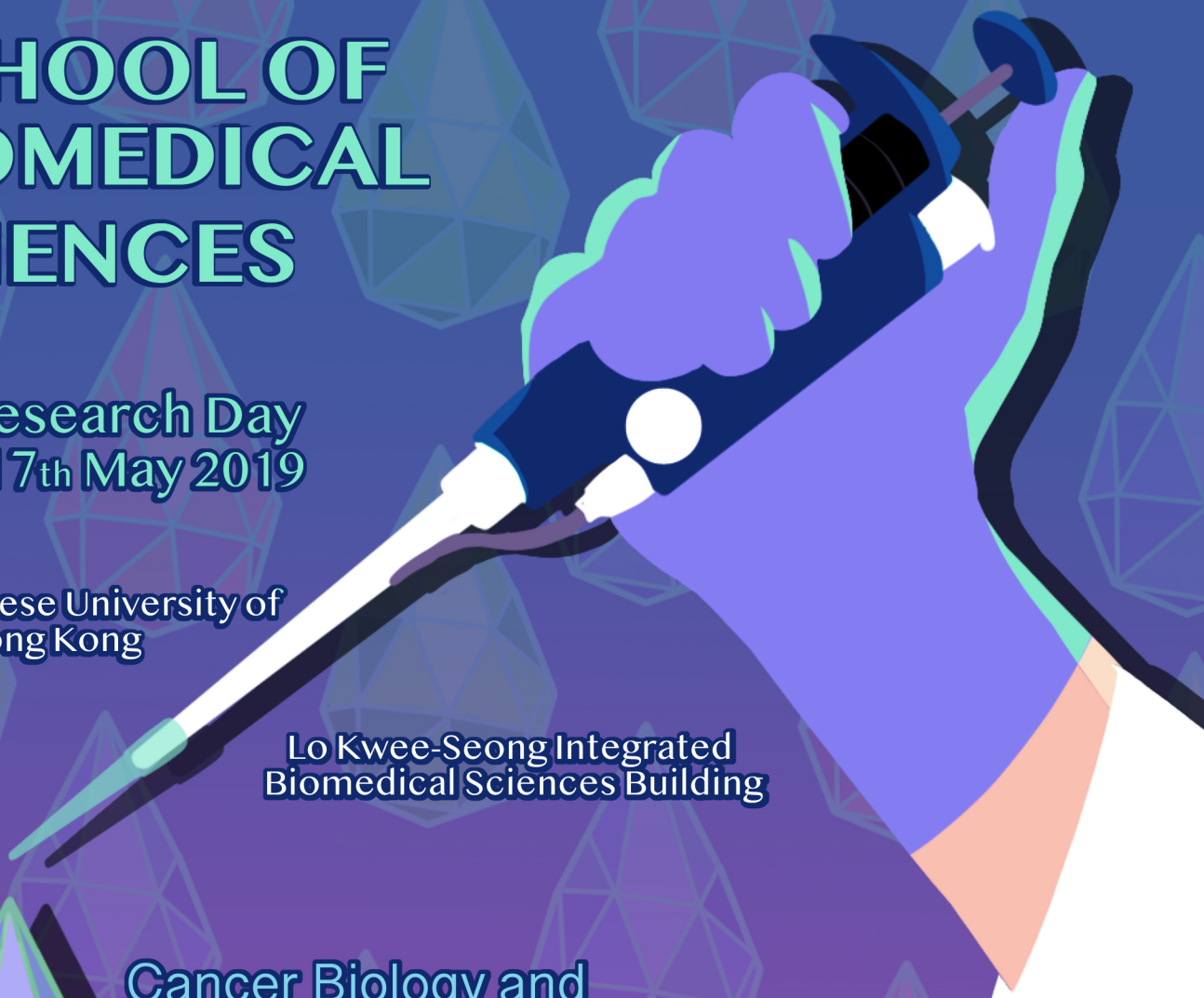
SCHOOL OF BIOMEDICAL SCIENCES



10th Research Day
16th - 17th May 2019

The Chinese University of Hong Kong

Lo Kwee-Seong Integrated Biomedical Sciences Building

Cancer Biology and Experimental Therapeutics

Developmental and Regenerative Biology

Neural, Vascular, and Metabolic Biology

香港中文大學
The Chinese University of Hong Kong

香港中文大學55周年
55th ANNIVERSARY OF CUHK

CU Medicine 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 2019

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Professor SO Hon Cheong

COVER: The three Thematic Research Programs of School of Biomedical Sciences, CUHK
Designed by Ms. Tong Lok Yee Sylvia, Dept. of Microbiology, Faculty of Medicine, CUHK

CONTENTS

Welcome Message from the Dean of Faculty of Medicine

It is my great pleasure to welcome all of you to the School of Biomedical Sciences (SBS) Research Day 2019.

This year marks the 10th anniversary of this flagship annual event of the School. It has successfully served as a significant platform to engage faculty and researchers in the School with distinguished researchers from the University and other institutions, to showcase accomplishments and to exchange research ideas.

Through strengthening academic links to further accelerate research collaboration, it is our earnest hope to solve some of the puzzles baffling biomedical scientists in their quest to bring hope and healing to patients. The School will continue to work closely with clinicians in the Prince of Wales Hospital and to forge closer partnerships with the industries for sustained growth and long-term development.

I trust that every one of you will benefit greatly from the animated and stimulating discussions and cross-pollination of ideas in this one-and-a-half-day event.

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 honoured to welcome you to the School of Biomedical Sciences Research Day 2019.

The Research Day comes to its 10th year. Since the formation in 2009, our School has been endeavoured to pursue research excellence. The theme-based research model has excelled in fostering synergies in research among School members in respective Thematic Research Programs. With the desirable growth in research capacity, our School will continue to play a leading role in pushing forward the frontiers of biomedical sciences in Pan-Asian region and the globe.

The Research Day is not only a platform for our School Members to showcase their latest research advances, but also a golden opportunity for high-calibre experts to interact. This year we are delighted to have Prof. Yu Jun from Department of Medicine & Therapeutics of the university as our keynote speaker. I hope the enriching programme will inspire you and open you doors for future scientific collaboration.

I would like to thank the members of the organizing committee for planning this event. Also, I wish to extend my sincere gratitude to all of the sponsoring companies for their generous support.

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

SBS Research Day 2019 Programme

16 May 2019 (Thursday)

Room G02, Lo Kwee-Seong Integrated Biomedical Sciences Building

09:00-09:20	**Opening Ceremony:** Prof. CHAN Ka Leung Francis (Dean of Faculty of Medicine) & Prof. CHAN Wai Yee (Director of School of Biomedical Sciences)
09:20-09:30	**Presentation of the prize for SBS Research Day 2019 Programme Book Cover / Banner Design Competition / Photo Taking**

Time	*Title of Presentation*	*Speaker*	*Abstract No.*
Keynote Lecture *Chairperson: Prof. CHAN M. Andrew (CUHK SBS)*			
09:30-10:10	Gut microbiota: What impact on colorectal neoplasm	Prof. YU Jun (MEDT)	Keynote
Session I (NVMB) *Chairpersons: Prof. TANG Leung Sang Nelson (CUHK CPY) & Prof. SHUM Sau Wun Alisa (CUHK SBS)*			
10:10-10:40	CRISPR-Cas9 genetically modified *Lactobacillus casei* for probiotic treatment of Inflammatory Bowel Disease	Prof. KWAN Yiu Wa (NVMB)	O1
10:40-11:10	Growth hormone-releasing hormone signaling in acute ocular inflammation	Prof. CHAN Sun On Hector (NVMB)	O2
11:10-11:30	***Tea Break***		
Session II (NVMB) *Chairpersons: Prof. YU Siu Bun Sidney (CUHK SBS) & Prof. PONOMAREV Eugene (CUHK SBS)*			
11:30-12:05	Protein arginine methylation as a regulator of hepatic cancer stemness and glucose metabolism	Dr. MA Kwai Yee Stephanie (HKU)	O3
12:05-12:35	Studies of traditional Chinese medicines in animal models of diseases	Prof. LAM Fu Yuen Francis (NVMB)	O4
12:35-13:05	TRPP proteins act through autophagy to exert cyto-protective role in human embryonic stem cell-derived cardiomyocytes	Prof. YAO Xiaoqiang (NVMB)	O5
13:05-14:30	***Lunch***		
Session III (CBET) *Chairpersons: Prof. WU Ka Kei William (CUHK AIC) & Prof. CHAN M. Andrew (CUHK SBS)*			
14:30-15:05	Computational study of clonal evolution guides targeted therapy in brain cancer	Dr. WANG Jiguang (HKUST)	O6
15:05-15:35	The energetic orphan estrogen-related receptor alpha in prostate cancer: new insights	Prof. CHAN Leung Franky (CBET)	O7
15:35-16:05	Translational genomic landscape of head and neck cancers	Prof. LUI Wai Yan Vivian (CBET)	O8
16:05-16:30	***Tea Break***		
Session IV (CBET) *Chairpersons: Prof. KWONG Joseph (CUHK OBG) & Prof. SO Hon Cheong (CUHK SBS)*			
16:30-17:00	Ghrelin mimetics in cancer supportive care	Prof. RUDD A. John (CBET)	O9
17:00-17:30	The genomes and microbiomes of *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* reveal a broad spectrum of dust mite allergens	Prof. TSUI Kwok Wing Stephen (CBET)	O10
17:30-18:00	Novel strategies of liver cancer immunotherapy by co-targeting myeloid-derived suppressor cells	Prof. ZHOU Jingying (CBET)	O11
18:30-20:00	***Conference Banquet (by invitation)***		

SBS Research Day 2019 Programme

17 May 2019 (Friday)

Room G02, Lo Kwee-Seong Integrated Biomedical Sciences Building

Time	*Title of Presentation*	*Speaker*	*Abstract No.*
Session V (DRB) *Chairpersons: Prof. WANG Huating (CUHK ORT) & Prof. KO Wing Hung (CUHK SBS)*			
09:00-09:35	Efficient RNA drug delivery using red blood cell extracellular vesicles	Dr. LE Thi Nguyet Minh (CityU)	O12
09:35-10:05	CRISPR-mediated knock-in of large DNA & potentials in gene therapy	Prof. FENG Bo (DRB)	O13
10:05-10:35	Zswim4, a novel regulator for BMP signaling pathway, is essential for embryonic development	Prof. ZHAO Hui (DRB)	O14
10:35-11:00	***Tea Break***		
Session VI (DRB) *Chairpersons: Prof. LI Gang (CUHK ORT) & Prof. JIANG Xiaohua (CUHK SBS)*			
11:00-11:30	The regulation of oxygen sensing and glucose metabolism in cartilage tissue engineering and regeneration	Prof. WAN Chao (DRB)	O15
11:30-12:00	Cellular based therapy for cartilage regeneration	Prof. JIANG Yangzi (iTERM / DRB)	O16
12:00-12:30	Mesenchymal stem cell-based therapy for non-alcoholic fatty liver disease	Prof. LEE Chien-Wei (iTERM / DRB)	O17
12:30-12:45	***Closing Remarks***		
12:45-14:00	***Closing Lunch***		

Abbreviations:
AIC = Department of Anaesthesia and Intensive Care
CityU = City University of Hong Kong
CPY = Department of Chemical Pathology
CUHK = The Chinese University of Hong Kong
HKU = The University of Hong Kong
HKUST = The Hong Kong University of Science and Technology
iTERM = Institute for Tissue Engineering and Regenerative Medicine
MEDT = Department of Medicine & Therapeutics
OBG = Department of Obstetrics and Gynaecology
ORT = Department of Orthopaedics and Traumatology
SBS = School of Biomedical Sciences

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

Keynote Lecture

Speaker Biography

Prof. YU Jun（于君）is a Professor of Department of Medicine and Therapeutics, Director of the Research Laboratory of Institute of Digestive Disease, and Associate Director of State Key Laboratory of Digestive Disease, The Chinese University of Hong Kong. She serves as Council Member of American Gastrointestinal Association (AGA) Oncology and Council Member of AGA Microbiome and Microbial Diseases, UAS; Council Member of Cancer Microbiome Consortium, UK; Associate Chairman of HK Scientist Association, Chang Jiang Scholar Chair Professor. She is Associate Editor for *Oncogene*, Editor for *Gut, Scientific Reports, J Gastroent Hepatol* etc.

Her academic education includes an MBBS, Master of Medicine MD, and Ph.D. Her areas of expertise include gastroenterology and hepatology, with research interests being molecular pathogenesis, microbiome and biomarkers of gastrointestinal cancers (gastric, colon, and liver), and non-alcohol steatohepatitis (NASH)/HCC in relation to the molecular pathogenesis and treatment response. Prof. Yu has over 380 peer-reviewed publications (83 papers IF>10, h index=62). She has over 20 patents on cancer early diagnostic markers and treatment targets. She obtained over 30 prestigious awards, including Science and Technology Progress Awards of He Liang and He Li Fund 2018; AGA Council Oncology Research Mentor Award 2017; The WuXi PharmaTech Life Science and Chemistry Award 2017; The State Natural Science Award 2016; The State Scientific and Technological Progress Award (Innovation Team) 2016; Croucher Senior Research Fellowship 2016; The State Science and Technology Progress Award 2012; First-class of Higher Education Outstanding Scientific Research Output Awards (Natural science) in 2010 and 2014; First-class Higher Education Outstanding Scientific Research Output Awards (Scientific and Technological Progress Award) 2012; Research Excellence Award CUHK 2009, etc.

Five recent representative publications

1. Liu D, Wong CC, Fu L, Chen H, Zhao L, Li C, Zhou Y, Zhang Y, Xu W, Yang Y, Wu B, Cheng G, Lai PB, Wong N, Sung JJY, **Yu J***. "Squalene epoxidase drives NAFLD-induced hepatocellular carcinoma and is a pharmaceutical target." ***Sci Transl Med***, 2018; 10(437). (Cover Story, with editorial).
2. Coker OO, Dai Z, Nie Y, Zhao G, Cao L, Nakatsu G, Wu WK, Wong SH, Chen Z, Sung JJY, **Yu J***. "Mucosal microbiome dysbiosis in gastric carcinogenesis." ***Gut***, 2018; 67(6):1024-1032.
3. Sun W, Zhang Y, Wong KC, Liu K, Yang Y, Wu B, Tong JH, Chan AW, Chan HL*, **Yu J***. "Increased expression of GATA Zinc Finger Domain Containing 1 via gene amplification promotes liver cancer by directly inducing PRL3." ***Hepatology***, 2018; 67(6):2302-2319.
4. Nakatsu G, Zhou H, Wu WKK, Wong SH, Coker OO, Dai Z, Li X, Szeto CH, Sugimura N, Lam TY, Yu AC, Wang X, Chen Z, Wong MC, Ng SC, Chan MTV, Chan PKS, Leung Chan FK, Sung JJY, **Yu J***. "Alterations in enteric virome associate with colorectal cancer and survival outcomes." ***Gastroenterology***, 2018; 155(2):529-541.e5.
5. Liang JQ, Teoh N, Xu L, Pok S, Li X, Chu ESH, Chiu J, Dong L, Arfianti E, Haigh WG, Yeh MM, Ioannou GN, Sung JJY, Farrell G*, **Yu J***. "Dietary cholesterol promotes steatohepatitis related hepatocellular carcinoma through dysregulated metabolism and calcium signaling." ***Nat Commun***, 2018; 9(1):4490.

* Corresponding author

Technical expertise

- ✧ Genome, epigenome and microbiome research on cancer pathogenesis
- ✧ Cancer biomarker and therapeutic target

Keynote Lecture

Abstract

Gut microbiota: What impact on colorectal neoplasm

YU Jun

Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

Cancer is a major disease burden globally. The gut microbiome and its role in carcinogenesis is a rapidly evolving research field (*Nat Biotechnol 2015*). Mounting evidence has suggested that the gut microbiota is implicated in a variety of cancers especially in the colorectal cancer (CRC). In this connection, detailed and holistic investigations into the gut metagenome in CRC initiation, progression, and response to therapies are imperative. With our work in metagenomic profiling in CRC, we were the first to reveal an interacting oral pathogen network in CRC in Chinese (*Nat Commun 2015, Gut 2017a*) and among different populations (*Microbiome 2018*). We were first to demonstrate a causative role of gut microbiota in CRC development, which revealed that faecal transplantation of samples from patients with colorectal cancer promotes intestinal carcinogenesis in germ-free and conventional mice (*Gastroenterology 2017a*). Our studies identified several bacterial species that were significantly enriched in colorectal cancer patients. Some microbes were novel and their relationships with colorectal cancer were investigated, especially pinpointing the specific causative role of *Peptostreptococcus anaerobius* (*Gastroenterology 2017b*) and *C. hathewayi* (*Cancer Res 2016*) in CRC. The molecular bases of how the novel microbes play roles in the formation of colorectal cancer were investigated. Pertinent to clinical practice, we identified *Fusobacterium* as a marker to improve the diagnostic performance of the fecal immunochemical test, which could serve as non-invasive diagnostic markers for the early CRC (*Gut 2017b; Clin Cancer Res 2017*). In addition to our studies of the bacteriome, we identified for the first time CRC-associated virome signatures that independently predicted patient survival in CRC (*Gastroenterology 2018*). Moreover, we recently identified the enteric fungal microbiota dysbiosis in colorectal cancer (*Gut 2018*). The findings provide new insights for the molecular pathogenesis of CRC and aid development of new microbiome-based strategies for the diagnosis and prevention of this vital malignancy (*Semin Cancer Biol 2018*).

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1. Xiao L, Feng Q, Liang S, ..., Yu J, Sung JJ, et al. A catalog of the mouse gut metagenome. *Nat Biotechnol*. 2015 Oct; 33(10):1103-1108.
2. Berry Nakatsu G, Li X, Zhou H, ..., Zhang J, Liang Q, Yu J*, Sung JJ*. Gut mucosal microbiome across stages of colorectal carcinogenesis. *Nat Commun*. 2015; 6:8727.
3. Yu J, Feng Q, Wong SH, Zhang D, et al. Metagenomic analysis of faecal microbiome as a tool towards targeted non-invasive biomarkers for colorectal cancer. *Gut*. 2017; 66(1):70-78. a
4. Dai Z, Coker OO, Nakatsu G, Chan FKL, Kristiansen K, Sung JJY, Wong SH*, Yu J*. Multi-cohort analysis of colorectal cancer metagenome identified altered bacteria across populations and universal bacterial markers. *Microbiome*. 2018 Apr 11; 6(1):70.
5. Wong SH, Zhao L, Zhang X, Nakatsu G, ..., Chan FK, Sung JJ, Wei H*, Yu J*. Gavage of fecal samples from patients with colorectal cancer promotes intestinal carcinogenesis in germ-free and conventional mice. *Gastroenterology*. 2017; 153(6):1621-1633.e6. a
6. Tsoi H, Chu ES, Zhang X, Sheng J, Nakatsu D, Ng SC, Chan AW, Chan FK, Sung JJ, Yu J*. Peptostreptococcus anaerobius induces intracellular cholesterol biosynthesis in colon cells to induce proliferation and causes dysplasia in mice. *Gastroenterology*. 2017; 152(6):1419-1433.e5. b
7. Jin Y*, Tang S, Li W, Ng SC, Chan MW, Sung JJ*, Yu J*. Hemolytic E. coli promotes colonic tumorigenesis in females. *Cancer Res*. 2016; 76(10):2891-2900.
8. Wong SH, Kwong TN, ..., Wu WK, Yu J, Sung JJ. Quantitation of faecal Fusobacterium improves faecal immunochemical test in detecting advanced colorectal neoplasia. *Gut*. 2017; 66(8):1441-1448. b
9. Liang Q, Chiu J, Chen Y, Huang Y, Higashimori A, Fang JY, Brim H, Ashktorab H, Ng SC, Ng SS, Zheng S, Chan FK, Sung JJ, Yu J*. Fecal bacteria act as novel biomarkers for non-invasive diagnosis of colorectal cancer. *Clin Cancer Res*. 2017; 23(8):2061-2070.
10. Nakatsu G, Zhou H, Wu WK, Wong SH, ..., Sung JY, Yu J*. Alterations in enteric virome associate with colorectal cancer and survival outcomes. *Gastroenterology*. 2018; 155(2):529-541.e5.
11. Coker OO, Nakatsu G, ..., Ng SC, Chan FKL, Sung JJY, Yu J*. Enteric fungal microbiota dysbiosis and ecological alterations in colorectal cancer. *Gut*. 2018 Nov 24. pii: gutjnl-2018-317178.
12. Wong SH, Kwong TNY, Wu CY*, Yu J*. Clinical applications of gut microbiota in cancer biology. *Semin Cancer Biol*. 2018 May 18. pii: S1044-579X(18)30026-9. doi: 10.1016/j.semcancer.2018.05.003. Review.

Session I (NVMB)

Speaker Biography

Prof. KWAN Yiu Wa（關耀華）obtained his Bachelor degree (Hons) from the Department of Pharmacology and Experimental Therapeutics of The Liverpool University (UK), and his PhD degree in the Department of Pharmacology and Physiology of The Strathclyde University (Glasgow, Scotland) after he received a scholarship from the Croucher Foundation. He went on to have his post-doctoral training, with the supports of the American Heart Association (USA), under Professor RS Kass (University of Rochester New York, New York, USA) prior to joining CUHK. He is a pharmacologist by training, and his main research interests are related to the pharmacology of different drugs in treating metabolic and vascular diseases e.g. type 2 diabetes mellitus, osteoporosis and pulmonary hypertension. He also has research interests in the utilization of alternative / un-conventional approaches such as recombinant probiotics in treating various diseases.

Five recent representative publications

1. Vong CT, Tseng HHL, **Kwan YW**, Lee SM, Hoi MPM. "Novel protective effect of O-1602 and abnormal cannabidiol, GPR55 agonists, on ER stress-induced apoptosis in pancreatic β-cells. " ***Biomed Pharmacother***, 2019; 111:1176-1186.
2. Chan BD, Wong WY, Lee MM, Cho WC, Yee BK, **Kwan YW**, Tai WC. "Exosomes in inflammation and inflammatory disease." ***Proteomics***, 2019; e1800149.
3. Zhou ZY, Huang B, Li S, Huang XH, Tang JY, **Kwan YW**, Hoi PM, Lee SM. "Sodium tanshinone IIA sulfonate promotes endothelial integrity via regulating VE-cadherin dynamics and RhoA/ROCK-mediated cellular contractility and prevents atorvastatin-induced intracerebral hemorrhage in zebrafish." ***Toxicol Appl Pharmacol***, 2018; 350:32-42.
4. Law ILG, Loo JFC, Kwok HC, Yeung HY, Leung CCH, Hui M, Wu SY, Chan HS, **Kwan YW**, Ho HP, Kong SK. "Automated real-time detection of drug-resistant Mycobacterium tuberculosis on a lab-on-a-disc by Recombinase Polymerase Amplification." ***Anal Biochem***, 2018; 544:98-107.
5. Tseng HHL, Vong CT, **Kwan YW**, Lee SM, Hoi MPM. "Lysosomal Ca^{2+} signaling regulates high glucose-mediated interleukin-1β secretion via transcription factor EB in human monocytic cells." ***Front Immunol***, 2017; 8:1161.

Technical expertise

- ✧ Ion channels gatings measurements
- ✧ Recombinant probiotics designs and uses
- ✧ Treatments for diabetes and osteoporosis

CRISPR-Cas9 genetically modified *Lactobacillus casei* for probiotic treatment of Inflammatory Bowel Disease

HO Michael Wai-hung[1], WONG Wing-Yan[2], LEUNG Tsz-Wing[2], LEE Magnolia Muk-Lan[2], CHAN Brandon Dow[2], TAI William Chi-Shing[2], KWAN Yiu Wa[1]

[1] School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.
[2] Department of Applied Biology & Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Hong Kong SAR, P.R. China.

Inflammatory bowel disease (IBD) is a chronic, relapsing-remitting intestine inflammatory disease. The progressive, destructive nature of the disease leads to complications including intestinal obstruction, abscesses, fistulas and cancer. An increasing trend in IBD incidence has been observed worldwide and currently, it is estimated that over 10 million people suffer from IBD (2018). Traditionally, the prevalence of IBD is higher in Western countries; however, in recent years there is a rapid increase in the incidence rate in newly industrialized countries such as some Asian countries. IBD is an early onset disease and requires lifelong treatment, greatly impacting a patient's quality of life and placing a significant burden on the public health system worldwide. As current treatments for IBD suffer from drawbacks in multiple aspects, including mild efficacy with severe side effects, long-term intolerance, and limited patient responses, novel IBD therapeutics are thus urgently needed.

Emerging evidence has suggested the roles of gut microbiota in human health, and loss of homeostasis in the gut microbiota, so-called dysbiosis, has been linked to the development of different diseases, including IBD. Probiotics have been defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host". Recent studies have demonstrated the beneficial effects of probiotics consumption in modulation of the gut environment and microbiome compositions for the treatment of various diseases. Thus, the use of probiotics to manipulate the activity of the gut microbiota to produce beneficial effects is a promising potential strategy for IBD therapy.

In our studies, using CRISPR/Cas9 technology, we have developed a genetically engineered strain of *Lactobacillus casei*, incorporating the peptide MW1 (with reported anti-inflammatory and anti-bacterial properties) into the bacterial genome. In the DSS-induced acute colitis mouse model, when compared with wild-type bacteria, daily oral consumption ($10x10^{10}$ cfu/ml) of the genetically modified *L. casei* ameliorated disease severity, reduced major *in vivo* pro-inflammatory mediators and pathways measured, and reduced key pathogenic gut microbiota while increasing several beneficial species collected in the gut. No apparent side effects were observed in all mice which consumed wild-type and genetically modified *L. casei*.

Altogether, we showed that in IBD mice model, oral consumption of genetically modified *L. casei* could significantly improve disease severity and key inflammatory and microbial indicators, when compared to wild-type probiotic treatments. Through our work, we have successfully demonstrated the strong potential for using genetically modified bacteria as edible probiotics for the treatment of diseases which shines light on a promising path towards the novel IBD therapeutics in the near future.

Session I (NVMB)

Speaker Biography

Prof. CHAN Sun-On Hector（陳新安）graduated from The Chinese University of Hong Kong with a BSc degree in Biology. He then studied a MPhil degree in the Department of Anatomy. He was awarded the Croucher Foundation Scholarship to study a DPhil programme in Neuroscience in University of Oxford, under the supervision of Prof. Ray Guillery.

After graduation, he moved back to Hong Kong and started to teach in the Department of Anatomy (now School of Biomedical Sciences) as a lecturer, Associate Professor and Professor. His major research interests are on development of visual pathway and recently mechanisms of ocular inflammation and its protection.

Five recent representative publications

1. Ren JL, Yu QX, Ma D, Liang WC, Leung PY, Ng TK, Chu WK, Pang CP, **Chan SO**. "Growth hormone-releasing hormone receptor mediates cytokine production in ciliary and iris epithelial cells during LPS-induced ocular inflammation." ***Experimental Eye Research***, 2019; 181:277-284. doi: 10.1016/j.exer.2019.02.021.
2. Hu F, Liu H, Su DQ, Chen H, **Chan SO**, Wang Y, Wang J. "Nogo-A promotes inflammatory heat hyperalgesia by maintaining TRPV1 function through stabilization of actin cytoskeleton in the rat dorsal root ganglion neuron." ***FASEB Journal***, 2019; 33(1):668-682. doi: 10.1096/fj.201800382RR.
3. Ren JL, Yu QX, Liang WC, Leung PY, Ng TK, Chu WK, Pang CP, **Chan SO**. "Green tea extract attenuates LPS-induced retinal inflammation in rats." ***Scientific Reports***, 2018; 8(1):429, doi:10.1038/s41598-017-18888-5.
4. Chu WK, Law KS, **Chan SO**, Yam JCS, Chen LJ, Zhang H, Cheung HS, Block NL, Schally AV, Pang CP. "Antagonists of growth hormone-releasing hormone receptor induce apoptosis specifically in retinoblastoma cells." ***Proceedings of National Academy of Sciences USA***, 2016; 113(50):14396-14401. doi:10.1073/pnas.1617427113.
5. Qin YJ, **Chan SO**, Chong KKL, Li BFL, Ng TK, Yip YWY, Chen H, Zhang M, Block NL, Cheung HS, Schally AV, Pang CP. "Antagonist of GH-releasing hormone receptors alleviates experimental ocular inflammation." ***Proceedings of National Academy of Sciences USA***, 2014; 111(51):18303-18308.

Technical expertise

✧ Confocal microscopy, immunohistochemistry, cell and tissue culture, axon tracing, brain slice imaging

Growth hormone-releasing hormone signaling in acute ocular inflammation

CHAN Sun-On Hector[1], LIANG Weicheng[1], YU Qiuxiao[1], PANG Chi-Pui[2]

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

Ocular inflammation is a major cause of visual impairment attributed to dysregulation of the immune system. Previously we have shown that the receptor for growth hormone-releasing hormone (GHRH-R) affects multiple inflammatory processes. To clarify the pathological roles of GHRH-R in acute ocular inflammation, we investigated the inflammatory cascades mediated by this receptor. In human ciliary epithelial cells, NF-κB subunit p65 was phosphorylated in response to stimulation with lipopolysaccharide (LPS), resulting in transcriptional activation of GHRH-R. Bioinformatics analysis and co-immunoprecipitation showed that GHRH-R had a direct interaction with JAK2. JAK2 was elevated in ciliary body and iris after treatment with LPS in a rat model of endotoxin-induced uveitis. This elevation augmented the phosphorylation of STAT3 and production of pro-inflammatory factors, including IL-6, IL-17A, COX2 and iNOS. In explants of iris and ciliary body, the GHRH-R antagonist, MIA-602, suppressed phosphorylation of STAT3 and attenuated expression of downstream pro-inflammatory factors after LPS treatment. A similar suppression of STAT3 phosphorylation was observed in human ciliary epithelial cells. *In vivo* studies showed that blocking of GHRH-R/JAK2/STAT3 axis with JAK2 inhibitor, Ruxolitinib, alleviated LPS-induced acute ocular inflammation, as indicated by the reduction in inflammatory cells and protein leakage in the aqueous humor, and repressed STAT3 target genes, IL-6, IL-17A, COX2 and iNOS in explants of rat ciliary body and iris and in human ciliary epithelial cells. Our findings indicate a functional role of GHRH-R/JAK2/STAT3 signaling axis in acute anterior uveitis, and suggest a novel therapeutic strategy based on treatment with antagonists targeting this signaling pathway.

Funding: Supported in part by the Research Grants Council General Research Fund to S.O.C. (Project No.: CUHK14113815).

Session II (NVMB)

Speaker Biography

Dr. MA Kwai Yee Stephanie（馬桂宜）obtained her B.Sc. and M.Sc. degrees from the University of British Columbia in Vancouver, Canada in 2000 and 2003, respectively. She then graduated with a Ph.D. degree in 2007 from The University of Hong Kong with an outstanding ranking and was awarded the Li Ka Shing Prize for the Best PhD Thesis of that year. Since then, she has been working at HKU where she is currently an Associate Professor in the School of Biomedical Sciences at the Li Ka Shing Faculty of Medicine. Dr. Ma's research interest is on exploiting stemness as a cancer cell vulnerability. According to the ISI Essential Science Indicator, Dr. Ma is currently listed as the top 1% of most cited scholars under the category of 'clinical medicine' and 'all fields'. She is also the recipient of the 2008 Young Scientist Award in Life Sciences from the Hong Kong Institution of Science, the 2012-13 Outstanding Young Researcher Award from HKU, the 2014 Croucher Innovation Award, the 2014 Scientific Research Outstanding Achievement Awards (Second-class Award in Science and Technology Section) from the Higher Education Institution of China, the 2017 University of British Columbia Alumni Builder Award (Canada) as well as the 2018 Ton Duc Thang University Scientific Prize - Rising Star Award (Vietnam). Dr. Ma is also recently elected as a Founding Member of the Young Academy of Sciences of Hong Kong.

Five recent representative publications

1. Chan LH, Zhou L, Ng KY, Wong TL, Lee TK, Sharma R, Loong JH, Ching YP, Yuan YF, Xie D, Lo CM, Man K, Artegiani B, Clevers H, Yan HH, Leung SY, Richard S, Guan XY, Huen MS, **Ma S**. "Protein arginine methyltransferase PRMT6 regulates RAS/RAF binding and MEK/ERK-mediated cancer stemness activities in hepatocellular carcinoma through CRAF methylation." ***Cell Rep***, 2018; 25(3):690-701.
2. Tong M, Che N, Zhou L, Luk ST, Kau PW, Chai S, Ngan ES, Lo CM, Man K, Ding J, Lee TK, **Ma S**. "Efficacy of annexin A3 blockade in sensitizing hepatocellular carcinoma to sorafenib and regorafenib." ***J Hepatol***, 2018; 69(4):826-839.
3. Chai S, Ng KY, Tong M, Lau EY, Lee TK, Chan KW, Yuan YF, Cheung TT, Cheung ST, Wang XQ, Wong N, Lo CM, Man K, Guan XY, **Ma S**. "Octamer4/microRNA-1246 signaling axis drives Wnt/β-catenin activation in liver cancer stem cells." ***Hepatology***, 2016; 64(6):2062-2076.
4. Ng KY, Chan LH, Chai S, Tong M, Guan XY, Lee NP, Yuan YF, Xie D, Lee TK, Dusetti NJ, Carrier A, **Ma S**. "TP53INP1 downregulation activates a p73-dependent DUSP10/ERK signaling pathway to promote metastasis of hepatocellular carcinoma." ***Cancer Res,*** 2017; 77(17):4602-4612.
5. Tong M, Fung TM, Luk ST, Ng KY, Lee TK, Lin CH, Yam JW, Chan KW, Ng F, Zheng BJ, Yuan YF, Xie D, Lo CM, Man K, Guan XY, **Ma S**. "ANXA3/JNK signaling promotes self-renewal and tumor growth and its blockade provides a therapeutic target for hepatocellular carcinoma." ***Stem Cell Reports***, 2015; 5(1):45-59.

Protein arginine methylation as a regulator of hepatic cancer stemness and glucose metabolism

MA Kwai Yee Stephanie

School of Biomedical Sciences and State Key Laboratory of Liver Research, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, P.R. China.

Arginine methylation is a common post-translational modification that plays pivotal roles in signal transduction. However, its function in human diseases is poorly understood. In this study, we found protein arginine methyltransferase 6 (PRMT6) to be frequently down-regulated in hepatocellular carcinoma (HCC) and its expression to negatively correlate with aggressive cancer features in HCC patients. Silencing of PRMT6 promoted the tumor-initiating, metastasis, therapy resistance and glucose metabolism potential of HCC cell lines and patient-derived organoids; while overexpression of PRMT6 led to an opposing effect. Findings of our lentiviral based functional studies was further substantiated by PRMT6 wild-type and catalytic inactive methyltransferase mutant overexpression. Consistently, loss of PRMT6 expression aggravated liver tumorigenesis in chemical-induced HCC PRMT6 knockout mice. Contrary to its usual localization in the nucleus where it has previously been identified to play a role in histone modification in other tumor types, we did not find PRMT6 to alter the H3R2 mark in HCC cells. Interestingly, we identified a previously unappreciated role of PRMT6 in the cytoplasm. Integrated transcriptome and protein-protein interaction studies revealed an enrichment of genes implicated in RAS signaling and that PRMT6 interacted with CRAF on arginine 100 and as a result hindered its RAS binding potential and altered its downstream MEK/ERK signaling. As a consequence, down-regulation of PRMT6 in HCC will result in activation of ERK-mediated cancer stemness via regulating CD133, SOX2 and NANOG, as well as ERK-mediated glucose metabolic reprogramming via regulating PKM2.

Session II (NVMB)

Speaker Biography

Prof. LAM Francis Fu Yuen（林富源）completed his PhD studies in Physiology and Pharmacology under the joint-supervision of Dr. Ian Rodger and Prof. William Bowman at the University of Strathclyde, Scotland. In his postdoctoral training, he worked as a Research Assistant and then as a Research Fellow under the leadership of Prof. William Ferrell at the University of Glasgow, Scotland. At that time, his research interest focused on the role of neurogenic inflammation in the development of arthritis.

Prof. Lam joined The Chinese University of Hong Kong initially as a lecturer in the Department of Pharmacology, and then he became an Associate Professor in the School of Biomedical Sciences. Since joining The Chinese University of Hong Kong, his research field has expanded into vascular pharmacology and the study of traditional Chinese medicines in inflammatory and vascular diseases. Recently, he also conducted studies on skin allergies and stroke. Prof. Lam has published a few book chapters and 75 peer-reviewed articles in international journals such as *Annals of Rheumatic Diseases*, *Arthritis and Rheumatism*, *British Journal of Pharmacology*, *Circulation*, *European Journal of Pharmacology*, *Hypertension*, *International Immunopharmacology*, *Journal of Cardiovascular Pharmacology*, *Journal of Ethnopharmacology*, *Life Sciences*, *Neuroscience*, *Phytomedicine*, and *Vascular Pharmacology*. Prof. Lam was a Visiting Research Staff of the Neurovascular Research Group of Glasgow and Paisley Universities, Scotland. He also served as a member of the Advisory Board of *Journal of Geriatric Cardiology*, a reviewer for international journals and grant awarding bodies, an Executive Committee Member of the Hong Kong Pharmacology Society, and a Council Member of the Board of Specialty Committee of Immunology of Traditional Chinese Medicine of World Federation of Chinese Medicine Societies.

Five recent representative publications

1. Deng Y, **Lam FFY**, Ng ESK, Lau CBS, Koon JCM, Leung PC, Fung KP. "A herbal formulation of Danshen and Gegen protects rat brains from injuries induced by focal and global ischaemia." ***J Adv Plant Sci***, 2018; 1:104.
2. Zhen X, Ng ESK, **Lam FFY**. "Protease activated receptor-3 on *in vivo* and *in vitro* rat models of ischemic stroke." ***Central South Pharmacy***, 2017; 15(6):780-785.
3. Zhen X, Ng ESK, **Lam FFY**. "Role of protease activated receptor-2 *in vivo* and *in vitro* rat models of ischemic stroke." ***Central South Pharmacy***, 2017; 15(5):595-600.
4. Yu COL, Leung KS, Fung KP, **Lam FFY**, Ng ESK, Lau KM, Chow SKH, Cheung WH. "The characterization of a full-thickness excision open foot wound model in n5-streptozotocin (STZ)-induced type 2 diabetic rats that mimics diabetic foot ulcer in terms of reduced blood circulation, higher C-reactive protein, elevated inflammation, and reduced cell proliferation." ***Exp Anim***, 2017; 66(3):259-269.
5. Zhen X, Ng ESK, **Lam FFY**. "Suppression of ischaemia-induced injuries in rat brain by protease-activated receptor-1 (PAR-1) activating peptide." ***Eur J Pharmacol***, 2016; 786:36-46.

Technical expertise

- ✧ Animal models of joint inflammation and stroke
- ✧ Vascular pharmacology

Studies of traditional Chinese medicines in animal models of diseases

LAM Francis Fu Yuen[1], NG Ethel Sau Kuen[1], DENG Yan[2], LI Edmund Kwok Ming[3], SHAW Pang Chui[4,5], LI Ming[4], HE Jun[6], LAU Clara Bik San[4,7], KOON Johnny Chi Man[4,7], LEUNG Ping Chung[4,7], FUNG Kwok Pui[1,4,7]

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

[2] Department of Obstetrics and Gynecology, [3] Department of Medicine & Therapeutics, [4] State Key Laboratory of Phytochemistry and Plant Resources in West China, [5] School of Life Sciences, [7] Institute of Chinese Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

[6] Key Laboratory of Biodiversity and Biogeography, Kunming Institute of Botany, Chinese Academy of Science, Kunming, Yunnan, P.R. China.

Traditional Chinese medicines (TCMs) had been used by Chinese medical practitioners to treat ailments for more than two thousand years. They continue to be popular remedies in Greater China in the present day. The theory and practice of TCMs are inherently different to those of Western medicines. Nevertheless, studies of TCM by modern scientific methods can increase evidence-based support and global recognition on their uses. Here, the efficacies of some TCMs were examined on animal models of diseases.

Aconiti Radix (AC) and *Aconiti Kusnezoffii Radix* (AK) are two TCMs commonly used to treat joint pain and arthritis. In Southwestern China, the root of *Aconitum vilmorinianum Kom*. (AV) has long been used as a local substitute for these herbs for analgesia and anti-inflammation, but its anti-arthritic effects have not been investigated. Therefore, the anti-arthritic effects of these three *Aconitum* herbs were compared in a rat model of monoarthritis induced by unilateral intra-articular injection of Freund's complete adjuvant. All three herbs exhibited anti-arthritis properties, but AV was found to produce the most significant improvement on allodynia, swelling, hyperaemia and vascular permeability in arthritic knee joints. These findings confirmed AV to be a good substitute of AC and AK for treatment of arthritis. A TCM combination of Lingzhi and San Miao San was also tested on the same monoarthritis model, and shown to produce analgesic and anti-inflammatory effects in arthritic rat knees. These findings concur to previous clinical studies that showed this TCM combination reduced pain in rheumatoid arthritis patients, and extend its possible benefit to suppression of inflammatory symptoms.

Danshen and Gegen are the dried roots of *Salvia miltiorrhiza* and *Pueraria lobata*, respectively. These two herbs can be used separately or as a combined formulation (DG) to treat cardiovascular diseases. The individual and combined effects of these two herbs were examined in a mouse model of pain and inflammation induced by acetic acid. DG or Gegen, but not Danshen, were found to relieve the pain symptom, and none of them reduced inflammation. In another study, the same DG formulation was tested in two rat models of stroke that were induced by global ischaemia and middle cerebral artery occlusion (MCAO), respectively. This DG formulation was found to ameliorate nitrative and oxidative stress to suppress ischaemia-induced injuries in rat brains. These findings indicate the therapeutic applications of DG could be extended to treatments of ischaemic stroke, in addition to its common usage in treatments of cardiovascular diseases.

Session II (NVMB)

Speaker Biography

Prof. YAO Xiaoqiang（姚曉強）obtained his degree of Bachelor of Science in Biology in 1981 from Department of Biology, Hangzhou University, Zhejiang, China. In 1984, he obtained his Master of Philosophy degree from Chinese Academy of Sciences. He then obtained his Ph.D. degree in 1991 from Department of Biological Sciences, The State University of New York at Buffalo, USA. After that, he had postdoctoral training in Department of Internal Medicine, Yale University School of Medicine, USA. In 1996, he became an Assistant Professor in Department of Physiology, The Chinese University of Hong Kong, and later was promoted to Associate Professor in 1999 and Professor in 2002. He is now the Chief of Neural, Vascular, and Metabolic Biology Thematic Research Program in the School of Biomedical Sciences, The Chinese University of Hong Kong.

His research interest is mostly on ion channels in cardiovascular system and cancer cells. These include TRP channels and K^+ channels. He has published more than 200 original articles with total citation of >8800 with h-factor of 52, including those in *Proc Natl Acad Sci USA, Nature Communications, Circulation Research, Journal of Clinical Investigation* and *Trends in Pharmacological Sciences.*

Five recent representative publications

1. Sun L, Meng Z, Zhu Y, Lu J, Li Z, Zhao Q, Huang Y, Jiang LW, **Yao X**. "TM9SF4 is a novel factor promoting autophagic flux under amino acid starvation." ***Cell Death Differ***, 2018; 25(2):368-379.
2. Lu J, Boheler KR, Jiang LW, Chan CW, Tse WW, Keung W, Poon ENY, Li RA, **Yao X**. "Polycystin-2 plays an essential role in glucose starvation-induced autophagy in human embryonic stem cell-derived cardiomyocytes." ***Stem Cells***, 2018; 36(4):501-513.
3. Lau OC, Shen B, Wong CO, Tjong YW, Lo CY, Wang HC, Huang Y, Yung WH, Chen YC, Fung ML, Rudd JA, **Yao X**. "TRPC5 channels participate in pressure-sensing in aortic baroreceptors." ***Nat Commun***, 2016; 7:11947.
4. Ma X, Chen Z, Hua D, He D, Wang L, Zhang P, Wang J, Cai Y, Gao C, Zhang X, Zhang F, Wang T, Hong T, Jin L, Qi X, Chen S, Gu X, Yang D, Pan Q, Zhu Y, Chen Y, Chen D, Jiang L, Han X, Zhang Y, Jin J, **Yao X**. "Essential role for TrpC5-containing extracellular vesicles in breast cancer with chemotherapeutic resistance." ***Proc Natl Acad Sci USA***, 2014; 111(17):6389-6394.
5. Du J, Ma X, Shen B, Huang Y, Birnbaumer L, **Yao X**. "TRPV4, TRPC1 and TRPP2 assemble to form a flow-sensitive heteromeric channel." ***FASEB J***, 2014; 28(11):4677-4685.

Technical expertise

✧ Ion channels and Ca^{2+} signalling in cardiovascular system and cancer

TRPP proteins act through autophagy to exert cyto-protective role in human embryonic stem cell-derived cardiomyocytes

LU Jun, YU Hongyan, YAO Xiaoqiang

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

Human embryonic stem cells (hESCs) and human-induced pluripotent stem cells (hiPSCs) provide an unlimited source of human cardiomyocytes for potential application in disease modeling, drug screening and cell-based heart therapies. These hESC- or hiPSC-derived cardiomyocytes (hESC-CMs or hiPSC-CMs) are suggested to have many properties of authentic human cardiomyocytes. In the present study, we utilized hESC-CMs as models to investigate the potential role of TRPP2 (polycystin-2 or PKD-2) and TRPP1 (polycystin-1 or PKD1) in autophagy. Our study demonstrates that TRPP2 and TRPP1 function to promote autophagy under glucose starvation, thereby protects cardiomyocytes from apoptotic cell death. The mechanism may involve TRPP2 interaction with ryanodine receptors to alter Ca^{2+} release from sarcoplasmic reticulum (SR), consequently modulating the activity of AMPK and mTOR, resulting in alteration of autophagy and apoptosis. We suggest that this scheme of TRPP2-autophagy-apoptosis may have important pathophysiological relevance in cardiomyopathy in patients with autosomal dominant polycystic kidney disease and ischemic heart diseases.

Acknowledgment: We thank the financial support from Hong Kong Research Grant Committee [AoE/M-05/12, GRF/14118516, RIF/R4005-18F] and Hong Kong Innovation and Technology Fund [ITF/096/18].

Session III (CBET)

Speaker Biography

Dr. WANG Jiguang（王吉光）is an Assistant Professor in Division of Life Science (LIFS) and Department of Chemical and Biological Engineering (CBE), The Hong Kong University of Science and Technology (HKUST). He has received his PhD degree from Academy of Mathematics and Systems Science (AMSS), Chinese Academy of Sciences (CAS) in 2011. Between 2011 and 2015, he was a Postdoctoral Research Scientist in the Department of Biomedical Informatics (DBMI) at Columbia University. From 2015, he was named as the Precision Medicine Fellow and promoted to an Associate Research Scientist at DBMI. He has established the Wang Genomic Laboratory at the end of 2016. He is now focusing on the application of data science in biology and medicine. His research interests include cancer genomics, noncoding RNA, medical image analytics, machine learning and precision medicine.

Five recent representative publications

1. Hu H*, Mu Q*, Bao Z*, Chen Y*, Liu Y*, Chen J, Wang K, Wang Z, Nam Y, Jiang B, Sa JK, Cho HJ, Her NG, Zhang C, Zhao Z, Zhang Y, Zeng F, Wu F, Kang X, Liu Y, Qian Z, Wang Z, Huang R, Wang Q, Zhang W, Qiu X, Li W, Nam DH, Fan X#, **Wang J**#, Jiang T#. "Mutational landscape of secondary glioblastoma guides MET-targeted trial in brain tumor." ***Cell***, 2018; 175 (6): 1665-1678.
2. Lee JK*, Liu Z*, Sa JK*, Shin S*, **Wang J***, …, Lee J#, Rabadan R#, Nam DH#. "Pharmacogenomic landscape of patient-derived tumor cells informs precision oncology therapy." ***Nature Genetics***, 2018; 50(10):1399-1411.
3. Lee J*, **Wang J***, Sa JK*, Ladewig E*, …, Rabadan R#, Nam DH#. "Spatiotemporal genomic architecture informs precision oncology in glioblastoma." ***Nature Genetics***, 2017; 49(4):594-599.
4. **Wang J**, Cazzato E, …, Nam DH#, Finocchiaro G#, Iavarone A#, Rabadan R#. "Clonal evolution of glioblastoma under therapy." ***Nature Genetics***, 2016; 48(7):768-776.
5. Pefanis E*, **Wang J***, Rothschild G*, Lim J*, …, Rabadan R#, Basu U#. "RNA exosome-regulated long non-coding RNA transcription controls super-enhancer activity." ***Cell***, 2015; 161(4):774-789.

Technical expertise

- ✧ Computational genomics
- ✧ Machine learning

Computational study of clonal evolution guides targeted therapy in brain cancer

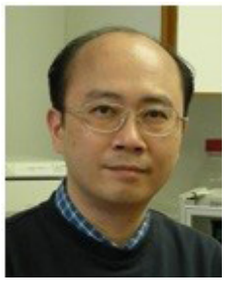
WANG Jiguang

Division of Life Science and Department of Chemical and Biological Engineering, The Hong Kong University of Science and Technology, Hong Kong SAR, P.R. China.

Recent progression of cancer genome projects has uncovered the mutational landscapes of many cancers, but how cancer cell evolves with and without therapy is still unclear. Scientists believe one major reason of treatment failure is the temporal-spatial dynamics of cancer cells. Actually, cancer cells are constantly evolving, with different groups of cells accumulating distinctive mutations. As the search for more effective cancer diagnostics and therapies continues, remained key questions include a) how to interpret intratumor heterogeneity (ITH); b) how to understand the tumors change over time and how to predict the impact of ITH on tumor progression; and c) how to disentangle the order in which mutations occur. Being able to predict how a tumor will behave based on signs seen early in the course of disease could enable the development of new diagnostics that could better inform treatment planning. In this talk, I will use brain tumor as an example to show our recent studies in this topic.

Session III (CBET)

Speaker Biography



Prof. CHAN Leung Franky（陳良）obtained his Ph.D. degree from The University of Hong Kong in 1989 and received his postdoctoral training in McGill University (Montreal, Canada) thereafter. He joined The Chinese University of Hong Kong as a lecturer in the Department of Anatomy in 1992 and is presently a full professor at the School of Biomedical Sciences. Prof. Chan has published more than 120 original research papers, including *Cancer Research, Oncogene, Journal of Pathology, Journal of Clinical Endocrinology and Metabolism, Endocrinology* and *PNAS.* Chan's primary research focus is on the hormonal carcinogenesis of prostate cancer. His current research topics include: (1) orphan nuclear receptors-mediated signaling pathways, (2) cancer stem cells in prostate cancer, (3) epithelial mesenchymal transition in metastasis, (4) molecular targeted therapy and immunotherapy of prostate cancer, and (5) signaling pathways involved in castration-resistant and neuroendocrine prostate cancer.

Five recent representative publications

1. Xu Z, Wang Y, Xiao ZG, Zou C, Zhang X, Wang Z, Wu D, Yu S, **Chan FL**. "Nuclear receptor ERRα and transcription factor ERG form a reciprocal loop in the regulation of TMPRSS2:ERG fusion gene in prostate cancer." ***Oncogene***, 2018; 37(48):6259-6274.
2. Jia L, Wu D, Wang Y, You W, Wang Z, Xiao L, Cai G, Xu Z, Zou C, Wang F, Teoh JY, Ng CF, Yu S, **Chan FL**. "Orphan nuclear receptor TLX contributes to androgen insensitivity in castration-resistant prostate cancer via its repression of androgen receptor transcription." ***Oncogene***, 2018; 37(25):3340-3355.
3. Xiao L, Wang Y, Xu K, Hu H, Xu Z, Wu D, Wang Z, You W, Ng CF, Yu S, **Chan FL**. "Nuclear receptor LRH-1 functions to promote castration-resistant growth of prostate cancer via its promotion of intratumoral androgen biosynthesis." ***Cancer Research***, 2018; 78(9):2205-2218.
4. Wang Z, Wu D, Ng CF, Teoh JY, Yu S Wang Y, **Chan FL**. "Nuclear receptor profiling in prostatospheroids and castration-resistant prostate cancer." ***Endocr Relat Cancer***, 2018; 25(1):35-50.
5. Cai G, Wu D, Wang Z, Xu Z, Wong KB, Ng CF, **Chan FL***, Shan Yu S. "Collapsin response mediator protein-1 (CRMP1) acts as an invasion and metastasis suppressor of prostate cancer via its suppression of epithelial-mesenchymal transition and remodeling of actin cytoskeleton organization." ***Oncogene***, 2017; 36(4):546-558.

The energetic orphan estrogen-related receptor alpha in prostate cancer: new insights

CHAN Leung Franky

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

Estrogen-related receptor alpha (ERRα, NR3B1, ESRRA) is an orphan member of the nuclear receptor superfamily. This receptor is constitutively active and its transactivation does not require binding of any known steroid hormones but dependent significantly on its co-activator PGC-1 α/β. Studies in past decades indicate that ERRα functions as a key transcriptional regulator of energy homeostasis and mitochondrial functions. Accumulating evidences show that ERRα play important roles in cancer growth regulation, via its regulation on energy metabolism (enhanced glycolysis or Warburg effect) and other non-metabolism pathways. Our previous studies show that ERRα exhibits a significant upregulation pattern and performs an oncogenic role in prostate cancer through different pathways, such as augmentation of HIF-1 signaling via its physical interaction with HIF-1α and formation of a reciprocal transcriptional loop with an oncogenic transcription factor ERG. In this lecture, the speaker will update its new roles in prostate cancer including transcriptional regulation of intratumoral androgen biosynthesis and zinc transport, based on some unpublished findings from his laboratory.

Session III (CBET)

Speaker Biography

Prof. LUI Wai Yan Vivian（呂偉欣）obtained her Ph.D. (Hons) training in Molecular Pharmacology at the University of Pittsburgh School of Medicine, USA, followed by post-doctoral trainings at Duke University and University of Pittsburgh, USA. Prof. Lui specializes in precision medicine development in head and neck cancers. Using genomics, proteomics, integrative genomic-proteomic discovery approaches, and a driver mutation screening platform (US patented, Co-inventor), Prof. Lui has contributed to major mutationally-driven drug sensitivity findings in head and neck cancer. Prof. Lui has published over 80 research articles in the area of precision medicine, cancer genomics and therapeutics in renowned scientific journals including *Cancer Discovery, Nature Comms., JAMA Oncology, PNAS* and *JNCI*, etc.

Five recent representative publications

1. Ngan HL, Wang L, Lo KW, **Lui VWY**. "Genomic landscapes of EBV-associated nasopharyngeal carcinoma vs. HPV-associated head and neck cancer." ***Cancers (Basel)***, 2018; 10(7):210.
2. Li Y*, Chung GTY*, **Lui VW***, To KF, Ma BB, Chow C, Woo JKS,Yip KY, Seo J, Hui EP, Mak MK, Rusan M, Chau NG, Or YY, Law MH, Law PP, Liu ZW, Ngan HL, Hau PM, Verhoeft K, Poon PH, Yoo SK, Shin J, Lee S, Lun SW, Jia L, Chan AW, Chan JY, Lai PBS, Fung C, Hung ST, Wang L, Chang AM, Chiosea S, Hedberg ML, Tsao SW, van Hasselt AC, Chan ATC, Grandis JR, Hammerman PS, Lo KW. "Exome and genome sequencing of nasopharynx cancer identifies NF-κB pathway activating mutations." ***Nature Communications***, 2017; 8:14121.
3. Van Allen EM*, **Lui VW***, Egloff AM*, Goetz EM, Li H, Johnson JT, Duvvuri U, Bauman JE, Stransky N, Zeng Y, Gilbert BR, Pendleton KP, Wang L, Chiosea S, Sougnez C, Wagle N, Zhang F, Du Y, Close D, Johnston PA, McKenna A, Carter SL, Golub TR, Getz G, Mills GB, Garraway LA, Grandis JR. "Genomic correlate of exceptional erlotinib response in head and neck squamous cell carcinoma." ***JAMA Oncology***, 2015; 1(2):238-244.
4. **Lui VW**, Peyser ND, Ng PK, Hritz J, Zeng Y, Lu Y, Li H, Wang L, Gilbert BR, General IJ, Bahar I, Ju Z, Wang Z, Pendleton KP, Xiao X, Du Y, Vries JK, Hammerman PS, Garraway LA, Mills GB, Johnson DE, Grandis JR. "Frequent mutation of receptor protein tyrosine phosphatases provides a mechanism for STAT3 hyperactivation in head and neck cancer." ***Proc Natl Acad Sci USA***, 2014;111(3):1114-1119.
5. **Lui VW**, Hedberg ML, Li H, Vangara BS, Pendleton K, Zeng Y, Lu Y, Zhang Q, Du Y, Gilbert BR, Freilino M, Sauerwein S, Peyser N, Xiao D, Diergaarde B, Wang L, Chiosea S, Seethala R, Johnson JT, Kim S, Duvvuri U, Ferris RL, Romkes M, Nukui T, Ng PKS, Garraway LA, Hammerman SP, Mills GB, Grandis JR. "Frequent mutation of the PI3K pathway in head and neck cancer defines predictive biomarkers." ***Cancer Discovery***, 2013; 3(7):761-769.

* Equal contributions

Technical expertise

- ✧ Functional genomics of cancer gene mutations
- ✧ Drug sensitivity genomics
- ✧ Drug target discovery by integrative genomics and proteomics

Translational genomic landscape of head and neck cancers

LUI Wai Yan Vivian

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

Head and neck cancer incidences reaches ~0.7 million new cases per year globally. In this talk, we will discuss about the genomic landscape of two virally-associated head and neck cancers, namely the Epstein-Barr Virus (EBV)-associated Nasopharyngeal cancer (NPC), and the human papillomavirus (HPV)-associated head and neck cancer. Our recent exome-reanalysis efforts identified for the first time several novel commonalities between EBV(+)NPC and HPV(+)HNC, which may essentially inform us the "essential common drives" for these oncovirus-associated head and neck cancers. Importantly, among these "common signals" are potential drug targets, which are to be investigated in the future for these cancers. We will also discuss on the major druggability differences for EBV(+)NPC, HPV(+)HNC, and HPV(-)HNC.

Conflict of Interest Disclosures:
VWYL served as a Consultant for Novartis Pharmaceuticals (HK) Limited (Oct 2015-Oct 2016), and obtained a research funding from the University-Industry Collaboration Program by the Innovation Technology Fund (ITF, The Government of the Hong Kong Special Administrative Region) and the Lee's Pharmaceuticals (HK) Limited (grant UIM/329 from May 2018-April 2020). Currently, VWYL also receives research fundings from the Research Grants Council, Hong Kong (#14168571, #17121616, General Research Fund), the Health and Medical Fund (HMRF#15160691, the Health and Medical Research Fund, the Food and Health Bureau, The Government of the Hong Kong Special Administrative Region), the Start-up Fund from the School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, and the Hong Kong Cancer Fund, Hong Kong SAR. As well as fundings from NIH (NCI) USA and Research Impact Fund from RGC.

Session IV (CBET)

Speaker Biography

Prof. RUDD John Anthony（陸臻賢）worked with Glaxo Group Research in the late 1980s to explore the potential use of the 5-HT_3 receptor antagonist, ondansetron, to antagonize chemotherapy- and drug-induced emesis. He was also part of a team that mapped 5-HT_3 receptor distribution in the human and ferret brainstem and first to show increases in of 5-HT in the plasma of patients receiving cisplatin-based chemotherapy. Pioneered the use of the ferret to model chemotherapy-induced acute and delayed emesis (now a gold standard model) and discovered that NK_1 tachykinin antagonists could be used to prevent the acute and delayed phases of emesis induced by cisplatin: now NK_1 tachykinin antagonists are a cornerstone of treatment for delayed emesis. Recently he collaborated with Helsinn on the development of the second generation 5-HT_3 and NK_1 receptor antagonists, palonosetron and netupitant, respectively. He has an ongoing interest in broad inhibitory anti-emetic drugs and works with several leading pharmaceutical companies to aid drug development. He is also examining the role of the brain-gut axis in mechanisms of neurodegenerative diseases.

Five recent representative publications

1. **Rudd JA**, Chan SW, Ngan MP, Tu L, Lu Z, Giuliano C, Lovati E, Pietra C. "Anti-emetic action of the brain-penetrating new ghrelin agonist, HM01, alone and in combination with the 5-HT_3 antagonist, palonosetron and with the NK_1 antagonist, netupitant, against cisplatin- and motion-induced emesis in *Suncus murinus* (house musk shrew)." ***Frontiers in Pharmacology***, 2018; 9:869, doi: 10.3389/fphar.2018.00869
2. Lu Z, Ngan MP, Lin G, Yew DTW, Fan X, Andrews PLR, **Rudd JA**. "Gastric myoelectric activity during cisplatin-induced acute and delayed emesis reveals a temporal impairment of slow waves in ferrets: effects not reversed by the GLP-1 receptor antagonist, exendin (9-39)." ***Oncotarget***, 2017; 8:98691-98707.
3. Tu L, Lu Z, Dieser K, Schmitt C, Chan SW, Ngan MP, Andrews PLR, Nalivaiko E, **Rudd JA**. "Brain activation by H_1 antihistamines challenges conventional view of their mechanism of action in motion sickness: a behavioral, c-fos and physiological study in *Suncus murinus* (house musk shrew)." ***Frontiers in Physiology***, 2017; 8:412.
4. Lu Z, Yeung CK, Lin G, Yew DTW, Andrews PLR, **Rudd JA**. "Insights into the central pathways involved in the emetic and behavioural responses to exendin-4 in the ferret." ***Autonomic Neuroscience: Basic and Clinical***, 2017; 202:122-135.
5. Kan KKW, Wai MK, Jones RL, **Rudd JA**. "Role of prostanoid $EP_{3/1}$ receptors in mechanisms of emesis and defaecation in ferrets." ***European Journal of Pharmacology***, 2017; 803:112-117.

Technical expertise

- ✧ *In vivo* experimentation in conscious animals using radiotelemetry for acquisition and analysis of blood pressure (including HRV, spectral analysis), temperature, gastric myoelectric activity, and other biopotentials
- ✧ Pharmacological assays for drug potency estimations
- ✧ Immunohistochemistry; c-Fos
- ✧ *In vivo* imaging for gastric emptying
- ✧ Microelectrode array for electrophysiological recordings from ICC and other cells
- ✧ Stereotaxic surgery for cannula placement and drug delivery
- ✧ Whole body plethysmography in conscious animals to examine respiratory function; safety pharmacology
- ✧ Memory testing and general activity protocols; taste aversion protocols

Ghrelin mimetics in cancer supportive care

TU Longlong[1], LU Zengbing[1], LIU Julia Y.H.[1], HUANG Ianto B.[1], NGAN Man P.[1], LAM Francis F.Y.[1], CHAN Sze-W.[2], GIULIANO Claudio[2], LOVATI Emanuela[2], PIETRA Claudio[2], RUDD John A.[1]

[1] School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.
[2] School of Health Sciences, Caritas Institute of Higher Education, Hong Kong SAR, P.R. China.
[3] Helsinn Healthcare SA., Research and Preclinical Development Department, Lugano, Switzerland.

Ghrelin is an orexigenic peptide that was originally isolated from rat stomach extracts. It is also synthesized in the hypothalamus. Ghrelin activates growth hormone secretagouge1A receptors (GHS-R1A) to exert a variety of biological effects including an ability to increase growth hormone secretion, stimulate feeding, and increase gastrointestinal motility and gastric acid secretion. Our previous studies showed that ghrelin antagonizes cisplatin-induced acute emesis in ferrets via central actions in the brain; this action was mimicked to some degree by anamorelin, which also improved food and water intake during acute and delayed emesis experiments. More recently, we also showed that the new orally bioavailable brain-penetrating GHSR-1A agonist, HM01, could antagonize cisplatin-induced acute emesis in *Suncus murinus* and could enhance the control of emesis by a combination of a 5-HT_3 and of a NK_1 antagonist anti-emetic regimen. The anti-emetic action of HM01 appears to extend to other chemotherapeutic agents and to the free radical generator, pyrogallol, which is consistent with an action to prevent emetic mechanisms in the periphery. Surprisingly, HM01 also prevented motion-induced emesis, which is mediated centrally, and is not known to involve free radicals. The unique mechanism of action of GHS-R1A mimetics to inhibit emesis is discussed relative to the need to discover new treatments for emesis control in man.

Session IV (CBET)

Speaker Biography

Prof. TSUI Kwok-Wing Stephen （徐國榮） is currently a professor in the School of Biomedical Sciences and directors of the Hong Kong Bioinformatics Centre and the Centre for Microbial Genomics and Proteomics in The Chinese University of Hong Kong (CUHK). In 1995, he received his Ph.D. degree in Biochemistry at CUHK and his thesis is related to the study of the human genome. He was then appointed as an Assistant Professor in the Biochemistry Department in 1997 and promoted to the full professorship in 2004. He was a former member of the International HapMap Consortium and worked on the single nucleotide polymorphisms of human chromosome 3p. During the SARS outbreak in 2003, his team was one of the earliest teams that cracked the complete genome of the SARS-coronavirus. Totally, he has published more than 210 scientific papers in international journals, including *Nature, New England Journal of Medicine, Lancet, PNAS, Circulation, Journal of Allergy and Clinical Immunology* and *Genome Biology*. He is very interested in bioinformatics, comparative genomics and molecular biology of clinical pathogens including human immunodeficiency virus, hepatitis B virus, influenza virus and *Mycobacterium tuberculosis*. Most recently, he cracked the genome, transcriptome and microbiome of two dust mite species, which can be linked to the house dust mite allergy.

Five recent representative publications

1. Liu XY, Yang KY, Wang MQ, Kwok JSL, Zeng X, Yang Z, Xiao XJ, Lau CPY, Li Y, Huang ZM, Ba JG, Yim AKY, Ouyang CY, Ngai SM, Chan TF, Leung ELH, Liu L, Liu ZG, **Tsui SKW**. "High-quality assembly of Dermatophagoides pteronyssinus genome and transcriptome reveals a wide range of novel allergens." ***J Allergy Clin Immunol***, 2018; 141(6):2268-2271.
2. Chan TF, Ji KM, Yim AKY, Liu XY, Zhou JW, Li RQ, Yang KY, Li J, Li M, Law PTW, Wu YL, Cai ZL, Qin H, Bao Y, Leung RKK, Ng PKS, Zou J, Zhong XJ, Ran PX, Zhong NS, Liu ZG, **Tsui SKW**. "The draft genome, transcriptome and microbiome of Dermatophagoides farinae reveal a broad spectrum of dust mite allergens." ***J Allergy Clin Immunol***, 2015; 135(2):539-548.
3. Leung TF, Ko FWS, Sy HY, **Tsui SKW**, Wong GWK. "Differences in asthma genetics between Chinese and other populations." ***J Allergy Clin Immunol***, 2014; 133(1):42-48.
4. Chan TM, Leung KS, Lee KH, Wong MH, Lau CK, **Tsui SKW**. "Subtypes of associated protein-DNA (TF-TFBS) patterns." ***Nucleic Acids Res***, 2012; 40(19):9392-9403.
5. Leung KS, Wong KC, Chan TM, Wong MH, Lee KH, Lau CK, **Tsui SKW**. "Discovering protein-DNA binding sequence patterns using association rule mining." ***Nucleic Acids Res***, 2010; 38(19):6324-6337.

The genomes and microbiomes of *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* reveal a broad spectrum of dust mite allergens

TSUI Kwok-Wing Stephen[1,2], YANG Yi Kevin[1,2], WANG Mingqiang[1,2], WAN Tsz-Yau Angel[1], QING Xiong[1], CHAN Ting-Fung[3], Leung Lai-Han Elaine[4], Liu Zhi-Gang[5]

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It is well known that house dust mites (HDMs) are predominant sources of inhalant allergens associated with allergic disease. Therefore, sequenced house dust mite (HDM) genomes would certainly advance our understanding of HDM allergens, a common cause of human allergies. To produce annotated *Dermatophagoides* (D.) farinae and *D. pteronyssinus* genomes, we developed a combined genomic-transcriptomic-proteomic approach for the elucidation of HDM allergens. High quality *D. farinae* and *D. pteronyssinus* genomes and transcriptomes were assembled with high-throughput DNA sequencing platforms including PacBio, Illumina HiSeq and ion torrent. The mite's microbiome composition was at the same time determined and the predominant genus was validated immunohistochemically. Putative allergens were then evaluated with immunoblotting, immunosorbent assays, and skin prick tests. In this study, 79.79-Mb and 66.85-Mb genomes of *D. farinae* and *D. pteronyssinus*, respectively, was constructed. Moreover, the full gene structures of canonical allergens and non-canonical allergen homologues were produced. Using mass spectrometry analysis of *D. farinae* protein spots reactive to pooled sera from HDM-allergic patients, novel major allergens were found. In *D. farinae*, the predominant bacterial genus among 100 identified species was Enterobacter (63.4%), among them *Enterobacter cloacae* and *Enterobacter hormaechei* were most predominant. KEGG pathway analysis revealed a phototransduction pathway in *D. farinae* as well as thiamine and amino acid synthesis pathways suggestive of an endosymbiotic relationship between *D. farinae* and its microbiome. In summary, high quality HDM genomes produced from genomic, transcriptomic, and proteomic experiments revealed allergen genes and a diverse endosymbiotic microbiome, providing a tool for further identification and characterization of HDM allergens and development of diagnostics and immunotherapeutic vaccines.

Session IV (CBET)

Speaker Biography

Prof. ZHOU Jingying（周京穎）obtained her Ph.D. degree in Microbiology from the AIDS Institute, Department of Microbiology, The University of Hong Kong (HKU) in 2013 and received the Awards for Outstanding Research Postgraduate Student (HKU). She continued her research as a postdoctoral fellow in Prof. Alfred Cheng's lab, School of Biomedical Sciences, The Chinese University of Hong Kong (CUHK) and became a Research Assistant Professor in 2018. Prof. Zhou has published in international journals including *Gut, Journal of Clinical Investigation, Cancer research* and served as co-inventor of two U.S. patents on DNA vaccines. She has received academic awards including recognitions from the American Association of Immunologists (AAI), United European Gastroenterology (UEG) and AstraZeneca. Prof. Zhou's current research interests are innate and adaptive immune regulation in cancer, with particular focus on the mechanisms of tumor microenvironment in hepatocellular carcinoma (HCC) and aiming at the enhancement of cancer immunotherapy.

Five recent representative publications

1. Sun H, Yang W, Tian Y, Zeng X, **Zhou J**, Mok MTS, Tang W, Feng Y, Xu L, Chan AWH, Tong JH, Cheung YS, Lai PBS, Wang HKS, Tsang SW, Chow KL, Hu M, Liu R, Huang L, Yang B, Yang P, To KF, Sung JJ, Wong GLH, Wong VWS, Cheng AS. "An inflammatory-CCRK circuitry drives mTORC1-dependent metabolic and immunosuppressive reprogramming in obesity-associated hepatocellular carcinoma." ***Nat Commun***, 2018; 9(1):5214.
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 AS. "Hepatoma-intrinsic CCRK inhibition diminishes myeloid-derived suppressor cell immunosuppression and enhances immune-checkpoint blockade efficacy." ***Gut***, 2018; 67:931-944.
3. Liu M*, **Zhou J***, Chen Z, Cheng AS. "Understanding the epigenetic regulation of tumours and their microenvironments: opportunities and problems for epigenetic therapy." ***J Pathol***, 2017; 241(1):10-24.
4. Cheung KL, Kwok HY, Huang YR, Chen M, Mo YF, Wu XL, Lam KS, Kong HK, Lau CK, **Zhou J**, Li JJ, Cheng L, Lee BK, Peng QL, Lu XF , An MH , Wang H, Shang S, Zhou BP, Wu H, Xu AM , Yuen KY, Chen Z. "Gut-homing Δ42PD1^{+}Vδ2 T cells promote innate mucosal damage via TLR4 during acute HIV type 1 infection." ***Nat Microbiol***, 2017; 2(10):1389-1402.
5. Tan Z, **Zhou J***, Cheung KL, Yu Z, Cheung KW, Liang J, Wang H, Lee BK, Man K, Liu L, Yuen KY, Chen Z. "Vaccine-elicited CD8+ T cells cure mesothelioma by overcoming tumor-induced immunosuppressive environment." ***Cancer Res***, 2014; 74(21):6010-6021.

* Co-first author

Technical expertise

- ✧ Immune cell isolation, culture and identification
- ✧ FACS analysis (cell subtypes, intracellular cytokine/chemokine/transcription factor staining)
- ✧ Hepatocellular carcinoma and mesothelioma mouse models
- ✧ DNA and viral vector vaccination

Novel strategies of liver cancer immunotherapy by co-targeting myeloid-derived suppressor cells

ZHOU Jingying, LIU Man, CHENG Alfred Sze-Lok

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

Hepatocellular carcinoma (HCC), mostly developed in fibrotic/cirrhotic liver, is a leading cause of cancer deaths worldwide. Although targeting the T cell co-inhibitory programmed death-1 (PD-1)/PD-1-ligand 1(PD-L1) axis shows promise against HCC, the overall response to this immune-checkpoint blockade (ICB) remains sub-optimal (<20%). With an aim to developing mechanism-based combination immunotherapy, we have recently reported enhancement of ICB efficacy by disrupting the HCC cell-myeloid-derived suppressor cell (MDSC) crosstalk (*Gut 2018; Nature Communication 2018*). Here we hypothesize that direct targeting of MDSCs can efficiently re-shape the immunosuppressive microenvironment to improve HCC immunotherapy.

By a mouse hepatoma cell Hepa1-6 orthotopic fibrotic HCC mouse model, we found that monocytic MDSC (M-MDSC) subset was dramatically expanded in murine fibrous liver and positively correlated with increased hepatic tumorigenicity. Hepatic stellate cell (HSC), as key profibrogenic stromal cell, stimulated immunosuppressive M-MDSC generation from human peripheral blood mononuclear cells (PBMCs). Mechanistically, activated HSCs initiated p38 MAPK-mediated enhancer remodeling and triggered monocyte-to-M-MDSC identity shifting. Enhancer inhibition by a clinically-trialed drug iBET-762 disrupted HSC-M-MDSC crosstalk and abrogated M-MDSC generation and immunosuppressive functions. Notably, combination of iBET-762 with anti-PD-L1 antibody significantly induced tumor-infiltrating T lymphocytes, leading to tumor eradication and prolonged host survival in fibrosis-associated HCC model. As we also showed profound suppression of HCC patient-derived M-MDSCs by enhancer inhibition, our results delineate an enhancer deregulation mechanism for M-MDSC generation in fibrous liver environment, highlighting a promising therapeutic strategy of combined enhancer and immune-checkpoint targeting for desmoplastic tumors.

This project is supported by Collaborative Research Fund C4017-14G, C4045-18W and the Focused Innovations Scheme 1907309.

Session V (DRB)

Speaker Biography

Dr. LE Thi Nguyet Minh graduated from the National University of Singapore in 2005 with a Bachelor degree in Life Sciences. She further received a Ph.D. degree in Computational and Systems Biology from the Singapore-Massachusetts Institute of Technology (MIT) Alliance under the guidance of Prof. Bing Lim and Prof. Harvey Lodish. From 2010 to 2015, she worked as a postdoctoral fellow with Prof. Judy Lieberman at Boston Children's Hospital and Harvard Medical School in the USA. She joined the Department of Biomedical Sciences at City University of Hong Kong (CityU) as a tenure-track Assistant Professor in August 2015.

Dr. Le is well recognised for her contributions to the field of microRNAs and cancer biology. Dr. Le was awarded several prestigious scholarships and fellowships during her studies such as the Lee Foundation study grant and the Singapore-MIT Alliance scholarship. She was one of the first three recipients of the L'Oréal Singapore for Women in Science National Fellowship. During her training at Harvard Medical School, she was awarded the Jane Coffin Childs fellowship, a prestigious postdoctoral fellowship in the USA. She also won a number of competitive travel scholarships and poster awards at international conferences. Dr. Le is currently leading a research group of 7 PhD students and 3 research assistants. The group focuses on functions of extracellular vesicles (EVs) in cancer microenvironment and application of RBCEVs in anti-cancer therapies.

Dr. Le is also a cofounder of Carmine Therapeutics and cochair of the Hong Kong RNA Club. More details can be found on https://lelabcityu.wordpress.com/.

Five recent representative publications

1. Chan KL[#], Peng B[#], Umar MI, Chan CY, Sahakyan AB, **Le MTN***, Kwok CK*. "Structural analysis reveals the formation and role of RNA G-quadruplex structures in human mature microRNAs." ***Chemical Communications***, 2018; 54(77):10878-10881.
2. Usman WM, Pham TC, Kwok YY, Vu TL, Ma V, Peng B, Chan YS, Wei L, Chin SM, Azad A, He AB, Leung AYH, Yang M, Shyh-Chang N, Cho WC, Shi J, **Le MTN***. "Efficient RNA drug delivery using red blood cell extracellular vesicles." ***Nature Communications***, 2018; 9(1):2359.
3. **Le MTN**, Hamar P, Guo C, Basar E, Perdigão-Henriques R, Balaj L, Lieberman J*. "miR-200-containing in extracellular vesicles promote metastasis of breast cancer cells." ***Journal of Clinical Investigation***, 2014; 124(12):5109–5128.
4. **Le MTN**[#], Shyh-Chang N[#], Khaw SL, Chin L, Teh C, Tay J, O'Day E, Korzh V, Yang H, Lal A, Lieberman J, Lodish HF*, Lim B*. "Conserved regulation of p53 network dosage by microRNA-125b occurs through evolving microRNA-target gene pairs." ***PLoS Genetics***, 2011; 7(9):e1002242.
5. **Le MTN**[#], Teh C, Shyh-Chang N, Xie H, Zhou B, Korzh V, Lodish HF*, Lim B*. "MicroRNA-125b is a novel negative regulator of p53." ***Genes & Development***, 2009; 23(7):862-876.

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Efficient RNA drug delivery using red blood cell extracellular vesicles

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Most of the current methods for programmable RNA drug therapies are unsuitable for the clinic due to low uptake efficiency and high cytotoxicity. Extracellular vesicles (EVs) could solve these problems because they represent a natural mode of intercellular communication.

However, current cellular sources for EV production are limited in availability and safety in terms of horizontal gene transfer. One potentially ideal source could be human red blood cells (RBCs). Group O-RBCs can be used as universal donors for large-scale EV production since they are readily available in blood banks and they are devoid of DNA. Here, we describe and validate a new strategy to generate large-scale amounts of RBC-derived EVs for the delivery of RNA drugs, including antisense oligonucleotides, Cas9 mRNA, and guide RNAs. RNA drug delivery with RBCEVs shows highly robust microRNA inhibition and CRISPR-Cas9 genome editing in both human cells and xenograft mouse models, with no observable cytotoxicity.

Session V (DRB)

Speaker Biography

Prof. FENG Bo（馮波）is an Associate Professor in the School Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong (CUHK). She is an active staff member in the Developmental and Regenerative Biology Thematic Research Program, Institute for Tissue Engineering and Regenerative Medicine, MOE Key Laboratory for Regenerative Medicine and CUHK-GIBH Joint Laboratory on Stem Cell and Regenerative Medicine. Prof. Feng graduated from Nankai University with B.Sc. (1993) and M.Sc (1996), and received her Ph.D. (2006) from National University of Singapore. After graduation, Prof. Feng joined Prof. Ng Huck Hui's lab in Genome Institute of Singapore as a postdoc. She worked on stem cells and reprogramming and published her works in *Nature Cell Biology, Cell Stem Cell* and *Nature*. In Nov 2010, Prof. Feng joined CUHK and her current research interest lies within the molecular mechanism that controls pluripotency and differentiation of ESCs/iPSCs, as well as development of new tools for stem cell research and applications.

Five recent representative publications

1. Zhang C, He X, Kwok YK, Wang F, Xue J, Zhao H, Suen KW, Wang CC, Ren J, Chen GG, Lai BS, Li J, Xia Y, Chan AM, Chan WY, **Feng B***. "Homology-independent multiallelic disruption via CRISPR/Cas9-based knock-in yields distinct functional outcomes in human cells." ***BMC Biology***, 2018; 16(1):151.
2. He X, Tan C, Wang F, Wang Y, Zhou R, Cui D, You W, Zhao H, Ren J, **Feng B***. "Knock-in of large reporter genes in human cells via CRISPR/Cas9-induced homology-dependent and independent DNA repair." ***Nucleic Acids Res***, 2016; 44(9):e85.
3. Hu J, Lei Y, Wong WK, Liu S, Lee KC, He X, You W, Zhou R, Guo JT, Chen X, Peng X, Sun H, Huang H, Zhao H, **Feng B***. "Direct activation of human and mouse Oct4 genes using engineered TALE and Cas9 transcription factors." ***Nucleic Acids Res***, 2014; 42(7):4375-4390.
4. Tsang WH, Wang B, Wong WK, Shi S, Chen X, He X, Gu S, Hu J, Wang C, Liu PC, Lu G, Chen X, Zhao H, Poon WS, Chan WY*, **Feng B***. "Lif-dependent primitive neural stem cells derived from mouse ES cells represent a reversible stage of neural commitment." ***Stem Cell Res***, 2013; 11(3):1091-1102.
5. **Feng B**, Jiang J, et al., Lufkin T, Ng HH. "Reprogramming of fibroblasts into induced pluripotent stem cells with orphan nuclear receptor Esrrb." ***Nat Cell Biol***, 2009; 11(2):197-203.

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Technical expertise

- ✧ Induced pluripotent stem cells
- ✧ Genome editing technology

CRISPR-mediated knock-in of large DNA & potentials in gene therapy

HE Xiangjun, ZHANG Chenzi, XUE Junyuan Katherine, ZHANG Zhenjie, FENG Bo

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

CRISPR/Cas9-induced site-specific DNA double-strand breaks (DSBs) can be repaired by homology-directed repair (HDR) or non-homologous end joining (NHEJ) pathways. Extensive efforts have been made to knock-in exogenous DNA to a selected genomic locus in human cells; which, however, has focused on HDR-based strategies and was proven inefficient. Here, we report that NHEJ pathway mediates efficient rejoining of genome and plasmids following CRISPR/Cas9-induced DNA DSBs, and promotes high-efficiency DNA integration in various human cell types. With this homology-independent knock-in strategy, integration of a 4.6 kb promoterless ires-eGFP fragment into the GAPDH locus yielded up to 20% GFP+ cells in somatic LO2 cells, and 1.70% GFP+ cells in human embryonic stem cells (ESCs). Quantitative comparison further demonstrated that the NHEJ-based knock-in is more efficient than HDR-mediated gene targeting in all human cell types examined. These data support that CRISPR/Cas9-induced NHEJ provides a valuable new path for efficient knock-in of large DNA in human ESCs and somatic cells, and hold potentials in a broad range of applications.

Session V (DRB)

Speaker Biography

Prof. ZHAO Hui（趙暉）is working at the School of Biomedical Sciences, The Chinese University of Hong Kong. He received his Bachelor Degree and Master Degree from Shandong University. He then went to Germany, and got his Ph.D. from the University of Essen, Germany. He had his post-doctoral training at the National Institutes of Health and Child Health and Development (NICHD) before he joined The Chinese University of Hong Kong in 2008. Professor Zhao Hui's research interests cover developmental biology and cancer biology. His laboratory studies the mechanism of neural crest differentiation, germ layer formation and cell migration, and how these multiple events affect the embryonic patterning. In the past few years, he also studied the tumorigenesis of neuroblastoma. Recently his group utilized TALEN and Cas9 nucleases to do gene targeting in Xenopus, zebrafish, and stem cells. He has published over 70 papers in high impact journals including *PNAS, Development, EMBO Journal, Nucleic Acids Research* and *Journal of Biological Chemistry*. He serves as reviewers for various magazines including *PNAS, Development*, and *Plos Biology*. His research is supported by the funds from the Ministry of Science and Technology, the National Natural Science Foundation of China and Hong Kong Research Grants Council.

Five recent representative publications

1. Li TF, Deng Y, Shi Y, Tian RJ, Chen YL, Zou L, Kazi JU, Rönnstrand L, Feng B, Chan SO, Chan WY, Sun J, **Zhao H**. "Bruton's tyrosine kinase potentiates ALK signaling and serves as a potential therapeutic target of neuroblastoma." ***Oncogene***, 2018; 37(47):6180-6194.
2. Shi Z, Wang F, Cui Y, Liu Z, Guo X, Zhang Y, Deng Y, **Zhao H***, Chen Y*. "Heritable CRISPR/Cas9-mediated targeted integration in Xenopus tropicalis." ***FASEB J***, 2015; 29(12):4914-4923.
3. Wang CD, Kam RTK, Shi WL, Xia Y, Chen XF, Cao Y, Sun J, Du Y, Lu G, Chen ZJ, Chan WY, Chan SO, Deng Y, **Zhao H**. "The proto-oncogene transcription factor Ets1 regulates neural crest development through Histone Deacetylase 1 to mediate output of bone morphogenetic protein signaling." ***J Biol Chem***, 2015; 290(36): 21925-21938.
4. Lei Y, Guo XG, Liu Y, Cao Y, Deng Y, Chen XF, Cheng HKC, Dawid IB, Chen YL, **Zhao H**. "Efficient targeted gene disruption in Xenopus embryos using engineered transcription activator-like effector nucleases (TALENs)." ***Proc Natl Acad Sci USA***, 2012; 109(43):17484-17489.
5. **Zhao H**, Han D, Dawid IB, Pieler T, Chen Y. "Homeoprotein hhex-induced conversion of intestinal to ventral pancreatic precursors results in the formation of giant pancreata in Xenopus embryos." ***Proc Natl Acad Sci USA***, 2012; 109(22): 8594-8599.

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Technical expertise

- ✧ Embryonic manipulation
- ✧ Genome editing
- ✧ Tumor biology
- ✧ Tissue engineering

Zswim4, a novel regulator for BMP signaling pathway, is essential for embryonic development

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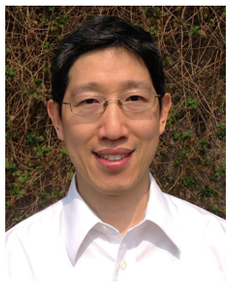
Developmental and Regenerative Biology Thematic Research Program, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, P.R. China.

The embryonic patterning refers to the generation of the complex organization of cell fates in space and time, which is regulated by the coordination of various signaling transductions. The BMP signaling is essential for the specification of the primary body axes, further differentiation of ectoderm, mesoderm and endoderm, and the maintenance of adult tissue homeostasis. In an attempt to understand the regulatory network of neural crest development, we identified Zinc finger SWIM domain-containing protein 4 (ZSWIM4), representing a group of proteins whose functions remain largely unknown. Zswim4 signal appeared in the dorsal blastopore lip at the onset of gastrula and then enriched at dorsal ectoderm at mid-gastrula stages. Its expression was detected in the anterior edge of the neural plate at neural stages, and in the lens, brain and some cranial nerves at the tailbud stage. Overexpression of Zswim4 in embryos causes a phenotype of inhibition of anterior axis and shortened body. Knockdown of Zswim4 disturbed embryo axis formation and a defect of eye development. In animal cap assay, the upregulation of *hox3, vent1, wnt8* induced by activation of BMP signaling are attenuated by the addition of Zswim4, suggesting that Zswim4 plays an inhibitory role in BMP signaling pathway. In line with this observation, the expression of vent1 and sizzled is decreased upon overexpression of *Zswim4* mRNA in two ventral blastomeres at the four-cell stage. The p-Smad1/5/8 is decreased upon *Zswim4* overexpression, while it is increased when Zswim4 expression was attenuated. Co-immunoprecipitation shows that Zswim4 physically interacts with Smad1. Furthermore, CRISPR/Cas9 was also used to disrupt *Zswim4* gene and establish a Zswim4 knockout Xenopus line for our future study. In summary, our data indicate that Zswim4 is a novel inhibitor of BMP signaling and plays an essential role during embryonic development.

Session VI (DRB)

Speaker Biography



Prof. WAN Chao（萬超） is an Associate Professor in School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong (CUHK). He is also a member of iTERM and MOE Key Laboratory for Regenerative Medicine, CUHK. Prof. Wan obtained his Ph.D. in Shanghai Jiaotong University School of Medicine in 2002, then worked as a resident Orthopaedic Surgeon in Longhua Hospital, Shanghai University of TCM. He pursued Postdoctoral training in School of Medicine, The Queen's University of Belfast, UK, and in School of Medicine, University of Alabama at Birmingham (UAB), USA until 2007. Before joining CUHK as an Assistant Professor in 2009, Prof. Wan was appointed as an Instructor in Department of Pathology, UAB, and an Instructor in Department of Orthopaedic Surgery, Johns Hopkins University School of Medicine. His research work has been published in international journals including *Proc Natl Acad Sci USA, J Clin Invest, Nat Med, Cell, Bone Res*, and *Biomaterials*. He was a recipient of British Orthopaedic Research Society Travelling Award, ICMRS Webster Jee Young Investigator Award, and ASBMR Harold Frost Young Investigator Award. His research work was supported by Hong Kong Research Grants Council, Health and Medical Research Fund, NSFC and MOST. He serves as an editorial board member of J Orthop Translat and Medical Reference Newspaper, Osteoporosis Channel, National Health and Family Planning Commission, P.R. China, and as a reviewer of more than 20 international journals in the field. His research interests include the molecular and cellular mechanisms of the oxygen sensing and growth factor pathways in skeletal development, degeneration and regeneration, and discovery of novel therapies for skeletal tissue repair or regeneration.

Five recent representative publications

1. Yang Z, Kou S, Wei X, Zhang F, Li F, Wang X, Lin Y, **Wan C***, Zhang W*, Sun F*. "Genetically programming stress-relaxation behaviour in entirely protein-based molecular networks." ***ACS Macro Lett***, 2018; 7:1468-1474.
2. Wang J*, Zhang F, Tsang WP, **Wan C***, Wu C. "Fabrication of injectable high strength hydrogel based on 4-arm star PEG for cartilage tissue engineering." ***Biomaterials***, 2017; 120:11-21.
3. Wang PZ, Zhang F, He Q, Wang J, Shiu HT, Shu Y, Tsang WP, Liang S, Zhao K, **Wan C***. "Flavonoid compound Icariin activates hypoxia inducible factor-1α in chondrocytes and promotes articular cartilage repair." ***PLoS One***, 2016; 11(2):e0148372.
4. Chen X, Gu S, Chen BF, Shen WL, Yin Z, Xu GW, Hu JJ, Zhu T, Li G, Ouyang HW, **Wan C**, Lee TL*, Chan WY*. "Nanoparticle delivery of stable miR-199a-5p agomir improves the osteogenesis of human mesenchymal stem cells via the HIF1a pathway." ***Biomaterials***, 2015; 53: 239-250.
5. Zhang F, He Q, Tsang WP, Garvey WT, Chan WY, **Wan C***. "Insulin exerts direct, IGF-1 independent actions in growth plate chondrocytes." ***Bone Research***, 2014; 2(2): 14012.

* Corresponding author

Technical expertise

✧ Transgenic mouse and skeletal disease animal models; biomaterials and skeletal tissue engineering; stem cell biology and mesenchymal lineage differentiation

The regulation of oxygen sensing and glucose metabolism in cartilage tissue engineering and regeneration

ZHAO Kai[1], SHU Yinglan[1], WANG Lin[1], ZHANG Fengjie[1], TSANG Wing Pui[1], WU Chi[2], SUN Fei[3], CHAN Wai Yee[1], WAN Chao[1]

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Articular cartilage is a thin layer of hyaline cartilage that consists of structural macromolecules including collagens, proteoglycans, glycoproteins and noncollagenous proteins. Being avascular and aneural, articular cartilage has very limited capacity of self-repair following injury or degeneration. Cartilage tissue engineering is considered as a promising approach for promoting articular cartilage repair. Chondrocytes are readily located in a hypoxic microenvironment during cartilage development or repair. Hypoxia inducible factor-alpha (HIF-α) is identified as a key mediator for chondrocyte adaptation to hypoxia, and involves in the regulation of cell survival, energy metabolism and differentiation. However, the detailed molecular mechanisms of the hypoxia/HIF-α pathway in regulation of the coordination of chondrocyte differentiation and energy metabolism during cartilage tissue engineering and regeneration remain to be elucidated. Using genetic, pharmacological and tissue engineering approaches we examined the roles of hypoxia or its memetic small molecules on the impact of chondrocyte fate control during cartilage tissue engineering and regeneration. We found that hypoxia (2% O_2) increased cartilaginous matrix synthesis and upregulated the expression of chondrogenic marker genes and proteins in the 3D complexes cultures than the normoxia controls. This was accompanied by increased glucose uptake, intracellular lactate and glutamate production of chondrocytes. Phosphofructokinase, liver (PFKL) was identified as an important mediator downstream of HIF-1α to regulate chondrocyte differentiation and glucose metabolism. In a mouse osteochondral defect model, transplantation of engineered cartilage tissue under hypoxia enhanced articular cartilage repair indicated by increased chondrogenic differentiation, cartilaginous matrix synthesis and inhibited cartilage hypertrophy compared with that under normoxia. Candidate small molecule HIF activators showed beneficial effects on promoting chondroprogenitor cell migration, differentiation and engraftment during articular cartilage repair. The newly generated bioscaffolds served as favorable matrix to support chondrocyte growth and differentiation in the above engineered or *in vivo* repair microenvironment. Our data suggest that targeting the oxygen sensing pathway is a potent approach to control chondrocyte fate during cartilage tissue engineering and regeneration.

Session VI (DRB)

Speaker Biography

Prof. JIANG Yangzi（姜洋子）received Bachelor (2007) and PhD (2012) in Zhejiang University, Hangzhou, China, and did her postdoctoral training (2012-2018) at University of Pittsburgh, PA, USA. Prof. Jiang joined The Chinese University of Hong Kong in 2018, and she is currently a research assistant professor at iTERM / SBS, CUHK. Prof. Jiang's previous research work has focused on creating tissue regeneration strategies of musculoskeletal system, particularly in bone and cartilage. Her publications cover the topics of stem cells, tissue engineering, cell transplantation, biomaterials, pathology of osteoarthritis, and translational medicine.

Prof. Jiang's lab has sought to understand the stem/progenitor cell origin (*Nat Rev Rheum*, 2015) and signaling pathways (*Arthritis Res Therapy*, 2015) of human articular cartilage in both healthy and disease conditions, and apply these knowledge to instruct the production of functional tissue replacements for clinical use. Prof. Jiang's work of taking the cartilage derived stem/progenitor cells for repair large-size of osteochondral defect (6-13 cm^2, ave 8.5 cm^2) in 15 young patients (*Stem Cells Transl Med*, 2016) has also paved a way for the autologous cell-based Tissue Engineering Techniques as Class III Therapeutics in China (*J Ortho Transl*, 2014), and many patients had been benefited from Prof. Jiang's work.

Five recent representative publications

1. He J[#], **Jiang Y**[#], Alexander PG, Ulici V, Zhu Y, Wu S, Tuan RS. "Infrapatellar fat pad aggravates degeneration of acute traumatized cartilage: a possible role for Interleukin-6." ***Osteoarthritis and Cartilage***, 2017; 25(1):138-145.
2. **Jiang Y**[#], Cai Y, Zhang W, Yin Z, Hu C, Tong T, Lu P, Zhang S, Neculai D, Tuan RS, Ouyang HW. "Human cartilage derived progenitor cells from committed chondrocytes for efficient cartilage repair and regeneration." ***Stem Cells Translational Medicine***, 2016; 5(6):1-12.
3. **Jiang Y**[#], Hu C, Yu S, Yan J, Peng H, Ouyang HW, Tuan RS. "Cartilage stem/progenitor cells are activated in osteoarthritis via interleukin-1β/nerve growth factor signaling." ***Arthritis Research & Therapy***, 2015; 17:327.
4. **Jiang Y**[#], Tuan RS. "Origin and function of cartilage stem/progenitor cells in osteoarthritis." ***Nature Reviews Rheumatology***, 2015; 11(4):206-212 .
5. Zhang W, Heng BC, **Jiang Y***, Ouyang HW*. "Clinical translation of autologous cell-based tissue engineering techniques as Class III therapeutics in China: Taking cartilage tissue engineering as an example." ***Journal of Orthopaedic Translation***, 2014; 2(2):56-65.

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Technical expertise

- ✧ Development of therapeutic strategies for musculoskeletal tissue regeneration
- ✧ The mechanism for degenerative and inflammatory diseases
- ✧ Cell based therapy and translational medicine
- ✧ Expertise key words: Osteoarthritis, Tissue Specific Stem Cells; Cartilage; Tissue Engineering; Cell-Based Therapy and Translational Medicine

Cellular based therapy for cartilage regeneration

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Cartilage is a specialized tissue with several interesting characteristics that highlight a trade-off between function and healing. On the one hand, cartilage is an incredibly robust tissue, with the principal function of providing mechanical support, especially in weight-bearing circumstances. On the other hand, most cartilage exhibits almost a complete lack of intrinsic healing abilities once damaged. These two characteristics, mechanical durability and healing resistance, both stem from the unique structure of cartilage. Adult hyaline cartilage tissue is composed of over 90% of extracellular matrix (ECM) and less than 2% chondrocytes in total volume. Adult human cartilage has limited self-repair ability, and damage to articular cartilage leads directly to the pathogenesis of osteoarthritis (OA), and OA progresses until the entire affected joint needs to be either fused or replaced.

Regenerative medicine aims to replace or regenerate human cells, tissues and organs to restore or establish normal function. The basic principle involves the application of cells, biomaterial scaffolds, and signaling molecules to promote endogenous regenerative capacity and/or the replacement of whole tissues with engineered constructs *in vitro* and *in vivo*. Autologous Chondrocyte Implantation/Transplantation (ACI/ACT) was first applied clinically to treat full-thickness chondral defects in knees by the Peterson group in 1994. Briefly, small amounts (~250 mg) of healthy cartilage were harvested from non-load bearing areas under arthroscopy, and the isolated chondrocytes were expanded *in vitro* for 2-3 weeks. The cultured cells were then injected into the defect area of cartilage and sealed with a sutured periosteal flap taken from the proximal medial tibia. The overall 0-5 year therapeutic efficacy was generally 70-90%, as evidenced by relief of symptoms and improvement of joint function. In a 10-20 year (mean,12.8 year) follow up study, 74% of the 224 patients that underwent ACI treatment reported their status as good or better than before surgery. ACI provides the possibility of regenerating cartilage tissues and restoring normal joint function, criteria which meet the basic clinical definition for functional cartilage repair. The limitation of ACI/ACT is that lack of cell sources, therefore different types of stem cells were studied and evaluated. Our recent study suggested that the tissue specific stem/progenitor cells that derivate from human adult articular cartilage can be enriched as proper cell sources for cartilage repair, which overcome the cell number and quality problem that we used to meet in the clinical application.

Session VI (DRB)

Speaker Biography

Prof. LEE Chien-Wei（李建緯）'s research interest focuses on ageing-related diseases, such as osteosarcopenia and nonalcoholic fatty liver disease. He also seeks to explore the translational application of mesenchymal stem cells. He has extensively studied the epigenetic regulation of MSCs and has discovered the hepatogenic lineage plasticity of mesenchymal stem cells. Prof. Lee has published in several leading journals such as *Gastroenterology, Stem Cell Reports, Translational Research* and *Scientific Reports.*

Prof. Lee has investigated the epigenetic modifiers governing the proliferation and differentiation process of MSCs. He has demonstrated that the manipulation of TGF-β1-DNA methyltransferases axis accelerates hepatogenic differentiation of MSCs and governs the cell fate switch of primary hepatocyte toward MSC-like cells. He also found dexamethasone-induced osteoporosis is epigenetically controlled by histone deacetylase 6. Now, the primary research theme of Prof. Lee's study is the therapeutic potential and the mechanisms of MSCs and their exosomes in nonalcoholic fatty liver disease and osteosarcopenia.

Four recent representative publications

1. **Lee CW***, Chen YF*, Wu HH*, Lee OK. "Historical perspectives and advances in mesenchymal stem cell research for the treatment of liver diseases." ***Gastroenterology***, 2018; 154(1):46-56.
2. **Lee CW**, Huang WC, Huang HD, Huang YH, Ho JH, Yang MH, Yang VW, Lee OK. "DNA methyltransferases modulate hepatogenic lineage plasticity of mesenchymal stromal cells." ***Stem Cell Reports***, 2017; 9(1):247-263.
3. **Lee CW**, Hsiao WT, Lee OK. "Mesenchymal stromal cell-based therapies reduce obesity and metabolic syndromes induced by a high-fat diet." ***Transl Res***, 2017; 182:61-74.
4. Rimando MG, Wu HH, Liu YA, **Lee CW**, Kuo SW, Lo YP, Tseng KF, Liu YS, Lee OK. "Glucocorticoid receptor and histone deacetylase 6 mediate the differential effect of dexamethasone during osteogenesis of mesenchymal stromal cells (MSCs)." ***Sci Rep***, 2016; 6:37371.

* Equal contribution

Technical expertise

- ✧ Stem cell biology and immunology
- ✧ Molecular cell biotechnology, WB, ELISA, Cloning, Protein expression, PCR, immunostaining, FASC, exosome isolation
- ✧ Cell culture (primary cell, stem cell and cell line) and cell-based assays
- ✧ Animal model in ageing, fatty liver, osteoporosis and sarcopenia

Mesenchymal stem cell-based therapy for non-alcoholic fatty liver disease

LEE Chien-Wei, LEE Oscar

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Obesity and its related diseases, such as nonalcoholic fatty liver disease (NAFLD), cause heavy socioeconomic burden and an alarming global health problem. In Hong Kong, 50% of the population is overweight or obese, and 14%-67% (increased with age) people suffer from NAFLD. NAFLD refers to a spectrum of hepatic histological abnormalities spanning from nonalcoholic fatty liver (NAFL), featured by simple steatosis, to nonalcoholic steatohepatitis (NASH), characterized by cellular injury and inflammatory infiltrates, then to fibrosis or cirrhosis. Currently, the effects of pharmacological agents for NAFLD treatment remain unsatisfactory. Therefore, the development of new therapeutic regimes for NAFLD is imperative. Human mesenchymal stem cells (MSCs) are well-established sources for tissue homeostasis and cell therapy because of their unique function in self-renewal, trophic support, differentiation potential. The convenient isolation, unlimited availability and cost-effective scale-up of MSCs make them have great potential for clinical application. We found that human MSCs, MSC-derived brown adipocytes (M-BA), and MSC lysate are able to treat high-fat diet induced NAFLD and acute liver diseases. Transplantation of those cells repressed lipid accumulation, macrophage infiltration, collagen deposition and inflammation in the liver of high-fat diet-fed mice through a paracrine effect.

On the other hand, exosomes derived from MSCs (MSC-exosomes), the major components of the MSC secretome, confer the therapeutic effects via their cargos, such as micro RNA, long non-coding RNA, proteins and lipids. MSC-exosomes, with high liver organotropism, possessed liver regeneration ability through inducing proliferation and repressing apoptosis in hepatocytes; MSC-exosomes also alleviated CCl4-induced liver fibrosis; however, the effect and mechanism of action of MSC-exosomes on NAFLD are still unknown. Together, we suggest that MSCs possess therapeutic potential in for the treatment of NAFLD.

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