28 - 29 SEPTEMBER 2023

12TH MODELS of PHYSIOLOGY & DISEASE SYMPOSIUM

Centre for Life Sciences, National University of Singapore

NUS National University of Singapore | Department of Physiology
Yong Loo Lin School of Medicine

NUS National University of Singapore | Immunology Translational Research Programme
Yong Loo Lin School of Medicine

28 - 29 SEPTEMBER 2023

12TH MODELS of PHYSIOLOGY & DISEASE SYMPOSIUM

Table of Content

28 - 29 SEPTEMBER 2023

12TH MODELS of PHYSIOLOGY & DISEASE SYMPOSIUM

Welcome Note

On behalf of the Organizing Committee, it is with great pleasure that we welcome you to the 12th Models of Physiology and Disease Symposium (Focus on Immuno-physiology). With the setting up of the various Translational Research Programmes in the Yong Loo Lin School of Medicine at the National University of Singapore, this is the first year that the symposium is jointly organized by the Department of Physiology and the Immunology Translational Research Programme.

With outstanding speakers, we hope this symposium will stimulate interest and discussion among the various communities in Singapore's biomedical research landscape and feature NUS as a centre of excellence for biomedical research both regionally and beyond. We hope this will open up discussion of opportunities to advance our understanding of basic mechanisms of diseases, therapeutic options and preventive measures. We have gathered renowned scientists from Singapore and overseas. We are also excited to have active participation of staff and students from our department and the Immunology Translational Research Programme.

We would like to thank all speakers, coordinators, student helpers, attendees and you for your participation. We are thankful for the support given by the Department of Physiology and the Immunology Translational Research Programme in planning and organizing the event. We are also grateful for the generous support from We also thank our sponsors Singlab, Miltenyi Biotec, Evident Scientific, Abcam, Global Cold Chain Solutions that made this symposium possible. Particular thanks go to the Lee Foundation and the Deanery of the Yong Loo Lin School of Medicine for their generous support.

Best Regards,

Herbert Schwarz & Andrew Tan

28 - 29 SEPTEMBER 2023

12TH MODELS of PHYSIOLOGY & DISEASE SYMPOSIUM

Welcome Note

Dear Friends and Colleagues,

It is with immense pleasure that I extend my warmest welcome to all of you at the 12th Models of Physiology and Disease Symposium.

This symposium was initiated in 2009 by the Department of Physiology at the NUS Yong Loo Lin School of Medicine. Since then, the symposium has served as a platform to foster knowledge exchange, drive meaningful discussions, and inspire collaborative efforts in human health and disease. I am very pleased to resume the 12th symposium this year which was held back for 3 years due to the COVID-19 pandemic. It is a great pleasure to jointly host the symposium with the Immunology Translation Research Programme (ITRP) this year.

We have an excellent line up of renowned international and local speakers. They bring with them a wealth of expertise and knowledge. I encourage everyone to actively engage, exchange ideas, and build networks that will foster growth and collaboration beyond these walls.

I extend my heartfelt appreciation to the organizers A/P Herbert Schwarz and Dr. Andrew Tan as well as members of the organizing committee for an excellent job in organizing this symposium. I extend my gratitude to our sponsors – NUS Yong Loo Lin School of Medicine, Lee Foundation, Singlab, Miltenyi Biotec, Evident Scientific, Abcam and Global Cold Chain Solutions – for their kind and generous support that has made this symposium possible.

I am confident that the next two days will be nothing short of exceptional. I wish you a very productive and inspiring conference.

Yours sincerely,

Reshma Taneja

Professor and Head

Department of Physiology, Yong Loo Lin School of Medicine

National University of Singapore

28 - 29 SEPTEMBER 2023

12TH MODELS of PHYSIOLOGY & DISEASE SYMPOSIUM

Welcome Note

Immunology is the study of how the organism can distinguish self from nonself. It's a multi-disciplinary science that is broad and connected to many disciplines, like the subject of physiology which is the study of how the human body functions. Hence, it is only natural that the Department of Physiology and Immunology Translational Research Programme (ITRP) collaborate to organize a symposium.

Together with the Organizing Committee, it is with great pleasure that I welcome you to the 12th Models of Physiology and Disease Symposium (Focus on Immune-physiology), jointly organized by Department of Physiology and ITRP at the Centre for Life Sciences, National University of Singapore. This is the first such collaboration and we hope to collaborate more with other departments for future events.

There is an outstanding line up of sessions and speakers from several countries. I hope that the symposium will continue to stimulate greater interest and discussion between the various communities in Singapore's biomedical research landscape and to feature NUS as a centre of excellence for biomedical research both regionally and beyond. Ending off the symposium, the ITRP bioinformatics core have organized a workshop to share hands-on skills on single cell analysis which is a useful and relevant skill that scientists should learn for their research.

I would also like to thank the organizers A/P Herbert Schwarz and Dr. Andrew Tan as well as members of the organizing committee for an excellent job in organizing this symposium. I extend my appreciation to our sponsors – NUS Yong Loo Lin School of Medicine, Lee Foundation, Singlab, Miltenyi Biotec, Evident Scientific, Abcam and Global Cold Chain Solutions – for their kind and generous support that has made this symposium possible.

I wish the 12th Models of Physiology and Disease Symposium a great success!

Veronique Angeli, Ph.D.
Director
Immunology Programme Life Science Institute, NUS
Immunology Translational Research Programme, NUS Yong Loo Lin School of Medicine
Associate Professor, Department of Microbiology and Immunology, NUS Yong Loo Lin School of Medicine

28 - 29 SEPTEMBER 2023

12TH MODELS of PHYSIOLOGY & DISEASE SYMPOSIUM

Programme

Day 1: Cancer and Immunology (Thursday, 28 September 2023)

8:15 - 8:50 AM	*Registration*
8:50 - 9:00 AM	**Opening Remarks by Reshma Taneja (HoD of Physiology) and Veronique Angeli (Director of ITRP)**

Session 1: Cancer Immunology

Chair: Nick Gascoigne

9:00 - 9:45 AM	**Michael Dustin** Engaging the immunological synapse to combat infection and cancer **University of Oxford, United Kingdom**
9:45 - 10:15 AM	**Shawn Chen** Cancer theranostics **National University of Singapore**
10:15 - 10:45 AM	*Tea Break*
10:45 - 11:15 AM	**Stephan Gasser** Off-the-shelf redirection of T cells to tumors **Roche, Switzerland**
11:15 - 11:45 AM	**Jinhua Lu** The winding roads to cancer vaccines, e.g. NY-ESO-1 **National University of Singapore**
11:45 - 11:55 AM	**Jyothsna Vasudevan** An in vitro human multicellular vascularized solid liver tumor model as a pre-clinical tool for assessing targeted drug delivery and adoptive cell therapy **National University of Singapore**
11:55 - 12:05 PM	**Emily Nickles** Characterization of anti-CD137L antibodies and their potential therapeutic application for treatment of autoimmune diseases **National University of Singapore**
12:05 - 12:15 PM	**Jiajun Tan** Whole tissue 3D imaging for the exploration of biological architectures **Mitenyi Biotec Asia Pacific Sponsor Talk**
12:15 - 1.30 PM	*Lunch*

Session 2: Immunophysiology of Disease

Chair: Derrick Ong

1.30 - 2:00 PM	**Enfu Hui** T cell costimulation in *cis* **University of California, San Diego**
2:00 – 2.30 PM	**Thai Tran** Deciphering the "Jekyll and Hyde" effects of corticosteroids in the treatment of influenza viral infections **National University of Singapore**
2.30 - 3:00 PM	**Gloryn Chia** Exploring alternative neoantigens for development of cancer vaccines **National University of Singapore**
3:00 – 3:10 PM	**Yajing Liang** DMTF1 promotes neural stem cell proliferation by regulating cell cycle gene expression via H2AZ **National University of Singapore**
3:10 - 3:40 PM	*Tea Break*

Chair: Karen Crasta

3:40 - 4:10 PM	**Lina Lim** Overcoming chronic stress-induced breast tumor development, growth and metastasis: an immune mediated mechanism? **National University of Singapore**
4:10 - 4:40 PM	**Haiyan Liu** IL-37 dampens immune suppressive functions of MDSCs via metabolic reprogramming in the tumor microenvironment **National University of Singapore**
4:40 - 5:10 PM	**Shruti Bhatt** Modeling and targeting therapy resistance in myeloid leukemia **National University of Singapore**
5:10 – 5:25 PM	**You Heng Chuah** CAMK2D serves as a molecular scaffold for RNF8-MAD2 complex to induce mitotic checkpoint in glioma **National University of Singapore**
6:00 - 9:30 PM	*Dinner (by invitation only)*

28 - 29 SEPTEMBER 2023

12TH MODELS of PHYSIOLOGY & DISEASE SYMPOSIUM

Programme

Day 2: New Technology (Friday, 29 September 2023)

8:15 - 8:50AM	*Registration*

Session 3: New Technology (Delivery Technology)
Chair: John Chua

9:00 - 9:45AM	**Richard Harbottle** DNA Vectors an alternative platform for genetic engineering German Cancer Research Center, Germany
9:45 - 10:15 AM	**Yi Yan Yang** Synthetic Macromolecules and Assemblies Overcoming Drug Resistance in Cancer Bioprocessing Technology Institute, Singapore
10:15 - 10:45 AM	*Tea Break*

Chair: Tsai Shih Yin

10:45 - 11:15 AM	**Giorgia Pastorin** Recent advances in nanomedicine for cancer treatment: Synthesis or Biomimicry? National University of Singapore
11:15 - 11:45 AM	**Yongliang Zhang** DUSP10 therapy for colorectal cancer treatment National University of Singapore
11:45 - 11:55 AM	**Previtha Dawn** LCK knockout CAR - T cells as a novel allogeneic platform National University of Singapore
11:55 - 12:05 PM	**Mugdha Vijay Patwardhan** GSTT2 and the response to BCG Immunotherapy National University of Singapore
12:05 - 12:15 PM	**Amrita Roy** Spatially mapping transcriptomic gene expression profiles using gold standard RNAscope in situ hybridization technology Singlab Sponsor Talk
12:15 - 12:20 PM	*Closing Remarks by Organizing Committee Chairmen and Lucky Draw*
12:20 - 1:20 PM	*Lunch*

Session 4: Digital Technology Workshop

1:20 - 1:50 pm	**Chengwei Zhong** Interpretable spatial dimensional reduction of spatial transcriptomics with STAMP National University of Singapore
1:50 – 2.20 PM	**Sethi Raman** ezSingleCell: An integrated one-stop single-cell and spatial omics analysis platform for bench scientists National University of Singapore
2:30 - 4:30 PM	**Jianzhou Cui** Hands-on teaching session on single cell analysis National University of Singapore

28 - 29 SEPTEMBER 2023

12TH MODELS of PHYSIOLOGY & DISEASE SYMPOSIUM

Speakers

Shruti BHATT

Assistant Professor, Department of Pharmacy, NUS

Link: https://pharmacy.nus.edu.sg/team/asst-prof-shruti-bhatt/

Xiaoyuan (Shawn) CHEN

Professor, Nasrat Muzzayyin Chair Professor in Medical and Technology,
Yong Loo Lin School of Medicine and Faculty of Engineering, NUS
Senior Investigator/Lab Chief, National Institutes of Health

Link: https://medicine.nus.edu.sg/circ/team/professor-xiaoyuan-shawn-chen/

Gloryn CHIA

Assistant Professor, Department of Pharmacy, NUS
Principal Investigator, iHealthtech

Link: https://pharmacy.nus.edu.sg/team/asst-prof-gloryn-chia/

Michael DUSTIN

Professor, Director of Research in Kennedy Institute of Rheumatology
University of Oxford

Link: https://www.kennedy.ox.ac.uk/team/michael-dustin

28 - 29 SEPTEMBER 2023

12TH MODELS of PHYSIOLOGY & DISEASE SYMPOSIUM

Speakers

Stephan GASSER

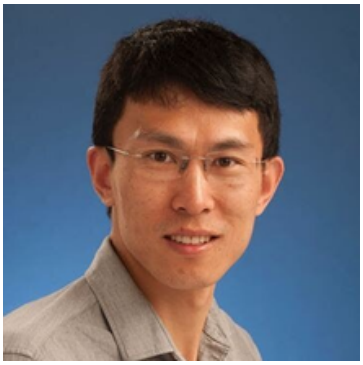
Senior Principal Scientist
Roche Innovation Center, Zurich, Switzerland
Assistant Professor in Immunology Programme of Life Sciences Institute (2007)

Link: linkedin.com/in/stephan-gasser-3a5ba59

Richard HARBOTTLE

Research Group Leader, DNA Vector Research Group
German Cancer Research Center
Deutsches Krebsforschungszentrum (DKFZ)

Link: https://www.dkfz.de/en/dna-vektoren/index.php



Enfu HUI

Associate Professor, Department of Cell and Developmental Biology
University of California, San Diego

Link: https://biology.ucsd.edu/research/faculty/enfuhui

Haiyan LIU

Associate Professor, Department of Microbiology and Immunology,
Life Science Institute, Immunology Translational Research Program, NUS

Link: https://medicine.nus.edu.sg/mbio/about-us/our-people/academic-staff/liu-haiyan.html

28 - 29 SEPTEMBER 2023

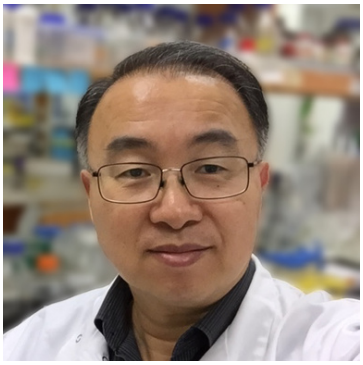
12TH MODELS of PHYSIOLOGY & DISEASE SYMPOSIUM

Speakers

Lina, Hsiu Kim LIM

Associate Professor, Department of Physiology,
Immunology Translational Research Program, NUS

Link: https://medicine.nus.edu.sg/phys/research/research-programs/immunology/lim-hsiu-kim-lina/



Jinhua LU

Associate Professor, Department of Microbiology and Immunology, NUS

Link: https://medicine.nus.edu.sg/mbio/about-us/our-people/academic-staff/lu-jinhua.html

Giorgia PASTORIN

Associate Professor, Assistant Dean (Research and Development), Faculty of Science,
Director of the Pharmaceutical Innovation and Research Center, NUS

Link: https://pharmacy.nus.edu.sg/team/a-prof-giorgia-pastorin/

Thai TRAN

Associate Professor, Department of Physiology, NUS

Link: https://medicine.nus.edu.sg/phys/research/research-programs/infectious-disease/thai-tran/

28 - 29 SEPTEMBER 2023

12TH MODELS of PHYSIOLOGY & DISEASE SYMPOSIUM

Speakers

Yi Yan YANG

Senior Principle Scientist and Group Leader, Bioprocessing Technology Institute, Agency for Science, Technology and Research (A*STAR)
Adjunct Professor (research), Department of Orthopaedic Surgery, NUS

Link: https://www.a-star.edu.sg/ibb/our-scientists/yi-yan-yang's-laboratory/yang-yi-yan

Yongliang ZHANG

Associate Professor, Department of Microbiology and Immunology, NUS

Link: https://medicine.nus.edu.sg/mbio/about-us/our-people/academic-staff/zhang-yongliang.html

Speaker's Abstracts

Michael DUSTIN

Title: Engaging the immunological synapse to combat infection and cancer

Abstract: The immunological synapses (IS) is the specialized contact between a T cell and antigen presenting cell that serves effector function for helper and cytotoxic T cells. A key feature of the IS is the transport of TCR microclusters to the centre, where signaling is terminated. We discovered using correlative light and electron microscopy that TCR were ectocytosed in the centre of the synapse. These vesicles also serve as an antigen specific carrier for CD40-ligand, a critical signal delivered by helper T cells[1]. We next adapted our technology to investigate how CD8 cytotoxic T cells (CTL) and NK cells use nanoscale protein "bombs" with a core of cytotoxic perforin and granzymes and a shell of thrombospondin-1 (TSP-1) that are secreted into the synaptic cleft to kill target cells[2]. We have referred to these "bombs" as supramolecular attack particles (SMAPs). Ashwin Jainarayanan, Vineeth Chandrasekar, Vinny Almeida, Amanda Wickl and Carol Leung have shown that enriched SMAP can slow or eliminate aggressive cancers in mouse models.

While the radially symmetric synapse has clear benefits for effector function, the control of proliferation is less clear. Work led by Alexander Leithner has recently developed a new method to selectively control the lateral mobility of one component in a synthetic bilayer at a time, which has revealed new requirements for costimulatory signaling by the ICAM1 integrin ligand based on mechanical feedback. The impact of mixtures of mobile and immobile ICAM1 is currently being investigated.

With Dr. Jemma Larson in the lab of Bruce Blazar, Ewoud Compeer and Olga Margaritaki have investigated the cytotoxic mechanisms of chimeric antigen receptor expressing CD8+ iTreg[3], as a novel approach to immunotherapy for B cell leukemias. The CAR CD8 iTreg have similar cytotoxicity to CD8 CTL, but produce lower levels of inflammatory cytokines and thus have less toxicity. They have found that CD8 iTreg make SMAPs with a shell of TSP-4 rather than TSP-1. Nagaja Capitani and Cosima Baldari, collaborators at the University of Siena have also found that culture human CD8 CTL also switch from TSP-1 to TSP-4 during in vitro expansion. The importance of this change in the composition of the SMAP shell from trimeric TSP-1 to pentameric TSP-4 is under study.

[1] Cespedes, P. F. et al. T-cell trans-synaptic vesicles are distinct and carry greater effector content than constitutive extracellular vesicles. Nat Commun 13, 3460 (2022). https://doi.org:10.1038/s41467-022-31160-3

[2] Balint, S. et al. Supramolecular attack particles are autonomous killing entities released from cytotoxic T cells. Science 368, 897-901 (2020). https://doi.org:10.1126/science.aay9207

[3] Bolivar-Wagers, S., Larson, J. H., Jin, S. & Blazar, B. R. Cytolytic CD4+ and CD8+ Regulatory T-Cells and Implications for Developing Immunotherapies to Combat Graft-Versus-Host Disease. Frontiers in Immunology 13 (2022). https://doi.org:10.3389/fimmu.2022.864748

28 - 29 SEPTEMBER 2023

12TH MODELS of PHYSIOLOGY & DISEASE SYMPOSIUM

Speaker's Abstracts

Xiaoyuan (Shawn) CHEN

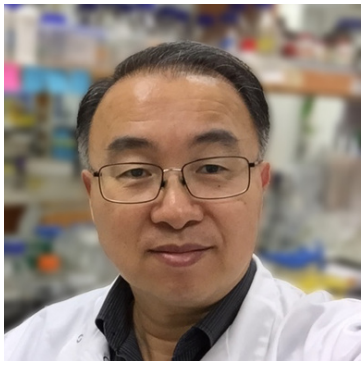
Title: Cancer theranostics

Abstract: Theranostics, the combination of ther(apy) and (diag)nostics, aims to develop molecular diagnostic tests and targeted therapeutics with the goals of individualizing treatment by targeting therapy to an individual's specific disease subtype and genetic profile. It can be diagnosis followed by therapy to stratify patients who will likely respond to a given treatment. This talk will highlight a few recent examples how we can target different types of cells (fibroblasts, macrophages, dendritic cells, and T cells) in the tumor microenvironment to develop new cancer diagnostics and therapeutics.

Stephan GASSER

Title: Off-the-Shelf Redirection of T Cells to Tumors

Abstract: Off the shelf T-cell bispecific antibodies (TCBs) targeting heme antigens have demonstrated promising efficacy in clinical development. Recently, the Food and Drug Administration granted accelerated approval for our CD20 targeting TCB Glofitamab. I will discuss how we combine TCBs with targeted costimulatory molecules and how we envisage extending the benefits of TCBs to solid cancers.



Jinhua LU

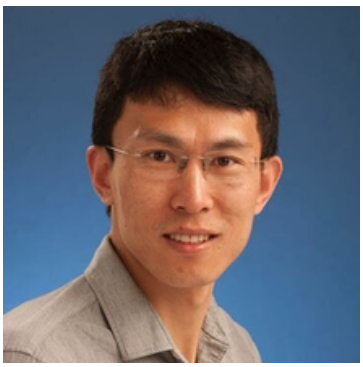
Title: The winding roads to cancer vaccines, e.g. NY-ESO-1

Abstract: Cancers are caused by genetic mutations that confer growth advantages. These mutations are often amplified through epigenetic precipitation. While these changes add immunogenicity to cancer cells, some escape immune surveillance and gain stronger malignancy. Immune checkpoint blockage only release limited tumor-specific immunity and, for many cancer patients, the response rates are limited to 20-40%. Late stage tumors are particularly suppressive to tumor-specific CD8 T cells. These tolerant CD8 T cells also require strong vaccines to reactivate. Effective cancer vaccines are expected to target the antigens from the extracellular space to the cytoplasmic MHC class I pathway. Tumors are immunogenically heterogeneous which require polyvalent vaccines to overcome tumor editing. However, there is currently no effective means to evaluate cancer vaccine immunogenicity. We recently discovered a peptide (P2M6) with dual TLR ligand and intracellular antigen delivery properties. With P2M6, we are developing a platform for cancer vaccine development.

28 - 29 SEPTEMBER 2023

12TH MODELS of PHYSIOLOGY & DISEASE SYMPOSIUM

Speaker's Abstracts



Enfu HUI

Title: T cell costimulation in cis

Abstract: Classically, T cell co-stimulation (signal 2) occurs in the secondary lymphoid organs, in which B7 ligands (CD80 and CD86), expressed by professional antigen-presenting cells (APCs), activate the main co-stimulatory receptor CD28 on T cells in trans. However, in peripheral tissues, APCs expressing B7 ligands are relatively scarce. This raises the questions of whether and how CD28 co-stimulation occurs in peripheral tissues. In this talk, I will present our recent evidence that T cells can receive CD28 stimulation through B7 ligands displayed by themselves via cis-B7:CD28 interactions. I will discuss both the functional consequence and cell biology basis of cis-B7:CD28 signaling.

Thai TRAN

Title: Deciphering the "Jekyll and Hyde" effects of corticosteroids in the treatment of influenza viral infections

Abstract: Corticosteroids (steroids) possess potent anti-inflammatory properties and are prescribed to manage hyperinflammatory complications, such as acute respiratory distress syndrome or pneumonia, associated with influenza A virus (IAV) infections. However, the use of steroids remains contentious due to its link with increased IAV infection and exacerbation of disease-related morbidity and mortality. The immunosuppressive nature of steroids is thought to explain the increased risk of viral infection. However, supplementary interferon (IFN) treatment to enhance innate anti-viral genes only partially offset the impact of steroids on innate immune responses, suggesting additional mechanisms remain to be fully elucidated. Previous work in our laboratory identified CD151, a tetraspanin, as a novel host factor in IAV replication. Surprisingly, preliminary studies also indicated that steroid treatment elevates CD151 expression in airway smooth muscle cells. Hence, our hypothesis posits that the heightened IAV replication, viral load, poor lung function, and mortality associated with steroid use are mediated by CD151. We validated that CD151 alone substantially enhances IAV load in human airway epithelial cells (hAECs) in vitro, highlighting its fundamental contribution to viral replication. Importantly, we showed that steroid-induced increase in viral load is contingent on the presence of CD151 in vitro, ex vivo, and in vivo infection models. At three days post IAV infection, steroid-treated CD151-null mice exhibited a lower lung damage score, better lung function, and more robust anti-viral immune response than wild-type steroid-treated mice. Our study highlights a promising novel avenue for refining steroid's 'Jekyll and Hyde' therapeutic properties to manage hyperinflammation resulting from influenza infections. By mitigating CD151 expression levels, the steroid-induced enhancement of IAV load, lung damage, and consequent poor lung function could be abolished while preserving the beneficial anti-inflammatory attributes of steroids in treating IAV infections.

28 - 29 SEPTEMBER 2023

12TH MODELS of PHYSIOLOGY & DISEASE SYMPOSIUM

Speaker's Abstracts

Gloryn CHIA

Title: Exploring alternative neoantigens for development of cancer vaccines

Abstract: The paradigm of cancer immunotherapy has been transformed by the emergence of neoantigens as potent targets for tailoring personalized cancer vaccines. However, the limited availability of somatic mutations in the majority of tumor types poses a challenge for effectively harnessing neoantigens. In this context, we explore alternative neoantigens that arise from non-mutational sources, such as epigenetic alterations and splicing changes in tumor cells. Through the analysis of post-transcriptional events in tumor cells, we unveil an unexplored spectrum of neoantigenic diversity that extends beyond traditional mutational landscapes. These alternative sources not only broaden the antigenic repertoire but also address the challenge of tumor types with limited mutational burdens, particularly in the development of cancer vaccines.

Lina LIM

Title: Overcoming chronic stress-induced breast tumor development, growth and metastasis: an immune mediated mechanism?

Abstract: "Stress" is linked to depression and anxiety in working adults and schooling children, and this itself is linked to a higher risk of disease. In a groundbreaking study, Robert Sapolsky researched free-roaming African Baboons and found that the dominant or alpha males were much less stressed and had lower heart rates and blood pressure than the submissive ones. Here I will show results in vitro and in vivo demonstrating that stress enhances cancer growth, migration and metastasis which can be reversed with inhibitors of the adrenergic pathway. On the other hand, maternal bonding and connection is related to and correlated with the secretion of oxytocin, or the "love hormone". Our published systematic review shows that oxytocin strengthens affectionate parenting in mothers and stimulatory parenting in fathers. Low levels of oxytocin are associated with various mental health disorders like anxiety, depression and post-traumatic stress disorder. Whether a lower oxytocin level can also lead to a higher risk of female cancers is also an interesting field which has not been investigated fully. I will show exciting results that systemic administration of oxytocin reduces stress-induced anxiety in vivo and stress-induced breast tumor development, growth and metastasis in vitro and in vivo. These studies pave the way for deeper understanding of stress in cancer and disease and finding interventions to reverse this is of utmost importance.

28 - 29 SEPTEMBER 2023

12TH MODELS of PHYSIOLOGY & DISEASE SYMPOSIUM

Speaker's Abstracts

Haiyan LIU

Title: IL-37 dampens immune suppressive functions of MDSCs via metabolic reprogramming in the tumor microenvironment

Abstract: IL-37 has been shown to inhibit tumor growth in various cancer types. However, the immune regulatory function of IL-37 in the tumor microenvironment is unclear. Recent studies have suggested that IL-37 could recruit natural killer cells and promote dendritic cell or macrophage functions to inhibit tumor development using subcutaneous or xenograft mouse models, which may not reflect the organ-specific tumor microenvironment. In this study, we established a humanized patient-derived xenograft (PDX) hepatocellular carcinoma (HCC) model and three murine orthotopic HCC models to study the function of IL-37 in the tumor microenvironment. We found that IL-37 inhibited HCC growth and promoted T cell activation. Further study revealed that IL-37 impaired the immune-suppressive capacity of myeloid derived suppressor cells (MDSCs). Pretreatment of MDSCs with IL-37 before adoptive transfer attenuated their tumor-promoting function in HCC tumor-bearing mice. Moreover, IL-37 promoted both glycolysis and OXPHOS in MDSCs, resulting in the upregulation of ATP release, which impaired the immune-suppressive capacity of MDSCs. Taken together, we demonstrated that IL-37 inhibited tumor development through dampening MDSC's immune-suppressive capacity in the tumor microenvironment via metabolic reprogramming, making it a promising target for future cancer immunotherapy.

Shruti BHATT

Title: Modeling and targeting therapy resistance in myeloid leukemia

Abstract: Despite of remarkable changes in therapeutic landscape of acute myeloid leukemia (AML) in past 5 years, relapsed AML patients still succumb to disease. In majority of patients, the common cause of death ultimately is the emergence multi-drug resistance at relapse. By using human cell lines, patient-derived xenografts (PDX) and primary tumors as our models, we investigated the basis of multi-drug resistance and methods for identifying drug sensitivity in relapsed AML. We found that reduction in mitochondrial apoptotic priming consistently accompanied the acquisition of multidrug resistance irrespective of the mechanism of drug action and genetic status of PDX models.

28 - 29 SEPTEMBER 2023

12TH MODELS of PHYSIOLOGY & DISEASE SYMPOSIUM

Speaker's Abstracts

Richard HARBOTTLE

Title: From Stem-Cells to T-Cells . . . .
DNA NanoVectors an Alternative Non-Integrating DNA Vector Platform for Regenerative Medicine and Immunotherapy

Abstract: Over the past decades, the field of gene and cell therapy has focussed predominantly on the use of viral vectors for genetically engineering cells. Viruses typically have limited capacity, are immunogenic, and can cause a range of cellular toxicities which can reduce their efficacy. Additionally, they are complex and expensive to produce to clinical standards, and in recent years, global manufacturing capacity has been overwhelmed by demand. The DNA Vector lab at the DKFZ has worked to develop an alternative genetic vector system which can be used as an effective replacement for viruses. This novel non-viral DNA nanovector platform can be quickly and economically produced and used in a range of applications including regenerative medicine and gene and cell therapy. These vectors are minimally sized circles of DNA which are designed and refined to contain no pathogenic sequences and comprise a novel composition including newly identified S/MAR motifs which provide their enhanced functionality including persistent expression and mitotic stability without genetic integration. S/MAR DNA nanovectors present a compelling alternative to viral vectors for introducing tumor-targeting Chimeric Antigen Receptors (CARs) or T Cell Receptors (TCRs) into immune cells, maintaining efficient and effective delivery. Additionally, they facilitate the generation of recombinant stem cells for applications in regenerative medicine. They are more versatile and are simpler and quicker to manufacture at scale, thus increasing the number of patients who can be treated while significantly reducing the vein-to-vein time of the treatment process which is particularly crucial for generating personalized therapies for aggressive tumours where every cellular product needs to be created uniquely and delivered promptly. This DNA nanovector system and improvements to it could potentially have an enormous impact in a range of fields including DNA vaccines, gene therapy, and the clinical application of recombinant T Cell Immunotherapy and personalised stem-cell medicine.

Yi Yan YANG

Title: Synthetic Macromolecules and Assemblies Overcoming Drug Resistance in Cancer

Abstract: Anticancer drug resistance is a huge problem in healthcare industry. Multiple drugs are employed to treat cancer patients to overcome the drug resistance issue, leading to severe harmful side-effects. In addition, this approach does not mitigate cancer metastasis. Recent research has been focused on macromolecular anticancer peptides and polymers. The anticancer macromolecules can eliminate cancer cells and cancer stem cells, preventing metastasis. However, they have non-specific toxicity due to the presence of cationic charge components. We have recently proposed a targeted delivery strategy to transport the anticancer polymers to tumor tissues through supramolecular assemblies. Specifically, we synthesized an anionic biodegradable polycarbonate and utilized it to form nanocomplexes with cationic anticancer polycarbonate via supramolecular self-assembly, neutralizing the cationic changes of anticancer polycarbonate. Biotin was conjugated to the anionic polycarbonate and served as a cancer cell-targeting ligand. The nanoparticles had sizes of <130nm with anticancer polycarbonate loading levels of 38%-49%. Unlike the small molecular anticancer drug doxorubicin, the nanocomplexes effectively inhibited the growth of both drug-susceptible MCF7 and drug-resistant MCF7/ADR human breast cancer cell lines with low half maximal inhibitory concentration (IC50). The nanocomplexes increased the anticancer polymer's in vivo half-life from 1h to 6 -8h, and rapidly killedBT474 human breast cancer cells primarily via an apoptotic mechanism. The nanocomplexes significantly increased the median lethal dose (LD50) and reduced the injection site toxicity of the anticancer polymer. They suppressed tumor growth by 32% -56% without causing any damage to the liver and kidneys. These supramolecular assemblies may be employed as a cancer treatment option in the future to overcome drug resistance.

28 - 29 SEPTEMBER 2023

12TH MODELS of PHYSIOLOGY & DISEASE SYMPOSIUM

Speaker's Abstracts

Giorgia PASTORIN

Title: Recent advances in nanomedicine for cancer treatment: Synthesis or Biomimicry?

Abstract: "Biomimicry" derives from Ancient Greek, and it encompasses the fusion of the word Bios (life), and mīmēsis (imitation), i.e. imitation of Nature. Cells are natural biological entities that secrete small (nano) extracellular vesicles (EVs) as a mean to transport information and biomelcules into other cells. Receiving cells are then equipped with recognition motifs that enable the selective internalization of these EVs. The imitation of this natural process that enables cells to communicate with both neighbouring and distant cells has inspired the development of new nanotechnological strategies to improve the delivery of drugs at their site of action. Scientists have recently exploited these EVs to either load them with drugs or to develop artificial EV mimetics that preserve biocompatibility and intrinsic targeting ability towards diseased cells.

Our group has recently conceived a nano-biohybrid system building on the idea of "combining the best of two worlds": these nano-Cell Vesicle Technology Systems (nCVTs), obtained through the fusion of cell-derived components with conventional synthetic materials, represent an unreported chimeric drug delivery system with ideal properties in terms of nano-size (which enables to reach and accumulate at the diseased area), surface cues (which preserve the targeting properties inherited from their original parent cells) as well as ease of loading and functionalization (from the synthetic components), which pave the way towards new advances in the field of nanomedicine.

Key references:
Nanoscale, 2018, 10, 6812, Nanoscale, 2020, 12, 18022, BIOMOLECULAR COMPOSITES, PCT No.10201706173U; patent filed in Jan 2020, Seminars in Cancer Biology, 2021, S1044-579X(21)00029-8

ZHANG Yongliang

Title: DUSP10 therapy for colorectal cancer treatment

Abstract: Colorectal cancer (CRC) is one of the most commonly diagnosed cancer worldwide. Challenges in CRC treatment include development of resistance to therapies, recurrence and patients' unsuitability for therapies, which could lead to unfavourable patent outcome. Understanding molecular mechanisms underlying the pathogenesis of CRC will help to develop novel therapies against CRC. Our study on a molecule known as Dual-specificity phosphatase 10 (DUSP10) demonstrated its potent tumor suppressive function in CRC. We therefore developed a patented technology by targeting DUSP10 (DUSP10 therapy) for CRC treatment. The efficacy of DUSP10 therapy in CRC was tested using various mouse models of CRC. The results showed that treatment with DUSP10 therapy could inhibit up to 80% of colon tumor development. It could also suppress CRC liver metastasis. In addition, DUSP10 therapy could be combined with other therapies such as immune checkpoint inhibitor therapy to achieve better outcomes. As such, the DUSP10 therapy is a promising novel therapeutic intervention for CRC which need to be further tested in clinical trials.

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12TH MODELS of PHYSIOLOGY & DISEASE SYMPOSIUM

Short Talks

Jyothsna VASUDEVAN

Department of Mechanobiology Institute
Research Fellow under Dr Andrea Pavesi

Title: An in vitro human multicellular vascularized solid liver tumor model as a pre-clinical tool for assessing targeted drug delivery and adoptive cell therapy

Abstract: The development of effective therapeutic strategies for solid tumors is limited due lack of pre-clinical models that can accurately predict patient treatment outcomes. Current state-of-the-art in vitro models fail to faithfully replicate crucial characteristics of the in vivo tumor microenvironment (TME), which comprises a diverse array of cell types like endothelial cells, fibroblasts, immune cells, and cancer cells, capable of either promoting tumor resistance or hindering targeted therapies. To address this issue, we have created an in vitro vascularized liver tumor model within a microfluidic device to assess drug delivery and immunotherapy approaches. Our model comprises of a tumor spheroid surrounded by a perfusable self-organized microvasculature bed with physiologically relevant permeability. The efficacy of Sorafenib was assessed by measuring tumor viability, quantified by the loss of cancer cells' fluorescence signal. Notably, the presence of vasculature resulted in increased cytotoxicity, emphasizing the significance of tumor-vascular interactions in testing therapeutic effectiveness in a more physiological-like setting. Furthermore, to validate immunotherapy, we introduced engineered immune cells, specifically chimeric antigen receptor (CAR) T-cells (CD133+ CAR-T) and transiently expressing T-cells engineered with a T cell receptor (HBV+ TCR-T cells), into the model. Our findings showed enhanced immune cell infiltration in the absence of vasculature, while their cytotoxicity was heightened in the presence of vasculature and extravasation. By conducting digital spatial transcriptomic analysis on standard paraffin-embedded sections of the cultured microtissue, we identified both known and novel genes involved in creating a pro-tumorigenic microenvironment. Overall, our platform effectively mimics crucial aspects of the in vivo TME, significantly improving the predictability of treatment outcomes with promising applications in personalized medicine.

Emily Nickles

Department of Physiology
Research Associate under Prof Herbert Schwarz

Title: Characterization of anti-CD137L antibodies and their potential therapeutic application for treatment of autoimmune diseases

Abstract: CD137, a potent co-stimulatory molecule, is expressed on activated T cells while its binding partner CD137L is expressed on antigen presenting cells. CD137-CD137L interaction induces bidirectional signaling, which drives a type 1 cellular immune response. Current literature demonstrates the ability of CD137 agonists to skew T cell polarization to a Th1 phenotype, thereby ameliorating Th2 or Th17 mediated autoimmune diseases such as lupus, allergic airway inflammation and collagen-induced arthritis. Despite reports highlighting the potential of targeting CD137 for treatment of autoimmune diseases, targeting CD137L has not been fully explored. In this study, 8 anti-CD137L antibodies were generated and characterized. Out of the 8 antibodies, clone P4A4 seems to be most promising as an antibody for therapeutic application. P4A4 can induce CD137L reverse signaling in the monocytic cell line THP-1 and in primary monocytes, evidenced by enhanced IL-8 secretion, which is indicative of agonistic activity. P4A4 additionally blocks CD137-CD137L interaction in sub-optimally activated peripheral blood mononuclear cells from healthy donors. P4A4 reduced expression of T cell activation and co-stimulatory molecules, production of T cell producing cytokines and T cell proliferation. In an in vivo acute GvHD humanized mouse model, P4A4 treated mice had better survival and showed reduced splenic T cell activation. Collectively, these results suggest that clone P4A4 should be further evaluated for treatment of autoimmune diseases.

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Short Talks

LIANG Yajing

Department of Physiology
Graduate student under Dr Derring Ong Sek Tong

Title: DMTF1 promotes neural stem cell proliferation by regulating cell cycle gene expression via H2AZ

Abstract: The neural stem cells (NSCs) contribute to brain development and homeostasis via their unique properties of self-renewal and differentiation. It is thought that NSC functional reserves decline over time, leading to the progressive loss of cognition and memory during aging. Thus, the molecular understanding of how NSC proliferation and dormancy are regulated holds the potential in developing therapeutic strategies to retard or even reverse brain aging. DMTF1 is a transcription factor that is proposed to be a haplo-insufficient tumor suppressor gene in cancer cells. However, the exact role of DMTF1 in NSC biology remains poorly understood. We found that DMTF1 depletion reduced the proliferation and self-renewal of mouse NSC in vitro. Interestingly, DMTF1 proximity proteomics identified novel protein interactions between DMTF1, the histone variant H2AZ and histone chaperones of H2AZ. DMTF1 and H2AZ ChIP-Seq analyses revealed that the majority of DMTF1 genome binding sites overlaps with that of H2AZ, mainly at the promoters of cell cycle genes. DMTF1 knockdown reduces H2AZ occupancy at the promoters of cell cycle genes, and downregulates cell cycle gene expression in mouse NSC, suggesting that DMTF1 may directly/indirectly regulate H2AZ chromatin deposition which in turn influences cell cycle gene expression. Unexpectedly, DMTF1 is downregulated in telomerase deficient NSC, an aging model of NSC, and DMTF1 overexpression can rescue the proliferation defect of telomerase deficient NSC. Our preliminary data supports a key role of DMTF1 in regulating NSC proliferation and suggests that boosting DMTF1 levels may enhance NSC functional reserves in the aging brain.

CHUAH You Heng

Department of Physiology
Graduate student under Dr Derring Ong Sek Tong

Title: CAMK2D serves as a molecular scaffold for RNF8-MAD2 complex to induce mitotic checkpoint in glioma

Abstract: The spindle assembly checkpoint (SAC) is an evolutionarily conserved mechanism employed by our cells to safeguard genomic fidelity, for the prevention of chromosome mis-segregation. In the presence of unattached kinetochores, the SAC activation leads to the formation of mitotic checkpoint complex (MCC), which is a potent inhibitor of the anaphase-promoting complex/cyclosome, blocking anaphase progression. Interestingly, there is extensive crosstalk between SAC proteins and DNA damage repair (DDR) factors. The E3 ubiquitin ligase RNF8, a well-established DDR factor, has been implicated in mitotic checkpoint, but its exact role remains unknown. Using RNF8 proximity proteomics, we show that RNF8 associates with MAD2 via its RING domain whereas its FHA domain binds transiently/weakly to the phospho-Thr287 of CAMK2D. In glioma stem cells (GSC), the overexpression of wild-type RNF8, but not the –FHA and RING mutants, impairs cell proliferation, blocks mitotic progression, and increases genomic instability. Mechanistically, RNF8 competes with p31comet for binding to MAD2 closed conformer, and the CAMK2D oligomers scaffold RNF8-MAD2 complexes to facilitate MCC generation, leading to SAC activation. Clinically, low RNF8 expression portends poor patient prognosis in multiple glioma patient cohorts. Finally, our mechanistic insights led to the identification of a novel PLK1/HSP90 inhibitor combination which effectively suppresses GSC proliferation and stemness. Collectively, our study has unveiled an E3 ligase-independent role of RNF8 in SAC regulation, dissected its underlying molecular mechanisms and highlighted the importance of RNF8 downregulation in glioma to avoid mitotic checkpoint activation.

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Short Talks

Previtha Dawn

Department of Microbiology and Immunology
Graduate student under Prof Nicholas Gascoigne

Title: LCK Knockout CAR-T Cells as a Novel Allogeneic Platform

Abstract: Chimeric antigen receptor (CAR) T therapy has shown remarkable success in treating liquid tumours but current approved therapies rely on autologous T cells which are expensive, difficult to manufacture and not readily available for patients. The production of safe and effective allogeneic CAR T cells is needed to increase accessibility of CAR-T therapy and broaden its application. The main approach to generate allogeneic CAR-T therapy is by disrupting T cell receptor (TCR) expression to minimize Graft-versus-Host Disease (GVHD). However, this approach has shown limited persistence in vivo and in clinical trials unlike the long-term durability of autologous CAR-T cells. Here, we propose a novel platform for allogeneic CAR-T therapy that retains the TCR but inhibits TCR signalling by knocking out the Lymphocyte-specific protein tyrosine kinase (LCK), a well-established kinase for TCR activation. This builds on previous work on LCK independent CAR T signalling. We generated LCK–CAR-T cells that showed similar or enhanced in vitro and in vivo efficacy against tumour cells compared to conventional CAR-T cells. LCK–T cells have reduced proliferation and intracellular cytokine staining against allogeneic PBMCs compared to T cells. In the xenogeneic GVHD mouse model, LCK–T cells showed reduced xenogeneic GVHD comparable to TCR– T cells. In murine major mismatched allogeneic models, LCK– T cells showed a reduction in GVHD symptoms compared to wildtype T cells. Compared to TCR–T cells, the LCK–T cells showed superior persistence and higher engraftment in allogeneic recipient mice.

Mugdha Vijay Patwardhan

Department of Surgery
Graduate student under Dr. Ratha Mahendran

Title: GSTT2 and the response to BCG Immunotherapy

Abstract: Whilst M. bovis Bacillus Calmette-Guérin (BCG) therapy remains the gold-standard for treatment of high-risk non-muscle invasive bladder cancer (BC), 30-40% of patients fail therapy, resulting in disease recurrence and progression. Glutathione-S-transferase theta 2 (GSTT2) is a member of the GST family. Loss of GSTT2 expression has been associated with modulation of intracellular ROS and BCG survival in BC cell lines. Retrospective analysis of BC patients revealed that patients with the GSTT2B deletion responded better to fewer instillations of BCG. To understand these responses, wild-type (WT) and GSTT2-knockout (KO) mice were implanted with MB49-PSA BC cells, in subcutaneous and orthotopic settings. Mice were treated with four weekly BCG instillations, after which the subcutaneous tumors and bladders were harvested for downstream analysis. Single-cell RNA sequencing of whole-bladders was used to identify cell clusters within the bladder, and analyze differential gene expression. Hmga2, Ahnak and Peak1 were found to be differentially expressed in bladders from WT and GSTT2-KO mice. These genes are known to be involved in pro- and anti-tumorigenic pathways such as epithelial-mesenchymal transition and inflammation. Additionally, quantitative real-time PCR analysis revealed differences in the expression of immune-related genes, especially markers of immune exhaustion such as PD-L1 and CTLA-4. Flow cytometry analysis of subcutaneous tumors also revealed differences in T-cell infiltration. Thus, loss of GSTT2 may influence the response to BCG therapy, through modulating downstream signaling pathways and immune responses. Elucidating such pathways can lead to a better understanding of the mechanism of BCG and its role as a therapy for BC.

Sponsor Talks

Jiajun TAN

Instrument Specialist, Miltenyi Biotec

Jiajun completed his PhD in 2020 in the International Graduate School in the BioNanoTechnology program, a joint program between Nanyang Technology University, Singapore, and the University of Natural Resources and Life Science, Vienna. During his PhD, he worked on engineering a Chimeric Antigen Receptor. He has since joined Miltenyi Biotec as an Instrument Specialist.

Link: https://www.miltenyibiotec.com/SG-en/

Talk Title:
Whole tissue 3D imaging for the exploration of biological architectures

Abstract:
Biological tissues are remarkably complex. Traditional microscopy analysis of whole biological tissues by mechanical sectioning is labor-intensive, time-consuming, and can result in the loss of information. These limitations happen again during the re-assembly into 3D reconstruction for analysis. Recent advancements in light sheet microscopy and tissue clearing have overcome these shortcomings. Tissue clearing renders tissues transparent, circumventing the need for physical sectioning, and allows for whole tissues to be imaged without the loss of information.
Here, we will introduce the UltraMicroscope – Miltenyi Biotec's 3D imaging solution, as well as the accompanying tissue-clearing reagents and antibodies.

Sponsor Talks

Amrita Roy
Singlabs

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Talk Title:
Spatially mapping transcriptomic gene expression profiles using gold standard RNAscope in situ hybridization technology

Abstract:
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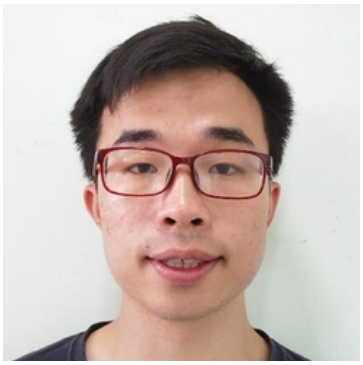
Digital Technology Workshop



Chengwei ZHONG

Title: Interpretable spatially aware dimension reduction of spatial transcriptomics with STAMP

Abstract: Spatial transcriptomics produces high-dimensional gene expression measurements while retaining their spatial context within tissues. Obtaining a biologically meaningful low dimensional presentation of the data is a crucial step toward data interpretation and downstream analysis. Here, we present STAMP, an interpretable spatially aware dimension reduction method built on a deep generative model that returns low dimensional topics of biologically relevant spatial domains and associated gene modules. STAMP recovered the anatomical structures of the mouse hippocampus and olfactory bulb with known gene markers highly ranked in the respective gene modules. In a lung cancer sample, it delineated cell states with supporting gene markers at a higher resolution than the original annotation and uncovered a topic of cancer associated fibroblasts. Finally, we expanded STAMP to account for batch effects and identify spatiotemporal patterns across chronologically consecutive samples of mouse embryo development. STAMP is implemented in Python and downloadable at https://github.com/JinmiaoChenLab/scTM.

Sethi RAMAN

Title: ezSingleCell: An integrated one-stop single-cell and spatial omics analysis platform for bench scientists

Abstract: ezSingleCell is an interactive and easy-to-use application for the analysis and integration of multiple single-cell and spatial omics data types. It integrates the best-performing publicly available methods and in-house novel algorithms for in-depth data analysis, integration, and interactive data visualization. By integrating the relevant tools to form a complete analysis pipeline, we save users from the hassles of choosing among the enormous diversity of available methods, installing individual packages, and reformatting the data for different analysis steps. In addition, ezSingleCell allows crosstalk between different datatypes such as use single cell to deconvolute spatial data in an unified interface. ezSingleCell takes input data in a variety of formats such as text files or Cell Ranger/ Space Ranger output and produces publication ready figures and tables. Users can customize the relevant parameters to ensure the quality and accuracy of their data analysis. Users can also download and store the R objects from ezSingleCell to perform additional offline analyses. ezSingleCell's streamlined interface can analyze a standard scRNA-seq dataset containing 3000 cells in less than five mins. ezSingleCell is also accompanied by an in-depth manual and video tutorials to guide users. Overall, these features make ezSingleCell a convenient and easy web service for single cell and spatial analysis without requiring prior programming knowledge. ezSingleCell is available in two forms: an installation-free web application (https://immunesinglecell.org/ezsc/) or a software package with a shinyApp interface (https://github.com/JinmiaoChenLab/ezSingleCell2) that runs on a personal computer with a low memory requirement of 8 Gb RAM.

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Workshop

Jianzhou CUI

Hands-on teaching session on single cell analysis

The workshop primarily focuses on scRNA sequencing analysis. By the end of the workshop, participants will be acquainted with the following topics:

Outline

Preprocessing Raw Data: This step involves data cleaning, filtering, and preparing it for further analysis.
Quality Control (QC): Ensuring that the data meets certain quality standards to ensure accuracy and reliability.
UMAP: Utilizing a dimensionality reduction technique to visualize high-dimensional data in a lower-dimensional space.
DEG (Differentially Expressed Genes) Analysis: Identifying genes that show significant differences in expression levels between different conditions or groups.
Heatmap: Creating a visual representation of data using colors to display values.
Cell Annotation: Automatic or manual annotation of cell types, provided the necessary markers are available.
Feature Plot: Generating graphical representations of specific features within the data.
Violin Plot: Creating a type of data visualization that displays the distribution of data across various categories.
Cell-to-Cell Communication Analysis: Investigating communication patterns between individual cells.
Trajectories Analysis: Studying the developmental paths and changes of cells over time.

Audience and Requirements

Investigators from any institution and from all career stages are welcome to attend, and we particularly encourage trainees and early-stage investigators to participate. There are several requirements to attend this training:

- Each participant must have a basic background in statistics.
- Each participant must be familiar with R.
- Each participant must bring their own computer with RStudio installed.

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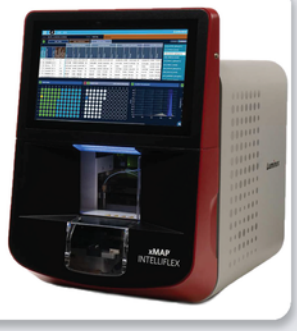
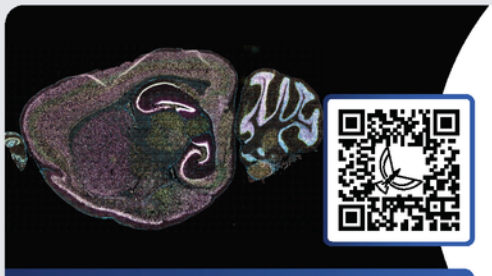


RNAscope: Visualize the invisible



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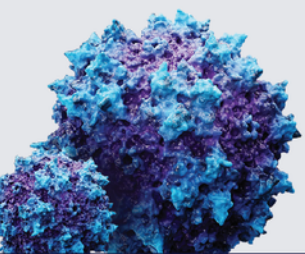

SingLab Technologies Pte Ltd
1003 Bukit Merah Central #03-03, Singapore 159836
(65) 6272 0788
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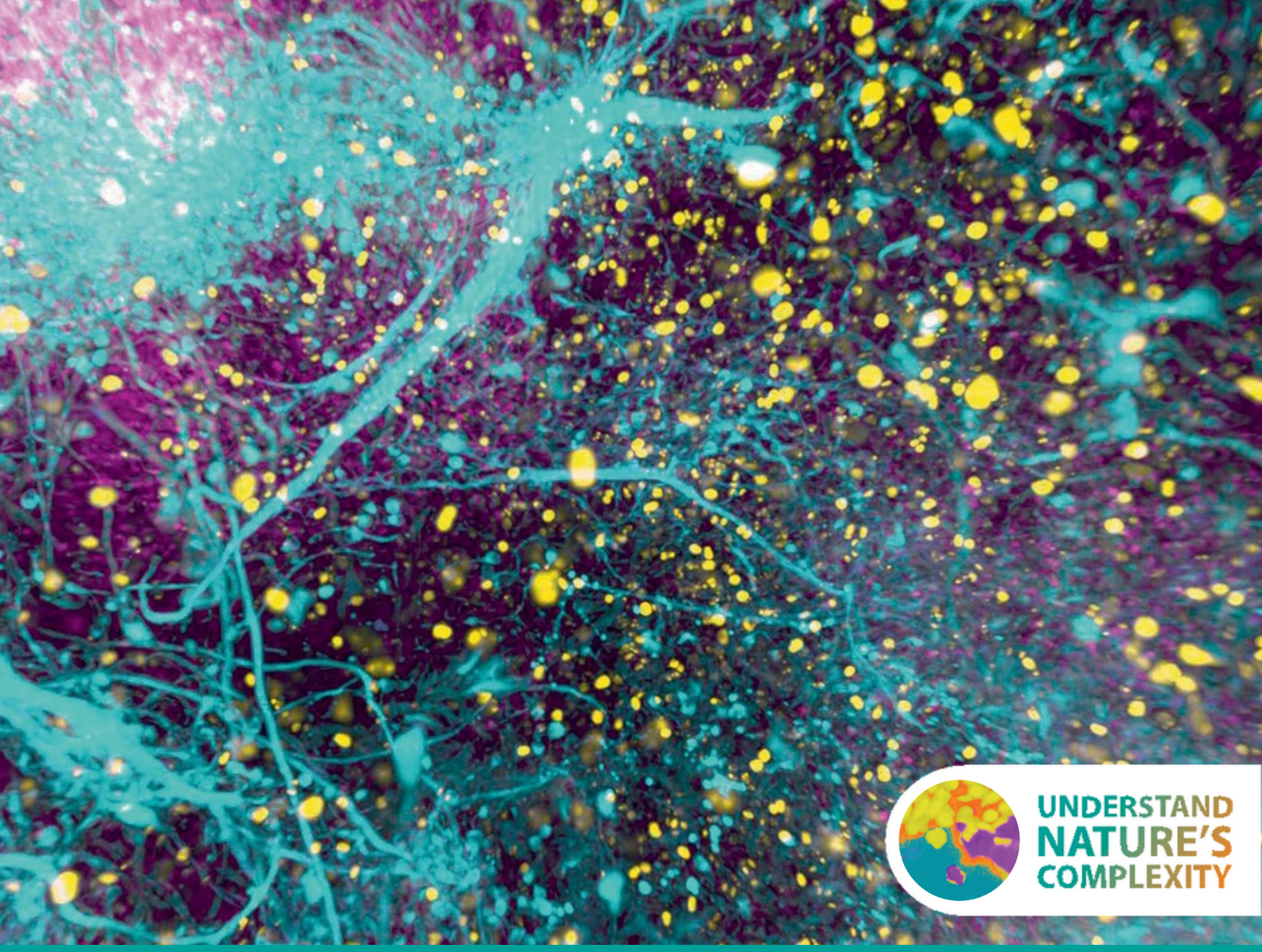

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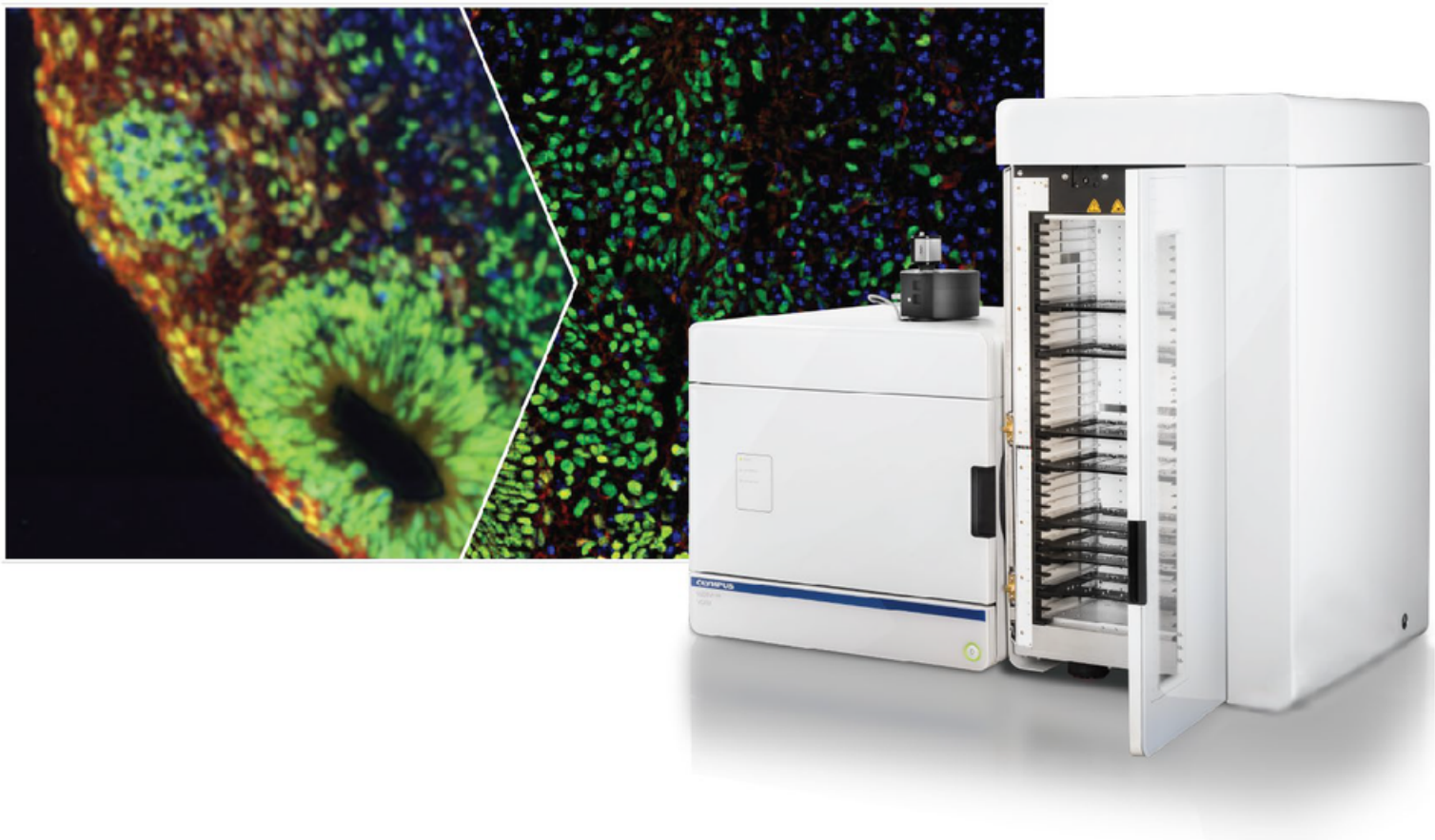

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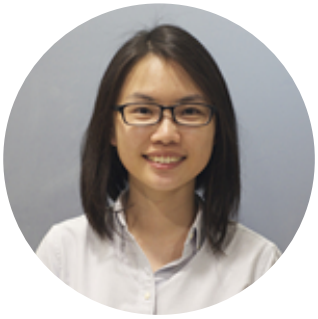
Committee

Herbert Schwarz
Associate Professor
Deputy Head, Department of Physiology
Immunology Translational
Research Programme

Tan Yong-Yi, Andrew
Assistant Professor
Department of Physiology
Healthy Longevity Translational
Research Programme

Cheng Man Si
Lab Tech
Physiology

Kelvin Koh Ting Wei
Lab Exec
Physiology



Chong Pey Rou
Lab Tech
Physiology

Nurul Suhana Ali
Lab Tech
Physiology

Sonja Chua
Scientific Manager
Immunology Translational Research Programme

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Yong Loo Lin School of Medicine

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