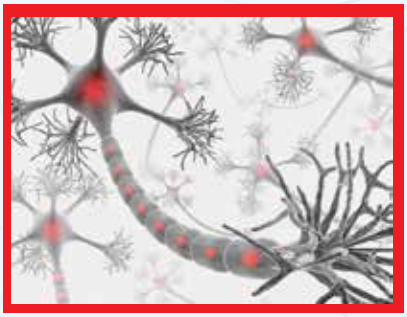
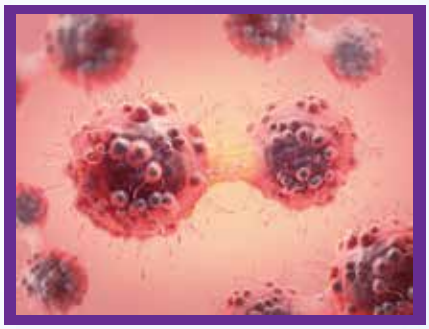


Neural, Vascular, and Metabolic Biology

9th SBS Research Day

Developmental and Regenerative Biology



Cancer Biology and Experimental Therapeutics

SCHOOL OF BIOMEDICAL SCIENCES

RESEARCH DAY 2018

Date: 17-18 May 2018 (Thu & Fri)

Venue: Lo Kwee-Seong Integrated Biomedical Sciences Building

香港中文大學
The Chinese University of Hong Kong

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

香港中文大學 生物醫學學院
CUSBS

School of Biomedical Sciences Research Day 2018

Members of the Organizing Committee

Professor HUANG Yu (Chairman)
Professor CHAN Wai Yee
Professor CHEUNG Chi Kwan Vincent
Professor KE Ya
Professor LAU Hang Yung Alaster
Professor LEE Tin Lap
Professor TIAN Xiaoyu
Professor ZHAO Hui

COVER: The three Thematic Research Programs of School of Biomedical Sciences, CUHK
Designed by Ms. Michelle Li, Dept. of Orthopaedics & Traumatology, Faculty of Medicine, CUHK

CONTENTS

Welcome Message from the Dean of Faculty of Medicine

It gives me great pleasure to welcome you to the School of Biomedical Sciences (SBS) Research Day 2018.

The SBS Research Day has served as a platform for faculty and researchers in the School to mingle and communicate with researchers and experts of different disciplines. Speakers with brilliant track record in the thematic research are invited to share with participants their latest scientific findings and research ideas. This annual flagship event has encouraged more spirited interactions among institutions and notable scientists and enabled the School to explore new opportunities in collaborative research.

Nowadays, universities worldwide, in addition to providing quality tertiary education and leading cutting-edge research, are also expected to make positive social impacts. Seizing opportunities enabled by rapid advances in biomedical sciences, the School will continue to work closely with clinicians in the Prince of Wales Hospital and to foster closer and long-term partnership with industries to accelerate bench-to-bedside research.

The 2018 SBS Research Day is a golden opportunity for the School to reflect on what has been achieved in the past year, thereby helping the School to re-calibrate its future plans on research and development. I trust that you will take home many thought-provoking ideas to stimulate further discussions beyond this one-and-a-half day programme. Let us work together to push the frontiers of science to bring healing and hope to patients.

Professor Francis K.L. Chan
Dean, Faculty of Medicine
Choh-Ming Li Professor of Medicine & Therapeutics
The Chinese University of Hong Kong

Welcome Message from the Director of School of Biomedical Sciences

I am delighted and honoured to welcome you all to the School of Biomedical Sciences Research Day 2018.

Being the first of its kind in Hong Kong, our School has adopted the theme-based research model since its establishment in June 2009. The thematic research programs have achieved a desirable integration of our academic members, and enhanced our overall research competitiveness, as well as increased the dynamics and synergies of selected fields of biomedical research. Capitalizing on our existing strengths and the developmental outlook, our School will continue to establish new links and plays an important role as a biomedical hub in the Pan-Asian region.

The Research Day is an important platform to bring together our School members, clinical colleagues and friends from other local institutions to share their up-to-date findings and views. This year, we are honoured to have Prof. Toshikazu USHIJIMA from National Cancer Center, Tokyo, Prof. Gareth SULLIVAN from University of Oslo and Prof. Raymond Chuen-Chung CHANG from The University of Hong Kong to be our guest speakers. I am particularly pleased to welcome 2 new colleagues of SBS, and 5 new colleagues jointly appointed by SBS and the newly established Institute for Tissue Engineering and Regenerative Medicine (iTERM) joining and some speaking at this Research Day. It is expected that this one-and-a-half-day event will be filled with comprehensive and stimulating discussions!

Once again, I would like to express my sincere gratitude to members of the organizing committee for their efforts and the sponsors for their generous support for this event.

Thank you for joining the SBS Research Day and wish all of you a great time with us!

Wai Yee Chan, Ph.D.
Professor of Biomedical Sciences
Director, School of Biomedical Sciences
The Chinese University of Hong Kong

SBS Research Day 2018 Programme

17 May 2018 (Thursday)

Room G02, Lo Kwee-Seong Integrated Biomedical Sciences Building

Time	Title of Presentation	Speaker	Abstract No.
09:00-09:10	**Welcome by Prof. CHAN Wai Yee (Director of School of Biomedical Sciences)**		
Session I (CBET) *Chairpersons: Prof. CHENG Sze Lok Alfred (CUHK SBS) & Prof. YU Jun (CUHK MEDT)*			
09:10-09:45	Epigenetic field: reality for risk diagnosis and potential for cancer therapy	Prof. USHIJIMA Toshikazu (NCCRI, Tokyo)	O1
09:45-10:00	***Tea Break***		
10:00-10:15	**Address by Prof. Rocky S. TUAN (Vice-Chancellor and President of CUHK) and presentation of the prize for SBS Research Day 2018 Programme Book Cover Design Competition / Photo Taking**		
10:15-10:45	Differential regulation of the pro-inflammatory biomarker, YKL-40/CHI3L1, by PTEN/ Phosphoinositide 3-kinase and JAK2/STAT3 pathways	Prof. CHAN M. Andrew (SBS)	O2
10:45-11:15	Epigenetic enhancement of liver cancer immunotherapy by specific inhibition of histone deacetylase 8	Prof. CHENG Sze Lok Alfred (SBS)	O3
11:15-11:30	***Tea Break***		
Session II (CBET) *Chairpersons: Prof. TANG Ming Kuen Patrick (CUHK ACP) & Prof. CHAN M. Andrew (CUHK SBS)*			
11:30-12:00	Could cancer be an immune disease?	Prof. CHEUNG Wing Tai (SBS)	O4
12:00-12:30	Identification of novel therapeutic targets for pancreatic cancer	Prof. CHEN Yangchao (SBS)	O5
12:30-13:00	Computational drug repositioning for psychiatric disorders	Prof. SO Hon Cheong (SBS)	O6
13:00-14:30	***Lunch***		
Session III (DRB) *Chairpersons: Prof. BIAN Liming (CUHK BME) & Prof. WAN Chao (CUHK SBS)*			
14:30-15:00	Bone graft revitalization via inflammatory modulation for enhanced bone repair	Prof. WANG Dan Michelle (iTERM / SBS)	O7
15:00-15:30	The controversial origin of pericytes - implications for cell-based therapies	Prof. BLOCKI Anna (iTERM / SBS)	O8
15:30-16:00	Growth factor bioprinting and computer vision-based cell tracking for musculoskeletal tissue engineering	Prof. KER Dai Fei Elmer (iTERM / SBS)	O9
16:00-16:25	***Tea Break***		
Session IV (DRB) *Chairpersons: Prof. CHAN Yiu Leung David (CUHK OBG) & Prof. LEE Tin Lap (CUHK SBS)*			
16:25-17:00	Enhanced functional longevity of hiPSC derived hepatocyte-like cells in 3D suspension culture	Prof. SULLIVAN Gareth (U Oslo)	O10
17:00-17:30	Approaches for restoring male fertility by targeting spermatogonia and sperm	Prof. FOK Kin Lam Ellis (SBS)	O11
17:30-18:00	Development-inspired engineering of artificial folded mucosa	Prof. CHAN Hon Fai (iTERM / SBS)	O12
18:30-20:00	***Conference Banquet (by invitation)***		

SBS Research Day 2018 Programme

18 May 2018 (Friday)

Room G02, Lo Kwee-Seong Integrated Biomedical Sciences Building

Time	Title of Presentation	Speaker	Abstract No.
Session V (NVMB) *Chairpersons: Prof. CHEUNG King Ho (HKBU SCM) & Dr. KO Ho Owen (CUHK MEDT)*			
09:00-09:35	Pathophysiological mechanisms of risk factors leading to development of Alzheimer's disease	Prof. CHANG Chuen Chung Raymond (HKU)	O13
09:35-10:05	Thrombocytes, glycolipids, amyloid and neurodegeneration	Prof. PONOMAREV Eugene (SBS)	O14
10:05-10:35	EMG-derived muscle-synergy patterns as recovery biomarkers in stroke survivors: Initial results from a Multi-Center Consortium	Prof. CHEUNG Chi Kwan Vincent (SBS)	O15
10:35-11:00	***Tea Break***		
Session VI (NVMB) *Chairpersons: Prof. TANG Leung Sang Nelson (CUHK CPY) & Prof. YAO Xiaoqiang (CUHK SBS)*			
11:00-11:30	Getting out of TRAPP: vesicle and beyond	Prof. YU Siu Bun Sidney (SBS)	O16
11:30-12:00	Molecular clock and vascular remodeling	Prof. TIAN Xiaoyu (SBS)	O17
12:00-12:30	How to abandon an old strategy: the critical role of a specific frontal-striatal pathway	Prof. YUNG Wing Ho (SBS)	O18
12:30-12:45	***Closing Remarks***		
12:45-14:00	***Closing Lunch***		

Abbreviations:
ACP = Department of Anatomical and Cellular Pathology
BME = Department of Biomedical Engineering
CPY = Department of Chemical Pathology
CUHK = The Chinese University of Hong Kong
HKBU = Hong Kong Baptist University
HKU = The University of Hong Kong
iTERM = Institute for Tissue Engineering and Regenerative Medicine
MEDT = Department of Medicine and Therapeutics
NCCRI = National Cancer Center Research Institute
OBG = Department of Obstetrics and Gynaecology
SBS = School of Biomedical Sciences
SCM = School of Chinese Medicine
U Oslo = University of Oslo

SBS Thematic Research Programs:
CBET = Cancer Biology and Experimental Therapeutics
DRB = Development and Regenerative Biology
NVMB = Neural, Vascular, and Metabolic Biology

Session I (CBET)

Speaker Biography

Prof. USHIJIMA Toshikazu （牛島俊和）is Chief of Division of Epigenomics, National Cancer Center Research Institute (NCCRI), Tokyo, graduated from the University of Tokyo School of Medicine in 1986. He started his research career at NCCRI in 1989, and was promoted to Chief of Carcinogenesis Division (now Division of Epigenomics) in 1999. He also served as the Senior Deputy Director of the Research Institute from 2011 to 2014. He developed one of the first genome-wide screening techniques for changes in DNA methylation, methylation-sensitive representational difference analysis (MS-RDA), in 1997 [PNAS, 1997]. Using MS-RDA, he identified a novel tumor-suppressor gene in gastric cancers, and isolated a very powerful prognostic marker in neuroblastomas [reviewed in Nat Rev Cancer, 2005]. His major contribution to cancer epigenetics is establishment of the concept "epigenetic field for cancerization" [reviewed in Clin Cancer Res, 2012]. Environmental factors, such as *Helicobacter pylori* infection and cigarette smoking, can induce aberrant DNA methylation of multiple genes in normal-appearing tissues, and accumulation of such aberrant DNA methylation produces an epigenetic field for cancer development. He conducted a prospective cohort study to demonstrate that measurement of DNA methylation in normal-appearing tissue can really tell a cancer risk [Gut, 2015; Gut, 2017]. He is now investigating the mechanisms of how aberrant DNA methylation is induced. He is serving as an editor for Cancer Letters (Associate Editor), Gastric Cancer (Associate Editor), and Cancer Science (Associate Editor), and as a board member for Cancer Prevention Research, Epigenomics, Clinical Epigenetics, and Genome Medicine. He served as a senior editor for Cancer Research (2010-2017). He is also serving as an International Scientific Steering Committee member of the International Human Epigenome Consortium, and has been serving as a grant reviewer in more than ten countries. He has received Incitement (1997) and Mauvernay (2009) awards of JCA, President award of NCC (2012), the Tahara Award of the Japanese Gastroenterological Carcinogenesis Society (2012), and the Uehara Helicobacter Award of the Japanese Helicobacter Society (2013).

Five recent representative publications

1. Yamashita S, Kishino T, Takahashi T, Shimazu T, Charvat H, Kakugawa Y, Nakajima T, Lee YC, Iida N, Maeda M, Hattori N, Takeshima H, Nagano R, Oda I, Tsugane S, Wu MS, **Ushijima T**. "Genetic and epigenetic alterations in normal tissues have differential impacts on cancer risk among tissues." ***Proc Natl Acad Sci USA,*** 2018; 115(6):1328-1333.
2. Maeda M, Nakajima T, Oda I, Shimazu T, Yamamichi N, Maekita T, Asada K, Yokoi C, Ando T, Yoshida T, Nanjo S, Fujishiro M, Gotoda T, Ichinose M, **Ushijima T**. "High impact of methylation accumulation on metachronous gastric cancer: 5-year follow up of a multicentre prospective cohort study." ***Gut,*** 2017; 66(9):1721-1723.
3. **Ushijima T**, Hattori N. "Molecular pathways: involvement of *Helicobacter pylori*-triggered inflammation in the formation of an epigenetic field defect, and its usefulness as cancer risk and exposure markers." ***Clin Cancer Res***, 2012; 18(4):923-929.
4. Chiba T, Marusawa H, **Ushijima T**. "Inflammation-associated cancer development in digestive organs: mechanisms and roles for genetic and epigenetic modulation." ***Gastroenterology***, 2012; 143(3):550-563.
5. Niwa T, Tsukamoto T, Toyoda T, Mori A, Tanaka H, Maekita T, Ichinose M, Tatematsu M, **Ushijima T**. "Inflammatory processes triggered by *Helicobacter pylori* infection cause aberrant DNA methylation in gastric epithelial cells." ***Cancer Res,*** 2010; 70(4):1430-1440.

Technical expertise

✧ DNA methylation analysis, epigenomic analysis; Translational research, biomarker development

Epigenetic field: reality for risk diagnosis and potential for cancer therapy

USHIJIMA Toshikazu, TAKESHIMA Hideyuki, MAEDA Masahiro

Division of Epigenomics, National Cancer Center Research Institute, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.

Aberrant DNA methylation can be present in normal tissues, involving a large number of passenger genes and a limited number of driver genes. Its accumulation level is associated with cancer risk in multiple types of cancers, and can exceed the importance of accumulation of point mutations, especially in inflammation-associated cancers [Yamashita, PNAS, 115:1328, 2018].

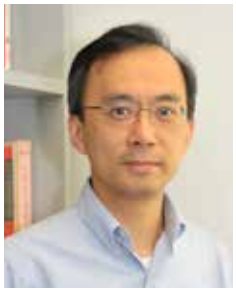
To bring these findings into clinical cancer risk diagnosis, we conducted a multicenter prospective study to predict who, among gastric cancer patients once cured by endoscopic treatment, would develop a metachronous gastric cancer using DNA methylation levels in gastric mucosae. After five-year follow-up of 795 patients, the quartile with the highest methylation levels was shown to have a 3-fold higher risk than the quartile with the lowest methylation levels [Asada, Gut, 64:388, 2015; Maeda, Gut, 66:1721, 2017]. We are now conducting another multicenter prospective study to predict who, among healthy people with *H. pylori* eradication, will develop a gastric cancer. We expect that, based upon the results of this new prospective study, people after *H. pylori* eradication can be stratified according to their individual gastric cancer risk.

As an inducer of aberrant DNA methylation, chronic inflammation has been known. It not only accelerates age-related methylation but also induces methylation of additional genes by inducing H3K27me3 [Takeshima, Carcinogenesis, 33:2384, 2012]. In methylation-causing inflammation, decreased *TET* expression, due to increased NF-κB activity and some miRNA expression, and increased DNMT activity, due to elevated nitric oxide production, are simultaneously present. This vicious combination is likely to induce aberrant DNA methylation in epithelial cells [Takeshima, MS in preparation].

Aberrant DNA methylation may be present not only in cancer cells but also in stromal cells. We conducted DNA methylation and H3K27me3 microarray analyses of (i) cancer-associated fibroblasts (CAFs), which are known to promote aggressiveness of cancer cells, (ii) fibroblasts in non-cancer tissues of cancer patients (NCAFs), and (iii) entirely normal fibroblasts (NFs). CAFs had distinct DNA methylation profiles compared to those of NF and NCAFs, and even NCAFs had distinct profile from NFs. Importantly, CAFs had increased expression of growth factors due to their epigenetic alterations. These showed that exposure to chronic inflammation induces aberrant DNA methylation also in stromal cells, and indicated that epigenetic alterations in stromal cells may become targets of cancer therapy [Maeda, MS in preparation].

Session I (CBET)

Speaker Biography



Prof. CHAN M. Andrew （陳文樂）obtained his Ph.D. degree in Molecular Biology from the Institute of Cancer Research at the Royal Marsden Hospital, University of London. He was a Fogarty International Fellow at the National Cancer Institute of the United States National Institutes of Health, and Faculty Members at the Mount Sinai School of Medicine and the Medical College of Wisconsin. Professor Chan is currently a member of the Cancer Biology & Experimental Therapeutics Thematic Research Program. Professor Chan serves on multiple governmental granting agencies and has published 64 peer-reviewed papers with some in high impact journals such as *Science, Nature Genetics, Cancer Cell, PNAS, Blood,* and *Nature Neuroscience*. The laboratory of Professor Chan focuses on various cancer cell signaling pathways in the initiation and progression of human cancer. His research involves understanding the regulatory mechanisms of the PTEN tumor suppressor in brain cancer and neurodevelopmental disorders, as well as the Ras-related GTPase, R-Ras, in tumor immune microenvironment.

Five recent representative publications

1. Wong CW, Or MY, Wang Y, Li L, Li J, Yan M, Cao Y, Luk HM, Tong TMF, Leslie NR, Lo IFM, Choy RKW, **Chan AM**. "Identification of a PTEN mutation with reduced protein stability, phosphatase activity, and nuclear localization in Hong Kong patients with Autistic features, neurodevelopmental delays, and macrocephaly." ***Autism Research***, 2017; In press.
2. Knafo S, Sanchez-Puelles C, Palomer E, Delgado I, Draffin JE, Wahle T, Kaleka K, Pereda-Perez I, Klosi E, Faber EB, Lozano-Montes L, Ortega-Molina A, Ordonez-Gutierrez L, Wandosell F, Vina J, Dotti CG, Gerges NZ, **Chan AM**, Spaller MR, Serrano M, Venero C, Esteban JA. "PTEN recruitment controls synaptic and cognitive function in Alzheimer's models." ***Nat Neurosci***, 2016; 19(3):443-453.
3. Yan X, He Y, Chen Y, Yu M, Singh G, Wang D, Hillery CA, **Chan AM**. "R-Ras regulates murine T cell migration and intercellular adhesion molecule-1 binding." ***PLoS One***, 2015; 10(12):e0145218.
4. Ray A, Basu S, Miller NM, **Chan AM**, Dittel BN. "An increase in tolerogenic dendritic cell and natural T regulatory cell numbers during EAE in *Rras*$^{-/-}$ mice results in attenuated disease." ***J Immunol***, 2014; 192(11):5109-5117.
5. Singh G, Hashimoto D, Yan X, Helft J, Ma G, Qiao RF, Kennedy CR, Chen S-H, Merad M, **Chan AM**. "R-Ras is required for Murine Dendritic cell maturation and CD4+ T-cell priming." ***Blood***, 2012; 119(7):1693-1701.

Technical expertise

- ✧ Signaling pathway analysis
- ✧ Mouse models of human cancer
- ✧ Biochemistry of small GTPases
- ✧ Cell based assays in monitoring diverse tumor cell parameters
- ✧ Cancer cell metabolism
- ✧ Primary culture of mouse astrocytes, neurons and neuroprogenitors, and various immune cells

Differential regulation of the pro-inflammatory biomarker, YKL-40/CHI3L1, by PTEN/Phosphoinositide 3-kinase and JAK2/STAT3 pathways

WANG Yubing[1], WONG Chi-Wai[1], YAN Mingfei[1], LI Lisha[1], LIU Tian[1], OR Mei Yu Penelope[1], TSUI Kwok Wing Stephen[1], WAYE Miu Yee Mary[2], CHAN M. Andrew[1]

[1] School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.
[2] The Nethersole School of Nursing, The Chinese University of Hongn Kong, Hong Kong SAR, P.R. China.

Constitutive activation of the phosphoinositide 3-kinase/AKT signalling pathway is commonly observed in high-grade gliomas with frequent loss of *PTEN* tumour suppressor. To identify transcriptomic profiles associated with a hyperactivated PI3K pathway, RNA-sequencing analysis was performed in a glioblastoma cell line stably expressing PTEN. RNA-sequencing revealed enriched transcripts of pro-inflammatory mediators, and among the genes that displayed highly differentially expression was the secreted glycoprotein YKL-40. Interestingly, treatment with chemical inhibitors that target the PI3K/AKT pathway elicited differential effects on YKL-40 expression in selected GBM cell lines, indicating that its expression displayed tumour cell-specific variations. This variability appeared to be correlated with the ability to transactivate the immune signalling molecules JAK2 and STAT3. Individual glioblastoma cell lines also displayed variability in the expression of a short variant (SV) of YKL-40. Unlike the full-length (FL) version, which was localised to all cell compartments, the short isoform could not be secreted and was only localised to the cytoplasm. Functionally, FL YKL-40 promoted cell proliferation, whereas SV YKL-40 suppressed it. Taken together, the differential expression of the immunomodulatory molecule YKL-40 may affect the local immune microenvironment or the treatment efficacy of selected PI3K pathway inhibitors.

Session I (CBET)

Speaker Biography

Prof. CHENG Sze Lok Alfred（鄭詩樂）is an Associate Professor in the School of Biomedical Sciences at The Chinese University of Hong Kong (CUHK). He completed his Ph.D. under the supervision of Prof. Joseph Sung in the Department of Medicine and Therapeutics at CUHK in 2002 and went on his postdoctoral training in Ohio State University until 2007. Prof. Cheng has published in international journals including *Molecular Cell, Nature Genetics, Journal of Clinical Investigation, Cancer Research, Gastroenterology, Gut* and *Journal of Hepatology*. He has received >20 academic honors and awards, including recognitions from the American Association of Cancer Research (AACR) and United European Gastroenterology (UEG). He was a recipient of the Most Promising Young Investigator Award by Hong Kong Government (2014) and CUHK (2015). He has been recently awarded the Asa Briggs Visiting Fellowship in 2017 by the University of Sussex and the Visiting Professorship in 2018 by the Southwestern Medical University. Until 2018, he has presided as Principal Investigator in 14 local and national competitive grants with a sum of over 20 million HK dollars. His current research focuses on the epigenetic mechanisms in tumors and their microenvironment, aiming at the enhancement of cancer immunotherapy.

Five recent representative publications

1. Mok MTS, Zhou J, Tang W, Zeng X, Oliver AW, Ward SE, **Cheng ASL**[*]. "CCRK is a novel signalling hub exploitable in cancer immunotherapy." ***Pharmacol Ther,*** 2018; pii: S0163-7258(18)30015-9. doi: 10.1016/j.pharmthera.2018.01.008.
2. Zhou J, Liu M, Sun H, Feng Y, Xu L, Chan AWH, Tong JH, Wong J, Chong CCN, Lai PBS, Wang HK, Tsang SW, Goodwin T, Liu R, Huang L, Chen Z, Sung JJ, Chow KL, To KF, **Cheng ASL**[*]. "Hepatoma-intrinsic CCRK inhibition diminishes myeloid-derived suppressor cell immunosuppression and enhances immune-checkpoint blockade efficacy." ***Gut***, 2017; pii: gutjnl-2017-314032. doi: 10.1136/gutjnl-2017-314032.
3. Cao Q, Anyansi C, Hu X, Xu L, Xiong L, Tang W, Mok MTS, Cheng C, Fan X, Gerstein M, **Cheng ASL**, Yip KY. "Reconstruction of enhancer-target networks in 935 samples of human primary cells, tissues and cell lines." ***Nat Genet***, 2017; 49(10):1428-1436. doi: 10.1038/ng.3950.
4. Tian Y, Wong VW, Wong GL, Yang W, Sun H, Shen J, Tong JH, Go MY, Cheung YS, Lai PB, Zhou M, Xu G, Huang TH, Yu J, To KF, **Cheng ASL**[*], Chan HL[*]. "Histone deacetylase HDAC8 promotes insulin resistance and ß-catenin activation in NAFLD-associated hepatocellular carcinoma." ***Cancer Res***, 2015; 75(22):4803-4816. doi: 10.1158/0008-5472.CAN-14-3786.
5. Feng H, Yu Z, Tian Y, Lee YY, Li MS, Go MY, Cheung YS, Lai PB, Chan AM, To KF, Chan HL, Sung JJ, **Cheng ASL**[*]. "A CCRK-EZH2 epigenetic circuitry drives hepatocarcinogenesis and associates with tumor recurrence and poor survival of patients." ***J Hepatol***, 2015; 62(5):1100-1111. doi: 10.1016/j.jhep.2014.11.040.

[*] Corresponding author

Technical expertise

✧ Nanoscale chromatin profiling; Immune cell profiling; Preclinical hepatocellular carcinoma models

Epigenetic enhancement of liver cancer immunotherapy by specific inhibition of histone deacetylase 8

YANG Weiqin[1#], ZHOU Jingying[1#], FENG Yu[1#], SUN Hangyong[2], CHAN Lam Stephen[3], CHEN Zhiwei[5], TO Ka Fai[4], CHENG Sze Lok Alfred[1]

[#] These authors contribute equally in this study.

[1] School of Biomedical Sciences, [2] Department of Medicine and Therapeutics, [3] Department of Clinical Oncology, [4] Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong, Hong Kong SAR, [5] AIDS Institute, The University of Hong Kong, Hong Kong SAR, P.R. China.

Background: Recent clinical trials of inhibition of immune-checkpoints such as the programmed death-ligand 1 (PD-L1)/PD-1 axis, which elicits antitumor T-cell responses in a broad spectrum of cancers, have also produced durable efficacy in a fraction of patients with advanced hepatocellular carcinoma (HCC). The heterogeneous responses to immune-checkpoint blockade therapy are attributable to the complex interplay between a range of cancer-cell-autonomous cues and the immunosuppressive tumor microenvironment. Our integrative epigenomics and functional analysis has previously elucidated a critical role of histone deacetylase 8 (HDAC8) in hepatic carcinogenesis (*Cancer Research* 2015;75:4803-16). In this study, we aimed to investigate the therapeutic potential of a potent and highly-selective HDAC8-specific inhibitor PCI-34051 in preclinical HCC model.
Methods: To investigate the immune-modulatory and anti-tumor effects of PCI-34051, we have established an orthotopic HCC mouse model via intrahepatic implantation of syngeneic luciferase-stably-transfected Hepa1-6 hepatoma cells in immunocompetent C57/BL6 and immunodeficient nude mice. The mice have been treated with vehicle, PCI-34051, anti-PD-L1 antibody, or combined therapy for 3 weeks. The tumorigenicity was assessed by *in vivo* luciferin imaging, and correlated with lymphoid and myeloid cell profiling.
Results: We demonstrated that HDAC8 inhibition by PCI-34051 significantly reduced HCC tumorigenicity in C57/BL6 (~5-fold; $p<0.01$) but not nude mice. Immune profiling revealed specific reduction in tumor-infiltrating regulatory T cells (Tregs; $p<0.05$) and significant increase in CD8+ T cells ($p<0.05$). The functional significance of Tregs was demonstrated by adoptive transfer, which completely abrogated PCI-34051-induced tumor regression. Notably, PCI-34051 treatment significantly enhanced the efficacy of anti-PD-L1 therapy ($p<0.01$). Combined PCI-34051 and anti-PD-L1 treatment resulted in complete tumor eradication in all of the co-treated mice, which exhibited significantly better survival rate than single treatment groups ($p<0.05$). More importantly, the combination therapy promoted long-term survival (>300 vs. 30 days in untreated control), which was associated with elevated CD8+ T effector and central memory cells.
Conclusions: Our data suggest that selective chromatin modifications by HDAC8 alter the tumor immune surveillance program and demonstrate the promising potential of rational combinatorial epigenetic immunotherapy to fully unleash T-cell responses, leading to long-term remission of HCC.
Acknowledgement: This work is supported by the RGC CRF (C4017-14G).

Session II (CBET)

Speaker Biography

Prof. CHEUNG Wing Tai（張榮泰）was trained initially in The Chinese University of Hong Kong as a biochemist and pharmacologist working on G protein-coupled receptor (GPCR)-regulated smooth muscle contraction and lipid metabolism. As a Croucher scholar, Dr. Cheung received his PhD degree in Cambridge University on molecular neurobiology studying orphan GPCRs. Postdoctoral training with Dr. John Rogers worked on calcium binding proteins. Dr. Cheung's laboratory is built on his life-long pursuit of GPCR being a valuable drug target, research themes are focused on pathophysiology of cancers and metabolic syndromes, and exploring protein engineering for therapeutic anti-GPCR antibody development.

Five recent representative publications

1. Jin L[#], Li ZF[#], Wang DK, Sun M, Qi W, Ma Q, Zhang L, Chu C, Chan EYM, Lee SST, Wise H, To KF, Shi Y, Zhou N[*], **Cheung WT**[*]. "Molecular and functional characterization of tumor-induced factor (TIF): Hamster homolog of CXCL3 (GROγ) displays tumor suppressive activity." ***Cytokine***, 2018; 102:62-75. doi: 10.1016/j.cyto.2017.12.019.
2. Feng L, Yuen YL, Xu J, Liu X, Chan MYC, Wang K, Fong WP, **Cheung WT**[*], Lee SST[*]. "Identification and characterization of a novel PPARα-regulated and 7α-hydroxyl bile acid-preferring cytosolic sulfotransferase mL-STL (Sult2a8)." ***J Lipid Res***, 2017; 58(6):1114-1131. doi: 10.1194/jlr.M074302. *(Paper is accompanied with an editorial Commentary by Paul Dawson and Kenneth Setchell)*
3. Leung SO, Gao K, Wang GY, Cheung BKW, Lee KY, Zhao Q, **Cheung WT**, Wang JZ. "Surrogate target cells expressing surface anti-idiotype antibody for the clinical evaluation of an internalizing CD22-specific antibody." ***MAbs,*** 2015; 7(1):66-76. doi: 10.4161/19420862.2014.985519.
4. Zhao Q, Wong PF, Lee SST, Leung SO, **Cheung WT**[*], Wang JZ[*]. "Generation of anti-idiotype scFv for pharmacokinetic measurement in lymphoma patients treated with chimera anti-CD22 antibody SM03." ***PLoS One***, 2014; 9(5):e96697. doi: 10.1371/journal.pone.0096697.
5. Jiang LL, Teng GMK, Chan EYM, Au SWN, Wise H, Lee SST, **Cheung WT**. "Impact of cell type and epitope tagging on heterologous expression of G protein-coupled receptor: a systematic study on angiotensin type II receptor." ***PLoS One***, 2012; 7(10):e47016. doi: 10.1371/journal.pone.0047016.

[#] Co-first author
[*] Corresponding author

Technical expertise

- ✧ Tissue organ bath pharmacology
- ✧ Phage-displayed Library
- ✧ Protein chemistry
- ✧ Protein engineering

Could cancer be an immune disease?

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Ovarian cancer is one of the devastating diseases as most of the patient (~60 %) are diagnosed at the advanced stage that cancer cells have already spread within the abdomen. Previously, using stable clones of Chinese hamster ovarian (CHO) cells that overexpressed GPCR MAS at different levels, our lab has established a mouse xenograft model of copy number variation (CNV)-mediated; GPCR MAS-driven epithelial ovarian cancer. RNA profiling indicated a high expression of GRO chemokines CXCL1 and CXCL3 in the transformed ovarian cells [*Int J Cancer* 125: 1316-1327 (2009)]. In search for the functional impacts of GRO chemokines on tumour formation, proteomic study indicated a specific expression of coactosin-like protein 1 (COTL1) in xenograft stroma. Consistent with previous reports that COTL1 enhanced leukotriene production, a complete leukotriene synthesis pathway was located in xenograft stroma by immunohistochemistry and qPCR. In addition to the GRO chemokine receptor CXCR2, leukotriene receptors were also detected abundantly in xenografts and neutrophils. Indeed, leukotriene LTB4, but not LTD4, triggered a chemotactic response in neutrophils. By contrast, leukotrienes did not exert any growth-promoting effects on the tumorigenic *Mas*-transformed ovarian cells (Mc0M80) nor cancer-associated fibroblasts (CAF). Of interest, cell growth of the tumorigenic Mc0M80 cells was significantly enhanced when the cells were co-cultured with neutrophils, but not with CAF. In agreement with the *in vitro* cell studies, co-injection of Mc0M80 cells and neutrophils marginally enhanced xenograft formation, and growth of xenografts was significantly suppressed by treatment with 5-lipoxygenase (5-LOX) inhibitor zileuton *in vivo*. These results suggested that cancer cell-derived GRO chemokines orchestrated the formation of a leukotriene signalling microenvironment that induced neutrophils infiltration. The recruitment of neutrophils in stroma promoted cancer cell growth, resulting in xenograft formation. Our work suggests stromal leukotriene-induced neutrophils infiltration plays critical role in tumour initiation and neutrophils would be a novel therapeutic target for cancers.

Session II (CBET)

Speaker Biography

Prof. CHEN Yangchao（陳揚超）is currently an Associate Professor at School of Biomedical Sciences, The Chinese University of Hong Kong (CUHK). He obtained his Ph.D. from Sun Yat-sen University in 2003 and later on was trained as a postdoctoral fellow at University of Washington, Seattle. He has been faculty member as Research Assistant Professor, Assistant Professor and Associate Professor at Faculty of Medicine CUHK since 2007. His research interests include epigenetics in cancer, histone modification particularly methylation, long and short non-coding RNAs, development of novel therapeutics for liver and pancreatic cancer. The ultimate goal of his lab is aimed at the identification of novel diagnostic markers and therapeutic targets for pancreatic and liver cancer.

Five recent representative publications

1. Li CH, Tang SC, Wong CH, Wang Y, Jiang JD, **Chen Y***. "Berberine induces miR-373 expression in hepatocytes to inactivate hepatic steatosis associated AKT-S6 kinase pathway." ***Eur J Pharmacol***, 2018; 825:107-118. doi: 10.1016/j.ejphar.2018.02.035.
2. Li CH, Xiao Z, Tong J, To KF, Fang X, Cheng ASL, **Chen Y***. "EZH2 coupled with HOTAIR to silence microRNA-34a by the induction of heterochromatin formation in human pancreatic ductal adenocarcinoma." ***Int J Cancer***, 2017; 140(1):120-129. doi: 10.1002/ijc.30414.
3. Xiao Z, Li CH, Chan SL, Xu F, Feng L, Wang Y, Jiang JD, Sung JJY, Cheng CHK, **Chen Y***. "A small-molecule modulator of the tumor-suppressor miR34a inhibits the growth of hepatocellular carcinoma." ***Cancer Res***, 2014; 74(21):6236-6247. doi: 10.1158/0008-5472.CAN-14-0855.
4. Li CH, Xu F, Chow SC, Feng L, Yin D, Ng TB, **Chen Y***. "Hepatitis B virus X protein promotes hepatocellular carcinoma transformation through interleukin-6 activation of microRNA-21 expression." ***Eur J Cancer***, 2014; 50(15):2560-2569. doi: 10.1016/j.ejca.2014.07.008.
5. Li CH, To KF, Tong JH, Xiao Z, Xia T, Lai PB, Chow SC, Zhu YX, Chan SL, Marquez VE, **Chen Y***. "Enhancer of zeste homolog 2 silences microRNA-218 in human pancreatic ductal adenocarcinoma cells by inducing formation of heterochromatin." ***Gastroenterology***, 2013; 144(5):1086-1097.e9. doi: 10.1053/j.gastro.2013.01.058.

* Corresponding author

Technical expertise

- ✧ Lentiviral vector mediated gene expression, RNAi and CRISPR/CAS9
- ✧ Long and short non-coding RNAs
- ✧ Large scale RNAi and CRISPR/CAS9 screening
- ✧ Functional Genomics and Proteomics

Identification of novel therapeutic targets for pancreatic cancer

CHEN Yangchao

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Pancreatic ductal adenocarcinoma (PDAC) exhibits a high mortality rate, and the overall survival has no improvement for over 30 years. The poor prognosis of PDAC is due to the rapid acquiring of chemoresistance to the first-line chemotherapeutic agent gemcitabine, and the lack of efficacious alternative therapeutic drugs. As such, our research team is eager to identify novel players including both protein-coding and non-code genes as the therapeutic targets against PDAC.

We have identified miR-218 as the tumor suppressor microRNA aberrantly suppressed by histone methyltransferase EZH2. Restoration of miR-218 and modulating the miR-218 regulating pathway were promising in inhibiting the development and progression of PDAC. We also found that miR-34a was regulated by EZH2 in PDAC cells and demonstrated that EZH2 suppressed miR-34a expression through trimethylation of H3K27 and heterochromatin formation. We further identified a small molecule modulator of miR-34a with strong anti-cancer efficacy *in vitro* and *in vivo* in animal models.

In addition, we explored the role of other non-coding RNAs as the therapeutic targets for PDAC. We recently showed that long non-coding RNA HOTTIP was remarkably overexpressed in PDAC cells, and HOTTIP could undergo both canonical and non-canonical pathways in PDAC cells that contributed to PDAC development. Furthermore, our team attempted to identify players associated with gemcitabine resistance. Through genome-wide RNAi screening, we identified LLGL1 protein that could sensitize PDAC cells to gemcitabine. We further showed that LLGL1 could be a promising biomarker for predicting PDAC patients' response to Gemcitabine treatment. Studies conducted by our team could provide critical players as potential therapeutic targets and promote the development of novel therapeutic treatments.

Session II (CBET)

Speaker Biography

Prof. SO Hon Cheong（蘇漢昌）received his Bachelor of Medicine and Bachelor of Surgery (MBBS) degree together with a PhD degree in 2012 from The University of Hong Kong (HKU). His PhD research focused on statistical and psychiatric genomics. He has received numerous awards for his academic achievement, including the Croucher Foundation Scholarship and the Dr. Stephen K.P. Chang Gold Medal for the best PhD thesis in the Faculty of Medicine, HKU. Prior to taking up the current academic post, he worked as a resident psychiatrist in Queen Mary Hospital and Castle Peak Hospital. He joined the School of Biomedical Sciences of The Chinese University of Hong Kong as an Assistant Professor in Jan 2016.

His main research interests include the development and application of novel statistical and computational methodologies to "omics" and clinical data in general. In particular, he is interested in uncovering the genetic architecture of complex diseases and predicting disease risk and phenotypes based on bioinformatics and clinical data. He has developed methodologies for evaluating the heritability explained by individual genetic variants and the entire set of markers on a genome-wide association study (GWAS) panel. He has also developed novel methods to combine genetic information with family history in improving risk prediction, as well as new ways to construct polygenic risk scores. He is one of the lead-authors in a schizophrenia GWAS in Chinese population, leading to discovery of a novel susceptibility loci on the X chromosome. His recent interest also includes bioinformatics approaches to repurposing drugs for new indications, and has developed several repurposing methodologies using GWAS and other "omics" data.

Five recent representative publications

1. **So HC**[*], Chau CK, Chiu WT, Ho KS, Lo CP, Yim SH, Sham PC. "Analysis of genome-wide association data highlights candidates for drug repositioning in psychiatry." ***Nat Neurosci***, 2017; 20(10):1342-1349. doi: 10.1038/nn.4618.
2. **So HC**[*], Sham PC[*]. "Exploring the predictive power of polygenic scores derived from genome-wide association studies: a study of 10 complex traits." ***Bioinformatics***, 2017; 33(6):886-892. doi: 10.1093/bioinformatics/btw745.
3. **So HC**[*], Sham PC[*]. "Improving polygenic risk prediction from summary statistics by an empirical Bayes approach." ***Sci Rep***, 2017; 7:41262. doi: 10.1038/srep41262.
4. Wong EH[#], **So HC**[#], Sham PC (2014). "Common variants on Xq28 conferring risk of schizophrenia in Han Chinese." ***Schizophr Bull***, 2014; 40(4):777-786. doi: 10.1093/schbul/sbt104.
5. **So HC**, Kwan JS, Cherny SS, Sham PC. "Risk prediction of complex diseases from family history and known susceptibility loci, with applications for cancer screening." ***Am J Hum Genet***, 2011; 88(5):548-565. doi: 10.1016/j.ajhg.2011.04.001.

[#] Co-first author

[*] Corresponding author

Technical expertise

- ✧ Bioinformatics and statistical genomics
- ✧ Neuropsychiatric genomics

Computational drug repositioning for psychiatric disorders

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[6] Centre for Genomic Sciences, The University of Hong Kong, Hong Kong SAR, P.R. China.

The time and cost for novel drug discovery is ever-increasing. Drug repositioning, i.e. using existing drugs for new therapeutic indications, represents a cost-effective approach to speed up drug development. With increased availability of large-scale "omics" data, computational methods will play an important role for prioritizing candidates suitable for repositioning. Here we will present an approach for repositioning by comparing imputed expression profiles from genome-wide association data and drug transcriptomes. We also propose another method based on the principles of gene-set analysis. In addition, we will present a framework to repositioning based on machine learning approaches including deep neural network. We focus our applications on psychiatric disorders since few repositioning studies were targeted towards these disorders. We found that the above methods successfully "re-discovered" known drugs for the studied diseases and revealed novel repositioning candidates that are supported by the literature.

Session III (DRB)

Speaker Biography

Prof. WANG Dan Michelle（王丹）completed her B.S and M.S in Dental Medicine from Sun Yat-Sen Medical University, her Ph.D in Oral Biology from the University of Pittsburgh as well as her postdoctoral training from the Department of Orthopaedic Surgery at Stanford University. She is a Research Assistant Professor at The Chinese University of Hong Kong with appointments in the School of Biomedical Sciences and the Institute for Tissue Engineering and Regenerative Medicine. Her research interests include cell-matrix interactions, stem cell biology, osteoimmunology, tissue engineering and regenerative medicine for bone-tendon and bone-ligament tissue unit repair.

Five recent representative publications

1. Ker DFE[#], **Wang D**[#], Behn AW, Wang ETH, Zhang X, Zhou BY, Mercado-Pagán AE, Kim S, Kleimeyer J, Gharaibeh B, Shanjani Y, Nelson D, Safran M, Cheung E, Campbell P, Yang YP. "Functionally graded, bone- and tendon-like polyurethane for rotator cuff repair." ***Advanced Functional Materials***. Accepted in March 2018.
2. **Wang D**, Gilbert JR, Taylor GM, Sodhi CP, Hackam DJ, Losee JE, Billiar TR, Cooper GM. "TLR4 inactivation in myeloid cells accelerates bone healing of a calvarial defect model in mice." ***Plast Reconstr Surg***, 2017; 140(2):296e-306e. doi: 10.1097/PRS.0000000000003541.
3. **Wang D**, Taylor GM, Gilbert JR, Sodhi CP, Hackam DJ, Losee JE, Billiar TR, Cooper GM. "Enhanced calvarial bone healing in CD-11c-TLR4$^{-/-}$ and Myd88$^{-/-}$ mice." ***Plast Reconstr Surg***, 2017; 139(4):933e-940e. doi: 10.1097/PRS.0000000000003206.
4. **Wang D**, Gilbert JR, Cray JJ Jr, Kubala A, Shaw MA, Billiar TR, Cooper GM. "Toll-like receptor 4 mediates the regenerative effects of bone grafts for calvarial bone repair." ***Tissue Eng Part A***, 2015; 21(7-8):1299-1308. doi: 10.1089/ten.TEA.2014.0215.
5. **Wang D**, Gilbert JR, Cray JJ Jr, Kubala A, Shaw MA, Billiar TR, Cooper GM. "Accelerated calvarial healing in mice lacking Toll-like receptor 4." ***PLoS One***, 2012; 7(10):e46945. doi: 10.1371/journal.pone.0046945.

[#] Co-first author

Technical expertise

- ✧ Musculoskeletal tissue engineering
- ✧ Osteoimmunology

Bone graft revitalization via inflammatory modulation for enhanced bone repair

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[4] Department of Surgery, University of Pittsburgh, Pittsburgh, PA, USA.

Inflammation, an integral component of the injury response, is involved not only in the host defense against infectious pathogens but also in tissue repair and regeneration, dynamically balancing its tissue-destructive and tissue-constructive properties. For decades, osteoimmunology has mostly focused on investigating osteoclasts and metabolic bone disease as they relate to pathologic bone resorption. Recently, interest has increased in elucidating the positive interactions between the immune and skeletal systems during the fracture healing process. To treat large bone defects in clinical practice, structural allografts are the most common alternatives to bone autografts. Despite the high clinical use of allografts, their inferior bone healing performance due to limited remodeling and revascularization poses a significant concern. As such, our research is focusing on exploring potential approaches by manipulating the local immune environment to achieve a robust allograft remodeling and revascularization for enhanced fracture repair.

Session III (DRB)

Speaker Biography

Prof. BLOCKI Anna graduated with a BSc degree in Molecular Biology from the University of Applied Sciences of Gelsenkirchen, Germany, in the top 5% of her cohort in 2008. Subsequently she joined the group of Prof. Michael Raghunath within the Department of Bioengineering (now Department of Biomedical Engineering) to pursue her PhD studies on "Peripheral blood: a simple cell source for the generation of angiogenic progenitors from monocytes". Prof. Blocki was able to secure a PhD scholarship from the Graduate Program in Bioengineering (GPBE) and was later admitted to the top-tier PhD programme, the NUS Graduate School for Integrative Sciences and Engineering (NGS). Her work on Blood Derived Angiogenic Cells (BDACs) allowed her to formulate the hypothesis of more than one origin of pericytes, which she followed up during her later research. Her focus on regenerative cell types and extracellular matrix (ECM) engineering inspired her also to investigate the therapeutic potential of the developed technologies in preclinical studies. This was realized during her first postdoctoral appointment at the Singapore Bioimaging Consortium (SBIC) at the Agency for Science Technology and Research (A*STAR) from December 2012 to April 2015. Following that, Prof. Blocki was able to secure a competitive postdoctoral fellowship from the Charité Universitätsklinikum Berlin that allowed her to work towards ECM-mimicking biomaterials and their potential clinical application. Since February 2018 she has joined the Institute for Tissue Engineering and Regenerative Medicine and the School of Biomedical Sciences as an Assistant Professor.

Five recent representative publications

1. **Blocki A**, Wang Y, Koch M, Goralczyk A, Beyer S, Agarwal N, Lee M, Moonshi S, Dewavrin JY, Peh P, Schwarz H, Bhakoo K, Raghunath M. "Sourcing of an Alternative Pericyte-Like Cell Type from Peripheral Blood in Clinically Relevant Numbers for Therapeutic Angiogenic Applications." ***Molecular Therapy***, 2015; 23(3):510-522.
2. **Blocki A**, Wang Y, Koch M, Peh P, Beyer S, Law P, Hui J, Raghunath M. "Not all MSCs can act as pericytes: functional *in vitro* assays to distinguish pericytes from other mesenchymal stem cells in angiogenesis." ***Stem Cells Dev***, 2013; 22(17):2347-2355.
3. **Blocki A**, Beyer S, Dewavrin JY, Goralczyk A, Wang Y, Peh P, Ng M, Moonshi SS, Vuddagiri S, Raghunath M, Martinez EC, Bhakoo KK. "Microcapsules engineered to support mesenchymal stem cell (MSC) survival and proliferation enable long-term retention of MSCs in infarcted myocardium." ***Biomaterials***, 2015; 53:12-24.
4. **Blocki A**, Löper F, Chirico N, Neffe AT, Jung F, Stamm C, Lendlein A. "Engineering of cell-laden gelatin-based microgels for cell delivery and immobilization in regenerative therapies." ***Clin Hemorheol Microcirc***, 2017; 67(3-4):251-259.
5. **Blocki A**, Löwenberg C, Jiang Y, Kratz K, Neffe AT, Jung F, Lendlein A. "Response of encapsulated cells to a gelatin matrix with varied bulk and microenvironmental elastic properties." ***Polymers for Advanced Technologies***, 2016; 28(10), doi: 10.1002/pat.3947.

Technical expertise

- ✧ Engineering of bio-instructive biomaterials to guide regeneration processes
- ✧ Deciphering of the extracellular matrix
- ✧ Blood-derived angiogenic cells (BDACs), their pericytic identity and their potential for clinical application

The controversial origin of pericytes - implications for cell-based therapies

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[*] Shared corresponding authorship

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[2] School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

[3] Institute for Clinical Hemostasiology and Transfusion Medicine, University Saarland, Homburg/ Saar, Germany.

[4] Institute of Chemistry and Biotechnology, Zurich University of Applied Sciences, Wädenswil, Switzerland.

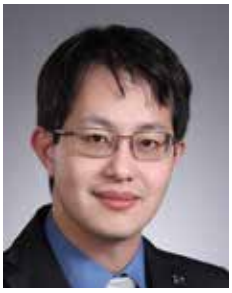
Pericytes wrap around endothelial cells in small blood vessels and are indispensable for proper vessel function. A couple of years ago pericytes have been identified to be mesenchymal stem cells. Mesenchymal stem cells, and especially their specialized subpopulation of pericytes, represent promising candidates for therapeutic angiogenesis applications, and have already been widely applied in pre-clinical and clinical trials. However, cell-based therapies of ischemic diseases have not resulted in significant long-term improvement. Interestingly, just recently pericytes from a hematopoietic origin were observed in embryonic skin. Additionally, a pericyte sub-population expressing leukocyte and monocyte markers was described during adult angiogenesis *in vivo*. Since mesenchymal stem cells do not express hematopoietic markers by definition, the latter cell type might represent an alternative hematopoietic pericyte population relevant to angiogenesis.

We therefore sourced blood-derived angiogenic cells (BDACs) from monocytes that closely resembled hematopoietic pericytes *in vitro*, which had only been observed *in vivo* thus far. BDACs displayed many pericytic features such as pericyte markers PDGFR and NG2, while expressing leukocyte markers CD45 and monocyte markers CD11b. At the same time, they lacked properties inherent to monocytes and macrophages such as the ability to phagocytose or the ability to be polarized. They also enhanced angiogenesis *in vitro* and *in vivo* and enhanced revascularization and functional tissue regeneration in a pre-clinical model of critical limb ischemia. Comparison between BDACs and mesenchymal pericytes in functional *in vitro* assays revealed that in direct co-culture BDACs enhanced, while mesenchymal pericytes impaired endothelial sprouting. In contrast only mesenchymal pericytes consistently stabilized endothelial tubular networks.

We therefore concluded that BDACs (while resembling hematopoietic pericytes) enhanced early stages of angiogenesis, while mesenchymal pericytes were responsible for blood vessel maturation and homeostasis. Since the formation of new blood vessels is crucial during therapeutic angiogenesis or during integration of implants into the host tissue, hematopoietic pericytes (and therefore BDACs) might offer an advantageous addition or even an alternative for cell-based therapies.

Session III (DRB)

Speaker Biography



Prof. KER Dai Fei Elmer（柯岱飞）completed his Ph.D. in Biological Sciences from Carnegie Mellon University and postdoctoral training from Department of Orthopaedic Surgery at Stanford University. He is an Assistant Professor at The Chinese University of Hong Kong with appointments in the School of Biomedical Sciences and the Institute for Tissue Engineering and Regenerative Medicine. His research interests include developing biomaterials and computer vision-based approaches for repairing injured bone-tendon and bone-ligament tissue units. His lab webpage is https://ker-lab.weebly.com/.

Five recent representative publications

1. **Ker DFE**, Chu B, Phillippi JA, Gharaibeh B, Huard J, Weiss LE, Campbell PG. "Engineering spatial control of multiple differentiation fates within a stem cell population." ***Biomaterials***, 2011; 32(13):3413-3422. doi: 10.1016/j.biomaterials.2011.01.036.
2. **Ker DFE**, Nain A, Weiss LE, Wang J, Suhan J, Amon C, Campbell PG. "Bioprinting of growth factors onto aligned sub-micron fibrous scaffolds for simultaneous control of cell differentiation and alignment." ***Biomaterials,*** 2011; 32(32):8097-8107. doi: 10.1016/j.biomaterials.2011.07.025.
3. **Ker DFE**, Weiss LE, Junkers SN, Chen M, Yin Z, Sandboth MF, Huh S, Eom S, Bise R, Osuna-Highley E, Kanade T, Campbell PG. "An engineered approach to stem cell culture: automating the decision process for real-time adaptive subculture of stem cells." ***PLoS One***, 2011; 6(11):e27672. doi: 10.1371/journal.pone.0027672.
4. Yin Z, Su H, **Ker DFE**, Li M, Li H. "Cell-sensitive phase contrast microscopy imaging by multiple exposures." ***Med Image Anal***, 2015; 25(1):111-121. doi: 10.1016/j.media.2015.04.011.
5. **Ker DFE**[#*], Wang D[#], Behn AW, Wang ETH, Zhang X, Zhou BY, Mercado-Pagan AE, Kim S, Kleimeyer J, Gharaibeh B, Shanjani Y, Nelson D, Safran M, Cheung E, Campbell P, Yang YP. "Functionally-Graded, Bone- and Tendon-Like Polyurethane for Rotator Cuff Repair." ***Advanced Functional Materials***, 2018; (accepted).

[#] Co-first author

[*] Co-corresponding author

Technical expertise

- ✧ Musculoskeletal tissue engineering
- ✧ Computer-aided tracking of cells

Growth factor bioprinting and computer vision-based cell tracking for musculoskeletal tissue engineering

KER Dai Fei Elmer[1,2], **WANG Dan**[1,2], **NAIN Amrinder**[3], **YANG Peter Yunzhi**[4,5,6], **WEISS Lee**[7,8], **CAMPBELL Phil**[8]

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[4] Department of Orthopaedic Surgery, Stanford University, California, USA.
[5] Department of Materials Science and Engineering, Stanford University, California, USA.
[6] Department of Bioengineering, Stanford University, California, USA.
[7] Robotics Institute, Carnegie Mellon University, Pittsburgh, USA.
[8] Engineering Research Accelerator, Carnegie Mellon University, Pittsburgh, USA.

Musculoskeletal diseases and trauma cost an estimated US $950 billion annually world-wide. In this study, inkjet-based growth factor bio-printing and computer vision-based cell tracking were used to study the effect of bioprinting musculoskeletal growth factors on musculoskeletal differentiation and facilitate stem cell expansion. Growth factor screening assays identified Fibroblast Growth Factor-2 (FGF-2) as a candidate tendon-promoting cue capable of increasing the tendon/ligament marker Scleraxis (SCX) in a variety of musculoskeletal progenitor cell lines and muscle-derived stem cells. Subsequent gene expression studies showed that FGF-2 increased *scx* expression in a manner similar to chick embryonic tendon development. Bio-printing of multiple musculoskeletal growth factors resulted in spatial control of bone-, tendon- and muscle-like cell differentiation on various biomaterials, engineering a primitive 'muscle-tendon-bone' unit. Computer vision-based cell tracking identified differences in cell morphologies with different growth factor treatment and could be used to perform real-time expansion of C2C12 myoblast cells. In summary, inkjet-based growth factor bioprinting and computer vision-based cell tracking hold promise to engineer and study complex tissues.

Session IV (DRB)

Speaker Biography

Prof. SULLIVAN Gareth is a group leader within the Norwegian Center for Stem Cell Research and Vice Director of the Hybrid Technology Hub - Centre of Excellence in Oslo (http://www.med.uio.no/hth/english/). He holds a PhD in molecular cell biology from the University of Dundee, Scotland and performed his post-doctoral research at the Centre of Regenerative Medicine, University of Edinburgh with Sir Prof. Ian Wilmut. In addition he has over 8 years industrial experience, as a CSO, working in both the toxicology and next generation sequencing fields. At the end of 2011 he established his own research group at the University of Oslo and Oslo University Hospital. Where his research focus turned to what dictates cellular fate decision, along with the utilization of induced pluripotent stem cells to study disease in the dish. The overall focus of the lab now is the development of faithful liver models using human pluripotent stem cells to allow the dissection of both debilitating metabolic pediatric diseases and infectious diseases. In addition to provide tools to investigate toxicology, reduce drug failure rates and enable regenerative medicine. The Sullivan group was first to demonstrate the generation of functional hepatocyte like cells from human iPSCs derived from different ethnic backgrounds (*Hepatology* 2010). This has led to the establishment of the first small molecule driven hepatocyte differentiation procedure (*Stem Cell Reports*, 2015) and is presently being translated to large-scale 3D liver organoid production, ultimately to provide a more physiological model.

Five recent representative publications

1. Siller R, **Sullivan GJ**. "Rapid Screening of the Endodermal Differentiation Potential of Human Pluripotent Stem Cells." ***Curr Protoc Stem Cell Biol***, 2017; 43:1G.7.1-1G.7.23. doi: 10.1002/cpsc.36.
2. Mathapati S, Siller R, Impellizzeri AR, Lycke M, Vegheim K, Almass R, **Sullivan GJ**. "Small-Molecule-Directed Hepatocyte-Like Cell Differentiation of Human Pluripotent Stem Cells." ***Curr Protoc Stem Cell Biol***, 2016; 38:1G.6.1-1G.6.18. doi: 10.1002/cpsc.13.
3. Siller R, Greenhough S, Naumovska E, **Sullivan GJ**. "Small-molecule-driven hepatocyte differentiation of human pluripotent stem cells." ***Stem Cell Reports***, 2015; 4(5):939-952. doi: 10.1016/j.stemcr.2015.04.001.
4. Siller R, Greenhough S, Park IH, **Sullivan GJ**. "Modelling human disease with pluripotent stem cells." ***Current Gene Therapy***, 2013; 13(2):99-110. doi:10.2174/1566523211313020004.
5. **Sullivan GJ**, Hay DC, Park IH, Fletcher J, Hannoun Z, Payne CM, Dalgetty D, Black JR, Ross JA, Samuel K, Wang G, Daley GQ, Lee JH, Church GM, Forbes SJ, Iredale JP, Wilmut I. "Generation of functional human hepatic endoderm from human induced pluripotent stem cells." ***Hepatology***, 2010; 51(1):329-335. doi: 10.1002/hep.23335.

Technical expertise

- ✧ Human pluripotent stem cells, cell biology, molecular biology, stem cell differentiation, genome editing (CRISPR), reprogramming, transcription, enhancer biology, disease modeling, biomaterial and nanomaterials.

Enhanced functional longevity of hiPSC derived hepatocyte-like cells in 3D suspension culture

SULLIVAN Gareth

Norwegian Center for Stem Cell Research and Vice Director of the Hybrid Technology Hub - Centre of Excellence in Oslo, Norway.

Acute liver failure is a debilitating syndrome, which is reflected in its high mortality rate of 60-80%. Throughout Europe there are more than 50,000 cases of sudden liver failure annually, where the only option for these patients is liver transplantation. However, there is a dearth of donors and this is reflected with only 20% of patients receiving a transplant. This is the main reason for the observed high mortality rates. Therefore alternative strategies to reduce this burden are required and one such approach would be access to suitable bio-artificial liver (BAL) devices. BALs could potentially allow liver recovery by providing a stop-gap between disease onset and identification of suitable donor, thus saving lives. Clinical trials by a few groups using developmental BALs have produced encouraging improvement with respect to patient neurological and biochemical status. But, in all cases have not demonstrated significant survival benefits, this in part is due to the cell types used, coupled with instability and low functionality. In order to develop an effective BAL, there are a number of key requirements; access to stable, highly functional hepatocyte equivalents, that mimic normal liver function long term.

As stated a major roadblock is the identification of a suitable surrogate cell type, we have chosen to utilise human pluripotent stem cell (hPSC) derived hepatocytes (iHEPs) to address this challenge, as hPSCs offer a potentially limitless supply of genetically defined material. There are numerous protocols available to derive iHEPs, with many claiming to be scalable. However the cell numbers required for a functional BAL is in the order of 10^{10} to 10^{11} cells, this is simply not achievable with conventional growth factor based methods, as the physical cost implications will be in the millions of USD. To address these shortcomings we have developed a small molecule driven protocol that massively reduces the financial burden of iHEP production. However, we still encountered the issue of long-term maintenance of these cells in conventional 2D culture. Therefore we further developed our small molecule approach to address this and translated our findings to produce 3D liver organoids. The derived organoids have the functional attributes of liver tissue, and can be generated in the numbers required for a BAL device (10^{10} to 10^{11} cells). More importantly we have massively reduced the cost, allowing the production of clinically relevant numbers of cells for the first time. In addition this cell source can provide functional, physiologically relevant cells for many other downstream applications including: drug discovery, drug interaction studies, disease / infectious disease modelling, as well as integration into multi-organ chip formats and toxicology.

Session IV (DRB)

Speaker Biography

Prof. FOK Kin Lam Ellis（霍建霖）obtained his Ph.D. in physiology from the School of Biomedical Sciences (SBS), The Chinese University of Hong Kong in 2009. He continued his research after graduation and then moved to the Department of Medicine, McGill University in Canada as Post-doc Fellow in 2012. He joined SBS as a Research Assistant Professor in 2015, and he became an Assistant Professor in 2017.

Dr. Fok's research mainly focuses on male reproduction and germline stem cell biology. His previous researches have uncovered the functions of a number of genes in spermatogenesis. He has also studied the sperm maturation process in detail and uncovered the dual role of a small peptide human β-defensin 1 in regulating the motility and bactericidal activity of sperm. During his training at McGill University, Dr. Fok has also looked into the biology of spermatogonial stem cells and revealed the involvement of a ubiquitin ligase in regulating the establishment and maintenance of spermatogonial stem cells. Over the years, Dr. Fok has published over 30 peer-review articles in decent journals including *Science Translational Medicine* and *Cell Research*. Dr. Fok has served as an invited reviewer for international journals and a grant reviewer for overseas funding bodies. He is also the review editor for the *Frontiers* journals.

Five recent representative publications

1. Li X[#], **Fok KL**[#], Guo J, Wang Y, Liu Z, Chen Z, Ruan YC, Yu SS, Zhao H, Jiang X, Chan HC. "Retinoic acid promotes stem cell differentiation and embryonic development by transcriptionally activating CFTR." ***Biochim Biophys Acta (Molecular Cell Research)***, 2018; 1865(4):605-615. doi: 10.1016/j.bbamcr.2018.01.005.
2. **Fok KL**[#], Bose R[#], Sheng K, Chang CW, Katz-Egorov M, Culty M, Su S, Yang M, Ruan YC, Chan HC, Iavarone A, Lasorella A, Cencic R, Pelletier J, Nagano M, Xu W, Wing SS. "Huwe1 regulates the establishment and maintenance of spermatogonia by suppressing DNA damage response." ***Endocrinology***, 2017; 158(11):4000-4016. doi: 10.1210/en.2017-00396.
3. Bose R, Sheng K, Moawad AR, Manku G, O'Flaherty C, Taketo T, Culty M, **Fok KL**, Wing SS. "Ubiquitin ligase Huwe1 modulates spermatogenesis by regulating spermatogonial differentiation and entry into meiosis." ***Sci Rep***, 2017; 7(1):17759. doi: 10.1038/s41598-017-17902-0.
4. Diao R[#], Wang T[#], **Fok KL**[#], Li X, Ruan YC, Yu MK, Cheng Y, Chen Y, Chen H, Mou L, Cai X, Wang Y, Cai Z, Zeng X, Chan HC. "CCR6 is required for ligand-induced CatSper activation and functions in human sperm." ***Oncotarget***, 2017; 8(53):91445-91458. doi: 10.18632/oncotarget.20651.
5. Diao R[#], **Fok KL**[#], Chen H, Yu MK, Duan Y, Chung CM, Li Z, Wu H, Li Z, Zhang H, Ji Z, Zhen W, Ng CF, Gui Y, Cai Z, Chan HC. "Deficient human β-defensin 1 underlies male infertility associated with poor sperm motility and genital tract infection." ***Sci Transl Med***, 2014; 6(249):249ra108. doi: 10.1126/scitranslmed.3009071.

[#] Co-first authors with equal contributions

Technical expertise

- ✧ Genetic engineering: CRISPR/Cas9, lentiviral gene delivery, mutagenesis
- ✧ Cell biology: spermatogonial stem cell culture, sperm analysis, flow cytometry
- ✧ Animal model: germ cell transplantation, conditional knock-out mice

Approaches for restoring male fertility by targeting spermatogonia and sperm

FOK Ellis[1], **CHEN Ziyi**[1], **CHEN Hao**[2]

[1] School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

[2] Institute of Biomedical and Pharmaceutical Sciences, Guangdong University of Technology, P.R. China.

Infertility affects 15% couples worldwide and male factor contributes to half of these cases. Male infertility thus affects roughly 30 million men around the globe, resulting in important social, psychological and financial impacts in family health and social planning. Male infertility is multi-faceted. While known causes such as maldescended testis and varicoceles contribute to ~40% of the infertile cases, approximately 30% of these cases are idiopathic that may attribute to defects in spermatogenesis, sperm maturation and/or sperm functions. Hitherto, the first-line regimens for male infertility of unknown causes are the assisted reproductive technologies (ART) including intrauterine insemination (IUI), conventional *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI). Although these procedures can bypass some fertility defects, the success rate of IUI remains low and ICSI may be associated with increased risk of congenital abnormalities in the offspring. Other emerging regimens include the transplantation of spermatogonial stem cells and the production of male gamete *in vitro*. Nonetheless, the low isolation and transplantation efficiency, and the low differentiation efficiency *in vitro* remain the major hurdle for these methods. In today's seminar, we will discuss two projects that explore the possibility of restoring male fertility by targeting spermatogonia and sperm. The first one uncovered the involvement of CD147 in defective acrosome reaction of asthenozoospermia, which shed light on a method to the improvement of fertilization rate in IVF. The second one revealed the role of connective tissue growth factor in spermatogonial migration, which may implicates in enhancing the efficiency of spermatogonial stem cell transplantation.

Session IV (DRB)

Speaker Biography

Prof. CHAN Hon Fai（陳漢輝） received his B.Eng. (Medical Engineering) in 2010 from The University of Hong Kong. He then pursued his M.S. and Ph.D. degree in Biomedical Engineering at Duke University under the support of Sir Edward Youde Memorial Fellowships for Overseas Studies. During his Ph.D. research, he developed a microfluidic platform to produce uniform-sized multicellular spheroids for controlling mesenchymal stem cell differentiation. He also investigated the effect of extracellular matrix on stem cell differentiation and hepatocyte behavior. To address the issue of poor mechanical property of hydrogel used in biomedical application, Hon Fai developed a tough hydrogel which can be 3D printed into different human body shapes for tissue repair.

After graduation in 2015, Hon Fai spent one year at Columbia University as a postdoctoral researcher. He performed high-throughput screening of synthetic genes for optimization of protein expression using microfluidic droplets. He joined Massachusetts Institute of Technology as a postdoctoral associate in 2016 where he developed biologically inspired folded hydrogel to recapitulate mucosal folding observed in many hollow or tubular organs in human body. In 2018, Hon Fai is appointed as an Assistant Professor at the Institute for Tissue Engineering and Regenerative Medicine and School of Biomedical Sciences at The Chinese University of Hong Kong.

Five recent representative publications

1. **Chan HF**, Ma S, Tian J, Leong KW. "High-throughput screening of microchip-synthesized genes in programmable double-emulsion droplets." ***Nanoscale***, 2017; 9(10):3485-3495. doi: 10.1039/c6nr08224f.
2. **Chan HF**, Zhang Y, Leong KW. "Efficient one-step production of microencapsulated hepatocyte spheroids with enhanced functions." ***Small***, 2016; 12(20):2720-2730. doi: 10.1002/smll.201502932.
3. Hong S[#], Sycks D[#], **Chan HF**[#], Lin S, Lopez GP, Guilak F, Leong KW, Zhao X. "3D printing of highly stretchable and tough hydrogels into complex, cellularized structures." ***Adv Mater***, 2015; 27(27):4035-4040. doi: 10.1002/adma.201501099.
4. Cao C, **Chan HF**, Zang J, Leong KW, Zhao X. "Harnessing localized ridges for high-aspect-ratio hierarchical patterns with dynamic tunability and multifunctionality." ***Adv Mater***, 2014; 26(11):1763-1770. doi: 10.1002/adma.201304589.
5. **Chan HF**, Zhang Y, Ho YP, Chiu YL, Jung Y, Leong KW. "Rapid formation of multicellular spheroids in double-emulsion droplets with controllable microenvironment." ***Sci Rep***, 2013; 3:3462. doi: 10.1038/srep03462.

[#] Co-first author

Technical expertise

- ✧ Tissue engineering
- ✧ Biomaterials
- ✧ Microfluidics

Development-inspired engineering of artificial folded mucosa

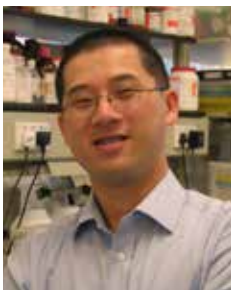
CHAN Hon Fai[1,2,3,4], ZHAO Ruike[3], PARADA German[5], MENG Hu[1,2], LEONG Kam[6], GRIFFITH Linda[3,4], ZHAO Xuanhe[3,7]

[1] Institute for Tissue Engineering and Regenerative Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.
[2] School of Biomedical Sciences, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.
[3] Department of Mechanical Engineering, Massachusetts Institute of Technology, Cambridge, USA.
[4] Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, USA.
[5] Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, USA.
[6] Department of Biomedical Engineering, Columbia University, New York, USA.
[7] Department of Civil and Environmental Engineering, Massachusetts Institute of Technology, Cambridge, USA.

The surfaces of many hollow or tubular tissues/organs in our respiratory, gastrointestinal, and urogenital tracts are covered by mucosae with folded patterns. The patterns are characterized into uniaxial and biaxial folds, and induced by mechanical instability of the mucosa under compression due to constrained growth during development. Changes in these patterns have been associated with diseases such as asthma. Recapitulating this folding process *in vitro* will facilitate the understanding and engineering of mucosa in various tissues/organs. However, scant attention has been paid to address the challenge of reproducing mucosal folding. Here we mimic the mucosal folding process using a cell-laden hydrogel film attached to a pre-stretched tough-hydrogel substrate. The cell-laden hydrogel constitutes of human epithelial cell lining on stromal component to recapitulate the physiological feature of mucosa. Relaxation of the pre-stretched tough-hydrogel substrate applies compressive strains on the cell-laden hydrogel film, which undergoes mechanical instability and evolves into uniaxial and biaxial morphological patterns. We predict the conditions for mucosal folding as well as the morphology of and strain in the folded artificial mucosa using a combination of theory and simulation, and the results are verified by cell culture experiments. We further demonstrate the function of the folded mucosa by analyzing cell deformation in response to the stretching of substrate, resembling the expansion of luminal diameter of organ/tissue such as stomach or bladder. Our results show that unfolding of the folded mucosa can accommodate the high stretch generated from the substrate compared with the stretching of flat mucosa, the former of which displays less severe nuclei deformation and preserves cell membrane integrity. This illustrates the important role played by mucosal folding. The work not only provides a simple method to fold artificial mucosa but also demonstrates a new paradigm in tissue engineering via harnessing mechanical instabilities of cell-laden scaffolds.

Session V (NVMB)

Speaker Biography



Prof. CHANG Chuen Chung Raymond（鄭傳忠）is the Lab Chief for the Laboratory of Neurodegenerative Diseases in the School of Biomedical Sciences, LKS Faculty of Medicine, member in The State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong. Dr. Chang is the organizer and Secretary of HKU Alzheimer's Disease Research Network. He organizes International Alzheimer's Disease Conference every year since 2000. This conference is now co-organized by 8 universities and Hong Kong Science Park. Dr. Chang's research interest is on four directions. (1) Pathophysiological changes of Alzheimer's disease (AD); (2) how different risk factors (post-operative cognitive dysfunctions, periodontitis, depression, cigarette smoking, air pollutants) stimulate systemic inflammation to affect neuroimmune responses leading to AD; (3) spreading of neurodegeneration in Parkinson's disease dementia; and (4) neurodegeneration of the retina and deterioration of visual functions in Alzheimer's disease. He has published over 132 peer-reviewed papers, 14 book chapters and edited 3 books in these areas. His *h*-index is 39 by Scopus. Dr. Chang is the Chief Editor for "American Journal of Alzheimer's Disease and Other Dementias", Senior Editor for "Journal of Neuroimmune Pharmacology", Associate handling Editor for "Journal of Alzheimer's Disease", "Frontiers in Neurology", "Frontiers in Neurosciences" and "Frontiers in Psychiatry". He is in the Scientific Advisory Board of International AD/PD Symposium, and Scientific Review Committee in Alzheimer Association. He is the member of editorial board of more than 20 different journals, and grant reviewer for different grant agencies/Foundations.

Five recent representative publications

1. Hung CHL, Cheng SSY, Cheung YT, Wuwongse S, Zhang NQ, Ho YS, Lee SMY, **Chang RCC**[*]. "A reciprocal relationship between reactive oxygen species and mitochondrial dynamics in neurodegeneration." ***Redox Biol***, 2018; 14:7-19. doi: 10.1016/j.redox.2017.08.010.
2. Liu AKL, Hurry MED, Ng OTW, DeFelice J, Lai HM, Pearce RKB, Wong GTC, **Chang RCC**[*], Gentleman SM[*]. "Bringing CLARITY to human brain: visualization of Lewy pathology in three-dimensions." ***Neuropathol Appl Neurobiol***, 2016; 42:573-587. Doi: 10.1111/nan.12293.
3. Poon DCH, Ho YS, You R, Tse J, Chu K, **Chang RCC**[*]. "PKR deficiency alters E. coli-induced sickness behaviors but does not exacerbate neuroimmune responses or bacterial load." ***J Neuroinflamm***, 2015; 12:212. Doi: 10.1186/s12974-015-0433-2.
4. Poon CH, Ho YS, Chiu K, Wong HL, **Chang RCC**[*]. "Sickness: From the focus on cytokines, prostaglandins, and complement factors to the perspectives of neurons." ***Neurosci Biobehav Rev***, 2015; 57:30-45. doi: 10.1016/j.neubiorev.2015.07.015.
5. **Chang RCC**[*], Ho YS[*], Wong S, Gentleman SM, Ng HK. "Neuropathology of cigarette smoking." ***Acta Neuropathol***, 2014; 127(1):53-69. doi: 10.1007/s00401-013-1210-x.

[*] Corresponding author

Technical expertise

- ✧ Alzheimer's disease
- ✧ Parkinson's disease
- ✧ Glaucoma
- ✧ Neurodegeneration
- ✧ Neuroimmunology
- ✧ Dementia

Pathophysiological mechanisms of risk factors leading to development of Alzheimer's disease

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[1] Laboratory of Neurodegenerative Diseases, School of Biomedical Sciences, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, P.R. China.

[2] State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong SAR, P.R. China.

Alzheimer's disease (AD) is an-aging-associated neurodegenerative disease. Epidemiological studies have revealed numerous risk factors leading to the development of AD. Accumulative evidence have shown that development of AD can be multi-hit processes by our own life style, diet, and living environment. It has been predicted that an increase of AD pathological factors may start 30 years before clinical symptoms of cognitive impairment. Therefore, it is important to understand the mechanisms of all these risk factors to find out any common pathway. The aim of our study is to elucidate the biological mechanisms of risk factors such as post-operative cognitive dysfunctions, periodontitis, environmental pollutants, depression, cigarette smoking leads to cognitive impairment and even to AD.

We elucidate a convergent pathway from different risk factors. We hypothesize that systemic inflammation/immune response is the key pathway conveying immune responses to the brain to initiate neuroimmune responses. This can then stimulate activation of microglia and astrocytes to sustain neuroimmune responses in the brain. Consequently, neuroimmune responses induce Alzheimer pathology (production of β-amyloid peptide and tau phosphorylation) and degeneration of synapses. Taking post-operative cognitive dysfunctions (POCD) as example, we have employed an experimental model of laparotomy in young and aged mice to investigate systemic inflammation. Concomitantly, activation of microglia, expression of cytokines and phosphorylation of tau were found even two weeks after laparotomy. We could even find cognitive impairment by Y-maze and novel object recognition tests. To prove our hypothesis, we fed the mice with non-steroid anti-inflammatory drug ibuprofen. As a result, all the above neuroimmune responses, tau phosphorylation and cognitive impairment were reverted back to normal.

Taken together, systemic inflammation/immune response perhaps is the convergent pathway conveying messages of the healthiness of the body to the brain. Consequently, this can affect progression of neurodegeneration or deposit the seed of Alzheimer pathology to the brain. This explains how POCD and even periodontitis can be risk factors for developing AD.

Acknowledgement: The study is partly supported by GRF17123217.

Session V (NVMB)

Speaker Biography

Prof. PONOMAREV Eugene（龐佑信）is currently appointed to the School of Biomedical Sciences, The Chinese University of Hong Kong, and his research interest is related to the immunological aspects of inflammation in the central nervous system (CNS) associated with neurodegenerative disease such as multiple sclerosis and Alzheimer's disease. Particularly he is interested in (1) epigenetic and transcriptional control of microglia/macrophage activation and polarization during CNS inflammation and (2) the role of platelets in the initiation of neuroinflammation. Both directions of his research program are currently supported by RGC and HMRF grants. Dr. Ponomarev is well known scientist in field of neuroinflammation and neurodegeneration and he is an author of more than 30 publications in top academic journals such as *Nature Medicine*, *Journal of Immunology*, *Journal of Neuroscience* and *Circulation Research*. Dr. Ponomarev serves in the editorial boards of number of International academic journals such as *Journal of Immunology, Journal of Neuroscience, Journal of Clinical Immunology, Annals of Neurology, Journal of Neuroinflammation, PLoS One, EMBO Reports* etc. Before his relocation to Hong Kong, Eugene Ponomarev spent 12 years in the USA working as a scientist in top academic institutions such as Brigham and Women's Hospital, Harvard Medical School (Boston MA) where he held the position of Assistant Professor and his work was supported by RO1 grant form National Institute of Health.

Five recent representative publications

1. Veremeyko T, Yung AWY, Dukhinova M, Kuznetsova IS, Pomytkin I, Lyundup A, Strekalova T, Barteneva N, **Ponomarev ED**. "Cyclic AMP pathway suppress autoimmune neuroinflammation by inhibiting functions of encephalitogenic CD4 T cells and enhancing M2 macrophage polarization at the site of inflammation." ***Front Immunol***, 2018; 9:50. doi: 10.3389/fimmu.2018.00050.
2. **Ponomarev ED**. "Fresh evidence for platelets as neuronal and innate immune cells: their role in the activation, differentiation and deactivation of Th1, Th17 and Tregs during tissue inflammation." ***Frontiers in Immunology***, 2018; doi: 10.3389/fimmu.2018.00406.
3. Starossom SC, Veremeyko T, Dukhinova M, Yung AWY, Weiner HL, **Ponomarev ED**. "Platelets play differential role during the initiation and progression of autoimmune neuroinflammation." ***Circ Res***, 2015; 117(9):779-792. doi: 10.1161/CIRCRESAHA.115.306847.
4. Veremeyko T, Siddiqui S, Sotnikov I, Yung A, **Ponomarev ED**. "IL-4/IL-13-dependent and independent expression of miR-124 and its contribution to M2 phenotype of monocytic cells in normal conditions and during allergic inflammation." ***PLoS One***, 2013; 8(12):e81774. doi: 10.1371/journal.pone.0081774.
5. Sotnikov I, Vermeyko T, Starossom SC, Barteneva N, Weiner HL, **Ponomarev ED**. "Platelets recognize brain-specific glycolipid structures, respond to neurovascular damage and promote neuroinflammation." ***PLoS One***, 2013; 8(3):e58979. doi: 10.1371/journal.pone.0058979.

Technical expertise

- ✧ Immune cell isolation from different organs and their identification; Cell cultures: neuronal and immune cells; Experimental Autoimmune Encephalitis (EAE); FACS analysis (cell subsets, intracellular staining); microRNA; Platelets / Glycolipids

Thrombocytes, glycolipids, amyloid and neurodegeneration

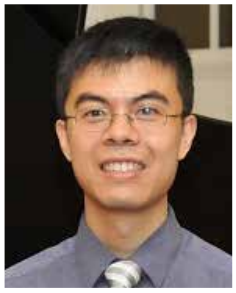
DUKHINOVA Marina, KUZNETSOVA Inna, KOPEIKINA Ekaterina, VEREMEYKO Tatyana, YUNG Amanda, LEVCHUK Kseniia, PONOMAREV Eugene

School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

While it is widely accepted that inflammation in the central nervous system (CNS) contributes to neurodegenerative diseases such as Alzheimer's disease (AD) and traumatic injury, it is not clear how inflammation in CNS is initiated during neurodegerative process in the absence of infection. It is also not clear whether inflammation in the CNS is beneficial or detrimental in case of AD. Our laboratory is interested in earliest events of initiation of neuroinflammation during neurodegenerative diseases and traumatic injury. One of the cells types that have capacity to immediately respond to neurovascular damage are platelets. Platelets are known to respond to a vascular damage, but their role in the neurodegenerative and neuroinflammatory diseases is not well known. We have previously found that administration of brain lipid rafts induced a massive platelet activation and degranulation. The brain-specific glycolipids (gangliosides) within brain lipid rafts were specifically recognized by the platelets and this recognition occurred during disruption of blood brain barrier, a hallmark of CNS inflammation. Current study revealed that interaction of platelets with brain lipid rafts in WT mice resulted in release of serotonin and platelet-activation factor that mediated microglia activation and recruitment of peripheral leukocytes and significantly stimulated neuronal activity. Moreover, activated platelets were capable of production of beta-amyloid fragments, with possible contribution to pathogenesis of AD. To test this, we created novel transgenic model with specific expression of human beta-amyloid in platelets. Overexpression of human beta-amyloid protein in mouse platelets resulted in systemic amyloidosis, cerebral amyloid angiopathy and Alzheimer's disease pathology. Thus, these studies determined a new role of platelets as "innate immune cells" that directly recognize a neuronal damage and contribute to inflammation and neurodegeneration in the CNS in various pathologies including AD.

Session V (NVMB)

Speaker Biography



Prof. CHEUNG Chi Kwan Vincent（張智鈞） is a native of Hong Kong at present an Assistant Professor at the School of Biomedical Sciences of The Chinese University of Hong Kong (CUHK), and an Adjunct Assistant Professor at the Division of Biomedical Engineering of The Hong Kong University of Science and Technology. He obtained his bachelor degree in Mathematics and Pharmacology & Therapeutics from the University of British Columbia, Vancouver, and subsequently, Ph.D. in Neuroscience and Biomedical Engineering from Massachusetts Institute of Technology (MIT) and the Harvard Medical School, and postdoc at the McGovern Institute for Brain Research of MIT. Vincent's research has focused on understanding how the central nervous system (CNS) controls voluntary movement and enables learning of motor skills. For many years, he has worked closely with MIT Institute Professor Emilio Bizzi on the theory that the CNS translates a motor intention into a suitable motor command by combining basic modules of movement known as muscle synergies. On the applied side, Vincent is interested in exploring how knowledge of movement modules may be translated into a new rehabilitation strategy for stroke survivors. He and his collaborators at the Spaulding Rehabilitation Hospital, Boston, and the San Camillo Rehabilitation Hospital, Venice, have recently proposed that distinctive muscle-synergy patterns may be used as markers of motor cortical damage in stroke patients. More recently, Vincent has utilized novel neural technologies such as optogenetics to elucidate the circuitries and principles underlying movement control. Vincent's papers have appeared in many journals including *PNAS, Journal of Neuroscience, Journal of Neurophysiology, Scientific Reports,* and *Neural Computation*. He has been invited to speak at both meetings of professional societies (e.g., Neural Control of Movement Society, Society for Neuroscience USA, and World Congress for Neurorehabilitation) and seminars for the general public (e.g., The Hong Kong Book Fair and The Hong Kong Electronics Fair).

Five recent representative publications

1. Caggiano V[#], **Cheung VCK**[#], Bizzi E. "An optogenetic demonstration of motor modularity in the mammalian spinal cord." ***Sci Rep***, 2016; 6:35185. doi: 10.1038/srep35185.
2. Devarajan K[*], **Cheung VCK**[*]. "A quasi-likelihood approach to non-negative matrix factorization." ***Neural Computation***, 2016; 28:1663-1693.
3. Devarajan K[*], **Cheung VCK**[*]. "On non-negative matrix factorization algorithms for signal-dependent noise, with application to electromyography data." ***Neural Comput***, 2014; 26(6):1128-1168. doi: 10.1162/NECO_a_00576.
4. Bizzi E[*], **Cheung VCK**[*]. "The neural origin of muscle synergies." ***Front Comput Neurosci***, 2013; 7:51. doi: 10.3389/fncom.2013.00051.
5. **Cheung VCK**, Turolla A, Agostini M, Silvoni S, Bennis C, Kasi P, Paganoni S, Bonato P, Bizzi E[*]. "Muscle synergy patterns as physiological markers of motor cortical damage." ***Proc Natl Acad Sci USA***, 2012; 109(36):14652-14656. doi: 10.1073/pnas.1212056109. **[Recommended by Faculty of 1000]**

[*] Corresponding author

[#] Co-First author

Technical expertise

- ✧ neurophysiology; electromyography; data mining; machine learning algorithms; motion analysis

EMG-derived muscle-synergy patterns as recovery biomarkers in stroke survivors: Initial results from a Multi-Center Consortium

CHEUNG Chi Kwan Vincent

School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

For any motor act, the CNS must assemble a coordinated pattern of muscle activities to achieve the intended motion and stabilize the joints whose motions are undesired. The computations behind this assembly are extraordinarily complicated, in that the hundreds of muscles spanning the hundreds of joints constitute a large search space of motor commands even for an apparently simple movement. The CNS may circumvent this complexity by generating muscle commands through the combination of a manageable number of pre-specified units, each of whose activation would simultaneously recruit a specific group of muscles. These units, variously called motor primitives, neuromotor modules, or muscle synergies, are in essence neural mechanisms for synchronizing motoneuronal activities for purposeful motor behaviors. Recent rodent optogenetic experiments of ourselves and others have argued that muscle synergies are encoded by spinal excitatory interneurons that are modulated by proprioceptive and descending drives. A similar organization may also exist in humans, as indicated by our recent EMG data obtained from human subjects during lower-limb adaptation.

Given the plausible neural origin of muscle synergies, it is sensible to ask whether altered muscle-synergy patterns in the affected arm of stroke survivors may serve as indicators of motor impairment, and whether distinct synergy patterns may predict rehabilitative outcome. We explore these questions by longitudinally tracking upper-limb muscle synergies (16 muscles) in diverse survivors with unilateral brain lesions (N=60) from 3 research centers (San Camillo Hospital, Venice; Spaulding Rehab Hospital, Boston; and The Chinese University of Hong Kong) undergoing 1 of 4 different interventions (training on virtual reality, Armeo, an EEG-driven hand exoskeleton, and standard PT/OT). In a previous cross-sectional study, we proposed that an altered affected-arm muscle synergy may either be a merging or fractionation of unaffected-arm synergies (*PNAS* 2012). Here, we found that across all subjects, after rehab training, increase in the muscle-synergy similarity between the affected and unaffected arms (inter-arm synergy similarity, or ISS) correlated strongly with a reduction of synergy merging or fractionation in the affected arm. Interestingly, subjects with smaller ISS pre-rehab tended to show more increase in ISS after intervention. Post-rehab increase in ISS correlated with post-rehab increase in upper-limb Fugl-Meyer (FM) score only in severely impaired (FM<=35), but not in mild-to-moderately impaired (FM>35), survivors. Overall, our results argue that the ISS has the potential to serve as a recovery biomarker with diagnostic and predictive values. Rehabilitative interventions may reduce impairment by restoring the compositions of muscle synergies in the affected arm, thus suggesting that the normative synergies could be the targets of new rehabilitative interventions.

Session VI (NVMB)

Speaker Biography

Prof. YU Siu Bun Sidney（余小彬）received his bachelor degree in Molecular and Cell Biology from the University of California, Berkeley. He did his Ph.D. study at the University of Texas, Southwestern Medical Centre at Dallas. During his Ph.D. study, he was first under the supervision of David G. Garbers, studying guanylyl cyclase receptor family in C. elegans, and later under Michael G. Roth, studying the structure and function of ArfGAP1 in vesicular transport. He then did his postdoctoral research studying vesicular transport under the mentorship of Susan Ferro-Novick at Yale. He was among the first to study the TRAPP (transport protein particle) complex in mammalian cells. After joining The Chinese University of Hong Kong, he continues to investigate this topic of research and expands into other related areas including lipid droplet homeostasis and hepatitis C virus pathogenesis.

Five recent representative publications

1. Luo MX, Li C, Tan R, Xu X, Wu WKK, Satoh A, Wang T, **Yu S.** "A RasGAP, DAB2IP, regulates lipid droplet homeostasis by serving as GAP toward RAB40C." ***Oncotarget***, 2017; 8(49):85415-85427. doi: 10.18632/oncotarget.19960.
2. Zhao S, Li CM, Luo MX, Siu GK, Gan WJ, Zhang L, Wu WK, Chan HC, **Yu S.** "Mammalian TRAPPIII Complex positively modulates the recruitment of Sec13/31 onto COPII vesicles." ***Sci Rep***, 2017; 7:43207. doi: 10.1038/srep43207.
3. Li C, Luo MX, Zhao S, Siu GKY, Liang Y, Chan HC, Satoh A, **Yu S**. "COPI-TRAPPII activates Rab18 and regulates its lipid droplet association." ***EMBO J***, 2017; 36(4):441-457. doi: 10.15252/embj.201694866.
4. Gan W, Zhang C, Siu KY, Satoh A, Tanner JA, **Yu S**. "ULK1 phosphorylates Sec23A and mediates autophagy-induced inhibition of ER-to-Golgi traffic." ***BMC Cell Biol***, 2017; 18(1):22. doi: 10.1186/s12860-017-0138-8.
5. Siu KY, Zhou F, Yu M, Zhang L, Wang T, Liang YH, Chen Y, Chan HC, **Yu S**. "Hepatitis C virus NS5A protein cooperates with phosphatidylinositol 4-kinase IIIα to induce mitochondrial fragmentation." ***Sci Rep***, 2016; 6:23464. doi: 10.1038/srep23464.

Technical expertise

- ✧ Protein purification
- ✧ Confocal microscopy and related imaging techniques

Getting out of TRAPP: vesicle and beyond

YU Sidney

School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

The Transport protein particle (TRAPP) was initially identified as a vesicle tethering factor for COPII coated vesicles in yeast. Three forms of TRAPP (TRAPPI, II, and III) have been discovered and they are responsible for various trafficking functions. In mammals, structures and functions of various TRAPP complexes are beginning to be understood, and so far, we only have solid evidence of the existence of mammalian TRAPPII and TRAPPIII. We have found that mammalian TRAPPII is involved in regulation of lipid droplet metabolism, a vital process in energy homeostasis. Such regulation appears to rely on the function of TRAPPII as an activator of Rab18, a small GTPase well-characterized in regulating lipid droplet metabolism. COPI coatomers have been reported to regulate lipid droplet metabolism. The interaction between COPI and TRAPPII is required for TRAPPII to exert its regulatory effect on lipid droplet. These results reveal a novel function of TRAPPII in mammalian cells.

Session VI (NVMB)

Speaker Biography

Prof. TIAN Xiaoyu（田小雨） is an Assistant Professor of the School of Biomedical Sciences, The Chinese University of Hong Kong (CUHK). She received PhD from CUHK Department of Physiology. She studied the therapeutic effect of PPARs on vascular dysfunction in hypertension and type 2 diabetes, and mitochondrial oxidative stress in endothelial cell function. After graduation, she continued as a postdoctoral fellow in the lab of Prof. Ajay Chawla, Cardiovascular Research Institute, The University of California San Francisco, studying macrophage dynamics in obesity-induced adipose tissue inflammation, and also in the atherosclerosis. She later joined CUHK again in 2015, and is now Assistant Professor. Her current research interests include the regulation of macrophage function by molecular clock components in the vascular microenvironment of cardiovascular diseases. She also works on adipose tissue inflammation and immune regulation of obesity and insulin resistance.

Five recent representative publications

1. Huo M, Huang Y, Qu D, Zhang H, Wong WT, Chawla A, Huang Y, **Tian XY**. "Myeloid Bmal1 deletion increases monocyte recruitment and worsens atherosclerosis." ***FASEB Journal***, 2017; 31(3):1097-1106. doi: 10.1096/fj.201601030R.
2. Cheang WS, Wong WT, Zhao L, Xu J, Wang L, Lau CW, Chen ZY, Ma RCW, Xu A, Wang N, **Tian XY**, Huang Y. "PPARδ is required for exercise to attenuate endoplasmic reticulum stress and endothelial dysfunction in diabetic mice." ***Diabetes***, 2017; 66(2):519-528. doi: 10.2337/db15-1657.
3. **Tian XY**, Ganeshan K, Hong C, Nguyen KD, Qiu Y, Kim J, Tangirala RK, Tontonoz P, Chawla A. "Thermoneutral housing accelerates metabolic inflammation to potentiate atherosclerosis but not insulin resistance." ***Cell Metab***, 2016; 23(1):165-178. doi: 10.1016/j.cmet.2015.10.003.
4. Ma S, **Tian XY**, Zhang Y, Mu C, Shen H, Bismuth J, Pownall HJ, Huang Y, Wong WT. "E-selectin-targeting delivery of microRNAs by microparticles ameliorates endothelial inflammation and atherosclerosis." ***Sci Rep***, 2016; 6:22910. doi: 10.1038/srep22910.
5. Cheang WS, **Tian XY**, Wong WT, Lau CW, Lee SS, Chen ZY, Yao X, Wang N, Huang Y. "Metformin protects endothelial function in diet-induced obese mice by inhibition of endoplasmic reticulum stress through 5' adenosine monophosphate-activated protein kinase-peroxisome proliferator-activated receptor δ pathway." ***Arterioscler Thromb Vasc Biol***, 2014; 34(4):830-836. doi: 10.1161/ATVBAHA.113.301938.

Technical expertise

- ✧ Vascular biology
- ✧ Adipose tissue inflammaiton

Molecular clock and vascular remodeling

TIAN Xiaoyu

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Peripheral circadian clock in vascular cells are important regulators of vascular function and homeostasis. Previous evidences showed that dysfunction of circadian clock either through exposure to abnormal day-night cycle or genetic ablation of core clock components Bmal1 or Clock promotes vascular stiffness and inflammatory responses. Clinical studies also showed that cardiovascular events such as stroke and myocardial infarction have clear circadian variation. Our previous study showed that deletion of Bmal1 in macrophages and monocytes promotes vascular inflammation and atherosclerosis. Our current work demonstrates that deletion of Bmal1 in macrophages also promotes vascular remodelling through MMPs associated with pro-fibrotic Type 2 cytokine signalling.

In angiotensin II induced hypertension, deletion of Bmal1 in macrophages enhances blood pressure increase and loss of 24 hrs circadian pattern. Endothelial function and vascular elasticity was impaired. Increased vascular smooth muscle thickness and more adventitial collagen deposition was found in arteries from hypertensive mice with Bmal1 deletion. High expression of matrix metalloproteinase MMPs were also found in vessels and in perivascular adipose tissue and adventitia. Interesting, these changes were associated with M2 alternative macrophage activation in perivascular adipose tissue. In cultured macrophages, Stat6 activation, and higher expression of markers for type 2 immune responses were further enhanced in Bmal1 knockout cells, which contribute to the pro-fibrotic changes in response to IL4. In addition, knockout of Bmal1 also enhances TGFb1 signaling through interaction with Smad2 and Smad3, leading to imbalance of MMPs and MMP inhibitor TIMPs, promoting vascular remodeling.

These results showed that disturbance of molecular clock system in perivascular macrophages contribute to vascular remodeling. These changes are associated with the non-canonical interaction of BMAL1 with other transcription factors such as Stat6 and Smad2/3 instead of direct effects regulated by clock-controlled genes.

Session VI (NVMB)

Speaker Biography

Prof. YUNG Wing Ho （容永豪）graduated from The Chinese University of Hong Kong (CUHK) in biology and biochemistry with first class honors. He was a recipient of the Commonwealth Scholarship and the Croucher Foundation Fellowship that supported his DPhil study and post-doctoral training in the University of Oxford, under the supervision of Prof. Julian Jack, FRS. He is currently Professor in the School of Biomedical Sciences and the Director of the Gerald Choa Neuroscience Centre, CUHK. He received the Master Teacher of the Year award, Faculty of Medicine in 2007 and the Research Excellence Award, CUHK in 2013. He has major research interests in neuroplasticity, neural circuitry and neurodegenerative diseases.

Five recent representative publications

1. Li Q, Ko H, Qian ZM, Yan LYC, Chan DCW, Arbuthnott G, Ke Y, **Yung WH**. "Refinement of learned skilled movement representation in motor cortex deep output layer." ***Nat Commun***, 2017; 8:15834. doi: 10.1038/ncomms15834.
2. Xu LH, Xie H, Shi ZH, Du LD, Wing YK, Li AM, Ke Y, **Yung WH**. "Critical role of endoplasmic reticulum stress in chronic intermittent hypoxia-induced deficits in synaptic plasticity and long-term memory." ***Antioxid Redox Signal***, 2015; 23(9):695-710. doi: 10.1089/ars.2014.6122.
3. Li Q, Qian ZM, Arbuthnott GW, Ke Y, **Yung WH**. "Cortical effects of deep brain stimulation: implications for pathogenesis and treatment of Parkinson disease." ***JAMA Neurol***, 2014; 71(1):100-103. doi: 10.1001/jamaneurol.2013.4221.
4. Huang Y, Wang JJ, **Yung WH**. "Coupling between GABA-A receptor and chloride transporter underlies ionic plasticity in cerebellar Purkinje neurons." ***Cerebellum***, 2013; 12(3):328-330. doi: 10.1007/s12311-013-0453-3.
5. Li Q, Ke Y, Chan DCW, Qian ZM, Yung KKL, Ko H, Arbuthnott G, **Yung WH**. "Therapeutic deep brain stimulation in Parkinsonian rats directly influences motor cortex." ***Neuron***, 2012; 76(5):1030-1041. doi: 10.1016/j.neuron.2012.09.032.

Technical expertise

- ✧ Electrophysiology
- ✧ Brain imaging
- ✧ Optogenetics
- ✧ Animal behavior

How to abandon an old strategy: the critical role of a specific frontal-striatal pathway

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Strategy-switching flexibility is a critical executive function essential for survival in an ever-evolving environment. This ability is often impaired in attentional deficit and hyperactivity disorder, schizophrenia, and early Parkinson's disease. To date, the underlying brain circuitry and receptor mechanisms of task-switching ability are not entirely clear. In this study, based on a cross-modal spatial-egocentric task in mice and employing a multi-disciplinary approach, we demonstrated the essential role of a projection from prelimbic cortex to specific sub-population of nucleus accumbens medium spiny neurons in strategy-switching flexibility via facilitation of the abandoning of an old strategy. This function is dependent on an intact dopaminergic tone in the nucleus accumbens utilizing presynaptic dopamine D1 and D2 receptors. Our results point to a critical role of a specific prelimbic cortex-nucleus accumbens sub-pathway in mediating strategy abandoning allowing the switching of one strategy to another in problem solving.

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