including the 2021 Young Investigator Award from the American Society for Biochemistry and Molecular Biology (ASBMB), and the Jefferson Fellowship in Medicine (2014), Phillip and Ruth Hettleman Prize for Artistic and Scholarly Achievement (2019) and the Yang Family Biomedicine Scholar (2020) from UNC, as well as recognitions of private foundations, such as American Cancer Society Scholar (2016), Leukemia & Lymphoma Society Scholar (2018), Janet D. Rowley Medical Research Award (2015) and Kimmel Scholar (2014).

His contributions the field include the demonstration, for the first time, that mis-regulation of histone modification reader is causal for oncogenicity using animal models (Nature 2009; as a work with Dave Allis). At his independent position, Dr. Wang identified novel histone reader proteins that mediate epigenetic regulation and, when mis-regulated, contribute to cancer development. Additionally, he demonstrated that phase separation of chromatin-binding factor can establish a type of multi-component condensates that not only enhance transcriptional outputs but also contribute to the formation of chromatin loops. Lastly, his team and collaborator are experienced in the development of small-molecule therapeutic agents such as PROTAC degraders for epigenetic factors.

Title: Chromatin Dysregulation, a Cancer Driver

ABSTRACT

Our research programs focus on mechanistic understanding of how chemical modifications of chromatin (including methylations of DNA and histone tails) regulate gene expression and cell fate determination during normal development, and how their deregulations lead to human diseases. Utilizing biochemical approaches, our laboratory recently identified and characterized novel proteins that specifically bind to histone lysine methylations. These histone modification 'readers' are crucially involved in gene/genome regulation, cell lineage specification and/or cancerous transformation. Importantly, discovery of small-molecule inhibitors to target chromatin modulators has become an area of intensive investigation and holds great promise for therapies. Our goal is to yield potential drug candidates with preclinical cancer models, which shall pave a way for translating new therapeutic approaches in future. During this meeting, we will report our research progresses along these exciting lines. (website: www.gregwanglab.com)



Wee Wei Tee

Associate Professor

NUS Medicine, National University of Singapore

Institute of Molecular and Cell Biology, A*STAR, Singapore

BIOGRAPHY

A/Prof Tee Wee Wei is a faculty member in the Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore. He is also a Senior Principal Investigator at the Institute of Molecular and Cell Biology (IMCB), A*STAR, where he serves as Division Director of Cancer Signalling and Therapy.

He obtained his PhD from the University of Cambridge under Prof. Azim Surani and subsequently trained with Prof. Danny Reinberg at New York University/HHMI. His research investigates the intersection of developmental biology, epigenetics and cancer, with a particular focus on how cancer cells hijack embryonic and germline programmes to acquire cellular plasticity, metastatic potential and therapeutic resistance. His laboratory aims to translate these fundamental discoveries into new therapeutic vulnerabilities and strategies for cancer treatment.

Title: Exploiting embryonic vulnerabilities in cancer

ABSTRACT

Cancer cells frequently reactivate developmental and germline programmes normally restricted to embryogenesis or reproductive tissues. Emerging evidence suggests that cancer cells can exploit these programmes to acquire plasticity, metastatic potential and therapeutic resistance.

Our work has explored this intersection between developmental and cancer biology. We identified the NELF transcriptional complex as a regulator of cellular plasticity in both totipotency and cancer: NELFA promotes the 2-cell-like embryonic state (Hu et al., Nature Cell Biology, 2020), while NELF rewiring in cancer drives epithelial–mesenchymal plasticity, stemness and metastasis (Zhang et al., Nature Communications, 2023). More recently, we showed that cancer cells aberrantly reactivate SYCP1, a germline-restricted meiotic protein, and repurpose it as a chromatin regulator controlling proliferation and DNA damage responses (Brennan et al., Science Advances, 2026).

Together, these studies suggest that cancer hijacks embryonic and germline machinery to establish malignant cell states and unique dependencies. I will discuss these findings and provide new updates on our efforts to identify and therapeutically exploit embryonic vulnerabilities in cancer.



Reshma Taneja

Professor

NUS Medicine, National University of Singapore

BIOGRAPHY

Professor Taneja received her Ph.D. from the Indian Institute of Science and went on to complete her postdoctoral training in the laboratory of Professor Pierre Chambon in France. She later established her own laboratory at the Mount Sinai School of Medicine in New York City before moving to Singapore in 2008.

She is currently the Head of the Department of Physiology at the National University of Singapore. During her time at NUS, she has received several awards recognizing both her research and teaching, including the Faculty Research Excellence Award, Faculty Teaching Excellence Award, NGS Teaching Commendation Award, and the Graduate Mentor of the Year Award.

Her research focuses on understanding the epigenetic and metabolic vulnerabilities of the paediatric cancer rhabdomyosarcoma, with the aim of identifying new therapeutic opportunities.

Title: Metabolic and signaling dependencies of tumor initiating cells in rhabdomyosarcoma

ABSTRACT

Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma in children and is characterized by a failure of myogenic precursor cells to undergo terminal differentiation. RMS comprises two major molecular subtypes: fusion-positive (FP-RMS), defined by the expression of the oncogenic PAX3-FOXO1 fusion protein, and fusion-negative (FN-RMS). Despite intensive multimodal therapy, outcomes for patients with high-risk disease remain poor, highlighting the urgent need for new therapeutic strategies.

The relatively quiet mutational landscape of RMS suggests that epigenetic deregulation may play a central role in tumour initiation, progression, and therapeutic resistance. Over the years, we have investigated the roles of chromatin regulators, including the histone methylation writers EHMT1/EHMT2 and the histone acetylation reader BRD4, in maintaining the myogenic differentiation block and promoting the aggressive phenotype of RMS cells.

In this seminar, I will discuss our findings on how epigenetic mechanisms contribute to RMS pathogenesis and tumour cell state. I will also present our ongoing work aimed at defining the metabolic dependencies of tumour-initiating cells in RMS. Together, these studies seek to uncover new vulnerabilities that can be therapeutically exploited to improve outcomes for children with this aggressive cancer.



Martin Bushell

Professor

Cancer Research UK Scotland Institute, Scotland

BIOGRAPHY

Prof. Martin Bushell completed his BSc (1996) and DPhil (1999) in Biochemistry at the University of Sussex. He subsequently undertook a Wellcome Trust International Travelling Fellowship at Stanford University, USA, from 2001 to 2005. Establishing his own laboratory at the University of Nottingham (2005–2010), he was awarded a BBSRC David Phillips Fellowship to investigate how gene expression is controlled at the translational level, with a particular focus on microRNAs.

In 2010, he relocated to the MRC Toxicology Unit in Leicester as a Programme Leader. During his tenure, he secured an MRC Non-Clinical Senior Fellowship (2010–2015) and served as Deputy Director of the Unit from 2011 to 2018.

In 2018, he moved his laboratory to Glasgow as a Senior Group Leader at the CRUK Scotland Institute (formerly the Beatson Institute). He was appointed Deputy Director of the Institute in 2022. Currently, his laboratory investigates how protein synthesis is controlled and regulated by cellular signalling, and how it orchestrates programmes of gene expression within the cancer environment.

Title: DDX6 is required to regulate ribosome traffic to control co-translational assembly of protein complexes

ABSTRACT

The DEAD-box helicase DDX6 is a known translational repressor and decay factor. While its role in RNA degradation is established, its mechanical function during active translation remains largely unexplored. Using TCP-seq and disome-profiling, we found DDX6 depletion minimally affects scanning or elongating ribosomes but triggers a dramatic redistribution of collided ribosomes. Strikingly, mRNAs with increased vs decreased collisions upon DDX6 depletion segregate distinctly by GC3 content (~80% vs ~40%). While global collision numbers remained static, DDX6 loss triggered a ZAK-dependent increase in p38(P), indicating these redistributed collisions become pathologically ribotoxic.

To dissect this mechanism, we employed DDX6-selective ribosome-profiling. We show DDX6 associates with elongating ribosomes at specific coding sequence positions with a clear off/on distribution. To assess co-translational assembly, we sequenced 30nt disome footprints, which originate from ribosomes linked through interacting nascent chains. We observe a profound spatial overlap, where 30nt disome footprints perfectly coincide with DDX6 association sites, suggesting DDX6 binds ribosomes during co-translational assembly. Furthermore, these regions are immediately preceded by collided ribosomes. Depleting DDX6 crucially reduces collisions at these positions, resulting in increased downstream collisions and globally reduced co-translational assembly.

Mechanistically, these DDX6-association sites exhibit a sharp gradient of decreasing GC3 content and increased downstream GA content, suggesting localised codon optimality dictates DDX6 recruitment. Building on findings that eIF4A2 clamps purine-rich RNA, we demonstrate DDX6 possesses similar clamping activity. We propose a model where DDX6 acts as a physical clamp, slowing the elongating ribosome to allow orchestrated co-translational assembly, while marking these pauses as “safe” to shield them from stress sensors. Our results reveal DDX6-mediated ribosome pausing is an essential checkpoint, orchestrating nascent chain interactions to ensure proper complex assembly and prevent ribotoxicity to maintain proteostasis.



Anthony Khong

Assistant Professor

NUS Medicine, National University of Singapore

BIOGRAPHY

Dr. Anthony Khong is an Assistant Professor in the Department of Physiology and the Cancer Science Institute at the National University of Singapore. He received his Bachelor of Science and Ph.D. from the University of British Columbia and completed his postdoctoral training at the University of Colorado Boulder before joining NUS in 2023.

Dr. Khong's research centers on RNA biology and biomolecular condensates, with a particular interest in how cells reorganize RNA and proteins during stress. During his time in the Roy Parker's Lab, he contributed to foundational studies defining the RNA composition and properties of stress granules. This work helped clarify that stress granules can arise through non-specific RNA aggregation, reshaping prevailing views of condensate assembly and informing how other RNA-protein structures may form. His current research builds on these insights to investigate how stress granules influence cancer-associated processes and cellular resilience under stress.

Title: Hypoxia-Induced Stress Granules Assemble with Minimal Translational Repression and Selectively Stabilize RNAs

ABSTRACT

Tumours employ adaptive responses to hypoxia that promote survival and proliferation. While transcriptional adaptations to low oxygen have been extensively studied, RNA-mediated mechanisms of hypoxic adaptation remain poorly understood. One such mechanism involves stress granules (SGs), messenger ribonucleoprotein (mRNP) condensates that assemble when non-translating mRNPs accumulate in the cytosol. Although SGs are frequently observed in hypoxic regions of solid tumours, the mechanisms governing their assembly, composition, and function during hypoxia remain largely unknown.

Here, we show that hypoxia-induced SGs are molecularly distinct from classical arsenite-induced SGs. Unlike arsenite SGs, hypoxia-induced SGs assemble independently of the integrated stress response and instead depend on HIF1 α -REDD1-mTORC1-4EBP1 axis. Remarkably, hypoxic SGs form with minimal global translational repression, suggesting that non-translating mRNPs condense at a reduced critical saturation concentration. This process additionally requires LARP1, an mTORC1-regulated RNA binding protein that we find interacts with the SG condensation factor G3BP1 during hypoxia. Together, these findings suggest that LARP1, G3BP1, and RNA cooperate to promote mRNP condensation under hypoxic conditions.

Using fluorescence-activated non-membrane condensate isolation, we define the RNA composition of hypoxia-induced SGs and uncover principles governing RNA recruitment and function. Similar to arsenite SGs, hypoxic SGs preferentially recruit long transcripts but lack the AU-rich sequence bias characteristic of arsenite SGs, revealing distinct RNA-partitioning principles. Importantly, SG recruitment protects select transcripts from RNA decay, thereby maintaining gene-expression programs associated with cell-cycle progression and prolonged hypoxic adaptation.

Together, our findings establish hypoxia-induced SGs as a distinct class of RNA condensates assembled through an mTORC1-dependent pathway under minimal translational repression. These condensates employ distinct RNA-recruitment principles and selectively stabilize transcripts, revealing how RNA condensation can reshape gene expression to promote cellular adaptation to hypoxia.



Eleonora Leucci

Associate Professor

KU Leuven, Belgium

BIOGRAPHY

Eleonora Leucci obtained her PhD in Medical Biotechnology from the University of Siena (Italy) in 2007. She then moved to BRIC, University of Copenhagen (Denmark) where she worked on small and long non-coding RNAs in the lab of Anders Lund as a postdoctoral fellow. Since 2012, she has moved to Belgium, where she was first a Marie Curie/VIB postdoctoral fellow in Chris Marine's lab and then an FNRS research associate at ULB, studying the role of lncRNAs in skin cancer. She received several national and international prizes in 2016 for her work on the lncRNA SAMMSON, and she was the recipient of the MRA Young Investigator Award 2018. Since 2017, Eleonora Leucci has led the laboratory for RNA cancer biology and heads the PDX platform TRACE at KU Leuven. Her lab studies RNA metabolism in cancer with a particular focus on the characterization of long non-coding RNAs important for therapy resistance.

Title: Contribution of lncRNAs to the generation of drug-tolerant persister cells

ABSTRACT

Long non-coding RNAs (lncRNAs) generated from remote areas of the human genome constitute a major source of innovation for the adaptation to the numerous stresses encountered by cancer cells during progression and therapy resistance. As such, research in this field offers a unique opportunity to study melanoma evolution and unveil potentially novel biology. Over the years, we have characterised several novel transcripts interacting with the translational machinery, either in the mitochondria or in the cytosol, and affecting the generation of drug-tolerant cells. These transcripts represent previously unexplored cancer-specific vulnerabilities and thus extend the palette of therapeutic opportunities to include RNA-based medicines.



Pedro Batista

Stadtman Investigator

National Cancer Institute, USA

BIOGRAPHY

Dr. Batista obtained his Licenciature, equivalent to a bachelor's degree, from the University of Lisbon. He completed his Ph.D. thesis research in the laboratory of Professor Craig C. Mello at the University of Massachusetts Medical School, where he studied the regulatory functions of endogenous RNA interference pathways in *C. elegans*. He received the Harold M. Weintraub Award for outstanding graduate studies. For his postdoctoral training, Dr. Batista joined the laboratory of Dr. Howard Chang at Stanford University, where his research focused on the role of the RNA post-transcriptional modification m6A in stem cell differentiation. This work was supported in part by a fellowship from the Damon Runyon Cancer Research Foundation. In November 2016, Dr. Batista joined the Laboratory of Cell Biology at the Center for Cancer Research as a Stadtman Tenure-Track Investigator, where he studies the interaction between the tumor microenvironment and RNA post-transcriptional regulation.

Title: ZNFX1 acts as a negative regulator of Natural Killer cell mediated cytotoxicity in HLRCC

ABSTRACT

Loss of FH activity, and the resulting accumulation of fumarate, induces the release of mitochondrial contents into the cytosol, activating innate immune pathways and triggering chronic inflammation that correlates with increased leukocyte infiltration in FH-deficient RCCs. Natural killer cells are leukocytes central to the innate immune system and exhibit potent cytotoxicity against physiologically stressed cells, including tumor cells, thereby potentially restraining tumor growth. NK cells are present in RCC, and their infiltration is associated with patient survival. Despite this infiltration, HLRCC tumors develop and metastasize, highlighting the presence of tumor microenvironmental factors that suppress NK function. We performed a targeted CRISPR screen to identify proteins involved in post-transcriptional RNA regulation that protect HLRCC cells from NK-mediated killing and identified ZNFX1 as a negative regulator of this response. Loss of ZNFX1 sensitizes cells to activation of innate immune pathways and to NK-mediated cytotoxicity. A targeted suppressor screen identified PKR as the driver of NK sensitivity in ZNFX1-deficient cells. We propose a model in which NK-cell delivery of cytotoxic granules activates innate immune signaling but is not sufficient, on its own, to kill the cells; this response is restrained by ZNFX1. These findings suggest that modulating innate immune pathways may sensitize solid tumor cells to NK cell activity.



Jiangbo Wei

Assistant Professor

Faculty of Science, National University of Singapore

BIOGRAPHY

Jiangbo received his B.S. in Chemistry from Peking University in 2015. He then pursued his Ph.D. study and postdoctoral research under the mentorship of Prof. Chuan He at the University of Chicago, where his work focused on the function of RNA modifications in gene expression and the epitranscriptomic regulation of chromatin and transcription. In December 2023, he was awarded the NUS Presidential Young Professorship, and in 2024 he joined the Departments of Chemistry and Biological Sciences as an Assistant Professor. He is also a Principal Investigator at the Cancer Science Institute of Singapore and a member of the National Initiative of RNA Biology and its Applications. His research integrates chemical biology, cell biology and epigenetics to develop RNA-centric technologies and to investigate the context-dependent regulation of RNA modifications, chromatin state, and their coupling in cancer, metabolic disorders, and development.

Title: Persistent mRNA m⁶A sustains BET inhibitor resistance in pancreatic cancer

ABSTRACT

Why epigenetic inhibitors work in some tumours and not in others remains a central challenge in cancer therapy. Here we show that the response to BET bromodomain inhibition in pancreatic cancer is set by whether the drug can shut down the mRNA m⁶A methyltransferase METTL3. An unbiased genome-wide CRISPR screen in resistant cells recovers METTL3. BET inhibition lowers METTL3 and m⁶A in responsive cells but not in resistant cells. Overexpressing METTL3 in responsive cells renders them resistant, and depleting it in resistant cells restores the response. The same screen also nominates a nuclear m⁶A reader. Epitranscriptome-wide profiling traces the dependency to an oncogenic cell-cycle regulator, whose transcript this reader stabilizes in the nucleus rather than in the cytoplasm, placing the decisive step on the pre-mRNA rather than after export. Removing the modification at that site is enough to resensitize resistant cells. Pharmacological inhibition of METTL3 reproduces the effect in resistant cells. In mice, combining either genetic or pharmacological loss of the enzyme with BET inhibition slows the growth of tumours that do not respond to the drug alone, including a patient-derived xenograft. Together, these findings show that a chromatin-directed drug acts through RNA methylation, and that persistent m⁶A accounts for much of the heterogeneity in BET inhibitor response.



Gerald Zamponi

Professor

University of Calgary, Canada

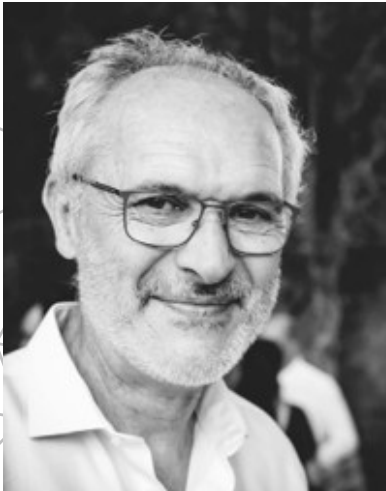
BIOGRAPHY

Dr. Gerald Zamponi is a Professor in the Cumming School of Medicine at the University of Calgary in the Department of Clinical Neurosciences. He previously served as Senior Associate Dean for Research the Head of the Department of Physiology and Pharmacology. He received his undergraduate training in Engineering Physics from the Johannes Kepler University in Austria, followed by a PhD in Neuroscience at the University of Calgary and postdoctoral work at the University of British Columbia in Canada. He is an elected Fellow of both the Royal Society of Canada, the Canadian Academy of Health Sciences, and the National Aacdemy of Inventors (USA).

Title: Targeting T-type calcium channel de-ubiquitination to treat chronic pain

ABSTRACT

Cav3.2 T-type calcium channels are important mediators of pain signaling. Their membrane expression is increased in chronic pain conditions and blocking them mediates analgesia. We discovered that this upregulation is due to aberrant deubiquitination of the channels by the deubiquitinase USP5 which directly binds to the intracellular domain III-IV linker region of the channels. USP5 expression is enhanced upon peripheral inflammation or injury and this then causes the channel to be deubiquitinated and become subject to reduced degradation. Validation of USP5 as a pain target in humans comes from clinical data on a pediatric patient with insensitivity to pain who harbours a USP5 missense mutation. A knock-in in mouse of this mutation phenocopies the patient's condition. The interaction between the channels and USP5 was validated as a new pharmacological target for pain therapeutics in a number of preclinical pain models in mice and rats. We identified a novel class of small organic molecules that target the interaction to cause pain relief, and demonstrate cardiovascular and kidney safety, as well as efficacy as orally bio-available analgesics. Hence, targeting the USP5 mediated upregulation of T-type channel activity without blocking ion flux through the channel per se is a novel for analgesia.



Emmanuel Bourinet

Professor

Institut de Genomique Fonctionnelle,
Montpellier, France

BIOGRAPHY

I hold a CNRS Research Director position with the French National Centre for Scientific Research and have led the "Calcium Channel Dynamics and Nociception" team at the Institute of Functional Genomics (IGF) in Montpellier, France, since 2005.

My research background centers on the structure-function relationships of voltage-gated calcium channels. I completed my PhD in Montpellier under the supervision of Prof. Joël Nargeot (1990–1993), studying calcium channels expressed from tissue mRNA injected into *Xenopus* oocytes and their regulation by protein kinases. I then joined the laboratory of Prof. Terry Snutch at the University of British Columbia in Vancouver, where I investigated various aspects of voltage-gated calcium channel function, including their modulation by GPCRs (such as opioid receptors) and the functional diversity arising from alternative splicing in the P/Q-type calcium channel family.

After securing a permanent CNRS junior researcher position, I returned to Montpellier and contributed to early molecular studies on T-type calcium channels. Building on this work, I established an independent research program focusing on the role of T-type channels in pain perception, expanding into rodent behavioral models. As a Principal Investigator since 2005, my team and collaborators aim to understand the contribution of calcium channels to the pathophysiology of somatosensation, focusing on peripheral sensory neurons and spinal circuits. We combine mouse genetics, electrophysiology, pharmacology, and behavioral analysis in preclinical models of chronic pain, and more recently, in the study of social and affective touch.

We strongly believe that preclinical findings require validation in human tissues to strengthen their translational potential. In collaboration with neurosurgeons and the organ donation coordination team at the Montpellier University Hospital, we established an access pipeline to perform molecular and ex vivo functional explorations on human dorsal root ganglia (DRG) and spinal cord tissues harvested from organ donors. Our research is framed around a reverse-translational strategy, prioritizing molecular pathways conserved between animal models and humans to maximize the potential for discovering mechanisms of pain pathophysiology.

From an administrative perspective, I have served on various evaluation committees, notably as a member and subsequently as President of the CNRS National Neuroscience Committee from 2017 to 2025.

Title: Targeting T-type calcium channel de-ubiquitination to treat chronic pain

ABSTRACT

Cav3.2 T-type calcium channels are important mediators of pain signaling. Their membrane expression is increased in chronic pain conditions and blocking them mediates analgesia. We discovered that this upregulation is due to aberrant deubiquitination of the channels by the deubiquitinase USP5 which directly binds to the intracellular domain III-IV linker region of the channels. USP5 expression is enhanced upon peripheral inflammation or injury and this then causes the channel to be deubiquitinated and become subject to reduced degradation. Validation of USP5 as a pain target in humans comes from clinical data on a pediatric patient with insensitivity to pain who harbours a USP5 missense mutation. A knock-in in mouse of this mutation phenocopies the patient's condition. The interaction between the channels and USP5 was validated as a new pharmacological target for pain therapeutics in a number of preclinical pain models in mice and rats. We identified a novel class of small organic molecules that target the interaction to cause pain relief, and demonstrate cardiovascular and kidney safety, as well as efficacy as orally bio-available analgesics. Hence, targeting the USP5 mediated upregulation of T-type channel activity without blocking ion flux through the channel per se is a novel for analgesia.



Soong Tuck Wah

Professor

NUS Medicine, National University of Singapore

BIOGRAPHY

Tuck Wah Soong was the Head of the Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore, from 2008 to 2017. He was Assistant Dean (Education) from 2006-2008 and is a senior faculty at the NUS Graduate School for Integrative Sciences and Engineering from 2004. He is the Deputy Programme Chair of the of the Neuroscience Translational Research Programme and a Principal Investigator of the Healthy Longevity and Cardiovascular and Metabolic Disease Translational Research Programmes.

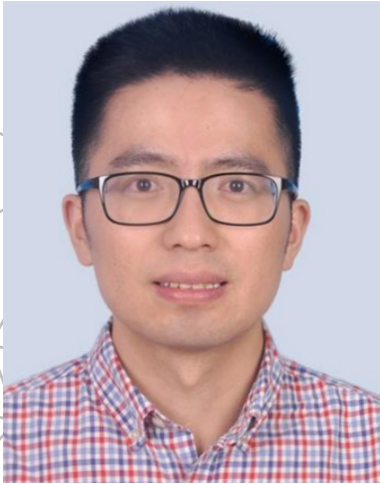
For research, Dr Soong was recognized by the Singapore Neuroscience Association with the “Excellence in Neuroscience” Research Award in 2013 and a Lifetime Achievement Award in 2025. He was awarded the Faculty Research Excellence Award twice (AY 2005/6 and AY 2012/2013), and the Faculty Outstanding Researcher Award for AY 2014/15. He was also awarded the Association for the study of Neurons and Disease or AND Investigator Award (Canada) in 2016 and the Dr C.S Paulose Research Excellence Award (India) in 2016. In 2024, he was an invited speaker of the Top 100 scientists’ seminar series of the Nanjing Medical University Tian Yuan Forum to celebrate the 90th anniversary of the university.

The research interests in his laboratory include: 1. Investigations into diversification of calcium channel function via alternative splicing and RNA editing and their implications in neurological disorders such as learning and memory, anxiety, circadian rhythm and metabolic disorders; 2. Investigations into galectin-Cav1.2 interactions and their implications in hypertension, heart diseases and in vascular dementia and 3. Investigations into the interplay of RNA editing of filamin A and oxygen-sensing pathways in cardiovascular and neurological disorders.

Title: Loss of Cav2.1_{EFa}-dependent Ca²⁺-dependent Facilitation resulted in ataxia and neurological disorders

ABSTRACT

Alternative splicing of Cav1.2 is a post-transcriptional mechanism that diversifies its structural potentially for optimal function. Here I will focus on work we have done on alternative splicing of mutually exclusive exons 37a/b that code for the EFa or EFb motif of Ca_v2.1 channels. Together with our collaborators we have shown that CaV2.1_{EFa} channels promote Ca²⁺-dependent facilitation and is developmentally regulated. We have also shown that in hippocampal neurons CaV2.1_{EFa} channels support paired-pulse depression while CaV2.1_{EFb} channels paired-pulse depression. The generation of the exon 37a conditional knock-out mice enabled us to address the physiological significance of CDF and its implications in neurological and neuropsychiatric disorders.



Hu Zhenyu

Senior Research Fellow

National Neuroscience Institute, Singapore

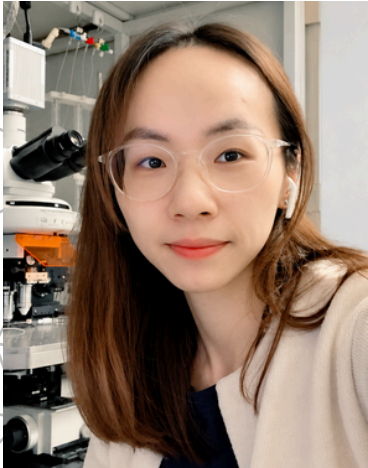
BIOGRAPHY

Dr Hu Zhenyu obtained his PhD degree in 2017 and subsequently completed post-doctoral training in Prof Soong Tuck Wah's lab at NUS, where he worked until 2024. He is currently a Senior Research Fellow at the Calcium Signaling Laboratory led by Assoc Prof Liao Ping at the National Neuroscience Institute, specialising in neurodegenerative and cardiovascular diseases by modulating voltage-gated calcium channels. His research focuses on understanding the calcium channel dysfunction mediated by its functional binding proteins, such as Galectins, Filamins and deubiquitinases, in the disease models of vascular dementia, hypertension and cardiac hypertrophy, with particular emphasis on development of novel peptide-based therapeutics.

Title: A Galectin-3-targeting peptide modulates Cav1.2 channel function in hypertension

ABSTRACT

Hypertension remains a leading risk factor for cardiovascular morbidity and mortality, highlighting the need for novel therapeutic strategies beyond conventional calcium channel blockers. Fine-tuning Cav1.2 calcium channel activity through its regulatory binding proteins represents an emerging approach to modulate vascular smooth muscle contraction and blood pressure. Here, we identified Galectin-3 as a previously unrecognized intracellular binding partner and positive regulator of Cav1.2 channels. Using molecular, biochemical, electrophysiological, structural, ex vivo, and in vivo approaches, we demonstrate that Galectin-3 binds to the intracellular II–III loop of Cav1.2, thereby increasing channel surface expression, current density, and open probability. Both Galectin-3 and Cav1.2 were significantly upregulated in arteries from spontaneously hypertensive rats and human patients, whereas smooth muscle-specific deletion of Galectin-3 reduced Cav1.2 expression, impaired vascular contractility, and lowered blood pressure in mice. Guided by in silico structural prediction and validated by site-directed mutagenesis, we developed iGal3BP, a peptide that selectively disrupts the Cav1.2–Galectin-3 protein interaction. In spontaneously hypertensive rats, iGal3BP accumulated in resistance arteries, reduced Cav1.2 protein expression, and produced a sustained antihypertensive effect. Furthermore, combined administration of iGal3BP with a Galectin-1 mimetic peptide, which negatively modulates Cav1.2 channels through a distinct mechanism, rapidly normalized systolic blood pressure within four hours and maintained normotension for up to 35 days. Collectively, these findings identify Galectin-3 as a critical regulator of Cav1.2 channel function and vascular contractility and establish disruption of the Cav1.2–Galectin-3 protein interaction as a promising peptide-based therapeutic strategy for hypertension. The study also highlights protein–protein interaction targeting as a novel paradigm for modulating voltage-gated calcium channels in cardiovascular disease.



Zhai Jing

Senior Research Fellow

NUS Medicine, National University of Singapore

BIOGRAPHY

Dr. Zhai Jing is a Senior Research Fellow from Ion Channel and Transporter Lab, in the Department of Physiology, working with Prof. Soong Tuck Wah. Her research focus on the physiological roles of RNA editing of voltage-gated calcium channel (Cav1.3). With the knockout mouse model, she had discovered the gain-of-function effect when knockout Cav1.3 RNA editing, which resulted in enhanced hippocampal-dependent learning and memory in the Cav1.3^{ΔECS} mice. However, trade-off effects were also observed from these mice. The Cav1.3^{ΔECS} mice developed obesity and glucose intolerance as well as disrupted circadian rhythmic activity in a gender specific manner. Her current work is to investigate the underlying mechanism of how loss of Cav1.3 RNA editing leads to these effects and more importantly why is it gender specific. Intriguingly, estrogen derived from the brain might be critical in regulating the neuronal activity in the hypothalamus.

Title: RNA editing of Cav1.3 modulates circadian rhythm through sex-dependent regulation by brain-derived estradiol : implications in metabolic health

ABSTRACT

The Cav1.3 channel contributes to a variety of neural functions, from neurodevelopment, learning and memory to addiction, mood and circadian regulation. From our recent published work, we demonstrated that loss of Cav1.3 RNA editing enhanced spatial learning and memory in the male Cav1.3^{ΔECS} mice. As RNA editing is a dynamic process that is not hardwired like in genetic mutation, we observed trade-offs and discovered that the male Cav1.3^{ΔECS} mice showed disturbance in sleep and were prone to over-weight tending towards obesity. The pace-making activity of SCN neurons were reduced in the Cav1.3^{ΔECS} male mice. Increased day activity and feeding behaviour were also observed from the Cav1.3^{ΔECS} male mice. The Cav1.3^{ΔECS} males consequently developed higher levels of fasting plasma glucose, fasting plasma insulin and glucose intolerance. Body weight gain and glucose dysregulation in Cav1.3^{ΔECS} males could however be rescued with day fasting for 6 weeks. These results highlight the functional significance of Cav1.3 channel editing in the modulation of circadian rhythm and feeding patterns that can result in metabolic dysregulation in the long run. Surprisingly this is subject to gender differences. In contrast to male, the female Cav1.3^{ΔECS} mice were protected against circadian disruption, obesity and have better metabolic health. Given that in rodents and humans, estrogen has been shown to play a pivotal role in the control of body weight, we pursued the possible role estrogen may play in this gender difference observed in the Cav1.3^{ΔECS} mice. We found that b-estradiol has direct inhibitory effect on Cav1.3 channel in SCN neurons. After measuring the level of b-estradiol in the CSF, we found that it is the brain-derived b-estradiol that was upregulated in the Cav1.3^{ΔECS} female mice that compensated for the excessive amount of Cav1.3 current due to lack of RNA editing. These findings suggested that the circadian regulation of RNA editing in Cav1.3 IQ-domain influences the SCN pace-making activity and loss of Cav1.3 RNA editing leads to male-specific circadian rhythmic disturbance and metabolic dysregulation.



Yousra El Ghaleb

Post Doctorate Fellow

Medical University of Innsbruck, Austria

BIOGRAPHY

Yousra El Ghaleb completed her Bachelor's in Psychobiology and Master's in Molecular Neurosciences at the University of Amsterdam, before pursuing her PhD at the Medical University of Innsbruck in the laboratory of Prof. Bernhard Flucher. During her PhD, she identified *CACNA1I* (coding for $Ca_v3.3$) for the first time as a disease gene for neurodevelopmental disorders — a landmark finding that became the foundation of her independent research program. This work was recognized with several awards, among them the Austrian State Prize "Award of Excellence 2022" for one of the best PhD dissertations in Austria.

Following a postdoctoral position in the Flucher lab, she was awarded the prestigious FWF ESPRIT grant in 2023 to establish her own research group at the Medical University of Innsbruck. With the help of many local and international collaborations the El Ghaleb lab focuses on elucidating the structural and functional disease mechanisms underlying *CACNA1I* channelopathies, combining electrophysiology, site-directed mutagenesis, and structural modeling to bridge the gap between channel dysfunction and patient phenotypes.

Title: Using Cross-Isoform Homology of Disease-Associated Voltage-Gated Ca^{2+} Channel Variants to Improve Pathogenicity Predictions

ABSTRACT

Voltage-Gated Ca^{2+} Channels (VGCCs) are pore-forming plasma membrane proteins activated by membrane depolarization, enabling Ca^{2+} entry along its electrochemical gradient. The ten mammalian VGCC isoforms are divided into high-voltage activated (HVA) channels, comprising Ca_v1 and Ca_v2 , and low-voltage activated (LVA) Ca_v3 channels. Mutations in all ten *Ca_v1*-encoding genes have been linked to channelopathies, from well-established associations such as $Ca_v2.1$ in familial hemiplegic migraine, to recently identified links between $Ca_v3.3$ and neurodevelopmental disorders.

In collaboration with the labs of Dr. Nadine Ortner and Dr. Norbert Weiss, we investigate whether pathogenic variants in highly conserved structural determinants of one VGCC isoform exert similar functional effects in other isoforms. Given the high sequence homology and conserved gating mechanisms across isoforms, we hypothesize that disease-associated variants at conserved residues may predict pathogenicity across channel subtypes. To test this, we inserted selected pathogenic variants into representative isoforms of HVA ($Ca_v1.3$ and $Ca_v2.1$) and LVA ($Ca_v3.2$ and $Ca_v3.3$) channels and characterize their functional consequences using patch-clamp electrophysiology, assessing current density, voltage dependence of activation and inactivation, and recovery and kinetics of inactivation.

Our data demonstrate that both the direction and severity of functional changes induced by homologous variants are consistent across VGCC isoforms, supporting a unified framework for variant interpretation with important implications for the diagnosis of calcium channelopathies.



Marina Chekulaeva

Principal Investigator

Max Delbrück Center for Molecular Medicine,
Germany

BIOGRAPHY

Marina Chekulaeva is a molecular biologist and RNA biologist whose work focuses on post-transcriptional gene regulation in neurons. She studied biochemistry and molecular biology before completing her PhD at EMBL Heidelberg, where she worked on RNA localization and translational control. She then trained as a postdoctoral researcher at the Friedrich Miescher Institute in Basel and at the University of Arizona, studying mechanisms of microRNA function.

Since 2013, she has led an independent research group at the Max Delbrück Center in Berlin. Her laboratory investigates how RNAs are localized, stabilized, and translated in subcellular compartments, with a particular focus on neurons and neurodegeneration. Her group combines molecular biology, genomics, imaging, and disease models to understand how local RNA regulation shapes neuronal function and how its disruption contributes to pathology.

Title: RNA localization in neurons and neurodegeneration

ABSTRACT

mRNA localization is regulated by localization elements, which are bound RBPs that target mRNAs to transport machinery, regulate their stability in a localization-dependent manner, or anchor them at a specific location in the cell. Despite the fact that thousands of mRNAs are localized in neurons, only a few localization elements and bound RBPs are known. To address this gap, we developed a protocol for transcriptome-wide mapping of neuronal localization. This approach identified localization elements in one-third of analyzed transcripts, suggesting that additional mechanisms contribute to localization. Our further work showed that depletion of mRNA destabilization elements functions as a mechanism that mediates the localization of housekeeping mRNAs to neurites.

A common feature in neurodegenerative diseases like ALS is the early loss of axons, pointing to defects in axonal localization and/or translation. ALS is associated with mutations in RNA-binding proteins such as FUS. To explore the role of local RNA metabolism in neurodegeneration, we established a FUS-ALS hiPSC-derived model. Analysis of the protein and mRNA expression profiles revealed a selective downregulation of proteins essential for neuromuscular junction function in FUS-ALS axons. This work sheds light on the mechanisms of ALS.



Christopher Chen Li-Hsian

Professor

NUS Medicine, National University of Singapore

BIOGRAPHY

Professor Christopher Chen is a Senior Clinician-Scientist at the Yong Loo Lin School of Medicine, National University of Singapore. His research training was at Oxford University and the Institute of Neurology, Queens Square, London. His major interests are in blood biomarkers, neuroimaging, prevention and treatment of stroke and dementia. He has over 600 publications and leads multiple studies and clinical trials. He aims to build regional collaborations in Brain Health through his roles as President of the Asian Society Against Dementia and the Asian Oceanian Association of Neurology.

Title: Multidomain Interventions for Brain Health to support Healthy Longevity

ABSTRACT

The SINGapore GERiatric Intervention Study to Reduce Cognitive Decline and Physical Frailty (SINGER) Study is a two-year clinical trial that aims to evaluate whether multidomain lifestyle intervention is effective in reducing cognitive decline and physical frailty in at risk elderly in Singapore.

Based on the FINGER trial which showed that it is possible to prevent cognitive decline using multidomain lifestyle interventions, SINGER is part of World Wide FINGERS.

Due to the Covid-19 pandemic, the SINGER trial was adapted to conduct lifestyle interventions remotely and to minimise face to face study visits with most of the research activities conducted online through a digital platform.

Participants receive guidance on diet, exercise, cognitive training and vascular monitoring so as to empower them to play an active role in their own healthy ageing.

The SINGER study recruited 1212 participants, completed interventions by end 2025 and the primary results will be reported in 2026. Pilot studies to enable implementation are ongoing.

Evidence-based interventions to prevent cognitive decline and physical frailty will play an important role in supporting Healthy Longevity.

Title:

Homozygous Hebp1 Deletion Mediate Amyloid Accumulation, Disrupts Spatial Neuromodulatory Networks, and Modulates Circuit Hyperexcitability in APP23 Mice

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Background:

Neural circuit dysfunction, neuroinflammation, and synaptic failure are central features of Alzheimer's disease (AD). Heme-binding protein 1 (Hebp1) has been implicated in neurodegeneration, but its contribution to amyloid- β (A β) pathology and neural network function remains unclear. Upon homozygous Hebp1 deletion in APP23 mice mediates amyloid plaque accumulation and altered survival in a gene-dosage-dependent manner. Spatial transcriptomic profiling showed preserved cellular architecture across hippocampal subregions but widespread transcriptional reorganization, including enrichment of cellular stress-response and chemical synaptic transmission pathways in the dentate gyrus and cornu ammonis. Despite this compensatory response, spatial metabolite-receptor interaction mapping revealed extensive disruption of intercellular signaling across the hippocampus and major subcortical projection centers, including the mammillary body and nucleus of the diagonal band. In contrast to control APP23 mice, which maintained robust GABAergic, glutamatergic, and cholinergic interactions, Hebp1-deficient mice exhibited widespread suppression of these networks. Subregion-specific analysis further identified reduced acetylcholine levels across hippocampal subfields, consistent with impaired long-range connectivity with diagonal band nucleus and mammillary body. In vivo electrophysiological recordings demonstrated that Hebp1 deletion modulated A β -associated circuit hyperexcitability altering neural circuit oscillations.

Presented by:

Aleksandr Mitriashkin (alexander.m@nus.edu.sg), National University of Singapore

Title:

Cryptic exon repression in Prdm13 by TDP-43 governs GABAergic interneuron development in the cerebellum

Kuah ZMB, Hong CJH, Joe S, Putri JK and Ling S-C

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Background:

TAR-DNA binding protein 43 (TDP-43) is a key regulator of RNA metabolism. Emerging evidence found cerebellar pathology in ALS patients, and aberrant TDP-43 inclusion has been documented in the cerebellum of motor-impaired FTLD patients. However, the physiological function of TDP-43 in the cerebellum remains poorly understood. To address this, we selectively deleted TDP-43 in Nestin-expressing progenitors (NEPs) in the cerebellum. The conditional ablation of TDP-43 in gliogenic NEPs does not perturb Bergmann glia (BGs) development. However, mature BGs lacking TDP-43 losses its characteristic localization and morphology, indicating the requirement of TDP-43 in the maintenance of BGs. Consequently, this led to the failure of granule neuron migration into the internal granule cell layer (IGL). In contrast, the conditional ablation of TDP-43 in Ascl1+ neurogenic NEPs results in the reduced generation of Pax2+ inhibitory progenitors which in turn led to fewer stellate and basket cells, but not Golgi cells of the IGL. Collectively, these cellular defects are accompanied with motor coordination deficit, and an approximately 30% reduction in cerebellum volume without disruption of gross laminar architecture. Mechanistically, TDP-43 represses a previously unreported cryptic exon in Prdm13, a chromatin modifier and transcriptional regulator required for GABAergic cell fate in the cerebellum and spinal cord. Blocking cryptic exon inclusion using CRISPR-dCas13-mediated RNA targeting restores the canonical splicing of Prdm13. Taken together, our results demonstrate a differential requirement of TDP-43 in gliogenic and neurogenic development in the cerebellum, and that TDP-43 sustains Prdm13 expression to ensure proper GABAergic cell fate specification.

Presented by:

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Title:**Machine Learning Framework for Endothelial Tissue State Predictions**

**Yudan Tang¹, Brandon Goh^{2,3}, Yunjin Li^{2,3}, Pistritu Dan-Valentin³,
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Background:

Endothelial cells lining the vasculature coordinate tissue-level responses through flow-induced mechanical signalling pathways, which, when dysregulated, perturbs vascular function and drives cardiovascular diseases. In response to perturbed mechanical forces including flow, the actomyosin network pulls on cell junctions, causing disrupted tissue permeability or leakiness. We previously showed that endothelial cell junctions exhibit morphologically distinct features, and ss such high dimensional features are yet to be translated into readouts of diseased states, novel machine learning based approaches are essential. Here, we developed a biologically informed convolutional neural network (U-Net) pipeline to predict junction morphology and tissue permeability from a library of immunofluorescence images capturing mechanosensitive proteins alongside paired in vitro permeability assays, under athero-protective unidirectional and athero-prone disturbed flow. Our model achieved high performance in segmenting cells from a tissue, predicting cellular shape parameters as well as functionally distinct junction morphologies. Permeability prediction using this model also achieved high accuracy when compared with the experimental findings. Thus, our machine learning model robustly predicts not only individual cell segmentation and shape parameters but also reflects the functional state of the endothelium. We are currently applying the trained models to ex vivo mouse arteries and veins, where our preliminary data strongly suggests that this computational model is applicable in a wide range of contexts including in vivo en-face endothelial tissues, regional variations of arteries and veins, as well as different junction proteins. This powerful computational framework will, therefore, allow us to uncover novel tissue-scale mechanobiological phenomena of endothelium across different vascular beds.

Presented by:

Brandon Goh Yeow Wee (wuyaohui@nus.edu.sg), Mechanobiology Institute

Title:

PYCR₁-Centered Metabolic-Redox Network Could Govern MCL-1-Dependent Venetoclax Resistance in Hematologic Malignancies

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Background:

Venetoclax (VEN) selectively inhibits the anti-apoptotic protein BCL-2 and is FDA-approved for treatment of specific hematologic malignancies. However, resistance remains a major challenge, with overexpression of BCL-2 family member MCL-1 representing a common mechanism of resistance. Here, we investigated PYCR₁ as a potential mediator of acquired VEN resistance in acute myeloid leukaemia (AML). Acquired VEN-resistant (VEN-R) MOLM14 and OCI-AML2 AML cells generated via prolonged VEN exposure exhibited elevated PYCR₁ expression and activity. PYCR₁ knockdown in VEN-R cells increased mitochondrial reactive oxygen species (ROS) and reduced cell viability, supporting a role for PYCR₁ in maintaining redox homeostasis and survival under VEN resistance. Mechanistically, we identified a previously uncharacterised interaction between PYCR₁ and AKT. Pharmacological inhibition of AKT reduced PYCR₁ levels, suggesting that AKT signalling may contribute to PYCR₁ regulation. Notably, PYCR₁ depletion reduced MCL-1 levels, while MCL-1 inhibition reciprocally decreased PYCR₁ levels, indicating a potential feedforward regulatory circuit involving AKT, PYCR₁, MCL-1, and ROS. In addition, PYCR₁ and MCL-1 were found to be transcriptionally upregulated in VEN-R cells, providing support for an alternative mechanism driving their increased expression. Following cessation of VEN treatment, PYCR₁ levels remained elevated after six weeks despite declining MCL-1 expression, suggesting that PYCR₁ upregulation may represent a more stable adaptation to VEN. Collectively, these findings implicate PYCR₁ in VEN resistance through its potential role in a metabolic-redox network. Further characterisation of this network may establish PYCR₁ as a therapeutic vulnerability for VEN re-sensitisation and inform combinatorial strategies to prevent or overcome acquired VEN resistance.

Presented by:

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Title:

SP4 disruption of neuronal maturation and excitatory/inhibitory balance in human iPSC-derived forebrain neurons

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Background:

Schizophrenia (SCZ) is a highly heritable neuropsychiatric disorder associated with both common and rare genetic variants. Among the implicated risk genes, SP4 encodes a brain-enriched zinc-finger transcription factor identified as a high-confidence SCZ risk gene. However, the consequences of SP4 loss on neuronal maturation and synaptic connectivity remain poorly understood, limiting our understanding of how SP4-associated risk contributes to SCZ pathophysiology.

To investigate this, we generated induced pluripotent stem cell (iPSC)-derived mixed forebrain neurons from wild-type (WT), SP4(+/-), and SP4(-/-) lines and assessed neuronal maturation, synaptic connectivity, and electrophysiological properties at DIV48 and DIV64. Expression of the forebrain and neuronal markers FOXG1 and MAP2 was largely preserved across genotypes, while intrinsic membrane properties remained unchanged. A transient reduction in CTIP2-positive deep-layer cortical neurons was observed only in SP4(-/-) neurons at DIV64, suggesting a limited effect on cortical subtype maturation.

In contrast, SP4 loss significantly altered synaptic phenotypes. Synapse density, measured by Homer1 and Synaptophysin co-localization, was increased in SP4-deficient neurons. SP4(+/-) neurons exhibited sustained increases at both timepoints, whereas SP4(-/-) neurons showed an early increase that normalized by DIV64, consistent with compensatory synaptic adaptation. Analysis of individual puncta revealed dynamic and compartment-specific synaptic remodeling following SP4 loss.

Patch-clamp recordings further demonstrated dose- and time-dependent disruption of excitatory and inhibitory signaling. Reduced spontaneous synaptic activity was observed at DIV48, followed by increased excitatory and inhibitory current amplitudes at DIV64, indicating a shift toward network hyperactivity. Together, these findings identify SP4 as a regulator of synaptic connectivity and excitatory-inhibitory homeostasis, providing mechanistic insight into SCZ-associated synaptic dysfunction.

Presented by:

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Title:**Mechanosensitive Regulation of Endothelial Dysfunction in Cardiovascular Aging**

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Background:

Perturbations in mechanical forces drive cardiovascular aging and disease, including atherosclerosis, stroke, and heart failure. Specifically, owing to their location at the blood–vessel interface, endothelial cells are continuously exposed to mechanical cues and are particularly susceptible to changes in their mechanical environment. Yet, the mechanisms linking these mechanical forces to age-associated endothelial dysfunction remain poorly understood. Here, we aim to identify novel genes involved in endothelial responses to mechanical force response during aging and under atherosclerosis-like conditions.

First, we developed microfluidic systems and substrates of varying stiffnesses to model hemodynamic flows seen in atherosclerotic and aged arteries respectively. We then built an integrated transcriptomic atlas using single-cell transcriptomic data from young (3 months old) and aged (2.5 years old) murine hearts and bulk RNA sequencing of human aortic endothelial cells (teloHAECs) exposed to physiological laminar or disturbed flow, modelling the haemodynamic environment of atherosclerosis-prone vessels. Through this integrative transcriptomic analysis, we identified mechanosensitive genes that are commonly regulated by aging and altered haemodynamic forces. These candidate genes span distinct functional categories, including junctional, actin-associated, and extracellular matrix-associated proteins, as well as nuclear transcription factors, suggesting potential roles in endothelial mechanotransduction across various length and time scales.

Our ongoing CRISPR-mediated screening in human pluripotent stem cell (hPSC)-derived endothelial cells cultured under defined flow and substrate stiffness conditions will reveal the functional role of these genes in endothelial barrier function, inflammatory signalling, proliferation, and mechanotransduction. Together, these studies will establish a mechanistic framework linking mechanochemical forces to endothelial signalling during cardiovascular aging and disease.

Presented by:

Hana Maldivita Tambrin (hana.tambrin@nus.edu.sg), Mechanobiology Institute

Title:

Divergent Roles of CNS Cell Types in Cholesterol Homeostasis and their Implication in Neuroglial Crosstalk

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Background:

Cholesterol is essential for cellular structure and function, acting as a key component of membranes and a precursor for steroid hormones and signaling molecules. Its levels are tightly regulated, including within the central nervous system (CNS), where cholesterol homeostasis is thought to operate independently from the periphery due to restrictive nature of the blood-brain barrier (BBB). While dysregulated cholesterol metabolism is associated with neurological and neurodegenerative disorders, it remains unclear how cholesterol dyshomeostasis can directly contribute to CNS pathology or influence systemic lipid regulation.

This study investigates the contribution of distinct CNS cell types to cholesterol metabolism and explores the potential bidirectional relationship between CNS and peripheral cholesterol regulation. Focusing on the key transcription factor SREBF-2, which regulates genes involved in cholesterol biosynthesis and uptake, we manipulated its expression in specific CNS cell types through cell-type-specific deletion and overexpression. Altering SREBF-2 levels in specific CNS cell types resulted in distinct outcomes, suggesting that each cell type contributed uniquely to cholesterol regulation in the CNS. Focusing on motor neurons, we found that those overexpressing SREBF2 developed normally but underwent premature degeneration by 3-month of age. Surprisingly, these mice did not show obvious motor deficits or paralysis with innervated neuromuscular junctions (NMJs) and no observable astrogliosis and microgliosis. Furthermore, SREBF2 overexpression in motor neurons boosted the myelination ability of oligodendrocytes in a non-cell-autonomous manner through ApoE-mediated cholesterol transfer, suggesting that increased myelination may help support the surviving neurons. Taken together, these results point to a complex, cell-type-specific regulation of cholesterol in the CNS and suggest that neuronal cholesterol metabolism can influence glial function and overall CNS health.

Presented by:

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Title:

Inducing Immunogenic Necroptosis to Overcome Immune Evasion in TP53-Mutated Acute Myeloid Leukaemia

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Background:

TP53-inactivated acute myeloid leukaemia (AML) is an aggressive subtype marked by profound treatment resistance, immune evasion, and poor survival. Standard chemotherapy, venetoclax-based regimens, and haematopoietic stem cell transplants rarely achieve durable remissions, highlighting the need for strategies to overcome immune resistance. Using isogenic AML models (TP53 WT, KO, mutants) expressing a model antigen, we found that TP53-inactivated AML cells broadly resisted TCR-T, CAR-T, and NK cytotoxicity, while inducing immune cell dysfunction in single-cell sequenced patient samples and in vitro systems. To define the molecular basis of this escape, we performed genome-wide CRISPR KO screens in TP53-inactivated and WT AML under T/NK pressure, integrated with transcriptomic and proteomic profiling. This revealed a dual dependency on inhibitors of apoptosis (IAPs: BIRC2, BIRC3, XIAP), which suppress extrinsic apoptosis, and death-inducing signalling complex (DISC) components (FADD, caspase-8, cFLIP), which restrain necroptosis. These suggest a unique vulnerability to apoptosis/necroptosis induction. Functional validation showed that IAP abrogation markedly amplified T/NK cytotoxicity, while targeting FADD or caspase-8 triggered rapid immune-driven necroptosis. Strikingly, the clinical caspase inhibitor Emricasan sensitised TP53-inactivated AML to immune killing and synergised with IAP antagonists, abolishing the threshold for TNF α -driven necroptosis. Blockade of RIPK1, RIPK3, or MLKL prevented this death, confirming pathway specificity. These vulnerabilities are independent of TP53 status, reflecting conserved dependencies on IAP-mediated apoptosis suppression and DISC-mediated necroptosis restraint. In TP53-inactivated AML, exploiting these nodes is particularly effective, where inhibiting the FADD-caspase-8-cFLIP axis with Emricasan (with/without IAP antagonists) overcomes immune resistance and supports integrating cell-death-promoting agents with immunotherapy for TP53-mutated AML.

Presented by:

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Title:

Dissecting *chrna3* Function: Single-Cell Transcriptomics Reveals Compensatory Pathways Underlying Drug Sensitivity and Comorbid Behaviours

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Background:

Substance use disorders are complex, multifactorial phenomena leading to substantial global health burdens. Human genetic studies link polymorphisms in the *CHRNA5-A3-B4* gene cluster, encoding nicotinic acetylcholine receptor subunits, to substance abuse and comorbid phenotypes like anxiety and circadian disruptions. Preclinical models that interrogate how these genetic drivers alter neural circuit function are critical for advancing precision medicine.

Using two CRISPR-Cas9-generated *chrna3* mutant zebrafish lines, we integrated a panel of behavioural assays, targeting drug preference and substance use associated comorbid disorder-like phenotypes, with single-cell RNA sequencing (scRNA-seq) to characterize the impact of *chrna3* dysfunction.

chrna3 mutants exhibited reduced aversion to both nicotine and alcohol during acute exposure, indicating a role in modulating shared reward processing and avoidance circuits. *chrna3* mutation reduced the efficacy of anxiolytic drugs, and altered baseline anxiety, circadian rhythm and feeding behaviours. Regional scRNA-seq revealed transcriptomic shifts across major neurotransmitter systems. Notably, *chrna3* dysfunction disrupted expression of circadian rhythm genes within the optic tectum and altered genes governing synaptic plasticity and neural development within the dorsal habenula.

Our findings demonstrate how *chrna3* functional impairment drives system-wide and region-specific neural alterations. By linking genetic variance to altered alcohol/nicotine sensitivity and comorbid anxiety, this work illustrates how functional genomic modelling in zebrafish can decode human GWAS hits and inform future personalized therapeutic strategies.

Presented by:

Joshua Raine (j.raine@nus.edu.sg), National University of Singapore

Title:

Repeat-containing intron expression links R-loops to disease progression in amyotrophic lateral sclerosis

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Background:

Intron retention is a known hallmark of ALS. Yet the contribution of disease associated repeat expansions within retained introns remains unknown. We hypothesised that aberrantly expressed repeat-containing intronic (RCIs) RNAs link intron retention to disease progression.

In our current study (accepted in principle at Nature Neuroscience), we have characterised RCI dysregulation in: i) 829 human induced pluripotent stem cell-derived motor neuron (hiPSC-MN), ii) 1,256 postmortem samples from 332 donors, iii) 322 ALS peripheral blood mononuclear cell (PBMC) samples, and iv) 244 ALS plasma miRNA-seq samples. We integrated our findings with genome instability assays in ALS patient-derived blood and loss-of-function experiments in hiPSC-MNs.

We find that RCIs formed a reproducible class of aberrantly expressed intronic RNAs across ALS postmortem tissue and hiPSC-MNs. Dysregulation was strongest in spinal cord, where cumulative RCI expression was higher in ALS than controls ($P < 0.001$). Increased expression was associated with earlier disease manifestation (log-rank=25.16; hazard ratio=1.85; $P < 0.0001$) and faster progression (log-rank=19.19; hazard ratio=1.85; $P < 0.0001$). Adding RCI expression to neurofilament light chain improved patient stratification by 17%. RCIs also showed increased genomic instability (GI-RCIs) in blood. SFPQ depletion selectively derepressed GI-RCIs, whereas depletion of other RNA-binding proteins had weaker effects. In PBMCs, RCIs carrying specific RNA-binding protein motifs predicted progression and were validated in an independent cohort of 226 patients. Furthermore, stable plasma RCI-derived microRNAs were able to stratify patients (244).

This data shows that SFPQ LOF contributes to ALS observed RNA dysregulation. The transcriptomic signature of this dysregulation is associated to patient progression in postmortem, iPSC-MNs, PBMCs and circulating miRNA species.

Presented by:

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Title:

OGDH inhibition induces SLC7A11 dependency and susceptibility to ferroptosis in rhabdomyosarcoma through ATF4-mediated stress response

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Background:

Rhabdomyosarcoma (RMS) is the most prevalent pediatric soft tissue, and is classified into two major subtypes – fusion-negative or embryonal rhabdomyosarcoma and fusion-positive or alveolar rhabdomyosarcoma. While standard treatment has increased survival of RMS patients, the outcome of those high risk or metastasis remains below 20%. Therefore, there is an urgent need for identifying novel therapeutic approaches in RMS. RMS cells differ significantly from myogenic-precursors in metabolic profile, exhibiting increased glutamine dependency, elevated glycolysis and OXPHOS. However, the metabolic vulnerabilities of RMS is poorly studied. To address this gap, we analyzed available database of dependency on metabolic genes in RMS (depmap.org) and identified that these cells are highly dependent on TCA cycle, and its enzyme 2-oxoglutarate dehydrogenase (OGDH). We found that OGDH expression is elevated in RMS, and its inhibition impaired proliferation, survival and migration. Our RNA-sequencing showed that OGDH inhibition increased expression of glutamate-cystine-exchanger, SLC7A11, crucial to protect cells from oxidative stress. OGDH inhibition also led to accumulation of ROS, decreased GSH/GSSG and NADPH/NADP, increased cystine uptake and glutamate release. Importantly, compared to control, OGDH inhibition increased cell death induced by SLC7A11 inhibitor, erastin, which was reversed by external fumarate, glutathione, cysteine, or ferroptosis-inhibitor ferrostatin-1. Lastly, OGDH inhibition induces expression of SLC7A11 by activating ATF4, which was also reversed by addition of cysteine and glutathione. Together, we have identified that RMS is dependent on OGDH, and its inhibition led to distorted metabolic and redox balance, increased dependency on SLC7A11 and susceptibility to ferroptosis, which can be potentially exploited.

Presented by:

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Title:

Complete TBK1 deletion attenuates microglial activation and slows disease progression in SOD1-ALS model mice

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Background:

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the selective death of upper and lower motor neurons. TBK1, encoding TANK-binding kinase 1 (TBK1), a ubiquitous serine/threonine kinase involved in the innate immune system and autophagy, has been identified as an ALS-causative gene, and loss of TBK1 activity has been linked to the development of ALS. Previous reports have shown that Tbk1 heterozygous knockout or Tbk1 kinase-dead mutation accelerated disease onset but extended survival in SOD1-linked ALS model mice associated with suppressed gliosis in the spinal cord. However, the effects of the complete deletion of TBK1 remained unknown, as Tbk1 homozygous knockout mice exhibit embryonic lethality due to RIPK1-dependent apoptosis.

To investigate the impact of complete TBK1 loss on neuroinflammation, we established Tbk1/Tnf double knockout (DKO) mice. The DKO mice developed normally due to the absence of tumor necrosis factor (TNF)-induced apoptosis. We next crossbred DKO mice with SOD1-linked ALS model (SOD1^{G93A}) to generate SOD1^{G93A}; Tbk1^{-/-} Tnf^{-/-} (G-DKO) mice. Compared with SOD1^{G93A}; Tnf^{-/-} (G-TKO) mice, G-DKO mice showed accelerated disease onset but significantly extended disease duration without altering lifespan. At the disease end-stage, microgliosis in the lumbar spinal cord was reduced in G-DKO mice compared with G-TKO mice. RNA-sequence analysis revealed significant downregulation of immune response pathway genes, including disease-associated microglia markers and interferon-inducible genes, in G-DKO microglia.

Our findings demonstrate for the first time that complete TBK1 deletion attenuates chronic microglial activation and slows disease progression in SOD1-ALS mice, highlighting TBK1-mediated interferon signaling as a potential therapeutic target requiring pathway-selective strategies.

Presented by:

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Title:

Dynamic regulation of RNA editing under low oxygen tensions

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Background:

Adenosine-to-Inosine RNA editing have long been established to be significantly upregulated under hypoxic conditions. In human cerebral organoids, RNA editing of Alu elements were upregulated. However, how hypoxia affects RNA editing of ion channels that are key regulators of neuronal excitability and plasticity remains unclear. Here, we explore the effects of hypoxia on RNA editing of ion channels and found that editing is regulated in a dynamic and precise manner. Specifically, we show that RNA editing of CaV1.3 is the most sensitive to changes in hypoxic conditions. To unravel the key mechanism underlying the regulation of ADAR2-mediated RNA editing under hypoxic conditions, we uncovered a novel interaction between ADAR2 and prolyl-hydroxylase protein, PHD2. Active PHD2 was found to significantly inhibit ADAR2 editing capacity. Acting in concert, the downregulation of SRSF9 protein expression under hypoxic conditions in neurons allows for a specific enhancement of ADAR2-mediated RNA editing of CaV1.3 transcripts.

Presented by:

Ng Shi Jun (shijun.ng@u.nus.edu), National University of Singapore

Title:**Key residues in HEBP1 couple heme binding to its subcellular localization and mitochondrial function**

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Background:

Alzheimer's disease (AD) is a disorder marked by memory and cognitive deficits caused by progressive neurodegeneration in the brain. Elevated level of heme-binding protein 1 (HEBP1) expression was observed in 3xTg-AD mice and in brains of patients with rapidly-progressing AD. Knocking out HEBP1 in neurons resulted in reduced heme-induced cell death. However, the specific role of HEBP1 remains elusive, with the role of heme binding in regulating HEBP1's function unknown. Here, we aimed to investigate this by first identifying a mutant HEBP1 variant with low binding affinity for heme to use as a comparison against HEBP1 wildtype (WT). By using homology modelling and molecular docking analysis, several possible key residues involved in heme-binding process were mapped. Further confirmation using tryptophan fluorescence quenching assays confirmed that Met59 and Ala63 contributed most critically to HEBP1's binding to heme, with mutations at M59E and M59E-A63E resulting in strongest reduction in heme-binding. When expressed in HeLa cells, both mutant variants showed increased localization to mitochondria and induced mitochondria aggregation, whereas HEBP1-WT was diffusely localized in the cytosol and did not redistribute mitochondria. Remarkably, HEBP1-WT significantly increased mitochondrial superoxide and mitochondrial iron levels, while mutants with reduced heme-binding did not significantly perturb them. Collectively, our findings highlight a role for heme in HEBP1's ability to regulate mitochondria oxidative stress and iron dyshomeostasis.

Presented by:

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Title:**Evaluating efficacy of Rapamycin taken over a lifespan on cognitive function****Ruijing Geng¹, Jiaqi Ding², Tirtha Das Banerjee³, Brian Kennedy^{1,5},****Ajay S. Mathuru^{1,4,5,6}**

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⁶Institute of Molecular and Cell Biology, A*STAR, Singapore, Singapore

Background:

Rapamycin, an inhibitor of the mechanistic target of rapamycin (mTOR) pathway, extends lifespan and improves healthspan across multiple model organisms. However, its long-term effects on cognitive function, particularly when administered prophylactically from early adulthood, remain incompletely understood. Here, we used the African turquoise killifish (*Nothobranchius furzeri*), a naturally short-lived vertebrate model of aging, to evaluate the effects of chronic rapamycin treatment on lifespan, cognition, reproduction, locomotion, and tissue physiology.

We established a scalable positive-reinforcement associative learning paradigm using an automated feeder that paired a visual cue with food delivery in individually housed adult killifish. Rapamycin was administered orally at 0.01 mg/kg/day beginning at 10–12 weeks of age. We additionally adapted a fluorescence in situ hybridization approach, RAM-FISH, to assess brain and tissue-specific gene-expression responses.

Killifish rapidly acquired the cue–reward association, with measurable behavioral changes emerging within one to two days and after 3 trials, demonstrating robust associative learning capacity. Chronic rapamycin treatment altered several age-related phenotypes, including reduced reproductive output and extended lifespan. These findings suggest that rapamycin may extend lifespan without compromising cognitive function and may contribute to preservation of cognitive health during aging.

Together, our automated behavioral platform and molecular profiling framework provide scalable tools for evaluating cognitive aging and geroprotective interventions in killifish, further supporting this species as a valuable vertebrate model for translational geroscience.

Presented by:**Ruijing Geng** (ruijing@nus.edu.sg), National University of Singapore

Title:**Transdermal Delivery for Estrogen Receptor Positive Breast Cancer Chemoprevention**

**Ryan Tze Liang Sia^{1,2}, Ayca Altay Benetti², Serene Si Ning Goh³, Camillo Benetti¹,
Giorgia Pastorin¹**

¹ Department of Pharmacy and Pharmaceutical Sciences, National University of Singapore, Singapore

² Department of Obstetrics and Gynaecology, National University of Singapore, Singapore

³ Yong Yoo Lin School of Medicine, National University of Singapore, Singapore; Department of General Surgery, Breast Division, National University Health System, Singapore; Saw Swee Hock School of Public Health, National University of Singapore, Singapore; National University Cancer Institute of Singapore, Singapore.

Electronic address: serene_sn_goh@nuhs.edu.sg.

Background:

Breast cancer (BC) is one of the most common malignancies among women and has caused an estimated 42,250 deaths in 2024 in the United States. Estrogen receptor positive (ER+) BC is responsible for 80% of these cases, and is the most common class of BC. Estrogen receptors are widely expressed in the glands of the breast and milk ducts. Therefore, selective estrogen receptor modulators (SERM)s can be used as a chemopreventive treatment. An example of a SERM is tamoxifen, which is one of the current chemopreventive options. However, there are a multitude of ramifications like vaginal bleeding and even a higher risk of endometrial cancer and cataracts. To solve this, researchers have utilised Z-endoxifen, which is a metabolite of tamoxifen, in phase I clinical trials. The patients were given liquid sachets that was applied to each breast daily, but they developed skin rashes. To tackle this problem, we have decided to utilise proniosomes, which are dry, anhydrous, packed vesicles coated with a water-soluble dry surfactant film, and can be hydrated to form niosomes on application on the skin. Formulation revealed about 35% encapsulation efficiency. Permeation experiments through human skin revealed that our loading of 400 µg of Z-endoxifen into 20 mg of proniosome gel showed $\sim 0.7 \mu\text{g}/\text{cm}^2$ over 48 hours, which shows that there is capability of permeation through the skin. These results recapitulate an alternative delivery strategy for the current treatment, with the elimination of side effects and a more effective delivery.

Presented by:

Ryan Sia Tze Liang (e1123682@u.nus.edu), National University of Singapore, Department of Pharmacy and Pharmaceutical Sciences

Title:**Mu-Opioid Receptor Modulates Drug Preference and Social Behaviour in Zebrafish****Goel T¹, Collado JW⁴, Raine J¹, Kibat C¹, Ding J¹, Banerjee TD², Mathuru AS^{1,3,4,5}**¹ Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore² Department of Biological Sciences, National University of Singapore, Singapore³ Institute for Digital Medicine (WisDM), Yong Loo Lin School of Medicine, National University of Singapore, Singapore⁴ Institute of Molecular and Cell Biology, A*STAR, Singapore⁵ Healthy Longevity Translational Research Programme, Yong Loo Lin School of Medicine, National University of Singapore, Singapore**Background:**

Nicotine and alcohol use disorders remain major public health concerns, with genetic factors contributing to individual vulnerability. The mu-opioid receptor, encoded by *OPRM1*, has been implicated in the responses of addictive substances; however, whether *OPRM1* independently influences responses to nicotine and alcohol remains unclear. We generated a stable *oprm1*-mutant zebrafish line using CRISPR-Cas9 and evaluated behavioural responses using the self-administration zebrafish assay (SAZA). Compared with wild-type siblings, *oprm1* mutants exhibited reduced avoidance of both nicotine and alcohol during acute self-administration. Following seven consecutive days of one-hour drug exposure, mutants also displayed altered behavioural adaptation, with a reduction in preference between acute and repeated exposure, particularly for nicotine, while wild-type responses remained comparatively stable. Whole-brain RNA sequencing revealed substance-specific transcriptomic effects of *oprm1* loss. Mutants exhibited fewer differentially expressed genes following nicotine exposure but a broader transcriptomic response following alcohol exposure compared with wild-type fish, including changes in genes associated with cholinergic, GABAergic, glutamatergic and dopaminergic signalling. Genotype-dependent changes in shoal cohesion and kinesis were also observed during acute alcohol exposure. Together, these findings suggest that *oprm1* influences the aversive effects of nicotine and alcohol and modulates subsequent behavioural and molecular adaptations to repeated exposure.

Presented by:

Tanisha Goel (tanishagoel@hotmail.com), National University of Singapore

Title:

FEZ1 Controls Autophagy Through ULK1-Dependent Phosphorylation During Human Cortical Development

Vidyawan V^{1,2,3,4}, Park SY^{1,2,3,4}, Mitriashkin A^{1,2,3,4}, Satnaliwala S^{1,2,4}, Yujie M⁵, Jun L⁶, Zhang Y⁶, Tan WH⁷, Chua JJE^{1,2,3,4}

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⁴ Neuroscience Translational Research Programme, National University of Singapore, Singapore

⁵ Cancer Science Institute of Singapore, National University of Singapore, Singapore

⁶ Department computer science, National University of Singapore, Singapore

⁷ Division of Genetics and Genomics. Boston Children's Hospital, USA

Background:

Major mental health disorders, including schizophrenia and autism spectrum disorder, are associated with disrupted neurodevelopment and synaptic dysfunction. Autophagy has emerged as an important regulator of brain development, with growing evidence that its disruption can affect neuronal migration and cortical organization. However, mechanisms controlling this process remain poorly understood.

We previously observed increased autophagy in neurons lacking FEZ1/UNC-76. Nevertheless, whether and how it regulates autophagy during brain development remains unclear. We observed that cerebral organoids generated from human iPSCs harbouring a novel human FEZ1 mutation derived from a patient diagnosed with a hitherto uncharacterised neurodevelopment disorder show abnormalities in rosette size and numbers. Significantly, patient cerebral organoids show higher levels of LC3II/I ratios, indicative of changes in autophagy in these organoids. Confirming these observations, transcriptomics analyses highlighted changes in the expression of key genes involved in the autophagy pathway. By in vitro kinase assays and computational modelling, we identify that ULK1/ATG1, the kinase initiating autophagy, phosphorylates FEZ1 at Ser316. Expression of FEZ1 G333R or S316A in HEK293 cells increased and decreased LC3II/I ratios, respectively. Our findings identify a key role of FEZ1 as an important target to regulate autophagy during human brain development, providing new mechanistic insights into neurodevelopmental disorders.

Presented by:

Vincencius Vidyawan (vino6@nus.edu.sg), National University of Singapore

Title:

Multimodal mapping reveals reversible brain network reorganisation in obesity

Yu Tuo^{1,2,#}, Coleen Roger^{3,4,#}, Azusa Saika¹, Roy Haast, Xing Qi Teo, Kuan Jin Lee, Feng Haosheng, Lim Jing Heng Jordan, Joanes Grandjean, Hasan Mohammad, Jean-Philippe Ranjeva, Yu Fu^{1,5,*}

¹Institute of Molecular and Cell Biology, Agency for Science, Technology and Research (A*STAR), Singapore

² Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

³Aix Marseille Université, CNRS, Centre de Résonance Magnétique Biologique et Médicale, Marseille, France

⁴ Assistance Publique-Hôpitaux de Marseille, Centre d'Exploration Métabolique par Résonance Magnétique, Hôpital Universitaire de la Timone, Aix Marseille University, Marseille, France

⁵ Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

* Correspondance: fu_yu@a-star.edu.sg

equal contribution

Background:

Obesity is increasingly recognised as a disorder of brain systems that assign value to food, integrate visceral state and regulate motivated behaviour, yet the whole-brain neural architecture underlying this condition and its reversibility remains incompletely understood. Here we combined ultra-high-field (11.7 T) rsfMRI with whole-brain 3D c-Fos immunostaining in mice, comparing chow-fed lean controls, high-fat-diet-induced obese mice and SGx-treated mice in which body weight was restored towards the lean range. Across both fALFF and c-Fos readouts, obesity produced widespread activity changes spanning cortical, subcortical and brainstem regions, a subset of which was reversed after SGx. Cross-modal concordance analysis isolated 17 regions concordantly rescued by SGx, and FC analysis identified 403 obesity-disrupted region pairs restored towards baseline, with a directional bias towards reversing obesity-induced hyperconnectivity. At the network level, obesity selectively eroded within-network integrity in the SAL and HPC systems while leaving the SMN internally unchanged but functionally isolated, and SGx rescued each signature. Both FC and fALFF features classified body-weight state with over-chance-level accuracy, with FC features being noticeably more effective than fALFF, and a compact FC-based ensemble classified body-weight state with >85% balanced accuracy on an unseen cohort, indicating that obesity is captured less by regional activity than by distributed inter-regional coupling. Finally, using a modified sDCM framework, we identified a directionally selective LC signature in which obesity amplified and SGx suppressed ascending LC→forebrain drive to LH, ORBvl and PL, while the descending limb was largely unaffected, nominating LH as a putative intermediary hub in obesity-related circuit reorganisation. These findings define systems-level neural signatures of hedonic-eating-induced obesity and provide computational avenues for identifying reversible circuit targets.

Presented by:

Yu Tuo (tuoyu@a-star.edu.sg), Department of Physiology, National University of Singapore

Title:**Targeting Galectin-3-associated neuroinflammation and CaV1.2 dysregulation in vascular cognitive impairment****Zhou Y^{1,3}, Hu Z^{1,2}, Liao P², Soong TW^{1,2,3,4}**¹ Department of Physiology, National University of Singapore, Singapore² Department of Research, National Neuroscience Institute, Singapore³ Institute for Functional Intelligent Materials, National University of Singapore, Singapore⁴ Neuroscience Translational Research Programme, National University of Singapore, Singapore**Background:**

Targeting Galectin-3-associated neuroinflammation and CaV1.2 dysregulation in vascular cognitive impairment
Chronic cerebral hypoperfusion contributes to vascular cognitive impairment and dementia, but the mechanisms linking neuroinflammation and CaV1.2 dysregulation to disease progression remain unclear. We investigated the involvement of galectin-3 (Gal-3) in these processes and evaluated iGal3BP, a peptide targeting Gal-3-associated signalling. Mice underwent bilateral carotid artery stenosis (BCAS) and were assessed at 2, 4 and 6 weeks. Behavioural abnormalities progressively worsened after BCAS, with several deficits emerging only at later time points. In treatment cohorts, iGal3BP improved behavioural outcomes and was associated with reduced Gal-3, CaV1.2, TLR4 and glial activation markers in the prefrontal cortex and hippocampus. In activated microglia, iGal3BP reduced Gal-3-associated inflammatory responses and abnormal calcium activity. By contrast, oxygen-glucose deprivation reduced neuronal CaV1.2 expression and calcium influx, and iGal3BP produced no further reduction in either measure. Although the peptide modestly reduced neuronal TUNEL positivity, Gal-3 was predominantly detected in proliferating contaminating microglia, suggesting indirect neuroprotection through attenuation of microglial inflammation. Preliminary studies in HEK293 cells were also consistent with increased lysosomal trafficking of Gal-3 and CaV1.2 following iGal3BP treatment, which may contribute to their reduced abundance and CaV1.2 activity. Together, these findings suggest that iGal3BP may alleviate BCAS-induced impairment through combined modulation of microglial inflammation and Gal-3–CaV1.2 protein homeostasis, although further genetic and lysosomal validation is ongoing.

Presented by:**Zhou YanRuo** (e1124883@u.nus.edu), Department of Physiology, National University of Singapore

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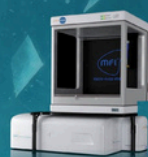
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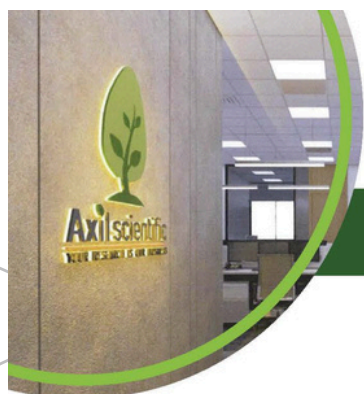
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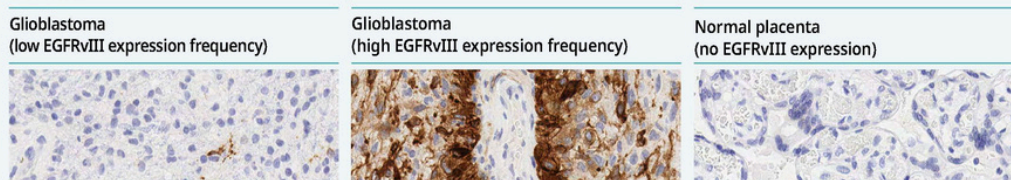
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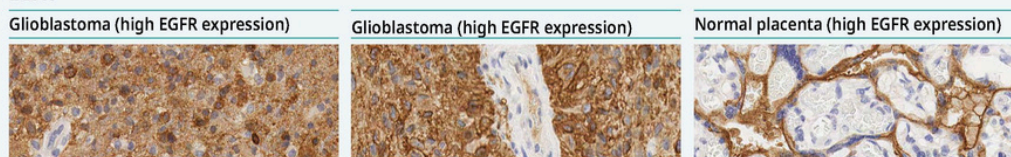
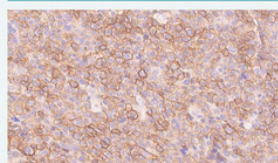


Figure 1. IHC-P staining showing EGFRvIII/EGFR expression using anti-EGFRvIII [EPR28380-83] (ab313646) and anti-EGFR [EP38Y] (ab52894). Positive staining in brown; hematoxylin nuclear counterstain in blue.

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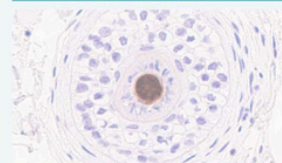


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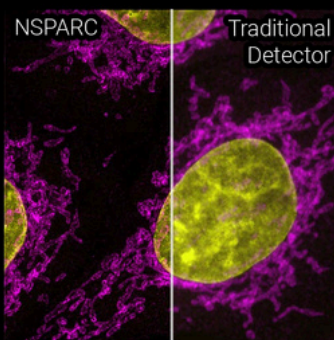
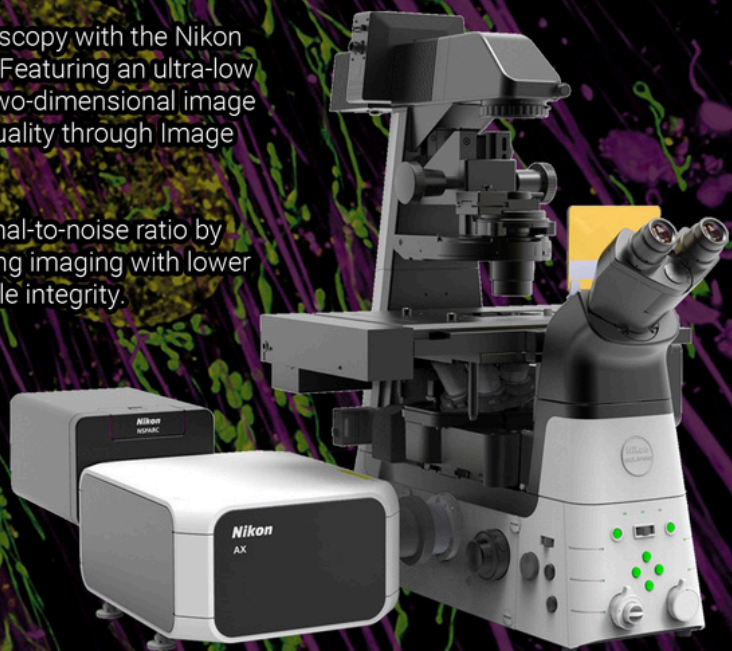


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As the Cancer Translational Research Programme at the NUS Yong Loo Lin School of Medicine, N2CR brings together over 130 members across NUS and NUHS to advance cancer discovery and translate research into better patient care. Through our two cross-cutting themes, SCOUT & COMPASS, as well as Site-Specific Resources (SSR), N2CR drives collaborative research in cancer origins, screening, molecular profiling, and precision oncology, with a focus on addressing the major challenges in Asian cancers.



Explore N2CR website



SCOUT

Screening and Carcinogenesis
- Origins in Unique Tissues
Decoding Cancer's Beginnings
for Healthier Tomorrow

COMPASS

Customised Oncology through Molecular Profiling and Strategic Selection
Charting the Future of Precision Oncology

FOCUS

Addressing Major Challenges in Asian Cancers

SITE-SPECIFIC RESOURCES (SSR)



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Shared Cancer Models, Smarter Research



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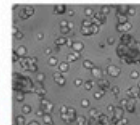


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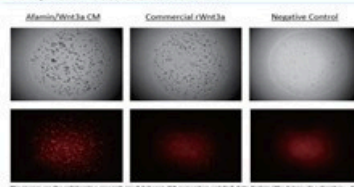
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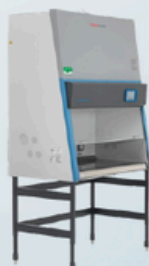
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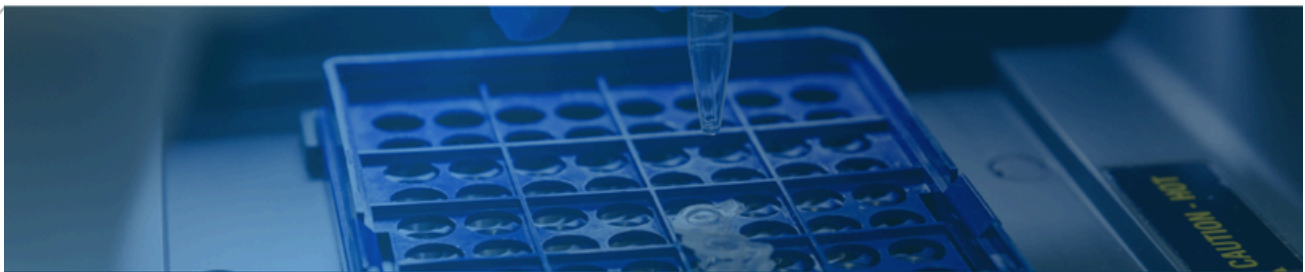
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