

LEE KONG CHIAN
SCHOOL OF
MEDICINE



Imperial College
London

STEM CELL SYMPOSIUM

REGENERATIVE MEDICINE AT A GLANCE

Tuesday, 22 May 2018

8.30AM to 6PM

Lee Kong Chian School of Medicine

Novena Campus

Toh Kian Chui Annex, Lecture Theatre

11 Mandalay Road, Singapore 308232

Keynote Speakers:

Juan Carlos Izpisua Belmonte

Professor

Roger Guillemin Chair

Salk Institute for Biological Studies

United States of America

Charles ffrench-Constant

Professor

Centre for Regenerative Medicine

University of Edinburgh

United Kingdom

Tuesday, 22 May 2018

Time	Programme
8.30am – 9.00am	<i>Arrival and Registration</i>
9.00am – 9.10am	<p>Opening Address</p> <p>Prof Philip INGHAM FRS <i>Professor of Developmental Biology, Principal Investigator, Developmental Genetics Laboratory, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore</i></p>
<p>Keynote Session 1</p> <p>Chairperson</p> <p>Prof Philip INGHAM FRS <i>Professor of Developmental Biology, Principal Investigator, Developmental Genetics Laboratory, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore</i></p>	
9.10am – 10.00am	<p>Cell, genetic and epigenetic approaches in ageing and ageing-associated diseases</p> <p>Prof Juan Carlos Izpisua BELMONTE <i>Roger Guillemin Chair and Professor, Gene Expression Laboratory, Salk Institute for Biological Studies, United States of America</i></p>
<p>Session 1: Regeneration <i>in situ</i> – <i>in vivo</i> Disease Modelling and Therapy</p> <p>Chairperson</p> <p>Prof Klaus Erik KARJALAINEN <i>Professor, School of Biological Sciences, College of Science, Nanyang Technological University, Singapore</i></p>	
10.00am – 10.30am	<p>LGR5+ stem cells in epithelial maintenance, repair and cancer of the stomach</p> <p>Nick BARKER <i>Institute of Medical Biology, A*STAR, Singapore University of Edinburgh, United Kingdom Kanazawa University, Japan</i></p>
10.30am – 11.00am	<i>Tea Break @ Lecture Theatre foyer</i>
11.00am – 11.30am	<p>Enhancing cellular therapy for ageing populations</p> <p>Simon COOL <i>Glycotherapeutics Group, Institute of Medical Biology, A*STAR, Singapore Orthopaedic Department, National University of Singapore</i></p>

<p>11.30pm – 12.00pm</p>	<p>A potent epidermal protease primes for rapid tissue responses upon loss of integrity</p> <p>Tom CARNEY <i>Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore</i></p>
<p>Session 2: Human Models of Development and Disease – The Power of <i>in vivo</i> Differentiation</p> <p>Chairperson</p> <p>Assoc Prof LIM Bing <i>Associate Vice President for Research Science, Merck Research Laboratory; Lead for External Collaborations and Research Integration, Translational Medicine Research Centre, Singapore Senior Group Leader, Cancer Stem Cell Biology, A*STAR, Singapore</i></p>	
<p>12.00pm – 12.30pm</p>	<p>Fleshing out the regulatory networks controlling human pancreas development</p> <p>Norris Ray DUNN <i>Institute of Medical Biology, A*STAR, Singapore Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore</i></p>
<p>12.30pm – 2.00pm</p>	<p><i>Lunch @ Lecture Theatre foyer</i></p>
<p>2.00pm – 2.30pm</p>	<p>Elucidation of coronary artery disease locus 6p24.1 using patient iPSC-derived vascular models</p> <p>Christine CHEUNG <i>Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore</i></p>
<p>2.30pm – 3.00pm</p>	<p>Model kidney development and disease using human PSC-derived kidney organoid</p> <p>XIA Yun <i>Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore</i></p>
<p>Session 3: Broadening the Capability – Technological Advancement</p> <p>Chairperson</p> <p>Prof Russell GRUEN <i>Professor of Surgery, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore Executive Director, NTU Institute for Health Technologies, Singapore Consultant General Surgeon, Tan Tock Seng Hospital, Singapore</i></p>	
<p>3.00pm – 3.30pm</p>	<p>Protein-RNA interactions implicated in neurodegenerative diseases</p> <p>Gene YEO <i>Department of Cellular and Molecular Medicine, University of California San Diego School of Medicine</i></p>

3.30pm – 4.00pm	<i>Tea Break @ Lecture Theatre foyer</i>
4.00pm – 4.30pm	<p>Global H3.3 dynamics defines its bimodal role in cell-fate transition</p> <p>Jonathan LOH <i>Institute of Molecular and Cell Biology, A*STAR, Singapore Graduate School of Integrative Sciences and Engineering, Department of Biological Sciences, National University of Singapore</i></p>
4.30pm – 5.00pm	<p>Genome-editing therapy via HITI (Homology-Independent Targeting Integration)</p> <p>Keiichiro SUZUKI <i>Institute for Advanced Co-Creation Studies, Graduate School of Engineering Science, Osaka University, Japan</i></p>
<p>Keynote Session 2</p> <p>Chairperson</p> <p>Prof Philip INGHAM FRS <i>Professor of Developmental Biology, Principal Investigator, Developmental Genetics Laboratory, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore</i></p>	
5.00pm – 5.50pm	<p>Biological functions and translational applications of CNS neural stem cell/extracellular matrix interactions</p> <p>Prof Charles FFRENCH-CONSTANT <i>Professorial Fellow, MRC Centre for Regenerative Medicine; Dean of Research, College of Medicine and Veterinary Medicine, University of Edinburgh, United Kingdom</i></p>
5.50pm – 6.00pm	<p>Closing Address: The Future of Regenerative Medicine – Leadership of Clinicians, Engineers, Biologists and Regulators</p> <p>Prof TEOH Swee Hin <i>Professor, Division of Bioengineering, School of Chemical and Biomedical Engineering, Nanyang Technological University, Singapore Fellow, Academy of Engineering, Singapore</i></p>
6.00pm – 9.00pm	<i>Networking @ Medical Library, Clinical Sciences Building, Level 20</i>

Cell, Genetic and Epigenetic Approaches in Ageing and Ageing-associated Diseases

Professor Juan Carlos Izpisua BELMONTE

Roger Guillemin Chair and Professor, Gene Expression Laboratory, Salk Institute for Biological Studies, United States of America

Prof Juan Carlos Izpisua Belmonte will describe different strategies for disease modelling including cell, genetic and epigenetic approaches. Prof Belmonte will dedicate special emphasis to the ageing process. Ageing can be defined as the progressive decline in the ability of a cell or organism to resist stress and disease. Recent advances in cellular reprogramming technologies have enabled detailed analyses of the ageing process, often involving cell types derived from aged individuals, or patients with premature ageing syndromes. In the presentation, Prof Belmonte will discuss how cellular reprogramming allows the recapitulation of ageing in a dish, describing novel experimental approaches to investigate the ageing process and ageing-associated diseases. Finally, the speaker will explore the role of epigenetic dysregulation as a driver of ageing, discussing how epigenetic reprogramming may be harnessed to ameliorate ageing hallmarks, both *in vitro* and *in vivo*. A better understanding of the reprogramming process may indeed assist the development of novel therapeutic strategies to extend a healthy lifespan.

About the Speaker



Prof Juan Carlos Izpisua Belmonte is currently a Professor at the Salk Institute for Biological Studies in La Jolla, California. He has a long and extensive background in developmental biology research, and has been a main catalyser in one of today's most promising areas of biomedicine: regenerative medicine. His work is helping to discover new molecules and specific gene/cell treatments to prevent and cure diseases affecting mankind both in the adult and embryonic stages. He has over 450 publications describing these results. His observations have been key in elucidating the cellular and molecular basis of tissue/organ

regeneration. His early work was pivotal to the understanding of fundamental genetic and cellular principles that govern vertebrae development, and tissue and organ regeneration. They constituted the basis of his conceptual discoveries and new methodologies for regenerative medicine including:

- Seminal discoveries towards understanding the molecular basis underlying somatic cell reprogramming.
- New methodologies for the differentiation of human stem cells into various cell types and organoids.
- Proof of concept that iPSC technology can be used for the generation of disease-corrected patient specific cells with potential value for cell therapy.
- Development of technologies that allow differentiation of human cells inside embryos of different species. These results may allow for the generation of human tissues and organs.
- Development of novel stem cell models of human ageing and ageing-associated diseases, and discovery of new drivers of ageing.
- Novel genetic and epigenetic technologies to both treat and prevent the transmission of mitochondrial and nuclear DNA-originated diseases

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

Nick BARKER

*Institute of Medical Biology, A*STAR, Singapore*

University of Edinburgh, United Kingdom

Kanazawa University, Japan

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

About the Speaker



Dr Barker was awarded a PhD in 1995 from the Berkshire University of Reading (England), followed by a postdoc at the University Medical Centre Utrecht in Hans Clevers Laboratory investigating the role of Tcf transcription factors in controlling expression of target genes regulated by the Wnt signal transduction pathway during development and carcinogenesis. The work led to the publication of a seminal paper in *Science*, which has now become one of the most cited papers in this field (currently > 2700 citations). In 2001, Dr Barker joined Semaia Pharmaceuticals, a company co-founded by Hans Clevers to develop colon cancer therapeutics targeted within the Tcf/ β -catenin signalling pathway. In 2006, he returned to the Clevers laboratory as staff scientist. The work led to the discovery that Lgr5 marks adult stem cells, which was reported in *Nature* (currently > 2100 citations). In 2010, Dr Barker was appointed as a senior principal investigator (lab head) at the Institute of Medical Biology, Singapore and promoted to Research Director in 2015. He is a visiting Professor at the Centre for Regenerative Medicine (CRM), Edinburgh, a Research Professor at Kanazawa University, Japan and an honorary faculty member at the University of Melbourne.

Enhancing Cellular Therapy for Ageing Populations

Simon COOL

*Glycotherapeutics Group, Institute of Medical Biology, A*STAR, Singapore
Orthopaedic Department, National University of Singapore*

Mesenchymal stem cells (MSCs) offer significant therapeutic potential for patients suffering age related articular cartilage damage. Their low number in bone marrow needs further culture expansion before clinical use. Endogenous FGF2 is critical to the expansion and naivety of such cells. The study shows that culture supplementation with selected heparan glycosaminoglycans that target endogenously produced FGF2 (termed HS8) creates an FGF2 gradient that provides signals to more distant MSCs. This results in a 2 to 3-fold increase in the MSC population without accelerated telomere loss, reduced colony-forming efficiency, or loss of tri-lineage potential. Such MSCs (MSCHS8) show enhanced efficacy for osteochondral repair. Full-thickness cartilage defects in rodent and porcine models treated with MSCHS8 have greatly enhanced healing outcomes with significant increases in ICRS I, ICRS II and O'Driscoll scores compared to MSCs culture in standard conditions. Magnetic Resonance Imaging and mechanical testing further confirm the therapeutic benefit of MSCHS8 treatment. These data highlight the critical role that heparan glycosaminoglycans can play in the bioprocessing of stem cells. Furthermore, this study strongly advocates for the further development of unique glycosaminoglycans capable of mimicking native cellular micro-environments as a strategy for clinical regeneration.

About the Speaker



Dr Simon Cool received his BSc (Hons) and PhD degrees from The University of Queensland, Australia, where he held a faculty position in the School of Biomedical Sciences. He was recognised with an Award for Excellence in Teaching in 2002 for his broad and deep contribution to enhancing the quality of learning and teaching. His studies have concentrated on the extracellular matrix compartment of skeletal tissue and how it guides stem cell behavior and wound repair.

He joined the Institute of Molecular and Cell Biology, A*STAR, Singapore in 2003 as Principal Investigator and then A*STAR's Institute of Medical Biology in 2008, to further his research in regenerative medicine. As Senior Principal Investigator of the Glycotherapeutics Group, he is developing novel glycosaminoglycan biomolecules to enhance wound repair and control adult stem cell behaviour. Most particularly, he has developed glycotherapeutic devices and adult stem cell-based therapies for the treatment of bone and cartilage injuries, cardiovascular diseases, and skin wounds and cosmetic applications. Dr Cool has filed 165 patents and his strong publication record (>120 publications) exemplifies the many successful projects he has led.

Dr Cool is a Professor (Adjunct Research) in the Orthopaedic Department at the National University of Singapore. He served as an elected council member for the Tissue Engineering and Regenerative Medicine International Society, Asia Pacific Chapter and Executive Editor for the journal *Gene*. He is currently Section Editor for the *Journal of Molecular Histology* and serves on the Editorial Boards of *Biomaterials* and *Stem Cells and Development*.

A Potent Epidermal Protease Primes for Rapid Tissue Responses Upon Loss of Integrity

Tom CARNEY

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

The vertebrate epidermis exists in a state of balance, continually turned over and replaced from a basal keratinocyte stem cell compartment. In addition, it is poised to respond rapidly to external insults or re-establish the barrier upon wounding. The mechanisms maintaining this poised state must permit an immediate, yet robust response.

The study has identified a protease and inhibitor system, present in the basal keratinocytes of mouse and zebrafish, essential for maintaining both epidermal integrity and quiescent inflammation. Upon loss of the inhibitor (or mis-expression of its cognate protease target), keratinocyte stem cells attain a migratory phenotype and the epidermis becomes inflamed, hallmarks of a regenerative response.

Carney and his colleagues have determined the cellular events resulting from dysregulation of this system, and identified a marked increase in Reactive Oxygen Species, which, along with activation of other critical pathways, initiates inflammation. Intriguingly, the epithelial defects are uncoupled from the inflammatory responses, and they have implicated the MAPK pathway and intracellular lipid signalling in the keratinocyte phenotype.

Together, this demonstrates that complex tissue scale outputs can be elicited by a simple, poised protease and inhibitor interaction within an epithelial stem cell compartment, which upon disruption, initiates responses seen upon injury or insult.

About the Speaker



Dr Tom Carney graduated from the Genetics Department at the University of Adelaide before embarking on a PhD in zebrafish developmental biology in the laboratory of Robert Kelsh at the University of Bath, UK, studying specification of neural crest derivatives. He continued zebrafish research as a postdoctoral fellow at the Max Planck Institute for Immunobiology in Freiburg, Germany from 2004, where he analysed a number of epidermal mutants, elucidating the role of novel extracellular matrix proteins and serine proteases in development. He took up an assistant Principal Investigator position in IMCB in October 2008, and then became a joint Assistant Professor at the Lee Kong Chian School of Medicine at NTU in 2014. His current research focuses on dermal and epidermal pathways in development and modelling human disease states in zebrafish.

Fleshing out the Regulatory Networks Controlling Human Pancreas Development

Norris Ray DUNN

*Institute of Medical Biology, A*STAR, Singapore*

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

The transcription factor gene Pancreatic and Duodenal Homeobox 1 (PDX1) encodes an evolutionarily conserved homeobox transcription factor expressed during the earliest stages of human pancreatic development. Strikingly, the loss of PDX1 results in complete pancreatic agenesis, a dramatic phenotype that emphasises the critical role PDX1 plays in coordinating the morphogenesis of this indispensable metabolic organ. The Dunn laboratory routinely models human pancreatic development *in vitro* by differentiating human pluripotent stem cells (hPSC) into early pancreatic progenitors (ePP). Using a protocol that tightly adheres to developmental logic, abundant PDX1+ ePP cells emerge after two weeks of *in vitro* culture. These ePP cells display a molecular signature that significantly overlaps with the developing human pancreatic primordium. Using a variety of “omics” and bioinformatic approaches, the lab has begun to construct a wiring diagram of those genes directly regulated by PDX1. Two such PDX1 targets are Regulatory Factor X 6 (RFX6) and Teashirt Zinc Finger Homeobox 3 (TSHZ3). In his presentation, the speaker will provide an update on the laboratory’s progress to functionalise these genes *in vitro* using a variety of novel, gene-edited hPSC lines.

About the Speaker



Dr Norris Ray Dunn obtained his PhD in Cell Biology in 1999 from Vanderbilt University under the supervision of Dr Brigid Hogan, FRS and then completed a post-doctoral fellowship in the laboratory of Dr Elizabeth Robertson FRS at Harvard University. In 2004, he joined ES Cell International Pte Ltd as a Research Scientist in the Diabetes Group, eventually being named Program Manager in 2005. In 2007, he joined the newly formed A*STAR Institute for Medical Biology where he remains as a Senior Principal Investigator. Dr Dunn also holds Adjunct Assistant Professor positions at the Lee Kong Chian School of Medicine at Nanyang Technological University (NTU) and the NTU School of Biological Science (SBS).

Elucidation of coronary artery disease locus 6p24.1 using patient iPSC-derived vascular models

Christine CHEUNG

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

Cardiovascular disease is the number one cause of mortality worldwide. Genome-wide association studies (GWAS) have identified many non-coding variants that are associated with coronary artery disease (CAD). However, the difficulty of elucidating genetic aetiology of non-coding variants has often impeded clinical application of GWAS findings. The study's goal is to interrogate the influence of an Asian susceptible locus 6p24.1 on vascular endothelial health. Cheung and colleagues have derived induced pluripotent stem cells (iPSCs) from CAD patients (with risk genotypes AA/AG) and normal individuals (with non-risk genotype GG). To elucidate how chromatin landscape is perturbed by the risk genotype, the study performed chromatin conformation capture assay. Findings revealed that the risk variant is a distal regulator of key genes implicated in atherosclerosis through long-range chromatin interactions. In establishing the genotype-to-phenotype link, the study was able to model functional differences in the iPSC-endothelial cells carrying risk versus non-risk genotypes. Taken together, this study would have broad relevance for investigating the functional genomics of other non-coding variants, holding promise for disease management guided by individual genetic risk profiles.

About the Speaker



Dr Christine Cheung is a Nanyang Assistant Professor at the Lee Kong Chian School of Medicine, Nanyang Technological University, and an awardee of the 2016 Nanyang Assistant Professorship. She received a PhD in Cardiovascular and Stem Cell Medicine from the University of Cambridge, and a BEng (First Class) from Imperial College London. Upon securing the competitive Independent Fellowship in 2012, she started up a research group at the A*STAR Institute of Molecular and Cell Biology, where she currently holds a joint appointment. To further her work, Dr Cheung received the Career Development Award and Young Investigator Grant from A*STAR. For her pioneering approach to create organ-specific blood vessels, she was recognised with the Young Investigator Prize from the British Society for Cardiovascular Research.

Model Kidney Development and Disease Using Human PSC-derived Kidney Organoid

XIA Yun

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

The number of people suffering from end-stage renal disease (ESRD), a consequence of many conditions including genetic defects, diabetes, cardiovascular disease, and hypertension, is increasing at an alarming rate. Cross-sectional studies have suggested that common genetic variants are associated with the development of kidney disease, and consequently ESRD. Due to the complex personal trait, it is premature to propose molecular genetic testing for diagnosis and treatment. Organoid differentiation represents the new paradigm of *in vitro* lineage specification that allows us to obtain organ miniatures from human pluripotent stem cell (PSC), including both embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). Xia and colleagues have developed a highly efficient differentiation protocol that involves a succession of culture conditions mimicking human kidney development. The generated kidney organoid presents segmented nephron structures, and a complex vasculature web. This differentiation platform provides an unprecedented opportunity to study human kidney development and disease pathogenesis in a patient-specific manner.

About the Speaker



Dr Xia Yun joined the Lee Kong Chian School of Medicine in September 2015. She finished her PhD training in Molecular and Cell Biology at the National University of Singapore in 2010. Passionate about stem cell biology and regenerative medicine, she joined Prof Juan Carlos Izpisua Belmonte's laboratory at Salk Institute for postdoctoral training. She has been working on *in vitro* specification of human pluripotent stem cells into renal-related lineages with Prof Belmonte. Currently, her laboratory research projects are focusing on understanding the molecular mechanisms underlying stem cell fate determination and lineage reprogramming with the ultimate goal of establishing reliable and safe strategies for managing kidney

diseases in a patient-specific manner.

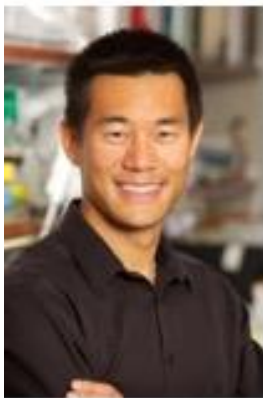
Protein-RNA Interactions Implicated in Neurodegenerative Diseases

Gene YEO

Department of Cellular and Molecular Medicine, University of California San Diego School of Medicine

The speaker will present his lab's interest in studying RNA-binding proteins that are implicated in neurodegenerative diseases. Mutations in RNA-binding proteins lead to defects in cytoplasmic RNA aggregates called stress granules. Yeo and colleagues utilise human iPSC systems to evaluate the components of stress granules, whereby modulation of these proteins lead to reduction of toxicity in animal models of amyotrophic lateral sclerosis.

About the Speaker



Prof Gene Yeo is an expert in RNA, computational biology, genomics and neurological diseases. He has a Bachelors degree in chemical engineering and economics from the University of Illinois, Urbana-Champaign and a Master's in business administration from the Rady School of Management at the University of California, San Diego. Funded by the Lee Kuan Yew Graduate Fellowship from Singapore, Prof Yeo earned a PhD in Computational Neuroscience from the Massachusetts Institute of Technology under the joint guidance of Dr Tomaso Poggio and Dr Christopher Burge. Using comparative genomics and statistical learning theory, he pioneered new computational approaches to attack the problem of splicing and

splicing-mediated gene regulation.

Prof Yeo was appointed the first Junior Fellow at the Crick-Jacobs Center for Theoretical and Computational Biology at the Salk Institute. His collaborative nature has generated successful projects and grants with experts in neuroscience and neurodegeneration, RNA processing, RNA-targeting CRISPR approaches and virology. He was awarded the Alfred P Sloan Fellowship in recognition of his work in computational molecular biology, as well as the inaugural Early Career award by the international RNA Society. In 2008, Prof Yeo was appointed an Assistant Professor at UCSD and was accelerated to Full Professor. Since 2003, he has authored over 100 peer-reviewed publications, invited book chapters, review articles and was Editor for several books on RNA-binding proteins. He successfully authored grants from the California Institute of Regenerative Medicine, served as Principal Investigator (PI) or co-PI on NIH R01, U01, U19 and U54 grants, and was funded by TargetALS, the ALS Association, Takeda, Genentech and Roche Pharmaceuticals.

Prof Yeo is on the Scientific Advisory Boards of several biotech companies, actively serves as a bioinformatics and business consultant to biotech and pharmaceutical companies, and is a co-founder at start-ups Enzerna, Eclipsebio, ProteoNA and Locana. He is on the Editorial Board of the journals Cell Reports and Cell Research. Prof Yeo is a Visiting Professor at the National University of Singapore, an Adjunct Senior Research Scientist at the Genome Institute of Singapore and a visiting researcher at the Molecular Engineering Laboratory under Nobel Laureate Sydney Brenner's auspices.

Global H3.3 Dynamics Defines its Bimodal Role in Cell-fate Transition

Jonathan LOH

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

Graduate School of Integrative Sciences and Engineering, Department of Biological Sciences, National University of Singapore

By investigating the global dynamic deposition of histone variants during cellular reprogramming, this study found that H3.3 maintains the identities of the parental cells by forming a regulatory node of multiple downstream genes. Removal of H3.3 at early time-point of reprogramming enhanced the efficiency of the process. H3.3 exhibited similar role in other cell fate reprogramming systems including transdifferentiation to haematopoietic progenitors and neuronal differentiation from mouse embryonic stem cells. Contrastingly, H3.3 deposition on genes associated with the newly reprogrammed cell lineage is essential as its depletion at the later phase abolished the process. Mechanistically, H3.3 deposition on regulatory elements and gene bodies by HIRA, and its K4 and K36 modifications are central to the activity of H3.3 in governing cell fate conversion. Finally, H3.3 safeguards fibroblast lineage by regulating MAPK cascade and collagen synthesis processes.

About the Speaker



Dr Jonathan Loh is a Senior Principal Investigator at the Institute of Molecular and Cell Biology where he also serves as the Programme Coordinator for the Stem Cell, Regenerative Medicine and Ageing research. Concurrently, he is a faculty member of the Graduate School of Integrative Sciences and Engineering, as well as the Department of Biological Sciences, National University of Singapore. He did his PhD research as an A*Star Scholar at the Genome Institute of Singapore under the mentorship of Dr Ng Huck Hui, where he mapped the transcriptional network of NANOG and Oct-4 in Embryonic Stem Cells (ESCs). During his postdoctoral fellowship at the Boston Children's Hospital, Harvard Medical School, he was under the tutelage of Dr George Daley. He pioneered the use of human blood cells for reprogramming to induce pluripotent stem cells. His laboratory is interested in dissecting the regulatory mechanisms regulating cell fate changes, and developing novel tools in deriving reprogrammed and differentiated cell types. His research has earned him several prestigious national and international accolades including the Singapore Young Scientist award, Singapore Youth award, World Technology Network Fellowship, MIT TR35 Asia Pacific award and the National Research Foundation Investigatorship award. He serves on the Executive Committee of the Stem Cell Society Singapore (SCSS) and the Committee for International Affairs at the International Society for Stem Cell Research (ISSCR).

Genome-editing Therapy via HITI (Homology-Independent Targeting Integration)

Keiichiro SUZUKI

Institute for Advanced Co-Creation Studies, Graduate School of Engineering Science, Osaka University, Japan

Targeted genome editing via engineered nucleases is revolutionising biomedical research and holds tremendous potential for clinical applications. Despite rapid advances in the field, *in vivo* targeted transgene integration is still infeasible because current tools are inefficient, especially for non-dividing cells, which compose most adult tissues. This poses a tremendous barrier for uncovering fundamental biological principles and developing treatments for a broad range of devastating genetic disorders. Based on CRISPR-Cas9, the study has devised a homology-independent targeted integration (HITI) strategy, which allows for robust DNA knock-in in non-dividing cells *in vitro* and, more importantly, *in vivo* (e.g., neurons and skeletal muscles of postnatal mammals). As proof of concept of its therapeutic potential, Prof Suzuki and colleagues demonstrated the efficacy of HITI in improving visual responses using a rat model of blindness, *retinitis pigmentosa*. The HITI method establishes new avenues for basic research and genome-editing therapies.

About the Speaker



Prof Keiichiro Suzuki began to learn DNA double-strand repair and genome-editing machineries in filamentous fungi when he was an undergraduate and a graduate student at Saitama University in Japan. He was a research associate of the Belmonte lab at the Salk Institute for Biological Studies from 2010 to 2017. He is a Professor at the Institute for Advanced Co-Creation Studies at Osaka University in Japan from 2017, where he has been developing highly efficient genome-editing methods for human stem cells, which are useful for gene correction of patient-derived human stem cells for disease modelling. His current interest is developing novel genome editing technologies for basic biology and gene therapy.

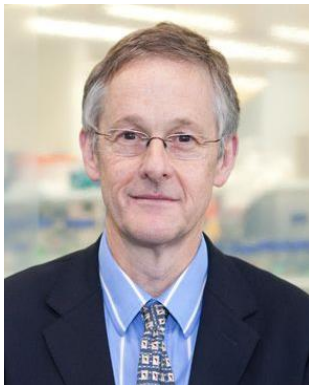
Biological functions and translational applications of CNS neural stem cell/extracellular matrix interactions

Professor Charles FFRENCH-CONSTANT

Professorial Fellow, MRC Centre for Regenerative Medicine; Dean of Research, College of Medicine and Veterinary Medicine, University of Edinburgh, United Kingdom

The mammalian brain contains a rich and distinct extracellular matrix, the function of which is poorly understood. Prof ffrench-Constant will describe studies on embryonic neural stem cells (NSC) and on all three adult NSC populations; those in hippocampus and subependymal zone and the widespread glial precursor cells that generate new oligodendrocytes throughout life. These studies all reveal instructive roles for cell/ECM interactions in NSC proliferation and differentiation, showing a number of different signalling pathways that regulate these interactions. Prof ffrench-Constant will consider how manipulation of these interactions might provide translational strategies for enhancing repair in the brain both by resident stem cells and by transplanted cells.

About the Speaker



Prof Charles ffrench-Constant is a clinician scientist who graduated with a MA in Physiology from the University of Cambridge and an MB, BChir in Medicine from Middlesex Hospital, London in 1980. He gained a MRCP in Internal Medicine in 1984 following training at the Hammersmith/University College Hospitals in 1984 and received a PhD in Neuroscience from UCL in 1986. He worked as a Post-Doctoral Fellow at MIT, Boston from 1987 to 1989 and in Zoology, Cambridge from 1989 to 1991, before being awarded a Junior Group Leader position in the Wellcome/CRC Institute at Cambridge from 1991 to 1996. He became a University Lecturer/Consultant at Addenbrookes Hospital, Cambridge in 1996, and was elected to the Chair of Neurological Genetics in 1999. He moved to the University of Edinburgh in 2007, becoming Director of the MRC Centre for Regenerative Medicine from 2010-5 during which time he led both the successful 2013 Centre renewal application and in 2014 a £11M bid to the UK Research Partnership Investment Fund for a new building to create an adjacent Centre for Tissue Repair. His work, funded by Wellcome Trust fellowship, programme and Investigator awards over 25 years, explores developmental and regenerative biology to develop new treatments for diseases of the CNS. He chaired the Wellcome Trust Molecular and Cellular Neuroscience panel from 2013 to 2017 and co-chaired the 2016 Myelin Gordon Research Conference. He is currently the Dean of Research for the College of Medicine and Veterinary Medicine at the University of Edinburgh, and Director of the Wellcome PhD programme in Translational Neuroscience.

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