The 4th NUS-CMU Joint Symposium

24th to 25th February 2022

NUS National University of Singapore

Department of Physiology
Yong Loo Lin School of Medicine

中國醫藥大學
China Medical University

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History

Physiology is the study of normal function in the body and how genes, proteins, organ systems interact to maintain health. It provides a foundation for the health sciences profession and life science research. Physiology education in Singapore began soon after the establishment of the Federated States Government Medical School in 1905. The importance of Physiology to medical education was recognised by the appointment of a separate lecturer in Physiology in 1906, followed by the appointment of Professor James Argyll Campbell as the first King Edward VII professor and endowed Chair in Physiology in 1912. The teaching of Physiology in the early days was focused on the basics of normal function with little correlation to clinical problems and application. However, by the 1970s, first year medical students were given the opportunity to visit hospitals where they were tutored by clinicians to help them apply Basic Physiology to clinical problems. Curriculum changes in the subsequent years emphasized a reduction in content, integration among preclinical subjects, independent learning and clinical relevance. Physiology is taught not only to medical but also dental, pharmacy and life science students. The teaching of Physiology to science students is a collaborative effort between the Department of Physiology, Faculty of Medicine and the Department of Biological Sciences, Faculty of Science.

A lot of the teaching of Physiology to life science students occurs not in classrooms but in the laboratories, where students work closely with research supervisors and mentors on research projects. There has been a very significant increase in the number of students doing research projects in Physiology in recent years, especially in the areas of Cell Physiology, Immunology and Neurobiology. The completion of the human genome sequence poses new challenges to understand function, especially how genes, proteins and organ systems interact to sustain function. Physiology education will be increasingly important in the undergraduate and graduate life science and medical curriculum. Further, the country's vision of being the biomedical R&D and healthcare hub for the region means that Physiology education must remain at the forefront to prepare the next generation of doctors, clinician-scientists, researchers and entrepreneurs.

中國醫藥大學
China Medical University

Brief Introduction

Established in 1958, China Medical University (CMU) in Taichung, Taiwan, has since developed into one of the world's premiere medical research universities with 9 colleges in total: the Colleges of Medicine, Chinese Medicine, Pharmacy, Life Sciences, Public Health, Health Care, Dentistry, Humanities and Technology, and Biomedical Engineering. Its Joint Commission International (JCI)-accredited hospitals have a total of over 6,000 beds, and it is the second largest healthcare system nationwide providing superb service of western and Chinese medicine. CMU is ranked as one of the top 300 universities by Academic Ranking of World Universities 2021, ranked top 350 by Times Higher Education (THE) World University Rankings 2021 and ranked top 100 by 2021 THE Asia University Rankings.

CMU trains both western medicine doctors and Chinese medicine doctors and implements the best integration of western and Chinese medicine at CMU Hospital providing outstanding medical service to patients. As a leader in several research fields with a culture of collaboration and innovation, CMU has made important breakthroughs in cancer treatment such as inventing combined target therapy and |immune checkpoint therapy to overcome difficult malignancies, lengthening the survival of glioblastoma patients, discovering ANK-199, a promising anticancer drug that treats head and neck cancer, and identifying the receptor protein IL-17RB that is strongly associated with pancreatic cancer. The Center of Excellence for Chinese Medicine is awarded with Top-Notch Center Grant by Ministry of Education (MOE) for 5 years and conducts many lines of clinical studies and discovery of mechanisms underlying the acupuncture-induced anesthesia via opioid-dependent and opioid-independent pathways. The Center of Excellence for New Drug Development is awarded with Top-Notch Center Grant by MOE and aims to develop novel drugs for 5 years.

International collaborative partnerships with prestigious institutions such as Stanford University, the M.D. Anderson Cancer Center, UC Irvine, National University of Singapore, Nanyang Technology University, and University of Tokyo have been firmly established. Additionally, over 80 international healthcare companies and venture capitalists are assisting the university with its knowledge transfer mission. Thus far, over 60 new drugs have emerged from CMU's research laboratories, as well as 10 spin-off companies.

Extracted from: https://english.cmu.edu.tw/intro_02.html

Scientific Programme

Day 1: 24 February 2022 (Thursday)

Time	Activity
09:00am - 09:10am	**Opening Speech** Yap Seng Chong, Medicine, National University of Singapore
09:10am - 09:20am	**Opening Speech** Mien-Chie Hung, China Medical University
	Theme 1: Cancer (Part I) (Moderator: Edward Chow, Cancer Science Institute)
09:25am - 09:50am	**Early intervention in cancer through the tumour suppressive mechanisms that maintain genome stability** Ashok Venkitaraman, Cancer Science Institute
09:50am - 10:15am	**Evading immune surveillance through tyrosine phosphorylation of the proliferating cell nuclear antigen PCNA** Shao-Chun Wang, China Medical University
10:15am - 10:40am	**Crosstalk between RNA editing and RNA splicing and its implication in cancer** Polly Chen, Cancer Science Institute
10:40am - 11:00am	**Break**
11:00am - 11:45am	**Marker-guided effective therapy (Mget) (Keynote)** Mien-Chie Hung, China Medical University
11:45am - 12:10pm	**Lineage- and stage-specific oncogenicity of master transcription factors** Takaomi Sanda, Cancer Science Institute
12:10pm - 12:35pm	**Diving into glioblastoma epigenetics** Derrick Ong, Physiology, National University of Singapore
12:40pm - 02:00pm	**Lunch Break**
	Theme 1: Cancer (Part II) (Moderator: Derrick Ong, Physiology, National University of Singapore)
02:00pm - 02:25pm	**Why do some tumors express one of the most potent T cell costimulatory molecules?** Herbert Schwarz, Physiology, National University of Singapore
02:25pm - 02:50pm	**Towards a New Strategy for Brain Tumor Immunotherapy** John S. Kuo, China Medical University
02:50pm - 03:15pm	**Aberrant Redox Signaling: An Enabling Cancer Hallmark?** Shazib Pervaiz, Physiology, National University of Singapore
03:15pm - 03:35pm	**Break**
03:35pm - 04:00pm	**Novel function of THEMIS2 in the enhancement of cancer stemness and chemoresistance by releasing PTP1B from MET** Lu-Hai Wang, China Medical University
04:00pm - 04:25pm	**Targeting cysteine metabolism for cancer therapy** Lih-Wen Deng, Biochemistry, National University of Singapore

Scientific Programme

Day 2: 25 February 2022 (Friday)

Time	Activity
	Theme 2: Aging (Part I)
	(Moderator: Tong-Wey Koh, Temasek Life Sciences Laboratory)
09:00am - 09:25am	**Addressing Human Ageing: No time like the Present**
	Brian Kennedy, Biochemistry, National University of Singapore
09:25am - 09:50am	**Exosomes from aneuploidy-induced senescent cells induce inflammatory signalling**
	Karen Crasta, Physiology, National University of Singapore
09:50am - 10:15am	**SAMS-1 coordinates HLH-30/TFEB and PHA-4/FOXA activities through histone methylation to mediate DR-induced autophagy and longevity**
	Allen Hsu, China Medical University
10:15am - 10:40am	**Mass Up Aging Skeletal Muscle- study of mTORC1 and sarcopenia**
	Shih-Yin Tsai, Physiology, National University of Singapore
10:40am - 11:05am	**Break**
	Theme 2: Traditional Chinese Medicine (Part II)
	(Moderator: Tong-Wey Koh, Temasek Life Sciences Laboratory)
11:05am - 11:30am	**Activation of Peripheral TRPM8 Mitigates Ischemic stroke by Topically Applied Menthol**
	Yi-Hung Chen, China Medical University
11:30am - 11:55am	**Deciphering the polypharmacology of natural products for the development of small molecule therapeutics: Is there too much of a good thing?**
	Christina Chai, Pharmacy, National University of Singapore
11:55pm - 12:20pm	**Pharmacological and immunomodulatory activities of pterostilbene**
	Hung-Rong Yen, China Medical University
12:30pm - 1:50pm	**Lunch Break**
	Theme 3: Stem Cells & Neuroscience
	(Moderator: Esther Wong, Physiology, National University of Singapore)
01:50pm - 02:15pm	**Novel peptides for helping osteoarthritis early diagnosis, lubrication and regenerative medicine**
	Shih-Chieh Hung, China Medical University
02:15pm - 02:40pm	**Epigenetic Plasticity in early development and cancer**
	Wee Wei Tee, Physiology, National University of Singapore
02:40pm - 03:00pm	**Break**
03:00pm - 03:25pm	**Distinct glial functions of TDP-43, a causal gene and the pathological hallmark for ALS-FTD spectrum diseases**
	Shuo-Chien Ling, Physiology, National University of Singapore
03:25pm - 03:50pm	**Using stem cells to understand and treat neurodegenerative disorders**
	Shi-Yan Ng, Physiology, National University of Singapore
04:00pm - 04:20pm	**Closing Speech**
	Herbert Schwarz, Physiology, National University of Singapore
	Mien-Chie Hung, China Medical University

Theme 1: Cancer (Part I)

Moderator

Name: Edward Chow

Principal Investigator, Cancer Science Institute of Singapore

Associate Professor, Pharmacology & Biomedical Engineering, National University of Singapore

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Speaker

Name: Ashok Venkitaraman

Distinguished Professor of Medicine, Cancer Science Institute of Singapore

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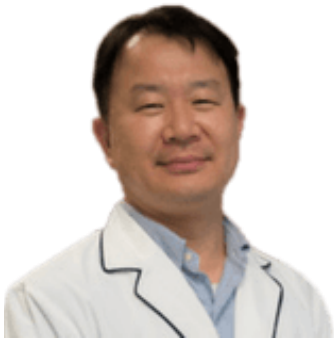
Early intervention in cancer through the tumour suppressive mechanisms that maintain genome stability

Genome instability occurs universally in human cancers, and arises early during their evolution. We discovered that inactivation of the hereditary breast & ovarian cancer susceptibility gene, BRCA2, induces genome instability associated with early-onset cancers in multiple organs, through functions in DNA repair, replication and segregation. Here, I will discuss recent work from my laboratory that reveals new tumour suppressive functions for BRCA2, and provides insights into early steps in carcinogenesis that promise future opportunities for early intervention in BRCA2 mutation carriers.

Speaker



Name: Shao-Chun Wang

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Evading immune surveillance through tyrosine phosphorylation of the proliferating cell nuclear antigen PCNA

Distant metastasis is the major cause of cancer-related death. However, how cancer metastasis is coordinated with the deregulated proliferation, another hallmark of cancer progression, has not been well understood. Elucidating the underlying mechanism is critical for the development of cancer therapies with durable response. Derailed cell division often sets off replication stresses in cancer cells which is expected to have profound effects in tumor development. Part of the research interests of my laboratory is to learn how cancer cells overcome the growth stress and succeed in disseminating to distant organs. Proliferating cell nuclear antigen (PCNA) is an indispensable component of the DNA replication machinery. Here we show that phosphorylation of PCNA on tyrosine 211 (pY211-PCNA) is responsible in reprogramming DNA metabolism and subsequently regulating the tumor microenvironment. Loss of pY211-PCNA results in replication fork stalling and biogenesis of single-stranded DNA (ssDNA) which requires the function of the essential ATP-dependent nuclease MRE11. The cytosolic ssDNA subsequently induced the inflammatory response through the cGAS/STING cascade, triggering a natural killer (NK) cell-dependent anti-tumor immunity to suppress distant metastasis. Consistently, the expression of pY211-PCNA is inversely correlated with cytosolic ssDNA and associated with poor survival in breast cancer patients. These results suggest that the genomic DNA metabolism is integrated with the programming of the tumor immune microenvironment which can be exploited for the development of novel tumor markers and therapeutic targets of cancer metastasis.

Speaker

Name: Leilei Polly Chen

Principal Investigator, Cancer Science Institute of Singapore

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Crosstalk between RNA editing and RNA splicing and its implication in cancer

RNA editing and splicing are the two major processes that dynamically regulate human transcriptome diversity. Despite growing evidence of crosstalk between RNA editing enzymes and splicing machineries, detailed mechanistic explanations and their biological importance in diseases, such as cancer are still lacking. In recent years, my team has found that RNA editing enzymes ADAR1 and ADAR2 (ADARs) significantly regulate canonical splicing and back-splicing of pre-mRNA transcripts through and beyond their RNA editing functions. We unravelled a binding tendency of ADARs to double-stranded RNAs (dsRNAs) that involves GA-rich sequences for editing and canonical splicing regulation. RNA editing affects not only the RNA nucleotide sequence but also secondary and tertiary structures of RNA molecules. We found that during back-splicing, ADARs-mediated editing changes can stabilize or destabilize dsRNA formed between reverse complementary matches (RCMs) within flanking introns via correcting A:C mismatches to I(G)-C pairs or creating I(G).U wobble pairs, thereby promoting or suppressing circular RNA biogenesis, respectively. Editing was also shown to favour the binding of RNA-binding proteins (e.g., SRSF7, PTBP1) to the action site to regulate canonical splicing and back-splicing. Furthermore, we found these ADARs-regulated splicing changes *per se* influence tumorigenesis, not merely byproducts of ADARs binding and editing.

Keynote Speaker

Name: Mien-Chie Hung

President, China Medical University

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Marker-guided effective therapy (Mget)

Anti-PD-1/PD-L1 therapy is a promising approach in cancer therapy. We showed that glycosylation of PD-L1 is required for its protein stability and interaction with PD-1 (Nature Communications 2016). We demonstrated TNFα as a major factor triggering cancer cell immunosuppression against T cell surveillance via stabilization of programmed cell death-ligand 1 (PD-L1) (Cancer Cell 2016). In collaboration with StCube Pharmaceuticals Inc., we have developed monoclonal antibodies against glycosylation-specific PD-L1. Impressive therapeutic effect was observed through antibody-drug-conjugate approach (Cancer Cell 2018a & Cancer Res 2020). Furthermore, we developed effective combination therapy by metformin-activated AMPK kinase to downregulates PD-L1 through alteration of glycosylation of PD-L1 and (Molecular Cell 2018). Our group has conducted a series of vigorous studies to identify additional potential targets to overcome PD-1/PD-L1 resistance and develop effective combination therapy including c-MET inhibitors (Gastroenterology 2019), IL-6/JAK1 pathway (J Clin Invest 2019), and Galectin-9 (Nature Comm 2021). These findings provide potential therapeutic strategies to enhance cancer immune therapy efficacy by targeting PD-L1 stabilization to combat multiple cancer types. We reported a novel PD-L1 function that is independent of its role in immune checkpoint in Nature Cell Biology 2020--PD-L1 in the nucleus harbors a nuclear transcriptional activity and promotes tumor pyroptosis downstream of TNFα. More recently, we further identified molecular mechanisms that caused resistance to anti-PD-1/PD-L1 therapy (J Clin Invest , 2021) and currently are developing new therapeutic approach to overcome the resistance. This talk will include our discoveries on developing therapies for lung or pancreatic cancers (Cancer Cell 2018b, 2018c); a new methodology to retrieve antigen by protein deglycosylaton improves predictive ability of PD-L1 as a biomarker for immunotherapy. (Cancer Cell 2019, AJCR in press). We identified the inhibition of the protein kinase activity of PCK1 as a potential treatment strategy in HCC (Nature 2020) and currently developed high throughput screening strategy to identify potential inhibitors for treatment.

During the pandemic, the research team at China Medical University in Taichung has successfully used our experience and expertise in cancer targeted therapy to target SARS-CoV-2. In this talk I will briefly summarize our results from screened multiple natural products libraries. (AJCR 2020,2021). For instance, both tannic acid and peimine have inhibitory effects on SARS-CoV2 infection. Tannic acid is a bioactive compound that can be found in berries and grapes, and peimine is an active ingredient of Chuan Bei. We found that tannic acid serves as a potent dual inhibitor of viral main protease Mpro and TMRPRSS2 protease on the host cells, and peimine inhibits several variants of SARS-CoV-2 cell entry via blocking the interaction between viral spike (S) protein and ACE2 on the host cells, respectively. The goal is to identify natural products that may help for prevention and therapy of Covid-19 through inhibition of SARS-CoV-2.

Speaker

Name: Takaomi Sanda

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Lineage- and stage-specific oncogenicity of master transcription factors

Master transcription factors (MTFs) are a type of transcription factors that determine cell identity and are required for normal development and cellular maintenance. MTFs often serve as oncogenes in a tissue- and stage-specific manner. They form unique transcriptional regulatory circuits and are regulated under large clusters of enhancers. One prime example is TAL1 that is required for normal hematopoiesis. TAL1 acts as an oncogene in T-cell acute lymphoblastic leukemia (T-ALL) but not in mature T-cell neoplasms or other cancers. Another example is ASCL1 that is essential for neuronal development. ASCL1 has been implicated in the adrenergic subtype of neuroblastoma and a fraction of small cell lung cancer but not in other cancers. Thus, these factors require specific cellular context to exert their oncogenic property. In this talk, I will present our latest findings on the mechanisms behind lineage- and stage-specific oncogenicity of MTFs.

Speaker

Name: Derrick Ong Sek Tong

President's Assistant Professor, Physiology, National University of Singapore

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Diving into glioblastoma epigenetics

Glioblastoma (GBM) is the most common and malignant adult brain tumor with an abysmal patient prognosis. The current standard of care for GBM remains to be aggressive surgery followed by radiotherapy, in combination with adjuvant temozolomide treatment. Tumor recurrence is almost inevitable due to the presence of glioma stem cells (GSCs), which exhibit stem cell–like traits, robust proliferation, invasiveness, and therapy resistance. We employ GSCs as an experimental model to uncover new GBM dependencies with the aim of innovating new therapeutic options for GBM. Here, I will outline some of our recent efforts in GBM epigenetics wherein we have uncovered that GBM (i) relies on biotin distribution to carboxylases and histones to sustain its metabolic and epigenetic requirements for proliferation, invasiveness and tumorigenicity; and (ii) employs E2F and STAT3 to provide transcriptional synergy for histone variant H2AZ activation to sustain its chromatin accessibility and tumorigenicity. Lastly, we will share our results of an unpublished study wherein we find the preferential downregulation of an E3 ubiquitin protein ligase in GBM. Notably, this E3 ubiquitin protein ligase appears to suppress GBM proliferation and tumorigenicity by promoting the spindle assembly checkpoint response via a non-canonical mechanism.

Theme 1: Cancer (Part II)

Moderator

Name: Derrick Ong Sek Tong

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Speaker

Name: Herbert Schwarz

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Why do some tumors express one of the most potent T cell costimulatory molecules?

The cytokine receptor CD137 (TNFRSF9, 4-1BB) is a potent costimulatory molecule for effector T cells (Teff), which strongly enhances anti-cancer immune responses. It was therefore quite surprising to find high expression of CD137 not only on Teff but also on certain malignant cells. We discovered that ectopic CD137 expression allows cancers to activate a negative feed-back mechanism which consists in the trogocytic transfer of CD137 to antigen presenting cells (APC) that express CD137 ligand, and where CD137 and CD137L form a complex that is internalized and degraded. This deprives APC of the immunostimulatory CD137L, and inhibits anti-cancer immune responses, thereby helping the cancer to escape immune surveillance. However, ectopic CD137 expression by malignant cells is also an Achilles heel of the cancer, that can be targeted by immunotherapy.

Speaker

Name: John S. Kuo

Vice President & Chair Professor, China Medical University

Yushan Scholar, Ministry of Education (Taiwan)

Professor, The University of Texas at Austin

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Towards a New Strategy for Brain Tumor Immunotherapy

The healthy blood-brain barrier (BBB) physically separates the central nervous system from the bloodstream and prevents effective delivery of many therapies to the brain. However, the BBB is pathologically disrupted by diseases such as brain tumors and exposes tumor cells and the surrounding extracellular matrix (ECM) to circulating blood that contains components of the immune system. For the incurable brain cancer, glioblastoma (GBM), contrast-enhanced magnetic resonance imaging (MRI) shows the tumor regions with BBB disruption, but the invasive tumor margin remains behind an intact BBB and does not usually enhance. This BBB heterogeneity makes it very difficult to effectively treat GBM, especially since therapeutically resistant GBM cells in the BBB-intact invasive margin are likely responsible for disease recurrence. Additionally, an immunosuppressive tumor microenvironment (TME) underlies the failure of current checkpoint inhibitor immunotherapies, and GBM patients only have a median patient survival of approximately two years despite aggressive treatments.

To address these challenges, we hypothesized that brain ECM-targeting moieties can specifically target the disrupted BBB and potentially deliver therapies to brain. We are developing new immunotherapies that targets and loads pathologically exposed ECM in BBB-disrupted regions of GBM, followed by release and distribution of immunostimulatory therapeutic agents throughout the entire tumor volume. Variable lymphocyte receptors (VLR) that preferentially associate with and bind brain ECM were identified from an immune VLR library via yeast surface display biopanning coupled with a moderate throughput ECM screen. Brain ECM-binding by VLR clones to murine and human brain tissue sections was confirmed. After systemic administration, P1C10, the lead brain ECM-targeting VLR candidate, specifically accumulated in brains with mannitol-disrupted BBB and at disrupted BBB regions in two different intracranial glioblastoma models. We also demonstrate P1C10's ability to deliver doxorubicin-loaded liposomes, resulting in significantly improved survival in glioblastoma-bearing mice. This 'proof of concept' study shows that specific VLRs can selectively target pathologically exposed brain ECM and deliver effective payloads to improve therapies for brain diseases.

Speaker

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Aberrant Redox Signaling: An Enabling Cancer Hallmark?

The process of carcinogenesis and/or its progression involves an intricate interplay between aberrant signaling networks that promote growth and proliferation coupled with defects or deficiencies in pathways that maintain tissue homeostasis. While amplified growth receptor signaling and activation of gene transcription have been well studied and strongly implicated in the acquisition of the cancer phenotype, there is also ample evidence that cellular redox milieu impacts cancer cell fate and response to therapy. To that end, mitochondrial metabolism has emerged as a critical gatekeeper that regulates cellular redox status and there is ample evidence to implicate aberrant redox signaling as an enabling hallmark of cancer cells. Our work over the years has contributed to the redox dichotomy of cell fate signaling in cancer cells, whereby mild oxidative stress promotes cell survival, growth and proliferation while overt oxidative stress creates an environment conducive for death execution. In our efforts to understand the underlying mechanisms of this divergent function of intracellular reactive oxygen species (ROS) in cancer cell fate determination, we have unraveled cellular targets that are amenable to redox regulation/modification(s), both at the transcriptional and post-translational levels. These include the apoptosis inhibitory protein Bcl-2, oncoproteins c-Myc and K-Ras, death receptor inhibitory protein c-FLIP, the putative tumor suppressor phosphatase PP2A and the master transcription factor NF-kB that drives inflammation and other hallmarks associated with cancer. Furthermore, we provide evidence to link drug resistance to a switch to mitochondrial OXPHOS, as well as aberrant redox signaling to mitochondrial morphology changes and mitophagy induction. These signaling networks, their interplay and impact on the biology of cancer cells will be discussed.

Speaker

Name: Lu-Hai Wang

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Academician, Academia Sinica

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Novel function of THEMIS2 in the enhancement of cancer stemness and chemoresistance by releasing PTP1B from MET

Triple negative breast cancer (TNBC) possesses poor prognosis mainly due to lack of effective endocrine or targeted therapies, aggressive nature and high rate of chemoresistance. Cancer stem cells (CSCs) are considered to play critical roles in cancer recurrence and chemoresistance. THEMIS2 was identified as the sole common elevated gene in three triple negative breast cancer (TNBC) and two ovarian CSC lines. We discovered an intrinsic signaling scaffold function of THEMIS2, which acts as a novel regulator of cancer stemness, promoting multiple cancer stemness properties including sphere formation, stemness markers expression, chemoresistance and tumorigenicity with low numbers of cancer cells implantation. For the first time, we demonstrated that THEMIS2 specifically enhanced MET activating phosphorylation by suppressing the association of protein-tyrosine phosphatases 1B (PTP1B) with p-MET and MET, which accounted mainly for THEMIS2-mediated effect on cancer stemness and chemoresistance. Increased THEMIS2 expression was associated with poor survival in TNBC patients and in patients from our breast cancer cohort. We found that non-cytotoxic dosages of cryptotanshinone (CPT) could potently inhibit cancer stemness, chemoresistance and tumorigenicity by suppressing expression of THEMIS2. Notably, stable overexpression of THEMIS2 is associated with enhanced sensitivity toward Capmatinib and CPT treatment. Expression levels of THEMIS2 and p-MET protein were positively correlated in the 465 breast cancer specimens. Our study revealed the novel oncogenic role of THEMIS2 and its underlying mechanism via suppressing PTP1B association with MET and thus leading to its activation. Our findings suggest that THEMIS2 could be a biomarker for MET targeted therapy and also provide a potential clinical application using low dosages of CPT for treatment of THEMIS2 positive TNBC.

Speaker

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Targeting cysteine metabolism for cancer therapy

Redox homeostasis and sustainable energy production are vital for cancer survival and growth. As cancer cells proliferate uncontrollably, metabolic substrate dwindles while reactive chemical species rise. To overcome these challenges, cancer cells evolve to switch to alternative metabolic substrate available and boost its anti-oxidative defense. Emerging studies implicate non-essential amino acid cysteine in these two pro-cancer processes, which in turn promote resistance to therapy. Here, we will discuss our recent observation that ovarian clear cell carcinoma (OCCC) exhibited profound dependence on the amino acid cysteine for survival. Mechanistic studies demonstrate cysteine deprivation can target both glycolytic and respiring OCCC through the elevation of oxidative stress and energy exhaustion, respectively. This work highlights the therapeutic potential of cysteine deprivation for OCCC.

Theme 2: Aging (Part I)

Moderator

Name: Tong-Wey Koh

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Speaker

Name: Brian Kennedy

Distinguished Professor, Biochemistry & Physiology, National University of Singapore

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Addressing Human Ageing: No time like the Present

Aging research has slowly gained momentum over the last three decades and now become a mature field of scientific endeavor. This has occurred only just in time, as aging is likely the largest medical challenge of the 21st Century. Aging is now recognized as the biggest risk factor for the onset of chronic diseases and the biggest predictor of complications in many infectious diseases. Given that over 20% of the population will be over 65 years of age in the not-too-distant future, it is imperative that strategies are developed to slow or reverse aging processes. Fortunately, as a result mostly of research in animal models, there are no shortage of interventions that have the potential to extend human healthspan. Delaying aging in animals is one thing, but validating them for efficacy in humans is entirely different. Here, I will discuss strategies to "get human" illustrating possible interventions that have a likelihood of success and discussing the possible clinical endpoints to test them in the clinic. People have tried to delay or reverse aging for millennia, and it certainly appears possible that this nearly ageless quest can be achieved in the near future.

Speaker

Name: Crasta Karen Carmelina

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Exosomes from aneuploidy-induced senescent cells induce inflammatory signalling

Communication between cells is quintessential for biological function and cellular homeostasis. Membrane-bound extracellular vesicles known as exosomes play pivotal roles in mediating intercellular communication in tumor microenvironments. These vesicles and exosomes carry and transfer biomolecules such as proteins, lipids and nucleic acids. In this talk, I discuss the implications for cancer progression on exosomes as emerging senescence-associated secretory phenotype (SASP) components from highly-aneuploid cells.

Speaker

Name: Allen Hsu

Professor, School of Medicine

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SAMS-1 coordinates HLH-30/TFEB and PHA-4/FOXA activities through histone methylation to mediate DR-induced autophagy and longevity

Dietary restriction (DR) is known to promote autophagy to exert its longevity effect. While S-adenosyl methionine synthetase-1 (SAMS-1) has been shown to be a key mediator of the DR response, little is known about the roles of S-adenosyl methionine (SAM) and SAM-dependent methyltransferase in autophagy and DR-induced longevity. In this study, we show that DR and SAMS-1 repress the activity of SET-2, a histone H3K4 methyltransferase, by limiting the availability of SAM. Consequently, the reduced H3K4me3 levels promote the expression and activity of two transcription factors, HLH-30/TFEB and PHA-4/FOXA, which are both known to regulate the transcription of autophagy-related genes. We then find that HLH-30/TFEB and PHA-4/FOXA act collaboratively on their common target genes to mediate the transcriptional response of autophagy-related genes and consequently the lifespan of the animals. Our study thus shows that the SAMS-1/SET-2 axis serves as a nutrient-sensing module to epigenetically coordinate the activation of HLH-30/TFEB and PHA-4/FOXA transcription factors to control autophagy and longevity in response to DR.

Speaker

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Mass Up Aging Skeletal Muscle- study of mTORC1 and sarcopenia

Aging is an emerging health issue worldwide. Sarcopenia is commonly related to aging and is a major risk factor for mortality. To date, there is no effective and approved pharmacological intervention to treat sarcopenia. The mechanisms to control skeletal muscle growth during aging is also not well understood. The mTORC1 signaling axis is a central hub regulating proteostasis and metabolism. Repression of the mTORC1 signaling cascade extends lifespan and promotes healthspan across model organisms. In contrast, genetically activating muscle mTORC1 signaling recapitulates sarcopenic features, including muscle atrophy and myopathy. Herein, we identified the following novel phenotypes associated with mTORC1 dysregulation in post-mitotic skeletal muscle. (1) While autophagic flux was reduced in mTORC1 hyper-activated skeletal muscle, our data show a previously unreported phenomenon where sustained mTORC1 activation impaired lysosomal acidification, thus inhibiting lysosomal degradation. We have also confirmed that this impaired lysosomal acidification upon fasting was conserved during natural aging in skeletal muscle, suggesting that lysosomal dysfunction might be driven by mTORC1-induced sarcopenia. (2) Additionally, excess cellular waste was taken up by mitochondria, leading to the accumulation of dysfunctional mitochondria and oxidative stress. (3) Lastly, we found that activating the mTORC1 downstream translation regulator 4EBP1 could rescue mTORC1-induced sarcopenia by expanding lysosomal degradation capacity to compensate for the autophagy impairment, consequently relieving proteotoxic stress resulting from the accumulation of damaged proteins and mitochondria. This work identifies 4EBP1 as a regulatory node in the translation-degradation axis, maintaining the proteomic integrity of skeletal muscle during ageing.

Theme 2: Traditional Chinese Medicine (Part II)

Moderator

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Speaker

Name: Yi-Hung Chen

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Activation of Peripheral TRPM8 Mitigates Ischemic stroke by Topically Applied Menthol

Currently, the only available pharmacological treatment for acute ischemic stroke is a thrombolytic. Here, we identified a unique, simple-to-use application method as an adjuvant therapy for ischemic stroke. Application of menthol, an agonist of transient receptor potential melastatin 8 (TRPM8), to paws derma attenuated infarct volumes and ameliorated sensorimotor deficits in stroke mice induced by middle cerebral artery occlusion (MCAO). Antagonism of TRPM8 or blocking conduction of peripheral nerve in the four paws reversed the reduction of infarct size and behavior performance in topically menthol treated mice. Topically applied menthol decreased oxidative stress and neuroinflammation. It is suggested that activation of peripheral TRPM8 expressed in the skin of paws has benefits for stroke recovery. Topical application of menthol could be a novel supplemental therapeutic strategy for stroke patients.

Speaker

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Deciphering the polypharmacology of natural products for the development of small molecule therapeutics: Is there too much of a good thing?

One the starting points in small molecule drug discovery is the identification of a suitable hit compound for further development as a drug for the treatment of a disease. Typically this can be discovered through high throughput screening of compound libraries using assays that are relevant to the disease, or *via* rational drug design should the target be known. Are there simpler methods to discover such hit compounds? Interestingly, a large number of natural products have been reported to have a diverse range of biological activities, in part due to its multiple targets that result in polypharmacology. Examples are berberine, resveratrol, curcumin and andrographolide; some of these are well-known actives in traditional medicines. In principle, the reported pharmacology of these natural products could be exploited as small molecule therapeutics. This presentation provides a perspective on how the polypharmacology of natural products could be exploited for drug development, as demonstrated with the natural product, andrographolide.

Speaker

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Pharmacological and immunomodulatory activities of pterostilbene

Asthma, a major noncommunicable disease, affects both adults and children and is associated with high morbidity compared with other chronic diseases. The glycolysis-associated activation of type 2 helper T (Th2) cells is the critical immunopathological mechanism involved in asthma deterioration. Long-term use of steroids as a medical treatment for asthma induces side effects and resistance. Pterostilbene (PS), a stilbenoid compound found in some Chinese herbal medicines and blueberry, exhibits antihyperglycemic and anti-inflammatory properties. Thus, we hypothesized that modulation of T cell immunity by pterostilbene may be an applicable intervention to treat asthma. Airway hyperresponsiveness (AHR), interleukin (IL)-4 and IL-13 levels, IgE, IgG, pulmonary infiltrated monocytes and eosinophils, and mucosubstances were measured in house dust mite (HDM)-induced asthmatic mice under PS treatment. Bioenergetic metabolism, PI3K-mTOR signaling, GATA3 expression, and histone acetylation in PS-treated Th2 cells were investigated. The immune response in the PS-treated PBMCs of patients with asthma was estimated. PS improved HDM-induced pulmonary allergic airway inflammation by inhibiting Th2 cell and eosinophil accumulation in HDM asthmatic mice. Targeting glycolysis resulted in IL-4 inhibition via the downregulation of mTOR, GATA3, and histone acetylation in PS-treated Th2 cells. Glucose supplementation rescued Th2 activation and eosinophilic maturation. PS reduced CD4+IL-4+ cells in the PBMCs of patients with asthma. PS attenuates HDM-induced asthma via inhibition of the Glut1/mTOR/GATA3 axis in Th2 cells, which supports the potential pharmaceutical application of PS treatment for asthma.

Theme 3: Stem Cell and Neuroscience

Moderator

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Speaker

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Novel peptides for helping osteoarthritis early diagnosis, lubrication and regenerative medicine

Osteoarthritis (OA) remains an unmet medical need, and there is no complete solution yet. Due to the nature of articular cartilage lacking blood vessels, most disease-modifying osteoarthritis drugs (DMOAD) are developed through intra-articular injection. Although methods for delivering therapeutic drugs and lubricants to articular cartilage have been established, peptides that target collagen II or hyaluronic acid (HA) cannot target OA cartilage, and therapeutic drugs and lubricants cannot be specifically delivered to OA cartilage. We hypothesized that the presence of OA-targeting peptide that can aid theranostics and regenerative medicine in OA. We carefully screened the phage display library and focused on the peptides that bound to territorial regions of articular cartilage, where collagen II degradation begins, and did not bind to other tissues, such as synovium and meniscus. We identified several peptides, such as C5-24 peptide, containing WXPXW consensus motifs that bind to collagen XII, a protein specifically expressed in human and animal OA models. We combined C5-24 peptide with magnetic resonance imaging detection reagents for clinical use, and used it for early diagnosis of OA in rat and pig models. OA-targeting peptides showed better static and kinetic friction characteristics than scrambled peptides, when conjugated with HA for rheological lubrication studies using human OA specimens. Furthermore, mesenchymal stem cell (MSC), through CD44 binding to HA conjugated with OA-targeting peptides, showed better capacity for OA homing and repair than those conjugated with scrambled peptides.

Speaker

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Epigenetic Plasticity in early development and cancer

The property of totipotency is widely considered to be exclusive to the zygote and early cleavage-stage embryos in vivo. However, recent studies in mouse embryonic stem cells (mESCs) showed that a rare subpopulation of cells can transit into an early-embryonic like state characterized by the expression of 2-cell (2C) stage restricted transcripts. The discovery of 2C-like mESCs has now opened up a window of opportunity to investigate the molecular basis of totipotency. Notably, the acquisition of totipotency is intimately linked to zygotic gene activation (ZGA) in vivo, a process that is highly important, yet very little is known about the molecular control. In our effort to discover novel regulators of the 2C-like state, we identify NELFA as a maternal factor that is important for 2C-gene expression. Crucially, induction of NELFA alone is sufficient to drive mESCs into a 2C-like state, while its loss supressed the activation of 2C genes. We further uncover novel molecular features of the 2C-like state, including specific epigenetic and metabolic changes, reminiscent to germline reprogramming. Our findings thus extend contemporary knowledge of how totipotency and/or ZGA may be regulated. We will present our latest findings in this meeting.

Speaker

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Distinct glial functions of TDP-43, a causal gene and the pathological hallmark for ALS-FTD spectrum diseases

Common genetic loci and pathological signatures have unified two seemingly different adult-onset neurodegenerative diseases, amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), which affect predominantly the motor system and cognition, respectively. In particular, mutations in TDP-43 are causal for both diseases coupled with the pathological TDP-43 inclusions present in the neurons and glia indicate that TDP-43 dysfunctions in these cells trigger ALS and FTD pathogenesis. Furthermore, TDP-43 aggregates, collectively known as TDP-43 proteinopathies, are common in aging human brains and in other neurodegenerative diseases, such as Alzheimer's disease (AD), underscoring the critical role of TDP-43 in brain health and diseases.

TDP-43 is ubiquitously expressed. Curiously, pathological TDP-43 also can be found in neurons, glia and other peripheral systems. Two key questions: the physiological functions of TDP-43 in different cell types, and whether the loss of TDP-43 in distinct glia contribute to ALS/FTD pathogenesis, remain unresolved. To this end, we systematically analyzed mice with TDP-43 deleted in distinct glia, including oligodendrocytes, Schwann cells and astrocytes. We uncovered that (1) TDP-43 is indispensable for oligodendrocyte survival and myelination by regulating cholesterol metabolism, (2) TDP-43 is required for maximize conduction velocity by maintaining paranodal assembly in Schwann cells, and (3) TDP-43 maintains the protective status of astrocytes. Loss of TDP-43 function in each of the distinct glia results in motor deficits without apparent damage to motor neurons. These results highlight that TDP-43 participate in different physiological role in distinct glia, and TDP-43 dysfunction in different glia may be an integral part of ALS pathogenesis.

Speaker

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Using stem cells to understand and treat neurodegenerative disorders

Induced pluripotent stem cells (iPSCs) are promising models of human diseases. Not only do they differentiate into disease-relevant cell types, these differentiated cells also retain disease-specific properties. To study the motor neuron disease Amyotrophic Lateral Sclerosis (ALS), we differentiate patient iPSCs into motor neurons and revealed that key mitochondrial deficiencies contribute to motor neuron degeneration. To investigate the effects of astrocyte-mediated toxicity in ALS, iPSCs were differentiated into astrocytes. By analyzing the secretome of ALS and healthy astrocytes, we found that ALS astrocytes secrete high amounts of free fatty acids which may contribute to motor neuron pathology in ALS. Having identified novel therapeutic targets for ALS at both the motor neuron and astrocyte levels, we continued to evaluate the effects of small molecule drugs in our iPSC-derived motor neurons and astrocytes. In this talk, I will discuss our lab's recent findings on reversing the metabolic dysfunctions in ALS and its effects on motor neuron health.

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