



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



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PROGRESS REPORT

JAN-DEC
2018

Li Ka Shing Institute of Health Sciences
李嘉誠健康科學研究所進度報告

Li Ka Shing Institute of Health Sciences Progress Report
李嘉誠健康科學研究所進度報告

2018

Li Ka Shing Institute of Health Sciences Progress Report 李嘉誠健康科學研究所進度報告

Li Ka Shing Medical Sciences Building
The Chinese University of Hong Kong, Prince of Wales Hospital
Shatin, The New Territories, Hong Kong SAR
The People's Republic of China

中華人民共和國香港特別行政區
新界 沙田 威爾斯親王醫院 李嘉誠醫學大樓



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EXECUTIVE SUMMARY

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香港中文大學
The Chinese University of Hong Kong

EXECUTIVE SUMMARY

報告摘要

2018 was another productive year for the Principal Investigators at the Institute in the pursuit of our mission to translate scientific developments into medical advances that would benefit the society and the patients. Over the past year, a number of our Principal Investigators were honoured with prestigious awards.

Professor Jun Yu, working on gastrointestinal diseases, was presented The Ho Leung Ho Lee Foundation Prize for Progress in Science and Technology, for her substantial medical discoveries and her contributions to the Chinese scientific community in recent years.

I would also like to extend my heartfelt congratulations to Professor Francis Chan and Professor Joseph Sung for their notable achievements in 2018. Professor Chan was the first Chinese honored with the American College



Dennis Lo

Director, Li Ka Shing Institute of Health Sciences
Li Ka Shing Professor of Medicine
The Chinese University of Hong Kong

of Gastroenterology International Leadership Award 2018, and he was also conferred the Honorary Doctorate Degree by Osaka City University. Furthermore, Professor Joseph Sung has been conferred Honorary Doctorate Degree by the University of Macau.

Principal Investigators from our Diabetes and Obesity research team were honored with prestigious awards over the year. Professor Juliana Chan received an Honorary Fellowship from Monash University, Australia, in recognition of her distinguished scientific achievements for the benefit of the community. Recently, the American Diabetes Association has announced that Professor Chan will be presented the 2019 Harold Rifkin Award for Distinguished International Service in The Cause of Diabetes. Additionally, Professor Ronald Ma, another key member of the team, was selected as Fellow of the American College of Endocrinologist.

One of our young Clinician-Scientists, Professor Gary Tse, has been granted with a highly competitive Croucher Foundation Clinical Assistant Professorship in recognition of his research excellence into cardiovascular physiology.

In particular, I am most honored to receive the 2018 Annual Achievement Award by the Chinese Society Clinical Oncology (CSCO) together with Professor Allen Chan, for our study on "Analysis of Plasma Epstein-Barr Virus DNA to Screen for Nasopharyngeal Cancer (NPC)". This award is one of the highest recognitions in China in the field of Clinical Oncology.

Furthermore, during the ceremony held on 15 March 2018, Professor Rossa Chiu and I were jointly awarded the Leaders of the Year Awards 2017 in the Commerce & Industry / Finance category, founded by the Sing Tao News Corporation Limited, for our work on cancer screening and non-invasive prenatal testing.

On the scientific front, our Principal Investigators have produced significant publications in their respective research areas in 2018.

Professor Rossa Chiu, working on molecular diagnosis, has presented a review on the current state of use of maternal blood DNA sequencing for fetal chromosomal and genetic assessment in the *New England Journal of Medicine*.

Professor Sunny Wong, Professor Jun Yu, Professor Siew Ng and other scientists have confirmed the association of colorectal cancer with bacteremia and uncovered novel associations for several novel species, including *Peptostreptococcus species*, *Clostridium septicum* and *Gemella morbillorum*. The team has expanded the list of microbes for which bacteremia should raise clinical red flags to exclude colorectal cancer and to highlight that the colonic microbial flora may contribute to colorectal cancer which provides support to the bacterial theory of carcinogenesis.

Professor Jun Yu and team also comprehensively profiled paired Non-alcoholic Fatty Liver Disease (NAFLD) induced Hepatocellular Carcinoma (HCC) tissues by utilising next-generation sequencing platforms, which revealed that Squalene Epoxidase (SQLE), and enzyme that catalyses the first oxygenation step in sterol biosynthesis, is highly expressed in NAFLD-HCC. They have established SQLE as a novel oncogene and therapeutic target in NAFLD-HCC. NAFLD-HCC is an emerging malignancy in the developed world.

I am very honoured to be named as one of the "Top 20 Translational Researchers" by the world-renowned scientific journal *Nature Biotechnology*, for 2 consecutive years in 2016 & 2017. *Nature Biotechnology* ranked the biotech's top translational researchers based on the total patents granted in a year and the most-cited patent for the past 5 years.

Together with the Institute's scientists and research teams, we would strive hard to further push forward the frontier of translational medicine in the coming years.

報告摘要

一年過去，李嘉誠健康科學研究所各首席研究員致力將科研成果轉化成各種創新醫學科技，惠及病人及整個社會。多位首席研究員的卓越科研成就及貢獻得到多方重視和認同，獲頒授不少重要獎項。

致力於消化疾病研究的于君教授獲何梁何利基金頒發2018年度科學與技術進步獎（醫學藥學獎），以表揚她近年在醫學領域取得的重大發現，以及對中國科學技術進步與創新的傑出貢獻。

我亦對消化疾病研究團隊陳家亮教授及沈祖堯教授於2018年獲得的成就致以衷心的祝賀。陳教授成為首位華人獲美國腸胃科醫學院頒發「國際領袖大獎」，同時亦獲日本大阪市立大學頒授名譽博士銜。而沈教授亦獲澳門大學頒授榮譽博士學位。

糖尿病與肥胖症研究團隊於過往一年亦收獲甚豐。陳重娥教授獲澳洲蒙納士大學頒發榮譽院士名銜，以表彰其在糖尿病研究領域上的貢獻。最近，美國糖尿病協會亦宣佈頒發2019年Harold Rifkin Award予陳教授，表揚陳教授在糖尿病研究方面的卓越成就和國際影響力。團隊另一重要成員馬清雲教授，亦獲選為美國內分泌醫學會院士。

此外，研究所其中一位新晉醫生科學家謝家偉教授，就著他於心血管生理學的研究，獲得裘槎基金會臨床助理教授席。

本人及陳君賜教授的其中一個研究項目證實了透過分析血漿內EB病毒（Epstein-Barr virus）DNA可在未有病徵前便有效地及早診斷出鼻咽癌，並獲中國臨床腫瘤學會頒發2018年度成就大獎，這是中國於臨床腫瘤學領域上的其中一個最高榮譽。

於2018年3月15日的頒獎典禮上，本人與趙慧君教授榮獲由星島報業集團舉辦的「2017年傑出領袖選舉」工商/金融組別獎項，這是對我們於癌症篩查及產前無創診斷技術研究工作的肯定。

在科研發展方面，研究所各首席研究員於本年內均在其專項範疇內取得卓越成就，並於各大國際權威學術期刊發表他們的研究成果。

分子診斷學的趙慧君教授於著名醫學期刊《新英倫醫學雜誌》發表了一份綜述，就著目前以母體血液DNA排序作胎兒染色體及基因檢測的應用狀況作出深入討論。

黃曦教授、于君教授、黃秀娟教授及其他科學家於研究中證實了大腸癌與菌血症的關係，並發現了幾個新的物種關聯，當中包括消化性鏈球菌、敗血性梭菌等。研究團隊擴大了結直腸癌相關微生物群的名單，包括一些不太為人所知的微生物，並指出對這些微生物的菌血症應該引起臨床警惕以排除結直腸癌。該研究亦強調結腸微生物菌群可能與結直腸癌有關，並為細菌致癌的學論提供了支持。

非酒精性脂肪性肝病（NAFLD）誘導的肝細胞癌（HCC）是發達國家新出現的惡性腫瘤。于君教授及其團隊全面分析了成對的NAFLD-HCC組織，揭示了SQLE（角鯊烯環氧酶）是一種催化甾醇生物合成中第一個氧合步驟的酶，在NAFLD-HCC中高表達。研究團隊建立了SQLE作為NAFLD-HCC中的新型致癌基因和治療靶標。SQLE抑制劑（特比萘芬）可能是預防和治療NAFLD-HCC的有前途的方法，為靶向NAFLD-HCC提供了新的方向。

除此之外，本人很榮幸能連續第二年獲權威科學期刊《自然—生物科技》選為「全球20位頂尖轉化研究科學家」之一。這是對本人及研究團隊於過去兩年獲得專利的項目，及專利被引用的次數，成功將醫學基礎研究成果有效地應用在臨床技術或藥物上的認同。

來年，我們將與研究所的科學家和研究團隊一起，繼續努力攜手走在轉化醫學研究的前沿。

盧煜明

香港中文大學
李嘉誠醫學講座教授 李嘉誠健康科學研究所所長



GOVERNANCE AND ADMINISTRATION

管治與行政

Steering Committee 督導委員會

The Steering Committee of the Li Ka Shing Institute of Health Sciences (LiHS) was formed in 2007. The twelfth meeting of the Steering Committee was held on 10 December 2018 and was attended by the committee members who gave invaluable recommendations on the future development and direction of the Institute.

李嘉誠健康科學研究所督導委員會於2007年正式成立。本年度的督導委員會會議於2018年12月10日舉行，會上各成員就研究所的未來發展發表了寶貴的意見。

Members 成員



Prof. Dennis Lo 盧煜明教授

Associate Dean (Research), Faculty of Medicine, CUHK
Li Ka Shing Professor of Medicine, CUHK
Director of LiHS, CUHK
Professor of Chemical Pathology, CUHK
香港中文大學醫學院副院長（研究）
香港中文大學李嘉誠醫學講座教授
香港中文大學李嘉誠健康科學研究所所長
香港中文大學化學病理學講座教授

Chairman 主席



Prof. Francis Chan 陳家亮教授

Dean of Medicine, CUHK
Choh-Ming Li Professor of Medicine & Therapeutics, CUHK
香港中文大學醫學院院長
香港中文大學卓敏內科及藥物治療學講座教授



Dr. Frieda Law 羅敏潔醫生

Representative of the Li Ka Shing Foundation
Consultant, Shantou University Medical College
李嘉誠基金會代表
汕頭大學醫學院顧問



Prof. Wai-yee Chan 陳偉儀教授

Pro-Vice-Chancellor / Vice-President, CUHK
Director, School of Biomedical Sciences, CUHK
Professor of Biomedical Sciences, CUHK
香港中文大學副校長（策略發展）
香港中文大學生物醫學學院院長
香港中文大學生物醫學講座教授



Prof. Hsiang-fu Kung 孔祥復教授*

Emeritus Professor of Virology, CUHK
Academician of the Chinese Academy of Sciences
香港中文大學榮休病毒學講座教授
中國科學院院士



Prof. Joseph Lau 劉允怡教授

Choh-Ming Li Research Professor of Surgery, Faculty of Medicine, CUHK
Academician of the Chinese Academy of Sciences
香港中文大學醫學院卓敏外科研究教授
中國科學院院士



Prof. Hui-yao Lan 藍輝耀教授

Assistant Dean (Research), Faculty of Medicine, CUHK
Choh-Ming Li Professor of Biomedical Sciences, CUHK
Associate Director of LiHS, CUHK
香港中文大學醫學院助理院長（研究）
香港中文大學卓敏生物醫學講座教授
香港中文大學李嘉誠健康科學研究所副所長



Prof. Guoping Zhao 趙國屏教授

Professor of Microbiology, CUHK
Academician of the Chinese Academy of Sciences
香港中文大學微生物學講座教授
中國科學院院士

Secretary 秘書

Ms. Cecilia Leung 梁欣欣女士

Assistant Secretary of LiHS, CUHK
香港中文大學李嘉誠健康科學研究所辦公室主任

Professor Hsiang-fu Kung had been serving as a member of the Steering Committee since the opening of the Institute, who had given invaluable recommendations on the development and direction of the Institute.

The Steering Committee and the Institute are in great sadness for the passing away of Professor Kung on 17 June 2019.

孔祥復教授由研究所成立至今一直擔任本督導委員會委員，為研究所的發展發表了寶貴的意見。

孔教授於2019年6月17日辭世，本督導委員會及研究所全人深表哀悼。

The Twelfth Meeting of the Steering Committee
(10 December 2018)

第十二次督導委員會會議
(2018年12月10日)

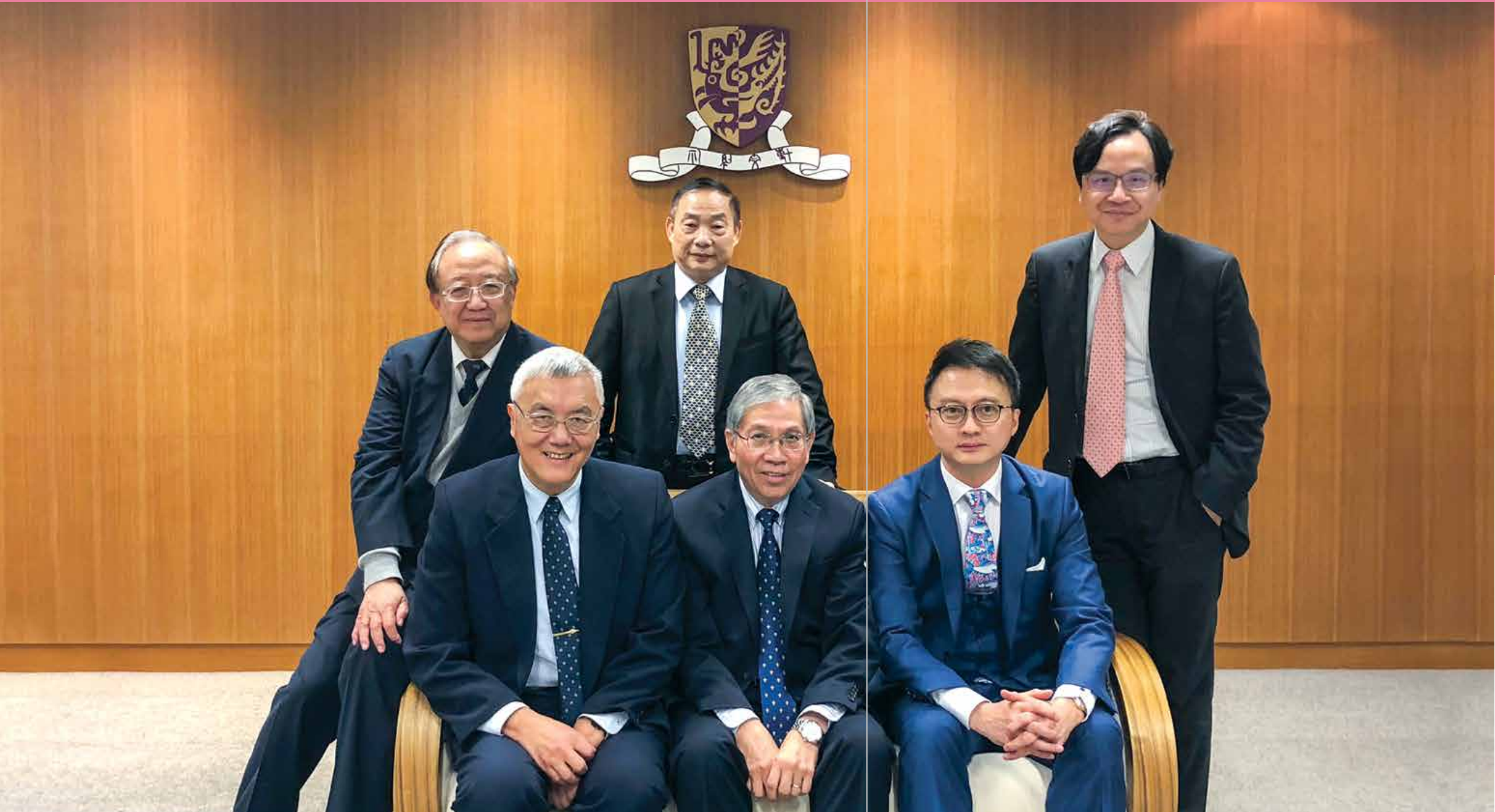
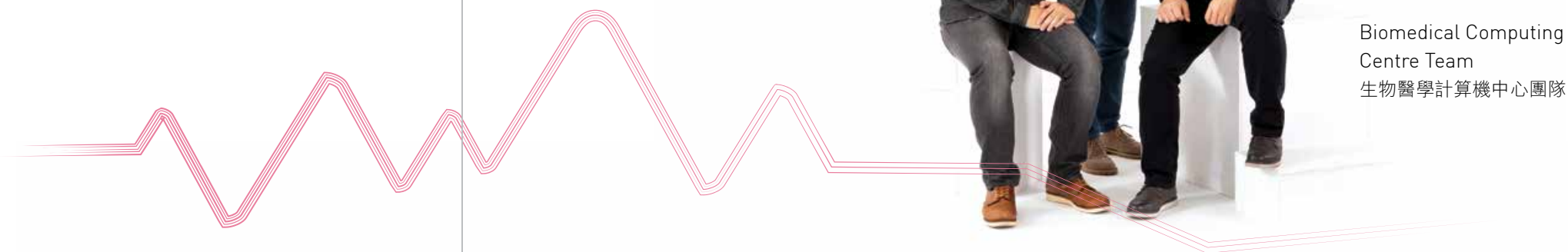


Photo from Left to Right 相片由左至右	Back Row 後排	Prof. Joseph Lau 劉允怡教授	Prof. Hui-yao Lan 藍輝耀教授	Prof. Dennis Lo 盧煜明教授
	Front Row 前排	Prof. Guoping Zhao 趙國屏教授	Prof. Wai-yee Chan 陳偉儀教授	Prof. Francis Chan (Chairman) 陳家亮教授 (主席)

LiHS Office 研究所辦公室

As of December 2018, a total of 12 staff members in the LiHS Office were in post, including administrative, scientific, research and technical staff. During the reporting period, the LiHS office oversaw the general administration of the Institute, the Li Ka Shing Medical Sciences Building, and the various core facilities, including the Biomedical Computing Centre, the Molecular Biology Core Facilities, and the Cell Biology Core Facilities.

截至2018年12月底，研究所辦公室共已聘任12名僱員，包括行政、科學、研究及技術人員，負責研究所的日常運作，並支援重點科研設施的運作，包括生物醫學計算機中心、分子生物學重點科研設施、和細胞生物學重點科研設施。



Biomedical Computing
Centre Team
生物醫學計算機中心團隊



Core Laboratory Team
重點科研設施團隊



THE LI KA SHING MEDICAL SCIENCES BUILDING

李嘉誠醫學大樓

THE LI KA SHING MEDICAL SCIENCES BUILDING

李嘉誠醫學大樓

The Li Ka Shing Institute of Health Sciences was housed inside the 11-storey Li Ka Shing Medical Sciences Building. As of December 2018, there were approximately 469 research personnel working in the Building. Principal Investigators and their research groups were allocated research space inside the Building following assessment by the Faculty's Research Space Allocation Committee, based on their track records in research. In addition, several multi-disciplinary research laboratories were allocated on a departmental and/or strategic basis.

With the full support from the University and the Faculty, the Institute will recruit additional top-notch research scientists in order to enhance our competitiveness in research.

李嘉誠健康科學研究所建於樓高11層的李嘉誠醫學大樓內。截至2018年12月，約有469名科研人員於大樓內工作。醫學院研究空間分配委員會根據各項目負責人及其隊伍的研究成果分配各隊伍在研究所內可使用的研究空間。另外，委員會亦根據所屬部門及策略性原則分配各個多範疇的實驗室。

在大學和醫學院的全力支持下，研究所將招聘更多出類拔萃的科學家以提升我們的科研實力。



11-Storey



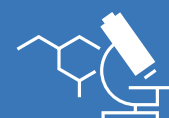
Diseases & Pathobiology



469 Research Personnel



New Technologies



Multi-disciplinary Research Laboratories



RESEARCH FACILITIES

研究設施

RESEARCH FACILITIES

研究設施

The Institute aims to provide an environment conducive to cutting-edge scientific research and technological innovations in biomedical sciences. With the many facilities at the Institute, the researchers at the University and the Faculty can focus on testing their hypotheses and realising their scientific dreams.

研究所致力為走在時代尖端的科研項目及創新技術提供良好的科研環境。所內的多元化設施讓中文大學及其醫學院的研究員能夠專注實驗及假設檢定，實現他們的科研夢想。

Biomedical Computer Centre 生物醫學計算中心

The **Biomedical Computing Centre** is one of the important facilities within the Institute and is a key part of the translational genomics focus of the Institute.

To cater for growing research needs on Next Generation Sequencing (NGS) and data analysis, the Centre continues to enhance its storage systems, system analysis workflow and computing systems in addition to the existing system resources.

生物醫學計算中心是研究所內的重要設施之一，亦是研究轉譯基因組學的重要一環。

為滿足次世代排序(NGS)和數據分析方面日益增長的研究需要，中心在原有的基礎設施和及系統建設之基礎上，持續加強其存儲系統、系統分析工作流程和計算系統，提升系統的存儲及運算能力，配合應對及支援日後研究及NGS排序的數據分析。

- Launching of a new high speed 2.16PB near-line storage system that has been integrated with the existing Tier 2 storage for raw sequencing and analysis data.

啟用全新的2.16PB高容量高速在線存儲系統，擴展第二層存儲器整體容量及負載能力，並增強整體儲存NGS原數據的存儲系統穩定性與數據傳輸性能。

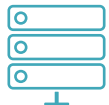
- Deployment of new analysis workflow under a new computing environment to enhance and strength the efficiency of NGS analysis works.

整合新系統分析工作流程，增強和擴展系統處理及操作分析工作的性能和效率。

- Deployment of new computing server for supporting Sequel Pacbio Sequencer and SMRTLink data analysis workflow, as well as expanding the storage capacity of Tier 2 data storage for NGS data analysis.

應用新增服務器及配合新擴展第二層高速存儲系統應用，擴展及增強Sequel Pacbio排序儀的整體工作及分析能力。



 32
Server Racks

 8PB
Petabytes Storage

 2,550.45
TeraFLOPS

 >6TB
RAM

 1,344 CPU Cores &
14,400 CUDA Cores

 100GE
backbone network
10GE and 40GE
to Servers and Storage Systems

Core Facilities
重點科研設施

The **Core Facilities** at the Institute include the following:

研究所內的**重點科研設施**包括：

■ Molecular Biology Core Facilities 分子生物學重點科研設施	■ Cell Biology Core Facilities 細胞生物學重點科研設施
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Molecular Biology Core Facilities
分子生物學重點科研設施

The **Molecular Biology Core Facilities** provide comprehensive molecular research platforms to perform four major functions: [Sample Quality Control](#), [Transfection](#), [Molecular Analysis](#), and [Data Analysis](#).

分子生物學重點科研設施為研究員提供全面的科研平台，進行樣本品質管制、基因轉染、分子分析及數據分析。

■ Sample Quality Control
樣本品質管制

Nucleic Acid Quantification and Quality Assessment
核酸定量分析和質量評估

To evaluate the sizing, quantity and quality of DNA and RNA, which is essential for many downstream applications.

評估DNA和RNA片段的長度、濃度和質量，以備後續實驗使用。



Agilent Bioanalyzer
生物分析儀



Invitrogen Qubit 2.0 Fluorometer
核酸蛋白螢光定量儀



Thermo Fisher Scientific Nanodrop
ND-1000 & ND-2000 Spectrophotometers
超微量分光光度計

■ Transfection 基因轉染

Electroporation
電脈衝穿孔

To transfect any DNA vectors (expression plasmids, shRNA vectors) into difficult-to-transfect cell lines and primary cell.

將DNA載體（表達質粒或shRNA載體）轉染成細胞株及原代細胞。



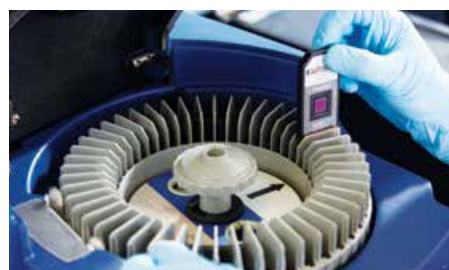
Amaxa Nucleofector II
電穿孔轉殖儀

■ Molecular Analysis 分子分析

Gene Expression Profiling, Analysis and Genotyping
基因表現模組及基因型態分析

To analyse genotyping, copy number variation, DNA methylation and gene expression profiling.

分析基因表型、拷貝數變異、基因甲基化及基因表達模譜。



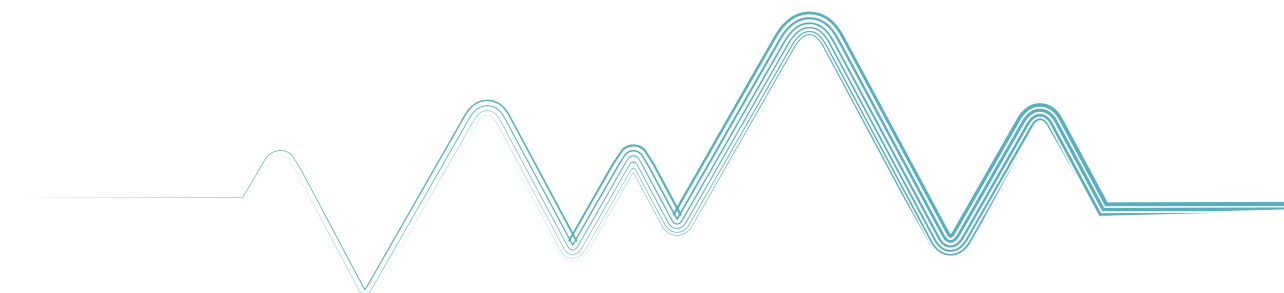
Life Technology QuantStudio12K Flex
Real-Time PCR System
定量實時聚合酶鏈鎖反應儀



Affymetrix Microarray System
微陣列分析儀



Illumina iScan Microarray System
芯片掃描系統



Bead-based Suspension 磁珠懸浮偵測

To quantify up to 100 analytes in a single sample (i.e. a flexible multiplex immunoassay system which uses colour-coded bead sets).

利用多重抗體陣列系統對樣本進行定量分析，可同時處理單一樣本內高達100種分析物。



BioRad BioPlex-200 Bead-based
Suspension Array System
珠子懸浮液相芯片系統

■ Data Analysis 數據分析

Data Analysis Workstation
數據分析工作平台

To analyse data generated by microarray analysis (i.e. an integrated and comprehensive data analysis tool).

對微陣列數據進行綜合分析。

GenomeStudio
基因組分析工作平台

Transcriptome Analysis Console
轉錄組分析控制台

Cell Biology Core Facilities 細胞生物學重點科研設施

The **Cell Biology Core Facilities** provide comprehensive cellular research platforms to perform three major functions: **Cell Selection**, **Cell Culturing** and **Cellular Imaging**.

細胞生物學重點科研設施為研究員提供全面的研究平台，進行細胞篩擇和培育細胞，及提供細胞成像。

■ Cell Selection 細胞篩擇

Microdissection 顯微切割

To isolate a single cell of interest or particular areas of samples by a contactless and contamination-free method.

利用非接觸及無污染技術，分離一個或一群目標細胞。

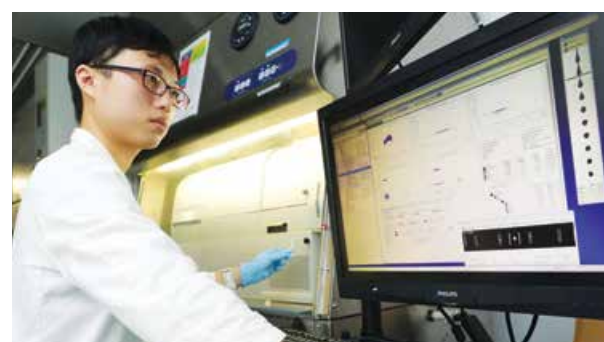


Leica LMD7000 Laser Micro-dissector
激光捕獲顯微切割器

Individual Cell Analysis & Collection 個體細胞分析與收集

To characterise and collect cells of interest as the cells pass through the sample stream and are interrogated by laser beam.

以雷射激光照射流動中的細胞，分類並收集目標細胞。



BD FACSaria Fusion Flow Cytometry Cell Sorter
流式細胞分選儀

■ Cell Culturing 細胞培養

Cell Expansion & Testing 細胞擴增和測試



Biosafety Cabinet
生物安全櫃

Cell Culture Facilities equipped with NSF49 certified Biosafety Cabinets, which facilitate the culturing of animal cells, animal cell lines and human cell lines. In view of increasing demand of cell culture facilities in recent years, Cell Culture Facilities have been expanded and enhanced in past years. The doubled capacity of cell culture facilities would benefit Principal Investigators from a wide spectrum of cell related specialties and speed up research work.

細胞培養設施內設有符合NSF49標準的生物安全櫃，可供研究員培育動物細胞、動物細胞株及人類細胞株。為配合日益增長的需求，研究所於去年擴充細胞培育設施，設施容量倍增後，有助提升研究效率並有利於研究與細胞相關的項目。

■ Cellular Imaging 細胞成像

Confocal Laser Scanning Imaging 共聚焦激光掃描顯微技術

To acquire optical sections, high resolution images, three-dimensional images for co-localisation analysis of subcellular structures, and dynamic processes for cellular research.

用於採集高分辨率圖像，包括用於亞細胞結構的共定位分析和細胞研究的動態過程的三維圖像。



Leica TCS SP8 Confocal Laser Scanning Microscope
共聚焦激光掃描顯微鏡

RESEARCH ACTIVITIES AND OUTPUTS

科研動態

RESEARCH ACTIVITIES AND OUTPUTS

科研動態

Research Areas and Teams

研究領域及隊伍

Research teams within the Institute can be grouped under two main areas, namely, “**Diseases and Pathobiology**” and “**New Technologies**”. Details of the research areas and their Principal Investigators are shown below:

研究所內的研究隊伍可大致分為兩大研究範疇，是為「**疾病及病理生物**」和「**創新技術**」。目前研究所屬下各個研究領域及小組的項目負責人詳列如下：



Diseases and Pathobiology 疾病及病理生物

Research Area 研究領域	Principal Investigator	首席研究員
Asian Cancers 亞洲癌症研究	Kwok-wai Lo Ka-fai To Nathalie Wong Qian Tao Siu-tim Cheung	羅國煒 杜家輝 王昭春 陶謙 張兆恬
Digestive Diseases 消化疾病研究	Jun Yu	于君
Vascular Medicine 血管疾病研究	Yu Huang Xiaoqiang Yao Gary Tse	黃聿 姚曉強 謝家偉
Diabetes and Obesity 糖尿病與肥胖症研究	Juliana Chan	陳重娥
Emerging Infectious Diseases 防疫研究	Shui-shan Lee	李瑞山
Molecular Microbiology 分子微生物學研究	Guoping Zhao Sunny Wong	趙國屏 黃曦
Inflammatory Diseases 炎症性疾病研究	Hui-yao Lan Erik Fung	藍輝耀 馮以文
Neuroscience 神經科學	Owen Ko	高浩
Reproduction and Development 生殖與發育研究	Ronald Wang	黃志超



New Technologies 創新技術

Research Area 研究領域	Principal Investigator	首席研究員
Molecular Diagnostics 分子診斷學	Dennis Lo Rossa Chiu Nelson Tang Allen Chan	盧煜明 趙慧君 鄧亮生 陳君賜
Fecal Microbiota Transplantation 腸道微生物移植研究	Siew Ng	黃秀娟
Stem Cells and Tissue Regeneration 幹細胞及組織再生研究	Oscar Lee Gang Li Kathy Lui Ling Qin	李光申 李剛 呂愛蘭 秦嶺
Genomics and Bioinformatics 基因組學與生物訊息學	Hao Sun Peiyong Jiang	孫昊 江培勇
Non-coding RNAs 非編碼核糖核苷酸研究	Huating Wang	王華婷
Cellular Signalling 細胞訊號轉導	William Wu	胡嘉麒

Publications and Other Research Outputs

學術著作及其他研究輸出

A summary of the publications and other research outputs of individual teams for the reporting period can be found in the [Appendix](#).

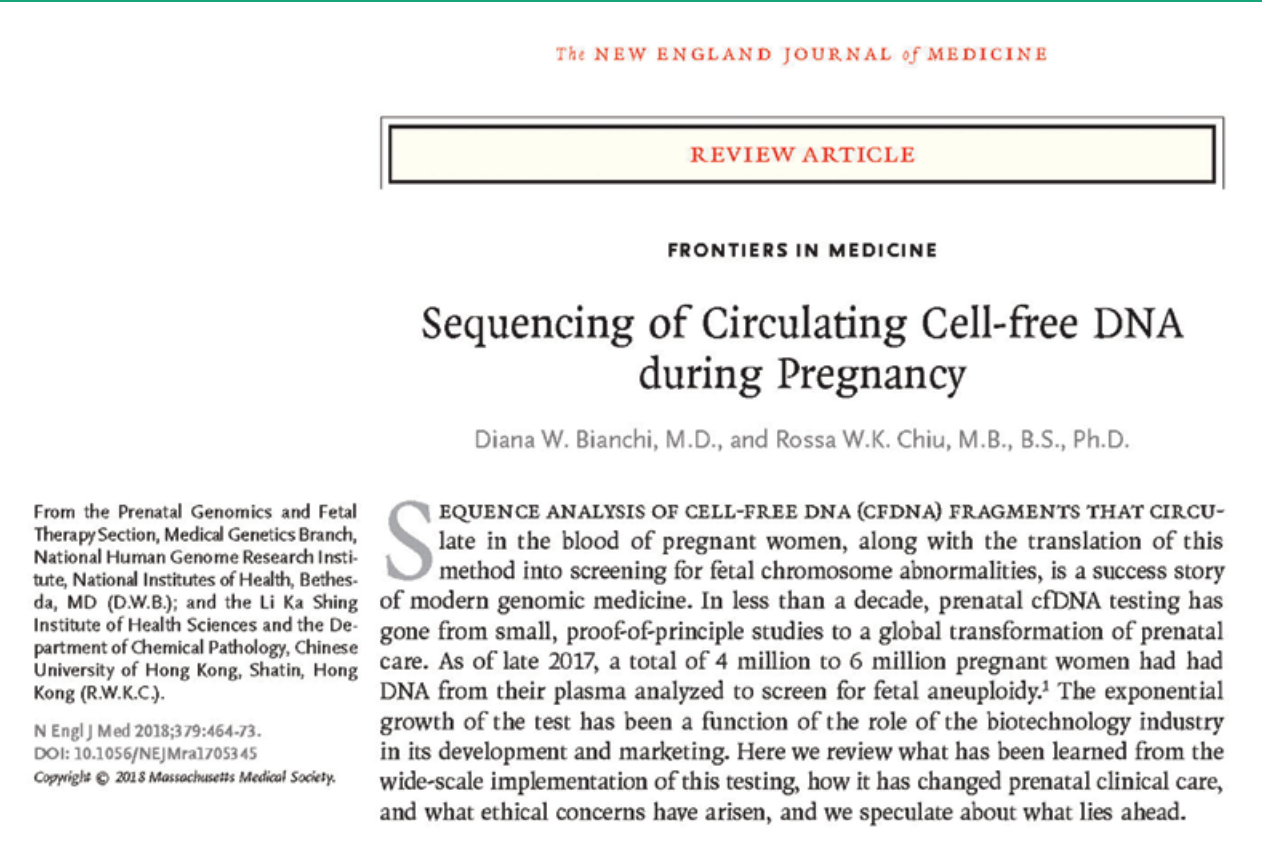
During this period, a total of **274** publications from these teams were published. Among the publications, **134** and **33** were published in journals with impact factors greater than **4** and **10**, respectively. Highlighted below are several major ones:

各小組的研究成果及著作詳列於[附錄](#)部分。過去一年，研究所屬下各研究小組共發表**274**篇學術論文，當中有**134**及**33**篇分別刊登於影響因子高於**4**及**10**的學術刊物。

■ Sequencing of Circulating Cell-free DNA during Pregnancy

Author(s): Rossa Chiu *et al.*

Journal: *New England Journal of Medicine* 2018;379(5):464-473



Introduction:

During pregnancy, small amounts of DNA from the placenta are released into the circulation of pregnant women. Analysis of these placental DNA molecules allows one to non-invasively assess the genetic makeup of the unborn child by accessing a maternal blood sample. In 2011, this maternal blood DNA based non-invasive approach of prenatal assessment has been clinically adopted for the screening of fetal chromosomal disorders, including Down syndrome. This approach has since been rapidly adopted worldwide and to date, about 6 million pregnancies opt for this form of prenatal screening each year. Due to the profound impact of this technology, a review on the current state of use of maternal blood DNA sequencing for fetal chromosomal and genetic assessment was presented in this article published in *The New England Journal of Medicine*, one of the highest impact journals in clinical medicine. The review also presented the renewed understanding of pregnancy physiology learned from the analysis of cell-free fetal DNA in maternal plasma, the social and ethical implications as well as the future directions of prenatal testing.

在懷孕的過程中，胎盤會釋放少量DNA到母體的循環系統，是以即使孩子還未出世，亦可透過分析孕婦血液樣本內的胎盤DNA分子以評估胎兒的基因組成而不會對胎兒構成任何風險。自2011年，以檢測母體血液DNA為本的無創產前檢測逐漸獲採納為臨床用途，開始應用於包括唐氏綜合症在內的胎兒染色體異常篩查，世界各地對此亦趨之若鶩，此類型的無創產檢如雨後春筍般在全球相繼推出，至今，每年約有六百萬名孕婦會選擇以此無創方式作產前檢測。科技發展一日千里，為產檢的臨床應用帶來龐大的衝擊和深遠的影響。有見及此，這篇刊登於世界頂尖醫學期刊《新英倫醫學雜誌》（The New England Journal of Medicine）的評論文章就目前以母體血液DNA排序作胎兒染色體及基因檢測的應用狀況作深入討論，同時，亦剖析如何從母體血漿內胎兒游離核酸的分析加深對懷孕生理的理解。文章亦涵蓋有關技術應用對社會、道德方面的影響，以至將來產前檢測的發展方向。

■ Association Between Bacteremia From Specific Microbes and Subsequent Diagnosis of Colorectal Cancer

Author(s): Sunny Wong, Jun Yu, Siew Ng, William Wu, Gary Tse *et. al.*

Journal: *Gastroenterology*. 2018;155(2):383-390.e8

Introduction:

Colorectal cancer has been associated with gut microbial dysbiosis and with bacteremia from certain microbes such as *Streptococcus gallolyticus*. Using a population-based health database, the team examined records of more than 13,000 patients who had been hospitalised for bacteremia. The study confirmed association of colorectal cancer with bacteremia and uncovered novel associations for several novel species including *Peptostreptococcus species*, *Clostridium septicum* and *Gemella morbillorum*. Most colorectal cancer cases were diagnosed within 1 year after the bacteremia episode. These findings confirm the known associations between colorectal cancer and certain bacterial species such as *S. gallolyticus* but also highlight the role of less well-known microbes.

This study is important in several aspects. Firstly, it expands the list of microbes, including less well-known ones, for which bacteremia should raise clinical red flags to exclude colorectal cancer. Although it is accepted that *S. gallolyticus* bacteremia should warrant colorectal workup, the awareness among clinicians is not ideal. This study reinforced the need for workup in patients with bacteremia from *S. gallolyticus* and other colorectal cancer-related bacteria. Colonoscopy should be contemplated in patients presenting with unusual bacteremia. Secondly, this study highlights that the colonic microbial flora may contribute to colorectal cancer, and provides support to the bacterial theory of carcinogenesis. Since many of these bacteria are common colonic symbionts within the large intestine,

their presence in the bloodstream suggests an abnormal entry from a dysbiotic mucosae, possibly through the neoplastic tissues. The increased access to blood vessels at the inflamed microenvironment may have facilitated these microbes to enter blood circulation causing bacteremia. Due to its impact, this study has been highlighted in several media including the *NEJM Journal Watch*, *MedScape*, *Mr Gut* and *Toutiao News*.

結直腸癌與腸道微生物失調和菌血症有密切的關係。利用一個大型的健康數據庫，研究小組檢查了超過13,000名因菌血症住院的患者記錄。該研究證實了大腸癌與菌血症的關係，並發現了幾個新的物種關聯，包括消化性鏈球菌、敗血性梭菌等，而大多數結直腸癌病例在菌血症發作後一年內確診。這些發現證實了結直腸癌與某些細菌種類之間的聯繫，但也提出了一些不太為人所知的細菌的影響。

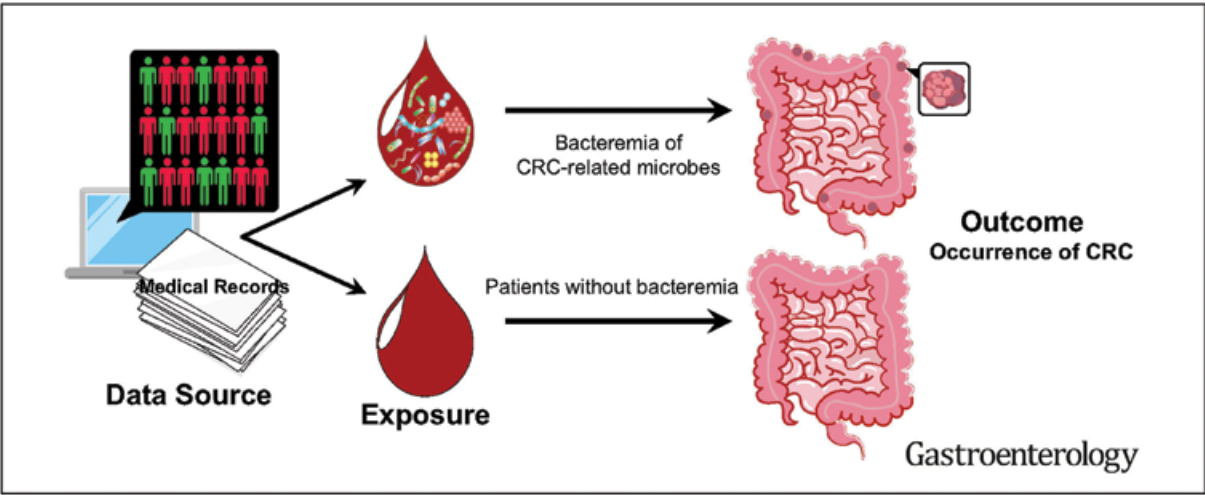
本研究在幾個方面是很重要的。首先，它擴大了結直腸癌相關微生物群的名單，包括一些不太為人所知的微生物，對於這些微生物的菌血症應該引起臨床警惕，以排除結直腸癌。這項研究加強了對溶血性鏈球菌和其他結直腸癌相關菌血症患者進行檢查的必要性。對於出現不正常菌血症的患者，應考慮採用內視鏡檢查。綜上所述，本研究強調了結腸微生物菌群可能與結直腸癌有關，並為細菌致癌的學論提供了支持。由於這些細菌中有許多是大腸內常見的結腸共生體，它們在血液中的存在表明一種異常的進入，可能來自於一種非生物的粘液，通過腫瘤組織進入。在發炎的微環境中，接觸血管的機會增加，可能促使這些微生物進入血液循環，導致菌血症。對於這項研究的影響，包括《新英格蘭醫學雜誌觀察》、《醫學景觀》、《Gut先生》和《今日頭條》在內的多家媒體都對其進行了重點報導。

Association Between Bacteremia From Specific Microbes and Subsequent Diagnosis of Colorectal Cancer



Thomas N. Y. Kwong,^{1,*} Xiansong Wang,^{1,2,5,*} Geicho Nakatsu,^{1,2} Tai Cheong Chow,¹ Timothy Tipoe,¹ Rudin Z. W. Dai,^{1,2} Kelvin K. K. Tsoi,^{3,4} Martin C. S. Wong,^{1,3} Gary Tse,² Matthew T. V. Chan,⁵ Francis K. L. Chan,^{1,2} Siew C. Ng,^{1,2} Justin C. Y. Wu,^{1,2} William K. K. Wu,^{1,5} Jun Yu,^{1,2} Joseph J. Y. Sung,^{1,2} and Sunny H. Wong^{1,2}

¹State Key Laboratory of Digestive Disease, Institute of Digestive Disease, Li Ka Shing Institute of Health Sciences, and CUHK Shenzhen Research Institute, The Chinese University of Hong Kong, Hong Kong; ²Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong; ³The Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong; ⁴Stanley Ho Big Data Decision Analytics Research Centre, The Chinese University of Hong Kong, Hong Kong; and ⁵Department of Anesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong



■ Squalene epoxidase drives NAFLD-induced hepatocellular carcinoma and is a pharmaceutical target

Author(s): Jun Yu *et al.*

Journal: *Science Translational Medicine*. 2018;10(437):eaap9840

Introduction:

Nonalcoholic fatty liver disease (NAFLD)-induced hepatocellular carcinoma (HCC) is an emerging malignancy in the developed world. The incidence of NAFLD is over 27% of the adult population in Hong Kong. However, the molecular mechanism of NAFLD-HCC remains poorly understood and no therapeutic drug is currently available for prevention or treatment of NAFLD-HCC. In this study, utilising next-generation sequencing platforms, Professor Jun Yu and her team comprehensively profiled paired NAFLD-HCC tissues, revealing that SQLE (squalene epoxidase), an enzyme that catalyses the first oxygenation step in sterol biosynthesis, is highly expressed in NAFLD-HCC. They constructed SQLE-transgenic mice and demonstrated that SQLE significantly increased incidence of NAFLD-HCC, suggesting that SQLE functions as an oncogene in NAFLD-HCC. Importantly, the team found that Terbinafine (SQLE inhibitor), a US FDA-approved drug, can be repurposed for the targeting of NAFLD-HCC. Terbinafine treatment in mice with HCC xenografts arrested growth and extended survival, and it reduced the incidence of NAFLD-HCC in SQLE transgenic mice with no apparent adverse effects. Collectively, in this study, the team established SQLE as a novel oncogene and therapeutic target in NAFLD-HCC. SQLE inhibitor (Terbinafine) may be a promising approach for the prevention and treatment of NAFLD-HCC, providing a new direction for targeting NAFLD-HCC.

This paper was selected for Press Release before publication in *Science Translational Medicine* April

2018 and as a Cover Story, along with an editorial in the same issue. Soon after its publication, three more commentaries and editorials on this article were published in major Journals of *Nature Reviews Drug Discovery* (May 2018), and *Nature Review Gastroenterology and Hepatology* (May 2018 and Dec 2018).

非酒精性脂肪性肝病 (NAFLD) 誘導的肝細胞癌 (HCC) 是發達國家新出現的惡性腫瘤。NAFLD的發病率超過香港成年人口的27%。然而，NAFLD-HCC的分子機制仍然知之甚少，目前沒有治療藥物可用於預防或治療NAFLD-HCC。在本研究中，利用新一代測序平臺，于君教授及其研究團隊全面分析了成對的NAFLD-HCC組織，揭示了SQLE（角鯊烯環氧酶）是一種催化甾醇生物合成中第一個氧合步驟的酶，在NAFLD-HCC中高表達。研究團隊構建了SQLE轉基因小鼠並證明SQLE顯著增加了NAFLD-HCC的發生率，表明SQLE是NAFLD-HCC的促癌基因。重要的是，他們發現美國FDA批准的藥物特比萘芬（SQLE抑制劑）可用于靶向預防NAFLD-HCC。特比萘芬抑制小鼠HCC異種移植瘤的物生長，並降低了SQLE轉基因小鼠NAFLD-HCC的發生率。總之，在這項研究中，團隊建立了SQLE作為NAFLD-HCC中的新型致癌基因和治療靶標。SQLE抑制劑（特比萘芬）可能是預防和治療NAFLD-HCC的有前途的方法，為靶向NAFLD-HCC提供了新的方向。

本文在2018年4月的《科學轉化醫學》雜誌上發表之前被選為新聞稿，並作為封面故事，以及同一期刊中的社論。在其出版後不久，另外三篇關於這篇文章的社論發表在主要期刊包括《自然評論藥物》（2018年5月），以及《自然評論胃腸病學和肝病學》（2018年5月和2018年12月）。

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

Squalene epoxidase drives NAFLD-induced hepatocellular carcinoma and is a pharmaceutical target

Dabin Liu,¹ Chi Chun Wong,¹ Li Fu,^{1,2} Huarong Chen,¹ Liuyang Zhao,¹ Chuangen Li,¹ Yunfei Zhou,¹ Yanquan Zhang,¹ Weiqi Xu,¹ Yidong Yang,³ Bin Wu,³ Gong Cheng,⁴ Paul Bo-San Lai,⁴ Nathalie Wong,⁵ Joseph J. Y. Sung,¹ Jun Yu^{1*}

Nonalcoholic fatty liver disease (NAFLD)-induced hepatocellular carcinoma (HCC) is an emerging malignancy in the developed world; however, mechanisms that contribute to its formation are largely unknown, and targeted therapy is currently not available. Our RNA sequencing analysis of NAFLD-HCC samples revealed squalene epoxidase (SQLE) as the top outlier metabolic gene overexpressed in NAFLD-HCC patients. Hepatocyte-specific *Sqle* transgenic expression in mice accelerated the development of high-fat, high-cholesterol diet-induced HCC. *SQLE* exerts its oncogenic effect via its metabolites, cholesteryl ester and nicotinamide adenine dinucleotide phosphate (NADP⁺). Increased *SQLE* expression promotes the biosynthesis of cholesteryl ester, which induces NAFLD-HCC cell growth. *SQLE* increased the NADP⁺/NADPH (reduced form of NADP⁺) ratio, which triggered a cascade of events involving oxidative stress-induced DNA methyltransferase 3A (DNMT3A) expression, DNMT3A-mediated epigenetic silencing of PTEN, and activation of AKT-mTOR (mammalian target of rapamycin). In human NAFLD-HCC and HCC, *SQLE* is overexpressed and its expression is associated with poor patient outcomes. Terbinafine, a U.S. Food and Drug Administration-approved antifungal drug targeting *SQLE*, markedly inhibited *SQLE*-induced NAFLD-HCC cell growth in NAFLD-HCC and HCC cells and attenuated tumor development in xenograft models and in *Sqle* transgenic mice. Suppression of tumor growth by terbinafine is associated with decreased cholesteryl ester concentrations, restoration of PTEN expression, and inhibition of AKT-mTOR, consistent with blockade of *SQLE* function. Collectively, we established *SQLE* as an oncogene in NAFLD-HCC and propose that repurposing *SQLE* inhibitors may be a promising approach for the prevention and treatment of NAFLD-HCC.

Grants
補助金及其他資助

Our Principal Investigators and their teams affiliated to the Institute have received grants of over **HK\$569M** during this reporting period. In particular, grants under the General Research Fund (GRF) scheme of the Research Grants Council (RGC) of **HK\$30M** are listed below:

此外，在本報告年度期間，研究所各項目負責人及其小組成員所取得的補助金及其他資助合計超過**港幣五億七百萬**，其中研究資助局的優配研究金共逾**港幣三千萬**，獲資助研究項目的詳情如下：

Project Title 研究題目	Principal Investigators / Research Team 研究所首席 研究員 / 小組	Amount (HK\$)
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2015 – 30/09/2018) PGE2-induced DNA methylation in gastric cancer: mechanisms and therapeutic implications	Jun Yu	852,552
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2016 – 31/12/2018) Functional characterization of squalene epoxidase in promoting fatty liver disease-associated liver cancer	Jun Yu	1,141,432
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2017 – 31/12/2019) Elucidation of a novel tumor suppressor gene tripartite motif 67 (TRIM67) in colorectal cancer	Jun Yu	1,154,550
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2017 – 31/12/2019) Incidence of non-alcoholic fatty liver disease and advanced fibrosis in patients with type 2 diabetes: A prospective cohort study using paired controlled attenuation parameter and liver stiffness measurements	Jun Yu	658,050
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2018 – 31/12/2020) Elucidating A novel tumor promoting gene Ring Finger Protein 6 in colorectal cancer	Jun Yu	1,229,089
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2018 – 31/12/2020) Inhibition of SLC25A22 synergizes with chemotherapy to induce KRAS-mutant colorectal cancer cell death through induction of endoplasmic reticulum stress	Jun Yu	1,203,589

Project Title 研究題目	Principal Investigators / Research Team 研究所首席 研究員 / 小組	Amount (HK\$)
Research Grants Council (RGC) – General Research Fund (GRF) (01/12/2018 – 30/11/2021) Regulation of autophagy by the novel tumor suppressor gene GGT7 in gastric cancer	Jun Yu	965,601
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2018 – 31/12/2020) When should low-dose aspirin be resumed after peptic ulcer bleeding? A double-blind, randomized controlled trial	Siew Ng	972,000
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2017 – 31/12/2019) Studies on the role of SREBP1 in EBV-induced metabolic reprogramming in NPC	Kwok-wai Lo	1,088,950
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2016 – 31/12/2018) Study on the role of Epstein-Barr Virus (EBV)-encoded microRNAs in controlling DNA damage repairs in EBV-associated nasopharyngeal carcinoma	Ka-fai To	1,187,649
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2017 – 31/12/2018) Target inhibition of ATM-mediated homologous recombination repair by Epstein-Barr virus miR-BARTs in nasopharyngeal carcinoma: molecular mechanisms and clinical implications	Ka-fai To	811,383
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2018 – 31/12/2020) Targeting YAP/TAZ activation to ameliorates endothelial dysfunction in diabetic mice	Yu Huang	1,126,512
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2017 – 31/12/2019) Targeting TFEB to reverse endothelial dysfunction in diabetic mice through induction of autophagy	Yu Huang	1,317,102
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2017 – 01/12/2019) TM9SF4 as a novel potassium channel and its role in autophagy	Xiaoqiang Yao	1,000,387

Project Title 研究題目	Principal Investigators / Research Team 研究所首席 研究員 / 小組	Amount (HK\$)
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2017 – 31/12/2018) The impact of gestational diabetes and vitamin D deficiency during pregnancy on children’s Cardiometabolic risk and methylation	Juliana Chan	998,652
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2018 – 31/12/2020) Genome-wide CRISPR screen for host factors associated with norovirus infections in stem cell-derived human intestinal enteroid model	Sunny Wong	1,132,030
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2018 – 31/12/2020) The Pathogenic role and therapeutic implication of a novel lncRNA np_9884 in type-2 diabetic kidney disease	Hui-yao Lan	1,222,113
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2016 – 31/12/2018) Is Smad7 a potential therapeutic target for preventing osteoporotic bone loss?	Gang Li	821,097
Research Grants Council (RGC) – General Research Fund (GRF) (05/09/2017 – 14/09/2020) Biomaterials-mediated bone formation and consolidation in distraction osteogenesis	Gang Li	1,098,710
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2017 – 31/12/2018) Unraveling the impact of hyperglycemia on survival and cell fate commitment of the human multipotent ISL1+ heart progenitors	Kathy Lui	902,460
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2018 – 31/12/2020) An Innovative Bio-intramedullary Nail with Osteogenic Mg-ions for Accelerating Bone Defect Repair: A Proof-of-Concept Study	Ling Qin	929,880
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2016 – 31/12/2018) Identification and functional characterization of super enhancer associated RNAs (seRNAs) in skeletal myogenesis using integrated genomic approach	Hao Sun	1,228,445
Research Grants Council (RGC) – General Research Fund (GRF) (01/12/2018 – 30/11/2020) Regulation of eosinophil/basophil-innate lymphoid type 2 cells axis by fundamental innate immunity inhibitor IL-37 in atopic dermatitis	Peiyong Jiang	739,525

Project Title 研究題目	Principal Investigators / Research Team 研究所首席 研究員 / 小組	Amount (HK\$)
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2015 – 31/12/2018) Integrating Large Intergenic Noncoding RNAs into Pax7 Mediated Regulatory Circuitry in Muscle Satellite Cells	Huating Wang	623,277
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2016 – 31/12/2018) Functional Characterization of YY1 in Skeletal Muscle Stem Cells and Muscle Regeneration	Huating Wang	1,182,869
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2016 – 31/12/2018) Is there a Link between Systemic Muscle Mass, Muscle Strength, Serum and Muscle Expression of Myokines and LBX1 with Bone Mineral Density and Bone Quality in Adolescent Idiopathic Scoliosis?	Huating Wang	593,675
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2017 – 31/12/2019) Mechanistic Exploration of Super-enhancer Associated seRNA Function in Skeletal Muscle Cells	Huating Wang	922,171
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2018 – 31/12/2020) Functional dissection of lncRNA SAM in skeletal muscle stem cells and muscle regeneration	Huating Wang	1,232,466
Research Grants Council (RGC) – General Research Fund (GRF) (01/03/2017 – 31/03/2020) Safety of Perioperative Dexamethasone in Major Noncardiac Surgery – A Randomized Noninferiority Trial	William Wu	190,857
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2016 – 31/12/2018) Targeting defective autophagy and its molecular sequelae in non-alcoholic fatty liver disease-related hepatocellular carcinoma	William Wu	813,275
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2016 – 31/03/2019) Dissecting an inflammatory-CCRK circuitry in non-alcoholic fatty liver disease-related hepatocarcinogenesis	William Wu	763,612
Total:		30,103,965

Theme-based Research Scheme
主題研究計劃

■ “Plasma DNA as a Platform Technology for Cancer Detection”
「血漿脫氧核糖核酸作為癌症檢測的平台」(T12-401/16-W)

The project was progressing smoothly during the reporting period. The Scientific Advisory Board conducted its first meeting on 4 September 2018 to assess the progress of the project.

2018年9月4日，主題研究計劃科學諮詢委員會舉行第一次會議，評核小組的研究成果。



Meeting of the Scientific Advisory Board of Theme-based Research Scheme Project
“Plasma DNA as a Platform Technology for Cancer Detection” [4 September 2018]

「血漿脫氧核糖核酸作為癌症檢測的平台」主題研究計劃科學諮詢委員會會議（2018年9月4日）

[In the photo, from left five to right: Professor Peiyong Jiang, Professor Allen Chan, Professor Dennis Lo, Professor Roger Reeves (Scientific Advisory Board Member), Professor Anne Cooke (Scientific Advisory Board Member), Professor Eddy Liew (Scientific Advisory Board Member), Professor Hao Sun, Dr. Jacky Lam) and other research team members.]

（相片中由左五至右為：江培勇教授，陳君賜教授，盧煜明教授，科學諮詢委員會會員Roger Reeves教授，科學諮詢委員會會員Anne Cooke教授，科學諮詢委員會會員Eddy Liew教授，孫昊教授，林偉棋醫生及其他研究團隊成員）

■ “Centre for Research into Circulating Fetal Nucleic Acids”
「母體血漿胎兒核酸研究中心」(T12-403/15-N)

The project was progressing smoothly during the reporting period. The Scientific Advisory Board conducted its third meeting on 5 November 2018 to assess the progress of the project.

2018年11月5日，主題研究計劃科學諮詢委員會舉行第三次會議，評核小組的研究成果。



Meeting of the Scientific Advisory Board of Theme-based Research Scheme Project
“Centre for Research into Circulating Fetal Nucleic Acids” [5 November 2018]

「母體血漿胎兒核酸研究中心」主題研究計劃科學諮詢委員會會議（2018年11月5日）

[In the photo, from left six to right: Professor Allen Chan, Professor Peiyong Jiang, Professor Rossa Chiu, Professor Howard S. Cuckle (Scientific Advisory Board Member), Professor Dennis Lo, Dr. Jacky Lam (right five) and other research team members]

（相片中由左六至右為：陳君賜教授，江培勇教授，趙慧君教授，科學諮詢委員會會員Howard S. Cuckle教授，盧煜明教授，林偉棋醫生（右五）及其他研究團隊成員）

SCIENTIFIC EXCHANGE AND VISITORS

學術交流及訪客

SCIENTIFIC EXCHANGE AND VISITORS

學術交流及訪客

During the reporting period, the Institute received a number of renowned academicians, experts and delegations from within and beyond the Territory. Some of them are highlighted as follows:

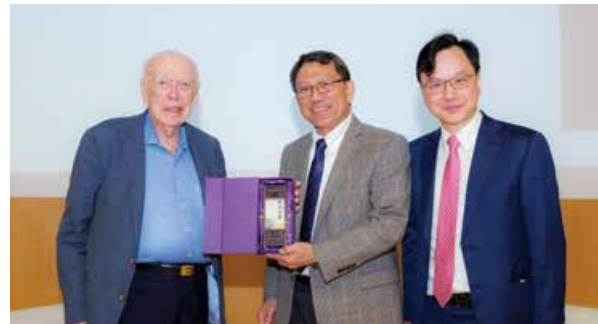
過去一年，研究所接待多位本港及海外著名學者、專家及訪問團，進行學術交流及參觀，詳列如下：

19 March 2018

2018年3月19日

Special lecture by Dr. James Watson, Nobel Laureate, Chancellor Emeritus of Cold Spring Harbor Laboratory. Dr. Watson is the co-discoverer of the DNA double helix.

James Watson博士（諾貝爾獎得主及Cold Spring Harbor Laboratory · Chancellor Emeritus）舉行講座。James Watson博士是DNA雙螺旋結構的共同發現者。



Professor Rocky Tuan (middle), Vice-chancellor, CUHK and Professor Dennis Lo, Director of the Institute presented souvenir to Dr. James Watson.



29 March 2018

2018年3月29日

Visit by Professor Rongping Mu, Secretary of Party Committee, Institutes of Science and Development, Chinese Academy of Sciences. The delegations visited the Institute and exchanged views on technological innovation in local universities, as well as collaboration with Mainland institutions.

中國科學院科技戰略諮詢研究院黨委書記穆榮平教授及代表團到訪研究所，並討論香港高等院校在科技創新及與內地合作的情況。

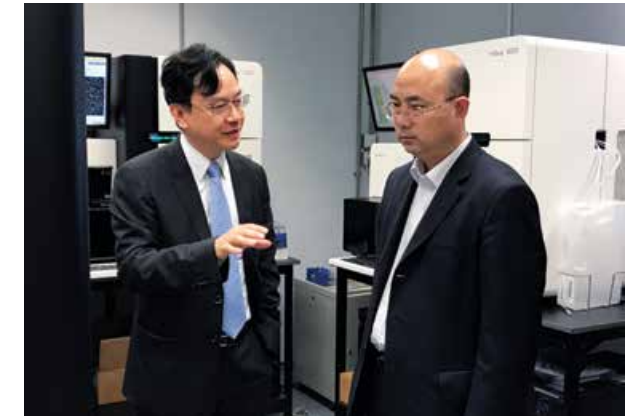


12 April 2018

2018年4月12日

Visit by Mr. Rui-jun Wang, Director-General of Guangdong Provincial Department of Science and Technology. The delegations visited the Institute and State Key Laboratory of Translational Oncology. They also discussed about enhancing innovation and technology co-operation between Hong Kong and Guangdong under the Greater Bay Area development.

廣東省科學技術廳王瑞軍廳長及代表團到訪研究所及轉化腫瘤學國家重點實驗室，討論如何加強粵港合作，推進粵港澳大灣區科技交流合作。



18 May 2018

2018年5月18日

Visit by Mr. Paul Chan, Financial Secretary of the HKSAR Government. The delegations visited various teaching and research facilities of the Faculty of Medicine, including the Institute.

香港特別行政區政府財政司司長陳茂波先生到訪香港中文大學醫學院，參觀了包括研究所在內的教學與科研設施。



26-27 May 2018

2018年5月26-27日

Professor Dennis Lo delivered the Opening Speech at “The Inaugural Joint Clinical and Translational Cardiology Conference”. The Conference was jointly organised by:

- The Chinese University of Hong Kong (Division of Cardiology, Department of Medicine & Therapeutics, Li Ka Shing Institute of Health Sciences, The Jockey Club School of Public Health, Faculty of Medicine; School of Life Sciences, Faculty of Science);
- The University of Hong Kong (Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, and Dr Li Dak-Sum Research Centre); and
- The Karolinska Institutet, Hong Kong (Ming Wai Lau Centre for Reparative Medicine).

The Conference served as a platform for knowledge transfer and exchange of ideas on the challenges and opportunities in research related to cardiovascular health. Academicians and clinicians also discussed about recent innovations and possible collaborations in the Asia-Pacific region.

盧煜明教授為「The Inaugural Joint Clinical and Translational Cardiology Conference」致開幕辭。此會議由以下團體共同舉辦：

- 香港中文大學醫學院內科及藥物治療學系心臟科、李嘉誠健康科學研究所、賽馬會公共衛生及基層醫療學院、理學院生物科學學院；
- 香港大學李嘉誠醫學院及李達三博士研究中心；及
- 卡羅琳斯卡學院劉鳴煒修復醫學中心。

此會議為學者及醫生提供一個知識傳遞平台，讓參加者交流有關心血管健康研究所遇到的挑戰與機遇。討論亦包括相關範疇最新科技發展及未來於亞太地區內協作計劃。



14 June 2018

2018年6月14日

Visit by delegations of Research Grant Council led by Professor Geoffrey L. Smith from University of Cambridge. Researchers in the Faculty and the Institute showcased their research achievements to the delegations during the visit.

由牛津大學Professor Geoffrey L. Smith率領的研究資助局代表團到訪香港中文大學醫學院，期間醫學院及研究所的科研人員向代表團成員展示了最新的研究成果。



5 July 2018

2018年7月5日

Seminar by Professor Willem H. Ouwehand, Director of NIHR BioResource – Rare Diseases at University of Cambridge and Wellcome Trust Sanger Institute & NHS Blood and Transplant, United Kingdom on “The 100,000 Genomes Project: Rare Diseases”.

Willem H. Ouwehand教授（英國劍橋大學Wellcome Trust Sanger Institute暨英國國民保健署Blood and Transplant轄下NIHR BioResource — Rare Diseases項目主任）舉行研討會，題目為「The 100,000 Genomes Project: Rare Diseases」。



15 August 2018

2018年8月15日

Seminar by Dr. Michelle Trenkmann, Associate Editor, *Nature Communications* on “Demystifying the Editorial Process – Behind the Curtain of Nature Family Journals”.

Michelle Trenkmann博士（自然通訊Associate Editor）舉行研討會，題目為「Demystifying the Editorial Process — Behind the Curtain of Nature Family Journals」。



8 November 2018
2018年11月8日

Seminar by Dr. Benjamin Fairfax, Principal Investigator, MRC Weatherall Institute of Molecular Medicine, University of Oxford, United Kingdom, on "Transcriptomic Mapping of Immune Cells in Cancer Therapeutic".

Benjamin Fairfax博士（英國牛津大學MRC Weatherall Institute of Molecular Medicine首席研究員）舉行研討會，題目為「Transcriptomic Mapping of Immune Cells in Cancer Therapeutic」。



9 November 2018
2018年11月9日

Seminar by Professor Paul Pharoah, Professor of Cancer Epidemiology, Strangeways Research Laboratory, University of Cambridge, United Kingdom, on "PREDICT: a Breast Cancer Prognostication and Treatment Benefit Model".

Paul Pharoah教授（英國劍橋大學Strangeways Research Laboratory，Professor of Cancer Epidemiology）舉行研討會，題目為「PREDICT: a Breast Cancer Prognostication and Treatment Benefit Model」。

3 December 2018
2018年12月3日

Seminar by Dr. Colin Crist, Associate Professor Department of Human Genetics, McGill University, Canada, on "Translational Control of Gene Expression Regulates Skeletal Muscle Stem Cell Quiescence and Self-renewal".

Colin Crist博士（加拿大麥基爾大學人類基因學系副教授）舉行研討會，題目為「Translational Control of Gene Expression Regulates Skeletal Muscle Stem Cell Quiescence and Self-renewal」。



6 December 2018
2018年12月6日

Seminar by Professor Mary Norton, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, USA, on "Prenatal Genetic Testing: What Patients Need to Know".

Mary Norton教授（美國加州大學Department of Obstetrics, Gynecology, and Reproductive Sciences）舉行研討會，題目為「Prenatal Genetic Testing: What Patients Need to Know」。

Scientific Exchange 學術交流

The 2018 East-West Alliance (EWA) Global Symposium was held at Shantou University Medical College, China from 17 to 18 November 2018. Professor Benny Zee, Professor Samuel Wong and Professor Sun On Chan from the Faculty of Medicine attended this meeting on behalf of The Chinese University of Hong Kong. The EWA is a global network of universities and medical schools that are supported by the Li Ka Shing Foundation. The Alliance aims to foster knowledge exchange and collaboration among leading medical institutions on high-impact research and educational projects. The theme of the 2018 EWA Global Symposium was "What Makes An Impactful Institution?"

2018年度東西方聯盟國際高峰會於2018年11月17日至18日期間假中國汕頭大學醫學院舉行，醫學院徐仲鎡教授、黃仰山教授及陳新安教授代表香港中文大學出席是次會議。「東西方聯盟」由15所獲李嘉誠基金會捐助的國際頂尖學府及醫學院組成，藉構建跨機構學術交流的平台，促進醫學研究及教育發展。本年度高峰會的主題為「What Makes An Impactful Institution?»。

Professor Samuel Wong, Professor Benny Zee and Professor Sun On Chan (third, fourth and fifth on second row, from left to right) at the 2018 East-West Alliance (EWA) Global Symposium

黃仰山教授、徐仲鎡教授及陳新安教授（第二排左起第三、四、五位）代表香港中文大學醫學院參加2018年度東西方聯盟國際高峰會

East-West Alliance Institutions 東西方聯盟屬下機構



The University of Hong Kong



Shantou University



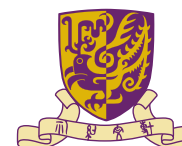
Stanford University

St. Michael's
Inspired Care.
Inspiring Science.

St. Michael's Hospital



Technion Israel Institute of Technology



The Chinese University of Hong Kong



University Medical Center Groningen



University of Alberta



University of California Berkeley



University of California San Francisco



University of Cambridge



University of Manitoba



University of Oxford



University of Michigan



The University of Melbourne



2018 EAST-WEST ALLIANCE (EWA) SYMPOSIUM

November 17-18, 2018

Shantou University Medical College, China

REPORT ON RESEARCH ACTIVITIES

科研活動報告

APPENDIX

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REPORT ON RESEARCH ACTIVITIES

科研活動報告

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腸道微生物移植研究

05

Vascular Medicine

血管疾病研究

02

Molecular Diagnostics

分子診斷學

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07

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11

**Reproduction and
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生殖與發育研究

13

Genomics and Bioinformatics

基因組學與生物訊息學

15

Cellular Signalling

細胞訊號轉導

08

Molecular Microbiology

分子微生物學研究

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神經科學

12

**Stem Cells and Tissue
Regeneration**

幹細胞及組織再生研究

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Non-coding RNAs

非編碼核糖核苷酸研究

NON-TECHNICAL SUMMARY

非技術性報告

Research activities of the Institute are highlighted below and detailed in the technical report which follows:

研究所各個研究領域的發展情況如下，有關各小組的科研工作詳情及其他動態則載於後頁的「技術性報告」部分：

01

Digestive Diseases 消化疾病研究

Gastrointestinal (GI) diseases, including GI cancers, inflammatory bowel diseases (IBD) and non-alcoholic fatty liver disease (NAFLD) are the major diseases in Hong Kong and they cause significant morbidity and mortality. The multidisciplinary team of physicians and scientists led by **Professor Jun Yu** specialises in GI research including: 1) elucidation of the genetic and epigenetic mechanisms underlying the pathogenesis of GI cancers; 2) investigation of the role of gut microbiota in GI cancers; 3) evaluation of the molecular mechanism and therapeutic targets of NAFLD; 4) identification of molecular biomarkers potentially useful for GI cancer diagnosis and prognosis.



Professor Jun Yu
于君教授

消化道疾病如消化道腫瘤，炎症性肝病和脂肪性肝病是香港常見病。于君教授帶領的研究團隊由跨學科醫生和科研人員組成，團隊的主要工作包括1) 闡述消化道腫瘤和疾病的分子機制；2) 研究消化道微生態和腫瘤的關係；3) 脂肪性肝病的機制和治療；4) 開發新的分子標誌物。

02

Molecular Diagnostics 分子診斷學



Professor Rossa Chiu
趙慧君教授

Professor Dennis Lo
盧煜明教授

This year, **Professor Dennis Lo**, **Professor Rossa Chiu** and their research team have further pushed the envelope in their research on circulating nucleic acids. Most notably, the team identified and reported the existence of preferred plasma DNA ends. Circulating DNA molecules exist as short fragments. Researchers have noticed that the fragmentation of plasma DNA appears to be non-random. However, it has not been known until the team's recent work that there exist locations in the genome which serve as preferential cutting sites for plasma DNA. The team has shown that these preferred cutting sites are specific down to particular nucleotide positions. Remarkably, the team's data reveal that the preferred cutting sites could be different for DNA originating from different tissue types. For example, in the prenatal context, DNA from the placenta exhibited different preferred end sites than maternal blood cells. The liver and liver tumour also release DNA with preferred end sites that are different from blood cells. As a result, the detection and quantification of DNA with such preferred cutting sites could potentially add another dimension to non-invasive prenatal diagnostics and liquid biopsy. With such pioneering work, Professor Dennis Lo was

named the "Top 20 Translational Researchers of 2017" by the authoritative scientific journal *Nature Biotechnology*. This is the second year that Professor Lo has received the honour and he was also the only Hong Kong scientist on the list.

今年，**盧煜明教授**、**趙慧君教授**及他們的研究團隊進一步挑戰游離核酸研究領域的極限，發表研究報告證實血漿DNA確實有偏好的斷點位置。一直以來，血漿游離DNA都是以片段的方式存在，科學家都相信該DNA的片段化並非隨機決定，奈何一直苦無證據。直到最近，盧教授及趙教授的團隊利用現今的DNA排序技術配合突破傳統框架的數據分析策略方案，發現基因組上果然有血漿DNA的偏好斷點位置，而那些斷點甚至乎仔細至某一特定的核苷酸位置。值得注視的是團隊的數據亦揭示不同組織釋放的DNA有著不同的偏好斷點，以孕婦血漿DNA為例，當中由胎盤釋放的DNA就跟來自母體血細胞的DNA展現不一樣的偏好斷點位置。另外，肝臟、肝腫瘤與血細胞所釋出的DNA亦各自帶有不同的偏好斷點。正因如此，檢測、量化這些帶有偏好斷點的DNA甚有發展潛力，有望為將來無創產檢及液體活檢增加嶄新的檢測層面。憑著領先創新的研究及對無創檢測的貢獻，盧煜明教授獲世界權威科學期刊《自然生物科技（*Nature Biotechnology*）》評為「2017年全球20位頂尖轉化研究科學家」，是次為盧教授連續第二年獲此殊榮，他亦是名單上唯一來自香港的科學家。



Professor Nelson Tang
鄧亮生教授

Professor Nelson Tang is the principal investigator of the Laboratory for Genetics of Disease Susceptibility. The research team led by Professor Tang are specialised in complex traits and genetic statistical analysis. His research covers genetic association studies, expression quantitative traits and genome-wide association study (GWAS) analysis. A patent has been recently granted for gene expression analyses. He is also teaching a bioinformatics course in the Faculty of Engineering.

The research team also has long-standing cooperation with international researchers. Professor Tang is also the associate director of a joint laboratory with Kunming Institute of Zoology of the Chinese Academy of Sciences (CAS). Recently, the team explored the genetic mechanism of Adolescent idiopathic scoliosis and Ageing.

鄧亮生教授是疾病易感性遺傳學實驗室的首席研究員。由鄧教授領導的研究小組專門從事複雜性狀的遺傳學和統計分析。他的研究涵蓋遺傳關聯研究，表達數量性狀和（GWAS）分析，最近亦獲得了一項專利用於基因表達分析。鄧教授也在工程學院教授生物訊息學課程。

研究小組長期與國際研究人員合作，包括中國科學院昆明動物研究所。當中他是聯合實驗室的副主任。最近，團隊發表了一個持續了10年的研究結果，我們開始了解青少年特發性脊柱側彎的遺傳機制。



Professor Allen Chan
陳君賜教授

Professor Allen Chan's research focus is to develop new diagnostic approaches based on the analysis of circulating nucleic acids. His team previously showed that the screening for nasopharyngeal cancers by plasma Epstein-Barr virus analysis could lead to significant improvement in treatment outcomes. In 2018, his team further improved this cancer-screening method through the use of the state-of-the-art DNA sequencing technology. The new technology has improved accuracy over the original method and, hence, for those who are tested positive, no further confirmation with an additional follow-up blood sample would be required. To recognize the contribution of Professor Allen Chan and Professor Dennis Lo in cancer screening research, The Chinese Society of Clinical Oncology bestowed them with the 2018 Annual Achievement Award.

由**陳君賜教授**帶領的團隊的研究重點是開發利用血漿脫氧核糖核酸（DNA）分析的新診斷方法。他的團隊證明通過血漿Epstein-Barr病毒分析篩查鼻咽癌可以顯著改善治療效果。在2018年，他們進一步通過使用最先進的DNA測序技術，改進了這項鼻咽癌篩查方法。相對於原來的的方法，新技術進一步提高了鼻咽癌篩查的準確性。因此，檢測呈陽性者，我們不需要收集額外的血液樣本來確認測試結果。為表揚陳君賜教授及盧煜明教授對癌症篩查研究的貢獻，中國臨床腫瘤學會頒授予他們「2018年度成就獎」。

03

Fecal Microbiota Transplantation 腸道微生物移植研究



Professor Siew Ng
黃秀娟教授

The team led by **Professor Siew Ng**, consisting of both clinicians and scientists, centers on fecal microbiota transplantation (FMT) for the treatment of various human diseases, including inflammatory bowel disease, obesity, graft versus host disease, multidrug resistant infections, and *Clostridium difficile* infections. This year, they discovered fungal dysbiosis correlates with lower efficacy of FMT. These findings were published in high impact journal and won several awards in International conferences. The team filed 3 patents related to FMT and is working with the Health Authority in Hong Kong to provide FMT as a service to subjects with recurrent *clostridium difficile* infections.

黃秀娟教授帶領的研究團隊由醫生和科學家組成，主要研究以腸道微生物移植（FMT）來治療各種疾病，包括炎症性腸病、肥胖、移植抗宿主病、多藥耐藥性感染和難辨梭菌感染。今年，他們發現真菌生態失調與FMT效果欠佳有關，這些研究結果已發表在高影響力期刊上，並在國際會議上獲得獎項。他們還提交了3項與FMT有關的專利，並正研究與香港醫管局合作，為患有復發性難辨梭菌感染的病人提供FMT服務。

04

Asian Cancers 亞洲癌症研究



Professor Nathalie Wong
王昭春教授



Professor Ka-fai To
杜家輝教授

Cancer is a leading cause of death in Hong Kong. In particular, the research team led by **Professor Ka-fai To**, **Professor Kwok-wai Lo** and **Professor Nathalie Wong** focuses on Nasopharyngeal cancer (NPC), hepatocellular carcinoma (HCC) and gastric carcinoma (GC) which are prevalent in our region and have distinctive ethnic and geographic occurrences. The team established a comprehensive Genome Map of Asian Cancers, including NPC and HCC using state-of-the-art technology of next generation sequencing in the past years. Their underlying principle is that the establishment of a genome map will offer a fundamental core that will greatly accelerate research progress on basic studies and clinical translations of these common cancers.

癌症是香港人死亡的主因之一，**杜家輝教授**、**羅國煒教授**及**黃昭春教授**所帶領的研究團隊特別關注本地流行和具獨特民族或地緣特徵的鼻咽癌，肝癌和胃癌。利用新一代測序技術，我們建立了亞洲人鼻咽癌和肝癌全面基因組圖譜，這將大大加快癌症的基礎研究和臨床轉化的進展。



Professor Kwok-wai Lo
羅國煒教授

Cancer is a gene disease with genetic and epigenetic abnormalities of multiple cancer genes. Epigenetic disruption of critical cancer genes, especially silencing of tumor suppressor genes (TSGs) by promoter CpG methylation, is frequently involved in tumorigenesis, even at the early pathogenic stage. Characterise the epi-genomic abnormalities of tumours leads to the identification of novel TSGs and non-invasive epigenetic biomarkers, as well as the elucidation of molecular pathogenic mechanisms. The research team led by **Professor Qian Tao** aims to study the epigenomes of common Hong Kong tumours and identify novel TSGs epigenetically inactivated as specific tumour markers.

在腫瘤的發展過程中，表觀遺傳異常破壞關鍵的腫瘤基因，特別是啟動子的甲基化沉默抑癌基因已成為腫瘤發生的一個重要起因。在全基因組層面詮釋腫瘤表觀遺傳組的變化可以發現新的抑癌基因，闡明腫瘤發生的分子病理機制及發展非侵入性的表觀遺傳標誌物。由**陶謙教授**帶領的腫瘤表觀遺傳學實驗室旨在通過研究香港常見腫瘤的表觀遺傳組學異常，鑒定新的抑癌基因及發展腫瘤早期診斷的分子標記物。



Professor Qian Tao
陶謙教授

Professor Siu-tim Cheung and her team focus on the investigation of molecular basis of human cancer, aim to improve treatment strategies and ultimately patient survival. The team has deciphered liver cancer expression profiles and metastasis associated genes. Continuation research included the study on novel targeted therapeutics, cancer immunotherapy and mechanism of drug resistance.

張兆恬教授及其團隊專注於研究人類癌症的分子基礎，旨在改善治療策略和患者最終生存率。該團隊已經解讀了肝癌表達基因譜和癌症轉移相關基因。接續研究包括新型靶向治療，癌症免疫治療和耐藥機制的研究。



Professor Siu Tim Cheung
張兆恬教授

05

Vascular Medicine 血管疾病研究

Autosomal dominant polycystic kidney disease (ADPKD) is a common disease with prevalence of 1:600 in population. The patients have kidney problem as well as heart problem. In the present study, **Professor Xiaoqiang Yao**'s team found that mutation in a protein named PKD2 is an important contributing factor leading to cardiomyopathy in ADPKD patients.

Professor Yu Huang's team has provided novel evidence on the molecular mechanisms underlying the development of atherosclerosis. The integrin-Gα13-RhoA-YAP pathway holds promise as a novel drug target against atherosclerosis. His team also revealed a significant role of microRNA 29a in the development of diabetic endothelial dysfunction. These studies further confirm the pathological role of increased oxidative stress in the vascular wall in diabetic vasculopathy.



Professor Yu Huang
黃聿教授

多囊性腎病（ADPKD）是一種常見疾病，人群中患病率為1：600。患者會有腎臟及心臟疾病。在本研究中，**姚曉強教授**的研究小組發現，一種名為PKD2的蛋白質突變是導致ADPKD患者心肌病的一個重要因素。

黃聿教授的團隊為動脈粥樣硬化形成的分子機制提供了新的理論依據。integrin-Gα13-RhoA-YAP通路有望成為抗動脈粥樣硬化藥物研發的新靶點。他的團隊還揭示了microRNA 29a在糖尿病內皮功能障礙中的重要作用。這些研究進一步證實了血管壁中氧化應激的增加在糖尿病血管病變中的病理學作用。



Professor Xiaoqiang Yao
姚曉強教授



Professor Gary Tse
謝家偉教授

Professor Gary Tse and his team focus on conducting meaningful translational research in understanding the pathology of atrial and ventricular arrhythmias, which are important conditions leading to thromboembolic events and sudden cardiac death, respectively. The team has unraveled the novel mechanisms by which immunosuppressive, anti-lipidemic and anti-diabetic medications exert protective effects against atrial fibrillation. Using a combination of genetic, pharmacological, biochemical and imaging approaches, they have identified their mechanisms of action, of which reductions in oxidative stress and prevention of mitochondrial dysfunction are critical to achieve reverse remodeling of the atria. For example, with collaborators from China, they found that the xanthine oxidase inhibitor allopurinol alleviated oxidative stress and prevented adverse atrial remodeling in the diabetic atria (Yang, ... Tse, Li and Liu, JAHA, 2018).

謝家偉教授及其團隊的研究重點是透過轉化型研究：去理解涉及心房及心室的心律不正的原因，這些疾病是導致血栓栓塞和心臟猝死的關鍵。研究團隊展示了免疫抑制劑、抗血脂藥物及抗糖尿病藥物，是對心房顫動具有保護作用之新機制。他們以糅合了遺傳學，藥理學，生物化學和造影的方法，確定其機制是透過減少氧化壓力和預防線粒體功能障礙，對心房的逆向重塑是至關鍵重要的 (Yang, ... , Tse, Li and Liu, JAHA, 2018年; 7 (10))。

06

Diabetes and Obesity 糖尿病與肥胖症研究

Led by a team of clinician scientists, the research portfolio of **Professor Juliana Chan** and her team transcends investigations of causes, trajectories, interventions and consequences of people with or at risk of developing diabetes during their different stages of life course. These include gestational diabetes, childhood obesity, young-onset diabetes, usual-onset diabetes and associated complications. Through a series of inter-linking projects, they have established cohorts, databases, biobanks and experimental models to advance their scientific knowledge through inter-institutional collaborations and development of their students and fellows. Through public private partnerships, they translate this knowledge into technologies, prototypes and services in pursuit of their ultimate goal of using genomic medicine, information technology and holistic care to predict, prevent and control diabetes.

在臨床醫生科學家團隊領導下，**陳重娥教授**及其團隊的研究項目覆蓋患有糖尿病或高風險人士，在生命不同階段的原因，軌迹，干預和後果，包括妊娠糖尿病，兒童肥胖，早發性及常見的糖尿病，和相關並發症。通過建立隊列，數據生物庫和實驗模型，培訓和機構合作，推進科學知識。透過公私合作，將知識轉化為技術，原型和服務，實現使用基因組醫學，信息技術和整合管理來預測，預防和控制糖尿病的最終目的。



Professor Juliana Chan
陳重娥教授

07

Emerging Infectious Diseases 防疫研究

The Emerging Infectious Diseases (EID) Laboratory specializes in the study of infections of public health importance in Hong Kong and around the world. In the past one year, the research team led by **Professor Shui-shan Lee** has focused on pre-exposure prophylaxis of HIV, influenza vaccination coverage and hepatitis C transmission. With the adoption of a cross-disciplinary approach, studies were conducted to explain the epidemiology of each infection and make projection on its transmission dynamics. To achieve the objectives of controlling the infections, an integration of laboratory studies, clinical investigations and field research has been made.

新發傳染病實驗室致鑽研香港等地具公共衛生影響的傳染病。在**李瑞山教授**的帶領下，過去一年重點探討愛滋病事前預防用藥、流感疫苗覆蓋、丙型肝炎病毒的傳播等。團隊進行跨領域研究，探討感染的傳播動力，並推算未來趨勢。項目涉及實驗室、臨床和社區研究。



Professor Shui-shan Lee
李瑞山教授

08

Molecular Microbiology 分子微生物學研究

Prof. Guoping Zhao is an expert of molecular microbiology and genomics. His group has been focusing on the genomics and functional genomics study to understand important bacterial metabolic regulation mechanisms. Since 2008, his team also has been exploring the systems and synthetic biology research strategy, emphasising technology innovation and integration/application to facilitate the bacterial physiology/metabolism research, particularly emphasising genome editing and bioinformatics analysis. Employing these advanced technology and research strategy, significant progress has been made in revealing the novel mechanisms of physiology and pathology of *Mycobacterium tuberculosis* and other pathogenic bacteria, particularly regarding to persistent infection and drug tolerance.



Professor Guoping Zhao
趙國屏教授

趙國屏教授，分子微生物學及基因組學專家。以系統合成生物學策略研究重要細菌的生理代謝調控。強調基因組編輯和生物信息分析技術創新，在結核分枝桿菌等致病菌持續性感染和藥物耐受相關生理病理研究中取得可喜成果。



Professor Sunny Wong
黃曦教授

The research focus of the Clinical Metagenomics team led by **Professor Sunny Wong** is to investigate the host-microbial crosstalk in the gastrointestinal tract, and to explore it for clinical applications. Using metagenomics, bioinformatics and cell biology techniques, the team has studied the digestive tract as an intricate ecosystem between the host and the gut microbiota. They have investigated the gastrointestinal tract ecosystem, especially pertaining to diseases including colorectal cancer, *Clostridioles difficile* infection and other gastrointestinal infections. Bridging between laboratory and hospital, the team endeavors to bring the scientific discoveries to clinical translation, and to improve human health through developing innovative diagnostics and therapeutics out of the gut microbiota.

透過基因排序、生物信息科技及功能性實驗，由**黃曦教授**帶領的團隊致力研究腸道內生態系統在疾病中的角色。他們的重點研究在於重要的腸胃科病，包括大腸癌、腸胃感染如難辨梭菌等。他們希望透過腸道生態的研究，發掘可用作臨床診斷及治療用途的嶄新產物，為人類的健康提供更多的保障。

09

Inflammatory Diseases

炎症性疾病研究

The research team led by **Professor Hui-yao Lan** has been working on the immune and molecular biological mechanisms of organ inflammation and fibrosis caused by various reasons. The study of epigenetic regulation of tumor microenvironment is also the focus of this team. Based on the new findings of the research, the team has made promising progress in the development of targeted Smad3 nanotherapy, silencing Smad3-dependent long non-coding RNAs, Smad3 gene-modified natural killer cell immunotherapy and Traditional Chinese Medicine for cancer therapy which were successful in animal experiments.



Professor Erik Fung
馮以文教授

Professor Erik Fung's research team focuses on heart failure and circulatory disorders. In collaboration with the CUHK Jockey Club Institute of Ageing, the team has been conducting a



Professor Hui-yao Lan
藍輝耀教授

藍輝耀教授領導的團隊一直致力於研究各種原因所導致的器官炎症和纖維化的免疫及分子生物學機理。對腫瘤微環境表觀遺傳調控的研究也是本團隊的重點。基於研究的新發現，本團隊在開發有針對性的Smad3靶向納米治療、Smad3基因修飾自然殺傷細胞的免疫療法和中藥抗癌藥已在動物實驗中取得了可喜的進展。

community-based study, undiagnosed heart Failure in frail older individuals (UFO), and have recruited over 300 older adults stratified by frailty status and the phenotypic cohort using physical performance measures and cardiac assessments. They endeavor to use 'omics' technologies for detailed profiling as they build upon the existing bio resource. Other ongoing studies include the Hypo-glycaemia nadir and cardiac Arrhythmias in frail insulin-injecting Elderly diabetics (HARE; with Geriatrics/Endocrinology), and an acute heart failure study (with Geriatrics/Emergency Medicine).

馮以文教授帶領的研究團隊主要集中在心臟衰竭和循環系統疾病。他們與香港中文大學賽馬會老年學研究所合作，進行了一項以社區為基礎的研究，名為「虛弱老年人士中未經診斷的心衰竭」(UFO)，並招募了300多名不同程度身體虛弱的老年人，因應他們的體能表現和心臟評估報告對其虛弱程度作出分類。團隊在現有的生物資料庫中，嘗使用「組學」技術進行詳細分析。同時其他正在進行的研究包括「使用胰島素的年老虛弱糖尿病患者與心律不正和不良臨床反應的危機」(HARE：與老年病學/內分泌學合作)和「急性心臟衰竭研究」(與老年醫學/急診醫學合作)。

10

Neuroscience

神經科學



Professor Owen Ko
高浩教授

Professor Owen Ko's team consists of members with diverse backgrounds in medicine, chemistry, biology and engineering. The team utilises a combination of imaging, biochemical and molecular tools to study (1) fundamental principles governing the operation of neural circuits and (2) neurovascular and immunological dysfunction in the pathogenesis of neurodegenerative diseases. The team seeks to enhance their basic understanding of how the brain works from a systems neuroscience perspective. Armed with novel tools and knowledge, they further aim to uncover pathogenesis underlying neurodegenerative diseases and to guide the development of novel diagnostic methods and treatments.

高浩教授及其團隊成員來自多種背景，包括醫學，化學，生物以及工程專業，融合運用影像學，生物化學，分子生物等多學科技術，圍繞兩個主要問題展開研究：(一)大腦神經迴路的運行機制，以及(二)神經退化性疾病病理過程中腦血管、免疫功能異常。他們著力從系統神經科學層面，進一步加強對大腦工作模式的理解，並基於全新的工具和發現，揭示神經退化性疾病的病理過程，並建立相關的診斷和治療方法。

11

Reproduction and Development 生殖與發育研究

This is the third year being as an official member of the institute, focusing on Reproductive and Development. **Professor Ronald Wang**'s team actively involved in clinical, basic and genetic studies of endometriosis, endometrium imaging, endometrial cancer, reproductive failure, polycystic ovary syndrome, preterm birth, preeclampsia, gestational diabetes mellitus, and cord blood stem cells with excellent progress and fruitful research output.



Professor Ronald Wang
黃志超教授

這是**黃志超教授**加入研究所的第三年，研究工作主要以生殖和發育為主。黃教授及其團隊積極參與了子宮內膜異位症、子宮內膜成像、子宮內膜癌、生殖失敗、多囊卵巢綜合徵、早產、先兆子癇、妊娠糖尿病和臍帶血幹細胞的臨床、基礎及遺傳學研究。團隊工作進展傑出，研究成果卓越。

12

Stem Cells and Tissue Regeneration 幹細胞及組織再生研究

Mesenchymal stem cells (MSCs) are adult stem cells and the key components for tissue regeneration in adulthood. The research team led by **Professor Gang Li** focuses on the biology and application of MSCs in the repair of bone, cartilage and tendon, in close collaboration with local and international clinicians and scientists. In the past year, the team continued their efforts in research on bone and cartilage regeneration; distraction osteogenesis and novel biomaterials. They have organised 1 international symposium, 1 Croucher Foundation summer course and 1 joint research meeting with Tainan University, Taiwan. They have obtained substantial funding support and our work has won 1 national award.



Professor Gang Li
李剛教授

間充質幹細胞是成人幹細胞，是成人組織再生的重要組成部分。**李剛教授**及其團隊的研究工作重點是與當地和國際臨床醫生和科學家密切合作，研究間充質幹細胞在骨、軟骨和肌腱修復中的作用應用。在過去的一年裡，團隊繼續致力於骨和軟骨再生、牽拉成骨技術和新型生物材料的研究。他們組織了1屆國際學術研討會，1屆裘槎基金會夏季研究生課程和1次與臺灣台南大學聯合研究會議。他們獲得了大量的政府和公司的研究資金支援，他們的工作獲得了1項國家獎。



Professor Kathy Lui
呂愛蘭教授

Cardiovascular disease is the leading cause of death worldwide. The research team led by **Professor Kathy Lui** has always been interested in regenerating the aged or damaged cardiovascular

system. They have studied the pathogenesis of and uncovered clinically relevant insights into therapeutic development targeting cardiovascular diseases. The team studied an unappreciated role of the immune system that directly regulates the development of cardiovascular diseases and regeneration. For instance, they reported that a particular subset of white blood cells called regulatory T-cells regulates vascular function and regeneration after injury. They have also been finalising a revised report on the role of these cells in regulating cardiomyocyte proliferation during heart development and regeneration.

心血管疾病是人類死亡的主要原因。**呂愛蘭教授**及其團隊一直對再生老化或受損的心血管系統感興趣。他們研究了針對心血管疾病的治療發展的臨床相關見解的發病機制和發現。團隊研究了免疫系統中一種未被重視的作用，它直接調節心血管疾病和再生的發展。例如，他們報導了稱為調節性T細胞的特定白細胞亞群調節血管功能和損傷後的再生。他們還最終確定了這些細胞在心臟發育和再生過程中調節心肌細胞增殖中的作用。

Ageing and increase in life expectancy is closely associated with the deterioration and injuries of the musculoskeletal system. Orthopaedic surgeries and their associated morbidities and mortalities impose huge socioeconomic and healthcare burden to patients, families, and the society. Hence, there is a need for new and improved surgical and non-surgical interventions or treatment. The multidisciplinary research team led by **Professor Ling Qin** has been developing innovative biomedical and tissue engineering products or supplements, clinical indication-orientated treatment regimens and protocols that utilise stem cells, bioactive and biodegradable materials/implants, endogenous and exogenous growth factors, and biophysical stimuli to enhance tissue regeneration for challenging musculoskeletal disorders. Their R&D strategies facilitate both anatomical and functional restoration to achieve good treatment outcomes, early rehabilitation, as well as reduce its associated morbidity and mortality.

人口老齡化和預期壽命的延長往往伴隨著肌肉骨骼系統的退化和損傷。骨科手術及相關的術後併發症和死亡率給患者及其家庭和社會帶來了巨大的經濟和醫療負擔。因此，現有的外科干預方式是有迫切需要改良的。由**秦嶺教授**

領的研究團隊利用交叉學科的研究方法，研發出新型生物醫學和組織工程材料以及機體補充劑，並且利用幹細胞、具有生物活性和可生物降解特質的材料/內置物、內源性和外源性的生長因子、以及生物物理刺激療法去改善疑難肌肉骨骼疾病的組織再生。他們的研發策略同時改善結構和功能恢復，以達到良好的治療效果及提早康復，并且降低相關的術後併發症和死亡率。



Professor Ling Qin
秦嶺教授

The Laboratory for Intelligent Orthopaedic Bio-Engineering Research led by **Professor Oscar Lee** focuses on the multi-disciplinary application of principles and expertise in stem cell biology, immunology, bioengineering and computer sciences to collectively develop advanced technologies in regenerative medicine, artificial intelligence and precision medicine for the diagnosis and treatment of orthopaedic problems, in particular, aging-related diseases such as osteoporosis, osteoarthritis, sarcopenia and musculoskeletal malignancies, so as to benefit the patients.

由**李光申教授**帶領的智能骨科生醫工程研究團隊，專注於跨領域結合，應用幹細胞生物學、免疫學、生醫工程及計算機科學的原理與研究方法，促進再生醫學、人工智能與精準醫學在骨科醫學上的應用，特別針對與高齡族群相關的骨質疏鬆症、關節炎、肌少症及骨骼肌肉系統腫瘤的病因深入研究，並帶來新的治療方法，以造福病患。



Professor Oscar Lee
李光申教授

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Genomics and Bioinformatics 基因組學與生物訊息學

The research team led by **Professor Hao Sun** has committed to use integrative genomic approaches to study the transcriptional regulation mechanism during different stages of stem cell development, as well as developing computational approaches for sequencing-based disease diagnosis.

生物資訊學是一門正在迅速興起的邊緣學科，它位於生物、電腦、數學等多個領域的交叉點上。隨著第二代基因測序技術的出現，生物資訊學已經成為生物醫學研究



Professor Hao Sun
孫昊教授

的重要領域。由**孫昊教授**所領導的生物資訊學研究小組致力於運用基因組學的研究的方法來研究干細胞的分化過程及其分子機理。



Professor Peiyong Jiang
江培勇教授

In this year, **Professor Peiyong Jiang** and his team have made a number of achievements in the bioinformatics area. Firstly, the team developed a bioinformatics approach for deciphering the preferred ends of plasma DNA associated with

cancer, offering a novel means for detection and monitoring of cancers. Secondly, the team developed a novel method for non-invasive screening of nasopharyngeal carcinoma (NPC), not only improving the overall accuracy on a population screening scale but also reducing two time-points to single time-point testing. This work has made a step toward the real clinical practice of NPC detection at its early stage. Thirdly, the team developed a sophisticated bioinformatics tool to enable integrative and synergistic analysis fragment sizes and fragment ends, shedding mechanistic insights into the generation of cell-free DNA.

這一年，**江培勇教授**和他的團隊在生物信息學領域取得了一系列的成就，包括：

- 1) 開發了一種生物信息學方法，用於破譯與癌症相關的血漿DNA偏好末端，為檢測和監測癌症提供了一種新方法。
- 2) 開發了一種新的鼻咽癌非侵入性篩查方法，不僅提高了人群篩查規模的整體準確性，而且從兩次不同時間取樣檢測減少到一次取樣檢測。這項工作向真正臨床意義的NPC早期檢測邁出了一步。
- 3) 開發了一種全新的生物信息學工具，以實現整合和協同分析片段長短和片段末端模式，從而對無細胞DNA生成的機制有進一步的認識。

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Non-coding RNAs 非編碼核糖核苷酸研究

Non-coding RNAs (ncRNAs) are fascinating molecules which perform a myriad of functions in regulating gene expression thus are key to determining the cell fate and identity. Through the past decade **Professor Huating Wang** and her team have explored the functional mechanisms in skeletal muscle stem cells (MuSCs). These cells normally lie in dormancy in adult muscles but upon damage they can be quickly activated to differentiate, fuse and repair damaged muscles. They have dissected gene regulatory mechanisms of a dozen of ncRNAs including microRNAs and long non-coding RNAs (lncRNAs) in orchestrating MuSC fate transition during the process of muscle regeneration. Findings from their studies have increased our understanding of both MuSC and ncRNA biology.



Professor Huating Wang
王華婷教授

非編碼RNA (ncRNA) 是一類有著精彩功能的生物大分子，其在調節基因表達中發揮無數功能，因此常常是決定細胞命運和身份的關鍵。在過去的十年中，由**王華婷教授**率領的研究團隊探索了其在骨骼肌幹細胞 (MuSCs) 的功能機制。這些細胞通常在成人肌肉中處於靜息狀態，但在肌肉受到損傷時，它們可以快速激活，分化，融合以修復受損肌肉。研究組已經剖析了包括microRNA和長鏈非編碼RNA (lncRNA) 的十幾種ncRNA的基因調控機制，詮釋了它們在肌肉再生過程中調節MuSC命運的功能。他們研究的結果大大增加了我們對MuSC和ncRNA生物學的理解。

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Cellular Signalling 細胞訊號轉導



Professor William Wu
胡嘉麒教授

Professor William Wu and his team are devoted to the pursuit of excellence in research on the molecular mechanisms of diseases of public-health significance, including infection, inflammation, cancer and chronic pain. They are particularly interested in molecules (e.g. host defense peptides) or cellular processes (e.g. autophagy) of emerging importance, the use of omics platforms and big data, and the study of disease development from an evolutionary perspective.

胡嘉麒教授及其團隊致力於開展與公眾健康密切相關的前沿性科學研究，包括感染、炎症、癌症與慢性疼痛等的分子機制研究。通過基因組學平台和大數據及進化醫學思路，發掘與疾病相關的新分子（如宿主防禦肽）或細胞過程（如自噬）。

TECHNICAL REPORT ON RESEARCH PROGRAMMES

研究項目：技術性報告



TECHNICAL REPORT ON RESEARCH PROGRAMMES

研究項目：技術性報告



01

Digestive Diseases

- Professor Jun Yu

03

Fecal Microbiota Transplantation

- Professor Siew Ng

05

Vascular Medicine

- Professor Yu Huang
- Professor Xiaoqiang Yao
- Professor Gary Tse

02

Molecular Diagnostics

- Professor Dennis Lo
- Professor Rossa Chiu
- Professor Nelson Tang
- Professor Allen Chan

04

Asian Cancers

- Professor Kwok-wai Lo
- Professor Ka-fai To
- Professor Nathalie Wong
- Professor Qian Tao
- Professor Siu-tim Cheung

06

Diabetes and Obesity

- Professor Juliana Chan

07

Emerging Infectious Diseases

- Professor Shui-shan Lee

09

Inflammatory Diseases

- Professor Hui-yao Lan
- Professor Erik Fung

11

Reproduction and Development

- Professor Ronald Wang

13

Genomics and Bioinformatics

- Professor Hao Sun
- Professor Peiyong Jiang

15

Cellular Signalling

- Professor William Wu

08

Molecular Microbiology

- Professor Guoping Zhao
- Professor Sunny Wong

10

Neuroscience

- Professor Owen Ko

12

Stem Cells and Tissue Regeneration

- Professor Oscar Lee
- Professor Gang Li
- Professor Kathy Lui
- Professor Ling Qin

14

Non-coding RNAs

- Professor Huating Wang

01 DIGESTIVE DISEASES

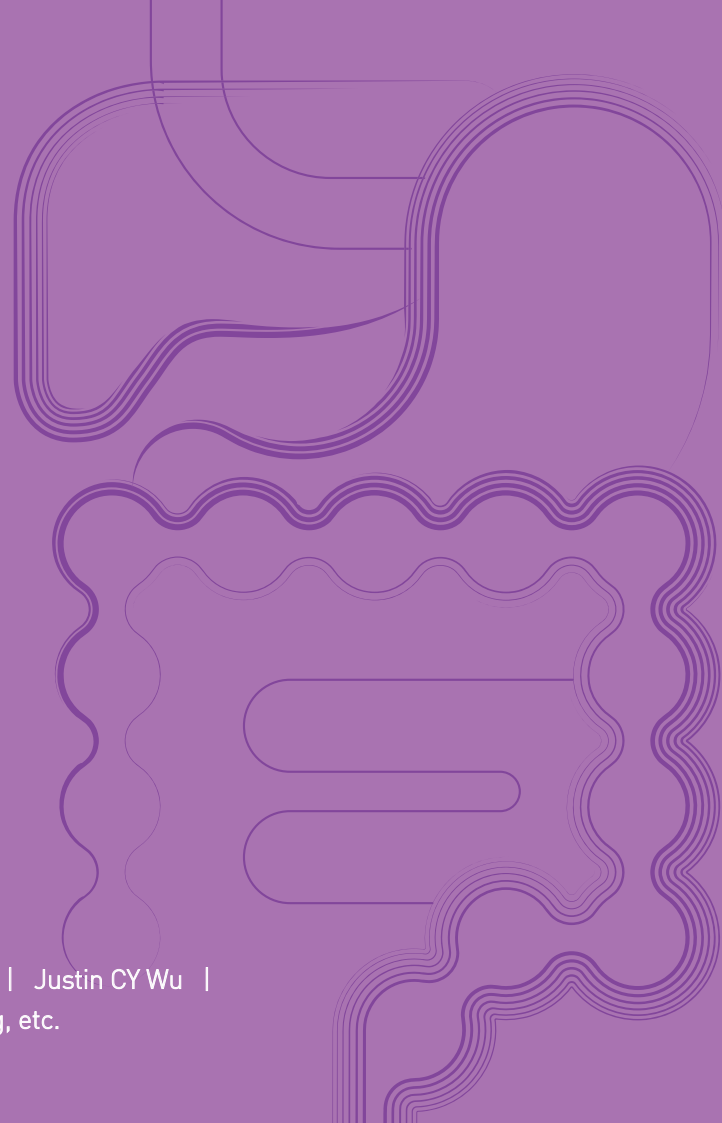


Principal Investigator
Professor Jun Yu



Team

Joseph JY Sung | Francis KL Chan | Henry LY Chan | Justin CY Wu |
Vincent WS Wong | Dennis CC Wong | Jessie Q Liang, etc.



■ Research Progress Summary

Colorectal Cancer:

Gut microbiota:

1. The team led by Professor Jun Yu was the first group to publish the alterations of enteric virome is associated with colorectal cancer (CRC) and patient survival. Using metagenomic data from 489 CRC patient and healthy subjects from 3 cohorts, they found that diversity of gut bacteriophage community was increased in patients with CRC compared to controls. Clinical subgroup analysis showed that dysbiosis of the gut virome was associated with early- and late-stage CRC. A combination of 4 taxonomic markers associated with reduced survival of patients with CRC (log-rank test, $P = 8.1 \times 10^{-6}$) independently of tumour stage, lymph node metastases, or clinical parameters. Their research indicates that enteric virome could be novel biomarkers of CRC.

2. The team retrospectively analysed population-wide dataset of Hong Kong patients hospitalised with bacteremia and demonstrated that the risk

of colorectal cancer was increased in patients with enriched bacterial species associated with CRC. They found that CRC risk was increased in bacteremia patients with *Bacteroides fragilis*, *Streptococcus gallolyticus*, *Fusobacterium nucleatum*, *Peptostreptococcus* species, *Clostridium septicum*, *Clostridium perfringens* or *Gemella morbillorum* compared with unexposed group, whereas no increased risk in patients with bacteremia caused by other microbes. This study informs clinicians that patients with bacterium from these species should be monitored for neoplastic lesions in colorectum.

3. They are the first to describe enteric fungal microbiota dysbiosis and ecological alterations in CRC. Faecal metagenomic sequences of 184 patients with CRC, 197 patients with adenoma and 204 control subjects from Hong Kong were analysed, revealing distinct mycobiomes in



early-stage and late-stage CRC. Basidiomycota: Ascomycota ratio was higher in CRC, with increase in Malasseziomycetes and decrease in Saccharomycete and Pneumocystidomycetes. Abundances of 14 fungal biomarkers distinguished CRC from controls with an area under the receiver-operating characteristic curve (AUC) of 0.74-0.93 in independent CRC cohorts. This study revealed CRC-associated mycobiome dysbiosis characterised by altered fungal composition and ecology, signifying that gut mycobiome might play a role in CRC.

4. The team performed a comprehensive meta-analysis of 526 metagenomic samples from Chinese, Austrian, American, and German and French cohorts, and identified seven bacterial species, including *Bacteroides fragilis*, *Fusobacterium nucleatum*, *Porphyromonas asaccharolytica*, *Parvimonas micra*, *Prevotella intermedia*, *Alistipes finegoldii*, and *Thermanaerovibrio acidaminovorans*, that are highly enriched in CRC across different populations. The seven enriched bacterial combined markers classified CRC cases from controls with an area under the receiver-operating characteristics curve (AUC) of 0.80 across different populations. The study identified potential diagnostic bacterial markers that are robust in different cohorts.

Molecular pathogenesis:

1. Using whole-genome sequencing of CRC clinical specimens, they identified a novel gene, Ring finger protein 6 (RNF6), a RING-domain E3 ubiquitin ligase that is amplified in CRC. They showed that RNF6 is upregulated in 73.5% of patients with CRC and was associated with RNF6 gene amplification. RNF6 promoted cell growth, cell-cycle progression, and epithelial-to-mesenchymal transition in CRC



cell lines. RNF6 also promoted colorectal tumour growth and lung metastasis in mouse models. Mechanistic studies revealed that RNF6 induced Wnt/ β -catenin signalling through promoting the ubiquitylation of transducin-like enhancer of split 3 (TLE3), a transcriptional repressor of the β -catenin/TCF4 complex. RNF6 expression and its gene amplification are independent prognostic factors for poor outcome of CRC patients.

Gastric Cancer:

Molecular pathogenesis:

1. Genomic-wide methylation array demonstrated that transcription factor forkhead box F2 (FOXF2) is preferentially methylated in gastric cancer. FOXF2 was silenced in gastric cancer cell lines and cancer tissues by promoter methylation. Overexpression of FOXF2 malignant phenotype in gastric cancer cell lines *in vitro* and *in vivo*. FOXF2 inhibited Wnt signalling by inducing β -catenin ubiquitination and degradation, independently of GSK-3 β . They demonstrated that FOXF2 induce transcription of E3 ligase interferon regulatory factor 2-binding protein-like (IRF2BPL), which mediates β -catenin ubiquitination and degradation. Multivariate Cox regression analysis further identified FOXF2 hypermethylation as an independent prognostic factor of poor survival in early-stage gastric cancer patients.

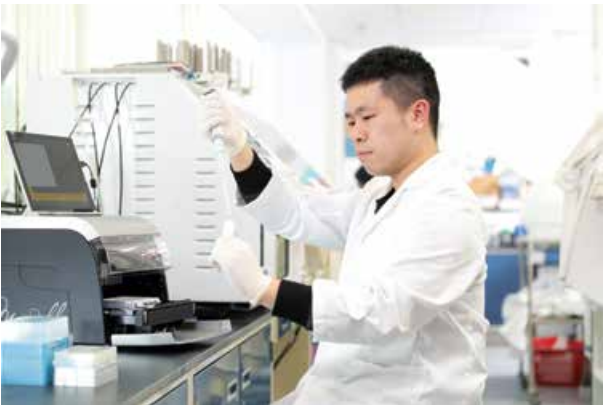
2. Genomic-wide methylation array have unveiled CAB39L as a novel tumour suppressor in gastric cancer. CAB39L mRNA was frequently silenced by promoter methylation in GC cell lines and tissues. Overexpression of CAB39L elicited the suppression of multiple cancer phenotypes both in GC cell lines and an orthotopic mouse model. CAB39L interacted with LKB1-STRAD complex and induced LKB1, leading to the phosphorylation and activation of AMPK α/β , which in turn, reversed the Warburg effect in GC, as evidenced by enhanced oxygen consumption rate and reduced extracellular acidification rate. In GC patients, CAB39L promoter hypermethylation was correlated with poor prognosis.

Non-alcoholic Fatty Liver Disease Associated Hepatocellular Carcinoma (NAFLD-HCC):

Molecular pathogenesis:

1. NAFLD-HCC is an emerging cancer in the developed world. RNA sequencing revealed squalene epoxidase (SQLE) as the top outlier metabolic gene overexpressed in NAFLD-HCC patients. Hepatocyte-specific Sqle transgenic expression in mice accelerated the development of high-fat, high-cholesterol diet-induced HCC. They showed SQLE exerts its oncogenic effect via its metabolites, cholesteryl ester and NADP⁺, which co-operatively induces PTEN-AKT-mTOR axis to promote cell proliferation. Terbinafine, a U.S. Food and Drug Administration-approved antifungal drug targeting SQLE, markedly inhibited SQLE-induced NAFLD-HCC cell growth in NAFLD-HCC and HCC cells and attenuated tumour development in xenograft models and in Sqle transgenic mice. Collectively, the team established SQLE as an oncogene in NAFLD-HCC and could be inhibitor to prevent or treat NAFLD-HCC. This paper was the cover story for April 2018

issue of *Science Translation Medicine*.
2. They analysed the molecular mechanism of NAFLD-HCC in mice fed with high-fat-non-cholesterol diet or high-fat-high-cholesterol diet. Dietary cholesterol induced larger volume and quantity of NASH-HCCs than non-cholesterol-induced HCCs in diethylnitrosamine-treated mice. Integrated genetic and expressional alterations in NASH-HCCs affected genes in five pathways including calcium, insulin, cell adhesion, axon guidance and metabolism. These findings shed light on the link of cholesterol to NASH and NASH-HCC and provide potential therapeutic targets.



Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Joseph Sung	Doctor of Education honoris causa Degree, University of Macau
Jun Yu	何梁何利基金科學與技術進步獎
Francis Chan	American College of Gastroenterology's 2018 International Leadership Award
Francis Chan	Honorary Doctorate Degree, Osaka City University
Francis Chan	廣東省科學與技術獎一等獎
Vincent Wong	廣東省科學與技術獎一等獎
Henry Chan	Chainuvati Lecturer, Thai Association for the Study of the Liver
Henry Chan	Okuda Lecturer, Asia Pacific Digestive Week
Dennis Wong	UEGW 2018 Travel Grant

Fellowships

Member's Full Name	Details
Joseph Sung	AGA Fellow, American Gastroenterology Association
Francis Chan	AGA Fellow, American Gastroenterology Association
Francis Chan	Honorary Fellowship of the Royal College of Physicians of Thailand
Jun Yu	AGA Fellow, American Gastroenterology Association
Jun Yu	Council member of International Cancer Microbiome Consortium, UK
Jun Yu	Council member of AGA Microbiome & Microbial Diseases in the Gastrointestinal Tract (MMDGT), USA
Jun Yu	Associate chairman of National Cancer and Microbiome Association China

Academic Editorship and Reviews

Member's Full Name	Details
Jun Yu	Associate Editor: Oncogene, The World Journal of Gastroenterology, Journal of Gastroenterology & Hepatology, Journal of Digestive Disease, Editorial board member, Gut, Journal of Gastroenterology & Hepatology Research, Scientific Reports, World Journal of Gastrointestinal Pharmacology and Therapeutics, Journal of Pathology & Laboratory Medicine, Journal of Next Generation Sequencing & Applications, Oncogenesis, The Open Hepatology Journal, Pragmatic and Observational Research, ISRN Gastroenterology, International Journal of Clinical Medicine, Insight Knowledge, The Open Gastroenterology Journal, etc.
Francis Chan	Associate Editor of Clinical Gastroenterology & Hepatology, Editorial board member of Precision and Future Medicine, Digestive Endoscopy, Digestive & Liver Diseases, Journal of Digestive Diseases, Encyclopedia of Gastroenterology, Elsevier
Vincent Wong	Associate editor of Clinical Gastroenterology and Hepatology, Editorial board member of PLoS One, Antiviral Therapy, Alimentary Pharmacology & Therapeutics, Journal of Hepatology, Hepatology, Hepatology Communications, JHEP Reports
Henry Chan	Associate editor of Journal of Hepatology, Hepatology International Liver Research, Seminars in Liver Research

Journal / Conference Reviews

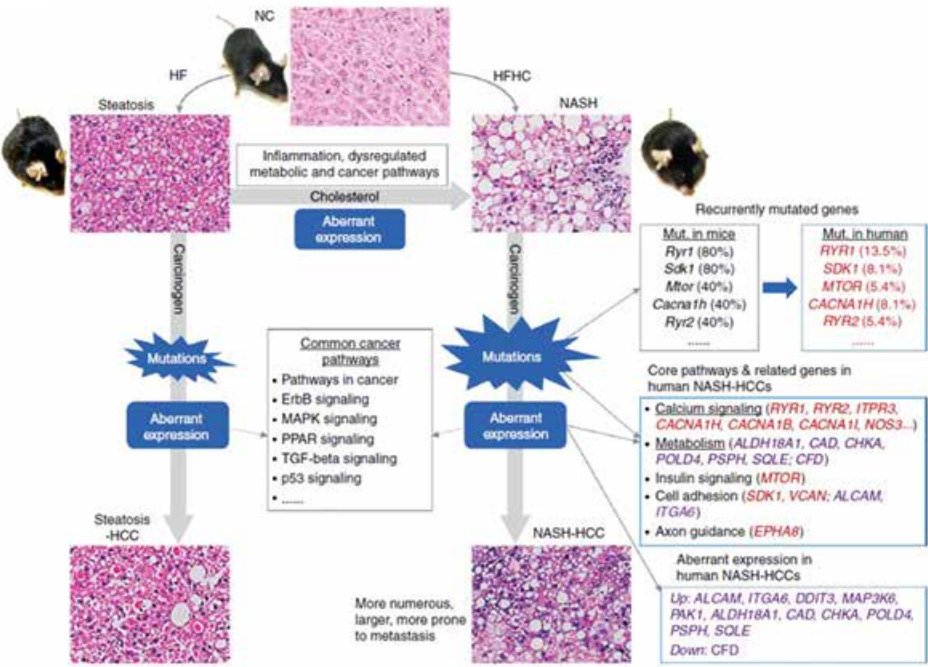
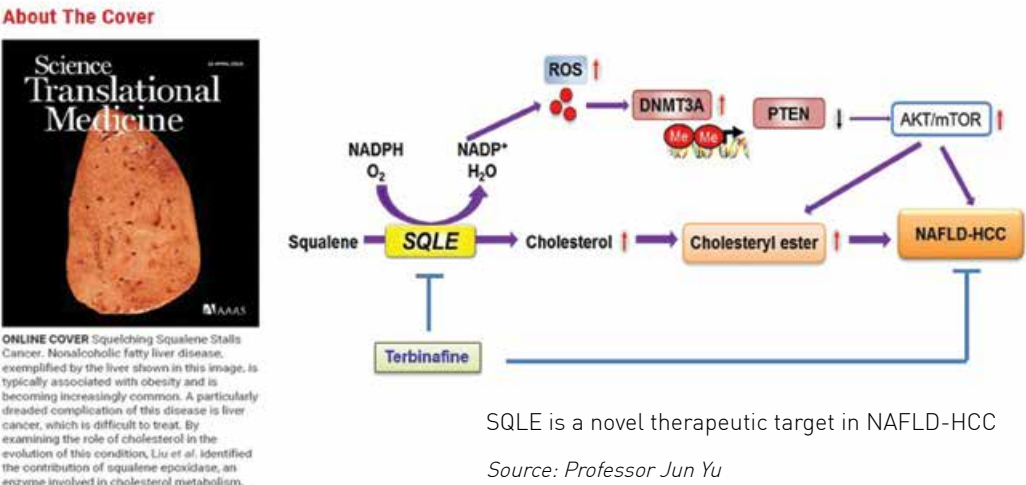
Member's Full Name	Details
Jun Yu	Journal: American Journal of Gastroenterology, American Journal of Pathology, Annals Oncology, BMC Cancer, BMC Gastroenterology, British Journal of Cancer, Alimentary Pharmacology & Therapeutics, Cancer, Cancer Letters, Cancer Research, Carcinogenesis, Cell Death & Disease, Clinical Cancer Research, Clinical Gastroenterology and Hepatology, Digestion, Digestive Diseases and Sciences, eBioMed, FEBS Letters, Gastroenterology, Gut, Hepatology, Human Molecular Genetics, The International Journal of Biochemistry & Cell Biology, Life Sciences, International Journal of Cancer, International Journal of Oncology, Journal of Gastroenterology and Hepatology, The Journal of Hematology & Oncology, Journal of Hepatology, Journal Of Molecular Medicine, Journal of Pathology, Liver International, Lancet, Mol Cancer Research, Mol Cancer Ther, Molecular Carcinogenesis, Molecular Oncology, Nature Reviews Gastroeneterology and Hepatology, New England Journal of Medicine, Oncogene, Plos One, Scand J Gastroenterology, Science Translational Medicine, Theranostics, Tumor Biology, Virchows Archiv

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Joseph Sung	Block Grant Projects	State Key Laboratory of Digestive Diseases Fixed Grant Funds	2016	Current	5,000,000
Joseph Sung	A Multi-centered Study: New Technologies and Plans for Colorectal Cancer Screening (MOST Ref. No.: 2017YFE0190700)	Ministry of Science and Technology - National Key Research Program	01/05/2018	31/10/2019	1,169,790
Joseph Sung	To Implement a Five-year multi-cancer Education and Prevention Programme for the Prevention of Obesity-related Cancers	The Hong Kong Jockey Club Charities Trust	01/01/2018	31/12/2022	35,360,000
Joseph Sung	The Diagnostic Accuracy of Using Faecal-DNA Test (COLOSAFE) for Colorectal Cancer Screening	Creative Biosciences (Guangzhou) Co., Ltd.	01/10/2018	31/03/2021	500,000
Joseph Sung	多癌種早期篩查診斷生物標誌物的效用驗證和推廣應用研究	國家重點研發計畫	01/08/2018	31/12/2020	RMB 7,400,000
Jun Yu	Functional Characterization of Squalene Epoxidase in Promoting Fatty Liver Disease-associated Liver Cancer	Research Grants Council - General Research Fund	01/01/2016	31/12/2018	1,141,432
Jun Yu	Elucidation of a Novel Tumor Suppressor Gene MAP9 in Regulating Chromosome Instability in Colon Cancer	Food and Health Bureau - Health and Medical Research Fund	01/01/2016	31/12/2018	1,195,728
Jun Yu	Elucidation of a Novel Tumor Suppressor Gene Tripartite Motif 67	Research Grants Council - General Research Fund	01/01/2017	31/12/2019	1,154,550
Jun Yu	Functional Investigation of a Novel Oncogenic Bacterium Peptostreptococcus Anaerobius in Colorectal Carcinogenesis	Food and Health Bureau - Health and Medical Research Fund	01/08/2018	31/07/2020	1,196,904
Jun Yu	Elucidating A novel Tumor Promoting Gene Ring Finger Protein 6 in Colorectal Cancer	Research Grants Council - General Research Fund	01/01/2018	31/12/2020	1,229,089
Jun Yu	Study on the Relationship Between Gut Microbe Dysbiosis and Ccolorectal Cancer	Science and Technology Program Grant, Shenzhen	01/07/2017	30/06/2020	RMB 2,000,000

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Jun Yu	Regulation and Mechanism of Tumor-intrinsic Oncogene Pathways in Mediating an Immune Suppressed Microenvironment in Hepatocellular Carcinoma	Research Grants Council – Collaborative Research Fund	01/06/2018	30/06/2021	7,544,147
Jun Yu	結直腸癌篩查生物標誌物及人群梯度篩查方案的前瞻	國家重點研發計畫	01/09/2018	31/12/2020	RMB 9,000,000
Francis Chan	Evaluation of Colorectal Cancer Screening Pilot Programme in Hong Kong: Awareness, Knowledge, Attitude, Perception, Practice and Satisfaction of Stakeholders	Food and Health Bureau – Health and Medical Research Fund	2015	2019	11,000,000
Francis Chan	消化道腫瘤標誌物試劑盒研發、多項聯合診斷體系的建立及其臨床應用	國家十三五慢病項目	01/09/2016	31/12/2020	RMB 1,000,000
Henry Chan	Plasma DNA as a Platform Technology for Cancer Detection	Research Grants Council – Theme-based Research Scheme	01/06/2016	31/05/2021	44,444,000
Vincent Wong	Incidence of Non-alcoholic Fatty Liver Disease and Advanced Fibrosis in Patients with Type 2 Diabetes: A Prospective Cohort Study Using Paired Controlled Attenuation Parameter and Liver Stiffness Measurements	Research Grants Council – General Research Fund	01/01/2017	31/12/2019	658,050
Qiaoyi Liang	Regulation of Autophagy by the Novel Tumor Suppressor Gene GGT7 in Gastric Cancer	Research Grants Council – General Research Fund	01/12/2018	30/11/2021	965,601
Qiaoyi Liang	Functional Importance and Clinical Application of the Novel Fusion Gene DDX5-POLG2 in Gastric Cancer	National Nature and Science Foundation of China	01/01/2018	31/12/2021	RMB 600,000
Qiaoyi Liang	Establishing a Best Panel of Stool-based Detection for Non-invasive Colorectal Neoplasm Screening	Health and Medical Research Fund – Research Fellowship Scheme	01/10/2017	30/09/2019	1,187,488
Chi Chun Wong	Functional Significance and Potential Clinical Application of SCNN1B, a Novel Tumor Suppressor Gene in Gastric Cancer	Food and Health Bureau – Health and Medical Research Fund	01/01/2016	31/12/2018	RMB 170,000

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Chi Chun Wong	PGE2-induced DNA Methylation in Gastric Cancer: Mechanisms and Therapeutic Implications.	Research Grants Council – General Research Fund	01/10/2015	30/09/2018	852,552
Chi Chun Wong	Inhibition of SLC25A22 Synergizes with Chemotherapy to Induce KRAS-mutant Colorectal Cancer Cell Death Through Induction of Endoplasmic Reticulum Stress.	Research Grants Council – General Research Fund	01/01/2018	31/12/2020	1,203,589
Chi Chun Wong	Mitochondrial Glutamate Transporter (SLC25A22) Promotes the Tumorigenicity of KRAS-mutant Colorectal Cancer Through Regulating DNA and Histone Methylation	National Natural Science Foundation of China	01/01/2018	31/12/2021	RMB 530,000



Dietary cholesterol promotes steatohepatitis related hepatocellular carcinoma through dysregulated metabolism and calcium signaling

Source: Professor Jun Yu

■ Publications

A. Journal Papers

1. Nakatsu G, Zhou H, Wu W, Wong S, Coker O, Dai Z, Li X, Szeto C, Sugimura N, Lam T, Yu A, Wang X, Chen Z, Wong M, Ng S, Chan M, Chan P, Chan F, Sung J, Yu J. Alterations in Enteric Virome Are Associated With Colorectal Cancer and Survival Outcomes. *Gastroenterology*. 2018;155(2):529-541.e5.
2. Kwong T, Wang X, Nakatsu G, Chow T, Tipoe T, Dai R, Tsoi K, Wong M, Tse G, Chan M, Chan F, Ng S, Wu J, Wu W, Yu J, Sung J, Wong S. Association Between Bacteremia From Specific Microbes and Subsequent Diagnosis of Colorectal Cancer. *Gastroenterology*. 2018;155(2):383-390.e8.
3. Coker O, Nakatsu G, Dai R, Wu W, Wong S, Ng S, Chan F, Sung J, Yu J. Enteric fungal microbiota dysbiosis and ecological alterations in colorectal cancer. *Gut*. 2018;68(4):654-662.
4. Liu D, Wong C, Fu L, Chen H, Zhao L, Li C, Zhou Y, Zhang Y, Xu W, Yang Y, Wu B, Cheng G, Lai P, Wong N, Sung J, Yu J. Squalene epoxidase drives NAFLD-induced hepatocellular carcinoma and is a pharmaceutical target. *Science Translational Medicine*. 2018;10(437):eaap9840.
5. Wang X, Li X, Zhang L, Wong S, Wang M, Tse G, Dai R, Nakatsu G, Coker O, Chen Z, Ko H, Chan J, Liu T, Cheng C, Cheng A, To K, Plewczynski D, Sung J, Yu J, Gin T, Chan M, Wu W. Oncogenes expand during evolution to withstand somatic amplification. *Annals of Oncology*. 2018;29(11):2254-2260.
6. Liang J, Teoh N, Xu L, Pok S, Li X, Chu E, Chiu J, Dong L, Arfianti E, Haigh W, Yeh M, Ioannou G, Sung J, Farrell G, Yu J. Dietary cholesterol promotes steatohepatitis related hepatocellular carcinoma through dysregulated metabolism and calcium signaling. *Nature Communication*. 2018;9(1):4490.
7. Zuo T, Wong S, Cheung C, Lam K, Lui R, Cheung K, Zhang F, Tang W, Ching J, Wu J, Chan P, Sung J, Yu J, Chan F, Ng S. Gut fungal dysbiosis correlates with reduced efficacy of fecal microbiota transplantation in *Clostridium difficile* infection. *Nature Communication*. 2018;9(1):3663.
8. Wong C, Li W, Chan B, Yu J. Epigenomic biomarkers for prognostication and diagnosis of gastrointestinal cancers. *Seminars in Cancer Biology*. 2019;55:90-105. [Review]
9. Wong S, Kwong T, Wu C, Yu J. Clinical applications of gut microbiota in cancer biology. *Seminars in Cancer Biology*. 2019;55:28-36. [Review]
10. Dai Z, Coker O, Nakatsu G, Wu W, Zhao L, Chen Z, Chan F, Kristiansen K, Sung J, Wong S, Yu J. Multi-cohort analysis of colorectal cancer metagenome identified altered bacteria across populations and universal bacterial markers. *Microbiome*. 2018;6(1).
11. Higashimori A, Dong Y, Zhang Y, Kang W, Nakatsu G, Ng S, Arakawa T, Sung J, Chan F, Yu J. Forkhead Box F2 Suppresses Gastric Cancer through a Novel FOXF2-IRF2BP1- β -Catenin Signaling Axis. *Cancer Research*. 2018;78(7):1643-1656.
12. Liu L, Zhang Y, Wong C, Zhang J, Dong Y, Li X, Kang W, Chan F, Sung J, Yu J. RNF6 Promotes Colorectal Cancer by Activating the Wnt/ β -Catenin Pathway via Ubiquitination of TLE3. *Cancer Research*. 2018;78(8):1958-1971.
13. Li X, Xu W, Kang W, Wong S, Wang M, Zhou Y, Fang X, Zhang X, Yang H, Wong C, To K, Chan S, Chan M, Sung J, Wu W, Yu J. Genomic analysis of liver cancer unveils novel driver genes and distinct prognostic features. *Theranostics*. 2018;8(6):1740-1751.
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B. Books / Book Chapters

1. Yu J. *Obesity, Fatty Liver And Liver Cancer*. 1st ed. Springer Singapore; 2018.
2. Lau J.K.C., Zhang X., Yu J. (2018) Animal Models of Non-alcoholic Fatty Liver Diseases and Its Associated Liver Cancer. In: Yu J. (eds) *Obesity, Fatty Liver and Liver Cancer. Advances in Experimental Medicine and Biology*, vol 1061. Springer, Singapore

C. Patents

- (1). US Patent:
 - Inventors: Jun Yu, Joseph JY Sung, Simond SM Ng, Yajuan Dong.
 - Title: A Novel Prognostic Marker for Colorectal Cancer- VSTM2A
 - U.S. Application No. 15/480107
 - Filed on 04/05/2017
- (2). US Patent:
 - Inventors: Yu Jun, Liu Dabin, Wong Chi-chun.
 - Title: Squalene Epoxidase in the Diagnosis and Treatment of Non-Alcoholic Fatty Liver Diseases.
 - U.S. Application No. 15/911,042
 - Filed on 2 March 2018
- (3). US Patent:
 - Inventors: KaKei Wu, Jun Yu.
 - Title: Use of Streptococcus Thermophilus for Treatment and Prevention of Colorectal Cancer
 - U.S. Application No. 62/799,162
 - Filed on 31 January 2019
- (4). China PCT:
 - Inventors: Jun Yu, Joseph JY Sung, Qiaoyi Liang.
 - Title: Tumor suppressor REC8 as a biomarker for gastric cancer
 - CN Patent Application No. 201810481334.3
 - Filed on 18 May 2018
- (5). Hong Kong patent:
 - Inventors: Jun Yu, Joseph JY Sung, Qiaoyi Liang.
 - Title: Faecal Bacterial Markers for Colorectal Cancer.
 - Patent Application No. 18111533.1
 - Filed on 14 Sep 2018

02

MOLECULAR DIAGNOSTICS

Circulating Fetal Nucleic Acids



Principal Investigators

Professor Dennis Lo
Professor Rossa Chiu



Team

Professor Allen Chan | Mr. Kam-wing Chan | Dr. Lisa Chan | Dr. Rebecca Chan | Dr. Alice Cheng |
Dr. Wanxia Gai | Dr. Diana Han | Dr. Macy Heung | Professor Peiyong Jiang | Ms. Yoyo Jin |
Mr. Chris Kum | Dr. Jacky Lam | Ms. Coral Lee | Ms. Elena Lo | Dr. Huimin Shang | Dr. Sarah Sin |
Professor Hao Sun | Professor Kun Sun | Ms. Patty Tse | Dr. Joaquim Vong | Dr. Lea Wang |
Miss Hing-ye Wong | Dr. Ting-ting Xie

Research Progress Summary

In the reporting year, Professor Dennis Lo, Professor Rossa Chiu and their research team have further pushed the envelope in their research on circulating nucleic acids, especially in the areas of prenatal and cancer diagnostics.

Prenatal Diagnosis

In 2016, the research team discovered that selected genomic locations were more likely to be found at the ends of plasma DNA molecules. A subset of such preferred ends exhibited selectivity for fetal- or maternal-derived DNA in maternal plasma. Further on the discovery, the team performed an integrative analysis of preferred end sites with the size characteristics of plasma DNA fragments. A maternal plasma DNA sequencing dataset, which was previously generated from 26 first-trimester pregnant women, was reanalysed. The plasma DNA sequencing reads were separated into short and long categories, namely set S and set L, respectively. A positive correlation was observed between the relative abundance of plasma DNA with set S versus set L preferred end sites and the fetal DNA fraction ($R = 0.79$, $P < 0.001$, Pearson correlation). In addition, the

team investigated whether the size-tagged preferred end sites could improve the non-invasive prenatal testing of fetal trisomy 21. They collected a dataset from a previous study, which contained 36 trisomy 21 cases and 108 control cases. Taking advantage of the reads covering the set S preferred ends, the trisomy 21 cases showed a significantly elevated normalized chr21 reads with set S preferred ends compared with the control cases ($P < 0.001$, Mann-Whitney U rank-sum test). The results suggested that the set S preferred end sites could potentially enhance trisomy 21 testing in assays designed to exploit their characteristics.

Interestingly, further analysis revealed that the fetal and maternal preferred ends were generated from different locations within the nucleosomal structure. Fetal DNA was frequently cut within the nucleosome core while maternal DNA was mostly cut within the linker region. Moreover, such short and long size-tagged ends were also observable in the plasma of non-pregnant healthy subjects. The finding suggested that the interrelationship of preferred DNA ends, chromatin accessibility, and plasma DNA size profile was likely to be a general one, extending beyond the context of pregnancy.



Besides DNA fragment end patterns, analysis of methylated fetal DNA was another research focus in the area of circulating nucleic acid in prenatal testing because DNA methylation in placental tissue was highly relevant to the normal growth and development of the fetus during pregnancy. Therefore, Professor Lo's research team aimed to develop an approach for reconstruction of the placental methylome with high accuracy and resolution in a completely non-invasive manner. They successfully established a novel size-based algorithm, FETal METHylome Reconstructor (FEMER), to non-invasively reconstruct the placental methylome by genomewide bisulfite sequencing and size-based analysis of maternal plasma DNA. By applying FEMER on a real clinical dataset, the goal achieved, thus providing a high-quality view of the placental methylome from maternal plasma DNA. FEMER could also predict the DNA methylation profile of CpG islands with high accuracy, which, in turn, showed potential in monitoring key genes involved in placental/fetal development.

To summarise, plasma DNA fragment end patterns shed light on the mechanism on how plasma DNA was generated. FEMER could enhance the non-invasive fetal/placental methylomic analysis. The research findings demonstrated promising utility in future developments in plasma DNA-based non-invasive molecular diagnostics in prenatal testing and monitoring.

Cancer Diagnosis

Circulating tumour-derived cell-free DNA (ctDNA) analysis offered an attractive non-invasive means for detection and monitoring of cancers. Hepatocellular carcinoma (HCC) is the predominant primary liver cancer and the incidence is the fifth highest in Hong Kong. This year, the research team developed an approach to detect the total pool of somatic mutations and demonstrated the existence of a class of ctDNA signature in the form of preferred plasma DNA end coordinates, which might improve the cost-effectiveness of liquid biopsy assessment for hepatocellular carcinoma.

The team sequenced the buffy coat, resected tumour, adjacent normal liver tissue, and plasma specimen obtained from the HCC patient. They

developed a strategy termed "dynamic threshold filtering" to remove apparent variants arising due to sequencing errors. By applying the filtering strategy, 11,466 plasma DNA variants were identified and their size profile was consistent with the expected profile of ctDNA. It was successfully demonstrated that scanning for somatic mutations in plasma without *a priori* tumour information was feasible.

Moreover, the team also looked for other types of ctDNA signatures. Cell-free DNA molecules were short and fragmented, but the fragmentation process was not random. By employing a liver transplantation model, it was found that liver-contributed cell-free DNA molecules ended more frequently at certain genomic coordinates than the non-liver-derived molecules. Moreover, the team investigated the ending patterns between cell-free DNA of the HCC patient and cell-free DNA of a patient with chronic HBV infection to identify tumour-associated cell-free DNA molecules. Majority of the tumour-associated preferred end coordinates were found to be in the intergenic regions (58%) or gene bodies (39%) while a small proportion were located at gene promoters (3%). The ratios of tumour- to non-tumour-associated preferred ends were significantly increased in the plasma samples of the 90 HCC patients compared with the plasma samples of other non-HCC participants ($P < 0.001$, Kruskal-Wallis test). Of note, the plasma samples were sequenced to a median depth of 1.5× haploid genome coverage only. By studying the size profiles, it was found that the cell-free DNA molecules with the tumour-associated preferred ends were shorter than those with their non-tumour-associated counterparts. These results were consistent with the fact that tumour-derived DNA in plasma was shorter than non-tumour-derived DNA in plasma. Plasma DNA end coordinates might serve as hallmarks of ctDNA that could be sampled readily and, hence, may improve the cost-effectiveness of liquid biopsy assessment.

Besides HCC, nasopharyngeal carcinoma (NPC) is another common cancer in Hong Kong and Southern China. In 1999, Professor Lo and his team developed a quantitative real-time polymerase chain reaction (PCR) test to detect Epstein-Barr virus (EBV) DNA in plasma of NPC patients. In 2013, the same test was moved from university laboratory into the community. The research team recruited more than 20,000 participants

and conducted a prospective study to investigate whether EBV DNA in plasma samples would be useful to screen for early NPC in asymptomatic persons. While plasma EBV DNA was persistently detectable in 97.1% of the NPCs identified, about 5% of the general population had transiently detectable plasma EBV DNA. This year, with the advancement of sequencing technology, the test further evolved. The team developed a sequencing-based counting and size profiling analysis on plasma EBV DNA to enhance population screening of nasopharyngeal carcinoma. It was found that NPC patients had significantly higher amounts of plasma EBV DNA with longer fragment lengths. By adopting the new analysis, NPC cases were detected at a positive predictive value (PPV) of 19.6%, which was superior compared with the PPV of 11.0% in the prospective screening study. The observed differences in the molecular nature of EBV DNA molecules in plasma of subjects with or without NPC were successfully translated into a sequencing-based test that had a high PPV for NPC screening.

There was no doubt that measurement of DNA derived from different tissues in the circulating DNA pool can provide important information of many pathological conditions. Though genome-wide bisulfite sequencing provided high-resolution analysis, it was expensive. So, the team tested an alternative. Through identifying differentially methylated regions in the liver and colon compared with other tissues, the team identified 2 markers and developed corresponding droplet digital PCR assays. Plasma concentrations of liver-derived and colon-derived DNA were measured for 40 liver cancer patients and 62 colorectal cancer patients (CRC). Among them, 27 colorectal cancer patients had shown liver metastases. In liver cancer patients, the concentration of liver-derived DNA correlated positively with the maximal dimension of the tumour ($R = 0.74$, Spearman correlation). In CRC patients, the plasma concentrations

of colon-derived DNA were increased compared with the 30 healthy controls. The receiver operating characteristic (ROC) curve analysis revealed that the absolute concentration of liver-derived DNA provided a better differentiation between CRC patients with and without liver metastasis compared with the fractional concentration. Quantitative analysis of plasma DNA with tissue-specific methylation patterns using droplet digital PCR was applicable for the investigation of cancers and assessing organ transplantation. This approach could also be useful for differentiating patients with and without metastases to other organs.

The project team's experience and efforts on prenatal and cancer diagnostics created synergistic effects and pushed forward the frontiers of molecular diagnostics. In the reporting period, the team published a total of 8 peer-reviewed articles and reviews in international journals. With the pioneering work on non-invasive prenatal diagnosis, Professor Dennis Lo was named the "Top 20 Translational Researchers of 2017" by the authoritative scientific journal *Nature Biotechnology*. This is the second year that Professor Lo received the honour and he was also the only Hong Kong scientist on the list. Lastly, having teamed up for more than a decade, it was remarkable and memorable that Professor Lo and Professor Rossa Chiu jointly triumphed Sing Tao News Corporation Limited's Leader of the Year 2017 in the Commerce & Industry/Finance category.



■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Dennis Lo Rossa Chiu	Sing Tao News Corporation Limited's Leader of the Year 2017 (Commerce and Industry/Finance Category)
Dennis Lo	InnoStars Award organised by Our Hong Kong Foundation
Dennis Lo	The Chinese Society of Clinical Oncology (CSCO) Annual Achievement Award 2018
Dennis Lo	2018年度高等學校科學研究優秀成果獎（科學技術）發明獎二等獎
Dennis Lo	Top 20 Translational Researchers of 2017 by the authoritative scientific journal Nature Biotechnology
Dennis Lo	Extraordinary Scientific Innovation Award, The Chinese Association for Science and Technology, USA
Dennis Lo	2018 Excellence in Genetics Research Award, Association of Chinese Geneticists in America
Dennis Lo	2018 Man of Hope (MOH) Award in the category of Health Advocate
Dennis Lo	The Fifth Biotechnology Get Together (2018) Award

Fellowships

Member's Full Name	Details
Dennis Lo	Fellow ad eundem of the Royal College of Obstetricians and Gynaecologists

Academic Editorship and Reviews

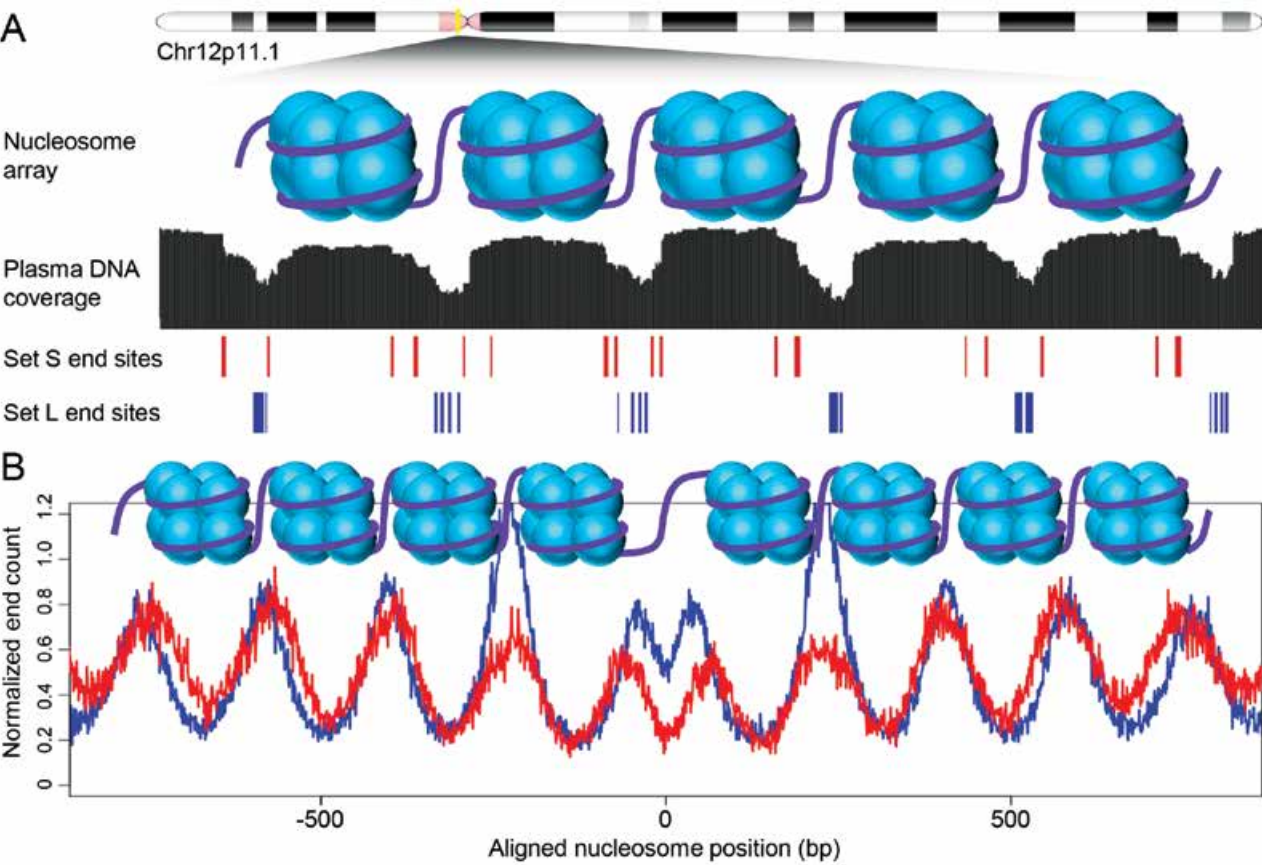
Member's Full Name	Details
Dennis Lo	<i>Frontiers in Molecular Biosciences</i> : Review Editor for Molecular Diagnostics and Therapeutics
Dennis Lo	<i>Clinical Chemistry</i> : Associate Editor
Dennis Lo	<i>Expert Reviews in Molecular Medicine</i> : Associate Editor
Dennis Lo	<i>npj Genomic Medicine</i> : Associate Editor
Dennis Lo	<i>Disease Markers</i> : Editorial Board Member
Dennis Lo	<i>Prenatal Diagnosis</i> : Editorial Board Member
Dennis Lo	<i>BioScience Trends</i> : Editorial Board Member
Dennis Lo	<i>Fetal Diagnosis and Therapy</i> : Editorial Board Member
Dennis Lo	<i>Journal of Molecular Biotechnology</i> : Editorial Board Member
Dennis Lo	<i>Chimerism</i> : Editorial Board Member
Dennis Lo	<i>Journal of Pathology</i> : Editorial Board Member
Dennis Lo	<i>Philosophical Transactions of the Royal Society B</i> : Editorial Board Member
Dennis Lo	<i>Journal of Genomes and Exomes</i> : Editorial Board Member
Dennis Lo	<i>Reproductive BioMedicine Online</i> : Editorial Board Member
Dennis Lo	<i>Marrow</i> : Editorial Board Member
Dennis Lo	<i>The Journal of Precision Medicine</i> : Editorial Board Member
Rossa Chiu	<i>Q&A Articles, Clinical Chemistry</i> : Associate Editor
Rossa Chiu	<i>Clinical Chemistry</i> : Editorial Board Member
Rossa Chiu	<i>Critical Reviews in Clinical Laboratory Sciences</i> : Editorial Board Member
Rossa Chiu	<i>Clinical Biochemistry</i> : Editorial Board Member
Rossa Chiu	<i>The Clinical Biochemist Reviews</i> : Editorial Board Member

Journal / Conference Reviews

Member's Full Name	Details
Dennis Lo	<i>Hong Kong Journal of Radiology</i>
Rossa Chiu	<i>Clinical Chemistry</i>
Rossa Chiu	<i>Clinical Chemistry and Laboratory Medicine</i>
Rossa Chiu	<i>American Journal of Obstetrics and Gynecology</i>
Rossa Chiu	<i>Obstetrics and Gynecology</i>
Rossa Chiu	<i>Prenatal Diagnosis</i>
Rossa Chiu	<i>The Journal of Obstetrics and Gynaecology Research</i>
Rossa Chiu	<i>Annals of Hematology</i>
Rossa Chiu	<i>Scientific Reports</i>

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Dennis Lo Rossa Chiu	Centre for Research into Circulating Fetal Nucleic Acids	Research Grants Council – Theme-based Research Scheme	01/01/2016	31/12/2020	37,286,000
Dennis Lo Rossa Chiu	Plasma DNA as a Platform Technology for Cancer Detection	Research Grants Council – Theme-based Research Scheme	01/12/2016	30/11/2021	28,570,000



Distribution of size-tagged preferred end sites around regions with well-positioned nucleosomes. (A) Snapshot of the plasma DNA coverage, set S, and set L preferred end sites. An illustration of the nucleosome arrays on chr12p11.1 region is shown. (B) Distribution of the preferred end sites surrounding the common open chromatin regions shared by placental tissues and T cells. An illustration of the nucleosome positions is shown. Red

and blue lines represent set S and set L preferred end sites, respectively. The aligned nucleosome positions as plotted on the x axis are in relation to the center of the common open chromatin regions.

Source: Kun Sun et al. "Size-tagged preferred ends in maternal plasma DNA shed light on the production mechanism and show utility in noninvasive prenatal testing" *PNAS* 2018;115:22:E5106-E5114 doi: 10.1073/pnas.1804134115

Publications

A. Journal Papers

1. Sun K, Lun FMF, Leung TY, Chiu RWK, Lo YMD, Sun H. Noninvasive reconstruction of placental methylome from maternal plasma DNA: Potential for prenatal testing and monitoring. *Prenatal Diagnosis*. 2018;38(3):196-203. doi:10.1002/pd.5214.
2. Cheng THT, Lui KO, Peng XL, Cheng SH, Jiang P, Chan KCA, Chiu RWK, Lo YMD. DNase1 Does Not Appear to Play a Major Role in the Fragmentation of Plasma DNA in a Knockout Mouse Model. *Clinical Chemistry*. 2018;64(2):406-408. doi:10.1373/clinchem.2017.280446. [Letter]
3. Sun K, Jiang P, Wong AIC, Cheng YKY, Cheng SH, Zhang H, Chan KCA, Leung TY, Chiu RWK, Lo YMD. Size-tagged preferred ends in maternal plasma DNA shed light on the production mechanism and show utility in noninvasive prenatal testing. *Proceedings of the National Academy*. 2018;115(22):E5106-E5114. doi:10.1073/pnas.1804134115.
4. Lam WKJ, Jiang P, Chan KCA, Cheng SH, Zhang H, Peng W, Tse OYO, Tong YK, Gai W, Zee BCY, Ma BBY, Hui EP, Chan ATC, Woo JKS, Chiu RWK, Lo YMD. Sequencing-based counting and size profiling of plasma Epstein-Barr virus DNA enhance population screening of nasopharyngeal carcinoma. *Proceedings of the National Academy*. 2018;115(22):E5115-E5124. doi:10.1073/pnas.1804184115.
5. Bianchi DW, Chiu RWK. Sequencing of Circulating Cell-free DNA during Pregnancy. *New England Journal of Medicine*. 2018;379(5):464-473. doi:10.1056/NEJMr1705345. [Review]
6. Gai W, Ji L, Lam WKJ, Sun K, Jiang P, Chan AWH, Wong J, Lai PBS, Ng SSM, Ma BBY, Wong GLH, Wong VWS, Chan HLY, Chiu RWK, Lo YMD, Chan KCA. Liver- and Colon-Specific DNA Methylation Markers in Plasma for Investigation of Colorectal Cancers with or without Liver Metastases. *Clinical Chemistry*. 2018;64(8):1239-1249. doi:10.1373/clinchem.2018.290304.
7. Leung CS, Yang KY, Li X, Chan VW, Ku M, Waldmann H, Hori S, Tsang JCH, Lo YMD, Lui KO. Single-cell transcriptomics reveal that PD-1 mediates immune tolerance by regulating proliferation of regulatory T cells. *Genome Medicine*. 2018;10(1):71. doi:10.1186/s13073-018-0581-y.
8. Jiang P, Sun K, Tong YK, Cheng SH, Cheng THT, Heung MMS, Wong J, Wong VWS, Chan HLY, Chan KCA, Lo YMD, Chiu RWK. Preferred end coordinates and somatic variants as signatures of circulating tumor DNA associated with hepatocellular carcinoma. *Proceedings of the National Academy*. 2018;115(46):E10925-E10933. doi:10.1073/pnas.1814616115.

02 MOLECULAR DIAGNOSTICS

Genetics of Disease Susceptibility



Principal Investigator
Professor Nelson Tang



Team

Raphael Chiu Yeung Chan (Microbiology) | Helen Fung Kum Chiu (Psychiatry) |
Linda Chiu Wah Lam (Psychiatry) | Ting Fan Leung (Paediatrics) |
Suk Ling Ma (Psychiatry) | Xiaoqiang Yao (School of Biomedical Sciences)



■ Research Progress Summary

Research Directions

1. Genetics of complex traits: to identify prevalent genetic variants causing common diseases in Han Chinese;
2. Statistical genetics and computational statistical analysis of big genetic and biological datasets;
3. Analysis of variation of the transcriptome using latest technology of next generation sequencing.

Research into Genetics of Disease Susceptibility (GDS)

The mission of the GDS laboratory is to identify disease predisposition genes for common diseases, also known as complex traits. The research group is involved in development of various analysis methods and wet laboratory validation of the results generated from such analysis. The team also participates in international consortiums in studies of healthy aging (including bone and

other phenotypes), breast cancer, and genetic susceptibility to adolescent idiopathic scoliosis and tuberculosis. With the advance in sequencing and other technology, the team acquires biological data in an unprecedented volume nowadays. The analysis and statistic method become limiting factor in handling such huge volume of data.



■ Research and Scholarship

Academic Editorship and Reviews

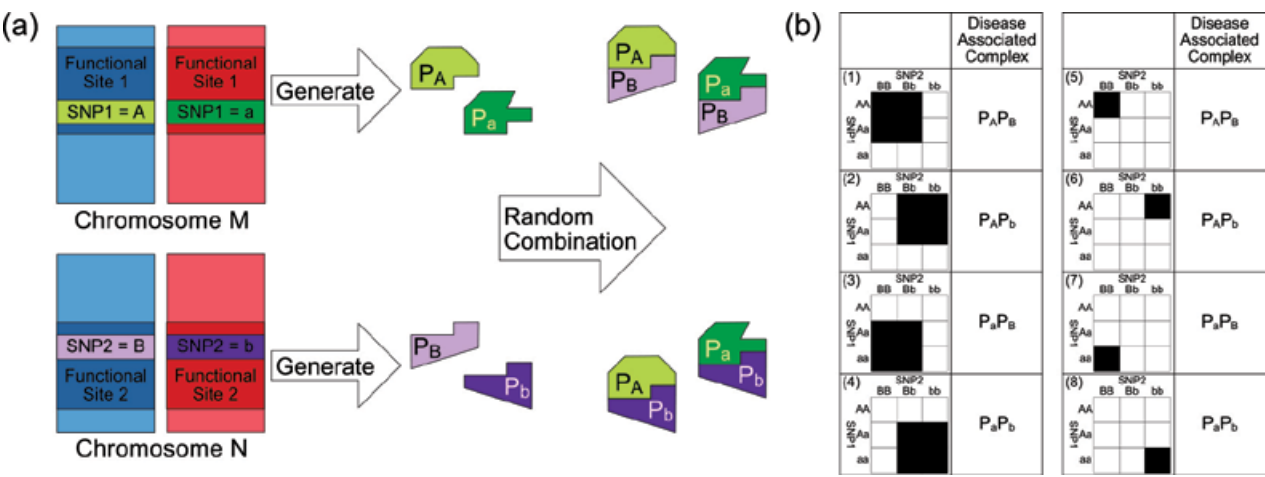
Member's Full Name	Details		
	Journal	Role	Period
Nelson Tang	Frontiers in Genetic Disorders	Editorial Board Member	Sep 2013 – present
Nelson Tang	Frontiers in Pediatrics	Editorial Board Member	Sep 2014 – present
Nelson Tang	Journal of Pediatric Biochemistry (Official Journal of the World Society of Child Science)	Editorial Board Member	Jun 2014 – present
Nelson Tang	Genes – Open Access Journal of Genetics & Genomics	Editorial Board Member	Aug 2018 – present

Journal / Conference Reviews

Member's Full Name	Details	
	Journal / Conference	Period
Nelson Tang	Pathology	Dec 2018
Nelson Tang	The 49 th Union World Conference on Lung Health	Feb 2018 – Oct 2018
Nelson Tang	Infection, Genetics and Evolution	Oct 2018
Nelson Tang	Frontiers in Genetics	Jan, Feb and Oct 2018
Nelson Tang	BMC Medical Genetics	Jan, Apr, Jun and Sep 2018
Nelson Tang	Scientific Reports	Apr 2018
Nelson Tang	European Journal of Medical Genetics	Apr 2018

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Nelson Tang	Expression and Functional Characterization of LBX1 in Adolescent Idiopathic Scoliosis	NSFC/RGC Joint Research Scheme	01/01/2017	31/12/2020	100,000
Nelson Tang	CUHK Jockey Club Institute of Ageing – Research Initiatives	CUHK Vice-Chancellor's One-off Discretionary Fund	01/01/2016	31/12/2019	12,000,000
Nelson Tang	Molecular Mechanism of Autophagy in Alzheimer's Disease	Chinese Academy of Sciences – International Partnership Program	01/01/2018	31/12/2019	1,000,000
Nelson Tang	Mitochondrial Heteroplasmy and Cognitive Decline	CUHK Research Committee – Direct Grant	29/06/2017	28/04/2019	69,650
Nelson Tang	An Integrated Trans-omics Approach to Diabetic Cardio-renal Complications: From Novel Discoveries to Personalized Medicine (Project Coordinator: Professor Ronald Ma)	Research Grants Council – Theme-based Research Scheme	01/01/2014	31/12/2018	47,000,000



A novel method to analysis gene-gene interaction in disease predisposition was proposed and applied to real patient datasets. In this figure, part (a) shows the bio-molecule interaction mechanism behind a 2nd order SNP-SNP interaction where SNP1 and SNP2 are both having genotype (major, minor). Meanwhile, part (b) shows the eight biologically plausible 2nd order genotype interaction patterns and their corresponding disease-associated complexes. Major alleles are represented by upper-case letters (i.e. A, B) and minor alleles are represented by lower-case letters (i.e. a, b).

Source: Lee KY, Leung KS, Tang NLS, Wong MH. Discovering Genetic Factors for psoriasis through exhaustively searching for significant second order SNP-SNP interactions. *Scientific Report* 2018;8(1):15186. doi:10.1038/s41598-018-33493-w.

■ Publications

A. Journal Papers

1. Xiao FH, Chen XQ, Yu Q, Ye Y, Liu YW, Yan D, Yang LQ, Chen G, Lin R, Yang L, Liao X, Zhang W, Zhang W, Tang NLS, Wang XF, Zhou J, Cai WW, He YH, Kong QP. Transcriptome evidence reveals enhanced autophagy-lysosomal function in centenarians. *Genome Research* 2018;28(11):1601-1610. doi:10.1101/gr.220780.117.
2. Xu L, Sheng F, Xia C, Qin X, Tang NLS, Qiu Y, Cheng JCY, Zhu Z. Genetic variant of PAX1 gene is functionally associated with adolescent idiopathic scoliosis in the Chinese population. *Spine (Phila Pa 1976)*. 2018;43(7):492-496. doi:10.1097/BRS.0000000000002475.

02 MOLECULAR DIAGNOSTICS

Plasma Nucleic Acids Research



Principal Investigator
Professor Allen Chan



Team

Jacky Wai Kei Lam | Irene Oi Lin Tse | Maggie Zi Jun Li |
Amy Fung Chu Tsang | Vivien Shen Lin | Patrick Pak Hang Lee



■ Research Progress Summary

Professor Allen Chan and his team completed a prospective clinical trial on using plasma Epstein-Barr virus (EBV) DNA for the screening of early asymptomatic nasopharyngeal carcinoma (NPC). They demonstrated that NPC screening can significantly detect cancer patients at earlier stages and improve their treatment outcomes. Professor Chan and his team is proceeding with the second phase of the study and are screening

all enrolled subjects at 4 years after the initial screening. This follow-ups study can address the optimal interval for NPC screening and if those non-cancer individuals with detectable plasma EBV DNA would have increased risk of developing NPC in the future. Professor Chan and Professor Dennis Lo have been bestowed with the Annual Achievement Award from the Chinese Society of Clinical Oncology (CSCO) in 2018.



■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Allen Chan	Annual Achievement Award from The Chinese Society of Clinical Oncology

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Allen Chan	Prospective 20,000-Person Nasopharyngeal Carcinoma (NPC) Screening Programme using Plasma Epstein-Barr Virus (EBV) DNA Analysis	Kadoorie Charitable Foundation	01/04/2013	31/03/2023	9,400,000



Receiving the Annual Achievement Award at the Annual Meeting of the Chinese Society of Clinical Oncology (CSCO)
Source: Professor Allen Chan

■ Publications

A. Journal Papers

1. Jiang P, Sun K, Tong YK, Cheng SH, Cheng THT, Heung MMS, Wong J, Wong VWS, Chan HLY, Chan KCA, Lo YMD, Chiu RWK. Preferred end coordinates and somatic variants as signatures of circulating tumor DNA associated with hepatocellular carcinoma. *Proceedings of the National Academy of Sciences*. 2018;115(46):E10925-E10933. doi:10.1073/pnas.1814616115.
2. Gai W, Ji L, Lam WKJ, Sun K, Jiang P, Chan AWH, Wong J, Lai PBS, Ng SSM, Ma BBY, Wong GLH, Wong VWS, Chan HLY, Chiu RWK, Lo YMD, Chan KCA. Liver- and Colon-Specific DNA Methylation Markers in Plasma for Investigation of Colorectal Cancers with or without Liver Metastases. *Clinical Chemistry*. 2018;64(8):1239-49. doi:10.1373/clinchem.2018.290304.
3. Lam WKJ, Jiang P, Chan KCA, Cheng SH, Zhang H, Peng W, Tse OYO, Tong YK, Gai W, Zee BCY, Ma BBY, Hui EP, Chan ATC, Woo JKS, Chiu RWK, Lo YMD. Sequencing-based counting and size profiling of plasma Epstein-Barr virus DNA enhance population screening of nasopharyngeal carcinoma. *Proceedings of the National Academy of Sciences*. 2018;115(22):E5115-E5124. doi:10.1073/pnas.1804184115.
4. Chan KCA, Chu SWI, Lo YMD. Ambient Temperature and Screening for Nasopharyngeal Cancer. *New England Journal of Medicine*. 2018;378(10):962-3. doi:10.1056/nejmc1800433. (Correspondence)
5. Cheng THT, Lui KO, Peng XL, Cheng SH, Jiang P, Chan KCA, Chiu RWK, Lo YMD. DNase1 Does Not Appear to Play a Major Role in the Fragmentation of Plasma DNA in a Knockout Mouse Model. *Clinical Chemistry*. 2017;64(2):406-8. doi:10.1373/clinchem.2017.280446. (Letters to Editor)

03 FECAL MICROBIOTA TRANSPLANTATION



Principal Investigator
Professor Siew Ng



Team

Laboratory of Fecal Microbiota Transplantation (FMT)



■ Research Progress Summary

In this reporting year, Professor Siew Ng's team has two major discoveries. The team identified that low abundance of fungi especially *Candida albicans* in stool of donor or recipient are associated with favourable fecal microbiota transplantation (FMT) outcomes. These novel findings highlight the importance of optimal and targeted donor selection, recipient stratification and donor-recipient matching in FMT practice. Secondly, they reported for the first-time alteration in the mucosa virobiota with functional distortion in patients with ulcerative colitis (UC). These findings highlight the importance of mucosal virobiota in UC pathogenesis and reconstituting gut virome homeostasis could be a potential treatment for UC. These works have been published in high impact journals including *Gut* and *Nature Communication* and won several awards in International conference. The team has filed 3 patents related to FMT.

The team has developed the first and most comprehensive longitudinal FMT registry in Asia—the *Asia-Pacific FMT registry*. The elucidation of the role of gut microbiome, including bacteriome, virome and fungome in health and disease as well as in FMT therapy will substantially aid the development of personalised gut microbiota-based therapy and enhanced efficacy of FMT. Currently, the team is working with the Hospital Authority in Hong Kong to provide FMT as a service to subjects with recurrent *Clostridium difficile* infections. This is cost effective and will benefit the patients and society.

Professor Siew Ng's team has also led the “*Frontiers in Fecal Microbiota Transplant*” meeting. With the endorsement of Asia-Pacific Association of Gastroenterology (APAGE) and Asia-Pacific Society for Digestive Endoscopy (APSDE), 14 experts from 7 countries in Asia Pacific met to discuss future directions and frontiers in FMT in Hong Kong. The goal was to identify key elements to shape forthcoming FMT research and practice for clinicians and scientists. A joint APAGE-APSDE official statement based on review of the literature and critical appraisal of current evidence focusing on donor and recipient factors to optimise FMT and mechanisms of FMT is currently being prepared.

The team has also established Asia's First Microbiota Transplantation & Research Centre New Strategies in Disease Prevention and Cure. The team is working on a pilot study to investigate the use of FMT to treat obese patients with type II diabetes mellitus. Preliminary results of this study were announced in a press conference held on 9 August 2018.

■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Siew Ng	Joanna and David B. Sachar M.D. International Award and Visiting Professorship in Inflammatory Bowel Disease, The Icahn School of Medicine, Mount Sinai, New York, USA
Siew Ng	Exemplary Teacher Award (Junior Medical Clerkship), The Chinese University of Hong Kong
Siew Ng	Teaching Grant Award to develop Electronic Learning Platform Development of Innovative Pedagogy in Undergraduate and Postgraduate Medical Education, The Chinese University of Hong Kong
Tao Zuo	Early Career Investigator (Certificate of Recognition), Digestive Disease Week. Washington, United States.

Fellowships

Member's Full Name	Details
Jingwen Zhang	Faculty Postdoctoral Fellowship Scheme, CUHK

Academic Editorship and Reviews

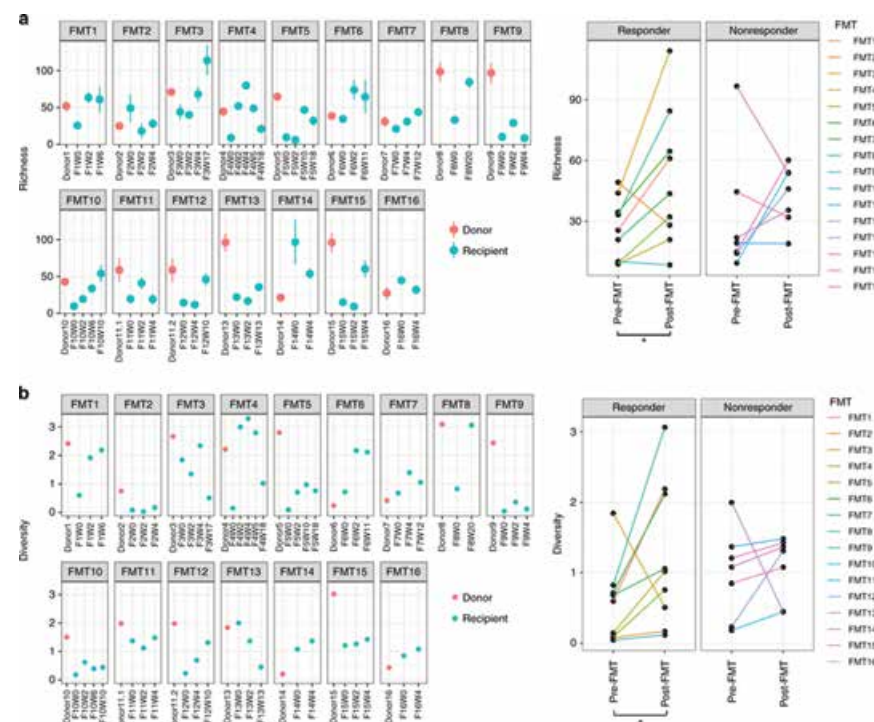
Member's Full Name	Details
Siew Ng	Associate Editor, Gut
Siew Ng	Editorial board member, Journal of Gastroenterology and Hepatology
Siew Ng	Editorial board member, Gastroenterology
Siew Ng	Editorial Board Member, World Journal of Gastroenterology
Siew Ng	Review Editor, Frontiers in Gastroenterology
Siew Ng	Editorial Board member, Inflammatory Intestinal Disease
Siew Ng	International Editorial Board Member, Indonesian Journal of Gastroenterology
Siew Ng	Editorial Board Member, Journal of Crohn's and Colitis
Siew Ng	Associate Editor, BMC Gastroenterology
Siew Ng	Editorial Board Member, Alimentary Pharmacology & Therapeutics

Journal / Conference Reviews

Member's Full Name	Details
Siew Ng	Abstract Reviewer for Digestive Disease Week, 2018, Washington, United States
Siew Ng	Invited Reviewer for Gastroenterology
Siew Ng	Invited Reviewer for Gut
Siew Ng	Invited Reviewer for Nature Review Gastroenterology & Hepatology
Siew Ng	Invited Reviewer for American Journal of Gastroenterology
Siew Ng	Invited Reviewer for Clinical Gastroenterology and Hepatology
Siew Ng	Invited Reviewer for Alimentary Pharmacology and Therapeutics
Siew Ng	Invited Reviewer for Gastrointestinal Endoscopy
Siew Ng	Invited Reviewer for Journal of Crohn's and Colitis
Siew Ng	Invited Reviewer for Inflammatory Bowel Disease
Siew Ng	Invited Reviewer for Journal of Gastroenterology and Hepatology
Siew Ng	Invited Reviewer for World Journal of Gastroenterology
Siew Ng	Invited Reviewer for Digestive Diseases and Sciences
Siew Ng	Invited Reviewer for BMC Gastroenterology
Siew Ng	Invited Reviewer for European Journal of Gastroenterol and Hepatol
Siew Ng	Invited Reviewer for Journal of Gastroenterology

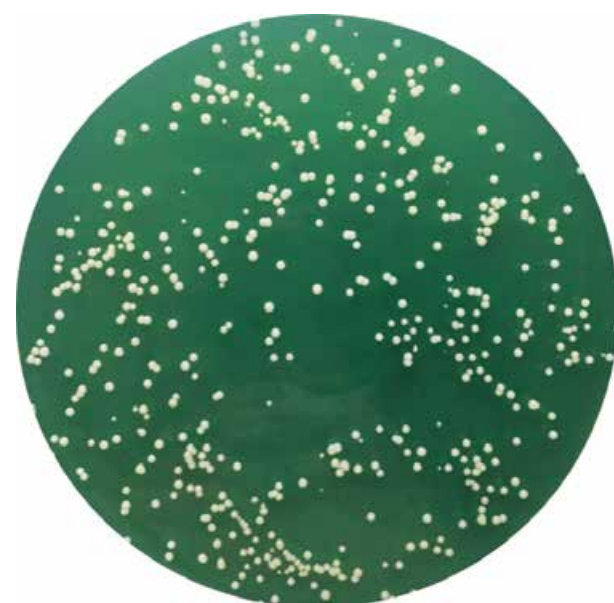
Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Siew Ng	When should low-dose aspirin be resumed after peptic ulcer bleeding? A double-blind, randomized controlled trial	Research Grants Council – General Research Fund	Jan 2018	Dec 2020	972,000
Siew Ng	PACIfIC: Prevalence, characteristics and genetics of adherent-invasive <i>Escherichia coli</i> in Crohn's disease patients: comparative study between France and Hong-Kong	ANR/RGC Joint Research Scheme	Feb 2018	Jan 2022	2,611,942
Siew Ng	A Prospective Study of Pregnant Women with and without IBD in order to better understand the patterns of bacterial transmission from the mother to the baby	Direct Grant for Research 2017/18, CUHK	Jun 2018	Jun 2019	71,000
Siew Ng	Microbiome and Inflammatory Bowel Disease	Vice-Chancellor Discretionary Fund (3 rd Round), CUHK	01/01/2018	01/12/2022	500,000



Source: Zuo T, Wong SH, Cheung CP, Lam K, Lui R, Cheung K, Zhang F, Tang W, Ching JYL, Wu JCY, Chan PKS, Sung JJY, Yu J, Chan FKL, Ng SC. Gut fungal dysbiosis correlates with reduced efficacy of fecal microbiota transplantation in *Clostridium difficile* infection. *Nature Communications*. 2018;9(1):3663.

Post-FMT alterations in the enteric mycobiota richness and diversity of CDI recipients in association with FMT response. Fecal fungal richness (a) and diversity (b) alterations in FMT recipients over the course of longitudinal follow-up and in their corresponding donors at baseline. Comparison of the fungal richness and diversity of pre-FMT samples and post-FMT samples collected at the last follow-up are shown in FMT responders and FMT nonresponders, respectively. Statistical significance was determined by paired Wilcoxon signed rank test, * $p < 0.05$. "F" indicates FMT-treated subject. "W" indicates weeks post-treatment.



Candida albicans colonies

Source: Professor Siew Ng



The team established Asia's First Microbiota Transplantation & Research Centre New Strategies in Disease Prevention and Cure.

Source: Press conference held by the Faculty of Medicine, The Chinese University of Hong Kong on 9 August 2018.

■ Publications

A. Journal Papers

- Hirai HW, Ching JYL, Wu JCY, Sung JJY, Chan FKL, Ng SC. Risk factors for advanced colorectal neoplasms in the proximal colon in 6218 subjects undergoing complete colonoscopy. *Journal of Gastroenterology and Hepatology*. 2019;34(1):113-119. [Epub ahead of Print]
- Park D, Hisamatsu T, Chen M, Ng S, Ooi C, Wei S, Banerjee R, Hilmi I, Jeon Y, Han D, Kim H, Ran Z, Wu K, Qian J, Hu P, Matsuoka K, Andoh A, Suzuki Y, Sugano K, Watanabe M, Hibi T, Puri A, Yang S. Asian Organization for Crohn's and Colitis and Asia Pacific Association of Gastroenterology consensus on tuberculosis infection in patients with inflammatory bowel disease receiving anti-tumor necrosis factor treatment. Part 2: Management. *Journal of Gastroenterology and Hepatology*. 2018;33(1):30-36. [Review]
- Kwong TNY, Wang X, Nakatsu G, Chow TC, Tipoe T, Dai RZW, Tsoi KKK, Wong MCS, Tse G, Chan MTV, Chan FKL, Ng SC, Wu JCY, Wu WKK, Yu J, Sung JJY, Wong SH. Association Between Bacteremia From Specific Microbes and Subsequent Diagnosis of Colorectal Cancer. *Gastroenterology*. 2018;155(2):383-390.e8.
- Mak WY, Mak OS, Lee CK, Tang W, Leung WK, Wong MTL, Sze ASF, Li M, Leung CM, Lo FH, Lam BCY, Chan KH, Shan EHS, Tsang SWC, Hui AJ, Chow WH, Chan FKL, Sung JJY, Ng SC. Significant Medical and Surgical Morbidity in Perianal Crohn's Disease: Results from a Territory-Wide Study. *Journal of Crohn's and Colitis*. 2018;12(12):1392-1398.
- Ng SC, Kaplan GG, Tang W, Banerjee R, Adigopula B, Underwood FE, Tanyingoh D, Wei SC, Lin WC, Lin HH, Li J, Bell S, Niewiadomski O, Kamm MA, Zeng Z, Chen M, Hu P, Ong D, Ooi CJ, Ling KL, Miao Y, Miao J, de Silva HJ, Niriella M, Aniwani S, Limsrivilai J, Pispongso P, Wu K, Yang H, Ng KK, Yu HH, Wang Y, Ouyang Q, Abdullah M, Simadibrata M, Gunawan J, Hilmi I, Goh KL, Cao Q, Sheng H, Ong-Go A, Chong VH, Ching JYL, Wu JCY, Chan FKL, Sung JJY. Population Density and Risk of Inflammatory Bowel Disease: A Prospective Population-Based Study in 13 Countries or Regions in Asia-Pacific. *American Journal of Gastroenterology*. 2018:107-115.
- Palmela C, Chevarin C, Xu Z, Torres J, Sevrin G, Hirten R, Barnich N, Ng SC, Colombel JF. Adherent-invasive *Escherichia coli* in inflammatory bowel disease. *Gut*. 2018;67(3):574-587.
- Wu WKK, Sun R, Zuo T, Tian Y, Zeng Z, Ho J, Wu JCY, Chan FKL, Chan MTV, Yu J, Sung JJY, Wong SH, Wang MH, Ng SC. A novel susceptibility locus in MST1 and gene-gene interaction network for Crohn's disease in the Chinese population. *Journal of Cellular and Molecular Medicine*. 2018;22(4):2368-2377.
- Park D, Hisamatsu T, Chen M, Ng S, Ooi C, Wei S, Banerjee R, Hilmi I, Jeon Y, Han D, Kim H, Ran Z, Wu K, Qian J, Hu P, Matsuoka K, Andoh A, Suzuki Y, Sugano K, Watanabe M, Hibi T, Puri A, Yang S. Asian Organization for Crohn's and Colitis and Asia Pacific Association of Gastroenterology consensus on tuberculosis infection in patients with inflammatory bowel disease receiving anti-tumor necrosis factor treatment. Part 2: management. *Intestinal Research*. 2018;16(1):17. [Review]
- Park D, Hisamatsu T, Chen M, Ng S, Ooi C, Wei S, Banerjee R, Hilmi I, Jeon Y, Han D, Kim H, Ran Z, Wu K, Qian J, Hu P, Matsuoka K, Andoh A, Suzuki Y, Sugano K, Watanabe M, Hibi T, Puri A, Yang S. Asian Organization for Crohn's and Colitis and Asia Pacific Association of Gastroenterology consensus on tuberculosis infection in patients with inflammatory bowel disease receiving anti-tumor necrosis factor treatment. Part 1: risk assessment. *Intestinal Research*. 2018;16(1):4. [Review]
- Zuo T, Kamm MA, Colombel JF, Ng SC. Urbanization and the gut microbiota in health and inflammatory bowel disease. *Nature Reviews Gastroenterology & Hepatology*. 2018;15(7):440-452. [Perspective]
- Zuo T, Wong SH, Cheung CP, Lam K, Lui R, Cheung K, Zhang F, Tang W, Ching JYL, Wu JCY, Chan PKS, Sung JJY, Yu J, Chan FKL, Ng SC. Gut fungal dysbiosis correlates with reduced efficacy of fecal microbiota transplantation in *Clostridium difficile* infection. *Nature Communications*. 2018;9(1):3663.

04

ASIAN CANCERS

Integrated Genome Research



Principal Investigators

Professor Ka-fai To
Professor Kwok-wai Lo
Professor Nathalie Wong



Team

Joanna Tong | Raymond Lung | Feng Wu | Walter Yeung | Ling Chow |
Shela Wong | Edith Tin | Kinki Chung | Sheree Lam



■ Research Progress Summary

Gastric Cancer

Gastric cancer also belongs one of research area. This year, the research team led by Professor Ka Fai To, Professor Kwok Wai Lo and Professor Nathalie Wong has published three original articles and three reviews on prestigious journals such as *Oncogene*, *Cancer Letters*, and *Cell Death & Disease*. They identified multiple driver oncogenes or signalling pathways, such as SRGAP1 (Slit-Robo GTPase-activating protein 1), PIEZO1, YAP1-TEAD4-CTGF axis in gastric carcinogenesis. The upregulated expression of these oncogenes was associated with poor disease-specific survival in gastric cancer. The team also confirmed the activation of potential oncogenes is partly due to the silence of several well-known tumour suppressive microRNAs, such as miR-124, miR-340, and miR-375. Their studies not only provided basic molecular mechanisms of gastric tumourigenesis, but also identified therapeutic targets for precision intervention. Apart from the research work, they actively summarised the research progress closely related with their research and reported them in Review articles, such as Amot family in driving tumourigenesis, Hippo pathway in immune escape, EBV-encoded miRNA in EBV associated gastric cancer. They hope their summary can help the researchers to understand the frontiers in cancer research and perform related research work from a novel angle.

Liver Cancer

Alternative splicing allows generation of cell-type specific mRNA transcripts and contributes to hallmarks of cancer. The research team led by Professor Nathalie Wong undertook long-reads sequencing analysis for alternative splicing in human hepatocellular carcinoma (HCC). A comprehensive alternative splicing landscape in HCC was defined with tumour-associated variants identified. Using the combined Sanger sequencing and TaqMan junction assays, unique and common expressions of spliced variants include enzyme regulators (ARHGEF2, SERPINH1), chromatin modifiers (DEK, CDK9, RBBP7), RNA-binding proteins (SRSF3, RBM27, MATR3, YBX1) and receptors (ADRM1, CD44v8-10, VDR, ROR1) were determined in HCC tumours. They further focused on functional investigations of ARHGEF2 variants (v1 and v3) that arise from the common amplified site chr.1q22 of HCC. The biological significance underscores two major cancer hallmarks, namely cancer stemness and EMT-mediated cell invasion and migration, although v3 is consistently more potent than v1. In sum, Professor Wong's team found novel isoforms and tumour-specific isoforms that arise from aberrant splicing, which can be common during liver tumourigenesis.



Nasopharyngeal Carcinoma (NPC)

By whole-genome sequencing, the team has built up comprehensive genomic landscapes of ~80 NPCs including established cell lines, xenografts and microdissected clinical specimens. With the transcriptome data, integrative informatics analysis was conducted to discover somatic alterations in both coding and noncoding regions (e.g. promoters, enhancers). In addition to the frequent mutated NF-B regulators reported in their recent whole-exome sequencing study, they have uncovered multiple novel somatic changes TGF-SMADs, ROBO-SLIT and NOTCH pathways that play roles in the tumourigenesis of EBV-associated NPC. The EBV transcriptome study has also demonstrated distinct transcription patterns of EBV-encoded microRNAs, (miR-BARTs), lytic genes and unique transcripts in NPC xenografts and clinical specimens. Functional study further revealed that multiple miR-BARTs negatively regulate the expression of a key DNA double-strand breaks (DSBs) repair gene, ATM, thereby controlling DNA damage repairs and inhibiting Zta-induced lytic reactivation. As an EBV-encoded oncoprotein, LMP1 plays a significant role in the development of NPC by virtue of its ability to engage multiple signalling pathways and cellular targets. In their recent study, they have uncovered a novel function of LMP1 in activation of SREBP1

activity and enhancement of FASN expression, thereby promoting *de novo* lipogenesis. The LMP1-mediated lipogenesis promotes tumour cell growth and contribute to the EBV-driven NPC pathogenesis. The therapeutic potential of utilising lipogenesis inhibitors in the treatment of locally advanced or metastatic tumours was proven in both *in vitro* and *in vivo* NPC models.

In their previous whole-transcriptome sequencing analysis, downregulation of a long non-coding RNA, maternally expressed gene 3 (MEG3), was identified in NPC samples. This finding suggests the possible role of MEG3 as a tumour suppressor in this distinctive disease. They confirmed the downregulation of MEG3 in NPC xenografts and biopsies. MEG3 is an imprinted gene located within chromosome 14q32, a common deleted region in NPC. Both DNA copy number loss and aberrant promoter methylation contributed to MEG3 inactivation. Treatment of demethylation agents successfully restored MEG3 expression. Ectopic expression of MEG3 in NPC cells inhibited *in vitro* and *in vivo* tumourigenicity. They further revealed the association between MEG3 activity and the p53 signaling cascade. Their findings support the role of MEG3 as a tumour suppressive long non-coding RNA in NPC and encourage the development of precise long non-coding RNA-targeted epigenetic therapy against this malignancy.



Research and Scholarship

Academic Editorship and Reviews

Member's Full Name	Details
Nathalie Wong	Associate Editor, Journal of Pathology
Nathalie Wong	Editorial Board Member, The Open Gastroenterology Journal
Nathalie Wong	Editorial Board Member, Liver Cancer Review Letters
Kwok-wai Lo	Member of Editorial Board, PLoS ONE

Academic Editorship and Reviews

Member's Full Name	Details
Kwok-wai Lo	Reviewer, Nature Communications
Kwok-wai Lo	Reviewer, Oncogene
Kwok-wai Lo	Reviewer, Journal of Pathology
Kwok-wai Lo	Reviewer, International Journal of Cancer

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Ka-fai To	Study on the role of Esptein-Barr Virus (EBV)-encoded microRNAs in controlling DNA damage repairs in EBV-associated nasopharyngeal carcinoma	Research Grants Council - General Research Fund	01/01/2016	31/12/2018	1,187,649
Ka-fai To	Target inhibition of ATM-mediated homologous recombination repair by Epstein-Barr virus miR-BARTs in nasopharyngeal carcinoma: molecular mechanisms and clinical implications	Research Grants Council – General Research Fund	01/01/2017	31/12/2018	811,383
Kwok-wai Lo	Systematic Development of Molecular Targets for Nasopharyngeal Carcinoma	Research Grants Council – Theme-based Research Scheme	01/01/2014	31/12/2018	55,610,000
Kwok-wai Lo	Studies on the role of SREBP1 in EBV-induced metabolic reprogramming in NPC	Research Grants Council – General Research Fund	01/01/2017	30/12/2019	1,088,950
Nathalie Wong	Regulation and Mechanism of Tumor-intrinsic Oncogene Pathways in Mediating an Immune Suppressed Microenvironment in Hepatocellular Carcinoma	Research Grants Council – Collaborative Research Fund	30/06/2018	29/06/2021	7,544,147

■ Publications

A. Journal Papers

1. Huang T, Zhou Y, Zhang J, Wong CC, Li W, Kwan JSH, Yang R, Chan AKY, Dong Y, Wu F, Zhang B, Cheung AHK, Wu WKK, Cheng ASL, Yu J, Wong N, Kang W, To KF. SRGAP1, a crucial target of miR-340 and miR-124, functions as a potential oncogene in gastric tumorigenesis. *Oncogene*. 2018. doi:10.1038/s41388-017-0029-7.
2. Cheung AHK, Chow C, Zhang J, Zhou Y, Huang T, Ng KCK, Or TCT, Yao YY, Dong Y, Fung JMW, Xiong L, Chan AKY, Lung WMR, Kang W, To KF. Specific targeting of point mutations in EGFR L858R-positive lung cancer by CRISPR/Cas9. *Laboratory Investigation*. 2018;98(7):968-976. doi:10.1038/s41374-018-0056-1.
3. Chong CCN, Chan AWH, Wong J, Chu CM, Chan SL, Lee KF, Yu SCH, To KF, Johnson P, Lai PBS. Albumin-bilirubin grade predicts the outcomes of liver resection versus radiofrequency ablation for very early/early stage of hepatocellular carcinoma. *Surgeon*. 2018;16(3):163-170. doi:10.1016/j.surge.2017.07.003.
4. Pan Y, Cheung ST, Tong JHM, Tin KY, Kang W, Lung RWM, Wu F, Li H, Ng SSM, Mak TWC, To KF, Chan AWH. Granulin epithelin precursor promotes colorectal carcinogenesis by activating MARK/ERK pathway. *Journal of Translational Medicine*. 2018;16(1):150. doi:10.1186/s12967-018-1530-7.
5. Lung RWM, Hau PM, Yu KHO, Yip KY, Tong JHM, Chak WP, Chan AWH, Lam KH, Lo AKF, Tin EKY, Chau SL, Pang JCS, Kwan JSH, Busson P, Young LS, Yap LF, Tsao SW, To KF, Lo KW. EBV-encoded miRNAs target ATM-mediated response in nasopharyngeal carcinoma. *Journal of Pathology*. 2018;244(4):394-407. doi:10.1002/path.5018.
6. Kang W, Huang T, Zhou Y, Zhang J, Lung RWM, Tong JHM, Chan AWH, Zhang B, Wong CC, Wu F, Dong Y, Wang S, Yang W, Pan Y, Chak WP, Cheung AHK, Pang JCS, Yu J, Cheng ASL, To KF. miR-375 is involved in Hippo pathway by targeting YAP1/TEAD4-CTGF axis in gastric carcinogenesis. *Cell Death & Disease*. 2018;9(2):92. doi:10.1038/s41419-017-0134-0.
7. Zhang J, Huang T, Zhou Y, Cheng ASL, Yu J, To KF, Kang W. The oncogenic role of Epstein-Barr virus-encoded microRNAs in Epstein-Barr virus-associated gastric carcinoma. *Journal of Cellular and Molecular Medicine*. 2018;22(1):38-45. doi:10.1111/jcmm.13354. [Editorial]
8. Huang T, Zhou Y, Zhang J, Cheng ASL, Yu J, To KF, Kang W. The physiological role of Motin family and its dysregulation in tumorigenesis. *Journal of Translational Medicine*. 2018;16(1):98. doi:10.1186/s12967-018-1466-y. (Review)
9. Zhang J, Zhou Y, Huang T, Wu F, Liu L, Kwan JSH, Cheng ASL, Yu J, To KF, Kang W. PIEZO1 functions as a potential oncogene by promoting cell proliferation and migration in gastric carcinogenesis. *Molecular Carcinogenesis*. 2018;57(9):1144-1155. doi:10.1002/mc.22831.
10. Ahmad M, Suhaimi SN, Chu TL, Abdul Aziz N, Mohd Kornain NK, Samiulla DS, Lo KW, Ng CH, Khoo ASB. Ternary copper(II) complex: NCI60 screening, toxicity studies, and evaluation of efficacy in xenograft models of nasopharyngeal carcinoma. PizzoSV., ed. *PLoS One*. 2018;13(1):e0191295. doi:10.1371/journal.pone.0191295.
11. Zhou Y, Huang T, Zhang J, Cheng ASL, Yu J, Kang W, To KF. Emerging roles of Hippo signaling in inflammation and YAP-driven tumor immunity. *Cancer Letter*. 2018;426:73-79. doi:10.1016/j.canlet.2018.04.004. (Review)
12. Lo AKF, Lung RWM, Dawson CW, Young LS, Ko CW, Yeung WW, Kang W, To KF, Lo KW. Activation of sterol regulatory element-binding protein 1 (SREBP1)-mediated lipogenesis by the Epstein-Barr virus-encoded latent membrane protein 1 (LMP1) promotes cell proliferation and progression of nasopharyngeal carcinoma. *Journal of Pathology*. 2018;246(2):180-190. doi:10.1002/path.5130.
13. Lee YY, Mok MT, Kang W, Yang W, Tang W, Wu F, Xu L, Yan M, Yu Z, Lee SD, Tong JHM, Cheung YS, Lai PBS, Yu DY, Wang Q, Wong GLH, Chan AM, Yip KY, To KF, Cheng ASL. Loss of tumor suppressor IGFBP4 drives epigenetic reprogramming in hepatic carcinogenesis. *Nucleic Acids Research*. 2018;46(17):8832-8847. doi:10.1093/nar/gky589.
14. Pan Y, Tong JHM, Kang W, Lung RWM, Chak WP, Chung LY, Wu F, Li H, Yu J, Chan AWH, To KF. EXOSC4 functions as a potential oncogene in development and progression of colorectal cancer. *Molecular Carcinogenesis*. 2018;57(12):1780-1791. doi:10.1002/mc.22896.

04

ASIAN CANCERS

Cancer Epigenetics



Principal Investigator
Professor Qian Tao



Team

Lili Li | Jie Luo | Xiangyu Wang | Shuang Tong |
Lisha Xie | Junyu Zhu | Yingjun Zhang

■ Research Progress Summary

Professor Tao's team has characterised the CpG methylomes of multiple tumours including esophageal (ESCC), nasopharyngeal (NPC), liver (HCC) and lung cancers. The identification of genome-wide CpG methylation alterations of tumours delineates the mechanistic link of epigenetic etiology in multiple carcinogenesis, and also provides clues of novel candidate tumour suppressor genes (TSG) inactivated in cancers. For example, the team identified the epigenetic disruption of 3p22-21.3 TSGs contributing to oncogenic STAT3 signaling activation in human tumorigenesis. They identified *DLEC1*, as a methylated 3p22.2 target gene in multiple tumors including ESCC, NPC and lung cancer. Their further study demonstrated the first evidence of tumour-specific *DLEC1* methylation in ESCC, as the most frequently methylated 3p22.2



TSGs (*RASSF1A*, *PLCD1* and *ZMYND10/BLU*) in tumours, which could also serve as a valuable biomarker. As a critical TSG regulated by p53, *DLEC1* inhibits the growth and metastasis of carcinoma cells through binding to STAT3 and further inhibiting its phosphorylation and other oncogenic signalling pathways. The team also identified the epigenetic disruption of other TSGs by promoter CpG methylation, including *ZNF382*,

ADAMTS9, *DACT2*, *ZFP82*, *SOX7*, *OVOL2* and *PBRM1*, contributing to multiple tumorigenesis and also as potential epigenetic biomarkers. In summary, the epigenomic work elucidates the epigenetic contribution of tumour-specific promoter methylation of critical TSGs in multiple carcinogenesis and also the epigenetic mechanism disrupting cell signalling pathway in cancers.



■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Zhangting Wang	1 st prize for posters during the joint Research Retreat of the State Key Laboratory of Oncology in South China, May 2018
Lili Li	2 nd prize for posters during the joint Research Retreat of the State Key Laboratory of Oncology in South China, May 2018

Fellowships

Member's Full Name	Details
Zhenfang Du	2018 AACR-AstraZeneca Cancer Research Fellowship

Academic Editorship and Reviews

Member's Full Name	Details
Qian Tao	Vice-President, The Epigenetics Society (since 2008)
Qian Tao	Reviewer for China State Natural Science Award (Ministry of Science and Technology, China) (國家科技部/國家科技獎評審專家)
Qian Tao	Panel member and reviewer for National Natural Science Foundation of China (NSFC) (中國國家自然科學基金NSFC/醫學科學領域評審組專家)
Qian Tao	Advisor Committee for Basic Research in Shenzhen (深圳市基礎研究專家諮詢委員會)
Qian Tao	Science and Technology Advisor Committee for Shenzhen (深圳市科技專家委員會)
Qian Tao	Academic Advisor, State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Hospital, Guangdong, China
Qian Tao	Academic Advisor, Key Laboratory of MOE, Cancer Research Institute, Central South University, Hunan, China
Qian Tao	Editorial board member/Academic Editor: Epigenomes, Cancer Comms, J Clin Epigenetics, Epigenetic Diag & Therapy, PLoS One.

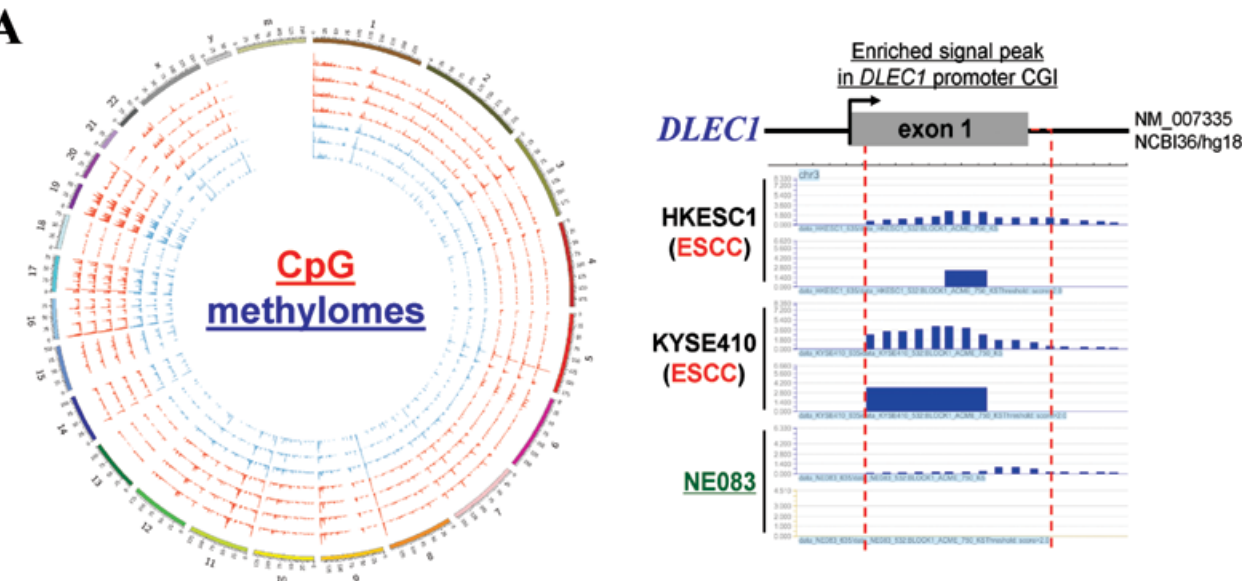
Journal / Conference Reviews

Member's Full Name	Details
Qian Tao	Reviewers for more than 50 Journals: Nature Communications, Blood, Cancer Research, Lancet, Cell Death and Differentiation, Epigenetics, Human Molecular Genetics, Journal of Pathology, Oncogenes, Lancet, Nucleic Acids Research, <i>et al.</i>
Qian Tao	Scientific Committee, September 14-16, 2018, Epigenetics section. The 2018 China Forum of Cancer Biomarkers, Zhengzhou, China
Qian Tao	Scientific Committee, October 27-28, 2018, 2 nd Clinical Molecular Diagnostics Forum, FuDan University, Shanghai, China
Qian Tao	Scientific Committee, November 10-11, 2018, "Immuno-Oncology", The 23 rd Annual Scientific Symposium of the Hong Kong Cancer Institute.
Qian Tao	Scientific Committee, December 21-22, 2018, The 2 nd meeting of NPC Biomarker committee, China anti-Cancer Association, Shenzhen, China
Qian Tao	Regular reviewer for 56 scientific journals/publishers, including Nature Communications, Blood, Cancer Research, Cell Death and Differentiation, Epigenetics, Human Molecular Genetics, Journal of Pathology, Lancet, Nucleic Acids Research, Oncogene.

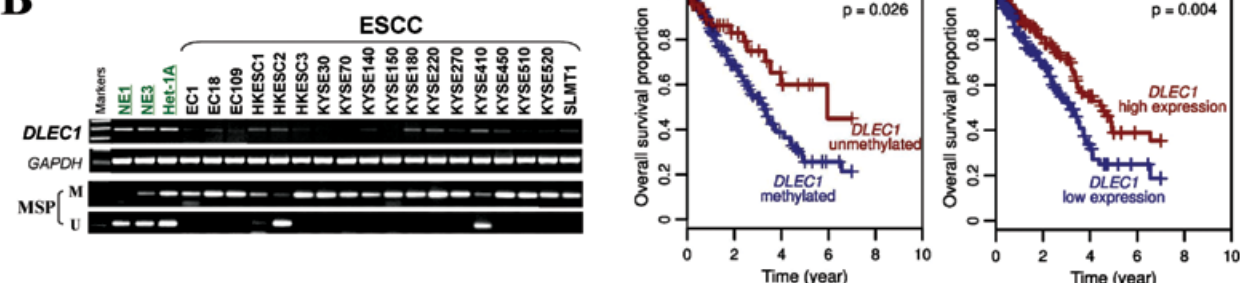
Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Qian Tao	Genome-wide Study of CpG Methylation of EB virus-associated Nasal Lymphoma Identifies Disrupted Transcription Program Derived from Silencing of Tumor Suppressor PAX5	Food and Health Bureau – Health and Medical Research Fund	01/09/2017	31/08/2019	1,015,032
Qian Tao	Mechanism Study of a New RhoA-signaling Antagonist in Esophageal Cancer Pathogenesis	The National Natural Science Foundation of China	1/2016	12/2019	RMB 570,000
Qian Tao	Systematic Development of Molecular Targets for Nasopharyngeal	Research Grants Council – Theme-based Research Scheme	1/2014	12/2018	55,610,000
Qian Tao	Innovation Platform of Oncology Pathogenesis and Targeted Therapy in Guangdong and Hong Kong	Guangdong- HK Joint Innovation Areas	6/2015	8/2018	RMB 2,000,000
Qian Tao	Epigenetic Disruption of Wnt/ β -catenin Signaling Pathway in the Development, Invasion and Metastasis of Breast Cancer	The National Natural Sciences Foundation of China – International Cooperation and Exchange	1/2015	12/2019	RMB 2,850,000

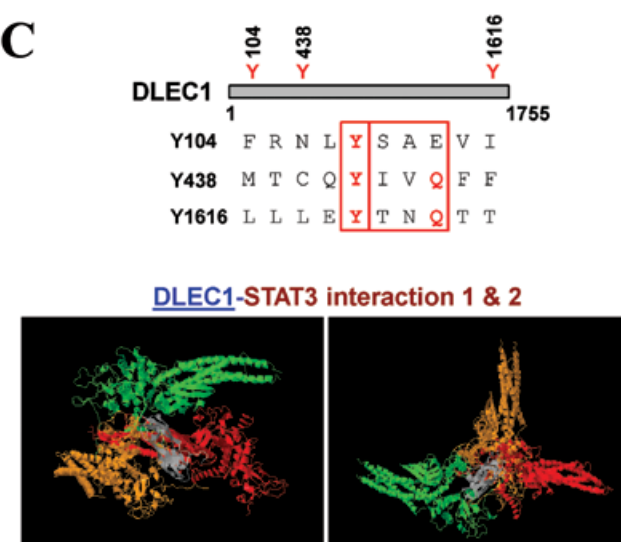
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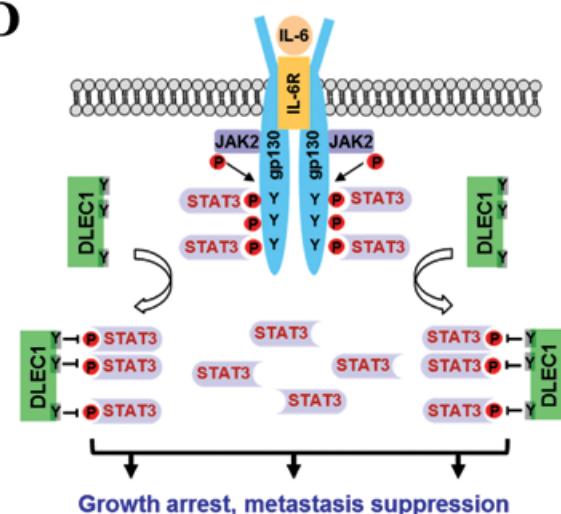
B



C



D



A novel mechanistic link between 3p22 alteration and oncogenic STAT3 signaling in human carcinogenesis. (A) CpG methylomes identify *DLEC1* methylation in multiple carcinomas. (B) *DLEC1* methylation is frequently detected in ESCC and correlated with poor survival. (C) Localization of the consensus STAT3-binding motifs (YXXQ) in the *DLEC1* protein (upper panel). Predicted models of *DLEC1*-

STAT3 protein docking (lower panel). (D) A schematic model showing the regulation of oncogenic STAT3 signaling activation by *DLEC1*. *DLEC1* suppresses STAT3 phosphorylation through binding to STAT3 via YXXQ motif and further interfering with JAK2-STAT3 interaction.

Source: Professor Qian Tao

Publications

A. Journal Papers

- Li L, Xu J, Qiu G, Ying J, Du Z, Xiang T, Wong KY, Srivastava G, Zhu XF, Mok TS, Chan AT, Chan FK, Ambinder RF, Tao Q. Epigenomic characterization of a p53-regulated 3p22.2 tumor suppressor that inhibits STAT3 phosphorylation via protein docking and is frequently methylated in esophageal and other carcinomas. *Theranostics*. 2018;8(1):61-77. doi:10.7150/thno.20893.
- Wen H, Ma H, Cai Q, Lin S, Lei X, He B, Wu S, Wang Z, Gao Y, Liu W, Liu W, Tao Q, Long Z, Yan M, Li D, Kelley KW, Yang Y, Huang H, Liu Q. Recurrent ECSIT mutation encoding V140A triggers hyperinflammation and promotes hemophagocytic syndrome in extranodal NK/T cell lymphoma. *Nature Medicine*. 2018;24(2):154-164. doi:10.1038/nm.4456.
- Zhang C, Xiang T, Li S, Ye L, Feng Y, Pei L, Li L, Wang X, Sun R, Ren G, Tao Q. The novel 19q13 KRAB zinc-finger tumour suppressor ZNF382 is frequently methylated in oesophageal squamous cell carcinoma and antagonises Wnt/ β -catenin signalling. *Cell Death & Disease*. 2018;9(5):573. doi:10.1038/s41419-018-0604-z.
- Shao B, Feng Y, Zhang H, Yu F, Li Q, Tan C, Xu H, Ying J, Li L, Yang D, Peng W, Tang J, Li S, Ren G, Tao Q, Xiang T. The 3p14.2 tumour suppressor ADAMTS9 is inactivated by promoter CpG methylation and inhibits tumour cell growth in breast cancer. *Journal of Cellular and Molecular Medicine*. November 2017. doi:10.1111/jcmm.13404.
- Zhang Y, Fan J, Fan Y, Li L, He X, Xiang Q, Mu J, Zhou D, Sun X, Yang Y, Ren G, Tao Q, Xiang T. The new 6q27 tumor suppressor DACT2, frequently silenced by CpG methylation, sensitizes nasopharyngeal cancer cells to paclitaxel and 5-FU toxicity via β -catenin/Cdc25c signaling and G2/M arrest. *Clinical Epigenetics*. 2018;10(1):26. doi:10.1186/s13148-018-0459-2.
- Qi XK, Han HQ, Zhang HJ, Xu M, Li L, Chen L, Xiang T, Feng QS, Kang T, Qian CN, Cai MY, Tao Q, Zeng YX, Feng L. OVOL2 links stemness and metastasis via fine-tuning epithelial-mesenchymal transition in nasopharyngeal carcinoma. *Theranostics*. 2018;8(8):2202-2216. doi:10.7150/thno.24003.
- Li L, Ma BBY, Chan ATC, Chan FKL, Murray P, Tao Q. Epstein-Barr Virus-Induced Epigenetic Pathogenesis of Viral-Associated Lymphoepithelioma-Like Carcinomas and Natural Killer/T-Cell Lymphomas. *Pathogens*. 2018;7(3):63. doi:10.3390/pathogens7030063. [Review]
- Ye L, Xiang T, Fan Y, Zhang D, Li L, Zhang C, He X, Xiang Q, Tao Q, Ren G. The 19q13 KRAB Zinc-finger protein ZFP82 suppresses the growth and invasion of esophageal carcinoma cells through inhibiting NF- κ B transcription and inducing apoptosis. *Epigenomics*. 2019;11(1):65-80. doi:10.2217/epi-2018-0092.
- Wang L, Fan Y, Zhang L, Li L, Kuang G, Luo C, Li C, Xiang T, Tao Q, Zhang Q, Ying J. Classic SRY-box protein SOX7 functions as a tumor suppressor regulating WNT signaling and is methylated in renal cell carcinoma. *FASEB J*. 2019;33(1):254-263. doi:10.1096/fj.201701453RR. [Epub in 2018]

04

ASIAN CANCERS

Biomarkers and Targeted Therapeutics



Principal Investigator
Professor Siu-tim Cheung



Team

Linda WC Ng | Katie SW Fung | Marcus HN Law | Elaine HL Siu |
Elaine YL Or | Carol Lee | Shin Yee Hui | Peter TC Li

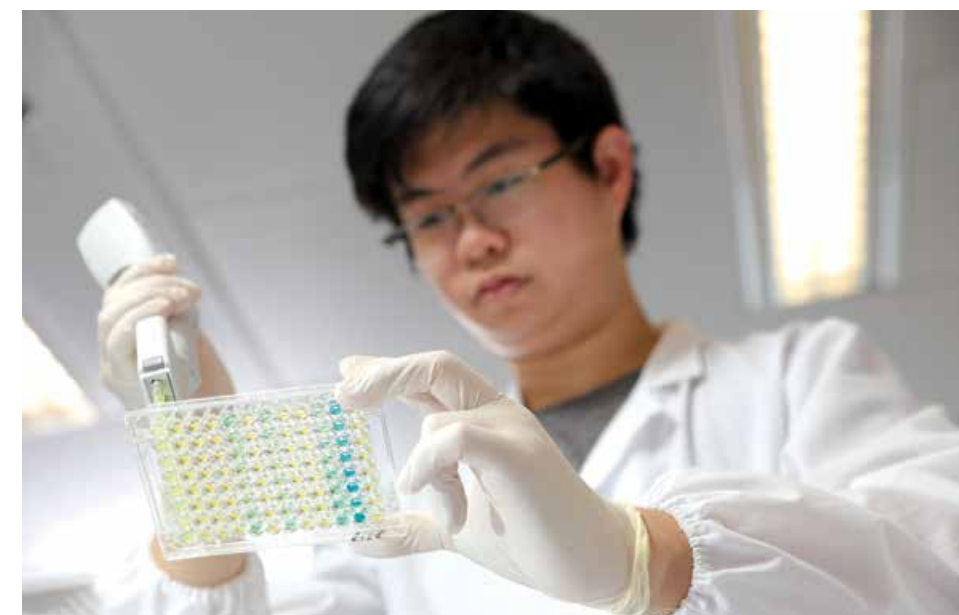


■ Research Progress Summary

Cancer Stemness Feature Control Drug Resistance and Recurrence

Transarterial chemoembolisation (TACE) is the most commonly used adjuvant therapy for liver cancer after surgery. Responses to TACE are variable due to tumour and patient heterogeneity. The team led by Professor Siu-tim Cheung had previously demonstrated that expression of Granulin-Epithelin Pre-cursor (GEP) and ATP-dependent binding cassette transporter ABCB5 in liver cancer stem cells was associated with chemoresistance and recurrence. The team further evaluates the association between GEP/ABCB5 expression and response to adjuvant TACE after curative resection for liver cancer. Patients were categorised into 3 risk groups according to their GEP/ABCB5 status for survival analysis: low risk (both low levels), intermediate risk (either one high level) and high risk (both high levels) groups. Early recurrence (recurrence within 2 years after resection) and disease-free survival were analysed. Patients with adjuvant TACE in the intermediate

risk group was associated with significantly better overall survival and 2-year disease-free survival than those who had surgery alone ($P = 0.036$ and $P = 0.011$, respectively). Adjuvant TACE did not offer any significant differences in the early recurrence rate, 2-year disease-free survival and overall survival for patients in low and high risk groups. This study further corroborate GEP/ABCB5 as liver cancer stemness markers, as TACE treatment cannot further decrease the low recurrence rate in the low risk group with both markers at low levels. Similarly, high risk group with both GEP/ABCB5 at high levels thus drug resistance even with TACE treatment. In summary, adjuvant TACE can provide survival benefits for liver cancer patients in the intermediate risk group. Clinical study is warranted to corroborate the use of cancer stemness biomarkers in patient selection for specific cancer treatment.



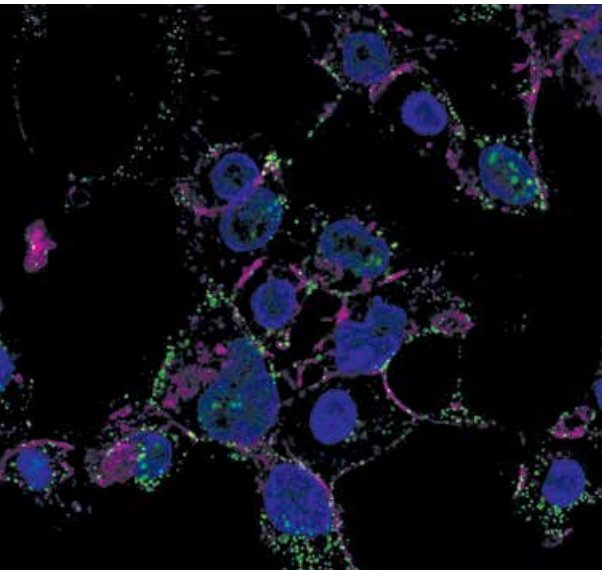
■ Research and Scholarship

Academic Editorship and Reviews

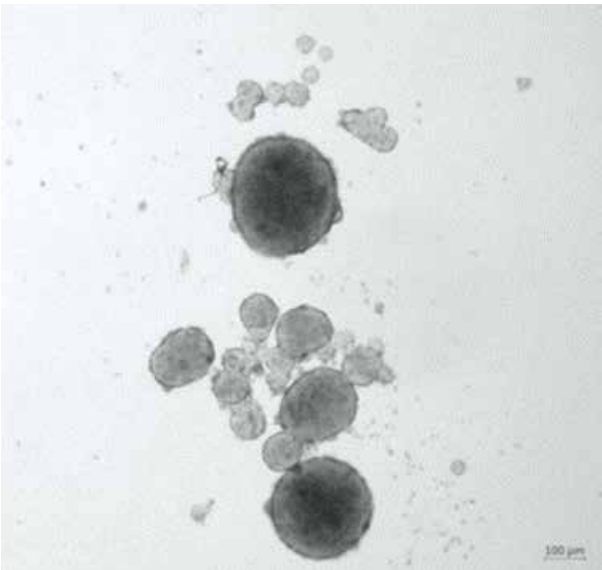
Member's Full Name	Details
Siu-tim Cheung	Academic Editor, PLOS ONE
Siu-tim Cheung	Reviewer, Hepatology
Siu-tim Cheung	Reviewer, Oncogene

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Siu-tim Cheung	Rational Combination of PD-L1/PD1 Targeting and Natural Killer Cells in Hepatocellular Carcinoma Treatment	Food and Health Bureau – Health and Medical Research Fund	01/04/2018	31/03/2020	981,720



Expression of specific drug transporter on the cancer cell surface indicating elevated drug resistance properties.
Source: Professor Siu-tim Cheung’s research: Cell image (unpublished)



Cancer cells grow as sphere (3-dimension) under targeted drug treatment indicating extraordinary drug resistance and cancer stemness features.
Source: Professor Siu-tim Cheung’s research: Cell image (unpublished)

■ Publications

A. Journal Papers

1. Siu EHL, Chan AWH, Chong CCN, Chan SL, Lo KW, Cheung ST. Treatment of advanced hepatocellular carcinoma: immunotherapy from checkpoint blockade to potential of cellular treatment. *Translational Gastroenterology and Hepatology*. 2018;3:89-89. doi:10.21037/tgh.2018.10.16 (Review)

2. Lin W, Yip YL, Jia L, Deng W, Zheng H, Dai W, Ko JMY, Lo KW, Chung GTY, Yip KY, Lee SD, Kwan JSH, Zhang J, Liu T, Chan JYW, Kwong DLW, Lee VHF, Nicholls JM, Busson P, Liu X, Chiang AKS, Hui KF, Kwok H, Cheung ST, Cheung YC, Chan CK, Li B, Cheung ALM, Hau PM, Zhou Y, Tsang CM, Middeldorp J, Chen H, Lung ML, Tsao SW. Establishment and characterization of new tumor xenografts and cancer cell lines from EBV-positive nasopharyngeal carcinoma. *Nature Communications*. 2018;9(1):4663. doi:10.1038/s41467-018-06889-5

B. Conference Papers

1. Siu EHL, Ng SSM, Chan AWH, Lau JYW, Lo KW, Chong CCN, Lai PBS, Chan SL, Law MHN, Ng LWC, Cheung ST. PD-L1 expression associated with treatment responses in colorectal cancer patients with XELOX/FOLFOX chemotherapy: potential of checkpoint blockage and natural killer cell-based immunotherapy. In: *The Annual Meeting of the American Association for Cancer Research*. April 14-18, 2018. Chicago, USA. Proceedings of the AACR.

C. Books / Book Chapters

1. Bateman A, Bennett HPJ and Cheung ST (Editors). Book: Progranulin. Methods and Protocols. Springer Protocols. Humana Press. New York: Springer Nature. *Methods in Molecular Biology*. 2018; 1806.

2. Bateman A, Cheung ST, Bennett HPJ. A brief overview of progranulin in health and disease. *Methods in Molecular Biology*. 2018; 1806: 3-15.

3. Yip CW, Cheung PFY, Wong NCL, Fung SW, Cheung ST (correspondence). Mouse monoclonal antibodies against progranulin (PGRN/GEP) as therapeutics in preclinical cancer models. *Methods in Molecular Biology*. 2018; 1806: 131-144.

4. Cheung PFY, Cheung ST (correspondence). Methods to analyze the role of progranulin (PGRN/GEP) on cancer stem cell features. *Methods in Molecular Biology*. 2018; 1806: 145-153.

D. Invited Lectures

1. Rational Combination of PD-L1/PD1 Targeting and Natural Killer Cells: Hepatocellular Carcinoma Preclinical Study. *Immuno-Oncology Summit*. August 27-31, 2018. Boston, USA.

05

VASCULAR MEDICINE

Basic Research



Principal Investigators

Professor Yu Huang
Professor Xiaoqiang Yao



Team

Laboratory of Vascular Medicine (Basic Research)

Research Progress Summary

Professor Yu Huang's team progresses well with focus on the impact of shear stress on endothelial function and in the process of identifying useful biomarkers for early prediction of vascular diseases.

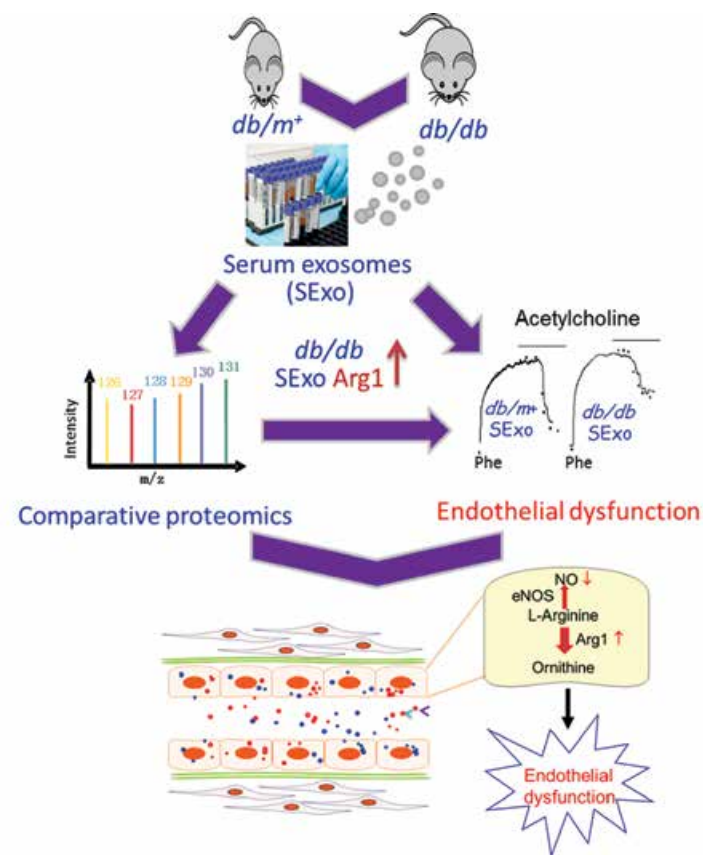
The team led by Professor Xiaoqiang Yao had novel findings that TM9SF4 is a novel factor that can promote autophagic flux in nutrient starvation condition, consequently protect cells from apoptotic cell death. His group also found that polycystin-2 plays an important role in promoting autophagic flux as a mechanism to protect cardiomyocytes from apoptotic cell death.



■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Yu Huang	The 9 th Asian Lecture on Vascular Biology at 8 th Scientific Meeting of Asian Society for Vascular Biology, Shanghai, China, 3 November 2018
Yu Huang	2017 Higher Education Outstanding Scientific Research Output Award (second-class award), Ministry of Education, People Republic of China (2017年度高等學校科學研究優秀成果獎 — 自然科學二等獎 · 2018)
Andy Cheng	1 st Prize of Young Investigator Award Competition (Oral Presentation) at 22 nd Scientific Meeting of Hong Kong Institute of Cardiovascular Science and Medicine, Hong Kong, 10 November 2018
Mingyu Huo	1 st Prize of Young Investigator Award Competition (Oral Presentation) at 22 nd Annual Scientific Meeting of Hong Kong Institute of Cardiovascular Science and Medicine, Hong Kong, 10 November 2018
Mingyu Huo	1 st Prize of Young Investigator Award Competition (Oral Presentation), The 17 th Conference of The Cardiovascular Society of Chinese Association of Pathophysiology and The 14 th China Congress of the International Society for Heart Research, Nanjing, China, 19-22 September 2018
Mingyu Huo	18 th World Congress of Basic and Clinical Pharmacology (WCP2018) Congress Bursary Award, Kyoto, Japan, 1-6 July 2018
Juan Huang	3 rd Prize of Young Investigator Award Competition (Oral Presentation) at 22 nd Scientific Meeting of Hong Kong Institute of Cardiovascular Science and Medicine, Hong Kong, 10 November 2018



Exosomes carrying an enzyme called arginase 1 isolated from diabetic db/db mice are delivered to vascular endothelial cells to lower bioavailability of arginine resulting in reduced production of nitric oxide in endothelial cells and related endothelial dysfunction.

Source: Professor Yu Huang

Fellowships

Member's Full Name	Details
Yu Huang	Member of the Biology and Medicine Panel, Hong Kong Research Grants Council, Hong Kong (December 2017-)
Yu Huang	Member of the Grant Review Board, Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (2013-)
Yu Huang	Panel Member of University of Macau Multi-Year Research Grant in Engineering and Science (2013-)
Yu Huang	Academic Committee Member of the Hong Kong Scholar Programme (香江學者計劃 · 2011-)
Yu Huang	President, Asian Society for Vascular Biology (2010-2018)
Yu Huang	Council Member, The Chinese Association of Pathophysiology (中國病理生理學會理事2010-2014 · 2014-2018)
Yu Huang	Vice-President, The Chinese Society of Vascular Medicine, Chinese Association of Pathophysiology (中國病理生理學會血管醫學專業委員會副主任委員 · 2015-)
Yu Huang	Vice-President, The Chinese Section, International Society of Heart Research (國際心臟研究會中國分會副主席 · 2016-2020)
Yu Huang	Executive Council Member of The Chinese Section, International Society of Heart Research (國際心臟研究會中國分會常務理事 · 2008-2012 · 2012-2016 · 2016-2020)
Yu Huang	Council Member of International Society of Heart Research – Chinese Committee of Translational Medicine (國際心臟研究會中國轉化醫學工作委員會理事 · 2014-2016)
Yu Huang	Executive Council Member of International Society of Heart Research – Chinese Committee of Translational Medicine (國際心臟研究會中國轉化醫學工作委員會常務理事 · 2016-2020)
Yu Huang	Council Member, The Chinese Society of Cardiovascular Pathophysiology (中國病理生理學會心血管專業委員會理事2008-2012 · 2012-2016 · 2016-2020)
Yu Huang	Executive Council Member, The Chinese Society of Cardiovascular Pharmacology, Chinese Pharmacological Society (中國藥理學會心血管專業委員會常務理事 · 2007-2011 · 2011-2015 · 2015-)
Yu Huang	Elected Council Member, The Chinese Society of Circulatory Physiology, Chinese Association for Physiological Sciences (中國生理學會循環生理專業委員會理事 · 2015-)

Academic Editorships and Reviews

Member's Full Name	Details
Yu Huang	Editor for British Journal of Pharmacology (UK, Jan 2018 - Dec 2022)
Yu Huang	Editorial Board Member, Cardiovascular Research (Europe, 2018-)
Yu Huang	Editorial Board Member, Journal Molecular and Cellular Cardiology (USA, 2018-)
Yu Huang	Associate Editor (Cardiovascular), Clinical and Experimental Pharmacology and Physiology (2014-)
Yu Huang	Associate Editor, Naunyn-Schmiedeberg's Archives of Pharmacology (Europe, 2012-)
Yu Huang	Editor, Drug Discoveries & Therapeutics (Japan, 2008-)
Yu Huang	Member of Editorial Board of Arteriosclerosis, Thrombosis and Vascular Biology, American Heart Association (USA) (2012-)

Journal / Conference Reviews

Member's Full Name	Details
Yu Huang	Review manuscripts for 1. Chemical Biology & Drug Design (UK) 2. Pharmaceutical Biology (USA) 3. Journal of Asian Natural Products Research (Taylor & Francis) 4. International Journal of Biological Sciences (China) 5. Toxicology and Applied Pharmacology (Elsevier) 6. Molecular Medicine Reports (Greece) 7. Expert Review of Cardiovascular Therapy (Taylor & Francis) 8. Genomic Medicine (UK) 9. Chinese Journal of Natural Medicines (China) 10. Journal of Chinese Medicine (China) 11. Indian Journal of Experimental Biology (India) 12. Experimental Gerontology (USA) 13. Journal of Herbal Medicine (UK) 14. Pharmacology Research & Perspectives 15. Molecular Medicine Reports (UK) 16. Diabetes Research and Clinical Practice (UK) 17. Fundamental & Clinical Pharmacology (Scandinavia) 18. Journal of American Heart Association (USA) 19. Cardiovascular Drug & Therapy (Europe) 20. Immunopharmacology And Immunotoxicology 21. Phytotherapy Research 22. The Journal of Nutritional Biochemistry 23. International Journal of Nanomedicine (USA) 24. European Journal of Pharmacology (Europe) 25. Endocrine (Italy) 26. Brazilian Journal of Pharmaceutical Sciences 27. Acta Physiologica Sinica (China) 28. Diabetes Care (USA) 29. Atherosclerosis (Europe) 30. Cell Reports (USA) 31. Biomedicine & Pharmacotherapy (USA) 32. Journal of Cellular and Molecular Medicine(USA) 33. Journal of Endocrinology (UK) 34. Microvascular Research (USA) 35. Case Reports in Nephrology and Dialysis (Europe) 36. Acta Pharmaceutica Sinica B (Elsevier) 37. ACS Chemical Neuroscience 38. Biomaterials (USA) 39. Journal of Clinical Investigation (USA) 40. Nature Communications (UK) 41. Jorntl Ceccular Physiology (USA) 42. Artificial Cells, Nanomedicine and Biotechnology (Taylor & Francis)

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Yu Huang	A multi-disciplinary study on the beneficial effects of PPARδ in physical exercise against diabetic vascular complications: cellular crosstalk and energy metabolism	Research Grants Council – Collaborative Research Fund	2017	2020	6,817,834
Yu Huang	Novel lipid-lowering independent benefits of statins against vascular dysfunction in metabolic syndrome	Food and Health Bureau – Health and Medical Research Fund	2017	2019	1,199,176
Yu Huang	Driving vascular regeneration against diabetic endothelial dysfunction with immune intervention	Food and Health Bureau – Health and Medical Research Fund	2017	2019	1,198,752
Yu Huang	Targeting YAP/TAZ activation to ameliorates endothelial dysfunction in diabetic mice	Research Grants Council – General Research Fund	2018	2021	1,126,512
Yu Huang	Conversion of white into brown adipocytes as a therapeutic strategy for obesity-related metabolic and vascular complications	Research Grants Council – Collaborative Research Fund	2018	2021	7,439,996
Yu Huang	Involvement of the Hippo pathway as a novel mechanism underlying the beneficial effect of metformin against diabetic vasculopathy and insulin resistance	Food and Health Bureau – Health and Medical Research Fund	2017	2018	1,200,000
Xiaoqiang Yao	TM9SF4 as a novel potassium channel and its role in autophagy	Research Grants Council – General Research Fund	Jan 2017	Dec 2019	1,000,387
Xiaoqiang Yao	Centre for Organelle Biogenesis and Function	Research Grants Council – Area of Excellence	Jan 2014	Dec 2021	47,250,000

■ Publications

A. Journal Papers

1. Xiang L, Zhang H, Wei J, Tian X, Luan H, Li S, Zhao H, Cao G, Chung A, Yang C, Huang Y, Cai Z. Metabolomics studies on db/db diabetic mice in skeletal muscle reveal effective clearance of overloaded intermediates by exercise. *Analytica Chimica Acta*. 2018;1037:130-139.
2. Liang C, Zhang Y, Zhuo D, Lo C, Yu L, Lau C, Kwan Y, Tse G, Huang Y, Yao X. Endothelial cell transient receptor potential channel C5 (TRPC5) is essential for endothelium-dependent contraction in mouse carotid arteries. *Biochemical Pharmacology*. 2018;159:11-24.
3. Cheng C, Bakar H, Gollasch M, Huang Y. Perivascular Adipose Tissue: the Sixth Man of the Cardiovascular System. *Cardiovascular Drugs and Therapy*. 2018;32(5):481-502. (Review)
4. Luo H, Chen C, Guo L, Xu Z, Peng X, Wang X, Wang J, Wang N, Li C, Luo X, Wang H, Jose P, Fu C, Huang Y, Shi W, Zeng C. Exposure to Maternal Diabetes Mellitus Causes Renal Dopamine D 1 Receptor Dysfunction and Hypertension in Adult Rat Offspring. *Hypertension*. 2018;72(4):962-970.
5. Gong Y, Luo J, Wang L, Huang Y. MicroRNAs Regulating Reactive Oxygen Species in Cardiovascular Diseases. *Antioxidants & Redox Signaling*. 2018;29(11):1092-1107. (Review)
6. Lu Z, Wei X, Sun F, Zhang H, Gao P, Pu Y, Wang A, Chen J, Tong W, Li Q, Zhou X, Yan Z, Zheng H, Yang G, Huang Y, Liu D, Zhu Z. Non-insulin determinant pathways maintain glucose homeostasis upon metabolic surgery. *Cell Discovery*. 2018;4(1).
7. Yang J, Wong L, Tian X, Wei R, Lai W, Au K, Luo Z, Ward C, Ho W, Ibañez D, Liu H, Bao X, Qin B, Huang Y, Esteban M, Tse H. A Familial Hypercholesterolemia Human Liver Chimeric Mouse Model Using Induced Pluripotent Stem Cell-derived Hepatocytes. *Journal of Visualized Experiments*. 2018;(139).
8. Tang T, Li Y, Li J, Wang K, Han Y, Dong W, Zhu Z, Xia N, Nie S, Zhang M, Zeng Z, Lv B, Jiao J, Liu H, Xian Z, Yang X, Hu Y, Liao Y, Wang Q, Tu X, Mallat Z, Huang Y, Shi G, Cheng X. Liver-heart crosstalk controls IL-22 activity in cardiac protection after myocardial infarction. *Theranostics*. 2018;8(16):4552-4562.
9. Amor S, Martín-Carro B, Rubio C, Carrascosa J, Hu W, Huang Y, García-Villalón A, Granado M. Study of insulin vascular sensitivity in aortic rings and endothelial cells from aged rats subjected to caloric restriction: Role of perivascular adipose tissue. *Experimental Gerontology*. 2018;109:126-136.
10. Leung O, Li J, Li X, Chan V, Yang K, Ku M, Ji L, Sun H, Waldmann H, Tian X, Huang Y, Lau J, Zhou B, Lui K. Regulatory T Cells Promote Apelin-Mediated Sprouting Angiogenesis in Type 2 Diabetes. *Cell Reports*. 2018;24(6):1610-1626.
11. Zhang H, Yang F, Guo Y, Wang L, Fang F, Wu H, Nie S, Wang Y, Fung M, Huang Y, Deng H, Qin Y, Ma X, Wei Y. The contribution of chronic intermittent hypoxia to OSAHS: From the perspective of serum extracellular microvesicle proteins. *Metabolism*. 2018;85:97-108.
12. Tian X, Ma S, Tse G, Wong W, Huang Y. Uncoupling Protein 2 in Cardiovascular Health and Disease. *Frontiers in Physiology*. 2018;9. (Review)
13. Zhang H, Liu J, Qu D, Wang L, Wong C, Lau C, Huang Y, Wang Y, Huang H, Xia Y, Xiang L, Cai Z, Liu P, Wei Y, Yao X, Ma R, Huang Y. Serum exosomes mediate delivery of arginase 1 as a novel mechanism for endothelial dysfunction in diabetes. *Proceedings of the National Academy of Sciences*. 2018;115(29):E6927-E6936.

14. Huang H, Xu C, Wang Y, Meng C, Liu W, Zhao Y, Huang X, You W, Feng B, Zheng Z, Huang Y, Lan H, Qin J, Xia Y. Lethal (3) malignant brain tumor-like 2 (L3MBTL2) protein protects against kidney injury by inhibiting the DNA damage-p53-apoptosis pathway in renal tubular cells. *Kidney International*. 2018;93(4):855-870.
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17. Liu X, Wang T, Wang Y, Chen Z, Hua D, Yao X, Ma X, Zhang P. Orai1 is critical for Notch-driven aggressiveness under hypoxic conditions in triple-negative breast cancers. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*. 2018;1864(4):975-986.
18. Lu J, Boheler K, Jiang L, Chan C, Tse W, Keung W, Poon E, Li R, 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.
19. Poon E, Hao B, Guan D, Jun Li M, Lu J, Yang Y, Wu B, Wu S, Webb S, Liang Y, Miller A, Yao X, Wang J, Yan B, Boheler K. Integrated transcriptomic and regulatory network analyses identify microRNA-200c as a novel repressor of human pluripotent stem cell-derived cardiomyocyte differentiation and maturation. *Cardiovascular Research*. 2018;114(6):894-906.

B. Books / Book Chapters

1. Tjong Y.W., Yao X. (2018) Methods for Evaluation of Vascular Endothelial Cell Function with Transient Receptor Potential (TRP) Channel Drugs. In: Boheler K., Gundry R. (eds) The Surfaceome. Methods in Molecular Biology, vol 1722. Humana Press, New York, NY

05

VASCULAR MEDICINE



Principal Investigator
Professor Gary Tse



Team

Bimal Gurung | Bijia Chen | Yan Yee Ting | Mingzhaung Chen | Francis Chen | Ming Xu Xie | Meng Yuan | Christien Ka Hou Li | Cheuk Wai Wong | Ishan Lakhani | Jenny Lai | Rachel Lai | Jeremy Wong | Lilianna Chung | Keith Leung | Alex Chau | Gabirel Wong | Dicken Kong | Kevin Ho | Joshua Hung | Sharen Lee | Samuel Woo | Matthew Lam | Ivan Ko | John Hung | Anthony Burtman | Konala Sunaina Reddy | Carly Wilson | Francis Cheng Pou Chan | Jasmine Chopra | Jonathan Chun Hin | Victor Mui | Chengsheng Ju | Tian Sang | Ryan Ho | Natalie Tsui | Lorraine Chiang | Ricko Wong | Chloe Cheung | Keith Lau | Thompson Kot | Man Ying So | Oi Ling Lau | Wenzhe Ye | Victoria Chan | Ka Wai Cheng | Gail Faan | Wai Lau | Po Yi Li | Lok Hei Tse | Enpei Zhang | Walter Wan | Dominic Lau



■ Research Progress Summary

Professor Gary Tse's team has taken a translational approach to investigate the mechanisms underlying cardiac arrhythmias and sudden cardiac death in both pre-clinical and clinical studies. Their work has related these phenomena to cardiac dynamics, such as the onset of alternans and abnormal electrical restitution. On the basic science side, his group recently applied time-domain, frequency-domain



and non-linear analyses to action potential time series to examine ventricular repolarisation variability in mouse models (Tse et al., *Frontiers in Physiology*, 2018;9:1578.). The next step of the team is to investigate whether these variability measures are predictive of arrhythmogenesis in different models. Using clinical cohorts, together with colleagues from Europe, they demonstrated that abnormal unipolar voltage mapping detected at the free wall of the right ventricular outflow tract can be used to predict ventricular fibrillation

inducibility in Brugada syndrome (Letsas et al., *Circulation: Arrhythmia and Electrophysiology*, 2018;11(2):e005928.). The team is currently working on combining different electrocardiographic (Tse et al., *Frontiers in Cardiovascular Medicine*, 2018;5:132) and restitution markers for risk stratification in Brugada syndrome patients (Tse et al., under review). The team has recently expanded their interests to include the more prevalent disease of heart failure (Zhang et al., *JAMDA*, 2018;pii:S1525-8610(18)30609-1).

■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Gary Tse	Junior Clerkship Exemplary Teachers' Award (2018) by the Department of Medicine and Therapeutics, The Chinese University of Hong Kong
Gary Tse	Guest Professorship in Cardiovascular Medicine (2018-2021) at the Dalian Medical University, People's Republic of China
Gary Tse	ECG Bayés Award (2018) by the International Society of Electrocardiology, International Society for Holter and Noninvasive Electrocardiology, Japanese Society for Holter and Noninvasive Electrocardiology and Japanese Society for Computerized Electrocardiology.
Gary Tse	Croucher Foundation Clinical Assistant Professorship (2016-2020)

Fellowships

Member's Full Name	Details
Gary Tse	Fellow, Academy of Medical Educators (FAcadMED)
Gary Tse	Fellow, Royal College of Physicians of Edinburgh (FRCP[Edin])
Gary Tse	Member through Distinction, Faculty of Public Health, Royal College of Physicians of the United Kingdom (MFPH (UK))
Gary Tse	Fellow, Heart Rhythm Society (FHRS)

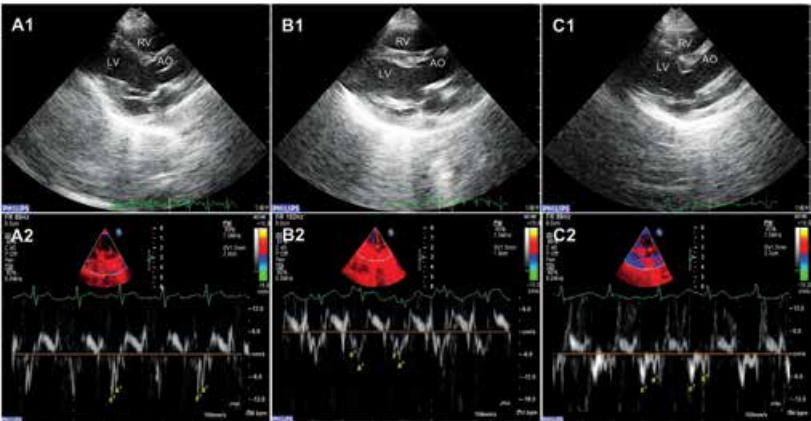
Academic Editorships and Reviews

Member's Full Name	Details
Gary Tse	Cardio-Oncology: Editorial Board Member
Gary Tse	Journal of Electrocardiology: Editorial Board Member
Gary Tse	Oxford Medical Case Reports: Editorial Board Member
Gary Tse	Frontiers in Physiology: Editorial Board Member, Section of Cardiac Electrophysiology (Review Editor)
Gary Tse	Frontiers in Physiology: Guest Associate Editor for Computational Physiology and Medicine
Gary Tse	Frontiers in Physiology: Topic Editor for "Recent Advances in Understanding the Basic Mechanisms of Atrial Fibrillation Using Novel Computational Approaches"
Gary Tse	Cardiology Research and Practice: Editor for Special Issue on "Atrial Fibrillation: Mechanisms and Management"
Gary Tse	Hong Kong Medical Journal: Epidemiology Advisor
Gary Tse	American Journal of Physiology
Gary Tse	Anatolian Journal of Cardiology
Gary Tse	Annals of Noninvasive Electrocardiology
Gary Tse	British Journal of Clinical Pharmacology
Gary Tse	Cardiovascular Therapeutics
Gary Tse	Circulation
Gary Tse	Clinical Cardiology
Gary Tse	Experimental and Therapeutic Medicine
Gary Tse	Europace
Gary Tse	Frontiers in Physiology

Member's Full Name	Details
Gary Tse	Hong Kong Medical Journal
Gary Tse	IEEE Journal of Biomedical and Health Informatics
Gary Tse	Journal of Visualized Experiments
Gary Tse	International Journal of Cardiology
Gary Tse	Journal of American Heart Association
Gary Tse	Journal of Critical Care
Gary Tse	Journal of Arrhythmia
Gary Tse	Journal of Cardiovascular Electrophysiology
Gary Tse	Journal of Electrocardiology
Gary Tse	Journal of Royal Society of Medicine
Gary Tse	Naunyn-Schmiedeberg's Archives of Pharmacology
Gary Tse	Oncotarget
Gary Tse	Oxford Medical Case Reports
Gary Tse	Pharmacology Reviews
Gary Tse	PLOS ONE
Gary Tse	SpringerPlus
Gary Tse	Scientific Reports
Gary Tse	Transactions on Biomedical Engineering

Journal / Conference Reviews

Member's Full Name	Details
Gary Tse	Invited Abstract Reviewer for European Society of Cardiology Congress
Gary Tse	Invited Reviewer for Medical Research Council Research Grant, United Kingdom (August 2018 – present)
Gary Tse	Invited Reviewer for Auckland Medical Research Foundation Research Grant, New Zealand (September 2017 – present)
Gary Tse	Invited Reviewer for Rosetrees Trust Medical Fellowship, United Kingdom (August 2017 – present)



Representative echocardiographic images of the left ventricle for the three different groups. Two-dimensional echocardiographic image of the control group, diabetic group and alogliptin-treated diabetic group (A–C, top) and Doppler tissue imaging (bottom). LV:left ventricle, RV:right ventricle; AO:aorta, e’ early diastolic mitral annular velocity, a’ late diastolic mitral annular velocity, n = 10 per group

Source: Zhang X, Zhang Z, Yang Y, Suo Y, Liu R, Qiu J, Zhao Y, Jiang N, Liu C, Tse G, Li G, Liu T. Alogliptin prevents diastolic dysfunction and preserves left ventricular mitochondrial function in diabetic rabbits. Cardiovasc Diabetol. 2018;17(1):160. doi:10.1186/s12933-018-0803-z.

■ Publications

A. Journal Papers

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3. Liang C, Zhang Y, Zhuo D, Lo CY, Yu L, Lau CW, Kwan YW, Tse G, Huang Y, Yao X. Endothelial cell transient receptor potential channel C5 (TRPC5) is essential for endothelium-dependent contraction in mouse carotid arteries. *Biochemical Pharmacology*. 2019;159:11-24. doi:10.1016/j.bcp.2018.11.002. [Epub ahead of print]
4. Zhang N, Tse G, Dahal S, Yang Y, Gong M, Chan CZY, Liu E, Xu G, Letsas KP, Korantzopoulos P, Li G, Liu T. Efficacy of Wenxin Keli plus amiodarone versus amiodarone monotherapy in treating recent-onset atrial fibrillation. *Cardiology Research and Practice*. 2018;2018:1-7. doi:10.1155/2018/6047271.
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9. Tse G, Bazoukis G, Roever L, Liu T, Wu WKK, Wong MCS, Baranchuk A, Korantzopoulos P, Asvestas D, Letsas KP. T-wave indices and atherosclerosis. *Current Atherosclerosis Reports*. 2018;20(11):55. doi:10.1007/s11883-018-0756-4.
10. Lei M, Gong M, Bazoukis G, Letsas KP, Korantzopoulos P, Li G, Bisleri G, Glover B, Li KHC, Tse G, Baranchuk A, Liu T. Steroids prevent early recurrence of atrial fibrillation following catheter ablation: A systematic review and meta-analysis. *Bioscience Reports*. 2018;38(5):BSR20180462. doi:10.1042/BSR20180462. [Review]
11. Shao Q, Meng L, Tse G, Sawant AC, Zhuo Yi Chan C, Bazoukis G, Baranchuk A, Li G, Liu T. Newly proposed electrocardiographic criteria for the diagnosis of left ventricular hypertrophy in a Chinese population. *Annals of Noninvasive Electrocardiology*. 2019;24(2):e12602. doi:10.1111/anec.12602.
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B. Conference Papers

1. Fan YT, Tse G, Shang Q, Yan BP, Tam LS, Lee AP. Inflammation-related impairment of left ventricular functional reserve in patients with systemic lupus erythematosus: A speckle-tracking exercise echocardiographic study. In: *EuroEcho-Imaging 2018*; Milan, Italy; 2018 Dec 5-8.
2. Bhardwaj A, Sawant AC, Tetewsky S, McCray W, Mammen M, Khan S, Manion C, Tse G, Liu T, Lee R, Curtis AB, Pershad A, Elkins P, Corbelli J. Superior survival with direct oral anticoagulants compared to warfarin in patients with atrial fibrillation and underlying cancer: Veterans affairs database study. In: *American Heart Association Scientific Sessions 2018*; Chicago, United States; 2018 Nov 10-12.
3. Tse G, Tian XY, Huang Y, Wong WT. Direct renin inhibition using aliskiren prevents endothelial dysfunction in renal arteries of spontaneously hypertensive rats. In: *The 27th Scientific Meeting of the International Society of Hypertension*; Beijing, China; 2018 Sep 20-23.
4. Sun Y, Li D, Tse G, Liu T, Xia Y. Difference in long-term cerebrovascular embolism risk between sustained atrial fibrillation and paroxysmal atrial fibrillation: A systemic review and meta-analysis. In: *The 29th Great Wall International Congress of Cardiology*; Beijing, China; 2018 Oct 11-14.

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7. Lakhani I, Gong M, Li G, Wong SH, Wu WKK, Wong MCS, Mu N, Dong M, Lip GYH, Mok VCT, Liu T, Tse G. Predictive value of neutrophil-to-lymphocyte ratio for clinical outcomes following stroke: A systematic review and meta-analysis. In: *European Society of Cardiology Congress 2018*; Munich, Germany; 2018 Aug 25-29.
8. Tse G, Li CKH, Gong M, Lakhani I, Bazoukis G, Letsas KP, Wu WKK, Wong SH, Li G, Wong MCS, Xia Y, Liu T. Catheter ablation for atrial fibrillation in heart failure patients: A systematic review and meta-analysis of randomized controlled trials. In: *European Society of Cardiology Congress 2018*; Munich, Germany; 2018 Aug 25-29.
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10. Wong R, Wong P, Zhang E, Chan CZY, Li G, Wong WT, Chan YS, Wong MCS, Liu T, Baranchuk A, Lip GYH, Lee APW, Tse G. Electrocardiographic evidence of atrial cardiomyopathy in mitral stenosis: a retrospective analysis in a Chinese cohort. In: *The 45th International Congress on Electrocardiology and the 18th Congress of the International Society for Holter and Noninvasive Electrocardiology*; Chiba City, Japan; 2018 Jun 28-30.
11. Yan BP, Chan CKY, Tse G, Wong MCS, To OTL, Lee VWY. Projected efficacy of statin mono- and combination therapy based on distance from baseline to target LDL-C level in acute coronary syndrome. In: *International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 8th Asia Pacific Conference*; Tokyo, Japan; 2018 Sep 8-11.
12. Bisleri G, Elbatarny M, Chacko S, Baranchuk A, Hong K, Kahn M, Tse G, Glover B. Simultaneous hybrid ablation of long-standing persistent atrial fibrillation: advanced mapping technologies to guide surgical ablation. In: *International Society for Minimally Invasive Cardiothoracic Surgery Annual Scientific Meeting 2018*; Vancouver, Canada; 2018 Jun 13-16.
13. Wong SH, Ho J, Wu JC, Ng SC, Sung JJ, Wu WK, Tse G. Prevalence of *Clostridium difficile* infection: A meta-analysis of global disease burden. In: *Digestive Diseases Week 2018*; Washington, United States; 2018 Jun 2-5.
14. Wong MCS, Huang J, Wang J, Huang J, Fung DH, Yu CP, Xiang HH, Tse G, Jiang JY. Increased risk of any-type colorectal neoplasia in asymptomatic individuals with family history of colorectal cancer: A systematic review and meta-analysis. In: *Digestive Diseases Week 2018*; Washington, United States; 2018 Jun 2-5.
15. Chen FM, Leung FP, Tse G, Wong WT. Type II cytokines are required for the resolution of injury in neonatal hearts following ischemic injury. In: *Arteriosclerosis, Thrombosis and Vascular Biology Scientific Sessions 2018*; San Francisco, United States; 2018 May 10-12.
16. Lakhani I, Gong M, Wong CW, Baranchuk A, Letsas K, Liu T, Tse G. Effects of minimizing ventricular pacing on the incidence of atrial fibrillation: A systematic review and meta-analysis of randomized controlled trials. In: *American College of Cardiology Scientific Session 2018*; Orlando, United States; 2018 Mar 10-12.
17. Yang Y, Zhao J, Qiu J, Li J, Liang X, Zhang Z, Zhang X, Fu H, Korantzopoulos P, Letsas K, Tse G, Li G, Liu T. Xanthine oxidase inhibitor allopurinol prevents oxidative stress-mediated atrial remodeling in alloxan-induced diabetes rabbits. In: *American College of Cardiology Scientific Session 2018*; Orlando, United States; 2018 Mar 10-12.

06

DIABETES AND OBESITY



Principal Investigator
Professor Juliana Chan



Team

Ronald CW Ma | Alice PS Kong | Andrea Luk | Elaine Chow | Wing Yee So | Risa Ozaki |
Kitty Cheung | Cadmon Lim | Heung Man Lee | Eric Lau | Guozhi Jiang | Dandan Mao | Claudia Tam |
Ming C Leung | Kwun Kiu Wong | Hou Yong | Huanyi Cao | Feifei Cheng | Lorena TF Cheung |
Chenzhao Ding | Baoqi Fan | Lee Ling Lim | Noel Ng | Kit Ying Tsoi | Fangying Xie | Ming Xing |
Wei Wei Zeng | Clara Lo | Annie Fung | Phil Xie | Dominic Fung



■ Research Progress Summary

In 2018, the Research Team led by Professor Juliana Chan continues with its overarching strategy of using big data, experimental studies and interventional programs to unravel the causes, trajectories and consequences of diabetes and its complications, with particular focus on genotype-phenotype-treatment-outcome interactions. Supported by the Research Grants Council - Theme-based Research Scheme (TRS), competitive grants (RGC, ITC, HMRF, NSFC-NHMRC, NIH), donations, proceedings from post-graduate and professional courses and contract research, they have nurtured a team of young clinicians, scientists, technologists and analysts with complementary skillsets to discover and apply new knowledge in the field of diabetes, endocrinology and clinical pharmacology.

The establishment of the 12-Centre Hong Kong Diabetes Biobank, supported by the RGC-TRS, has led to their newly awarded RGC Research Impact Fund led by Professor Ronald Ma where the team will empower the patients with genomic information using a randomised clinical trial (RCT) design. In addition to being one of the principal investigators (PIs) of the International Type 2 Diabetes Genetics Consortium and Accelerating Medicines Partnership Type 2 Diabetes Knowledge Portal, supported by the Foundation of the NIH with industrial support, Professor Ma is assembling an international consortium to discover and validate their genomic discoveries in diabetic complications. Through the RGC-TRS, they have established strategic partnerships with local and international experts to use big data and state of the art methodologies to discover and validate novel and potentially druggable disease pathways. Using a similar strategy, Professor Ma continues to make progress in the field of polycystic ovarian syndrome and gestational diabetes for prevention of diabetes and obesity in our young generation.

On a translational front, Professor Juliana Chan has been commissioned by the Food and Health Bureau to lead a project to discover novel biogenetic markers and sequences in familial young-onset diabetes followed by a RCT to compare the effects of precision medicine versus usual care in patients with young onset diabetes. In collaboration with basic scientists from the School of Biomedical Science, Professor Alice Kong is training several postgraduate students to examine the effects of oxidative stress and inflammation on beta cell biology as well as using their biobanks to discover biogenetic markers predictive of cancer in diabetes, supported by ITC. Meanwhile, Professor Juliana Chan is working closely with the Department of Microbiology to discover the mechanisms of the diabetes-cancer link and the potential anti-cancer and anti-diabetic effects of TCM.

In addition to being the medical director of the Phase 1 Clinical Trial Centre, Professor Andrea Luk, supported by RGC, is developing a panel of genetic variants of MODY (maturity onset diabetes of the young) for disease classification. She is currently working on a large HA big database consisting of 0.8 million patients to document the incidence of type 1 diabetes and the clinical course of young-onset diabetes. Supported by a HMRF grant, she will refine the Chinese Diabetes Outcome Model to simulate multiple events in people with diabetes over a 15-year horizon. Dr. Elaine Chow, a clinical pharmacologist with interest in endocrinology, has successfully developed the glucose/insulin clamp techniques at the Phase 1 Clinical Trial Centre to examine beta-cell function. Using this technique, she is evaluating the effects of novel technologies on this important parameter. Supported by the ITC, she is working closely with a local biotech company, to develop a novel continuous glucose monitoring system (CGMS) for registration in Europe and China to be followed by large scale clinical trials.

As a team of clinician scientists, the various PIs are running multiple phase 2-4 clinical trials of novel compounds at CFDA (renamed as NMPA: National Medical Products Administration) accredited clinical trial unit in the field of diabetes, obesity and cardiovascular-renal complications, supported by multinational companies. In anticipation of the

growing burden of young-onset diabetes, the team is sending fellows to overseas institutions to learn new technology in glucose sensing and insulin delivery system to address their unmet needs. Through this large number of complementary projects, they are currently training a team of fellows and students to explore the effects of sleep, nutrition, genetic counselling and various care models in diabetes.

As an International Diabetes Federation (IDF) Centre of Education and IDF Center of Excellence in Diabetes Care, the team continues to share their translational research and practices with local and overseas visitors and institutions. At the same time, several of the PIs are serving as members of steering committees in international projects in epidemiology and clinical trials in the field of diabetes and related fields, as well as grant reviewers of the ITC, RGC and HMRF panels. While more than 10 PhD students have graduated during this period, they are expecting more students/fellows to join the group in the coming years. To complement these scholastic activities, they have been sending students/fellows to leading institutions in UK, USA and Australia to learn new laboratory and analytical skills as well as inviting global experts to visit their unit to foster collaborations in pursuit of prediction, prevention and control of diabetes and its co-morbidities.

■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
CUHK-PWH Diabetes Care and Research Team	CUHK Hong Kong Institute of Diabetes and Obesity and PWH Diabetes and Endocrine Centre was recognised by the International Diabetes Federation (IDF) as an IDF Centre of Education and IDF Centre of Excellence in Diabetes Care for our commitment of using research to improve care and inform policy
Guozhi Jiang	AASD Investigator Award 2018 for the 10 th Asian Association for the Study of Diabetes (AASD), Kuala Lumpur, Malaysia, 22-25 November, 2018.
Noel Yat-hey Ng	Young Investigator Award, Oral presentation (1 st place), 20 th Diabetes and Cardiovascular Risk Factors East Meets West Symposium, Hong Kong, 30 September, 2018.
Baoqi Fan	“2018 Summer Institutes Scholarship” funded by the USA NIH National Institute of General Medical Sciences to participate in the 23 rd Summer Institute in Statistical Genetics, organised by the Department of Biostatistics, School of Public Health, University of Washington, Seattle, WA, USA (9-27 July 2018)
Baoqi Fan	“2018 Hong Kong Society of Endocrinology, Metabolism and Reproduction Training Fellowship” to participate in the 23 rd Summer Institute in Statistical Genetics, organised by the Department of Biostatistics, School of Public Health, University of Washington, Seattle, WA, USA (9-27 July 2018)
Clara Lo	Australasian Association of Clinical Biochemists AIM 2018/CMS meeting, Sydney, Australia, Poster prize
Feifei Cheng	Recipient of Global Scholarship Programme for Research Excellence 2018 to visit University of Sydney
FeiFei Cheng	Selected from all international applications to attend the 13 th World Health Organization/International Diabetes Federation (IDF) Cambridge Diabetes Seminar 2019, Cambridge, 31 March - 6 April 2019.
Chenzhao Ding	54 th Annual Meeting of European Association for the Study of Diabetes Travel Grant (1-5 October 2018)
Annie Chi-hua Fung	Bronze Medal, Dean’s Outstanding Research Award 2018, CUHK
Lee-ling Lim	Reviewer of the Year 2018, Journal of Diabetes
Lee-ling Lim	“2018 Summer Institutes Scholarship” funded by the USA NIH National Institute of General Medical Sciences to participate in the 23 rd Summer Institute in Statistical Genetics, organised by the Department of Biostatistics, School of Public Health, University of Washington, Seattle, WA, USA (9-27 July 2018)
Lee-ling Lim	“2018 Hong Kong Society of Endocrinology, Metabolism and Reproduction Training Fellowship” to participate in the 23 rd Summer Institute in Statistical Genetics, organised by the Department of Biostatistics, School of Public Health, University of Washington, Seattle, WA, USA (9-27 July 2018)

Fellowships

Member's Full Name	Details
Juliana Chan	2018 Honorary Fellowship of the Monash University, Australia
Ronald Ma	Fellow of the American College of Endocrinologists (FACE)

Academic Editorships and Reviews

Member's Full Name	Details
Juliana Chan	International Advisor: The Lancet Diabetes and Endocrinology
Juliana Chan	Editorial Board Member: Diabetes Metabolism Research Review
Ronald Ma	Regional Editor, Diabetic Medicine
Ronald Ma	Assistant Editor, Journal of Diabetes Investigation
Ronald Ma	Editorial Board Member : PLoS Medicine, Obesity Reviews, Nutrition, Metabolism and Cardiovascular Diseases, Journal of Diabetes Investigation
Alice Kong	Associate Editor, Primary Care Diabetes
Alice Kong	Editorial Board Member, Diabetes Technology & Therapeutics
Andrea Luk	Editorial Board: Diabetic Medicine

Journal / Conference Reviews

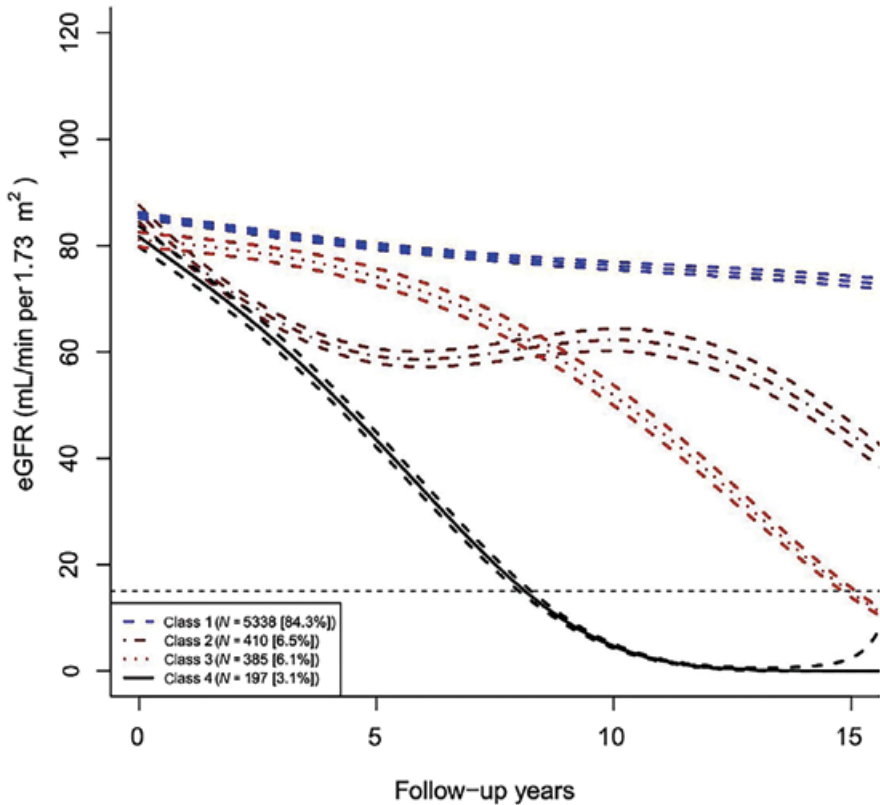
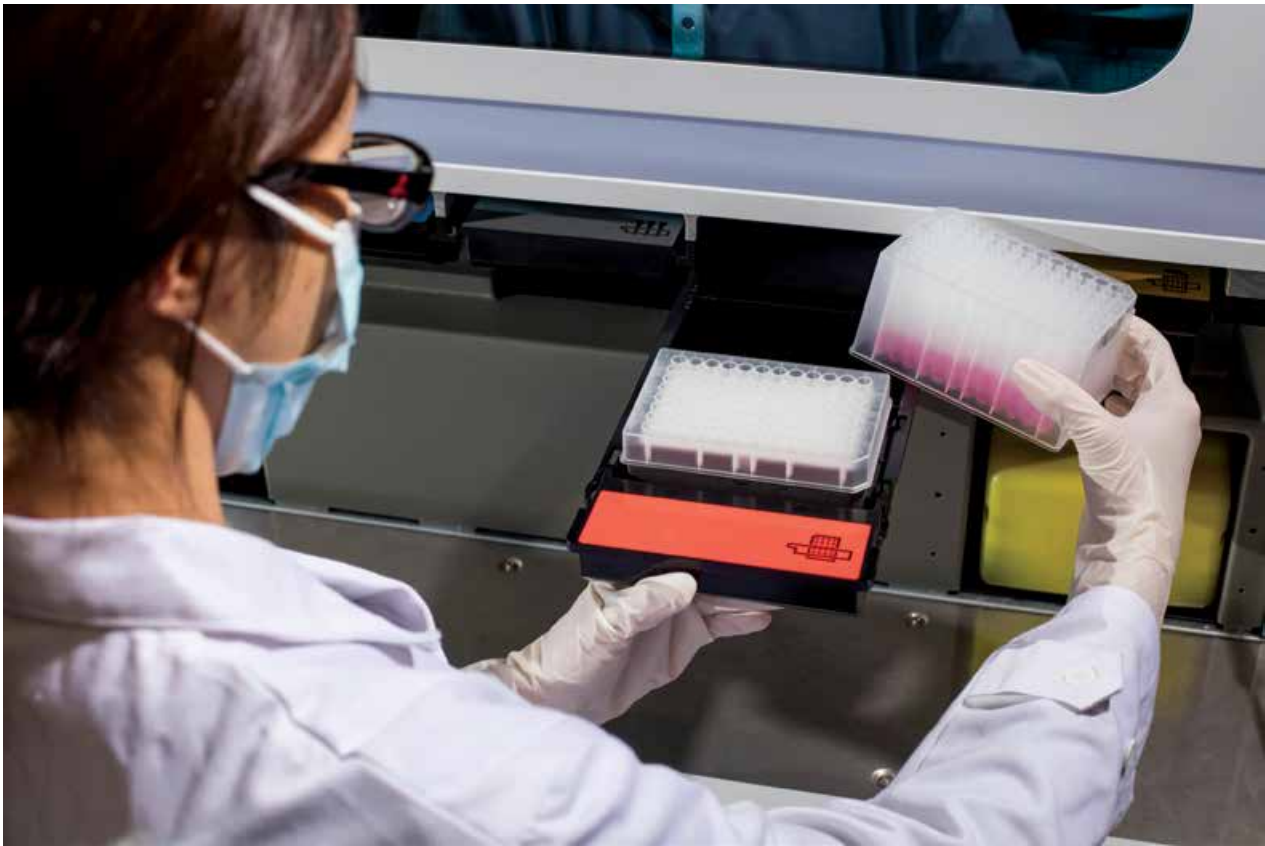
Member's Full Name	Details
Ronald Ma (Chair) Juliana Chan (Co-chair)	Gordon Research Conference- Epigenetic Mechanisms and Their Role in the Development of Diabetes, 27 May - 1 June 2018, Hong Kong
Ronald Ma	Lead, Diabetes and Women Stream, International Diabetes Federation World Diabetes Congress 2019, Busan, Korea

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Juliana Chan	JADE Mobile Application	Pfizer	2017	2018	USD 119,000
Juliana Chan	Diabetic Kidney Disease – Treat to Multiple Targets (DKD-TMT) Program (JADE Implementation Program	Pfizer	2013	2018	USD 995,037
Juliana Chan	Evaluation of a Percutaneous Optical Fibre Glucose Sensor (FiberSense) Across the Glycemic Range with Rapid Glucose Excursions Using the Glucose Clamp	Powder Pharmaceuticals Inc.	2016	2018	758,862
Juliana Chan	Identifying the Epigenomic Fingerprint of Coronary Heart Disease in Chinese Adults with Type 2 Diabetes	National Natural Science Foundation of China – National Health and Medical Research Council of Australia Joint Research Scheme	2016	2020	RMB 3,500,000
Ronald Ma	Validation of Novel Protein Markers for the Prediction of Diabetic Kidney Disease	The Chinese University of Hong Kong Technology and Business Development Fund	30/06/2018	29/06/2019	100,000
Ronald Ma	Precision Medicine in Diabetes	The Chinese University of Hong Kong – Shanghai Jiao Tong University Joint Research Fund	01/02/2018	31/01/2020	2,000,000
Ronald Ma	Early Growth Genetics and Cardiometabolic Risk in Chinese Adolescents	Food and Health Bureau – Health and Medical Research Fund	01/05/2018	30/04/2020	1,200,000
Ronald Ma	The Impact of Gestational Diabetes and Vitamin D Deficiency During Pregnancy on Children’s Cardiometabolic Risk and Methylation	Research Grants Council – General Research Fund	01/01/2017	31/12/2018	998,652
Ronald Ma Juliana Chan	An Integrated Transomics Approach to Diabetic Cardiorenal Complications: From Novel Discoveries to Personalized Medicine (T12-402/13N)	Research Grants Council – Theme-based Research Scheme	2014	2018	60,330,000

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Ronald Ma	Genetic Variants for Type 2 Diabetes and Diabetic Complications in East Asians: The Hong Kong Diabetes Registry Sponsored by the Accelerating Medicines Partnership Type 2 Diabetes Project	Foundation of the National Institutes of Health (USA)	2016	2018	3,013,920
Ronald Ma	A Randomized Double-blind, Placebo controlled, Parallel-group, Multicenter, Event-driven Phase III Study to Investigate the Efficacy and Safety of Finerenone on the Reduction of Cardiovascular Morbidity and Mortality in Subjects with Type 2 Diabetes Mellitus	Bayer HealthCare Limited	2016	2019	1,413,250
Alice Kong	Early Detection of Liver Cancer in Type 2 Diabetes Using Serum MicroRNA	Innovation and Technology Fund	2017	2018	1,396,790
Alice Kong	Explore Characteristics of Patients Treated with Premix and Basal Insulin in Asian Patients with Type 2 Diabetes Mellitus (T2DM) – The JADE Register	Lilly	2017	2019	USD 140,400
Elaine Chow	Effectiveness and Safety Study of the Percutaneous Optical Fibre Glucose Sensor (FiberSense) for Home Use in Diabetic and Prediabetic Individuals	Powder Pharmaceuticals Inc.	2017	2020	991,590
Elaine Chow	A Pilot Study to Describe the Glycaemic Variability of Insulin Glargine 300U/ml Versus NPH in Insulin Naïve T2DM Patients Following a Patient-adjusted Insulin Algorithm in Hong Kong	Sanofi Investigator Initiated Study	2017	2020	991,590



Trajectories of estimated glomerular filtration rate (eGFR) and 95% confidence intervals derived from the joint latent class model for a hypothetical 55-year-old man with 5 years of disease duration and no proteinuria at baseline.

Source: Jiang GZ et al. Progression of diabetic kidney disease and trajectory of kidney function decline in Chinese patients with Type 2 diabetes. *Kidney International*. 2019 Jan; 95(1):178-187. doi: 10.1016/j.kint.2018.08.026.

■ Publications

A. Journal Papers

1. Jiang G, Luk AOY, Tam CHT, Xie F, Carstensen B, Lau ESH, Lim CKP, Lee HM, Ng ACW, Ng MCY, Ozaki R, Kong APS, Chow CC, Yang X, Lan H, Tsui SKW, Fan X, Szeto CC, So WY, Chan JCN, Ma RCW, Ma RCW, Chan JCN, Huang Y, Lan H, Lok S, Tomlinson B, Tsui SKW, Yu W, Yip KYL, Chan TF, Fan X, So WY, Szeto CC, Tang NLS, Luk AO, Tian X, Jiang G, Tam CHT, Lee HM, Lim CKP, Chan KKH, Xie F, Ng ACW, Cheung GPY, Yeung M, Mai S, Xie F, Zhang S, Yu P, Weng M. Progression of diabetic kidney disease and trajectory of kidney function decline in Chinese patients with Type 2 diabetes. *Kidney International*. 2019;95(1):178-187. doi:10.1016/j.kint.2018.08.026. [Epub ahead of print]
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3. Tam CHT, Ma RCW, Yuen LY, Ozaki R, Li AM, Hou Y, Chan MHM, Ho CS, Yang X, Chan JCN, Tam WH. The impact of maternal gestational weight gain on cardiometabolic risk factors in children. *Diabetologia*. 2018;61(12):2539-2548. doi:10.1007/s00125-018-4724-x.
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17. Cheung LTF, Chan RSM, Ko GTC, Lau ESH, Chow FCC, Kong APS. Diet quality is inversely associated with obesity in Chinese adults with type 2 diabetes. *Nutrition Journal*. 2018;17(1):63. doi:10.1186/s12937-018-0374-6.

B. Conference Papers

1. Chow E, Krivánková L, Krivánek R, Lee V, Tsui V, Müller A, Chan JCN Evaluation of a percutaneous optical fibre glucose sensor (Fibersense) across the glycemic range with rapid glucose excursions using the glucose clamp. In: *Advanced Technologies & Treatments for Diabetes (ATTD)*, Vienna, Austria (Feb 2018)
2. Chow E, Zhang GZ, Chan Katie, Luk A, Ma RCW, Tomlinson B, Chan JCN Effect of CYP2C19 *2 and *3 variants on sulphonylurea monotherapy treatment failure in Chinese patients with Type 2 diabetes In: *18th World Congress of Basic and Clinical Pharmacology (WCP2018)*, Kyoto, Japan
3. Chow E, Leung C, Luk A, Ke C, Lee V, Tsui V, Krivánková L, Krivánek R, Müller A, Chan JCN Effectiveness And Safety Of A Novel Percutaneous Optical Fiber Continuous Glucose Sensor (FiberSense) In: *Clinic And Home Use In Patients With Diabetes*. Diabetes Technology Meeting, Maryland, USA (Nov 2018)

07 EMERGING INFECTIOUS DISEASES



Principal Investigator
Professor Shui-shan Lee



Team

Dr. Denise Pui-chung Chan | Dr. Kai-man Kam | Dr. Grace Chung-yan Lui |
Dr. Chin-man Poon | Dr. Ngai-sze Wong | Dr. Wing-wai Yew



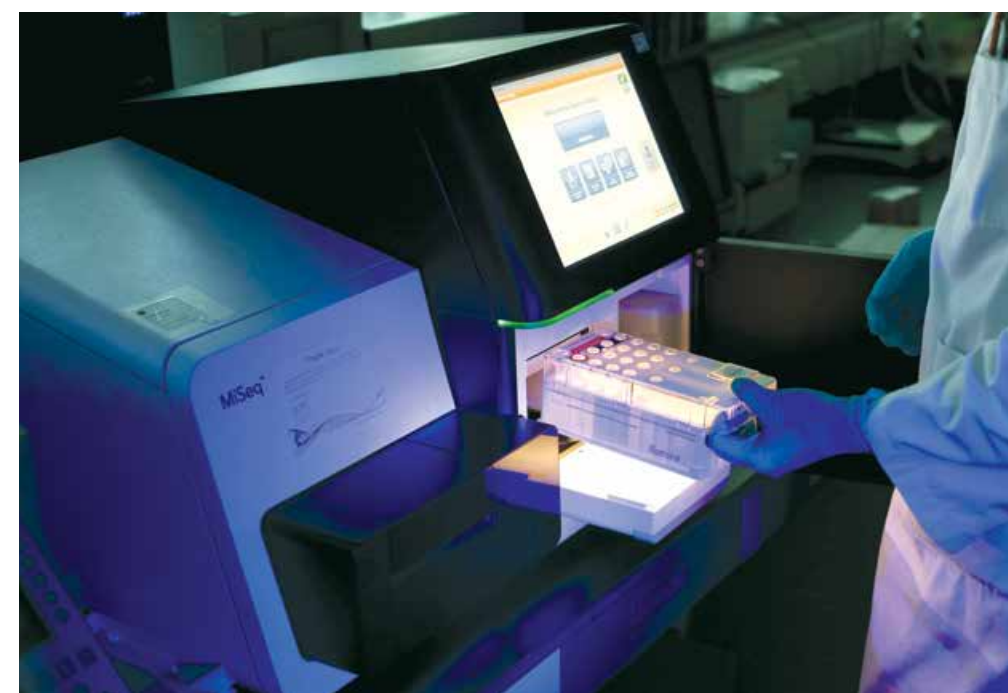
■ Research Progress Summary

As a research centre specialising in emerging infections, research foci of the Emerging Infectious Diseases Research Team have varied from year to year, focusing on conditions of concern. On an ongoing basis, the team examines transmission dynamics of human immunodeficiency virus (HIV) and other emerging infections, manages clinical cohorts, explores HIV comorbidities, conducts analyses on outbreaks. For the year 2018, the highlights were HIV pre-exposure prophylaxis; sexual transmission of hepatitis C virus (HCV); and influenza vaccination uptake in healthcare workers.

HIV Pre-exposure Prophylaxis

Pre-exposure prophylaxis (PrEP) is currently one most important means of preventing virus transmission in the community. Following release of promising results from several large-scale clinical trials and subsequent US Food and Drug Administration (FDA) approval of the use of co-formulated tenofovir disoproxil fumarate / emtricitabine (TDF/FTC) for PrEP, uptake has so far been slow in most parts of the world. The team pioneered Hong Kong's first pair of clinical trials on PrEP, which were rolled out in late 2017 and then mid-2018. The first study tested the feasibility and acceptability of partially self-financed mode of delivering daily PrEP while the second study compared daily with on-demand PrEP using a cross-over design. As of the end of 2018, over 100 men who have sex with men

(MSM) with high risk sexual behaviours have enrolled in the studies. Behavioural monitoring was performed using a novel online diary, while various point-of-care tests were piloted to track HIV/STI risks and adverse reactions in PrEP users. Early results on the practicality of PrEP, and the profile of risk compensation, were shared at international conferences and Hong Kong's government committees. The cross-disciplinary team is simultaneously working on social behavioural studies, qualitative research, as well as mathematical modelling that predicts PrEP's outcome in the setting of Hong Kong. The PrEP studies were supported by Council for the AIDS Trust Fund and Health and Medical Research Fund of the Hong Kong SAR Government.



Sexual Transmission of HCV

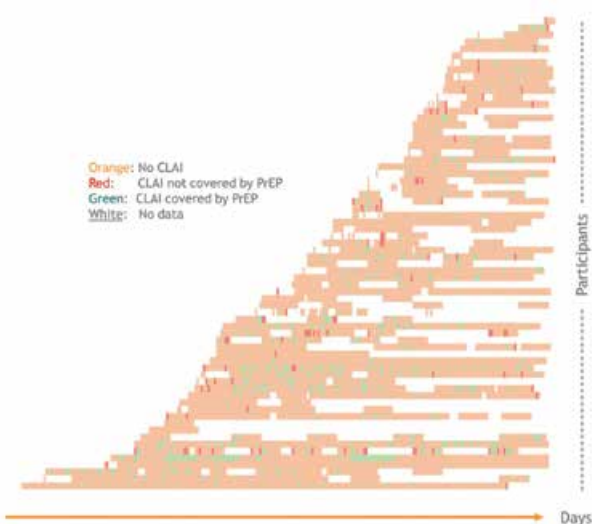
HCV has long known to be efficiently transmitted through contaminated transfusion and needle sharing among people who inject drugs (PWID). Sexual transmission of HCV was previously thought to be exceedingly uncommon. In the past decade, HCV outbreaks were repeatedly reported among MSM as a result of virus exposure through unprotected anal sex. In 2015, the team reported, for the first time, the emergence of a monophyletic genotype 3a cluster in HIV infected MSM in Hong Kong. An ongoing study founded on an acute HCV infection cohort was conducted, the results of which showed that transmission has stemmed from outbreaks centring on HIV infected MSM. The monophyletic cluster has given way to a more diverse pattern of further dissemination with the inclusion of genotype 1b. The analyses confirmed that there was no spilling over of infection from PWID whose HCV prevalence had been high at 80% locally. They observed that the epidemiological pattern was distinctly different in other neighbouring cities. The research team is working with collaborators in Tokyo and Taipei to decipher the transmission dynamics in the Asia Pacific. A preliminary study on sequences from the 3 cities identified 9 independent clusters belonging to 5 genotypes (1b, 2a, 2c, 3a, and 6a), each of which occurring in one city without overlapping except

for one 3a sequence from Taipei that was closely related genetically to the Hong Kong cluster. With the support of Health and Medical Research Fund, the team is beginning a new follow-up study by Next Generation Sequencing.

Suboptimal Seasonal Influenza Vaccination Uptake in Healthcare Workers

Seasonal influenza is an important health threat. Vaccination of healthcare workers could contribute to a reduction of disease burden and minimises virus transmission in the healthcare setting. Since 2005, the team has been, on a yearly basis, monitoring the vaccination coverage of nurses as a surrogate to reflect the health protection effects of seasonal influenza vaccination. Unfortunately, the study showed that the coverage had been falling from over 50% over 10 years ago to about 30% in recent years. Their latest study covering the period 2014 to 2018 showed that higher proportion of long term care facility (LTCF) nurses were not vaccinated because it was not a work requirement, compared to those based in hospitals/clinics. In 2018, the team’s effort was enhanced by the introduction of a comparative study to understand factors associated with vaccination uptake in Hong Kong, Singapore and Brunei. Effectiveness and adverse reactions aside, cultural values did play a role in shaping vaccination decisions.

Pre-exposure prophylaxis (PrEP) at work – (left) clinical trial poster; and (right) heat map showing temporal distribution of condomless anal intercourse (CLAI) in PrEP users



Source: Professor Shui-shan Lee

Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Shui-shan Lee	Daniel Yu Professor of Infectious Diseases
Ngai-sze Wong	International Scholarship Award, 22 nd International AIDS Conference at RAI Amsterdam, the Netherlands, 23-27 July 2018.
Donald Kwan	Li Po Chun Charitable Trust Fund Postgraduate Scholarship

Academic Editorship and Reviews

Member's Full Name	Details
Shui-shan Lee	Editor, International Journal of Infectious Diseases
Shui-shan Lee	Academic Editor, Medicine (Baltimore)
Shui-shan Lee	Assistant Editor, Addiction
Ngai-sze Wong	Academic Editor, PLoS One

Journal / Conference Reviews

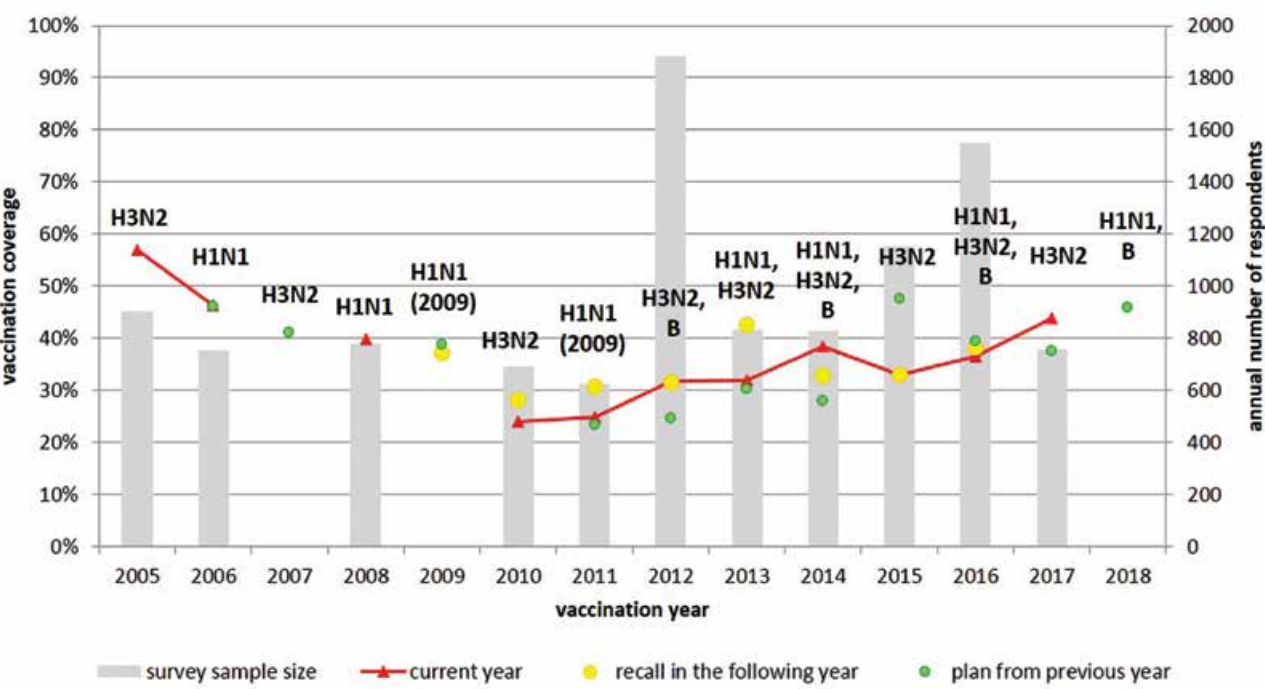
Member's Full Name	Details
Shui-shan Lee	Manuscript Reviewer, BMC Infectious Diseases
Shui-shan Lee	Manuscript Reviewer, Biomedical and Environmental Sciences
Shui-shan Lee	Manuscript Reviewer, AIDS & Behavior
Shui-shan Lee	Manuscript Reviewer, Lancet Respiratory Medicine
Shui-shan Lee	Conference Abstract Reviewer, 22 nd International AIDS Conference, Amsterdam, 23-27 July 2018
Shui-shan Lee	Conference Abstract Reviewer, 18 th International Congress on Infectious Diseases, Buenos Aires, 1-4 March 2018
Ngai-sze Wong	Manuscript Reviewer, Annals of Medicine
Ngai-sze Wong	Manuscript Reviewer, PLoS One
Ngai-sze Wong	Manuscript Reviewer, BMC Infectious Diseases
Ngai-sze Wong	Manuscript Reviewer, Sexually Transmitted Infections
Ngai-sze Wong	Manuscript Reviewer, International Journal of Environmental Research and Public Health
Kai-man Kam	Manuscript Reviewer, International Journal of Tuberculosis and Lung Diseases
Kai-man Kam	Manuscript Reviewer, Journal of Clinical Microbiology
Chin-man Poon	Manuscript Reviewer, PLoS One
Grace Chung-yan Lui	Manuscript Reviewer, International Journal of Tuberculosis and Lung Diseases
Grace Chung-yan Lui	Conference Abstract Reviewer, 3 rd Asia Pacific AIDS & Co-infections Conference (APACC), Hong Kong, 28-30 June 2018

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Shui-shan Lee	Pre-exposure prophylaxis with on-demand versus daily TDF/ FTC in MSM at high risk of HIV infection - a crossover study	Council for the AIDS Trust Fund	01/07/2018	30/06/2021	1,980,457
Shui-shan Lee	Update on clinical and public health HIV management in Hong Kong (HIV Manual)	Council for the AIDS Trust Fund	01/09/2018	31/08/2020	354,747
Ngai-sze Wong	The triggering factors of TB reactivation among HIV patients on highly active antiretroviral therapy (HAART)	Food and Health Bureau - Health and Medical Research Fund Commissioned Research on Control of Infectious Diseases (Phase III)	01/11/2018	31/10/2019	305,376
Denise Pui-chung Chan	Acceptability of STI test by post in Hong Kong	Centre for Health Protection	24/08/2018	23/08/2019	443,405
Grace Chung-yan Lui	Incidence and progression of fatty liver disease and liver fibrosis in newly diagnosed HIV-infected individuals initiating anti-retroviral therapy	Council for the AIDS Trust Fund	01/03/2018	28/02/2021	1,184,820
Grace Chung-yan Lui	Glycaemic control, diabetic complications, and mortality in HIV-infected individuals with diabetes	Council for the AIDS Trust Fund	01/02/2018	31/01/2019	225,082
Grace Chung-yan Lui	Optimization of antibiotics treatment duration in bloodstream infections with a serum procalcitonin-based algorithm	CUHK Research Committee - Direct Grant	30/06/2018	29/06/2019	147,831
Grace Chung-yan Lui	Outcomes of carbapenem-resistant Enterobacteriaceae infections in Hong Kong	Food and Health Bureau - Health and Medical Research Fund Commissioned Research on Control of Infectious Diseases (Phase III)	01/12/2018	30/11/2019	333,528
Denise Pui-chung Chan	A modelling study for assessing the effect of expended HCV testing and direct-acting antiviral therapy on the HCV epidemic among HIV-positive MSM in Hong Kong	Council for the AIDS Trust Fund	01/09/2018	31/08/2019	160,786

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Denise Pui-chung Chan	Seroepidemiology study of dengue infection among healthy adults in Hong Kong	Food and Health Bureau - Health and Medical Research Fund Commissioned Research on Control of Infectious Diseases (Phase III)	01/12/2018	30/11/2019	283,000
Chin-man Poon	Evaluation of the Seroepidemiology of Hepatitis A and B in the General Population for Informing the Development of New Hepatitis Vaccination Strategies in Hong Kong	Food and Health Bureau - Health and Medical Research Fund	01/06/2018	31/05/2020	1,196,480
Chin-man Poon	Time associated evolvement of networking pattern and its association with STD/ HIV transmission risk in HIV-positive MSM in Hong Kong	Council for the AIDS Trust Fund	01/10/2018	30/09/2019	348,549

Coverage of seasonal influenza vaccination in nurses and the prevailing influenza virus type by year, 2005 to 2018.



Source: Professor Shui-shan Lee

■ Publications

A. Journal Papers

1. Wong NS, Kwan TH, Tsang OTY, Lee MP, Yam WC, Lam W, Leung WS, Chan JMC, Ho KM, Lee SS. Pre-exposure prophylaxis (PrEP) for MSM in low HIV incidence places: should high risk individuals be targeted? *Scientific Reports*. 2018;8(1):11641. doi:10.1038/s41598-018-30101-9.
2. Yew WW, Yoshiyama T, Leung CC, Chan DP. Epidemiological, clinical and mechanistic perspectives of tuberculosis in older people. *Respirology*. 2018;23(6):567-575. doi:10.1111/resp.13303. [Review]
3. Wong NS, Chen L, Tucker JD, Zhao P, Goh BT, Poon CM, Yang L, Yang B, Zheng H, Huang S. Distribution of reported syphilis cases in South China: spatiotemporal analysis. *Scientific Reports*. 2018;8(1):9090. doi:10.1038/s41598-018-27173-y.
4. Kwok KO, Li KK, Lee SS, Chng PHY, Wei VWI, Ismail NH, Mosli N, Koh D, Lai A, Lim JW. Multi-centre study on cultural dimensions and perceived attitudes of nurses towards influenza vaccination uptake. *Journal of Hospital Infection*. November 2018. doi:10.1016/J.JHIN.2018.11.017.
5. Song R, Guan S, Lee SS, Chen Z, Chen C, Han L, Xu Y, Li A, Zeng H, Ye H, Zhang F. Late or lack of vaccination linked to importation of yellow fever from Angola to China. *Emerging Infectious Diseases*. 2018;24(7):1383-1386. doi:10.3201/eid2407.171868. [Letter]
6. Yew WW, Chan DP, Singhal A, Zhang Y, Lee SS. Does oxidative stress contribute to adverse outcomes in HIV-associated TB? *Journal of Antimicrobial Chemotherapy*. 2018;73(5):1117-1120. doi:10.1093/jac/dkx509.
7. To KW, Lee SS. HIV pre-exposure prophylaxis in South East Asia: A focused review on present situation. *International Journal of Infectious Diseases*. 2018;77:113-117. doi:10.1016/j.ijid.2018.10.027. [Review]
8. Lee SS, Petersen E. Overcoming 'purview paradox' to make way for the effective implementation of PrEP in preventing HIV transmission. *International Journal of Infectious Diseases*. 2018;77:105-106. doi:10.1016/j.ijid.2018.10.018. [Editorial]
9. Wong NS, Lee S, Lee SS. Differing pattern of influenza vaccination uptake in nurses between clinical and long term care facilities setting, 2014-2018. *International Journal of Infectious Diseases*. 2018;75:8-10. doi:10.1016/j.ijid.2018.07.009. [Short Communication]
10. To KW, Kam KM, Chan DPC, Yip WH, Chan KP, Lo R, Ng S, Ngai J, Lee SS. Utility of GeneXpert in analysis of bronchoalveolar lavage samples from patients with suspected tuberculosis in an intermediate-burden setting. *Journal of Infection*. 2018;77(4):296-301. doi:10.1016/j.jinf.2018.06.011.

B. Conference Papers

1. Poon CM, Lee SS. Spatio-temporal patterns of annual activity of hand, foot and mouth disease between 2005 and 2016 in Hong Kong. In: *XVIII International Congress on Infectious Diseases*; Buenos Aires, Argentina; 2018 Mar 1-4.
2. Chan DPC, Lam JC, Chan TC, Liang VD, Ng TK, Lee SS, Kam KM. Molecular epidemiology of *Mycobacterium tuberculosis* in Hong Kong showed reactivation cases took over recently transmitted cases. In: *XVIII International Congress on Infectious Diseases*; Buenos Aires, Argentina; 2018 Mar 1-4.
3. Chan DPC, Ho S, Lam JC, Chan TC. Community-based HIV and STI screening in men who have sex with men in Hong Kong. In: *XVIII International Congress on Infectious Diseases*; Buenos Aires, Argentina; 2018 Mar 1-4.

4. Kwan TH, Lee SS. Self-perceived body image types of MSM and its association with HIV risk behaviours: results from factor analysis. In: *15th Annual Scientific Meeting of Stanley Ho Centre for Emerging Infectious Diseases*; Hong Kong, Hong Kong; 2018 Jun 12.
5. Kwan TH, Lui GCY, Wong NS, Lee KCK, Chan DPC, Lee SS. The pattern of risk compensation in MSM enrolled in a pilot PrEP project. In: *3rd Asia Pacific Conference on AIDS and co-infections*; Hong Kong, Hong Kong; 2018 Jun 28-30.
6. Wong NS, Kwan TH, Chan KCW, Tsang OTY, Lee MP, Chan DPC, To SWC, Yam WC, Lee SS. Derivation of population mixing patterns from virus sequence data and their impacts on the modelling of HIV epidemics in MSM. In: *3rd Asia Pacific Conference on AIDS and co-infections*; Hong Kong, Hong Kong; 2018 Jun 28-30.
7. Kwan TH, Wong NS, Lee SS. HIV infected heroin users' 1-year discontinuation rate from methadone maintenance treatment: results from survival analysis. In: *3rd Asia Pacific Conference on AIDS and co-infections*; Hong Kong, Hong Kong; 2018 Jun 28-30.
8. Kwan TH, Lee SS. Differential preference of PrEP modalities among men who have sex with men. In: *3rd Asia Pacific Conference on AIDS and co-infections*; Hong Kong, Hong Kong; 2018 Jun 28-30.
9. Poon SCM, Wong NS, Leung J, Lee CK, Lee SS. Awareness and acceptance of blood donors as regards the relaxation of blood donation deferral policy for men who have sex with men in Hong Kong. In: *3rd Asia Pacific Conference on AIDS and co-infections*; Hong Kong, Hong Kong; 2018 Jun 28-30.
10. Wong NS, Chan KCW, Chan W, Lin A, Leung CC, Lee SS. TB incidence among HIV-patients tested positive at baseline LTBI screening. In: *3rd Asia Pacific Conference on AIDS and co-infections*; Hong Kong, Hong Kong; 2018 Jun 28-30.
11. Wong NS, Leung CC, Chan KCW, Chan WK, Lin AWC, Lee SS. The importance and clinical relevance of baseline LTBI screening in HIV patients. In: *22nd International AIDS Conference*; Amsterdam, Netherlands; 2018 Jul 23-27.
12. Kwan TH, Wong NS, Chan KCW, Tsang OTY, Leung WS, Ho KM, Lee MP, Chan SN, Lui GCY, Lee SS. Behavioural profile of viral hepatitis co-infected MSM at HIV diagnosis. In: *22nd International AIDS Conference*; Amsterdam, Netherlands; 2018 Jul 23-27.
13. Kwan TH, Wong NS, Wong ELY, Yeoh EK, Poon CM, Lee SS. Healthcare service utilisation and health outcomes among HIV-positive methadone users: a record linkage study. In: Joint Hong Kong College of Community Medicine (HKCCM) and Royal Australasian College of Medical Administrators (RACMA) Conference; Hong Kong, Hong Kong; 2018 Sep 5-8.
14. Kwan TH, Wong NS, Lui GCY, Lee KCK, Lee SS. Acceptability of an incentivised PrEP programme for men who have sex with men at high risk of HIV infection in Hong Kong: an implementation study. In: *The Lancet and the Chinese Academy of Medical Sciences Health Summit*; Beijing, China; 2018 Oct 27-28.
15. Kwan TH, Wong NS, Lui GCY, Lee KCK, Lee SS. Adherence of MSM Participating in a partially self-financed pilot PrEP project and its association with behavioural risk profiles. In: *HIV Glasgow 2018*; Glasgow, United Kingdom; 2018 Oct 28-31.
16. Wong NS, Wong BCK, Chan DPC, Liang DC, Lee SS. Concurrent transmission of HCV and bacterial STI in HIV-infected MSM. In: *HIV Glasgow 2018*; Glasgow, United Kingdom; 2018 Oct 28-31.

08

MOLECULAR MICROBIOLOGY

Clinical Microbial Genomics

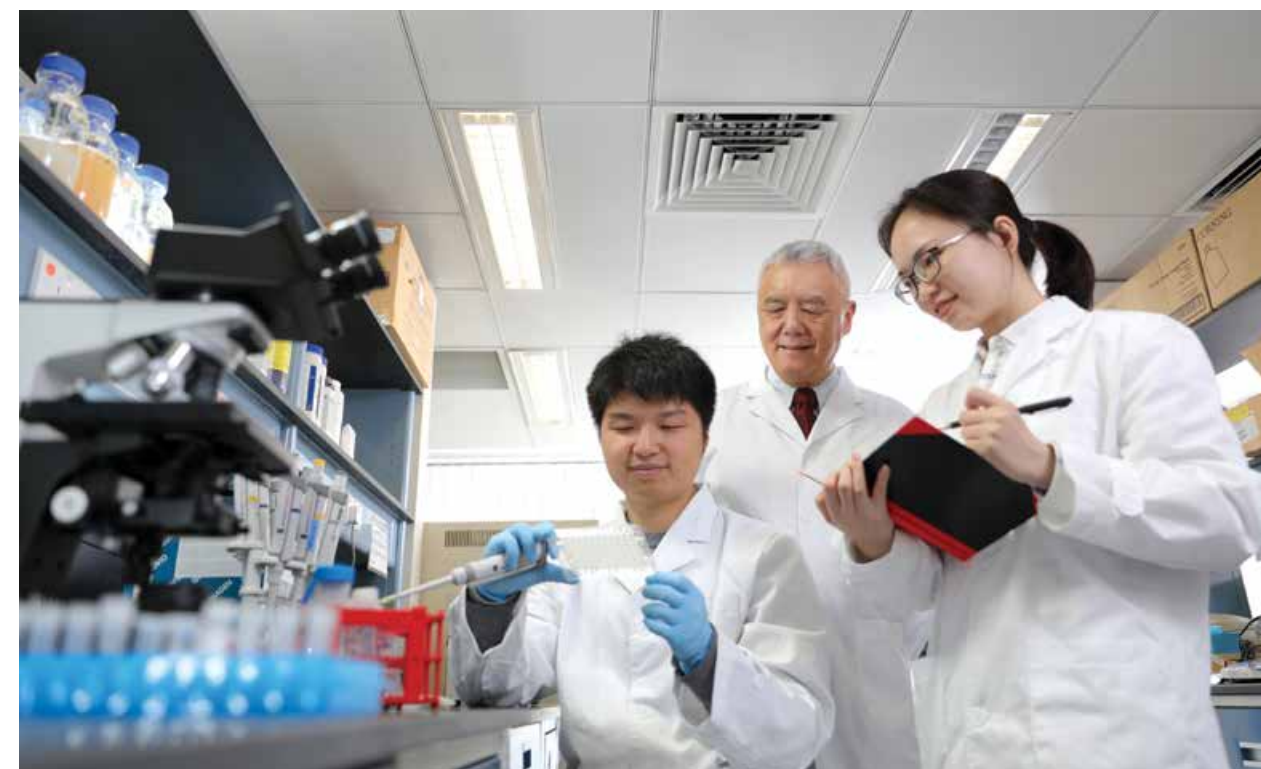


Principal Investigator
Professor Guoping Zhao



Team

Yuchen Channy Wei



■ Research Progress Summary

Mycobacterium tuberculosis (Mtb), the causative agent of tuberculosis, is an extraordinary human pathogen that has latently infected one-third of the world population and causes 9 million new cases and about 1.5-2 million deaths each year worldwide.

The Research team led by Professor Guoping Zhao has been studying the genomics of *Mtb* since 2008 via sequencing the genome of the classical avirulent strain H37Ra (*PLoS ONE* 3(6): e2375). His team demonstrated that mycobacterial MazG is a 5-OH-dCTP-specific housecleaning enzyme involved in a pathway preventing the CG to TA mutation and ensuring the persistent infection of *Mtb* in mouse (*PLoS Pathog* 9: e1003814. 2013). The team further showed that mycobacterial MazG counteracts antibiotic killing of stationary-phase mycobacteria that leads to the novel mechanism of which, antibiotics induced oxidation to dCTP contributed to antibiotic lethality via induction of DNA double-strand breaks (DSB) (*PNAS* 115(9), 2210-2215, 2018).

Professor Zhao's team has been implementing systems and synthetic biology research strategy upon bacteria since 2008. The team's decade's effort was rewarded by three significant breakthroughs in 2018 with respect to (1) Genome synthesis/editing (*Nature* 560, 331-335), (2) Revealing the trans-cleavage activity of Cas12a (*Cell Research* 28, 491-493) and developed a novel nucleic acid detection system — HOLMES (*Cell Discovery* 4, 20), (3) Identification of a novel ornithine-ammonia cycle in nitrogen fixation cyanobacteria based on metabolic flux technology (*Nat Chem Biol* 14, 575-581).

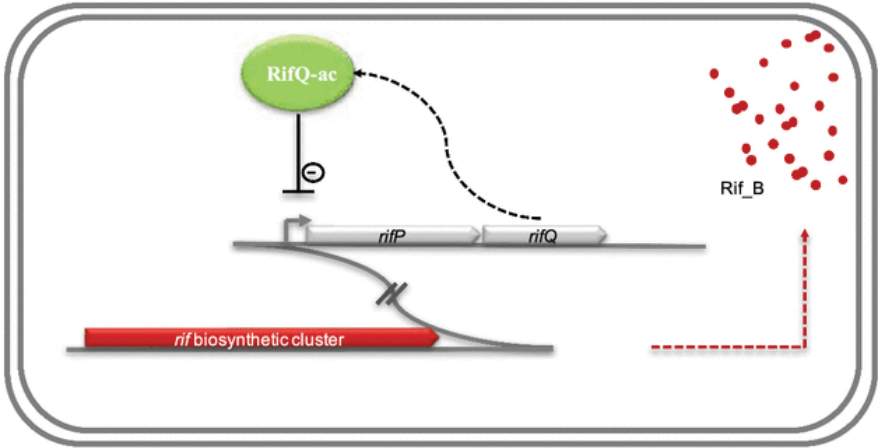
Professor Zhao's team is continuing to explore the mechanisms of physiology and pathology of *Mtb* and other pathogenic bacteria, employing these advanced technology and research strategy — systems and synthetic biology.



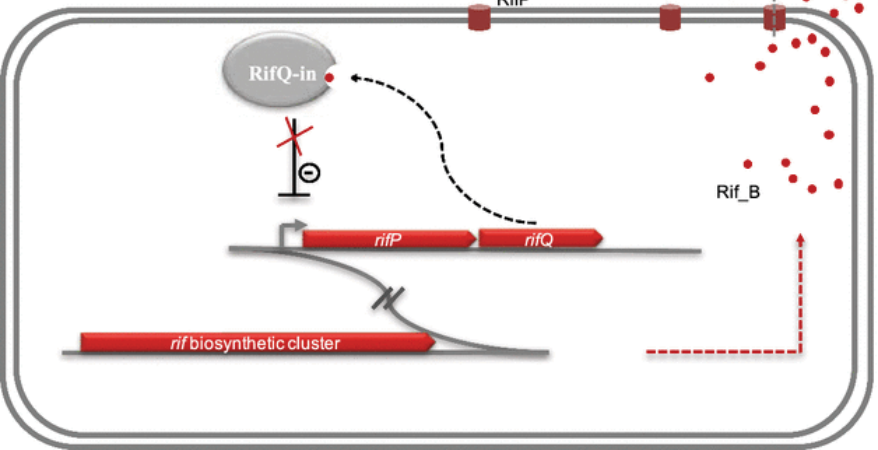
Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount
Guoping Zhao	面向天然產物生物合成的人工細胞	中國科學院國際大科學計畫培育專項	01/01/2018	31/12/2022	RMB 8,100,000

Early growth phase



Late growth phase



A proposed feedback model for RifQ-mediated regulation of rifamycin biosynthesis and export in *A. mediterranei*. At the early growth phase, RifQ represses Rif_B export, accelerating the accumulation of intracellular Rif_B. When the intracellular Rif_B concentration reaches a threshold, rifamycin B was able to inactivate RifQ by either direct binding or an unknown manner, and the export of Rif_B is remarkably promoted, reducing the intracellular concentration of Rif_B

Source: Lei C, Wang J, Liu Y, Liu X, Zhao G, Wang J. A feedback regulatory model for RifQ-mediated repression of rifamycin export in *Amycolatopsis mediterranei*. *Microbial Cell Factories*. 2018;17(1):14. doi:10.1186/s12934-018-0863-5

Publications

A. Journal Papers

1. Fan XY, Tang BK, Xu YY, Han AX, Shi KX, Wu YK, Ye Y, Wei M, Niu C, Wong KW, Zhao GP, Lyu LD. Oxidation of dCTP contributes to antibiotic lethality in stationary-phase mycobacteria. *Proceedings of the National Academy of Sciences of the United States of America*. 2018;115(9):2210-2215. doi:10.1073/pnas.1719627115.
2. Lei C, Wang J, Liu Y, Liu X, Zhao G, Wang J. A feedback regulatory model for RifQ-mediated repression of rifamycin export in *Amycolatopsis mediterranei*. *Microbial Cell Factories*. 2018;17(1):14. doi:10.1186/s12934-018-0863-5.
3. Li SY, Cheng QX, Liu JK, Nie XQ, Zhao GP, Wang J. CRISPR-Cas12a has both cis- and trans-cleavage activities on single-stranded DNA. *Cell Research*. 2018;28(4):491-493. doi:10.1038/s41422-018-0022-x.
4. Li SY, Cheng QX, Wang JM, Li XY, Zhang ZL, Gao S, Cao RB, Zhao GP, Wang J. CRISPR-Cas12a-assisted nucleic acid detection. *Cell Discovery*. 2018;4(1):20. doi:10.1038/s41421-018-0028-z. [Letter]
5. Li Z, Liu X, Wang J, Wang Y, Zheng G, Lu Y, Zhao G, Wang J. Insight into the Molecular Mechanism of the Transcriptional Regulation of amtB Operon in *Streptomyces coelicolor*. *Frontiers in Microbiology*. 2018;9. doi:10.3389/fmicb.2018.00264.
6. Shao Y, Lu N, Wu Z, Cai C, Wang S, Zhang LL, Zhou F, Xiao S, Liu L, Zeng X, Zheng H, Yang C, Zhao Z, Zhao G, Zhou JQ, Xue X, Qin Z. Creating a functional single-chromosome yeast. *Nature*. 2018;560(7718):331-335. doi:10.1038/s41586-018-0382-x.
7. Zhang H, Liu Y, Nie X, Liu L, Hua Q, Zhao GP, Yang C. The cyanobacterial ornithine-ammonia cycle involves an arginine dihydrolase. *Nature Chemical Biology*. 2018;14(6):575-581. doi:10.1038/s41589-018-0038-z.

08 MOLECULAR MICROBIOLOGY

Clinical Meta-genomics



Principal Investigator
Professor Sunny Wong



Team

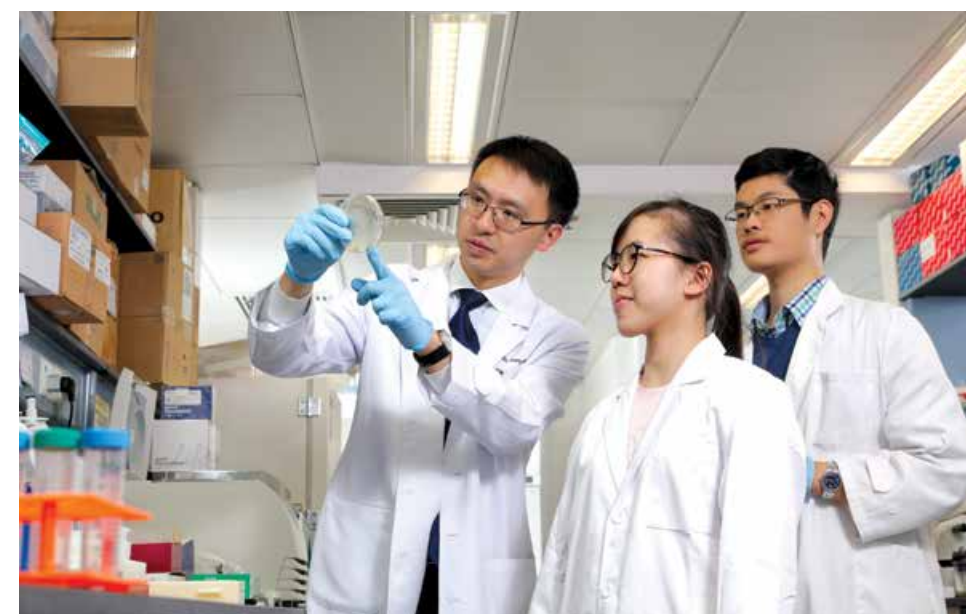
Thomas Kwong | Emily Kong |
Timothy Tipoe | T. C. Chow

■ Research Progress Summary

The major research focus of the research team is to investigate the gut host-microbe relationships in context of digestive diseases, particularly gastrointestinal cancers and infections. Building upon their previous works (Wong *et al*, *Gastroenterology* 2017) (Dai *et al*, *Microbiome* 2018), the research team led by Professor Sunny Wong has continued to study the metagenomic landscape in colorectal and gastric cancer. Their works have led to publication of a major study to report the risk of colorectal cancer in patients who have been had bacteremia (Kwong *et al*, *Gastroenterology* 2018). These findings confirm the known associations between colorectal cancer and certain bacterial species such as *Bacteroides fragilis* and *Streptococcus bovis*, but also highlight the role of less well-known microbes including *Peptostreptococcus spp*, *Clostridium septicum* and *Gemella morbillorum*. Many of the identified bacteria are typically part of the colonic flora, and their presence in the bloodstream suggests possible disruption of epithelial barriers by pre-existing neoplasia and associated proinflammatory microenvironment. This study also highlights the need for colonic workups for patients with bacteremia involving these species. Due to the significant impact, this study was highlighted in several journals and media including the *NEJM*

Journal Watch, *MedPage Today*, *Mr Gut* and others. Furthermore, the team has continued to study on gastrointestinal infections including those by *Clostridioides difficile*. Following their previous works on the epidemiology and antibiotic resistance patterns of *C difficile* in Hong Kong (Ho J *et al*, *Emerg Infect Dis* 2017) (Chow VC *et al*, *Sci Rep* 2017), the collaborative works have further depicted the virulence mechanisms of the infection (Chan H *et al*, *J Cell Mol Med* 2018). They are prospectively collecting clinical samples for further works in these areas.

The team has been an active player for dissemination of scientific knowledge in 2018. Members of the research team have presented at international conferences, including the International *Clostridium difficile* Symposium, the World Endoscopy Organisation Workshops, the Asia Pacific Digestive Week and other international meetings. Collectively, these translational works have brought them closer to understanding the mechanisms and translating discoveries on these diseases. These works are only possible with the enormous support from the Li Ka Shing Institute of Health Sciences.



■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Sunny Wong	Distinguished Research Paper Award for Young Investigators, Hong Kong College of Physicians

Fellowships

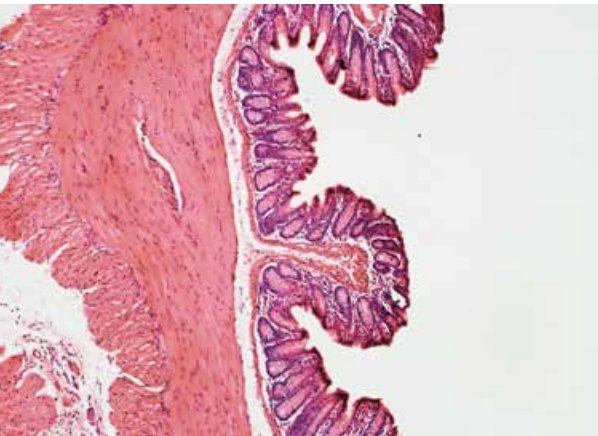
Member's Full Name	Details
Sunny Wong	Fellowship of the Royal College of Pathologists (UK)

Academic Editorships and Reviews

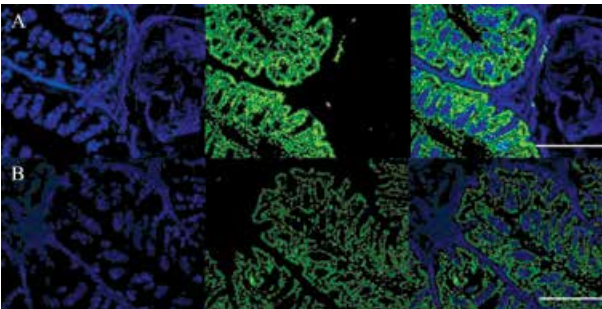
Member's Full Name	Details
Sunny Wong	Editor, Journal of Gastroenterology and Hepatology (since Aug 2018)
Sunny Wong	Guest Editor, Frontiers in Microbiology
Sunny Wong	Guest Editor, Seminars in Cancer Biology (till Aug 2018)
Sunny Wong	Editorial Board Member, Scientific Reports

Journal / Conference Reviews

Member's Full Name	Details
Sunny Wong	Conference Abstract Reviewer, Asia Pacific Digestive Week
Sunny Wong	Conference Abstract Reviewer, Hawaii International Conference on System Sciences



Histology of the colonic mucosae in a model mouse after oral gavage of potential carcinogenic bacteria
Source: Professor Sunny Wong



Fluorescence images of small intestines in a model mouse after oral gavage of experimental nanoparticles
Source: Professor Sunny Wong

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Sunny Wong	A Comparative Study to Investigate the Gut Microbiota of HIV Patients with Metabolic Syndrome	Council for the AIDS Trust Fund	01/04/2018	31/03/2019	453,735
Sunny Wong	Combining Stool Microbial DNA and Micro-RNA Markers for Detection of Colorectal Neoplasia	Hong Kong College of Physicians Young Investigator Research Grant	01/10/2016	30/09/2018	50,000
Sunny Wong	Clarifying the Mechanisms of Ribotype 002 Virulence in <i>Clostridium Difficile</i> Infection	Research Grants Council – General Research Fund	01/01/2017	31/12/2020	1,050,589
Sunny Wong	Gut Microbiota Across Early Stages of Synucleinopathy: From High-risk Relatives, REM Sleep Behavior Disorder to Early Parkinson's Disease	Food and Health Bureau - Health and Medical Research Fund	01/01/2018	31/05/2020	1,190,664
Sunny Wong	Genome-wide CRISPR Screen for Host Factors Associated with Norovirus Infections in Stem Cell-derived Human Intestinal Enteroid Model	Research Grants Council – General Research Fund	01/01/2018	31/12/2020	1,132,030
Sunny Wong	Elucidating the Role of Autophagy in the Pathogenicity of <i>Clostridium Difficile</i> Infection	Food and Health Bureau - Health and Medical Research Fund	10/09/2016	09/09/2018	1,199,040

■ Publications

A. Journal Papers

1. Kwong TNY, Wang X, Nakatsu G, Chow TC, Tipoe T, Dai RZW, Tsoi KKK, Wong MCS, Tse G, Chan MTV, Chan FKL, Ng SC, Wu JCY, Wu WKK, Yu J, Sung JJY, Wong SH. Association Between Bacteremia From Specific Microbes and Subsequent Diagnosis of Colorectal Cancer. *Gastroenterology*. 2018;155(2):383-390.e8. doi:10.1053/j.gastro.2018.04.028.
2. Dai Z, Coker OO, Nakatsu G, Wu WKK, Zhao L, Chen Z, 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;6(1):70. doi:10.1186/s40168-018-0451-2.
3. Chan H, Zhao S, Zhang L, Ho J, Leung CCH, Wong WT, Tian Y, Liu X, Kwong TNY, Chan RCY, Yu SSB, Wang MHT, Tse G, Wong SH, Chan MTV, Wu WKK. *Clostridium difficile* toxin B induces autophagic cell death in colonocytes. *Journal of Cellular and Molecular Medicine*. 2018;22(4):2469-2477. doi:10.1111/jcmm.13555.
4. Tipoe TL, Wu WKK, Chung L, Gong M, Dong M, Liu T, Roever L, Ho J, Wong MCS, Chan MTV., Tse G, Wu JCY, Wong SH. Plasminogen Activator Inhibitor 1 for Predicting Sepsis Severity and Mortality Outcomes: A Systematic Review and Meta-Analysis. *Frontiers in Immunology*. 2018;9. doi:10.3389/fimmu.2018.01218
5. Dai Z, Wong SH, Yu J, Wei Y. Batch effects correction for microbiome data with dirichlet-multinomial regression. *Bioinformatics 2019*; 35(5): 807-814. [Epub in 2018]
6. Zuo T, Wong SH, Cheung CP, Lam K, Lui R, Cheung K, Zhang F, Tang W, Ching JYL, Wu JCY, Chan PKS, Sung JJY, Yu J, Chan FKL, Ng SC. Gut fungal dysbiosis correlates with reduced efficacy of fecal microbiota transplantation in *Clostridium difficile* infection. *Nature Communications*. 2018;9(1):3663. doi:10.1038/s41467-018-06103-6.
7. Zuo T, Wong SH, Lam K, Lui R, Cheung K, Tang W, Ching JYL, Chan PKS, Chan MCW, Wu JCY, Chan FKL, Yu J, Sung JJY, Ng SC. Bacteriophage transfer during faecal microbiota transplantation in *Clostridium difficile* infection is associated with treatment outcome. *Gut*. 2018;67:634-643. doi:10.1136/gutjnl-2017-313952.
8. Nakatsu G, Zhou H, Wu WKK, Wong SH, Coker OO, Dai Z, Li X, Szeto CH, Sugimura N, Lam TYT, Yu ACS, Wang X, Chen Z, Wong MCS, Ng SC, Chan MTV, Chan PKS, Chan FKL, Sung JJY, Yu J. Alterations in Enteric Virome Are Associated With Colorectal Cancer and Survival Outcomes. *Gastroenterology*. 2018;155(2):529-541.e5. doi:10.1053/j.gastro.2018.04.018.
9. Coker OO, Nakatsu G, Dai RZ, Wu WKK, Wong SH, Ng SC, Chan FKL, Sung JJY, Yu J. Enteric fungal microbiota dysbiosis and ecological alterations in colorectal cancer. *Gut 2019*; 68(4): 654-662. doi:10.1136/gutjnl-2018-317178. [Epub in 2018]
10. 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. doi:10.1136/gutjnl-2017-314281.
11. Zhang L, Hu W, Cho CH, Chan FK, Yu J, Fitzgerald JR, Cheung CK, Xiao ZG, Shen J, Li LF, Li MX, Wu JC, Ling TK, Chan JY, Ko H, Tse G, Ng SC, Yu S, Wang MH, Gin T, Ashktorab H, Smoot DT, Wong SH, Chan MT, Wu WK. Reduced lysosomal clearance of autophagosomes promotes survival and colonization of *Helicobacter pylori*. *Journal of Pathology*. 2018;244(4):432-444. doi:10.1002/path.5033.

12. Wu WKK, Sun R, Zuo T, Tian Y, Zeng Z, Ho J, Wu JCY, Chan FKL, Chan MTV, Yu J, Sung JJY, Wong SH, Wang MH, Ng SC. A novel susceptibility locus in MST1 and gene-gene interaction network for Crohn's disease in the Chinese population. *Journal of Cellular and Molecular Medicine*. 2018;22(4):2368-2377. doi:10.1111/jcmm.13530.
13. Wang X, Li X, Zhang L, Wong SH, Wang MHT, Tse G, Dai RZW, Nakatsu G, Coker OO, Chen Z, Ko H, Chan JYK, Liu T, Cheng CHK, Cheng ASL, To KF, Plewczynski D, Sung JJY, Yu J, Gin T, Chan MTV, Wu WKK. Oncogenes expand during evolution to withstand somatic amplification. *Annals of Oncology*. 2018;29(11):2254-2260. doi:10.1093/annonc/mdy397.
14. Zhang L, Zhang Y, Wong SH, Law PTY, Zhao S, Yu J, Chan MTV., Wu WKK. Common Deregulation of Seven Biological Processes by MicroRNAs in Gastrointestinal Cancers. *Scientific Reports*. 2018;8(1):3287. doi:10.1038/s41598-018-21573-w.
15. Cao L, Wang S, Zhang Y, Wong KC, Nakatsu G, Wang X, Wong S, Ji J, Yu J. Zinc-finger protein 471 suppresses gastric cancer through transcriptionally repressing downstream oncogenic PLS3 and TFAP2A. *Oncogene*. 2018;37(26):3601-3616. doi:10.1038/s41388-018-0220-5.
16. Li X, Xu W, Kang W, Wong SH, Wang M, Zhou Y, Fang X, Zhang X, Yang H, Wong CH, To KF, Chan SL, Chan MTV, Sung JJY, Wu WKK, Yu J. Genomic analysis of liver cancer unveils novel driver genes and distinct prognostic features. *Theranostics*. 2018;8(6):1740-1751. doi:10.7150/thno.22010.
17. Degenhardt F, Wendorff M, Wittig M, Ellinghaus E, Datta LW, Schembri J, Ng SC, Rosati E, Hubenthal M, Ellinghaus D, Jung ES, Lieb W, Abedian S, Malekzadeh R, Cheon JH, Ellul P, Sood A, Midha V, Bk T, Wong SH, Schreiber S, Yamazaki K, Kubo M, Boucher G, Rioux J, Lenz TL, Brant SR, Franke A. Construction and benchmarking of a multi-ethnic reference panel for the imputation of hla class i and ii alleles. *Human Molecular Genetics 2018*. doi: 10.1093/hmg/ddy443. [Epub ahead of print]
18. Tian Y, Liu X, Jia M, Yu H, Lichtner P, Shi Y, Meng Z, Kou S, Ho IHT, Jia B, Cheng BCP, Lam CKM, Tsang S, Wong SH, Yu J, Cheng CHK, Gin T, Wu WKK, Chen Z, Chan MTV. Targeted Genotyping Identifies Susceptibility Locus in Brain-derived Neurotrophic Factor Gene for Chronic Postsurgical Pain. *Anesthesiology*. 2018;128(3):587-597. doi:10.1097/ALN.0000000000001977.

B. Book / Book Chapter

1. Lau HS and Wong SH (2018). Obesity, Microbiota and Non-Alcoholic Fatty Liver Disease. In: Yu J (Ed). Obesity, Fatty Liver and Liver Cancer. *Advances in Experimental Medicine and Biology, vol 1061*. Singapore: Springer Nature.

09 INFLAMMATORY DISEASES



Principal Investigator
Professor Hui-yao Lan



Team

Xiaoru Lan | Patrick MK Tang | Guangyu Lian | Thomas SK Mak | Biao Wei | Choilai Chung | Hui Yang |
Yuyan Qin | Huijun He | Jie Li | Jiaoyi Chen | Yueyu Gu | Philip CT Tang | Jinhong Li | Junzhe Chen |
Lin Wang | Jingyi Sheng | Qixia Shen | Jian Zhang | Yongke You | Honglian Wang | Zhongjing Hu |
Wingyin Lam | Travis HW To | Vivian Xue | Jing Zhu



■ Research Progress Summary

In 2018, the research team of Inflammatory Diseases has secured a number of grants for their research projects, including a General Research Fund from the Hong Kong Research Grants Council for the study of Smad3-dependent long non-coding RNAs (lncRNAs) in diabetic kidney disease, and a Health and Medical Research Fund for the treatment of diabetes by inhibiting the TGF- β /Smad3 signalling pathway. Meanwhile, the development of new drugs to inhibit Smad3 phosphorylation for treatment of cancer has been supported by the Hong Kong Innovation and Technology Fund. These have greatly encouraged the team to continue the research into the new mechanisms of TGF- β /Smad3 signalling in diabetic complications, tissue fibrosis and tumour microenvironment. Depending on their novel finding that the deletion of Smad3 prevents the phenotype as well as heart and kidney complications in type 2 diabetic mice, they successfully treated type 2 diabetic db/db mice by targeting Smad3-dependent long non-coding RNAs (lncRNAs) which led to a publication in pioneering diabetic journal (*Diabetes*.2018;67:731-44.) They have also successfully treated obstructive renal fibrosis by targeting TGF- β /Smad3-dependent lncRNAs which was published in *Molecular Therapy* (2018; 26:148-161).

The team is also working hard to develop new drugs with the cohort. They found that mice lacking Smad3 are largely resistant to tumour growth, invasion, metastasis and death. Smad3 targeted nanomedicines and novel Smad3 inhibitors as anticancer drugs and immunotherapy is making progress in animal experiments in their laboratory. Research into the Smad3-dependent cancer microenvironment has improved natural killer (NK) cell immunotherapy (*Cancer Immunology Research*. 2018; 6:965-977) and traditional Chinese medicine therapy brings new light to the treatment of cancer as shown in *Molecular Therapy* (2018; 26:2255-2266). The team was also awarded an Innovation and Technology Fund for the development of nanomedicine for cancer treatment. Research on the Smad3-dependent tumour microenvironment will continue to be the research direction of the team in the next few years.

The team has always attached importance to academic cooperation and communications. This year, team members have delivered speeches and awarded at the international, regional and local academic conferences which improved the academic standards and enhanced the reputation of The Chinese University of Hong Kong. Research training is another goal of their team. Over the past year, 5 PhD students, 7 post-doctoral fellows (2 from Hong Kong-China Scholar Program) and 6 researchers have been trained in their laboratory. Based on the excellent progress of all research projects, the team released 17 peer-reviewed papers in 2018.

In summary, 2018 was a year worthy of our respect, and Professor Lan and his team look forward to achieving even greater goals in 2019.

■ Research and Scholarship

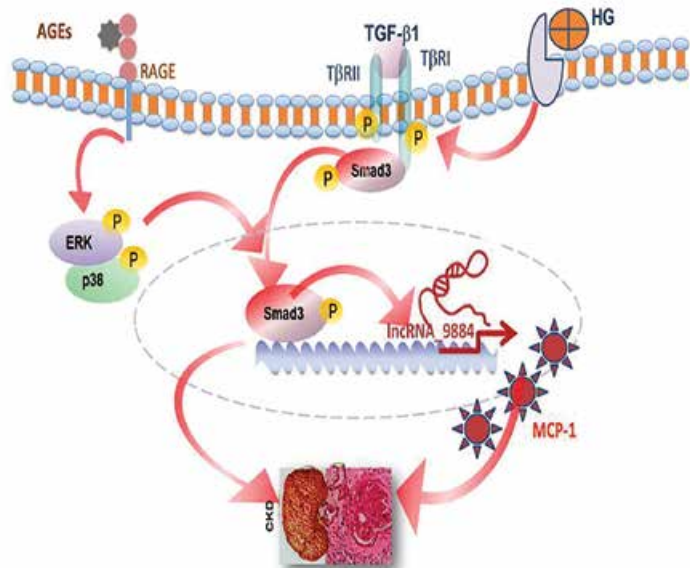
Research Awards and Recognitions

Member's Full Name	Details
Patrick MK Tang	Young Investigators Award, International Society of Nephrology Frontiers, Tokyo, 25 Feb 2018
Patrick MK Tang	Young Investigators Award, The East Meets West Symposium, Hong Kong, 30 Sep 2018
Patrick MK Tang	Poster Award, The State Key Lab of Oncology in South China Retreat meeting, Zhuhai, 26-27 May 2018
Hui-yao Lan	Consultant of Guangdong, Hong Kong and Macao Medical Health and Pathology Alliance Committee, 2019-2022
Hui-yao Lan	Expert Consultation on Hygiene and Health Cooperation in Guangdong, Hong Kong and Macau Greater Bay Area, 2018-2021
Hui-yao Lan	Honorary Chairperson of the 1 st Board of Specialty Committee of Research on Safety of Clinical Usage of Drugs of Would Federation of Chinese Medicine Societies, 2016-2020
Hui-yao Lan	Vice Chairperson of 2 nd Board of Specialty Committee of Immunology of TCM of World Federation of Chinese Medicine Societies, 2018-2023

Grants and Consultancy

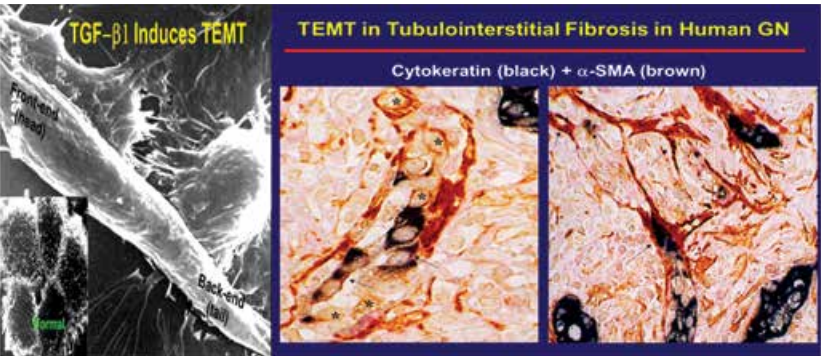
Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Hui-yao LAN	Development of a novel nanodrug SCND-SIS3 for Effective Anticancer Therapy	Innovation and Technology Commission - Innovation and Technology Fund	01/01/2018	30/06/2019	1,393,800
Hui-yao LAN	The Pathogenic role and therapeutic implication of a novel lncRNA np_9884 in type-2 diabetic kidney disease	Research Grants Council – General Research Fund	01/01/2018	31/12/2020	1,222,113
Hui-yao LAN	Novel Mechanisms and Therapeutic Implication of P2Y12 inhibitor, Clopidogrel, in Renal Fibrosis	Food and Health Bureau – Health and Medical Research Fund	01/07/2018	30/06/2020	1,200,000

TGFβ/Smad signaling is a key pathway leading organ fibrosis



TGF- β /Smad signalling is a key pathway leading organ fibrosis

Source: Professor Hui-yao Lan



TGF- β induces tubular epithelial-myofibroblast transition (TEMT) *in vitro* and in fibrosing kidney

Source: Professor Hui-yao Lan

■ Publications

A. Journal Papers

1. Lian GY, Wang QM, Tang PMK, Zhou S, Huang XR, Lan HY. Combination of asiatic acid and naringenin modulates NK cell anti-cancer immunity by rebalancing Smad3/Smad7 signaling. *Molecular Therapy*. 2018;26(9):2255-2266. doi:10.1016/j.ymthe.2018.06.016.
2. Wang QM, Tang PMK, Lian GY, Li C, Li J, Huang XR, To KF, Lan HY. Enhanced cancer immunotherapy with Smad3-silenced NK-92 cells. *Cancer Immunology Research*. 2018;6(8):965-977. doi:10.1158/2326-6066.CIR-17-0491.
3. Li J, Tang Y, Tang PMK, Lv J, Huang X, Carlsson-Skewir C, Da Costa L, Aspesi A, Fröhlich S, Szczęśniak P, Lacher P, Klug J, Meinhardt A, Fingerle-Rowson G, Gong R, Zheng Z, Xu A, Lan H. Blocking macrophage migration inhibitory factor protects against cisplatin-induced acute kidney injury in mice. *Molecular Therapy*. 2018;26(10):2523-2532. doi:10.1016/j.ymthe.2018.07.014.
4. Tang PMK, Zhou S, Li CJ, Liao J, Xiao J, Wang QM, Lian GY, Li J, Huang XR, To KF, NG CF, Chong CCN, Ma RCW, Lee TL, Lan HY. The proto-oncogene tyrosine protein kinase Src is essential for macrophage-myofibroblast transition during renal scarring. *Kidney International*. 2018;93(1):173-187. doi:10.1016/j.kint.2017.07.026.
5. Tang PMK, Tang PCT, Chung JYF, Hung JSC, Wang QM, Lian GY, Sheng J, Huang XR, To KF, Lan HY. A novel feeder-free system for mass production of murine natural killer cells in vitro. *Journal of Visualized Experiments*. 2018;(131). doi:10.3791/56785.
6. Liu BC, Tang TT, Lv LL, Lan HY. Renal tubule injury: a driving force toward chronic kidney disease. *Kidney International*. 2018;93(3):568-579. doi:10.1016/j.kint.2017.09.033. [Review]
7. Zhang Y, Meng XM, Huang XR, Lan HY. The preventive and therapeutic implication for renal fibrosis by targeting TGF- β /Smad3 signaling. *Clinical Science*. 2018;132(13):1403-1415. doi:10.1042/CS20180243.
8. Tang Y, Mak SK, Xu AP, Lan HY. Role of C-reactive protein in the pathogenesis of acute kidney injury. *Nephrology*. 2018;23:50-52. doi:10.1111/nep.13454.
9. Tang PMK, Zhang YY, Mak TSK, Tang PCT, Huang XR, Lan HY. Transforming growth factor- β signalling in renal fibrosis: from Smads to non-coding RNAs. *Journal of Physiology*. 2018;596(16):3493-3503. doi:10.1113/JP274492. [Review]
10. Tang PMK, Zhang YY, Lan HY. LncRNAs in TGF- β -driven tissue fibrosis. Non-coding RNA. 2018;4(4):26. doi:10.3390/ncrna4040026. [Review]
11. Tang Y, Liang P, Chen J, Fu S, Liu B, Feng M, Lin B, Lee B, Xu A, Lan HY. The baseline levels and risk factors for high-sensitive C-reactive protein in Chinese healthy population. *Immunity & Ageing*. 2018;15(1):21. doi:10.1186/s12979-018-0126-7.
12. Lan HY, Nikolic-Paterson DJ. Editorial: Advances in mechanisms of renal fibrosis. *Frontier in Physiology*. 2018;9. doi:10.3389/fphys.2018.00284. [Editorial]
13. Zhang J, Sheng J, Dong L, Xu Y, Yu L, Liu Y, Huang X, Wan S, Lan HY, Wang H. Cardiomyocyte-specific loss of RMP causes myocardial dysfunction and heart failure. *Cardiovascular Research*. December 2018. doi:10.1093/cvr/cvy307.

14. Zhou G, Sun X, Qin Q, Lv J, Cai Y, Wang M, Mu R, Lan H, Wang QW. Loss of Smad7 promotes inflammation in rheumatoid arthritis. *Frontiers in Immunology*. 2018;9. doi:10.3389/fimmu.2018.02537.
15. Huang H, Xu C, Wang Y, Meng C, Liu W, Zhao Y, Huang XR, You W, Feng B, Zheng ZH, Huang Y, Lan HY, Qin J, Xia Y. Lethal (3) malignant brain tumor-like 2 (L3MBTL2) protein protects against kidney injury by inhibiting the DNA damage-p53-apoptosis pathway in renal tubular cells. *Kidney International*. 2018;93(4):855-870. doi:10.1016/j.kint.2017.09.030.
16. Liu W, Chen B, Wang Y, Meng C, Huang H, Huang XR, Qin J, Mulay SR, Anders HJ, Qiu A, Yang B, Freeman GJ, Lu HJ, Lin HY, Zheng ZH, Lan HY, Huang Y, Xia Y. RGMb protects against acute kidney injury by inhibiting tubular cell necroptosis via an MLKL-dependent mechanism. *Proceedings of the National Academy of Sciences*. 2018;115(7):E1475-E1484. doi:10.1073/pnas.1716959115.
17. Chan GCW, Wu HJ, Chan KW, Yiu WH, Zou A, Huang XR, Lan HY, Lai KN, Tang SCW. N-acetyl-seryl-aspartyl-lysyl-proline mediates the anti-fibrotic properties of captopril in unilateral ureteric obstructed BALB/C mice. *Nephrology*. 2018;23(4):297-307. doi:10.1111/nep.13000.
18. Sun SF, Tang PMK, Feng M, Xiao J, Huang XR, Li P, Ma RCW, Lan HY. Novel lncRNA Erbb4-IR promotes diabetic kidney injury in db/db mice by targeting miR-29b. *Diabetes*. 2018;67(4):731-744. doi:10.2337/db17-0816.

B. Conference Papers

1. Li JH, Yang H, Tang Y, Lv J, Tang PMK, Huang XR, Xu AP, Zheng ZH, Lan HY. Macrophage migration inhibitory factor promotes acute kidney injury via enhancing CD74/NF- κ B/Mincle/Syk inflammation circuit. In: *International Society of Nephrology Frontiers*; Tokyo, Japan; 2018 Feb 22-25.
2. Tang PMK, Tang PCT, Huang XR, Ma RCW, Lee TL, To KF, Lan HY. Neural transcription factor Pou4f1 is essential for macrophage-myofibroblast transition driven kidney fibrosis. In: *International Society of Nephrology Frontiers*; Tokyo, Japan; 2018 Feb 22-25.
3. Lan HY. TGF-Smad signaling in tumor microenvironment. In: *International ITU Molecular Biology and Genetics Student Congress*; Istanbul, Turkey; 2018 Oct 5-7.
4. Lan HY. Role of Macrophages in Progression from AKI to CKD. In: *Silk Road Forum of Kidney Disease and The ISN Regional Training Center Conference*; Lanzhou, China; 2018 Aug 17-18.
5. Lan HY. TGF-beta promotes cancer via the Smad3-dependent tumor microenvironments. In: *5th Macau Symposium on Biomedical Sciences*; Macao; 2018 Jun 8-9
6. Lan HY. Non-Coding RNAs as a Therapeutic Strategy for Diabetic Nephropathy, New Progress in Nephrology In: *International Society of Nephrology Forum*; Hangzhou, China; 2018 Jun 1-2.
7. Lan HY. Macrophage-to-Myofibroblast Transition in Tissue Scarring. In: *NCKU for Biomedical Engineering and Cancer Research*; Taiwan; 2018 Oct 12.
8. Lan HY. miRNA as a therapeutic strategy for the complications of diabetes. The Epigenomics of Diabetes and Other Metabolic Diseases. In: *Gordon Research Conference*; Hong Kong; 2018 May 27 - Jun 1

09 INFLAMMATORY DISEASES

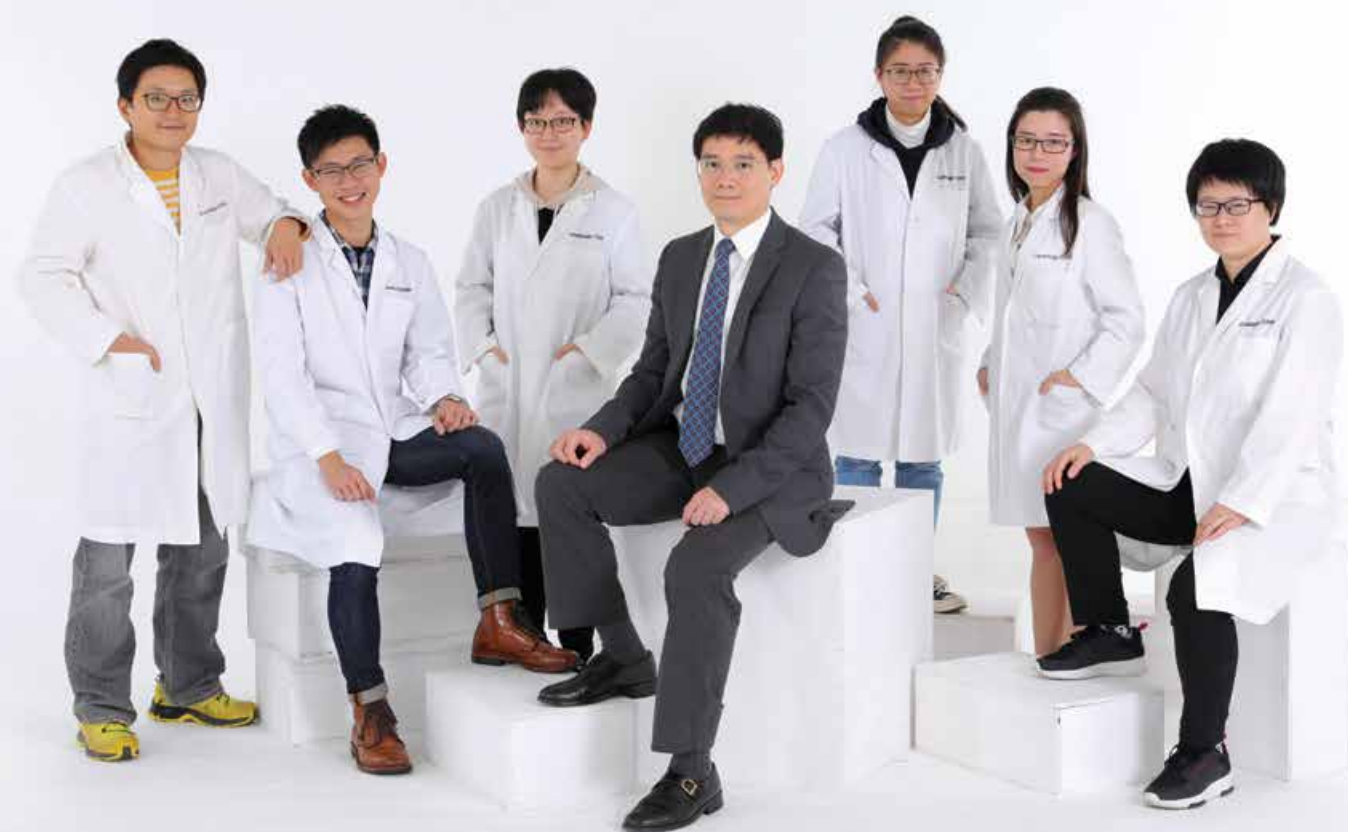


Principal Investigator
Professor Erik Fung



Team

King Fai Cheng | Cheng Leong | Ting Lui |
Xiaobo Yang | Qi Li | Suyi Xie | Simin Liu



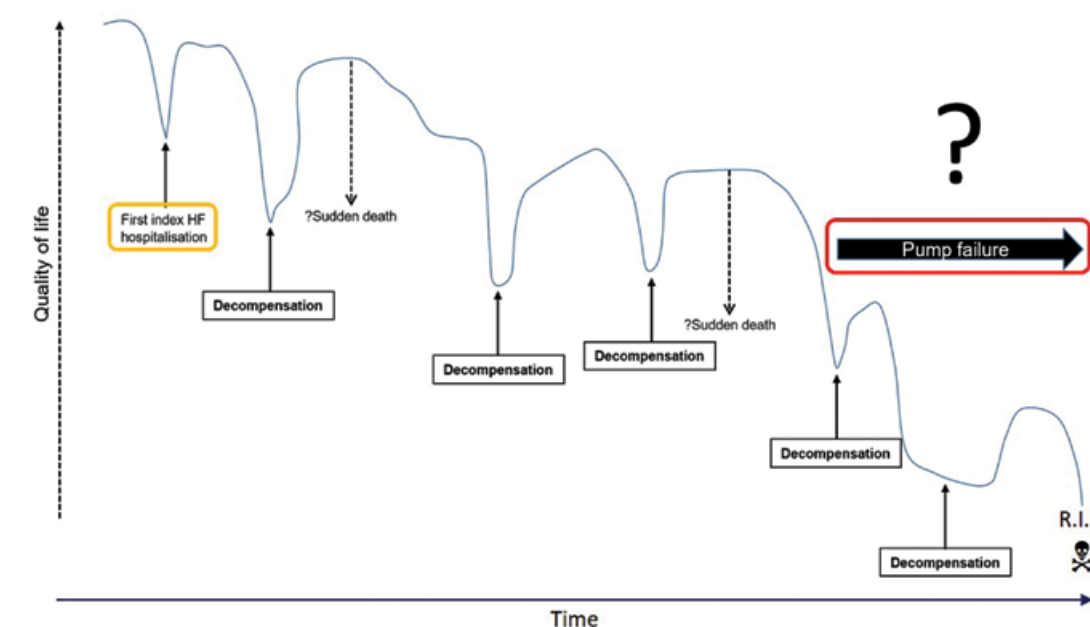
■ Research Progress Summary

In 2018, Professor Erik Fung and his research team have been working for different aspects. For knowledge transfer activities, they have been preparing a patent application for a novel valve implant device. For academic forums, Professor Fung has been the Chairman of the 2nd Asia Pacific Advanced Heart Failure Forum (APAHFF 2018) forum which was attended by over 250 people and international experts from over 15 countries. The Conference Proceedings from APAHFF 2018 will be published as abstracts in *Heart Asia*, a BMJ Publishing Group cardiology journal. Professor Fung was also served as Abstract Editor of 33 abstracts.

Professor Fung and his team have participated in various conferences and poster presentations, which include "Association between oxygen uptake efficiency slope (OUES), an effort-independent measure of cardiorespiratory fitness (VO_2max), and robust/pre-frail status in an elderly Chinese population." Heart Failure 2018 - European Society of Cardiology, Vienna, Austria. 26–29 May 2018, (Poster P2018); "Diastolic dysfunction, heart failure and frailty in the community-living elderly in Hong Kong: findings from the Undiagnosed heart Failure

in frail Older individuals (UFO) study." INOVA Advanced Heart Failure Symposium, Washington D.C., USA. 13 Oct 2018 and "Peak oxygen uptake (VO_2max) is superior to oxygen uptake efficiency slope (OUES) in discriminating between pre-frail and robust status and predicts mortality in ambulatory older adults living in the community." 21st British Society for Heart Failure Annual Autumn Meeting, London, UK. 29–30 Nov 2018.

For invited lectures and oral presentations, Professor Fung has participated in "Pharmacological therapies for heart failure: clinical cases & review." Hospital Authority Headquarters, Kowloon, Hong Kong SAR. 8 Feb 2018, "Pericardial Diseases." ECHO ASIA 2018, Asian-Pacific Association of Echocardiography, Jeju Island, Korea. 24–26 May 2018 and "Performance of cardiopulmonary exercise capacity and physical fitness indicators in differentiating pre-frail and robust elderly". 2018 Canadian Cardiovascular Congress, Toronto, Ontario, Canada. 20–23 Oct 2018. (Moderated presentation, Session: Exercise in The Elderly to Regeneration in Infancy [010]; Chair: Susanna Mak MD. 20 Oct 2018).



The diagram illustrates the natural history of heart failure from first index hospitalisation to death. The research group is interested in the study of heart failure from early on in life until development of decompensated and end-stage heart failure.

Source: Professor Erik Fung

■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Erik Fung	INOVA Advanced Heart Failure Symposium Travel Grant

Academic Editorship and Reviews

Member's Full Name	Details
Erik Fung	Associate Editor, Heart Asia (a BMJ Publishing Group journal)

Journal / Conference Reviews

Member's Full Name	Details
Erik Fung	Reviewer of Heart Asia
Erik Fung	Reviewer of Chest
Erik Fung	Reviewer of Scientific Reports

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Erik Fung	Biomarker Profiling of Heart Failure and Frailty in the Elderly	CUHK Research Committee – Direct Grant	30/06/2017	29/06/2018 (extension 31/08/2018)	150,000
Erik Fung	VerlCiguaT Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA)	Merck Sharp & Dohme Corp	31/01/2017	31/01/2020	Nil
Erik Fung	ETNA-AF Global: Non-interventional study on edoxaban treatment in routine clinical practice for patients with nonvalvular atrial fibrillation in Hong Kong (ETNA-AF-Hong Kong)	Daiichi Sankyo Hong Kong Limited	30/06/2017	29/06/2021	66,594
Erik Fung	Characterising the hazards of cardiac arrhythmias and adverse clinical outcomes accompanying hypoglycaemic nadir in frail elderly diabetics on insulin: a prospective, longitudinal, observational, follow-up study	Food and Health Bureau - Health and Medical Research Fund	01/04/2018	31/03/2021	1,197,580
Erik Fung	Assessing the eFFects of sILdenafil in Adults with pulmonary arTerial hypertension (AFFILIATE) study.	Pfizer Pharmaceutical Company	31/01/2018	30/01/2023	Nil

■ Publications

A. Journal Papers

1. Fung E, Hui E, Yang X, Lui L, Cheng K, Li Q, Fan Y, Sahota D, Ma B, Lee J, Lee A, Woo J. Heart failure and frailty in the community-living elderly population: What the UFO Study will tell us. *Frontier in Physiology*. 2018;9:234. doi:10.3389/fphys.2018.00347. (Perspective)

2. Fung E, Yang X, Newton P, Ferguson C, Gastelurrutia P, Lupón J, Bayés-Genís A, Jha S, Macdonald P. Letter by Fung et al Regarding Article, “Frailty and clinical outcomes in heart failure: A systematic review and meta-analysis”. *Journal of the American Medical Directors Association*. 2018;19(12):1143-1146. doi:10.1016/j.jamda.2018.09.035. (Letter)

3. Yang X, Lupón J, Vidán M, Ferguson C, Gastelurrutia P, Newton P, Macdonald P, Bueno H, Bayés-Genís A, Woo J, Fung E. Impact of frailty on mortality and hospitalization in chronic heart failure: A systematic review and meta-analysis. *Journal of the American Medical Directors Association*. 2018;7(23):e008251. doi:10.1161/jaha.117.008251. (Review)

4. Fung E. 23 Anticoagulation for mechanical circulatory support. *APAHFF Abstracts* 2017. 2018. doi:10.1136/heartasia-2018-apahff.23. (Editorial)

B. Conference Papers

1. Yu D, Li P, Fung E, Yuen J, Woo J, Chair S, Lee V, Choi K, Lo R. 22 Supportive cardiology: an innovative practice model to integrate palliative care into the management of advanced heart failure. *APAHFF Abstracts* 2017. 2018. doi:10.1136/heartasia-2018-apahff.22.

2. Fung E, Lui LT, Yau F, Leung J, Woo J. Association between oxygen uptake efficiency slope (OUES), an effort-independent measure of cardiorespiratory fitness (VO2max), and robust/pre-frail status in an elderly Chinese population. *European Journal of Heart Failure* 2018;20 (S1):528.

3. Fung E, Lui LT, Yau F, Leung J, Woo J. Performance of cardiopulmonary exercise capacity and physical fitness indicators in differentiating pre-frail and robust elderly. *Canadian Journal of Cardiology*. 2018;34:S6-S7.

10 NEUROSCIENCE



Principal Investigator
Professor Owen Ko



Team

Danny Chan | Eva Zhao | Kuan-jung Wu | Yanyan Yang |
Leo Yan | Junzhe Huang | Hei-ming Lai | Samuel Sy |
Richard Li | Caroline Chen



■ Research Progress Summary

Laboratory Construction

After initial phase of building up the laboratory and recruitment, Professor Owen Ko has now established a team of 10 researchers and finished construction of all major equipment needed. With the laboratory's emphasis on imaging, they have custom-built all their major imaging infrastructure. Main platforms the team has constructed are as follows:

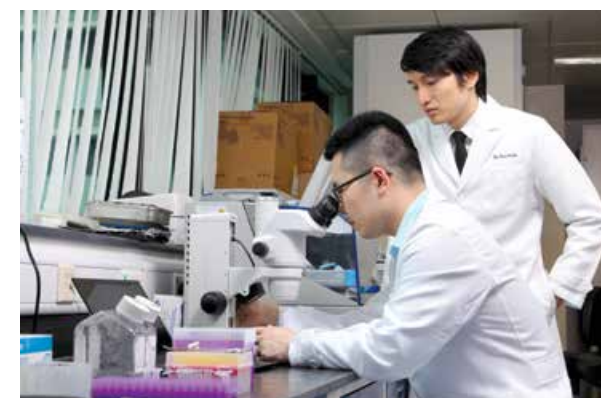
1. Two-photon fluorescence excitation microscope with integrated animal behavioral platform for in vivo imaging of neuronal network structure and activity;
2. Intrinsic signal imaging macroscope for localisation of brain regions participating in specific sensory processing tasks (e.g. visual processing);
3. Light-sheet fluorescence microscope for zebrafish larva whole-brain imaging of neuronal structure and activity;
4. Standard biochemical equipment and culture facilities.

Research Theme 1: Neural Circuitry Mediating Sensorimotor Behaviour

The team is currently investigating neural circuits underlying sensorimotor behaviour in two model systems:

(i) *Danio rerio* (Zebrafish) larvae

Several days post-fertilisation, zebrafish larvae already exhibit a rich repertoire of innate behaviors, including phototaxis, optomotor and optokinetic responses, prey capture, escape responses, rheotaxis and chemosensory attraction / avoidance. As a model organism for neuroscience, larval zebrafish offers the distinct advantages of relatively high optical transparency and more tractable number of neurons in the brain (in the order of 10^5), permitting the interrogation of brain-wide activities mediating sensorimotor transformation with cellular resolution. The team is interested in fundamental questions of how neural circuits in the brain integrates sensory information originating from bilateral sensory organs to drive avoidance or escape behavior in response to signals of danger. To this end, they have constructed an integrated high-speed light-sheet microscopy and microfluidics system, to precisely manipulate sensory environment of zebrafish larvae while performing volumetric whole-brain imaging of neuronal activities. They seek to characterise the brain-wide dynamics mediating chemosensory processing by larval zebrafish and uncover the circuit principles governing the integration of chemical signals from the bilateral nasal placodes and olfactory bulbs for the generation of appropriate avoidance responses.





(ii) *Mus musculus* (Mouse)

To optimise survival, animals must be able to associate sensory cues with the need to perform corresponding motor responses. These processes involve coordinated neural activity and signal flow across primary sensory areas, association areas, and motor areas. Often, sensorimotor tasks also necessitate the acquisition of novel motor sequences from an existing motor repertoire. To understand sensorimotor learning, the team must uncover how neuronal populations across different brain regions encode various aspects of task-relevant information, such as sensory features, predicted outcomes, and the generation of complex sequences of motor commands.

In their laboratory, Professor Ko and his team have developed a platform in which animals learn to execute motor tasks in response to visual cues, while neuronal activities are recorded from different visual and motor areas by multiphoton microscopy. Combined with retrograde tracing and molecular techniques, they seek to uncover rules governing the encoding of distinct task-related and motor sequence information along pathways connecting higher visual areas to association and motor areas.

Research Theme 2: Neurovascular and Immunological Dysfunction in Neurodegenerative Diseases

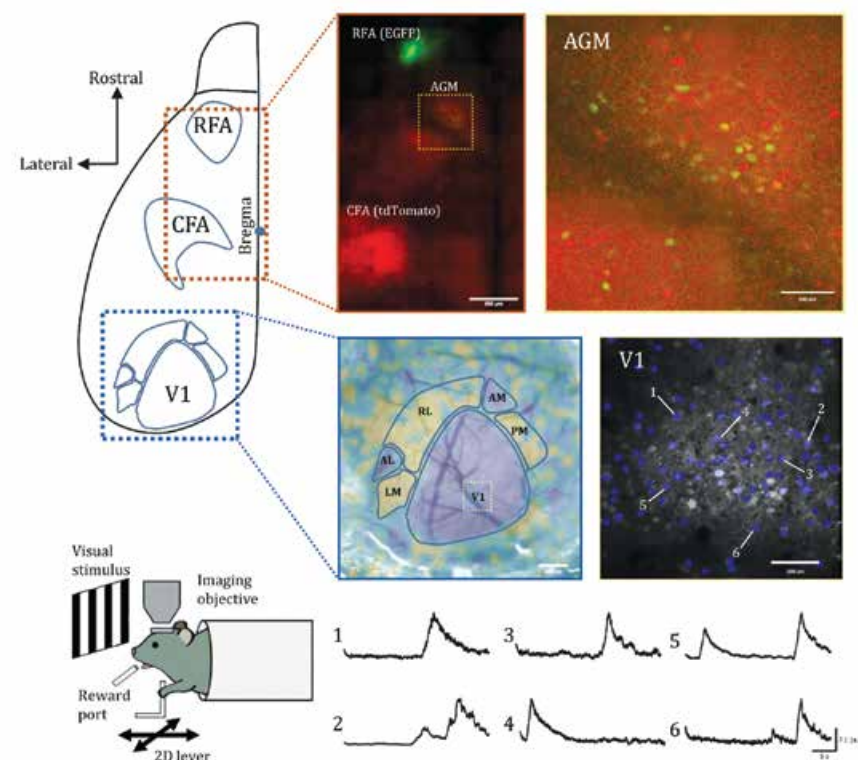
(i) *Neurovascular biology and dysfunction in neurodegenerative diseases*

Brain function critically relies on cerebrovascular health, which depends on the integrity of two key aspects of its vasculature: the blood-brain-barrier (BBB) and neurovascular coupling. BBB prevents exposure of the brain parenchyma to potential neurotoxic substances. Neurovascular coupling ensures the instantaneous fulfilment of heterogeneous and dynamic metabolic demands that arise from locally activated neuronal processing. Both BBB integrity and neurovascular coupling are regulated by neurovascular units (NVU), which are comprised of neurons, astrocytes and vascular mural cells including endothelial cells, vascular smooth muscle cells in the arterioles, and pericytes in the capillaries.

Mechanistic studies in animals modelling pathological processes affecting NVU integrity have increasingly revealed the contribution of neurovascular defects to neurodegeneration in dementia. Cerebral small vessel disease (SVD), a dominant cause of cognitive impairments in the elderly population, is a primary neurovascular disorder. On the other hand, compromised BBB and impaired neurovascular coupling are also prominent features in Alzheimer's disease (AD). In their investigation of SVD and AD, the team employs a combination of *in vivo* functional imaging, *in vitro* structural imaging and single-cell RNA sequencing (in collaboration with Professor Dennis Lo and Professor Rossa Chiu) to study mechanisms underlying neurovascular dysfunction. They aim to reveal (1) how normal NVU integrity is maintained, and (2) mechanisms by which aging and other disease-specific risk factors in SVD and AD culminate in NVU dysfunction.

(ii) *Neuroimmunology in the pathogenesis of Parkinson's disease*

Over the past decades, dozens of genetic loci and mutations associated with Parkinson's disease (PD) have been identified. However, the mechanisms by which such mutations cause PD remain elusive due the complexity of dynamical changes in gene regulation and protein. Neuroinflammation plays an important role in PD and other neurodegenerative diseases. The team is interested in the immunological linkage between the PD-associated genetic mutations (e.g. the LRRK2 G2019S mutation) and pathogenesis of PD. With support from the Margaret K. L. Cheung Research Center for Management of Parkinsonism, they employ a combination of *in vitro* neuronal and glial cell culture, *in vivo* genetic manipulation, and imaging techniques, to study the mechanisms where specific PD-associated mutations mediate neuroinflammatory responses that contribute to dopaminergic neuron loss in PD.



Schematics of *in vivo* behavioural and neuronal dynamics imaging platform. The animal is head-mount and performs visuomotor tasks, while simultaneous *in vivo* two-photon imaging can be carried out to reveal neuronal dynamics in different cortical forelimb area (RFA, labelled by EGFP) and caudal forelimb area (CFA, labelled by tdTomato); (2) Medial agranular cortex (AGM), where the RFA and CFA projecting neurons are labelled by EGFP and tdTomato respectively; and (3) the primary visual cortex (V1) with surrounding higher visual areas (HVAs, identified by intrinsic signal optical imaging). GCaMP6s labelled neurons allowed imaging of neuronal activities (regions of interest are highlighted in blue, while calcium transients of six selected neurons in V1 are shown).

Source: Professor Owen Ko

■ Research and Scholarship

Fellowships

Member's Full Name	Details
Eva Zhao	Young Investigator Travel Fellowship, 9 th International Conference of the International Society of Vascular Behavioral and Cognitive Disorders

Journal / Conference Reviews

Member's Full Name	Details
Owen Ko	Abstract reviewer, 9 th International Conference of the International Society of Vascular Behavioral and Cognitive Disorders

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Owen Ko	Characterization and Validation of Novel MRI Amyloid Contrast Agents	Videns Incorporation Ltd	01/10/2017	31/12/2018	25,000,000
Owen Ko	Investigating the Pathogenesis of Cerebral Small Vessel Disease	CUHK Faculty of Medicine – Faculty Innovation Award (Clinical Lecturer Scheme)	01/10/2017	30/09/2020	750,000
Owen Ko	Scientific Advisor	Aptorum Group Limited	2018	2018	N/A
Owen Ko	Scientific Advisor	Videns Incorporation Limited	2018	2018	N/A

■ Publications

A. Journal Papers

- Sy KHS, Ho LWC, Lau WCY, Ko H, Choi CHJ. Morphological diversity, protein adsorption, and cellular uptake of polydopamine-coated gold nanoparticles. *Langmuir*. 2018;34(46):14033-14045. doi:10.1021/acs.langmuir.8b02572.
- Wang X, Li X, Zhang L, Wong SH, Wang MHT, Tse G, Dai RZW, Nakatsu G, Coker OO, Chen Z, Ko H, Chan JYK, Liu T, Cheng CHK, Cheng ASL, To KF, Plewczynski D, Sung JJY, Yu J, Gin T, Chan MT V, Wu WKK. Oncogenes expand during evolution to withstand somatic amplification. *Annals of Oncology*. 2018;29(11):2254-2260. doi:10.1093/annonc/mdy397.
- Zhang L, Hu W, Cho CH, Chan FK, Yu J, Fitzgerald JR, Cheung CK, Xiao ZG, Shen J, Li LF, Li MX, Wu JC, Ling TK, Chan JY, Ko H, Tse G, Ng SC, Yu S, Wang MH, Gin T, Ashktorab H, Smoot DT, Wong SH, Chan MT, Wu WK. Reduced lysosomal clearance of autophagosomes promotes survival and colonization of *Helicobacter pylori*. *Journal of Pathology*. 2018;244(4):432-444. doi:10.1002/path.5033.

B. Conference Papers

- Zhao L, Yan LYC, Chen XY, Li ZQ, Sy SKH, Tian XY, Huang Y, Mok VCT, Ko H. Investigating the therapeutic potential of glucagon-like peptide-1 receptor (GLP-1R) agonist in cerebral small vessel disease. In: *9th International Conference of the International Society of Vascular Behavioral and Cognitive Disorders*; Hong Kong; 2018 Nov 14-17.

11

REPRODUCTION & DEVELOPMENT



Principal Investigator
Professor Ronald Wang



Team

Hui Xu | Nina Ching Yan Chu | Simon Long Cui | Alex Bo Liang | Linda Ling Wu | Alan Wing Kwong Chan | Emma Yujing Xiong | Fangrong Wu | Ricky Qi Wu | Zinnat Hasina | Ying He | Melody Di Mao | Yi Song | Kennes Sze Wan Hung | Rachel Rui Zhe Zhang | Ya Ting Gao | Dorris Rui Dong | Chris Shing Shing Lok



Research Progress Summary

Professor Ronald Wang and his team from the Department of Obstetrics and Gynaecology focus on the field of Reproduction and Development. The team covered wide spectrum of clinical, basic and genetic studies of female and male reproduction, and embryo and fetal development in human and mice. For Reproduction, the research team focused on studying diseases in endometrium and ovary, including recurrent reproductive failure (e.g. recurrent miscarriage, recurrent implantation failure, endometrial imaging), endometriosis (e.g. clinical trial, angiogenesis, immunosuppression), endometrial cancer (e.g. lncRNA and HIF dysregulation), polycystic ovary syndrome (clinical trial and secondary analysis), etc. For development, the research team focused on the abnormal neurodevelopmental mechanism (e.g. cerebellar ataxia, Down's syndrome), embryopathy in maternal disease (e.g. pregestational and gestational diabetes), placental function (e.g. preterm birth, preeclampsia, hormonal expression), cord blood stem cells (e.g. mononuclear cells for neonatal cerebral ischemia and anaemia) and drug safety during pregnancy (e.g. melamine, Chinese herbal medicine), etc.

In 2018, the team has published 1 review, 15 papers and 1 book chapter (all LiHS acknowledged, 10 as 1st/last/corresponding author) and obtained 5 research grants (2 as PI including 1 HMRP and 1 Direct Grant; and 3 as Co-I including 1 ITF, 1 OG Trust Fund and 1 Direct Grant).

Currently the team has 12 PhD students, 4 of them will submit their thesis in 2019.



■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Ronald Wang	Professor (Honorary), Faculty of Medicine, Jinan University, Guangzhou
Ronald Wang	Professor (Honorary), School of Basic Medical Science, Zhejiang Chinese Medical University, Hangzhou
Kennes Wan Hung Sze	CUHK, PhD Student Exchange Programme 2018-19 HK\$29,000 to have academic exchange to Department of Medical Biochemistry and Biophysics, Karolinska Institute

Fellowships

Member's Full Name	Details
Simon Long Cui	Faculty Postdoctoral Fellowship, Faculty of Medicine, CUHK
Alex Bo Liang	Faculty Postdoctoral Fellowship, Faculty of Medicine, CUHK
Linda Ling Wu	Faculty Postdoctoral Fellowship, Faculty of Medicine, CUHK

Academic Editorships and Review

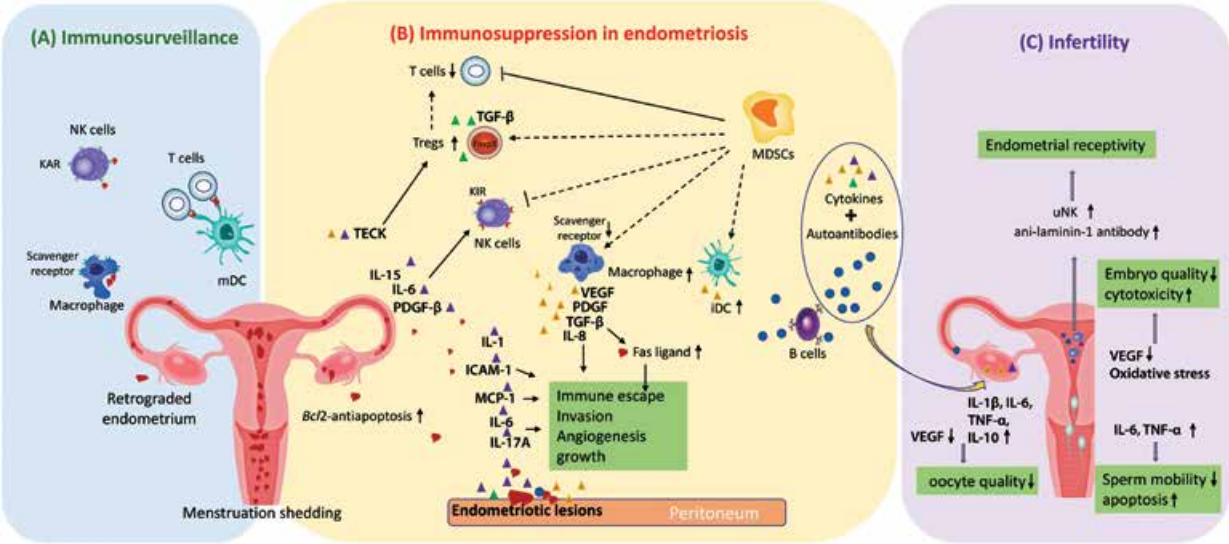
Member's Full Name	Details
Ronald Wang	National Medical Research Council, Singapore

Journal / Conference Reviews

Member's Full Name	Details
Ronald Wang	British Medical Journal
Ronald Wang	Free Radical Biology and Medicine
Ronald Wang	FASEB Journal
Ronald Wang	Scientific Report
Ronald Wang	Journal of Agricultural and Food Chemistry
Ronald Wang	Human Reproduction
Ronald Wang	European Journal of Obstetrics & Gynecology and Reproductive Biology
Ronald Wang	Reproductive BioMedicine Online
Ronald Wang	Journal of Ethnopharmacology
Ronald Wang	Evidence-Based Complementary and Alternative Medicine
Ronald Wang	BMC Complementary and Alternative Medicine

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Ronald Wang	A Multicentre Randomised Double-blind, Placebo-controlled Trial of Chinese Medicine and/or Progesterone in Women with Threatened Miscarriage – a Trial Centre in Hong Kong (15160971)	Food and Health Bureau – Health and Medical Research Fund	01/03/2018	29/02/2020	1,095,000
Hui Xu	Immunosuppression Mediated by Myeloid-derived Suppressor Cells (MDSCs) in Endometriosis and a Potential Therapeutic Target for Endometriosis. (2017.044)	CUHK Research Committee – Direct Grant	01/07/2018	30/06/2019	145,000
Ronald Wang	Cervicovaginal Fluid Biomarker for the Identification of Spontaneous Preterm Birth (ITS/252/17FX)	Innovation and Technology Fund	01/04/2018	31/03/2020	1,870,200
Ronald Wang	The Association of Vitamin D Level with Children’s Cardiometabolic Risk. (2017.042)	CUHK Research Committee – Direct Grant	25/06/2018	24/06/2019	71,000
Ronald Wang	The Relationship Between Toll-like Receptors and Chronic Endometritis around the Time of Embryo Implantation in Women with Recurrent Miscarriage.	SOGHK HKOG Trust Fund	1/1/2018	31/12/2018	30,000



Schematic representation of the complex pathophysiology of endometriosis with immunity. Endometrium flow through fallopian tube into peritoneal cavity during menstruation.

Source: Autoimmunity Review 17(10): 945-955.

■ Publications

A. Journal Papers

1. Wang J, Man GCW, Chan TH, Kwong J, Wang CC. A prodrug of green tea polyphenol (–)-epigallocatechin-3-gallate (Pro-EGCG) serves as a novel angiogenesis inhibitor in endometrial cancer. *Cancer Letter*. 2018;412:10-20. doi:10.1016/j.canlet.2017.09.054.
2. Yang X, Wang CC, Lee WYW, Trovik J, Chung TKH, Kwong J. Long non-coding RNA HAND2-AS1 inhibits invasion and metastasis in endometrioid endometrial carcinoma through inactivating neuromedin U. *Cancer Letter*. 2018;413:23-34. doi:10.1016/j.canlet.2017.10.028.
3. Chu CY, Fung KP, Wang CC. Effects of low-dose melamine exposure during pregnancy on maternal and fetal kidneys in rats. *Environmental Toxicology*. 2018;33(3):370-380. doi:10.1002/tox.22525.
4. Wang JZ, Xiong YJ, Man GCW, Chen XY, Kwong J, Wang CC. Clinicopathological and prognostic significance of blood microvessel density in endometrial cancer: a meta-analysis and subgroup analysis. *Archives of Gynecology and Obstetrics*. 2018;297(3):731-740. doi:10.1007/s00404-018-4648-1.
5. Li J, Wu Q, Wu XK, Zhou ZM, Fu P, Chen XH, Yan Y, Wang X, Yang ZW, Li WL, Stener-Victorin E, Legro RS, Ng EHY, Zhang H, Mol BWJ, Wang CC. Effect of exposure to second-hand smoke from husbands on biochemical hyperandrogenism, metabolic syndrome and conception rates in women with polycystic ovary syndrome undergoing ovulation induction. *Human Reproduction*. 2018;33(4):617-625. doi:10.1093/humrep/dey027.
6. Liang B, Wu L, Xu H, Cheung CW, Fung WY, Wong SW, Wang CC. Efficacy, safety and recurrence of new progestins and selective progesterone receptor modulator for the treatment of endometriosis: a comparison study in mice. *Reproductive Biology and Endocrinology*. 2018;16(1):32. doi:10.1186/s12958-018-0347-9.
7. Liu Y, Chen X, Huang J, Wang CC, Yu MY, Laird S, Li TC. Comparison of the prevalence of chronic endometritis as determined by means of different diagnostic methods in women with and without reproductive failure. *Fertility and Sterility*. 2018;109(5):832-839. doi:10.1016/j.fertnstert.2018.01.022.
8. Zhang T, Zhou J, Man GCW, Leung KT, Liang B, Xiao B, Ma X, Huang S, Huang H, Hegde VL, Zhong Y, Li Y, Kong GWS, Yiu AKW, Kwong J, Ng PC, Lessey BA, Nagarkatti PS, Nagarkatti M, Wang CC. MDSCs drive the process of endometriosis by enhancing angiogenesis and are a new potential therapeutic target. *European Journal of Immunology*. 2018;48(6):1059-1073. doi:10.1002/eji.201747417.

9. Wu F, Chen X, Liu Y, Liang B, Xu H, Li TC, Wang CC. Decreased MUC1 in endometrium is an independent receptivity marker in recurrent implantation failure during implantation window. *Reproductive Biology and Endocrinology*. 2018;16(1):60. doi:10.1186/s12958-018-0379-1.
10. Chen X, Liu Y, Cheung WC, Zhao Y, Huang J, Chung JPW, Wang CC, Li TC. Increased expression of angiogenic cytokines in CD56+ uterine natural killer cells from women with recurrent miscarriage. *Cytokine*. 2018;110:272-276. doi:10.1016/j.cyto.2018.01.013.
11. Chu KO, Chan KP, Chan SO, Ng TK, Jhanji V, Wang CC, Pang CP. Metabolomics of Green-Tea Catechins on Vascular-Endothelial-Growth-Factor-Stimulated Human-Endothelial-Cell Survival. *Journal of Agricultural and Food Chemistry*. 2018;66(48):12866-12875. doi:10.1021/acs.jafc.8b05998.
12. Zhang C, He X, Kwok YK, Wang F, Xue J, Zhao H, Suen KW, Wang CC, Ren J, Chen GG, Lai PBS, 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. doi:10.1186/s12915-018-0616-2.
13. Zhang T, DeCarolis C, Man GCW, Wang CC. The link between immunity, autoimmunity and endometriosis: a literature update. *Autoimmunity Reviews*. 2018;17(10):945-955. doi:10.1016/j.autrev.2018.03.017. [Review]

B. Book / Book Chapter

1. Liang B, Wang CC. 2018 Morphology-based whole embryo culture for developmental toxicity of drugs. In: Teratogenicity Testing: Methods and Protocols. *Methods in Molecular Biology*. Luís Félix Eds. Springer. Ch. 8, pp 177-189.

12

STEM CELLS AND REGENERATION

Intelligent Orthopaedic Bio-Engineering Research

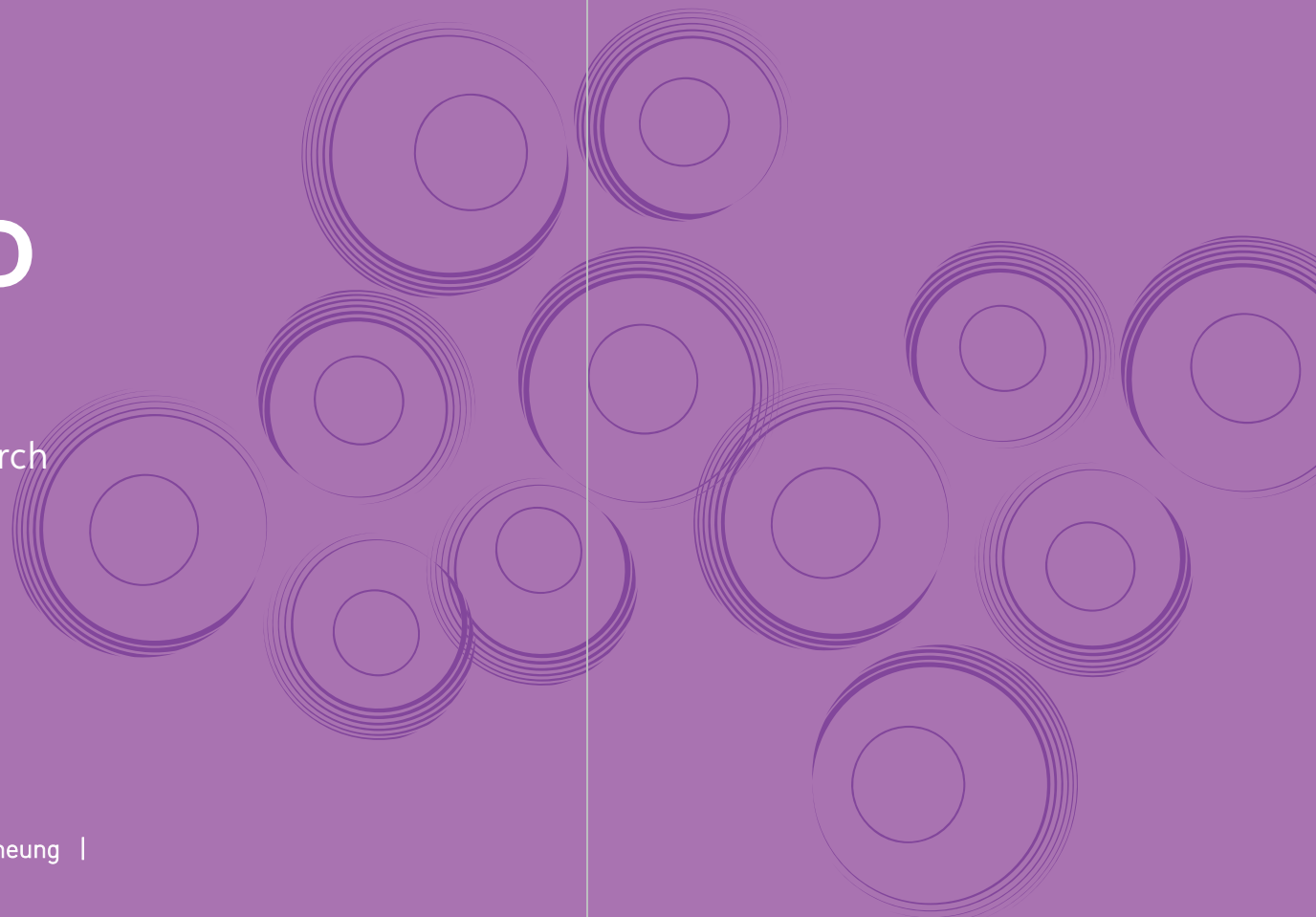


Principal Investigator
Professor Oscar Lee



Team

Chien-wai Lee | Carol Lau | Zoey Lin | Stella Cheung | Tina Cheung |
Jason Wan | Rita Shin | Belle Wang



■ Research Progress Summary

As a newly established research team started in August 2018, Professor Oscar Lee and his team focus on creating collaboration networks and seeking potential grant applications. The team has established solid intra-departmental and inter-departmental research collaborations in CUHK, and even collaborations between universities in HK and Mainland China. For instances, Professor Lee has cooperated with Professor Christopher Cheng in the School of Biomedical Sciences, CUHK for an Innovation and Technology Fund Tier 3 proposal, which focuses on “Development of Exosomes from Mesenchymal Stem Cells as Therapeutics for Acute Liver Failure”. Professor Lee along with Professor CW Lee has initiated a collaboration on “Stem cell therapy for the treatment of liver disease” with Professor Kenneth Lee in the

School of Biomedical Sciences and Professor Vivas Chan in the Institute for Tissue Engineering and Regenerative Medicine, CUHK. What is more, Professor Lee and Dr. Carol Lau have started a new collaborative project with Professor Jianfang Wang, Department of Physics, CUHK, which is about “Characterization of chemical composition of osteosarcoma tissues using Surface-Enhanced Raman Scattering (SERS)”. Importantly, Professor Lee has been invited by Professor Changshun Shao from Soochow University, Mainland China for jointly applying a National Natural Science Foundation of China (NSFC) / Research Grants Council (RGC) Joint Research Scheme proposal, titled “Development of Novel Stem Cell-based Immunotherapeutics for Systemic Lupus Erythematosus”.



Besides, Professor Lee and his team members also enthusiastically participated in knowledge transfer activities by giving seminars in the Department of Orthopaedics and Traumatology and in the Institute for Tissue Engineering and Regenerative Medicine (iTERM) Lunchtime Seminar Series. Professor Lee also gave a talk on cellular therapy for liver diseases in the 2nd Retreat of the Max Planck-GIBH Center for Regenerative Biomedicine (MGCRB) and CUHK-MPI-GIBH Joint Symposium on Stem Cell and Molecular Medicine which was held in CUHK. He was also invited as symposium speaker in Hebei Medical University and in the Institute of Engineering in Medicine, University of California, San Diego.

In the past months, team members actively participated and contributed to different seminars and workshops about the regulation of advanced therapy products, translation of laboratory research to clinical applications, and new technologies in biopharmaceutical research. Professor Oscar Lee, Professor CW Lee, Dr. Carol Lau, and Miss Zoey Lin joined and obtained certificates of the following seminars: Aseptic Processing for Sterile Products organised by Hong Kong Institute of Biotechnology Limited on 23-25 October 2018; Qualification and Application of Raman and NIR Spectroscopy Techniques in Regulated Pharma Industries by HKIB on 13 Nov 2018; and Hong Kong GMP Seminar by Department of Health HKSAR on 20-21 Nov 2018.

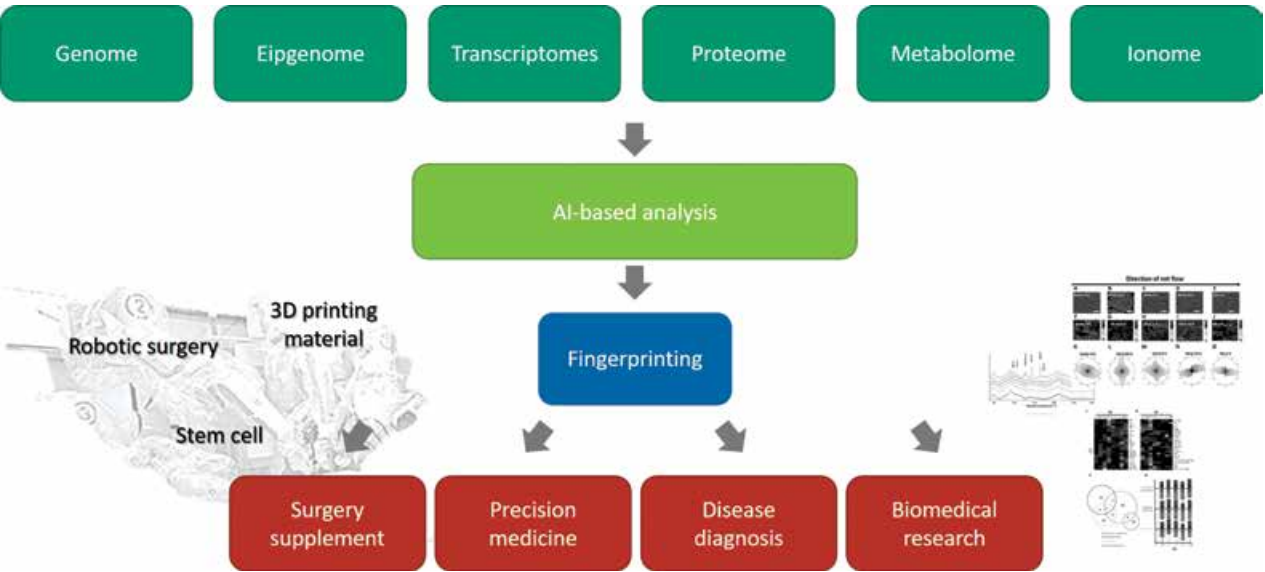
■ Research and Scholarship

Academic Editorships and Reviews

Member's Full Name	Details
Oscar Kuang-sheng Lee	Associate Editor, Cytotherapy (Since 2018)
Oscar Kuang-sheng Lee	Associate Editor, Stem Cell Research & Therapy (2015 – current)

Journal / Conference Reviews

Member's Full Name	Details
Oscar Kuang-sheng Lee	Board of Reviewers, 2019 Annual meeting of the Orthopaedic Research Society (ORS)



Development of AI-based platforms in precision medicine for musculoskeletal diseases

Source: Laboratory for Intelligent Orthopaedic Bio-Engineering Research, Department of Orthopaedics and Traumatology, Faculty of Medicine, The Chinese University of Hong Kong (http://www.ort.cuhk.edu.hk/maintheme_programs-point.html#LIOBER)

12

STEM CELLS AND REGENERATION

Adult Stem Cell Biology and Applications



Principal Investigator
Professor Gang Li



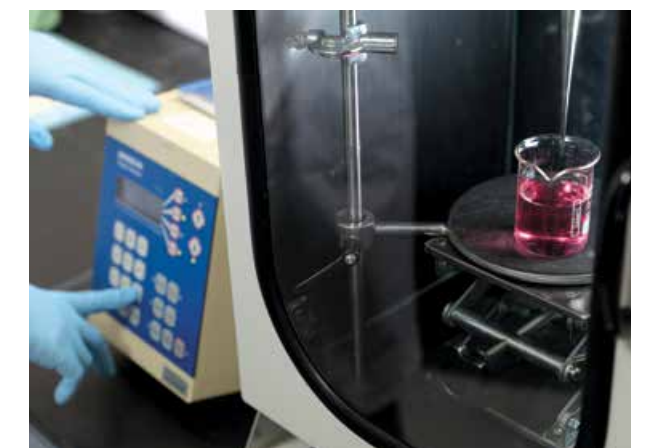
Team

Wayne Lee | Sien Lin | Meiling Zhu | Lu Feng | Bin Wang | Yan Wang | Liu Shi |
Weiping Lin | Yujia Wang | Yucong Li | Qi Pan | Haixing Wang | Xiaoting Zhang |
Yuan Li | Zhengmeng Yang | Shanshan Bai | Jianping Hang | Jessica Lo



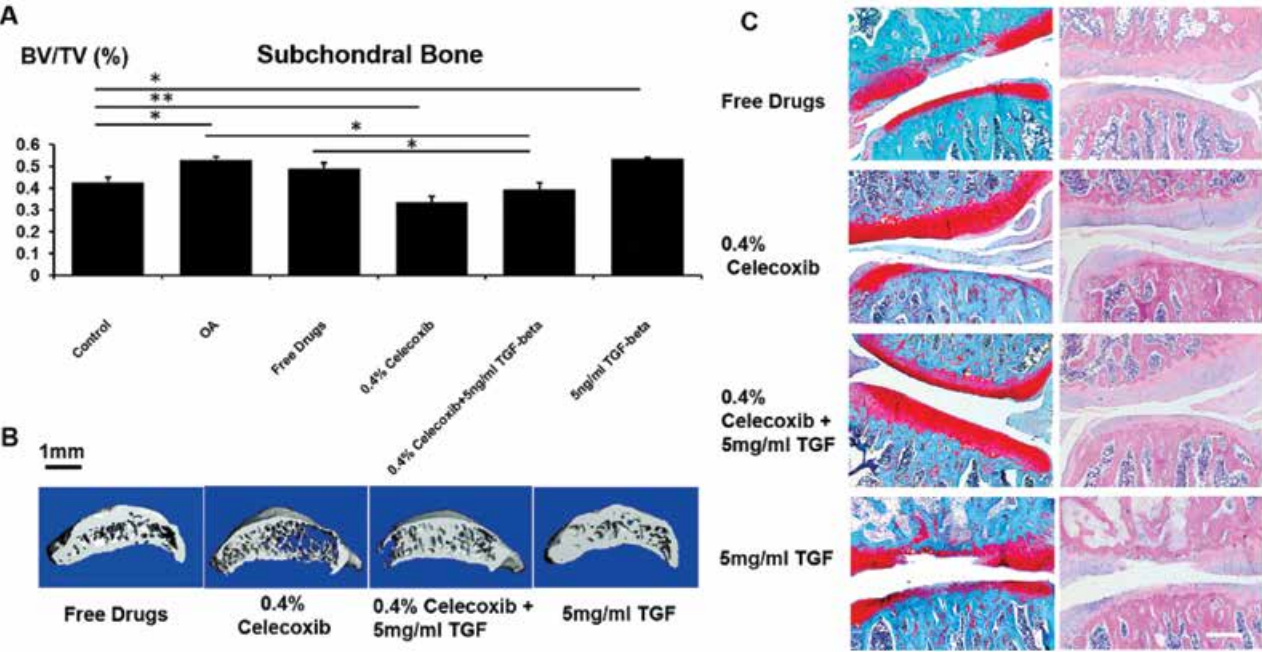
■ Research Progress Summary

In 2018, the research team has 18 members (1 research associate professor, 4 postdoctoral fellows, 1 research associate, 2 research assistants, 1 visiting fellow, 9 PhD students) with the following research projects carried out: (1) development of applications and products of secretomes derived from fetal and adult human mesenchymal stem cells; (2) biological roles of microRNAs and non-coding RNAs in bone and cartilage regeneration; (3) conducting industry contract research works on pre-clinical studies of biological compounds and biophysical stimulations; and (4) engaging in international collaborations and educational programs. These projects progress as planned, with production of more than 16 peer-reviewed publications and over HK\$ 8 million research grants secured by the team in 2018. In 2018, Professor Li has also successfully organised the 8th CUHK International Symposium on Stem Cell Biology and Regenerative Medicine; the 2nd Croucher Foundation Summer Course on Stem Cells Biology and Regenerative Medicine, and co-organised the International Conference on Mechanobiology for



Regeneration & 1st NCKU-CUHK Joint Forum on Cell Therapy & Tissue Engineering. Professor Li has been invited to give keynote speeches and lectures at various national and international conferences and meetings for more than 20 times in 2018, and served as visiting professors at many prestigious universities such as Monash University, Australia; University of Malaya, Malaysia; Sichuan University, China; South-East University Medical School, China; The Airforce Medical University, China, etc., He is also a council member of 4 prestigious

national research societies, and editorial board member for 4 international journals. He actively engaged in knowledge transfer and provided advice/consultation service for Hong Kong Science Park, local and international healthcare related industries. In 2018, Professor Gang Li has won the 1st Class Award in China Medical Science, China International Exchange and Promotion Association for Medical and Healthcare. (華夏醫學科技獎一等獎：「肢體複雜組織缺損修復重建關鍵技術的創新及應用」)



Co-delivery of Celecoxib and TGF- β 1 by the PCL-CD polymersomes reduces aberrant subchondral bone formation and attenuates articular cartilage degeneration in animal osteoarthritic knees. (A) Quantitative analysis and (B) 3D reconstruction of subchondral bone by μ CT scanning. BV/TV (BV: bone volume; TV: total defect volume) in subchondral bone determined by μ CT ($n = 6$). (C) Safranin-O/Fast green and Hematoxylin/Eosin staining of the histological sectioning of the rat knee joints 6 weeks after the injection. (C+T: 0.4% Celecoxib + 5 mg/ml TGF- β 1 free drug group; PS+C+T: PCL-CD polymersome encapsulated 0.4% Celecoxib + 5 mg/ml TGF- β 1 group; PS+C: PCL-CD polymersome encapsulated 0.4% Celecoxib group; PS+T: PCL-CD polymersome encapsulated 5 mg/ml TGF- β 1 group.

Source: Zhu M, Wei K, Lin S, Chen X, Wu CC, Li G, Bian L. Bioadhesive Polymersome for Localized and Sustained Drug Delivery at Pathological Sites with Harsh Enzymatic and Fluidic Environment via Supramolecular Host-Guest Complexation. *Small*. 2018;14(7):1702288. doi:10.1002/smll.201702288

Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Gang Li	華夏醫學科技獎一等獎：「肢體複雜組織缺損修復重建關鍵技術的創新及應用」 1 st Class Award in China Medical Science, China International Exchange and Promotion Association for Medical and Healthcare (2018-12)
Gang Li	Distinguished Tang Aoqing Guest Professorship, Jilin University, China
Gang Li	Adjunct Professor, Australian Regenerative Medicine Institute (ARMI), Monash University, Australia
Gang Li	Visiting Professor, Department of Orthopaedic Surgery and Traumatology, University of Malaya, Malaysia
Gang Li	Visiting Professor, Guang Dong Medical College, Dongguan, China
Gang Li	Visiting Scholar, Department of Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand
Gang Li	Visiting Professor, Xijing Orthopadeic Hospital, The Air Force Medical University, Xian, China
Gang Li	Visiting Professor, Shenzhen Baoan People's Hospital, Shenzhen, China
Gang Li	Visiting Professor, China Medical University, Shenyang, China
Gang Li	Visiting Professor, South Eastern University Medical School, Nanjing, China
Gang Li	Council member, Chinese Orthopaedic Research Society, Chinese Orthopaedic Association 中國骨科醫學會基礎醫學組委員
Gang Li	General Secretary, Division of Limb Deformity Correction and Reconstruction, Chinese Association of Orthopaedic Surgeons
Gang Li	Chairman of China Branch, International Limb Lengthening and Reconstruction Societies (ILLRS) and Association from Study and Application of the Methods of Ilizarov (ASAMI) (國際肢體延長和重建學會·Ilizarov方法研究和應用協會中國部主席)

Fellowships

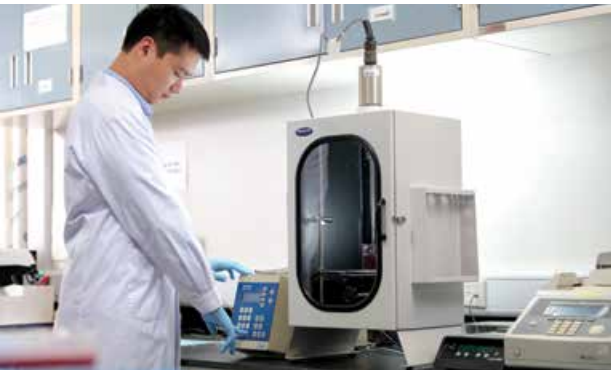
Member's Full Name	Details
Gang Li	Fellow of International Combined Orthopaedic Research Societies

Academic Editorship and Reviews

Member's Full Name	Details
Gang Li	Associate Editor, Journal of Orthopaedic Translation
Gang Li	Member of Editorial Board, Calcified Tissue International
Gang Li	Member of Editorial Board, Bone and Joint Research
Gang Li	Member of Editorial Board, Bone

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Gang LI	Biomaterials-mediated Bone Formation and Consolidation in Distraction Osteogenesis	Research Grants Council – General Research Fund	05/09/2017	14/09/2020	1,098,710
Gang LI	Is Smad7 a Potential Therapeutic Target for Preventing Osteoporotic Bone Loss?	Research Grants Council – General Research Fund	01/01/2016	31/12/2018	821,097
Gang LI	PEMF Effects on MSCs Chondrogenic Differentiation and Cartilage Lesion Repair	Orthofix Company, USA	31/12/2017	31/12/2019	2,478,510
Gang LI	血管和神經化促進組織工程骨形成的機制研究	The National Natural Science Foundation of China	01/03/2015	31/12/2019	RMB 600,000
Gang LI	A Micro Array Chip based Single Cell Manipulation System for Characterization of Electrical Stimulation Induced Stem Cell Differentiation	The National Natural Science Foundation of China – Research Grant Council Joint Research Scheme	01/01/2016	31/12/2019	400,000
Gang LI	Development of Bio-scaffold Encapsulating Human Fetal Mesenchymal Stem Cells Secretion for Promoting Difficult Skin Wound Healing	Hong Kong Innovation Technology Commission	01/03/2017	28/02/2019	1,969,301
Gang LI	Development of Bio-scaffold Encapsulating Human Fetal Mesenchymal Stem Cells Secretion for Promoting Difficult Skin Wound Healing	Hong Kong Innovation Technology Commission Internship	01/03/2017	28/02/2019	904,624
Gang LI	Functional Bone Regeneration in Challenging Bone Disorders and Defects	Research Grants Council – Theme-based Research Scheme	01/11/2017	31/10/2022	33,333,333



Publications

1. Suen WCW, Lee WYW, Leung KT, Pan XH, Li G. Natural killer cell-based cancer immunotherapy: A review on 10 years completed clinical trials. *Cancer Investigation*. 2018;36(8):431-457. doi:10.1080/07357907.2018.1515315. (Review)
2. Chen Y, Zhang D, Ho KW, Lin S, Suen WCW, Zhang H, Zha Z, Li G, Leung PS. GPR120 is an important inflammatory regulator in the development of osteoarthritis. *Arthritis Research & Therapy*. 2018;20(1):163. doi:10.1186/s13075-018-1660-6.
3. Liu Y, Feng L, Wang H, Wang Y, Chan HC, Jiang X, Fu W, Li G, Zhang J. Identification of an anti-inflammation protein, annexin A1, in tendon derived stem cells (TDSCs) of cystic fibrosis mice: A comparative proteomic analysis. *PROTEOMICS – Clinical Applications*. 2018;12(6):1700162. doi:10.1002/prca.201700162.
4. Lin S, Cui L, Chen G, Huang J, Yang Y, Zou K, Lai Y, Wang X, Zou L, Wu T, Cheng JCY, Li G, Wei B, Lee WYW. PLGA/ β -TCP composite scaffold incorporating salivianolic acid B promotes bone fusion by angiogenesis and osteogenesis in a rat spinal fusion model. *Biomaterials*. 2019;196:109-121. doi:10.1016/j.biomaterials.2018.04.004.
5. Kang H, Jung HJ, Kim SK, Wong DSH, Lin S, Li G, Dravid VP, Bian L. Magnetic manipulation of reversible nanocaging controls *in vivo* adhesion and polarization of macrophages. *ACS Nano*. 2018;12(6):5978-5994. doi:10.1021/acsnano.8b02226.
6. Qin L, Chen CH, Genant HK, Guo XD, Li G, O’Keefe R, Richards RG, Tang T, Chan K. The impact of translational orthopaedic research: Journal of Orthopaedic Translation indexed in Science Citation Index Expanded. *Journal of Orthopaedic Translation*. 2018;12:A1-A2. doi:10.1016/j.jot.2018.01.004. (Editorial)
7. Zhang YJ, Chen X, Li G, Chan KM, Heng BC, Yin Z, Ouyang HW. Concise review: Stem cell fate guided by bioactive molecules for tendon regeneration. *STEM CELLS Translational Medicine*. 2018;7(5):404-414. doi:10.1002/sctm.17-0206. (Review)
8. Feng L, Shi L, Lu Y, Wang B, Tang T, Fu W, He W, Li G, Zhang J. Linc-ROR promotes osteogenic differentiation of mesenchymal stem cells by functioning as a competing endogenous RNA for miR-138 and miR-145. *Molecular Therapy - Nucleic Acids*. 2018;11:345-353. doi:10.1016/j.omtn.2018.03.004.
9. Shi L, Feng L, Liu Y, Duan J, Lin W, Zhang J, Li G. MicroRNA-218 promotes osteogenic differentiation of mesenchymal stem cells and accelerates bone fracture healing. *Calcified Tissue International*. 2018;103(2):227-236. doi:10.1007/s00223-018-0410-8
10. Wu T, Zhang J, Wang B, Sun Y, Liu Y, Li G. Staphylococcal enterotoxin C2 promotes osteogenesis of mesenchymal stem cells and accelerates fracture healing. *Bone & Joint Research*. 2018;7(2):179-186. doi:10.1302/2046-3758.72.BJR-2017-0229.R1.
11. Peng X, Wu X, Zhang J, Zhang G, Li G, Pan X. The role of CKIP-1 in osteoporosis development and treatment. *Bone & Joint Research*. 2018;7(2):173-178. doi:10.1302/2046-3758.72.BJR-2017-0172.R1.

12

STEM CELLS AND REGENERATION

Stem Cell and Vascular Regeneration



Principal Investigator
Professor Kathy Lui



Team

Kevin Yang | Rachel Tam | Cai Liang | Jiatao Li | Xisheng Li |
Di Liu | Jeffrey Leung | Vicken Chan | Michael Yu | Tiffany Fung



■ Research Progress Summary

During the past years, Professor Kathy Lui and her team have been studying the pathogenesis of cardiovascular complications associated with diabetes; and developing new strategies including human pluripotent stem cells, therapeutic modified mRNAs, monoclonal antibodies and temporal yet precise lineage-tracing mouse models with the hope to improve cardiovascular function and promote cardiovascular regeneration especially hyperglycemic conditions. Specifically the team has been carrying out a few novel projects: (1) the role of hyperglycemia in second heart field and heart progenitor development; (2) the role of adaptive immune system in the pathogenesis of cardiovascular diseases; and (3) therapeutic modification of diseased model's immune system for driving cardiovascular regeneration. In particular, the team has uncovered the role of immune system in the pathogenesis and repair of the cardiovascular system.

In 2018, two immunologists shared the Nobel Prize in Physiology and Medicine for their contribution on cancer therapy by inhibition of negative immune regulation via CTLA-4 and PD-1. These checkpoint molecules inhibit effector T-cell survival and function, but their role in regulatory T-cells has been elusive. The team's studies report that immune tolerance through proliferation of regulatory T-cells requires a functional PD-1 signalling (Leung CS et al., *Genome Medicine*, 2018). Moreover, they reported that regulatory T-cells also directly facilitate endothelial cell regeneration after ischemic injury in type-2 diabetes (Leung OM et al., *Cell Reports*, 2018). Currently, they have been revising a manuscript that also documents the role of these cells in regenerating the injured heart. That explains why they lost their capability to regenerate a damaged heart through development. The team will introduce in more details after the manuscript published next year.

■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Kathy Lui	Member, The Young Academy of Sciences of Hong Kong
Kathy Lui	Member, Task Force on the Regulation of Advanced Therapy Products, Department of Health

Fellowships

Member's Full Name	Details
Kevin Yang	Research Committee Research Fellowship 2018
Rachel Tam	Faculty Postdoctoral Fellowship 2018

Academic Editorships and Reviews

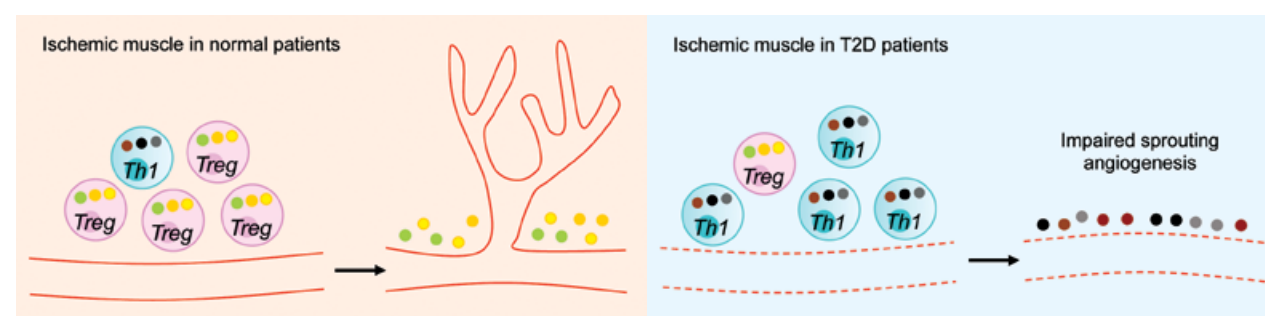
Member's Full Name	Details
Kathy Lui	Associate Editor, Stem Journal
Kathy Lui	Editorial Board Member, Scientific Reports

Journal / Conference Reviews

Member's Full Name	Details
Kathy Lui	Reviewer, Cellular and Molecular Immunology
Kathy Lui	Reviewer, Development
Kathy Lui	Reviewer, International Journal of Molecular Sciences
Kathy Lui	Reviewer, Journal of Cardiovascular Development and Disease
Kathy Lui	Reviewer, Stem Cell Reports
Kathy Lui	Reviewer, Oncotarget
Kathy Lui	Reviewer, Frontiers in Endocrinology
Kathy Lui	Reviewer, Stem Cell Research and Therapy

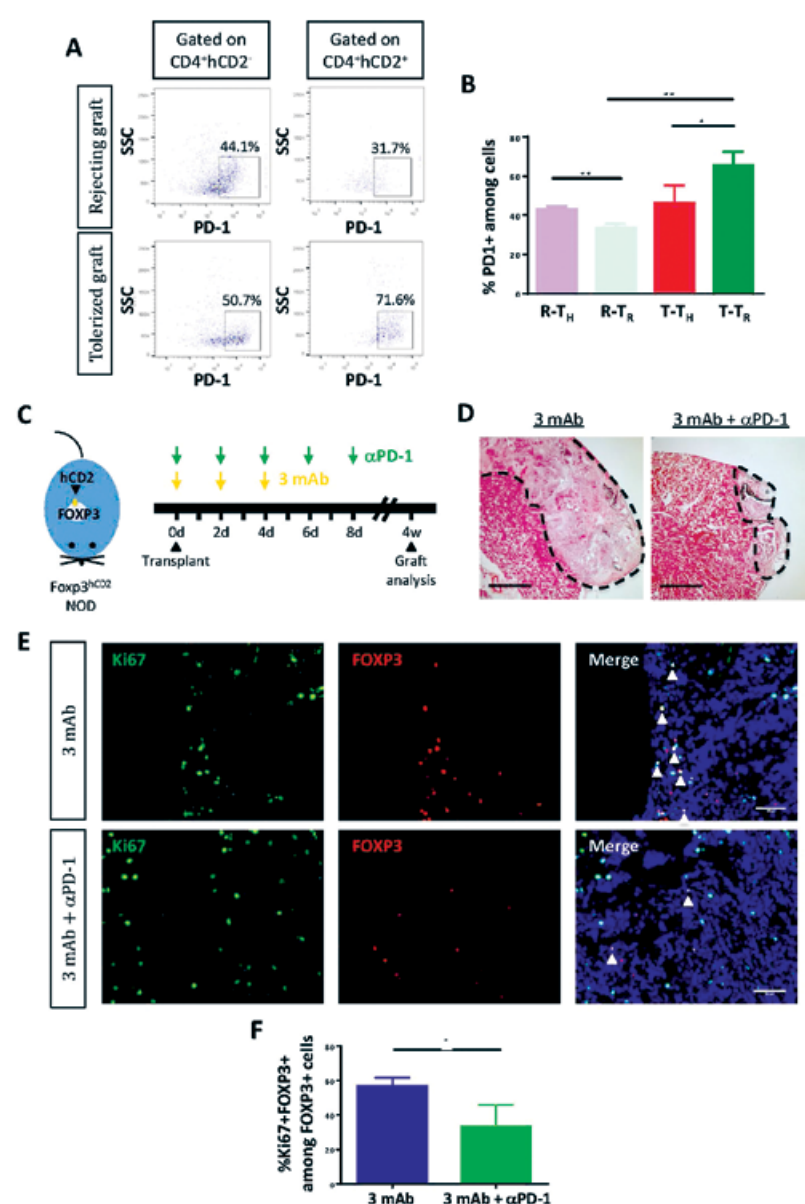
Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Kathy Lui	Driving Pancreatic Beta Cell Regeneration by VEGF Modified mRNA	Research Grants Council – Early Career Scheme	01/01/2016	31/12/2018	816,435
Kathy Lui	Driving Pancreatic Beta Cell Regeneration by VEGF Modified mRNA	Education fund from Research Grants Council – Early Career Scheme	01/01/2016	31/12/2018	50,000
Kathy Lui	Studying the Effect of Hyperglycemia on Development of the Multipotent Islet1+ heart Progenitors with Implications on Congenital Heart Diseases Using Human Embryonic Stem Cells	Seed Fund from Lui Chi Woo Institute of Innovative Medicine (CARE programme)	01/01/2016	31/12/2018	400,000
Kathy Lui	Transplantation of Vascularized Pancreatic Beta Cells Derived from Human Stem Cells for Type-1 Diabetic Recipients	Food and Health Bureau – Health and Medical Research Fund	01/06/2016	31/5/2018	1,199,992
Kathy Lui	Unraveling the Impact of Hyperglycemia on Survival and Cell Fate Commitment of the Human Multipotent ISL1+ Heart Progenitors.	Research Grants Council – General Research Fund	01/01/2017	31/12/2018	902,460
Kathy Lui	Driving Vascular Regeneration Against Diabetic Endothelial Dysfunction with Immune Intervention.	Food and Health Bureau – Health and Medical Research Fund	01/06/2017	31/5/2018	1,198,752
Kathy Lui	Modelling Human Congenital Heart Disease in Diabetes Using the ISL1-Cre lineage Tracing Human Pluripotent Stem Cells	Faculty of Medicine, CUHK – Innovation Award	01/01/2017	31/12/2021	2,500,000
Kathy Lui	Unraveling the Impact of Hyperglycemia on Human Second Heart Field Development	The Croucher Foundations’ Croucher Innovation Award	01/01/2017	31/12/2021	5,000,000
Kathy Lui	A Multi-disciplinary Study on the Beneficial Effects of PPARD in Physical Exercise Against Diabetic Vascular Complications: Cellular Crosstalk and Energy Metabolism.	Research Grants Council – Collaborative Research Fund	30/06/2017	29/6/2020	500,000
Kathy Lui	Joint R&D of Magnesium-based Orthopaedic Implants	Research Grants Council – Collaborative Research Fund	01/04/2018	31/03/2021	500,000



Regulatory T-cells of the immune system regulate endothelial cell regeneration after ischemic injury. More CD4⁺ helper T-cells and less regulatory T-cells (Treg) are found in ischemic tissues of T2D patients with peripheral artery diseases. CD4⁺ Th1 cells inhibit yet Treg potentiate de novo sprouting angiogenesis in T2D.

Source: Leung OM et al., *Cell Reports*, 2018



Proliferation of regulatory T-cells in tolerated transplants requires functional PD-1 signaling. (A) Flow cytometric analysis and (B) quantification showing expression of PD-1 in CD4⁺hCD2⁺ (T_H) or CD4⁺hCD2⁺ (T_R) cells of rejecting and tolerated grafts, respectively. (C) A schematic diagram showing the protocol for antibody treatments. (D) H&E staining showing graft rejection following treatment with αPD-1 mAb in addition to coreceptor and costimulation blockade (3 mAb). Scale bars: 1000 μm. (E) Immunostaining and (F) quantifications of Ki67⁺FOXP3⁺ cells among total FOXP3⁺ cells in 3 mAb- and 3 mAb + αPD-1 mAb-treated grafts, respectively. Arrows indicate Ki67⁺FOXP3⁺ cells. Scale bars: 50 μm. *P < 0.05. (A-F) n = 5 per group

Source: Leung CS et al., *Genome Medicine*, 2018

Publications

A. Journal Papers

- Tang J, Li Y, Huang X, He L, Zhang L, Wang H, Yu W, Pu W, Tian X, Nie Y, Hu S, Wang QD, Lui KO, Zhou B. Fate Mapping of Sca1⁺ Cardiac Progenitor Cells in the Adult Mouse Heart. *Circulation*. 2018;138(25):2967-2969. doi:10.1161/CIRCULATIONAHA.118.036210 (Letter)
- He L, Li Y, Huang X, Li Y, Pu W, Tian X, Cai D, Huang H, Lui KO, Zhou B. Genetic lineage tracing of resident stem cells by DeaLT. *Nature Protocols*. 2018;13(10):2217-2246. doi:10.1038/s41596-018-0034-5
- Leung CS, Yang KY, Li X, Chan VW, Ku M, Waldmann H, Hori S, Tsang JCH, Lo YMD, Lui KO. Single-cell transcriptomics reveal that PD-1 mediates immune tolerance by regulating proliferation of regulatory T cells. *Genome Medicine*. 2018;10(1):71. doi:10.1186/s13073-018-0581-y
- Liu K, Yu W, Tang M, Tang J, Liu X, Liu Q, Li Y, He L, Zhang L, Evans SM, Tian X, Lui KO, Zhou B. A dual genetic tracing system identifies diverse and dynamic origins of cardiac valve mesenchyme. *Development*. 2018;145(18):dev167775. doi:10.1242/dev.167775
- Leung OM, Li J, Li X, Chan VW, Yang KY, Ku M, Ji L, Sun H, Waldmann H, Tian XY, Huang Y, Lau J, Zhou B, Lui KO. Regulatory T Cells Promote Apelin-Mediated Sprouting Angiogenesis in Type 2 Diabetes. *Cell Report*. 2018;24(6):1610-1626. doi:10.1016/j.celrep.2018.07.019
- Li Y, Zhao H, Huang X, Tang J, Zhang S, Li Y, Liu X, He L, Ju Z, Lui KO, Zhou B. Embryonic senescent cells re-enter cell cycle and contribute to tissues after birth. *Cell Research*. 2018;28(7):775-778. doi:10.1038/s41422-018-0050-6 (Letter)
- Ku M, Ke E, Sabouri-Ghomi M, Abadejos JR, Freeman B, Nham A, Phillips N, Yang KY, Lui KO, Kirak O. Deconstructive somatic cell nuclear transfer reveals novel regulatory T-cell subsets. *Journal of Allergy and Clinical Immunology*. 2018;142(3):997-1000.e4. doi:10.1016/j.jaci.2018.04.038 (Letter)
- Li Y, Lui KO, Zhou B. Reassessing endothelial-to-mesenchymal transition in cardiovascular diseases. *Nature Reviews Cardiology*. 2018;15(8):445-456. doi:10.1038/s41569-018-0023-y (Review)
- Li Y, He L, Huang X, Bhaloo SI, Zhao H, Zhang S, Pu W, Tian X, Li Y, Liu Q, Yu W, Zhang L, Liu X, Liu K, Tang J, Zhang H, Cai D, Ralf AH, Xu Q, Lui KO, Zhou B. Genetic Lineage Tracing of Nonmyocyte Population by Dual Recombinases. *Circulation*. 2018;138(8):793-805. doi:10.1161/CIRCULATIONAHA.118.034250
- Li J, Tan J, Martino MM, Lui KO. Regulatory T-Cells: Potential Regulator of Tissue Repair and Regeneration. *Frontiers in Immunology*. 2018;9. doi:10.3389/fimmu.2018.00585 (Review)
- Zhang H, Lui KO, Zhou B. Endocardial Cell Plasticity in Cardiac Development, *Diseases and Regeneration*. *Circulation Research*. 2018;122(5):774-789. doi:10.1161/CIRCRESAHA.117.312136 (Review)
- Tang J, Zhang H, He L, Huang X, Li Y, Pu W, Yu W, Zhang L, Cai D, Lui KO, Zhou B. Genetic Fate Mapping Defines the Vascular Potential of Endocardial Cells in the Adult Heart. *Circulation Research*. 2018;122(7):984-993. doi:10.1161/CIRCRESAHA.117.312354
- Tang J, Lui KO, Zhou B. Replenishing the damaged heart with oxygen by nature-inspired photosynthesis. *Future Cardiology*. 2018;14(2):101-103. doi:10.2217/fca-2017-0088 (Editorial)
- Cheng THT, Lui KO, Peng XL, Cheng SH, Jiang P, Chan KCA, Chiu RWK, Lo YMD. DNase1 Does Not Appear to Play a Major Role in the Fragmentation of Plasma DNA in a Knockout Mouse Model. *Clinical Chemistry*. 2018 Feb;64(2):406-408. doi: 10.1373/clinchem.2017.280446. (Letter)

12

STEM CELLS AND REGENERATION

Innovative Orthopaedic Biomaterial and Drug Translational Research

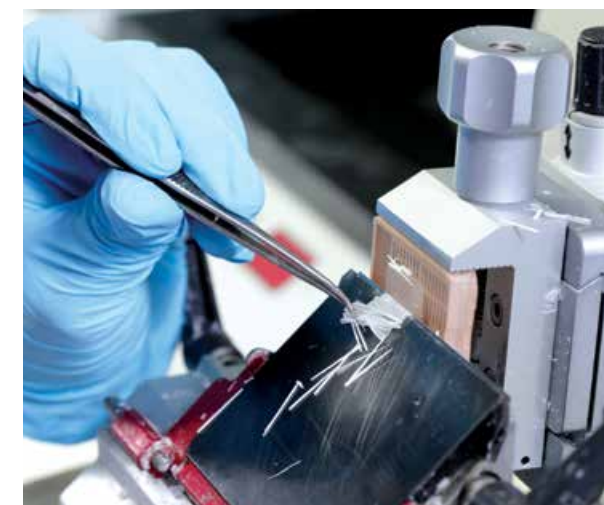


Principal Investigator
Professor Ling Qin



Team

Ziyi Chen | Dick Chow | Can Cui | Bingyang Dai | Xuan He | Le Huang | Xu Li |
Ye Li | Jie Mi | Qianqian Pang | Wenxue Tong | Jiali Wang | Jiankun Xu | Hao Yao |
Ri Zhang | Nianye Zheng | Lizhen Zheng | Liangbin Zhou | Li Zou | Hai Yue Zu



■ Research Progress Summary

Professor Ling Qin and team focus on the research and development of innovative orthopaedic implants and drugs or supplements for prevention and treatment of skeletal disorders and injuries with limited healing potential, including patients with impaired healing capacity, large bone defects, and healing at different tissue types such as the bone-tendon/bone-cartilage interface. He has been developing innovative biomedical and tissue engineering products, clinical indication-orientated treatment regimens and protocols that utilise stem cells, bioactive and biodegradable materials (e.g. biodegradable Magnesium (Mg)), endogenous and exogenous growth factors, and external biophysical stimuli to enhance musculoskeletal tissue regeneration. The goal of his research is to facilitate not only anatomical but more importantly also functional restoration to achieve early rehabilitation and reduce disease associated morbidity and mortality.

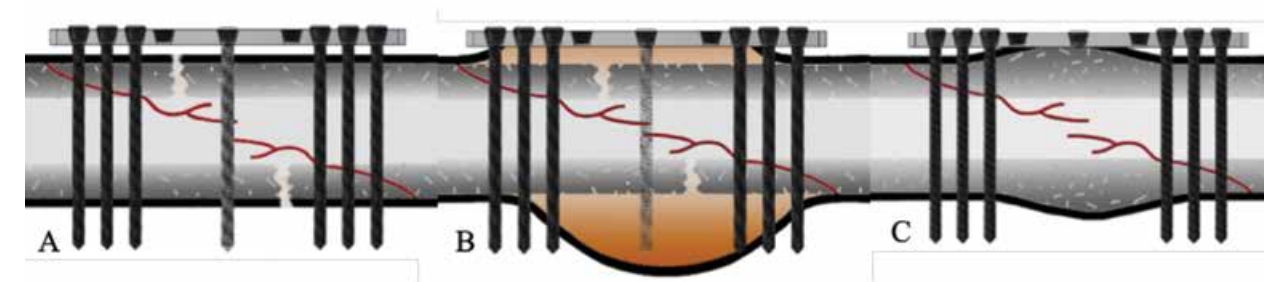


Being multidisciplinary in nature, Professor Qin and his team have been collaborating with local and international engineers and material scientists for developing innovative biomaterials and drugs, such as to redesign the current commercially available implant to incorporate with Mg-based components. Recently, they have tested different Mg-based alloys and have applied different coating to prevent the rapid degradation. One innovative approach is that the team has modified current commercially available implants to incorporate Mg-based components to enhance bone healing. This hybrid

implant, with both conventional titanium metal and Mg components, can deliver Mg to fracture sites also have great potential in facilitating and enhancing fracture healing, which could accelerate an early initiation of mobility and rehabilitation of patients with fractures. They have been working on Collaborative Research Fund and Theme-based Research Scheme which are funded previously and meanwhile also secured one General Research Fund and one Innovation and Technology Fund Tier 2 that enhances the team's collaborations with industrial sectors.

Design of innovative interlocking Ti-Mg hybrid locking screw by Professor Qin's team. This locking screw consists of a Mg-based screw body and a titanium screw head. The screw will be used to stabilize fractured bone with locking plate. The Mg-based screw body will degrade over time and the released Mg ions will stimulate the healing of the fracture.

Source: Mr. Wing Ho Chau



An improved fracture healing mechanism in this application is shown by using our Ti-Mg hybrid locking screw and plate system (A, B and C). A: Fracture is fixed with locking plate and screws. B: the healing process of the fracture fixed with locking plate and screws. This design will leave some space between the plate and bone surface, which will induce callus formation and enhance fracture healing. C: The impaired healing part is avoided and the overall healing quality is enhanced compared to fixation with compression plate.

Source: Mr. Wing Ho Chau

■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Ling Qin, Dick Chow, Jiali Wang, Jiankun Xu	Gold Medal with Congratulations of Jury, The 46 th Edition of the International Exhibition of Inventions of Geneva (11-15 April, 2018)
Jiankun Xu	Savio L-Y. Woo Young Researcher Award, International Symposium on Ligament & Tendon – XVII (21 April, 2018)
Wenxue Tong	Third Young Investigator Prize, the 12 th International Congress on Orthopaedic Advanced Techniques and Clinical Translational Research & the 1 st Young Investigator Forum of International Chinese Musculoskeletal Research Society (4-6 May, 2018)
Jiankun Xu	Second Young Investigator Prize, the 12 th International Congress on Orthopaedic Advanced Techniques and Clinical Translational Research & the 1 st Young Investigator Forum of International Chinese Musculoskeletal Research Society (4-6 May, 2018)
Wenxue Tong	Best Poster of the International Combined Orthopaedic Research Societies, ORS 2018 Annual Meeting (March 9-13, 2018)
Dick Chow	Shihao Liu-Xianyi Zhu Memorial Best Paper Awardee, 9 th International Conference on Osteoporosis and Bone Research, (17-20 Oct, 2018)
Xiaodan Chen	Shihao Liu-Xianyi Zhu Memorial Best Paper Awardee, 9 th International Conference on Osteoporosis and Bone Research, (17-20 Oct, 2018)
Ye Li	Shihao Liu-Xianyi Zhu Memorial Best Paper Awardee, 9 th International Conference on Osteoporosis and Bone Research, (17-20 Oct, 2018)
Jiankun Xu	Webster Jee Travel Award, 9 th International Conference on Osteoporosis and Bone Research, (17-20 Oct, 2018)
Jiankun Xu	Best Oral Presentation Award, 4 th Asia-Pacific Bone & Mineral Research Meeting and Osteoporotic Fracture Prevention & Treatment Conference 2018 (11-13 May, 2018)
Jiankun Xu	PGS Research Output Award 2017, CUHK
Ling Qin, Jiali Wang, Jiankun Xu	2018年中華醫學科技獎獲獎二等獎（第3完成人）「股骨頭壞死的基礎、臨床研究及轉化應用」

Academic Editorships and Reviews

Member's Full Name	Details
Ling Qin	Editor-in-Chief, Journal of Orthopaedic Translation
Ling Qin	Editorial Advisory Board Member, Recent Patents on Biomedical Engineering
Ling Qin	Member, International Society of Musculoskeletal and Neuronal Interactions
Ling Qin	Member, World Journal of Rheumatology
Ling Qin	《中華創傷骨科雜誌》第三屆編委
Ling Qin	Associate Editor, Orthopaedic Surgery (English version of Chin J Orthop Surg)
Ling Qin	Member, Journal Recent Patents on Mechanical Engineering.
Ling Qin	International Review Panel, European Cells & Materials Journal European Cells & Materials Journal
Ling Qin	Editor Board Member, Current Osteoporosis Report

Journal / Conference Reviews

Member's Full Name	Details
Ling Qin	Reviewer, 4 th Asia-Pacific Bone & Mineral Research Meeting and Osteoporotic Fracture Prevention & Treatment Conference 2018 (11-13 May, 2018)

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Ling Qin	Functional Bone Regeneration in Challenging Bone Disorders and Defects	Research Grant Council – Theme-based Research Scheme	01/11/2017	31/10/2022	33,333,000
Ling Qin	Joint R&D of Magnesium-based Orthopaedic Implants	Research Grant Council – Collaborative Research Fund	01/03/2018	28/02/2021	5,545,807
Ling Qin	An Innovative Bio-intramedullary Nail with Osteogenic Mg-ions for Accelerating Bone Defect Repair: A Proof-of-Concept Study	Research Grant Council – General Research Fund	01/01/2018	31/12/2020	929,880

■ Publications

A. Journal Papers

1. Tian L, Tang N, Ngai T, Wu C, Ruan Y, Huang L, Qin L. Hybrid fracture fixation systems developed for orthopaedic applications: A general review. *Journal of Orthopaedic Translation*. 2019;16:1-13. doi:10.1016/j.jot.2018.06.006. (Review)
2. Chow DH, Zheng L, Tian L, Ho K-S, Qin L, Guo X. Application of ultrasound accelerates the decalcification process of bone matrix without affecting histological and immunohistochemical analysis. *Journal of Orthopaedic Translation*. September 2018. doi:10.1016/j.jot.2018.08.001.
3. Lai Y, Cao H, Wang X, Chen S, Zhang M, Wang N, Yao Z, Dai Y, Xie X, Zhang P, Yao X, Qin L. Porous composite scaffold incorporating osteogenic phytomolecule icariin for promoting skeletal regeneration in challenging osteonecrotic bone in rabbits. *Biomaterials*. 2018;153:1-13. doi:10.1016/j.biomaterials.2017.10.025.
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7. Tian L, Sheng Y, Huang L, Chow DHK, Chau WH, Tang N, Ngai T, Wu C, Lu J, Qin L. An innovative Mg/Ti hybrid fixation system developed for fracture fixation and healing enhancement at load-bearing skeletal site. *Biomaterials*. 2018;180:173-183. doi:10.1016/j.biomaterials.2018.07.018.
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9. Zheng N, Liu X, Zhang R, Ho I, Chen S, Xu J, Yao H, Wang J, Yue J, Wang X, Qin L. Jingshu Keli attenuates cervical spinal nerve ligation-induced allodynia in rats through inhibition of spinal microglia and Stat3 activation. *Spine Journal*. 2018;18(11):2112-2118. doi:10.1016/j.spinee.2018.06.354.
10. Hu Y, Zhang T, Huang H, Cheng W, Lai Y, Bai X, Chen J, Yue Y, Zheng Z, Guo C, Qin L, Zhang P. Fracture healing in a collagen-induced arthritis rat model: Radiology and histology evidence. *Journal of Orthopaedic Research*. 2018;36(11):2876-2885. doi:10.1002/jor.24060.

11. Huang L, Wang X, Cao H, Li L, Chow DHK, Tian L, Wu H, Zhang J, Wang N, Zheng L, Yao X, Yang Z, Qin L. A bone-targeting delivery system carrying osteogenic phytomolecule icaritin prevents osteoporosis in mice. *Biomaterials*. 2018;182:58-71. doi:10.1016/j.biomaterials.2018.07.046.
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13. Li ZR, Cheng LM, Wang KZ, Yang NP, Yang SH, He W, Wang YS, Wang ZM, Yang P, Liu XZ, Luo YZ, Sun W, Wang HT, Zheng LZ, Wang XL, Qin L. Herbal Fufang Xian Ling Gu Bao prevents corticosteroid-induced osteonecrosis of the femoral head—A first multicentre, randomised, double-blind, placebo-controlled clinical trial. *Journal of Orthopaedic Translation*. 2018;12:36-44. doi:10.1016/j.jot.2017.11.001.
14. Zheng LZ, Wang JL, Kong L, Huang L, Tian L, Pang QQ, Wang XL, Qin L. Steroid-associated osteonecrosis animal model in rats. *Journal of Orthopaedic Translation*. 2018;13:13-24. doi:10.1016/j.jot.2018.01.003 (Review)
15. Li L, Long J, Li L, Cao H, Tang T, Xi X, Qin L, Lai Y, Wang X. Quantitative determination of residual 1,4-dioxane in three-dimensional printed bone scaffold. *Journal of Orthopaedic Translation*. 2018;13:58-67. doi:10.1016/j.jot.2017.06.004.
16. Yu W, Li R, Long J, Chen P, Hou A, Li L, Sun X, Zheng G, Meng H, Wang Y, Wang A, Sui X, Guo Q, Tao S, Peng J, Qin L, Lu S, Lai Y. Use of a three-dimensional printed polylactide-coglycolide/tricalcium phosphate composite scaffold incorporating magnesium powder to enhance bone defect repair in rabbits. *Journal of Orthopaedic Translation*. 2019;16:62-70. doi:10.1016/j.jot.2018.07.007. (Epub ahead of print)
17. Yan X, Wan P, Tan L, Zhao M, Qin L, Yang K. Corrosion and biological performance of biodegradable magnesium alloys mediated by low copper addition and processing. *Materials Science and Engineering C*. 2018;93:565-581. doi:10.1016/j.msec.2018.08.013.

B. Patent and Trademark Registrations

1. Hybrid Implant System and Manufacturing Method, US Patent (Application no. 15/874,532)
2. Registration of Trade Mark: Mgmax (健鎂牌)

13 GENOMICS AND BIOINFORMATICS



Principal Investigator
Professor Hao Sun



Team

Yile Huang | Yingzhe Ding | Ji Yuan | Anqi Lv |
Liangqinag He | Zhiming He | Fengyuan Chen

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■ Research Progress Summary

In the reporting period, Professor Hao Sun and his team are funded by 13 different grants from RGC/GRF, NSFC-RGC, HMRF, and TBR, for studying of transcriptional regulation mechanisms in muscle stem cells as well as next generation data analysis for plasma DNA/RNA sequencing. His team also published 7 papers on *Nature Methods*, *Nature Communications*, and *Bioinformatics* et al.



Noninvasive reconstruction of the placental methylome

Source: *Prenatal Diagnosis* Vol 38(3) 2018

■ Research and Scholarship

Fellowships

Member's Full Name	Details
Karl So	Postdoctoral Fellowship from Faculty of Medicine

Academic Editorship and Reviews

Member's Full Name	Details
Hao Sun	Associate Editor of Journal of Clinical Biochemistry

Journal / Conference Reviews

Member's Full Name	Details
Hao Sun	Reviewer of Bioinformatics
Hao Sun	Reviewer of Clinical Biochemistry
Hao Sun	Reviewer of Frontier Genomics
Hao Sun	Reviewer of Journal of Clinic Chemistry

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Hao Sun	Functional Dissection of lncRNA SAM in Skeletal Muscle Stem Cells and Muscle Regeneration	Research Grants Council – General Research Fund	01/01/2018	31/12/2020	1,232,466
Hao Sun	LncFunNet: an Integrated Computational Framework for Identification of Functional Long Noncoding RNAs in Mouse Skeletal Muscle Cells	Direct Grant for Research 2017/2018	30/06/2018	29/06/2019	71,000
Hao Sun	Mechanistic Exploration of Super-enhancer Associated seRNA Function in Skeletal Muscle Cells	Research Grants Council – General Research Fund	01/01/2017	31/12/2019	922,171
Hao Sun	Plasma DNA as a Platform Technolgy for Cancer Detection	Focused Innovations Scheme C	01/12/2016	30/11/2021	2,093,500
Hao Sun	Plasma DNA as a Platform Technolgy for Cancer Detection	CUHK Matching Fund for TRS	01/12/2016	30/11/2021	4,444,000
Hao Sun	Centre for Research into Circulating Fetal Nucleic Acids	Research Grants Council – Theme-based Research Scheme	01/01/2016	31/12/2020	48,828,000
Hao Sun	Identification and Functional Characterization of Super Enhancer Associated RNAs (seRNAs) in Skeletal Myogenesis Using Integrated Genomic Approach	Research Grants Council – General Research Fund	01/01/2016	31/12/2018	1,228,445
Hao Sun	Elucidation of the Role of Pax7 in Muscle Stem Cells	Research Grants Council – Collaborative Research Fund	30/06/2015	29/06/2018	5,221,440
Hao Sun	Transplantation of Vascularised Pancreatic Beta Cells Derived from Human Stem Cells for Type-1 Diabetic Recipients	Food and Health Bureau – Health and Medical Research Fund	01/06/2016	31/05/2018	1,199,992
Hao Sun	Is Smad7 a Potential Therapeutic Target for preventing Osteoporotic Bone Loss?	Research Grants Council – General Research Fund	01/01/2016	31/12/2018	821,097
Hao Sun	Functional Characterization of YY1 in Skeletal Muscle Stem Cells and Muscle Regeneration	Research Grants Council – General Research Fund	01/01/2016	31/12/2018	1,182,869

Publications

A. Journal Papers

1. Yuan J, Zhou J, Wang H, Sun H. Skmdb: An integrated database of next generation sequencing information in skeletal muscle. *Bioinformatics* 2019; 35(5): 847-855.doi: 10.1093/bioinformatics/bty705. [Epub in 2018]
2. Sun K, Wang J, Wang H, Sun H. GeneCT: a generalizable cancerous status and tissue origin classifier for pan-cancer biopsies. *Bioinformatics*. 2018;34(23):4129-4130. doi:10.1093/bioinformatics/bty524.
3. Zhou J, Huang Y, Ding Y, Yuan J, Wang H, Sun H. lncFunTK: a toolkit for functional annotation of long noncoding RNAs. *Bioinformatics*. 2018;34(19):3415-3416. doi:10.1093/bioinformatics/bty339. (Editorial)
4. Sun K, Lun FMF, Leung TY, Chiu RWK, Lo YMD, Sun H. Noninvasive reconstruction of placental methylome from maternal plasma DNA: Potential for prenatal testing and monitoring. *Prenatal Diagnosis*. 2018;38(3):196-203. doi:10.1002/pd.5214.
5. Bao X, Guo X, Yin M, Tariq M, Lai Y, Kanwal S, Zhou J, Li N, Lv Y, Pulido-Quetglas C, Wang X, Ji L, Khan MJ, Zhu X, Luo Z, Shao C, Lim DH, Liu X, Li N, Wang W, He M, Liu YL, Ward C, Wang T, Zhang G, Wang D, Yang J, Chen Y, Zhang C, Jauch R, Yang YG, Wang Y, Qin B, Anko ML, Hutchins AP, Sun H, Wang H, Fu XD, Zhang B, Esteban MA. Capturing the interactome of newly transcribed RNA. *Nature Methods*. 2018;15(3):213-220. doi:10.1038/nmeth.4595.
6. Yao M, Zhou X, Zhou J, Gong S, Hu G, Li J, Huang K, Lai P, Shi G, Hutchins AP, Sun H, Wang H, Yao H. PCGF5 is required for neural differentiation of embryonic stem cells. *Nature Communications*. 2018;9(1):1463. doi:10.1038/s41467-018-03781-0.
7. Li Y, Chen X, Sun H, Wang H. Long non-coding RNAs in the regulation of skeletal myogenesis and muscle diseases. *Cancer Letter*. 2018;417:58-64. doi:10.1016/j.canlet.2017.12.015. (Review)

13

GENOMICS AND BIOINFORMATICS



Principal Investigator
Professor Peiyong Jiang



Team

Olivia Tse | Wenlei Peng | Harry Chan | Silvia Deng | Coral Lee | Lu Ji |
Haiqiang Zhang | Sam Chu | Ze Zhou | Meng Ni | Yingming Jiao



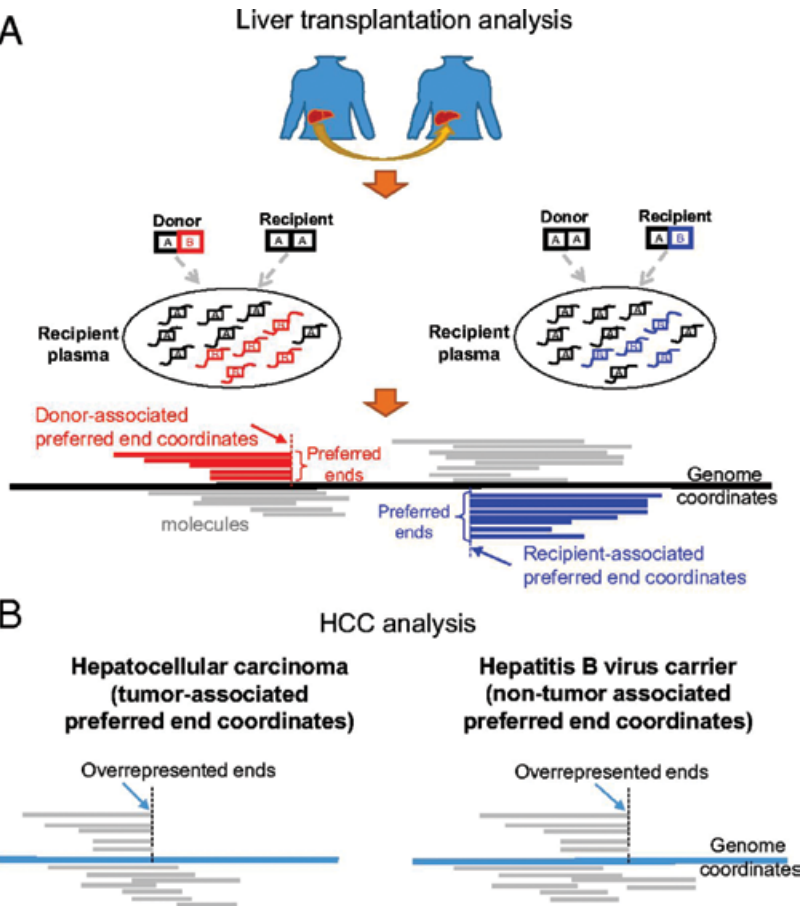
■ Research Progress Summary

In this academic year, Professor Peiyong Jiang and his team have made several important achievements in the bioinformatics area. Cell-free DNA fragmentation is a non-random process. The team made use of such non-randomness to develop a bioinformatics approach for identifying the genomic coordinates which are preferentially cut for generating plasma DNA, termed preferred end coordinates. This analysis further revealed that a great number of preferred ends were associated with cancer, opening up new possibilities for detection and monitoring of cancers. On the other hand, the team took advantage of the biological properties of plasma EBV DNA fragmentation to develop a novel bioinformatics platform for non-invasive screening of nasopharyngeal carcinoma (NPC) at its early stage. Such biological properties of plasma EBV DNA fragmentation were involved with the size lengthening of EBV DNA fragments that was specific to NPC. The integrative analysis of EBV DNA count and size not only improved the overall accuracy on a population screening scale but also reduce two time-points to single time-point testing. Third, the team developed a sophisticated bioinformatics platform to enable integrative and synergistic analysis fragment sizes and fragment ends of plasma DNA, shedding mechanistic insights into the generation of cell-free DNA.

■ Research and Scholarship

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Peiyong Jiang	Plasma DNA as a platform technology for cancer detection	Research Grants Council – Theme-based Research Scheme	01/06/2016	31/05/2020	44,444,000
Peiyong Jiang	Research into Circulating Fetal Nucleic Acids	Research Grants Council – Theme-based Research Scheme	01/01/2016	31/12/2020	37,286,000
Peiyong Jiang	Using Cell-free DNA Size to Improve Noninvasive Prenatal Testing	Innovation and Technology Fund	01/04/2018	30/09/2019	657,800
Peiyong Jiang	Regulation of eosinophil/basophil-innate lymphoid type 2 cells axis by fundamental innate immunity inhibitor IL-37 in atopic dermatitis	Research Grants Council – General Research Fund	01/12/2018	30/11/2020	739,525



Schematic illustration of the principle of identifying cell-free DNA end signatures. (A) SNP-based end signature analysis. (B) Nonpolymorphism based end signature analysis.

Source: Jiang P, Sun K, Tong Y, Cheng S, Cheng T, Heung M, Wong J, Wong V, Chan H, Chan K, Lo Y, Chiu R. Preferred end coordinates and somatic variants as signatures of circulating tumor DNA associated with hepatocellular carcinoma. *Proceedings of the National Academy of Sciences*. 2018;115(46):E10925-E10933.

■ Publications

A. Journal Papers

- Jiang P, Sun K, Tong Y, Cheng S, Cheng T, Heung M, Wong J, Wong V, Chan H, Chan K, Lo Y, Chiu R. Preferred end coordinates and somatic variants as signatures of circulating tumor DNA associated with hepatocellular carcinoma. *Proceedings of the National Academy of Sciences*. 2018;115(46):E10925-E10933.
- Gai W, Ji L, Lam W, Sun K, Jiang P, Chan A, Wong J, Lai P, Ng S, Ma B, Wong G, Wong V, Chan H, Chiu R, Lo Y, Chan K. Liver- and Colon-Specific DNA Methylation Markers in Plasma for Investigation of Colorectal Cancers with or without Liver Metastases. *Clinical Chemistry*. 2018;64(8):1239-1249.
- Lam W, Jiang P, Chan K, Cheng S, Zhang H, Peng W, Tse O, Tong Y, Gai W, Zee B, Ma B, Hui E, Chan A, Woo J, Chiu R, Lo Y. Sequencing-based counting and size profiling of plasma Epstein-Barr virus DNA enhance population screening of nasopharyngeal carcinoma. *Proceedings of the National Academy of Sciences*. 2018;115(22):E5115-E5124.
- Sun K, Jiang P, Wong A, Cheng Y, Cheng S, Zhang H, Chan K, Leung T, Chiu R, Lo Y. Size-tagged preferred ends in maternal plasma DNA shed light on the production mechanism and show utility in noninvasive prenatal testing. *Proceedings of the National Academy of Sciences*. 2018;115(22):E5106-E5114.
- Cheng T, Lui K, Peng X, Cheng S, Jiang P, Chan K, Chiu R, Lo Y. DNase1 Does Not Appear to Play a Major Role in the Fragmentation of Plasma DNA in a Knockout Mouse Model. *Clinical Chemistry*. 2017;64(2):406-408. [Letter]
- Zhu J, Dong J, Ji L, Jiang P, Leung T, Liu D, Ng L, Tsang M, Jiao D, Lam C, Wong C. Anti-Allergic Inflammatory Activity of Interleukin-37 Is Mediated by Novel Signaling Cascades in Human Eosinophils. *Frontier in Immunology*. 2018;9.

14 NON-CODING RNAs



Principal Investigator
Professor Huating Wang



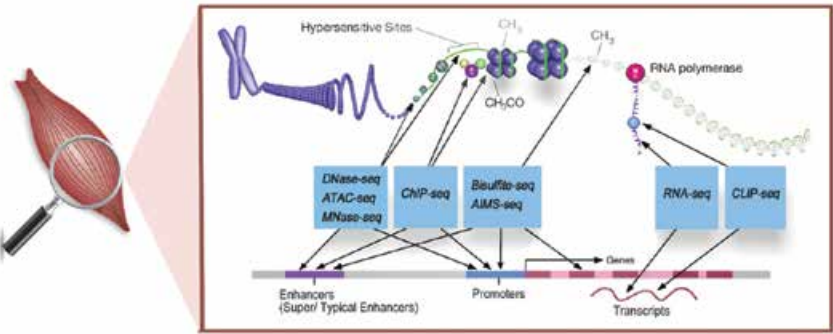
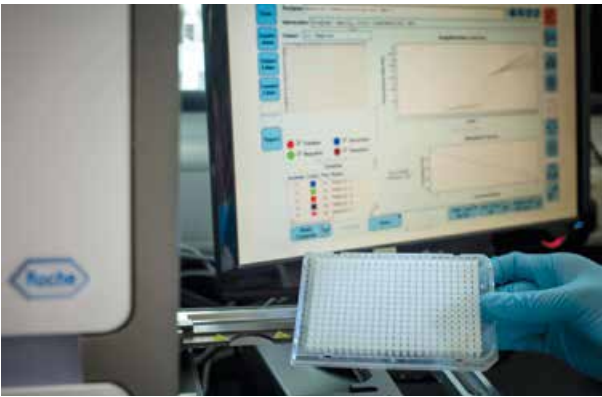
Team

Xiaona Chen | Yu Zhao | Fengyuan Chen | Yuying Li |
Suyang Zhang | Guang Xue | Yang Li | Zhiming He



■ Research Progress Summary

During the past year, the team led by Professor Huating Wang continued the work on RNA binding proteins (RBPs) and RNA protein complex in regulating gene expression in skeletal muscle stem cells and muscle regeneration. Specifically, they have been focusing on the following projects: (1) to elucidate transcriptome wide lncRNA-RBP binding events and identify key RBPs that are important for lncRNA localisation; (2) to study the functional roles of Dhx36 in skeletal muscle stem cells and muscle regeneration; (3) to characterise 3D genome organisation in sarcopenia, a muscle weakening condition associated with aging.



SKmDB: an integrated database of next generation sequencing information in skeletal muscle.

Source: Yuan J, Zhou J, Wang H, Sun H. SKmDB: an integrated database of next generation sequencing information in skeletal muscle. *Bioinformatics*. 2019;35(5):847-855. doi:10.1093/bioinformatics/bty705

■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Fengyuan Chen	Faculty Postdoctoral Fellowship awarded by Faculty of Medicine, CUHK
Huating Wang	FASEB Meeting Best Talk Award
Liangqiang He	再生醫學教育部重點實驗室開放基金

Journal / Conference Reviews

Member's Full Name	Details
Huating Wang	Bone Research , Journal paper reviewer
Huating Wang	Cell Research, Journal paper reviewer
Huating Wang	Nucleic Acid Research , Journal paper reviewer
Huating Wang	Oncogene, Journal paper reviewer

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Huating Wang	Functional Dissection of lncRNA SAM in Skeletal Muscle Stem Cells and Muscle Regeneration	Research Grants Council – General Research Fund	01/01/2018	31/12/2020	1,232,466
Huating Wang	Epigenetic Mapping in Human Skeletal Muscle Stem Cells	Hong Kong Epigenomics Project (EpiHK) fund	01/08/2018	31/12/2023	1,000,000
Huating Wang	Functional Characterization of YY1 in Skeletal Muscle Stem Cells and Muscle Regeneration	Research Grants Council – General Research Fund	01/01/2016	31/12/2018	1,182,869
Huating Wang	Integrating Large Intergenic Noncoding RNAs into Pax7 Mediated Regulatory Circuitry in Muscle Satellite Cells	Research Grants Council – General Research Fund	01/01/2015	31/12/2018	623,277
Huating Wang	Elucidation of the Role of Pax7 in Muscle Stem Cells	Research Grants Council – Collaborative Research Fund	01/08/2015	31/07/2018	750,000
Huating Wang	Identification and Functional Characterization of Super Enhancer Associated RNAs (seRNAs) in Skeletal Myogenesis using Integrated Genomic Approach	Research Grants Council – General Research Fund	01/01/2016	31/12/2018	1,086,500
Huating Wang	Is there a Link between Systemic Muscle Mass, Muscle Strength, Serum and Muscle Expression of Myokines and Lbx1 with Bone Mineral Density and Bone Quality in Adolescent Idiopathic Scoliosis?	Research Grants Council – General Research Fund	01/01/2016	31/12/2018	593,675
Huating Wang	Mechanistic Exploration of Super-enhancer Associated seRNA Function in Skeletal Muscle Cells	Research Grants Council – General Research Fund	01/01/2017	31/12/2019	922,171
Huating Wang	Investigate the role of satellite cell derived M-CSF in regulating macrophage function during skeletal muscle regeneration	Research Grants Council – PROCORE-France/ Hong Kong Joint Research Scheme	01/01/2018	01/01/2020	86,400
Huating Wang	Mechanistic investigation of Linc-p27 function in skeletal muscle satellite cell and muscle regeneration	CUHK Direct Grant	30/06/2018	29/06/2019	71,000

Publications

A. Journal Papers

1. Peterson JM, Wang DJ, Shettigar V, Roof SR, Canan BD, Bakkar N, Shintaku J, Gu JM, Little SC, Ratnam NM, Londhe P, Lu L, Gaw CE, Petrosino JM, Liyanarachchi S, Wang H, Janssen PML, Davis JP, Ziolo MT, Sharma SM, Guttridge DC. NF- κ B inhibition rescues cardiac function by remodeling calcium genes in a Duchenne muscular dystrophy model. *Nature Communications*. 2018;9(1):3431. doi:10.1038/s41467-018-05910-1.

2. Yuan J, Zhou J, Wang H, Sun H. Skmdb: An integrated database of next generation sequencing information in skeletal muscle. *Bioinformatics* 2019; 35(5): 847-855.doi: 10.1093/bioinformatics/bty705. [Epub in 2018]

3. Sun K, Wang J, Wang H, Sun H. GeneCT: a generalizable cancerous status and tissue origin classifier for pan-cancer biopsies. BergerB, ed. *Bioinformatics*. 2018;34(23):4129-4130. doi:10.1093/bioinformatics/bty524.

4. Yao M, Zhou X, Zhou J, Gong S, Hu G, Li J, Huang K, Lai P, Shi G, Hutchins AP, Sun H, Wang H, Yao H. PCGF5 is required for neural differentiation of embryonic stem cells. *Nature Communications*. 2018;9(1):1463. doi:10.1038/s41467-018-03781-0.

5. Zhou J, Huang Y, Ding Y, Yuan J, Wang H, Sun H. lncFunTK: a toolkit for functional annotation of long noncoding RNAs. ValenciaA, ed. *Bioinformatics*. 2018;34(19):3415-3416. doi:10.1093/bioinformatics/bty339. [Editorial]

6. Bao X, Guo X, Yin M, Tariq M, Lai Y, Kanwal S, Zhou J, Li N, Lv Y, Pulido-Quetglas C, Wang X, Ji L, Khan MJ, Zhu X, Luo Z, Shao C, Lim DH, Liu X, Li N, Wang W, He M, Liu YL, Ward C, Wang T, Zhang G, Wang D, Yang J, Chen Y, Zhang C, Jauch R, Yang YG, Wang Y, Qin B, Anko ML, Hutchins AP, Sun H, Wang H, Fu XD, Zhang B, Esteban MA. Capturing the interactome of newly transcribed RNA. *Nature Methods*. 2018;15(3):213-220. doi:10.1038/nmeth.4595.

7. Li Y, Chen X, Sun H, Wang H. Long non-coding RNAs in the regulation of skeletal myogenesis and muscle diseases. *Cancer Letter*. 2018;417:58-64. doi:10.1016/j.canlet.2017.12.015. [Review]

B. Conference Papers

1. Zhao Y, Zhou J, He L, Sun H, Wang H. "Functional investigation of seRNAs in skeletal myogenic differentiation". In: *Keystone Symposia: Noncoding RNAs: Form, Function, Physiology 2018*

2. Chen X, Xue G, Yuan J, Sun H, Wang H. "Mechanistic investigation of Linc-p27 function in skeletal muscle satellite cell and muscle regeneration". In: *The 4th China Muscle Symposium 2018*

3. Li Y, Yuan J, Zhang S, Chen F, Zhao Y, Lu L, Zhou L, Sun H, Wang H "Functional study of long noncoding RNA SAM in skeletal muscle stem cells and muscle regeneration". In: FASEB meeting, Steamboat, Colorado, USA, 2018 July

4. Zhao Y, Zhou J, He L, Sun K, Chen X, Li Y, Bao X, Estedan MA, Sun H, Wang H "MyoD induced enhancer RNA interacts with hnRNPL protein via CAAA motif to activate target gene transcription during myogenic differentiation". In: *International Human Epigenome Consortium Annual Meeting 2018 Oct*

15 CELLULAR SIGNALLING

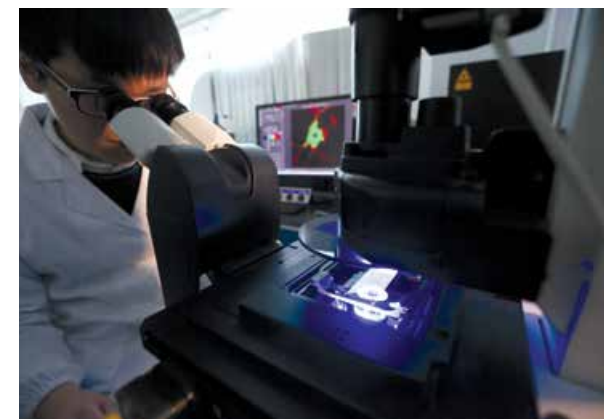
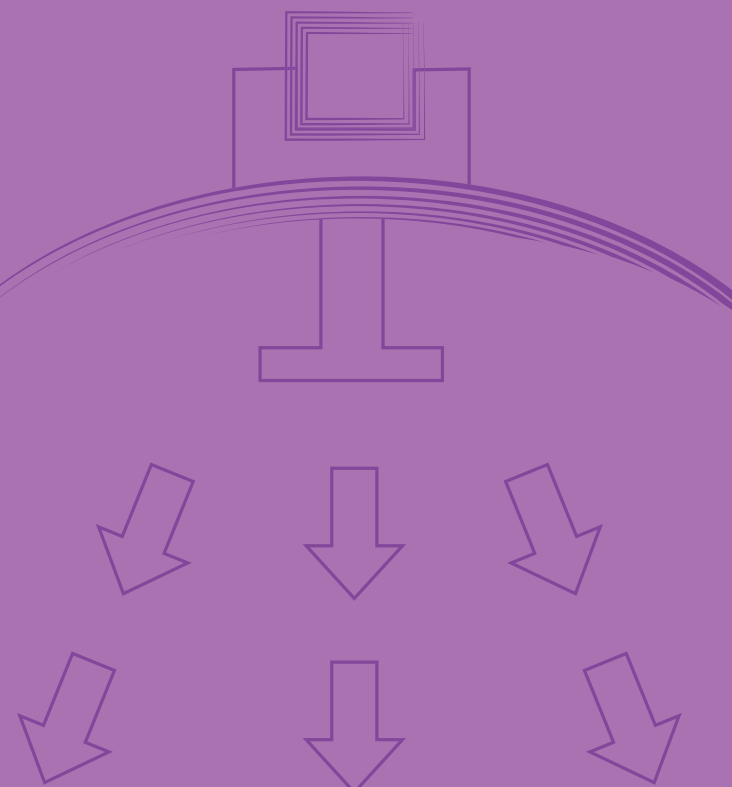


Principal Investigator
Professor William Wu



Team

Tony Gin | Matthew TV Chan | Lin Zhang | Xiaodong Liu | Wei Hu |
Idy HT Ho | Yuanyuan Tian | Jeffery Ho | Qing Li | Hung Chan |
Xiansong Wang | Judeng Zeng | Yidan Zou | Yuchen Zhang | TP Tam



■ Research Progress Summary

Evolutionary Medicine – Cancer genomics was investigated from an evolutionary perspective. The research team led by Professor William Wu found that oncogenes expand in size whereas tumour-suppressor genes move closer to small oncogenes in the course of evolution to withstand oncogenic somatic amplification. Their findings have shed new light on the previously unappreciated influence of gene size on oncogene amplification and elucidated how cancers have shaped our genome to its present configuration.

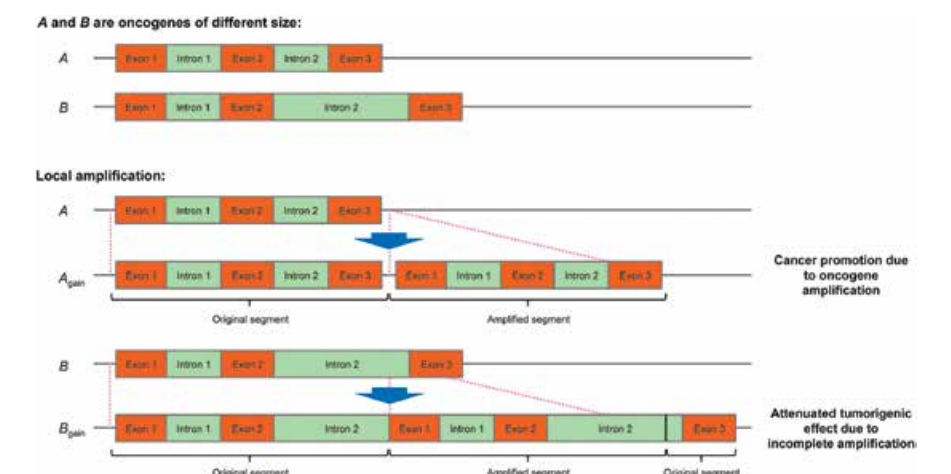
Autophagy – The team found that *Helicobacter pylori*, one of the most prevalent infectious pathogens in the world, could subvert autophagy into a pro-survival mechanism through inhibition of lysosomal clearance of autophagosomes. Disruption of autophagosome formation offers a novel strategy to

reduce *H. pylori* colonisation in human stomachs. In another study, they found that autophagy could serve as a pro-death mechanism mediating the cytotoxic action of Toxin B secreted by *Clostridium difficile* in colonocytes. Defective lysosomal clearance of autophagosomes was also found to be involved in the development of non-alcoholic steatohepatitis.

Pain Mechanism – Chronic postsurgical pain affects 9 to 80% of patients, but genetic determinants are not well identified. By targeted genotyping, the team found that a genetic variant of BDNF rs6265G>A is associated with decreased risk of chronic postsurgical pain. Mice with corresponding genetic alteration also exhibited less pain response in a plantar incision model of chronic postsurgical pain.

Proposed mechanism of survival advantage underlying larger gene size of oncogenes.

Source: *Annals of Oncology* 2018;29(11):2254-2260.



■ Research and Scholarship

Fellowships

Member's Full Name	Details
William Wu	Fellow of Royal College of Physicians of Edinburgh, UK

Academic Editorships and Reviews

Member's Full Name	Details
William Wu	Guest Editor of Seminars in Cancer Biology
William Wu	Editorial Board Member of Scientific Reports
William Wu	Editorial Board Member of Journal of Pharmacy and Pharmacology

Journal / Conference Reviews

Member's Full Name	Details
William Wu	Ad hoc reviewer for Oncogene

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
William Wu	Co-inhibition of Autophagy and Proteasome for Treatment of Malignant Pleural Mesothelioma	Pneumoconiosis Compensation Fund Board	01/08/2017	31/07/2019	2,146,552
William Wu	Preservation of Gut Barrier Function by Cathelicidin in Severe Sepsis	Food and Health Bureau – Health and Medical Research Fund	01/09/2017	31/08/2019	1,199,152
William Wu	Elucidating the Role of Autophagy in the Pathogenicity of <i>Clostridium difficile</i> Infection	Food and Health Bureau – Health and Medical Research Fund	10/09/2016	09/09/2018	1,199,040
William Wu	Targeting Defective Autophagy and its Molecular Sequelae in Non-alcoholic Fatty Liver Disease-related Hepatocellular Carcinoma	Research Grants Council – General Research Fund	01/01/2016	31/12/2018	813,275
William Wu	The Role of Autophagy in CD24-driven Colorectal Tumorigenesis	The Natural Science Foundation of Guangdong Province, Department of Science and Technology of Guangdong Province	01/08/2015	01/08/2018	RMB 100,000

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Tony Gin	Safety of Perioperative Dexamethasone in Major Noncardiac Surgery – A Randomized Noninferiority Trial	Research Grants Council – General Research Fund	01/03/2017	31/03/2020	190,857
Matthew Chan	Role of Intestinal Microbes in Sepsis	Australian and New Zealand College of Anaesthetists – Project Grant	01/01/2018	31/12/2018	AU\$ 70,000
Matthew Chan	Pharmacokinetics of Oseltamivir in Critically Ill Patients with Severe Influenza	Food and Health Bureau – Commissioned Research on Control of Infectious Diseases	01/04/2015	30/09/2019	290,000
Lin Zhang	Activating Mucolipin for Restoring Lysosomal Function in the Control of Helicobacter Pylori Colonization	Food and Health Bureau – Health and Medical Research Fund	01/09/2017	31/08/2019	1,198,360
William Wu	Development of a Novel Dentotropic Antimicrobial Peptide to Prevent Dental Caries	Food and Health Bureau – Health and Medical Research Fund	01/04/2018	31/03/2020	708,384
William Wu	Targeting Sphingosine Kinase 1 for Alleviating Intestinal Epithelial Injury in Sepsis	Food and Health Bureau – Health and Medical Research Fund	17/09/2018	24/01/2019	943,030
William Wu	Regulation of Autophagy by the Novel Tumor Suppressor Gene GGT7 in Gastric Cancer	Research Grants Council – General Research Fund	01/12/2018	30/11/2021	965,601
William Wu	Elucidation of a Novel Tumor Suppressor Gene Tripartite Motif 67 (TRIM67) in Colorectal Cancer	Research Grants Council – General Research Fund	01/01/2017	31/12/2019	1,154,550
William Wu	Functional Characterization of Squalene Epoxidase in Promoting Fatty Liver Disease-associated Liver Cancer	Research Grants Council – General Research Fund	01/01/2016	31/12/2018	1,141,432
William Wu	Dissecting an Inflammatory-CCRK Circuitry in Non-alcoholic Fatty Liver Disease-related Hepatocarcinogenesis	Research Grants Council – General Research Fund	01/10/2016	31/03/2019	763,612
William Wu	Bufalin, a Traditional Chinese Medicine (TCM) Compound, for Chemoprevention of Colorectal Cancer	Food and Health Bureau – Health and Medical Research Fund	01/09/2016	29/02/2020	1,030,704

■ Publications

A. Journal Papers

1. Wang X, Li X, Zhang L, Wong SH, Wang MHT, Tse G, Dai RZW, Nakatsu G, Coker OO, Chen Z, Ko H, Chan JYK, Liu T, Cheng CHK, Cheng ASL, To KF, Plewczynski D, Sung JJY, Yu J, Gin T, Chan MTV, Wu WKK. Oncogenes expand during evolution to withstand somatic amplification. *Annals of Oncology*. 2018;29(11):2254-2260. doi:10.1093/annonc/mdy397.
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B. Books / Book Chapters

1. Wu WKK, Zhang L, Chan MTV. Autophagy, NAFLD and NAFLD-related HCC. In: Obesity, Fatty Liver and Liver Cancer 2018 pp. 127-138 Singapore: Springer
2. Zhang L, Hu W, Ho J, Fitzgerald RJ, Gin T, Chan MTV, Wu WKK. Antimicrobial peptides in the host-microbiota homeostasis. In: Antimicrobial Peptides in Gastrointestinal Diseases 2018 pp. 23-33 Elsevier

INTERVIEWS OF PRINCIPAL INVESTIGATORS

與首席研究員對話





Interview with Professor Oscar Lee

李光申教授

Born and raised in Taiwan, Professor Oscar Lee completed his Medical Degree and training in Taiwan before pursuing postgraduate study at the University College London under the supervision of Professor Gordon Blunn. Prof. Lee then returned to Taiwan and has been very actively involved in clinical duties, teaching and research for more than 10 years. Prof. Lee is a renowned orthopaedic surgeon and stem cell scientist. He specialises in adult joint reconstruction and musculoskeletal tumour surgeries. Prof. Lee has joined The Chinese University of Hong Kong as Professor at the Department of Orthopaedics and Traumatology, and Institute for Tissue Engineering and Regenerative medicine since 2018.

01

You have been working and teaching in Taiwan since returning from the UK for your Master and PhD studies. What contributes to your decision in moving to Hong Kong to continue your career? Any special pushing or pulling factors?



I am recruited under the Global Strategic Recruitment Scheme of The Chinese University of Hong Kong. Our new Vice-chancellor, Prof. Rocky Tuan, is one of the important reasons for me to make the decisions, as Prof. Tuan and I have known each other for a long time and we have worked together academically in

a journal called *Stem Cell Research and Therapy*, of which he is the Editor-in-Chief and I serve as the Associate Editor for years. We do have a very close working relationship. When I was approached by Prof. Tuan, he shared with me his vision about the establishment of the Institute for Tissue Engineering and Regenerative Medicine. On top of the fact that many of the clinical professors in the Department of Orthopaedics and Traumatology in CUHK are my friends, so I decided to take these opportunities and challenges to move to Hong Kong.

Another reason is the changes in global atmosphere or the environment. In the past, Hong Kong is famous for the financial industry, manufacturing and logistics, but not that much in bio-technology. Since the launching of some new schemes by the current Chief Executive, lots of efforts and resources have been devoted to the development of bio-technology,



which shows the determination of developing bio-technology in Hong Kong. I believe I would have better opportunities to further translate my findings or inventions from the laboratory into applications. The solid financial industry is of great support and a lot of other supporting systems, for example the legal system and the accounting system, are all very well established in Hong Kong. The solid infrastructure is already there, and the Greater Bay Area projects launch by the Mainland China is of course going to bring a lot of opportunities to Hong Kong. All these are reasons attributing to my decision of moving to Hong Kong.



02

Having been working and living in Taiwan for a long time, how do you find your current life in Hong Kong? Any challenges in adapting to the pace or environment in Hong Kong?

“ Hong Kong is a cosmopolitan city with good fusion of Western and Eastern cultures, which I would describe as a wonderful place where East meets the West. There are a lot of traditional Chinese cultures being very well preserved and kept in Hong Kong. As an ethnic Chinese, I am very much into it. I do enjoy the life here in Hong Kong. On top of that, Hong Kong is a very modern and westernised city. So far, I have integrated into the working environment reasonably well because of my previous experiences of studying and working in the UK. There are still certain similarities between cities like London and Hong Kong. I do enjoy working and living here in Hong Kong.

Hong Kong people do walk very fast and that people work and live at a very rapid pace. This is something pretty new and fresh to me and I do enjoy that. And for myself, I am actually a fast walker too, so I am very much into this speed or rhythm. ”

03

Why would you decide to be an orthopaedic surgeon? Is being an orthopaedic surgeon related to your research interest in Stem Cell? When have you started your research interest in Stem Cell?

“ All these starts from my experiences or my hobby in the early years. When I was a teenage boy, my favorite toys are the tool kits, such as the screw drivers, saws, hammers etc. When I was in my final clinical year and taking the clinical rotations back in many years ago, I noticed that there were the saws, drills, screw drivers, all displayed in the surgical theatre of one specialty, which I can apply all my favourite toys and that is the orthopaedics surgery. That was so fascinating and amazing to me. I then immediately decided that I wanted to become an orthopaedics surgeon upon graduation, which I did.

During medical training, I realised that regenerative medicine was an important trend. As an orthopaedics surgeon, I have better access to tissues or sources to stem cell, which has exerted my research interest. I decided to spend a couple of years after my medical

training to engage myself in research related to stem cells on full-time basis. This is the reason why I moved to London to do my Master and PhD study. I was the first PhD graduate from the Centre for Biomedical Engineering of University College London with Stem Cell but not metallic implants as thesis topic. The Centre for Biomedical Engineering is historically very strong and has contributed substantially to the development of artificial metallic implants. My PhD supervisor, Prof. Gordon Blunn, is a marine biologist by training and his expertise is in Hydroxyapatite. Hydroxyapatite is the constituent of the skeleton of coral and that material happens to be excellent in allowing osteo-integration in bone cell ingrowth. Gordon is a biomedical engineer with a strong biology background. He supervised me, and we jointly decided the research direction. I do enjoy my days in UCL. ”



Lab reunion party in summer 2018.

04

How do you see the development of Stem Cell study in the near future?

“ I would say it is time for translational application now because of the massive evidence as a result of joint efforts of researchers of this field. Stem cells may contribute substantially and may well serve as a game changer for the treatments of lots of diseases and injuries, in particular for the elderly. Now, Hong Kong is facing the challenges that the citizens have

the highest life expectancies on average when comparing to the rest of the world, meaning that we need to work out new ways not only to keep our citizens to live longer, but also to let them live better. Stem Cells have a lot of functions in terms of anti-aging, regeneration and repairing. It is time for further translational studies, not only pre-clinically, but also clinically. ”

05

How about the current research environment in Hong Kong for the development of Stem Cell study?

“ In the past couple of months, I have been attending various sessions organised by the Government for opinion collections. I have contributed my previous experiences during the sessions since I am the vice-president of the International Society for Cell and Gene Therapy, and I have facilitated the legislation of the clinical use of Stem Cells in Taiwan. I think the Government has been working very hard in terms of legislation and the promotion of applying Stem cell technology to the clinical patients in order to benefit the patients' medical needs.

There are a lot of outstanding basic scientists and clinicians working on Stem Cells in Mainland China. As long as there are mechanisms for integrations of expertise between the laboratory bench and bedside, there are going to be some good developments. Hong Kong being a part of China would have a lot of potentials. Hong Kong has always served as a hub to connect Mainland China with the rest part of the world. I think we should leverage and make good use of our unique position and the competitive strengths. ”

06

How would the applications of Stem Cell study contribute to the development of precision or personalised medicine?

Stem Cell has a whole lot to do with the personalised or precision medicine. We all know that diseases are caused by not only genetic background, but also there are the lifestyle and environmental factors. Stem Cell in a sense is a perfect type of personalised medicine or medication if you were to help individual not only to combat diseases but also to preserve a number of functions or tissues. Stem Cell is definitely going to play an important role in terms of the development of precision or personalised medicine.

07

In the 2016 International Conference on Biomedical and Bioinformatics Engineering, you shared about how to integrate the concept of Precision medicine in your research, to apply the study of Mesenchymal Stem Cells (MSC) in treating liver diseases. You have devoted for more than 20 years in research of MSC, what we find interesting is that you are an orthopaedic surgeon, why would you spend time in MSC for treating liver diseases at the very beginning? You have a few important publications on liver diseases as well. Can you share with us more about that? How would these research results relate to your current research directions?

Adult stem cell, such as Mesenchymal Stem Cells (MSC) which are harvested from bone marrow or adipose tissues, are of embryonically mesoderm origin. We are among the first few groups to discover that these MSC can differentiate into hepatocytes which are of endodermal origin. This has a strong implication in terms of stem cell biology, i.e. adult stem cell is more plastic than we can ever think of. I am an orthopaedic surgeon but there is no boundary in science. I stick to this side track for a while, and then some of my group members follow along that line of research and then we have published some good works in terms of the applications of MSC for liver diseases treatments. It is not surprising afterwards that John B. Gurdon and Shinya Yamanaka, who were the winners of Nobel Prize in Medicine in 2012, have collectively demonstrated the plasticity or the possibility of re-programming of cells, in the terminally differentiated mice cells. Again, it is another source of evidence that the cells in our body may be more capable than we ever think of in terms of differentiation potentials.



Prof. Lee's former students and lab members at National Yang-Ming University threw a celebration party for his birthday.

08

How would you compare the research environment, resources and culture among Taiwan, the UK and Hong Kong? And how about the study or teaching environment as well?

Competitions are fierce and very similar in various places. For the UK, in particular, because of the political atmosphere of BRITXIT, certain negative impacts have been resulted. For example, the exchange of personnel is going to be more difficult between the rest of the European countries with UK. This is going to be detrimental to the overall scientific research environment in the UK.

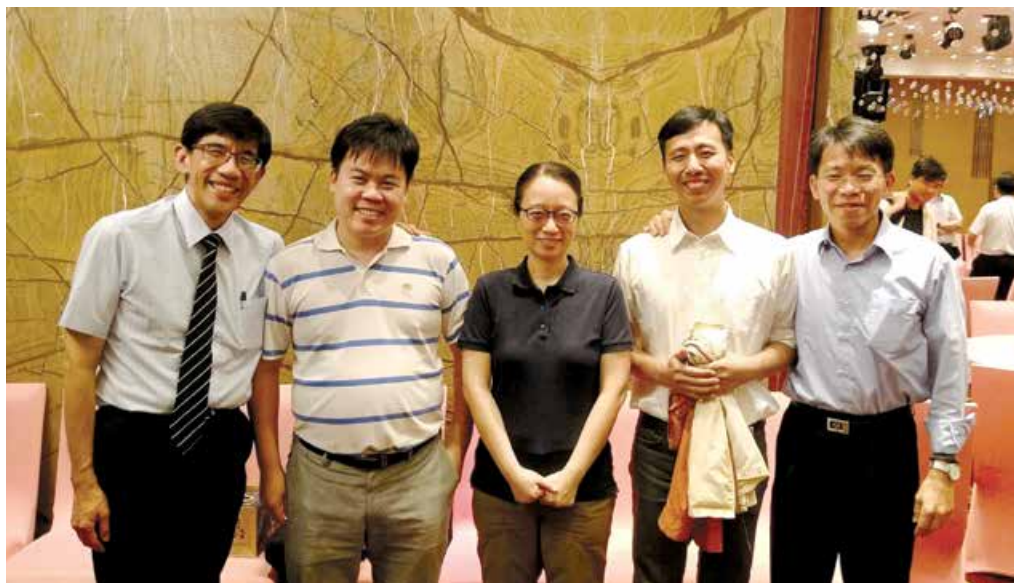
For Hong Kong, we are now enjoying not only the connections that we have already established over the years among the world, but now we are also a hub to attract and absorb the top elites from Mainland China. We do have advantages in attracting young talents to engage in the field of biomedical research.

When compare to Taiwan, Taiwan has a population of 23 Million, which is three times of that in Hong Kong. But Taiwan is relatively more isolated, and English is not the major official language, so I think Hong Kong does have its competitive advantages.

09

Apart from being a surgeon, a senior management in hospital, and a scientist, you have also supervised more than 40 PhD and Master students. Can you share with us more on your time management? Anything special you can share with us on your teaching experiences?

“Focus” is the most important keyword. I try to focus only one thing at a time, I concentrate, and I prioritize my tasks by making petitions and good use of time, so that I can finish my tasks properly. All in all, education is the most important mission among all these tasks of mine, because the fostering or nurturing of the next generation scientist and clinicians to me are very important. I personally do prefer to the British style of the one-on-one mentoring. If my students do not come to me, I would then suppose they are all right to be on their own and they are independent because they are postgraduate students. Whenever they need me, they will make appointments with me, and no matter what time they request, I would never let them down. Sometimes, there are appointments at 7 am or 8 pm, and my students and I are used to it. This is the way that I can keep track of the progress of my students which I find to be useful.



Prof. Lee's former trainees all do well and become independent investigators now.

10

What advices would you give to fellow students who are interested in developing their career as a clinician-scientist?

First, being a clinician-scientist is fun and rewarding. You make yourself a leader in terms of the progress or advances in both basic sciences and clinical medicine of your own specific field. The intangible achievements cannot be measured by the amount of money you made, but by the sense of satisfaction you gained. This is my piece of advice to the next generation, medical students, junior doctors, or postgraduate students, or for those who begin to consider going on these career tracks.

Clinicians follows what textbooks said, but being a clinician-scientist, you are the one who put your say or opinions on the textbooks. In other words, clinician-scientists write the textbook for the peer to read and follow. This is something very fascinating.

11

Being a new Principal Investigator of the Institute, what are your visions and goals, say in 5 years' time?

I hope that in 5 years' time, I can be very fluent in Cantonese. I should be able to speak Cantonese as well as I do in speaking in English or Putonghua, which is my mother-tongue.

On top of that, I would really like to be an integral part of the Faculty of Medicine in CUHK, and I also would like to exert my influences on the next generation, medical students and clinicians, to encourage them to choose to become clinician-scientists. So far, there are very few in Hong Kong, and we do need more clinician-scientists who are enthusiastic in teaching and doing research. So that, we can further strengthen the research advantages of the CUHK as a whole. This is something I would like to achieve in 5 years' time.



Interview with Professor Sunny Wong

黃曦教授

Professor Sunny Wong is a clinician-scientist specialising in internal medicine and digestive diseases. He is a medical graduate at The Chinese University of Hong Kong and then he pursued the Doctor of Philosophy in Clinical Medicine at the University of Oxford after a year at the hospital as House Officer in Hong Kong. Upon returning from the UK, Prof. Wong became a resident at the hospital for a few years before joining the Faculty of Medicine, CUHK in 2012 as an Honorary Clinical Tutor. He then received Clinical Assistant Professorship from the Croucher Foundation in 2013 at The Chinese University of Hong Kong. Prof. Wong is currently Assistant Professor at the Department of Medicine and Therapeutics.

01

After finishing your undergraduate study at the CUHK and then a year at the hospital as House Officer, you went to University of Oxford to pursue a PhD in Clinical Medicine. Why would you decide to take a PhD during that time?



I have been interested in research, especially laboratory and translational research, for a long time. Pursuing a PhD provided me a chance to go deep into a research topic, and gave me few years of full-time research experiences without distractions. The research component of a PhD was much more profound than that in an undergraduate programme, and it has significantly consolidated my foundation in scientific research. I have learned different research methodologies and skills required to do research.



In 2006, Prof. Wong graduated from The Chinese University of Hong Kong.

02

How does the pursue of PhD affect your research direction, career, or your decision to be a clinician-scientist?



My PhD experience was instrumental to my career development as a clinician-scientist. During the PhD study, I have learnt a lot on research topics and skills across disciplines. My research topic on genetics is closely linked to molecular biology, cell biology and bioinformatics, and it also has a paramount impact on the development of personalised medicine. My studies have allowed me to delve deep into one topic, at the same time given me the chance to keep pace with advanced medical development.

Hong Kong has been in the forefront of biomedical research, yet many developed countries are still ahead in infrastructure, personnel and research capabilities. The different perspectives in other countries did give me inspirations and strong motivation to be a clinician-scientist.



03

You have devoted a lot of time and effort in the study related to Gastrointestinal diseases and clinical meta-genomics, especially on human microbiota. How do you see the development of these studies in the near future? How would the applications of human microbiota research contribute to the development of personalised medicine?



We have learnt about the existence of human microbiota for a long time, through health products like probiotics.

With the advancements in sequencing technology, there is a surge in our knowledge on microbiota, especially on its composition. Now, we are moving on to study how microbes can affect each other and the host to cause diseases. It is foreseeable that there will be a lot of revolutionary studies in the coming decade. There will be emerging biomarkers or therapeutics coming from these microbiota researches. There are great clinical potentials from studies on the human microbiota.

Furthermore, the human microbiota is highly relevant to the development of personalised

medicine. Similar to our genetic makeup, the microbiota in each of us is highly unique and personal. The microbiota brings direct impacts on our health, not only on the digestive system, but also our general health especially in our immune and metabolic physiology. If we take the individual differences into considerations while making clinical decisions, it may be more comprehensive and effective in achieving the health-improving goals. For example, there are recent research studies showing that microbiota may affect immunotherapy in cancer patients, with which modulation may enhance its therapeutic efficacy in the future. This is one of the many examples of translating research in human microbiota.



04

What would be your next step in research related to human microbiota? What would you require for the compositions of your research team?



As mentioned in the previous questions, we would continue to work on the mechanistic relationships between microbiota with various diseases, including gastrointestinal infections and neoplasms. The other main research direction would be on clinical applications, on how we translate the findings into treatments or diagnostics tools.

To work on these research directions, a team with people of diverse background and skill sets would be required. We would need biologists to study the mechanisms, statisticians and bioinformaticians to analyse and interpret the data, and microbiologists to understand the role of different microbes.



05

Apart from clinical duties, research work, you have also engaged in a lot of international conferences or symposiums, and media & community activities. Why would you spend so much time in these kinds of “knowledge-transfer” activities?



Reaching out and connecting to the community is important. To share the knowledge with the public would increase the societal impact and raise awareness of the public. It is also a very effective way in promoting our research and recruiting potential volunteers for projects.

On a professional level, by sharing research findings and ideas at international conferences or symposiums, other researchers can make good use of the information in their study to further advance the field. Knowledge-transfer is always a reciprocal action. Through sharing and discussions, we can come up with new ideas which may guide future research direction and facilitate collaborations.



In 2006, Prof. Wong graduated from The Chinese University of Hong Kong.

06

Having been studying in Hong Kong and the UK, and with your own experiences in supervising or mentoring students, how would you describe the differences or focuses of education between these two places?

“ In general, Asian students are diligent and efficient in finishing their tasks, whereas students from western countries are more reflective with original ideas. This may have come down to their learning style and educational background. As a mentor myself, I think it is important for students to develop an inquisitive and logical mind as a researcher. Every student is unique, and I always try to personalise their education experiences according to their background, learning style and character. ”



Prof. Wong at the University of Oxford for his Doctoral Degree.

07

In terms of Bio-tech development, how would you describe the current situations in Hong Kong? What should be improved in order to encourage more research activities in Hong Kong?

“ There are a lot of well-developed systems in Hong Kong, such as our healthcare and higher education. We have world leading universities with great researchers and scientists, as well as well-constructed hospitals with good clinical follow-ups and electronic records. There is also excellent research infrastructure in Hong Kong, including the Research Ethics Committees and Clinical Trial Centers that are important for clinical research and trials. Furthermore, there are increasing supports from the government on translational medical research and bio-technology development, with more funding opportunities and infrastructure. ”

To build up the biotechnology sector in Hong Kong, I think we will need more interdisciplinary collaborations and supports from other downstream industries. This will be needed to translate scientific findings into clinical applications. For example, there are lots of good lawyers in the commercial sector, but we probably will need more lawyers who specialises in Intellectual Property related regulations in the biotechnology sector. The support from the government and other related industries are important for the biotechnology sector to take off and fly. ”

08

You have so many different roles and commitment in various activities as we have mentioned before. Can you share with us more on your time management?

“ I try to prioritise and group similar tasks together. For example, I usually have my clinical duties and teachings on Mondays and Tuesdays, so that I can focus on patient care while medical students can learn from us at the same time. I have regular research meetings with my team once a week, and I always try to keep meetings short and succinct. I usually meet my research team members for technical details, and post-graduate students for their progress separately. ”

What advices would you give to fellow students who are interested in developing their career as a clinician-scientist?



I would advise students to leave their comfort zones, go out and explore the world. With more support from the Faculty and with the Global Physician-Leadership Programme, students have a lot more opportunities to participate in research or leadership activities both locally and in overseas. I hope our students will cherish these chances to broaden their horizon, acquire different perspectives and sharpen their logical skills. Acquiring knowledge is important, but learning how to ask and propose a research question is another issue. Logical skills may even be more crucial than factual knowledge.

If students are really interested in doing research, a research MPhil or PhD will be very useful. It also depends how much time they would like to commit in research.



Prof. Wong at the conference "Cancer: From Biology to Treatment" co-organized by Faculty of Medicine, The Chinese University of Hong Kong (CUHK) and Erasmus University Medical Centre (Erasmus MC), the Netherlands on 11 May 2016.



Prof. Wong participated at the Digestive Disease Week 2016 at San Diego, California with the team.

Being a Principal Investigator of the Institute, what are your visions and goals, say in 5 years' time?



I hope to secure more supports and funding which will allow me to conduct in-depth research at larger scale. It is an exciting time with more funding from the Government into translational biotechnology research. As mentioned before, I look forward to devote more efforts in inter-disciplinary research, which may involve collaborations with chemists, engineering and other scientists. This will be essential to generate innovative research that can be utilised to benefit mankind.



FROM SCIENCE TO IMPACTS

從科學到影響





Interview with Professor Allen Chan

陳君賜教授

Nasopharyngeal Carcinoma (NPC) is one of the most common cancers in Southern China and prevails in Chinese population. Based on the unique relationship between NPC and Epstein-Barr virus (EBV), Professor Allen Chan and his team has used circulating EBV DNA analysis in blood plasma for screening early cancers in asymptomatic individuals. From 2013 to 2016, the team has recruited over 20,000 apparently healthy volunteers to this study. This large-scale prospective study provides the first conclusive evidence that circulating DNA analysis is useful for the screening of early asymptomatic cancers. Plasma DNA analysis has potential to be applied for the detection of other cancers or diseases.

01

When compared to surgical biopsies, liquid biopsy is considered as a more convenient and non-invasive alternative to obtain information about a cancer. Is blood the only “liquid” to be used in liquid biopsy? How can scientists or doctors obtain information from just a few milliliters of blood?

For liquid biopsy, any bodily fluid can be used for molecular analysis. In addition to blood, we can also use urine, peritoneal fluid or cerebrospinal fluid for analysis, which would provide us with different information about our body.

Blood is comprised of different cells and cell-free plasma. Liquid biopsy usually refers to the analysis of either circulating tumour cells or circulating cell-free DNA derived from cancer cells.

In cancer patients, cancer cells can sometimes be shed from the tumour to the blood giving rise to circulating tumour cells. However, the concentration of circulating cells is very low, typically less than one tumour cells in one million blood cells, and is usually observed in patients with advanced or metastatic cancer. On the other hand, in the cell-free plasma, tumour-derived DNA can sometimes account for a few percent of the total DNA even in patients with relatively small cancers. Therefore, the analysis of circulating tumour DNA represents a noninvasive method to investigate the molecular changes in the cancer.

02

Why did you choose Nasopharyngeal Carcinoma (NPC) as your focus with liquid biopsy but not other types of cancers? How is the current situation of NPC in Hong Kong or in Asia?

Nasopharyngeal Carcinoma (NPC) is one of the most common cancers in Southern China.

The pathogenesis of NPC is closely related to a virus called Epstein-Barr virus (EBV). In our Southern China, almost all NPC tumor tissues harbour the EBV genome. In our previous study, we showed that EBV DNA is detectable in the plasma of 95% NPC patients but only 5-7% of healthy subjects. The analysis of plasma EBV DNA is relatively inexpensive and the turn-around time is only a few hours. Therefore, plasma EBV DNA analysis is a suitable tool for large-scale cancer screening studies.



Professor Chan holding health talks in community for potential subjects.





The venue setup for health talks and blood taking session in community.



Blood samples taking from subjects after the health talks.

03

What tests are currently used for the detection of NPC? How effective are the existing methods for the screening or diagnosis of NPC? What are the main differences between the conventional and the liquid biopsy screening method?

“ Nasal endoscopy is the choice of investigation for the diagnosis of NPC. If a tumour is observed during endoscopy, a biopsy can be taken for histological examination to confirm the presence of NPC.

Over the last few decades, the testing for antibodies against EBV is frequently performed in subjects who are suspected of having NPC. However, the test for EBV antibodies is not particularly useful for the detection of early NPC because a large proportion of patients with early NPC would be negative for EBV antibodies. In contrast, EBV DNA is directly derived from the cancer cells. The testing for EBV DNA is more sensitive than antibody tests for picking up early cancers.



04

You have initially recruited around 20,000 participants. Any difficulties you and your team have encounter while recruiting and handling such large number of subjects? Can you share with us any challenges or interesting experiences during the study?



During the 4 years period of the study, our team organised health talks in community centres of different district every weekend. After the talks, subjects who are eligible to the study would be invited to join our study. I am grateful to all my team members who worked very hard over the weekends of these 4 years to recruit the study subjects.

In the beginning of our study, we were afraid that not many people would be interested to participate in the study. However, after we have been interviewed by a TV programme and talked about our study, over 20,000 subjects were enrolled through our online registration system to the different health talk sessions within 24 hours.

In our study, 34 subjects were subsequently confirmed of having NPC through screening. Many of them were diagnosed with very early stage cancer. Three patients who have their cancer diagnosed at stage I came to one of our meetings with Sir Michael Kadoorie to thank him in person for funding this study.



05

In your study, 1112 participants had detectable Epstein-Barr virus DNA in plasma at baseline, but then only 309 had detectable Epstein-Barr virus DNA in plasma and at follow-up. Why is there such a discrepancy?



EBV infection is actually very common. Over 95% of adults in Hong Kong would have been infected with EBV. After acute infection, EBV would go into a latent phase and reside within resting B lymphocytes. Reactivation of latent EBV could occur when the immunity of a person is low. Therefore, approximately 5% of subjects without NPC would have detectable EBV DNA in plasma. This viral reactivation is typically transient. In 2/3 of these subjects, the EBV DNA would become undetectable within 4 weeks. Therefore, we would retest subjects with initial positive plasma EBV DNA results 4 weeks later and perform further confirmatory investigation on those who have persistently positive results on the two occasions.

The clinical significance for persistently positive plasma EBV DNA in subjects without an identifiable NPC is not completely clear. It is possible that these subjects may have higher risk for future development of NPC. We are currently following up of all the recruited subjects and performing another round of screening to further investigate this.



06

NPC is a common type of cancer in Hong Kong and Southern China. Do you think a population-wide screening of NPC should be promoted in Hong Kong? Is the current EBV DNA screening technology mature enough for such large-scale screening?

PP The long-term survival of NPC is over 95% for patients diagnosed with stage I. The mortality and morbidity are much worse for patients presented with locally advanced or metastatic cancer. Unfortunately, over 75% of NPC patients present with advanced disease (stages III or IV) without screening because early NPC is relatively asymptomatic. Our study demonstrated that NPC screening using plasma EBV DNA analysis can significantly shift the stage distribution of NPC patients to earlier stage (70% early stage) resulting in substantial improvement in survival. As NPC is one of the commonest cancers in Hong Kong and Southern China, we believe that a population-wide NPC screening programme can lead to significant reduction in mortality and treatment-associated morbidity of NPC in the region.

The analysis for plasma EBV DNA is relatively inexpensive, rapid and simple. This technology is mature for large-scale clinical application. PP



Professor Dennis Lo and Professor Allen Chan were presented the 2018 Annual Achievement Award at The 21st Annual Meeting of Chinese Society of Clinical Oncology (CSCO).

07

How would you see the development of this liquid biopsy technology to be generalised to the screening of other types of cancers or diseases? What would be the future research directions?

PP In our study, we used NPC as a model to demonstrate that even small cancers can release substantial amount of DNA into the circulation to allow sensitive detection. This information is an important basis for the development of other cancer screening strategies based on liquid biopsy.

However, as I have mentioned NPC is closely associated with EBV infection so that EBV DNA can be used as a surrogate marker for detecting NPC. For other cancers not associated with viral infection, other non-virus-associated DNA markers would need to be used. Development of these DNA-based tumor markers is the research focus of our group.

In addition, as mentioned before, we are performing another round of screening on the 20,000 subjects we have recruited. The aim of this second round screening is to address the optimum interval for screening and whether subjects with detectable plasma EBV DNA but not identifiable cancer in the first round of screening would have increased risk of future development of NPC. PP

08

In your opinion, what do you think are the essential elements in translating scientific research findings in the laboratory to “real” impacts for the society? Any advices you would like to give to fellow researchers who are working on “From Science to Impacts”?

PP To translate scientific discoveries into clinically useful products like diagnostic tests and treatment, it usually requires large-scale clinical trials to demonstrate the clinical utility of the product.

Using our NPC screening study as an example, we need to make good arrangements for our study subjects, handle a huge number of samples and clinical information. We also need to report the laboratory results to our participants in a timely manner so that subsequent investigations can be promptly arranged. The key element behind this is a devoted and efficient team.

After carrying out these clinical studies, we then need to work with government agencies or industrial partners to make these new products available as clinical services.

In my personal experience, the process of bringing your invention into real-clinical service that can benefit patients is enjoyable. This satisfaction worth all the efforts that you have paid to bring this a reality. PP

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