

NUS - Kanagawa Symposium 2023 Advances in Cancer Research

PROGRAMME BOOKLET

NUS - KANAGAWA SYMPOSIUM 2023

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SYMPOSIUM ORGANISERS



Toshio SUDA

Senior Principal Investigator Cancer Science Institute of Singapore

Professor NUS Centre for Cancer Research (N2CR) Department of Medicine, Yong Loo Lin School of Medicine National University of Singapore



Alan Prem KUMAR

Research Assistant Professor NUS Centre for Cancer Research (N2CR) Department of Pharmacology, Yong Loo Lin School of Medicine National University of Singapore



Yohei MIYAGI

Director Kanagawa Cancer Center Research Institute

WELCOME MESSAGE

Dear Friends, Colleagues and Participants,

On behalf of the Organising Committee, it is a pleasure to welcome you warmly to the NUS-Kanagawa Symposium 2023: Advances in Cancer Research.

We are delighted to co-host this event with our organising partners: Kanagawa Prefecture Government (KPG), Kanagawa Cancer Center (KCC), Yokohama City University (YCU) and Central Institute for Experimental Animals (CIEA).

Our researchers at the National University of Singapore (NUS) have a long history of collaboration with KPG and Japanese research institutions. This includes the establishment of a Memorandum of Understanding (MOU). First inked in November 2013 and re-signed in June 2016, the MOU was established between KPG, the Agency for Science, Technology and Research (A*STAR), NUS and the National University Health System (NUHS) to enhance collaboration in research and development between both Japanese companies and research institutes and Singapore researchers for the discovery, development and commercialisation of drugs, therapeutics, diagnostic tests and medical devices.

Our institute and KPG have a common goal in furthering the research and development of strategies and cutting-edge technologies that can promote healthy ageing and better prepare our societies for the super-aged state. Indeed, researchers from NUS and Japanese institutions have had a long-standing partnership in research focused on "ME-BYO", which is a concept that health spans a spectrum ranging from healthy to sick and that the individual's health should be actively improved or maintained daily.

In alignment with our common goal, the theme for this year's symposium is "Advances in Cancer Research". With topics ranging from various cancer types to proteome and RNA biology to biobanking and mouse models, the programme this year covers topics both pertinent and crucial to the development of cancer research. This symposium presents the perfect opportunity to foster new collaborations and deepen our connections with each other.

We would like to thank His Excellency Yuji Kuroiwa for his support of the NUS-Kanagawa Symposium, Professor John Wong for gracing this symposium and Professor Chng Wee Joo for opening the symposium. We are grateful to all speakers and attendees for your participation.

I wish you all a fruitful and rewarding NUS-Kanagawa Symposium 2023!

Thank you.

With warmest regards, **Professor Toshio Suda** *Chairman of Organising Committee NUS-Kanagawa Symposium 2023: Advances in Cancer Research*

GUEST OF HONOUR

John Eu-Li WONG

Isabel Chan Professor in Medical Sciences National University of Singapore (NUS)

Executive Director Centre for Population Health, NUS

Senior Advisor National University Health System (NUHS) Singapore

BIOSKETCH

Dr John Eu-Li Wong is the Isabel Chan Professor in Medical Sciences; Executive Director, Centre for Population Health, National University of Singapore (NUS); and Senior Advisor, National University Health System (NUHS) Singapore.

A medical oncologist-haematologist, Professor Wong obtained his medical degree from NUS and did his post graduate training in both Singapore and the United States (US), at the New York Hospital-Cornell Medical Center, where he was the Chief Resident in Medicine, and Memorial Sloan-Kettering Cancer Center.

He was the founding director, National University Cancer Institute, Singapore; jointly founded the Cancer Therapeutics Research Group, a multinational consortium of nine academic institutions; served on the International Education Council for Molecular Targeted Therapy for Cancer, the American Society of Clinical Oncology International Affairs Committee, and the International Oncology Foundation Advisory Board.

He is Co-Chair of the US National Academy of Medicine Commission for a Global Roadmap for Healthy Longevity; Commissioner, Lancet Commission on 21st Century Global Health Threats; Member, Advisory Committee, Harvard University's T.H. Chan School of Public Health, The Culinary Institute of America, and the Association Montessori Internationale on Healthy Aging, Diet and Lifestyle.

He sits on the Editorial Board, Journal of the American Medical Association, received an honorary Degree of Doctor Philosophiae Honoris Causa from the Hebrew University of Jerusalem, is an international member of the US National Academy of Medicine, and an elected member of Academia Europaea. He is a Fellow of the Academy of Medicine Singapore, the Royal College of Physicians in Edinburgh and London, and the American College of Physicians.



NUS-Kanagawa Cancer Symposium

Advances in Cancer Research

Monday 4th September – Tuesday 5th September 2023 Centre for Life Sciences (CeLS) Auditorium <u>Programme</u>

1st Day

Monday 4 th September 2023				
<u>Time</u>	ltem	<u>Duration</u>		
1230 onwards	Registration	-		
	(CeLS Foyer)			
(1300 – 1320)	<u>Opening Address</u>			
1300 - 1303	Yuji Kuroiwa	3 mins		
	Governor, Kanagawa Prefectural Government			
	(Video Message)			
1303 – 1310	Yohei Miyagi	7 mins		
	Director, Kanagawa Cancer Center Research Institute			
1310 – 1320	Chng Wee Joo	10 mins		
	Vice President (Biomedical Sciences Research), Office of the Deputy President (Research and			
	Technology), NUS			
	Yong Loo Lin Professor in Medical Oncology & Vice Dean (Research), Yong Loo Lin School of Medicine, NUS			
	Group Director of Research, National University Health System			
	Senior Consultant, National University Cancer Institute, Singapore, NUHS			
	Senior Principal Investigator, Cancer Science Institute of Singapore, NUS			
	Theme: Leukemia			
	Chairperson: Toshio Suda			
1320 – 1340	Chng Wee Joo	20 mins		
	MAF-Driven Metabolic Reprogramming Mediates H3K27			
	Hyperacetylation to Regulate Super Enhancer-Associated Genes			
	hyperacetylation to Regulate Super Enhancer-Associated Genes			
1340 - 1400	Ong Sin Tiong	20 mins		
	Associate Professor, Duke-NUS Medical School			
	What Can Ma Leave from Cinels Call Chudies in Chuquis Muslaid			
	What Can We Learn from Single Cell Studies in Chronic Myeloid			
	Leukaemia?			
1400 – 1420	Hideaki Nakajima	20 mins		
	Professor and Chairman, Department of Stem Cell and Immune Regulation,			
	Yokohama City University Graduate School of Medicine			
	Deciphering the Mechanism of Chemoresistance in Poor-Risk AMI			
	Deciphering the Mechanism of Chemoresistance in Poor-Risk AML			

	Theme: Gastric Cancer & Tumour Niche Chairperson: Hideaki Nakajima	
1420 – 1440	Patrick Tan Professor, Senior Vice Dean of Research, Duke-NUS Medical School Chief Scientific Officer, Genome Institute of Singapore Senior Principal Investigator, Cancer Science Institute of Singapore, NUS	20 mins
	Genomic Landscapes of Gastric Pre-malignancy	
1440 – 1500	Shiro Koizume Chief Scientist, Kanagawa Cancer Center Research Institute	20 mins
	Malignant Phenotypes of Ovarian Cancer Induced Under Lipid Starvation and Hypoxia Condition	
1500 – 1530	Introduction of Industry Representatives	30 mins
1530 – 1600	Coffee Break	30 mins
	Theme: Proteome and RNA Biology Chairperson: Makoto Suematsu	
1600 - 1620	Dennis Kappei Principal Investigator, Cancer Science Institute of Singapore, National University of Singapore Assistant Professor, Department of Biochemistry, Yong Loo Lin School of Medicine, NUS Identification of Biomarkers and Therapeutic Targets in Gastric	20 mins
1620 - 1640	Cancer by Label-Free Quantitative Mass Spectrometry Jordan Ramilowski	20 mins
	Associate Professor, Yokohama City University Bioinformatics Laboratory Coordinated Expression of Long Noncoding-RNA Regulates Lineage Commitment of Classical Dendritic Cells	
1640 - 1700	Polly Leilei Chen Associate Professor and Principal Investigator, Cancer Science Institute of Singapore, National University of Singapore RNA "Mutations" in Cancer: Are They Silent?	20 mins
1700 – 1720	Anthony Khong Principal Investigator, Cancer Science Institute of Singapore, National University of Singapore Assistant Professor, Department of Physiology, Yong Loo Lin School of Medicine, NUS Stress Granules Promote p21 Expression and Chemoresistance	20 mins
	Stress Grandies Fromote p21 Expression and enemoresistance	

NUS-Kanagawa Cancer Symposium

Advances in Cancer Research

Monday 4th September – Tuesday 5th September 2023 Centre for Life Sciences (CeLS) Auditorium

Programme

2 nd	Day
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Tuesday 5 th September 2023			
<u>Time</u>	ltem	<u>Duration</u>	
	Theme: Immunology		
0900 - 0920	Chairperson: Dennis Kappei Tomohiko Tamura Professor, Department of Immunology, Yokohama City University Graduate School of Medicine	20 mins	
	Chromatin and the Transcription Factor IRF8 in the Regulation of Myeloid Cell Development		
0920 – 0940	Tetsuro Sasada Director, Cancer Vaccine and Immunotherapy Center, Chief, Division of Cancer Immunotherapy, Kanagawa Cancer Center Research Institute Predictive Biomarkers of Immune Checkpoint Inhibitors for Development of Personalized Immunotherapy	20 mins	
	Theme: Biobanking & Mouse Models Chairperson: Yohei Miyagi		
0940 – 1000	Shinya Sato Section head, Morphological Information Analysis laboratory Kanagawa Cancer Center Research Institute Analysis of Cancer Adipocyte Microenvironment Using High Quality and Diverse Data Modalities of Biobank in the Kanagawa Cancer Center	20 mins	
1000 - 1010	Teja Celhar Senior Research Scientist, Singapore Immunology Network, A*STAR Central Institute for Experimental Animals (CIEA) Transgenic Expression of Human Cytokines Impacts the Tumor Immune Microenvironment in Humanized NOG mice	10 mins	
1010 - 1020	Takeshi Takahashi General Manager, Dept. of Basic Research for Laboratory Animals Central Institute for Experimental Animals (CIEA)	10 mins	

	Induction of Anti-Tumor Immunology by Immune-Checkpoint Inhibitors in Humanized Mice	
1020 - 1040	Coffee Break	20 mins
	Theme: Renal & Brain Cancer	
4040 4400	Chairperson: Tomohiko Tamura	20 :
1040 – 1100	Hisashi Hasumi Associate Professor, Department of Urology, Yokohama City University	20 mins
	Development of Foundation of the Precision Medicine for Kidney Cancer	
1100 - 1120	Derrick Ong Assistant Professor, Department of Physiology, National University of Singapore NUS Centre for Cancer Research	20 mins
	Towards a Better Molecular Understanding of Glioblastoma Pathogenesis	
1120 - 1140	Kensuke Tateishi	20 mins
	Associate Professor and Principal Investigator, Department of Neurosurgery and Medical Life Science, Yokohama City University	
	Translational Research Platform for Malignant Brain Tumors	
1140 - 1200	Makoto Suematsu	20 mins
	Director, Central Institute for Experimental Animals	
	Imaging Metabolomics Deciphers Cancer Metabolism to Translate	
	into Medicine	
	Theme: Aging	
	Chairperson: Toshio Suda	
1200 - 1205	Yuichi Tei /Ung-il Chung Executive Board Member, Vice President and Dean, School of Health Innovation, Kanagawa University of Human Services, Kanagawa, Japan Professor, Department of Bioengineering, The University of Tokyo Graduate Schools of Engineering and Medicine, Tokyo, Japan Advisor to the Governor of Kanagawa Prefecture	5 mins
1205 – 1225	Hiroto Narimatsu	20 mins
	Director and Professor, Center for Innovation Policy,	
	Kanagawa University of Human Services Division Chief, Kanagawa Cancer Center Research Institute	
	Community-Based Intervention and Robot Suit HAL	
	Closing Address	
1225 – 1235	John Eu-Li Wong	10 mins
-	Isabel Chan Professor in Medical Sciences Executive Director, Centre for Population Health, National University of Singapore Senior Advisor, National University Health System (NUHS) Singapore	
1235	End of Symposium - Lunch	
==00		

DAY 1 | 4 SEPTEMBER 2023 Leukemia

CHNG Wee Joo

Vice President (Biomedical Sciences Research), Office of the Deputy President (Research and Technology), NUS

Yong Loo Lin Professor in Medical Oncology & Vice Dean (Research), Yong Loo Lin School of Medicine, NUS

Group Director of Research, National University Health System

Senior Consultant, National University Cancer Institute, Singapore, NUHS

Senior Principal Investigator, Cancer Science Institute of Singapore, NUS



MAF-driven Metabolic Reprogramming Mediates H3K27 Hyperacetylation to Regulate Super Enhancer-Associated Genes

Overexpression of transcription factor MAF is found in about 50% of multiple myeloma cases, and associated with the prognostically unfavorable t(14;16) translocation subtype. Genetic alterations can modify the epigenome through metabolite availability that act as substrates in histone modifications, but how this translates into specificities in gene regulation is unclear. Here, we report a novel involvement of MAF in metabolically-driven histone acetylation, including the superenhancer (SE) mark H3K27ac, through altering acetyl-CoA metabolism. To sustain the hyperacetylated chromatin state, MAF acquired the metabolic flexibility to utilize glutamine in addition to glucose, feeding metabolites into the tricarboxylic acid (TCA) cycle as acetyl-CoA sources. Systematic loss-of-function studies indicated that metabolic enzymes citrate synthase (CS) and ATP-citrate lyase (ACLY) are central to this process, and blocking citrate export from mitochondrial via CRISPR/Cas9 targeting of SLC25A1 synonymously abolished H3K27ac. Silencing of MAF also displayed defective mitochondrial oxidative phosphorylation attributed to reduced metabolic flux through TCA cycle and downregulation of electron transport chain complex I/II expression, without affecting mitochondrial DNA content. We assessed the genome-wide epigenetic profile of H3K27ac by conducting ChIP-seq and co-occupy with MAF binding sites to draw insights into MAF oncogenic transcriptome segregated by promoterand SE-regulated genes. Lastly, we identified novel t(14;16)-specific SE genes by imposing stepwise filtering criteria on our published SE dataset and overlapping with MAF RNA-seq. This led us to the prioritization of ZC3H3 for further investigation, and dependency experiments suggested that knockdown of ZC3H3 inhibited cell growth specifically in the t(14;16) subtype. Altogether, we delineated a non-canonical epigenetic role of MAF in connection to its altered metabolic state. This study is part of our framework to characterize and identify metabolic dependencies in genetic high-risk MM subtypes towards the aim of metabolic disruptions as a new direction in myeloma therapy.

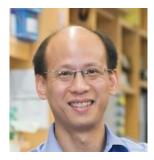
BIOSKETCH

Professor Wee Joo Chng is a Yong Loo Lin Professor in Medical Oncology and Vice Dean of Research at the Yong Loo Lin School of Medicine, National University of Singapore, where he is also a Senior Principal Investigator at the Cancer Science Institute of Singapore. He is concurrently the Director of the National University Cancer Institute, Singapore and the Group Director of Research, at the National University Health System.

Professor Chng sits on many international professional committees, such as the International Myeloma Working Group and the Asian Myeloma Network. He is involved in a number of Grant Review Committees, Conference Organising Committees, Advisory Boards and Steering Committees of Global Clinical Trials. He has authored more than 300 publications in many reputed journals and delivered talks at national and international conferences, and also actively participates in clinical trials. He has won multiple awards for his outstanding research including the NUHS Research Excellence Award, the International Myeloma Foundation's Brian GM Durie Outstanding Achievement Award, the National Medical Excellence Outstanding Clinician Scientist Award, the National Medical Research Council Senior Translational Research (STaR) Award, the National University of Singapore Young Research Award, and the Celgene Future Leaders in Haematology Award.

ONG Sin Tiong

Associate Professor Duke-NUS Medical School, Singapore



What Can We Learn from Single Cell Studies in Chronic Myeloid Leukemia?

The promise of cancer targeted therapies to elicit consistent and durable responses across the majority of cancer patients has not been realized, including in chronic myeloid leukaemia (CML). Here, despite the availability of highly potent drugs against the causative oncogenic BCR::ABL1 kinase, CML patients continue to experience widely heterogeneous responses to BCR::ABL1 tyrosine kinase inhibitors (TKI). To gain insight into the biologic basis of response heterogeneity, we generated a single-cell atlas from the pre-treatment bone marrow (BM) from 24 CML patients with differential TKI responses. We then employed a suite of computational approaches, including machine learning, to identify eight statistically significant features correlating with either sensitivity or extreme resistance to imatinib and BC transformation. We find that a combination of early LSC fate decisions, NK cell states, an inflammatory BM microenvironment, together with genetic mutations and cell cluster expansions contribute to differential TKI responses. Importantly, each patient presents with a unique constellation of prognostic factors, not all acting in the same direction, that determine treatment outcome. This new understand highlights the biologic complexity underlying primary resistance and response heterogeneity to cancer targeted therapies, while also identifying avenues for improved prognostication and novel therapeutic approaches. Our findings also have broad implications for cancer targeted therapies in general, and indicate that pre-existing factors, together with those acquired under the selective pressure of drug therapy, ultimately determine a given patient's response to targeted therapies.

BIOSKETCH

Dr. Ong is a practising haematologist/oncologist who studies mechanisms of cancer drug resistance at the Cancer & Stem Cell Biology Signature Research Programme in Duke-NUS Medical School in Singapore. Dr. Ong received his undergraduate degree in Medical Sciences from Cambridge University. He performed his internal medicine training at Addenbrooke's Hospital Cambridge and National University Hospital Singapore, and his subspecialty training at the University of Chicago. In 2007, Dr. Ong was recruited back to Singapore to join Duke-NUS, where he expanded his research portfolio to include genomics-based studies, drug development, as well as solid tumours, such as lung and brain cancers. His Singapore-based discoveries include the first East Asian gene variant to confer general resistance to cancer targeted therapies, novel drug targets in the cancer cell's translational machinery, and bioinformatics-based approaches to dismantling cancer cell states. He has partnered with A*STAR entities in Singapore to also develop novel MNK kinases (ETC-206) which are currently in clinical trials. His work has been published in Nature Medicine, Cancer Research, Blood, Leukemia, and the Proceedings of the National Academy of Sciences. He has received past and current funding from the US NIH, National Medical Research Council Singapore, and the Lymphoma and Leukemia Society.

Hideaki NAKAJIMA

Professor and Chairman Department of Stem Cell and Immune Regulation Yokohama City University Graduate School of Medicine



Deciphering the Mechanism of Chemoresistance in Poor-Risk AML

Overcoming therapeutic resistance has been a major challenge in improving outcome of poor risk acute myeloid leukemia (AML). Gene expression profiling enabled us to stratify the prognosis of AML, and it revealed a number of genes associated with its worse prognosis. For instance, higher expression of *PRDM16* is a hallmark useful to identify a group of patients with high relapse rate due to chemoresistance in pediatric AML. We have been investigating the mechanism of chemoresistance in poor risk AML using a mouse or cell line model with modulated *Prdm16* expression as well as multiomics data from patient samples. Our effort has revealed an intriguing relationship between this poor prognostic factor, resistance to cytarabine, a key drug for AML treatment, and the energy metabolism in AML cells.

BIOSKETCH

Dr. Nakajima is an adult hematologist and a physician scientist, currently appointed as Professor and Chairman of Department of Hematology and Clinical Immunology in Yokohama City University School of Medicine. He is an executive board member of Japanese Society of Hematology (JSH) and the Japanese Society of Internal Medicine, as well as a member of International Members Committee and the Awards Committee of American Society of Hematology (ASH). He started his research career with studies on differentiation inducing therapy of acute myeloid leukemia (AML) at Keio University School of Medicine, which led to his pioneering works on signaling and transcriptional regulation of hematopoiesis at St. Jude Children's Research Hospital and the University of Tokyo. His current research focuses on the epigenetic and transcriptional regulation of myeloid malignancies, clonal hematopoiesis, and hematopoietic stem cells.

DAY 1 | 4 SEPTEMBER 2023 Gastric Cancer & Tumour Niche

Patrick TAN

Professor, Senior Vice Dean of Research Duke-NUS Medical School

Chief Scientific Officer Genome Institute of Singapore

Senior Principal Investigator Cancer Science Institute of Singapore, NUS

Genomic Landscapes of Gastric Pre-malignancy

Intestinal metaplasia (IM) is a pre-malignant condition of the gastric mucosa associated with increased gastric cancer (GC) risk. We analyzed 1256 gastric samples (1152 IMs) from 692 subjects through a prospective 10-year study. We identified 26 IM driver genes in diverse pathways including chromatin regulation (ARID1A) and intestinal homeostasis (SOX9), largely occurring as small clonal events. Analysis of clonal dynamics between and within subjects, and also longitudinally across time, revealed that IM clones are likely transient but increase in size upon progression to dysplasia, with eventual transmission of somatic events to paired GCs. Single-cell and spatial profiling highlighted changes in tissue ecology and lineage heterogeneity in IM, including an intestinal stem-cell dominant cellular compartment linked to early malignancy. Expanded transcriptome profiling revealed with incomplete histology, antral/intestinal cell types, ARID1A mutations, inflammation, and microbial communities normally associated with the healthy oral tract. We demonstrate that combined clinical- genomic models outperform clinical-only models in predicting IMs likely to progress. Our results raise opportunities for GC precision prevention and interception by highlighting strategies for accurately identifying IM patients at high GC risk and a role for microbial dysbiosis in IM progression.

BIOSKETCH

Prof. Patrick Tan is Senior Vice Dean of Research at Duke-NUS Medical School and Chief Scientific Officer at the Genome Institute of Singapore. He is a Senior Principal Investigator at the Cancer Science Institute of Singapore, Executive Director of PRECISE (Precision Health Research Singapore) coordinating Singapore's National Precision Medicine program, and Professor (adjunct) at Duke University, USA. He received his B.A. (summa cum laude) from Harvard University and MD PhD degree from Stanford University, where he received the Charles Yanofsky prize for Most Outstanding Graduate Thesis in Physics, Biology or Chemistry. Other awards include the President's Scholarship, Loke Cheng Kim scholarship, Young Scientist Award (A-STAR), Singapore Youth Award (twice), Chen New Investigator Award (Human Genome Organization), President's Science Award, Japanese Cancer Association International Award and Public Administration Medal (Silver). In 2018, he received the American Association for Cancer Research (AACR) Team Science Award as Team Leader. He is an elected member of the American Society for Clinical Investigation (ASCI), the Bioethics Advisory Committee (BAC), a Board Member of the International Gastric Cancer Association, Board of Reviewing Editors for Science, and on advisory committees for Venture Corporation, Qatar Precision Health Institute, and Riyadh Biotech City (Saudi Arabia).



Shiro KOIZUME

Chief Scientist Kanagawa Cancer Center Research Institute



Malignant Phenotypes of Ovarian Cancer Induced under Lipid Starvation and Hypoxia Condition

Tumor microenvironment is generally hypoxic because of limited oxygen supply due to inefficient vasculature. Hypoxia-inducible factors (HIFs) are major mediators required for adaptation to such stress conditions. HIFs bind to and activate target genes as enhancers of transcription. Given that hypoxic tumor tissues are supplied with varied levels of blood components, multiple molecular mechanisms are required to facilitate cancer cell survival. We found that absence of long-chain fatty acids and cholesterol together with hypoxia causes synergistic activation of genes such as ICAM1 and CD69 in a HIFs dependent manner in ovarian clear cell carcinoma (CCC) cells. This process is mediated by degradation of lipid droplet through lipophagy. Furthermore, we demonstrated that ICAM-1 and CD69 proteins can enhance viability and epithelial-mesenchymal transition of CCC cells, thereby promoting tumor growth. Thus, tumor conditions with severe microenvironment with lipid starvation and hypoxia could be a potential target for treating CCC.

BIOSKETCH

1997 Graduate School of Pharmaceutical Sciences Hokkaido University 2005-2010 Research Scientist, Kanagawa Cancer Center Research Institute, Japan 2010- Present Chief Scientist, Kanagawa Cancer Center Research Institute, Japan Specialty and Present Interest: Gene regulatory mechanisms associated with cancer progression, Cancer-associated thromboembolism.

DAY 1 | 4 SEPTEMBER 2023 Proteome and RNA Biology

Dennis KAPPEI

Principal Investigator Cancer Science Institute of Singapore, National University of Singapore

Assistant Professor NUS Centre for Cancer Research (N2CR) Department of Biochemistry, Yong Loo Lin School of Medicine, NUS



Identification of Biomarkers and Therapeutic Targets in Gastric Cancer by Label-Free Quantitative Mass Spectrometry

While next-generation sequencing technologies have revolutionized the field of precision medicine by providing information about changes at both the DNA and RNA level, the analysis of protein expression landscapes lacks behind. This is unfortunate since RNA levels often primarily serve as a proxy for the functionally relevant protein expression levels due to widespread accessibility of next-generation sequencing technologies although RNA levels only correlate with protein expression data with a correlation coefficient of ~0.5 globally.

With proteins as the ultimate actionable molecules, we here explored proteomics profiling as the next level for diagnosis and identification of putative novel therapeutic targets. In a proof-of-concept example, we performed label-free quantitative mass spectrometry analysis to generate deep expression proteomes for both a panel of gastric cancer cell lines and primary tumor samples. Through this data set, we exemplify the potential of coordinated discovery of putative biomarkers/drug targets based on association with clinical data while simultaneously identifying matched cellular models.

BIOSKETCH

Dennis Kappei is a Principal Investigator and the Head of the Quantitative Proteomics Core at the Cancer Science Institute of Singapore (CSI) and an Assistant Professor in the Department of Biochemistry in the Yong Loo Lin School of Medicine at the National University of Singapore. Dr Kappei obtained his MS degree from Ecole Normale Supérieure and University Paris VI and pursued his graduate studies at the Max Planck Institute of Molecular Cell Biology and Genetics under the roof of the Dresden International Graduate School for Biomedicine and Bioengineering.

Jordan RAMILOWSKI

Associate Professor Yokohama City University Bioinformatics Laboratory



Coordinated Expression of Long Noncoding-RNA Regulates Lineage Commitment of Classical Dendritic Cells

Genomic loci encoding for long noncoding RNAs (IncRNAs), transcripts 200 nt or longer and without protein coding potential, are more prevalent in mammalian genomes than those encoding for mRNAs. Regardless, only a small fraction (5-10%) of all IncRNAs are actively transcribed in each cell state. Such restricted expression patterns suggest cell type-specific functions of IncRNAs, yet majority of IncRNAs remain functionally uncharacterized. Taking advantage of own unique *in-vivo* dendritic cells (cDCs) differentiation multi-omics data, we have created a comprehensive atlas of ~8,000 known and novel IncRNAs and analyzed ~1,000 IncRNA expressed in our system. Analyzing chromatin 3D-structure and modification and gene expression data, we have uncovered many interacting genomic loci enriched in active enhancer marks (H3K27ac) and actively transcribing enhancer IncRNAs (e-IncRNAs). Using bioinformatics approaches we are now investigating spatiotemporally roles of these e-IncRNAs in regulating myelopoiesis.

BIOSKETCH

Jordan Ramilowski graduated with a Ph.D. in Physical Chemistry from Utah State University (US). In 2011, Dr. Ramilowski moved to RIKEN Yokohama Institute (Japan) where he worked as a Bioinformatics Researcher largely focusing on understanding roles of long non-coding RNAs in gene regulation. Since 2020, Dr. Ramilowski has been appointed a Bioinformatics Associated Professor at the Advanced Medical Research Center at Yokohama City University, where he is primarily investigating regulatory roles of long non-coding RNAs (Inc-RNAs) in immune cell differentiation and pathology.

Polly Leilei CHEN

Associate Professor and Principal Investigator Cancer Science Institute of Singapore, NUS Centre for Cancer Research (N2CR) National University of Singapore



RNA "Mutations" in Cancer: Are They Silent?

RNA editing introduces changes in RNA sequences encoded by the genome. In humans, the most common type of editing is the conversion of adenosine to inosine (A-to-I), which is catalysed by adenosine deaminases acting on RNA (ADAR) family of proteins. A-to-I RNA editing has the potential to recode proteins, alter pre-mRNA splicing, mediate RNA interference, affect transcript stability and subcellular localization, among others. Over the past years, we have made contributions to current understanding of how RNA editing by the ADAR enzymes and their associated factors promotes carcinogenesis, providing important novel insights into this poorly understood biological process and its role in human cancer. In this talk, I would like to highlight our findings on the causes and functional consequences of RNA editing dysregulation in cancer and the therapeutic potentials of targeting RNA editing for cancer treatment.

BIOSKETCH

Dr Polly Leilei Chen received her Bachelor of Medicine and completed her medical training in China and then pursued her PhD (2010) at the University of Hong Kong. In 2014, Dr Chen joined National University of Singapore (NUS) as a Principal Investigator at Cancer Science Institute of Singapore and Assistant Professor in the Department of Anatomy. She was promoted to Associate Professor in 2021. Dr Chen is an EMBO Young Investigator and Asian RNA Research Ambassador. She currently places her research focus on functional and mechanistic investigation of RNA changes (particularly RNA editing and splicing) leading to cancer initiation and development; and the development of novel cancer therapies targeting these cancer-associated RNA changes.

Anthony KHONG

Principal Investigator Cancer Science Institute of Singapore, NUS

Assistant Professor NUS Centre for Cancer Research (N2CR) Department of Physiology, Yong Loo Lin School of Medicine, NUS

Stress Granules Promote p21 Expression and Chemoresistance

During the integrated stress response, most mRNAs exit translation, and many coalesce into ribonucleoprotein condensates known as stress granules. Stress granules also form during chemotherapy and can promote cancer cell survival and chemoresistance by an unknown mechanism. Herein, we provide several lines of evidence that stress granules enhance cell survival by promoting cell cycle exit. First, we see a correlation between spontaneous stress granule formation and cell-cycle exit under non-stress conditions. Second, cells deficient in proteins required for stress granule formation, such as G3BP1/2 proteins, are less likely to exit the cell cycle under non-stress, stress, and chemotherapeutic conditions. Third, rescuing stress granule formation in G3BP1/2 double knockout cells with an artificially reconstructed G3BP1 analogue gene (GFP-synthetic) that rescues stress granule formation restores the fraction of non-cycling cells to wildtype levels. The mechanism by which stress granules promote cell cycle exit is by stimulating p21 expression, leading to the inhibition of Rb phosphorylation. These results suggest that stress granules are important regulators of cell cycle exit, and targeting stress granules with inhibitors would be effective adjuvant chemotherapy to limit the development of chemoresistance in treating human tumours.

BIOSKETCH

Dr. Khong is an assistant professor at the Cancer Science Institute of Singapore and the Department of Physiology at the National University of Singapore. Dr. Khong obtained his Bachelor of Science at the University of British Columbia in 2008. He then obtained his Doctorate of Philosophy in Biochemistry and Molecular Biology at the University of British Columbia in 2015. Dr. Khong completed his postdoctoral training at the University of Colorado Boulder under the supervision of Professor Roy Parker in April 2023. In his academic career, he published 18 papers, including seven first-author research articles, and was awarded a Banting Postdoctoral Fellowship. Dr. Khong's main research areas are RNA biology and stress granules, a model biomolecular condensate that forms during cellular stress. Dr. Khong's recent research has provided fundamental insights into why cells build stress granules. Specifically, his studies have led to the idea that stress granules form as a biophysical consequence of extensive mRNA-mRNA aggregation during translational shutoff. Moreover, his recent study indicates stress granules promote chemoresistance by promoting cell-cycle exit. Dr. Khong plans to continue dissecting how stress granules and RNA granules modulate gene expression and participate in cancer biology at the National University of Singapore.



DAY 2 | 5 SEPTEMBER 2023 Immunology

Tomohiko TAMURA

Professor Department of Immunology, Yokohama City University Graduate School of Medicine



Chromatin and the Transcription Factor IRF8 in the Regulation of Myeloid Cell Development

The establishment of appropriate gene expression patterns is essential for cell differentiation. We have shown that the transcription factor IRF8 is required for the development of dendritic cells (DCs) especially cDC1s and monocytes, whereas it inhibits neutrophil differentiation. High, low or null expression of IRF8 in myeloid progenitors promotes differentiation toward cDC1s, monocytes, or neutrophils, respectively, via epigenetic regulation of distinct sets of enhancers. Regarding the regulation of Irf8 itself, it has multiple enhancers that function in a cell lineage- and differentiation stage-specific manner. I will also show our recent data regarding dynamic changes in higher-order chromatin structures and the physical and functional cooperation between the Irf8 enhancers during DC differentiation. I hope these findings help deepen our understanding of the fundamental role of chromatin regulation and key transcription factors in cell differentiation.

BIOSKETCH

Dr. Tamura obtained M.D. and Ph.D. at Yokohama City University. As a clinician, he specialized in hematopoietic stem cell transplantation. As a basic scientist, he has been studying the role of transcription factors in myeloid cell development and function at NICHD, NIH, the University of Tokyo, and Yokohama City University, particularly from the viewpoint of chromatin. He loves listening to classical and jazz music using sophisticated audio systems.

Tetsuro SASADA

Director Cancer Vaccine and Immunotherapy Center Chief Division of Cancer Immunotherapy, Kanagawa Cancer Center Research Institute



Predictive Biomarkers of Immune Checkpoint Inhibitors for Development of Personalized Immunotherapy

Immune checkpoint inhibitor (ICI) therapy has opened a new era of anti-tumor therapy, but only a part of patients can benefit from it. The identification and development of predictive biomarkers for ICIs are thus urgently required. However, current available biomarkers, such as PD-L1 expression and tumor mutational burden, do not allow to unambiguously identify patients who do or do not benefit from ICIs. In addition, tumor tissues for analyzing them are often difficult to obtain timely and repeatedly. We thus focus on biomarkers in peripheral blood that can be easily monitored in a minimally invasive manner. Recently, we have demonstrated the clinical significance of circulating systemic markers, such as profiling of amino acids and cytokines, as predictive factors of ICIs. In this symposium, I will present our recent data and discuss potential mechanisms to develop personalized immunotherapy.

BIOSKETCH

Dr. Sasada received MD (1987) and PhD (1997) from Kyoto University, Kyoto, Japan. After his training in gastroenterological surgery and immunology, he worked as the Director of the Immune Assessment Core at the Cancer Vaccine Center in Dana-Farber Cancer Institute, Boston from 2006 to 2010. After then, from 2010 to 2014, he studied cancer peptide vaccines at Kurume University School of Medicine, Fukuoka, Japan. In 2014, he moved to Kanagawa Cancer Center, Yokohama, Japan, and has been involved in the preclinical and clinical development of novel cancer immunotherapies.

DAY 2 | 5 SEPTEMBER 2023 Biobanking & Mouse Models

Shinya SATO

Section Head Morphological Information Analysis laboratory, Kanagawa Cancer Center Research Institute



Analysis of Cancer Adipocyte Microenvironment Using High Quality and Diverse Data Modalities of Biobank in the Kanagawa Cancer Center

The Kanagawa Cancer Center Biobank (Biospecimen Center) holds high-quality frozen tissue, serum, plasma, and DNA samples derived from cancer patients with accompanying clinical information, totaling approximately 50,000 specimens. The biobank maintains the quality of biospecimens through rapid specimen collection and management by dedicated staff. In addition, in recent years, the biobank has supported the creation of organoids and patient derived xenografts by providing fresh surgical materials. As an example of utilizing the diverse data modalities of our biobank samples, we present our study of the cancer-adipocyte microenvironment in metastases. Using biobank specimens, we have shown that adipocytes in the bone microenvironment may promote progression via tumor immune evasion and induction of cancer-associated fibroblasts. Furthermore, we have succeeded in measuring the concentration of adipocyte-derived secreted factors using serum and in producing organoids and PDX from metastatic seeding sites. We are now conducting a detailed and comprehensive analysis of the role of adipocytes in the cancer microenvironment using biobank derived multiple data modalities.

BIOSKETCH

Dr. Sato graduated from Nagoya City University School of Medicine in 2003. After initial training at the Aichi Cancer Center, he worked as a pathologist in the Department of Experimental Pathology, performing diagnostic work and studying metastatic microenvironment in rats. In 2016, he joined Prof. Alissa Weaver in the Department of Cancer Biology at Vanderbilt University to study the relationship between extracellular vesicles and metastasis, and showed that cancer cell-derived extracellular vesicles are involved in angiogenesis in the cancer microenvironment. After returning to Japan in 2019, he joined the Kanagawa Cancer Center Research Institute, where he continues to study cancer-adipocyte interactions using cell, animal, and biobank materials.

Teja CELHAR

Senior Research Scientist Singapore Immunology Network, A*STAR Central Institute for Experimental Animals (CIEA)



Transgenic Expression of Human Cytokines Impacts the Tumor Immune Microenvironment in Humanized NOG Mice

Immunodeficient mice engrafted with human hematopoietic stem cells (HSC), i.e. humanized mice, are emerging as important pre-clinical immuno-oncology models. To overcome poor engraftment of certain human lineages, humanized mice can be engineered to express a variety of human cytokines. While the effects of these cytokines on the reconstitution of the human immune system have been well documented, limited data is available on how they impact the human tumor immune microenvironment (TIME).

Here we have performed a detailed comparison of NOD/Shi-*scid IL2rg^{null}* (NOG) mice with transgenic strains NOG-hIL-6, NOG-hGM-CSF/hIL-3 (NOG-EXL) and NOG-hIL-34. All strains were engrafted with HSC from the same donor and transplanted with the human head and neck squamous cell carcinoma (HNSCC) line HSC4. At endpoint we collected the serum for cytokine measurement and analyzed the TIME by FACS and single-cell RNA sequencing (scRNA-Seq).

BIOSKETCH

Dr. Teja Celhar received her MSci in Pharmacy and Ph.D. in Biomedicine from the University of Ljubljana, Slovenia. She joined the Singapore Immunology Network in 2010 as a research fellow in Dr. Anna-Marie Fairhurst's Autoimmunity lab. During her postdoctoral training, she gained extensive knowledge of murine models of disease, particularly systemic lupus erythematosus. She joined the "Humanized NOG Mice for Immuno Therapy – HuNIT" platform in April 2019, where she is involved in the isolation and characterization of CD34⁺ hematopoietic stem/progenitor cells, generation of human immune system humanized mice and evaluation of novel models for Immuno-Oncology and Autoimmunity.

Takeshi TAKAHASHI

General Manager Dept. of Basic Research for Laboratory Animals Central Institute for Experimental Animals (CIEA)



Induction of Anti-Tumor Immunology by Immune-Checkpoint Inhibitors in Humanized Mice

Immune checkpoint inhibitors, including anti-PD-1 antibodies, have been tested in humanized mice, especially HSC-engrafted model, for the evaluation of anti-tumor activity. Nevertheless, the reports have been not always consistent in terms of tumor rejection, which would be partly due to different immunosuppressive features of each human tumor. CIEA developed a NOG sub-strain lacking mouse Fc receptor genes (FcRg and FcgRIIb, hence no functional FcgR receptors on the surface). This novel model (NOG-FcgR KO) induced strong anti-tumor immune responses by administration of anti-PD-1 antibody (Nivolumab), resulting in rejection of some tumor cell lines and PDX cell lines, which were resistant in conventional NOG mice. The rejection was accompanied with increased infiltration of human T cells into tumor. Our results indicate that there are some immune suppressive mechanisms in NOG mice imposed by mouse FcgR, which are alleviated in NOG-FcgR KO. This model is also practically applicable to development of extensive range of immune checkpoint inhibitors and possible candidates for combination therapy.

BIOSKETCH

- 2011- Head, Immunology Laboratory, Laboratory Animal Research Department, Central Institute for Experimental Animals (CIEA)
- 2006-2011 Assistant Prof., Dept. of Microbiology and Immunology, Tohoku University
- 2004-2006 Visiting Scientist, Deutsches Rheuma-Forschungszentrum Berlin
- 2003-2004 Visiting Scientist, Stanford University
- 2001-2003 Assistant Prof., Institute for frontier medical sciences, Kyoto University
- 1999-2001 Postdoc. fellow, Institute for frontier medical sciences, Kyoto University
- 1998-1999 Postdoctoral fellow, Tokyo metropolitan Institute for gerontology
- 1994-1998 Osaka University Graduate school of Medicine (Ph.D. 1998)

DAY 2 | 5 SEPTEMBER 2023 Renal & Brain Cancer

Hisashi HASUMI

Associate Professor Department of Urology, Yokohama City University



Development of the Foundation of Precision Medicine for Kidney Cancer

Kidney cancer is a complexed disease which arises from a variety of nephron cells under alterations of diverse kidney cancer-associated genes. Kidney cancer research was initiated by kindred analysis of hereditary kidney cancer patients and recent advances in multi-omics analyses using next generation sequencing have furthered our understanding on renal tumorigenesis. In this talk, I present our efforts towards the identification of kidney cancer-associated genes, functional analyses of those genes and the integrative approaches of clinical aspects with multi-omics analyses including single-cell RNA-seq, WES and WGS, which have in part elucidated renal tumorigenesis, tumor microenvironment, intra-/inter- tumor heterogeneity associated with normal nephron developmental machinery. In addition, I demonstrate our newly developed kidney cancer organoid model derived from genetically engineered human iPS cells which may partly recapitulate a natural history of renal tumorigenesis.

BIOSKETCH

Dr. Hasumi is a urologic surgeon who has been focusing on renal tumorigenesis under dysregulation of kidney cancer-associated genes. His aim is to develop the foundation of precision medicine for kidney cancer.

Derrick ONG

Assistant Professor NUS Centre for Cancer Research (N2CR) Department of Physiology, Yong Loo Lin School of Medicine National University of Singapore



Towards a Better Molecular Understanding of Glioblastoma Pathogenesis

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, therapy resistance and extensive plasticity. We employ patient-derived GSCs as an experimental model to uncover new GBM dependencies that contribute to GBM clinical hallmarks. Here, I will outline some of our efforts towards a better molecular understanding of GBM pathogenesis, and how some of our basic science findings may be translated into the clinic.

BIOSKETCH

Derrick is the President's Assistant Professor at the Department of Physiology, National University of Singapore (NUS). He obtained his PhD (Chemical Biology) at The Scripps Research Institute (CA) where he trained under Dr Jeffery Kelly, a pioneer in proteostasis. For his postdoctoral work, Derrick was mentored by Dr Ronald DePinho, a world expert in aging and cancer, first at Dana Farber Cancer Institute/ Harvard Medical School, and then University of Texas MD Anderson Cancer Center. His major research interest lies in the area of glioblastoma and cancer epigenetics.

Kensuke TATEISHI

Associate Professor and Principal Investigator Department of Neurosurgery and Medical Life Science Yokohama City University



Translational Research Platform for Malignant Brain Tumors

The major treatment approach for malignant brain tumors includes surgery, radiation, and chemotherapy. To provide personalized treatment, integrated information with histopathological and genomic characterization is crucial. Here, we present an overview of our translational research for malignant brain tumors. As a routine practice, we integrate preoperative imaging, intraoperative diagnosis with rapid immunohistochemistry and quantitative PCR based genomic assessment for establishing multidisciplinary treatment strategy during surgery. Frozen tumor specimens are stored for future experiments and primary culture is performed in all cases. Tumor cells are implanted into immunodeficient mice brain to form patient-derived xenograft (PDX) model. We also assess drug and radiosensitivity for primary cultured cells and xenograft cells for establishing personalized therapy. Comprehensive genomic information is obtained for patient tumor and corresponding PDX. These data are feedback for preclinical and clinical research. Using this system, we have experienced 269 glioma and 52 malignant lymphoma cases. This translational research platform may play an important role on basic and clinical research for malignant brain tumors.

BIOSKETCH

Dr. Tateishi is currently working as a neurosurgeon and principal investigator at Yokohama City University (YCU) and YCU hospital. His team's research goal is to elucidate tumor progressive mechanism and to establish novel therapeutic strategy for malignant brain tumors, including glioma and primary central nervous system lymphoma. To complete this, they have established the large scale of patient-derived xenograft models. Using these models, they are conducting translational research with collaborators.

Makoto SUEMATSU

Director Central Institute for Experimental Animals



Imaging Metabolomics Deciphers Cancer Metabolism to Translate into Medicine

Imaging metabolomics includes imaging mass spectroscopy (IMS) and surface-enhanced Raman spectroscopy (SERS). IMS requires high-energy laser irradiation to induce ionization of metabolites on frozen tissues that hampers visualization of redox metabolites without auto-oxidation. To overcome difficulties, we developed surface-enhanced Raman scattering imaging (SERS) assisted by infrared laser which enables visualization of reactive sulfur species (RSS) in cancer tissues. Application of SERS allowed us to visualize RSS in frozen ovarian cancer tissue slices collected the debulking surgery. Results suggest that cystathionine γ -lyase (CSE) is responsible for overproduction of polysulfide as an independent marker distinguishing non-responders from responders to post-operative platinum-based chemotherapy. Furthermore, polysulfides determine overall survival of patients with clear cell carcinoma (CCC) who turned out less sensitive to cisplatin than those with serous adenocarcinoma. Chemoresistance of CCC include inactivation of cisplatin with endogenous polysulfides, shedding light on effectiveness of polysulfide-degrading compound such as ambroxol to unlock chemoresistance. The lecture will highlight on roles of RSS in cancer chemoresistance.

BIOSKETCH

Dr. Suematsu, Professor and Chair at Department of Biochemistry, Keio University, is a physician scientist who is interested in how gases such as NO, CO and H2S exert their biological actions. This concept shed light on mechanisms by which cancer utilizes the gas-responsive receptors to take advantage of energy maintenance for survival. His carrier as Dean of Keio University School of Medicine enabled to launch "Supercentenarian Medical Research Center" that contributed to global collaboration in aging sciences. In April 2015, he was appointed by the late prime minister Abe to be the founding president of Japan Agency for Medical Research and Development (AMED). He concluded MOC in January 2016 with NIH to accelerate global data sharing in the field of rare and undiagnosed diseases, etc. From April 2023, he became Professor Emeritus, Keio University, and Director of Central Institute of Experimental Animals.

DAY 2 | 5 SEPTEMBER 2023 Ageing

Yuichi TEI / Ung-il CHUNG

Executive Board Member, Vice President and Dean, School of Health Innovation, Kanagawa University of Human Services, Kanagawa, Japan

Professor, Department of Bioengineering, The University of Tokyo Graduate Schools of Engineering and Medicine, Tokyo, Japan



Advisor to the Governor of Kanagawa Prefecture

BIOSKETCH

Dr. Chung graduated from the University of Tokyo School of Medicine to obtain MD in 1989. After working as Resident and Clinical Fellow in Internal Medicine at the University of Tokyo Hospital, he entered and graduated from the University of Tokyo Graduate School of Medicine to obtain PhD in 1997. In 1998, he was appointed Instructor in Medicine, Harvard Medical School, and then Assistant Professor of Medicine in 2001. In 2002, he came back to his alma mater. In 2007, he became Professor, the University of Tokyo Graduate School of Engineering, and in 2016, he also became Professor, Graduate School of Medicine. Since 2019, he also serves as Dean and Professor, at School of Health Innovation, Kanagawa University of Human Services and since 2021, as Executive Board Member and Vice President as well.

He specializes in skeletal biology/regenerative medicine and biomaterial science. He promotes industry-academia cooperation projects to measure and visualize health status of each individual for health personalization and behavior change. He attempts to systematize and academicize ME-BYO concept for social implementation. He also studies the role of morality in innovation management.

Hiroto NARIMATSU

Director and Professor

Center for Innovation Policy, Kanagawa University of Human Services

Division Chief, Kanagawa Cancer Center Research Institute

Community-Based Intervention and Robot Suit HAL

The population-based genomic cohort study called the Kanagawa ME-BYO prospective cohort study (ME-BYO cohort) aims to explore gene-environmental interactions in non-communicable diseases (NCDs) and evaluate the risks of developing diseases that can adversely affect an individual's quality of life (QOL). The data collected from the ME-BYO cohort study will be used to establish an effective strategy for healthy aging based on the ME-BYO concept. Furthermore, new projects such as the ME-BYO INDEX and the development of preventive care systems using Robot Suit HAL have been initiated to develop new technologies that can serve as preventive interventions. This presentation will provide an update on the latest progress of these new projects.

BIOSKETCH

Physician and researcher.

Through a cross-appointment system, Dr. Narimatsu is enrolled at both Kanagawa Cancer Center and Kanagawa University of Human Services, working toward a society where people can design their own health through innovation. He is also involved in the implementation of innovation in the community as the Chairman of CIKOP, Specified Nonprofit Corporation, based in Yamagata and Kanagawa Prefectures.





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