



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



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PROGRESS REPORT 2019

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

Li Ka Shing Institute of Health Sciences Progress Report JAN - DEC 2019
李嘉誠健康科學研究所進度報告 2019年1月至12月



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

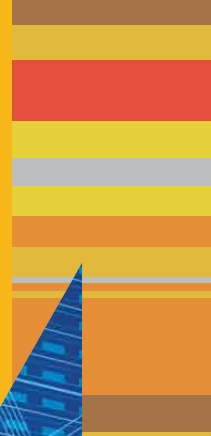
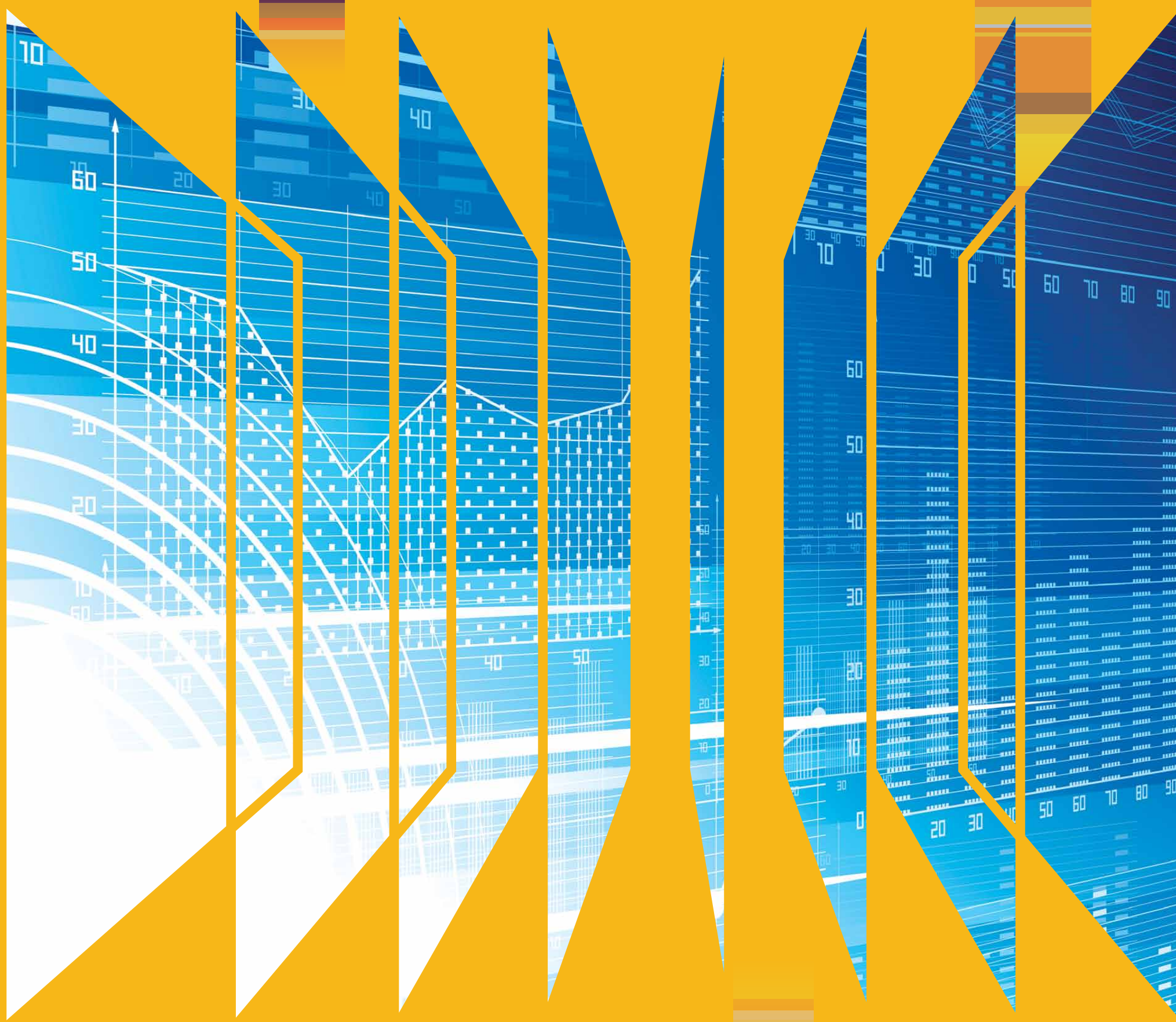
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EXECUTIVE SUMMARY

報告摘要



EXECUTIVE SUMMARY

報告摘要

Over the past year, Principal Investigators at the Institute had continued to push forward the research frontiers in their fields. Such efforts are a reflection of the Institute's mission to translate scientific developments into clinical applications that would benefit patients and have a positive impact on healthcare. A number of our Principal Investigators were honoured with prestigious awards over the past year.

In particular, I was most honoured to receive the Fudan-Zhongzhi Science Award 2019 during its Prize Presentation Ceremony on 15 December 2019 in Shanghai. This Award was first founded in 2015 by the Fudan University and the Zhongzhi Enterprise Group, in recognition of fundamental research on cell-free DNA molecules and leadership in developing new diagnostic testing.



Dennis Lo

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

I am also very pleased to report that through the work of our circulating nucleic acids group, Professor Rossa Chiu and myself were named two of the "Top 20 Translational Researchers of 2018" by the world-renowned and authoritative scientific journal *Nature Biotechnology*. This is the third consecutive year for myself to receive this honour and am pleased to note the scientific, healthcare and commercial impact generated by this body of work.

Professor Siew Ng, working on gastroenterology, and Professor Ronald Ma, working on diabetes, were both selected as Croucher Senior Medical Research Fellows, by the Croucher Foundation, in recognition of their achievements in scientific research in medicine and the support that gives to the next generation of clinician-scientists. The Senior Medical Research Fellowships from the Croucher Foundation are one of the most highly regarded research awards in Hong Kong.

Professor Allen Chan, specialising in plasma nucleic acids research for cancer detection and monitoring, was awarded with the Lo Ying Shek Chi Wai Foundation Meritorious Research Award and also being conferred as the Inaugural Lo Ying Shek Chi Wai Foundation Scholar, on 23 March 2019. The Award was established in 2018 with an aim of recognising selected young clinician-scientists who have achieved excellence in medical research output with publications in top tier reputable medical journals.

Principal Investigators from our Diabetes and Obesity research team were honoured with some prestigious awards over the years. Professor Juliana Chan received the 2019 Harold Rifkin Award for Distinguished International Service in the Cause of Diabetes. This international award was first established in 1991 in recognition of outstanding research, evaluation and care in diabetes, from an international perspective with an international impact. Professor Chan is the first awardee from Hong Kong.

I would also like to congratulate Professor Nelson Tang who was presented a Bronze Medal in the 47th International Exhibition of Inventions

of Geneva, for his work on single cell population gene expression biomarkers.

On the scientific front, our various Principal Investigators have achieved remarkable progress and produced significant publications in their respective research areas in 2019.

In particular, Professor Jun Yu and her research team, working on gastrointestinal diseases, has discovered that an anaerobic bacterium *Peptostreptococcus anaerobius* (*P. anaerobius*), was particularly prevalent in colorectal cancer (CRC) patients as compared to individuals. Colorectal Cancer (CRC) is the number one cancer in Hong Kong. Emerging evidence implicates a role of the gut microbiota in CRC. The team has demonstrated an important role of *P. anaerobius* in CRC and has proved that targeting integrin signalling might be a therapeutic approach for CRC intervention. This important finding, which was published in *Nature Microbiology*, might facilitate the development of therapy for CRC patients.

Furthermore, Dr. Jacky Lam and colleagues, have further advanced the technology for screening nasopharyngeal cancer (NPC) with plasma Epstein-Barr (EBV) DNA. Their research findings highlighted a synergistic effect of combining the methylation analysis with the analysis of other molecular characteristics of plasma EBV DNA in the reduction of the false positives. The combined analysis of the three parameters (i.e. methylation, count and size) of plasma EBV DNA yielded a positive predictive value almost 3 times of that of a current PCR-based protocol. This improvement would have a substantial public health impact if a mass screening programme based on this combined analysis of plasma EBV DNA is to be launched in endemic regions. This paper was published in *Nature Communications* and the team has filed a patent application for this technology.

As always, we look forward to future advances from our Principal Investigators and research teams in 2020.

報告摘要

過去一年，李嘉誠健康科學研究所各首席研究員繼續努力攜手走在轉化醫學研究的前沿。這些努力反映了研究所的使命，將科學發展轉化為惠及病人的臨床應用，並對社會醫療保健方面產生積極影響。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。

本人很榮幸能於2019年12月15日在上海舉行的頒獎典禮上獲頒發第四屆「復旦一中植科學獎」。這個獎項於2015年由復旦大學及中植企業集團創辦，旨在表彰在數學、物理學和生物醫學三個學科領域作出原創性和突破性科研成果的全球科學家。

就著游離核酸的研究成果，本人及趙慧君教授獲世界權威科學期刊《自然生物科技》選為「2018年全球20位頂尖轉化研究科學家」其中兩位，而本人更是

連續第三年獲此殊榮。我樂見這項研究對科學、醫療保健和商業等方面產生重要影響。

致力於腸胃病學研究的黃秀娟教授及糖尿病研究的馬青雲教授均獲裘槎基金會頒授「裘槎優秀醫學科研者獎2020」，以表彰其卓越醫學科研成就和對栽培新一代年青醫學科學家的貢獻。這是香港其中一個最高殊榮的科研獎項。

從事研究血漿核酸癌症檢測的陳君賜教授於2019年3月23日榮獲「羅鷹石慈慧基金傑出研究獎」，亦為首位獲得該獎項的傑出學者。「羅鷹石慈慧基金傑出研究獎」於2018年由羅鷹石慈慧基金創立，獎項旨在肯定香港年輕的臨床科學家對醫學研究的貢獻及成就。

糖尿病及肥胖症研究團隊亦收獲甚豐。陳重娥教授獲頒授國際年度獎「2019 Harold Rifkin 糖尿病傑出國際服務獎」。此獎項成立於1991年，以表揚在糖尿病研究、評估及治理等各範疇的優秀表現，同時具有環球視野及國際影響力的學者。陳教授為首位香港得獎者。

此外，我亦祝賀鄧亮生教授於「第四十七屆日內瓦國際發明展」中獲得銅獎，以肯定他於單細胞群基因表達生物標記物的研究工作的成績。

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。

專注消化系統疾病研究的于君教授及其團隊，發現一種厭氧菌 *Peptostreptococcus anaerobius* 在結腸癌患者體內普遍存在。結腸癌是香港頭號癌症，新發現的證據顯示腸道微生物在結腸癌中發揮重要作用。團隊證明厭氧菌在結腸癌扮演重要角色，而整合素信號通路的靶向治療可能成為治療結腸癌的全新方向。這項重要的發現已刊載於《自然微生物學》，有望推進結腸癌治療方法的研發。

與此同時，林偉棋醫生及其團隊成員在與人類疱疹病毒相關的鼻咽癌篩查技術取得極大進展。他們的研究證明透過結合甲基化分析，以及對血漿中人類疱疹病毒核酸其他分子特徵分析所產生的協同效應，有效減低檢測出現假陽性結果的機會；同時綜合分析血漿中人類疱疹病毒之核酸甲基化、數量和大小等三個參數，可以取得比現時以聚合酶反應為基礎的檢測方法高近三倍的陽性預測值。由此可以預見當未來在鼻咽癌流行的地區進行大規模篩查的時候，此項改善將對公共衛生產生重大影響。這項研究的成果已於《自然通訊》發表，團隊同時已為此技術申請專利。

一如既往，我們期待研究所的科學家及研究團隊在2020年取得更豐碩的研究成果。

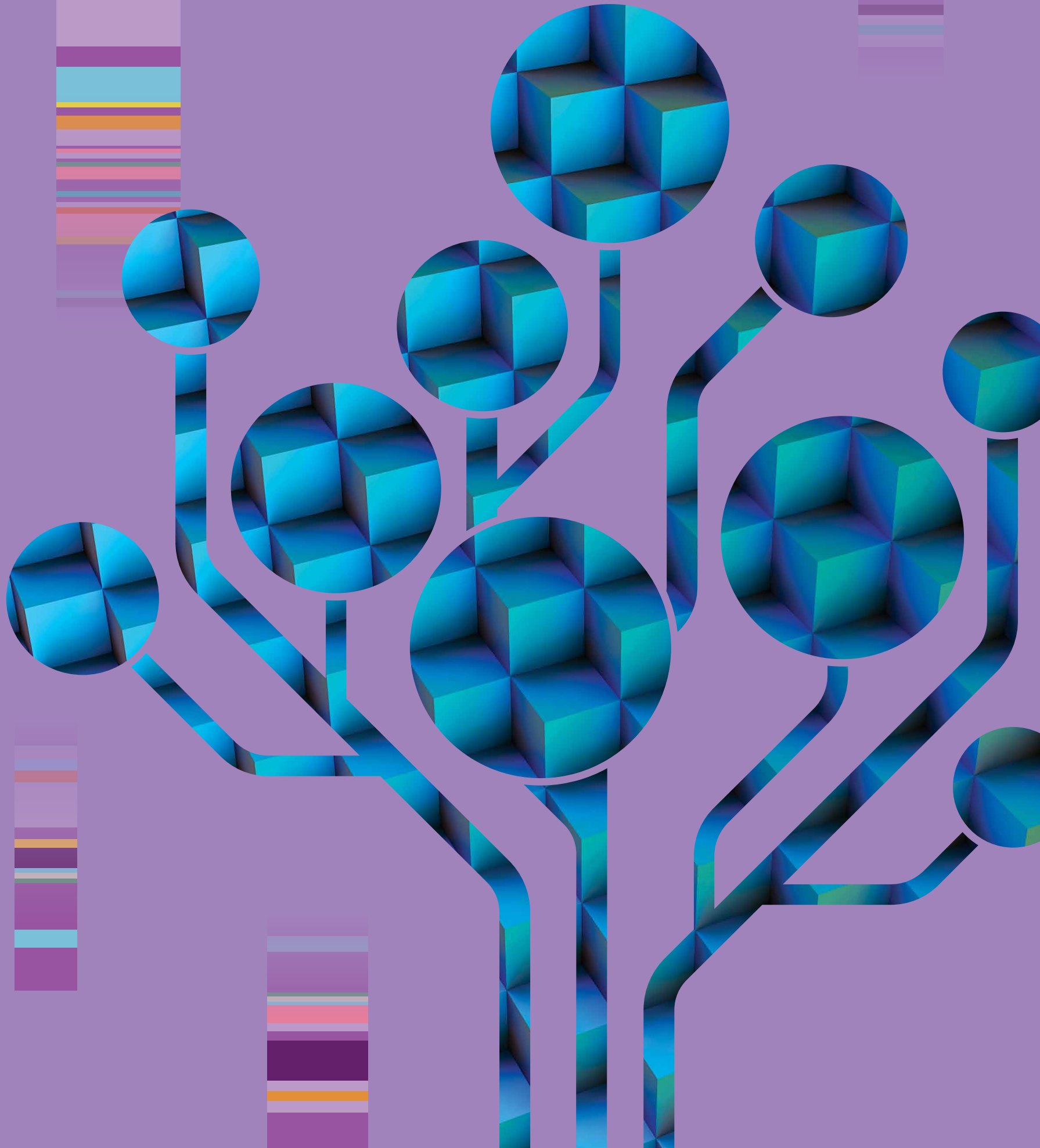
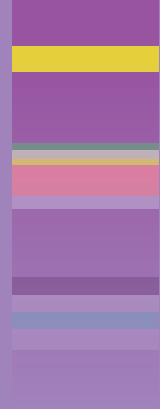
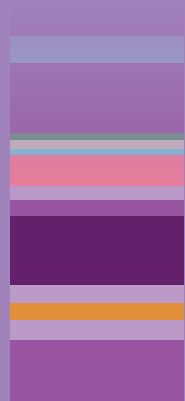


盧煜明

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



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 thirteenth meeting of the Steering Committee was held on 18 December 2019 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2019年12月18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。

Chairman

主席



Professor 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

Members

成員

Professor Dennis Lo 盧煜明教授

Associate Dean (Research), Faculty of Medicine, CUHK
Li Ka Shing Professor of Medicine, CUHK
Chairman, Department of Chemical Pathology, Faculty 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
香港中文大學化學病理學系系主任
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



Members

成員



Professor Wai-yee Chan 陳偉儀教授

Pro-Vice-Chancellor/Vice-President, CUHK
Director, CUHK-BGI Innovation Institute of Trans-omics
Director, Institute for Tissue Engineering and Regenerative Medicine (iTERM), CUHK
Professor of Biomedical Sciences, CUHK
香港中文大學副校長(策略發展)
香港中文大學一華基因跨組學創新研究院院長
香港中文大學組織工程與再生醫學研究所所長
香港中文大學生物醫學講座教授

Professor Tony Mok 莫樹錦教授

Chairman, Department of Clinical Oncology
CUHK Li Shu Fan Medical Foundation
Professor of Clinical Oncology, CUHK
香港中文大學腫瘤學系主任
香港中文大學李樹芬醫學基金腫瘤學教授



Professor Ling Qin 秦嶺教授

Assistant Dean (Mainland Affairs), Faculty of Medicine, CUHK
Professor, Department of Orthopaedics and Traumatology, Faculty of Medicine, CUHK
香港中文大學醫學院助理院長(內地事務)
香港中文大學矯形外科及創傷學系教授



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助理秘書長



The Thirteenth Meeting of the Steering Committee (18 December 2019)

第十三次督導委員會會議
(2019年12月18日)

Photo from left to right
相片由左至右

Professor Tony Mok
莫樹錦教授

Professor Wai-yee Chan
陳偉儀教授

Professor Dennis Lo
盧煜明教授

Professor Francis Chan (Chairman)
陳家亮教授 (主席)



LiHS Office 研究所辦公室



As of December 2019, 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2019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。



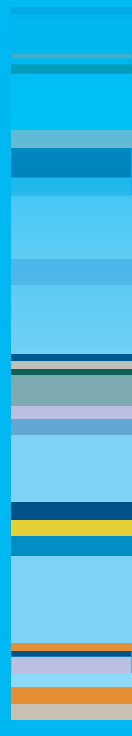
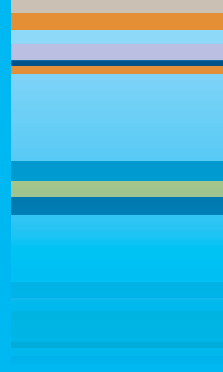
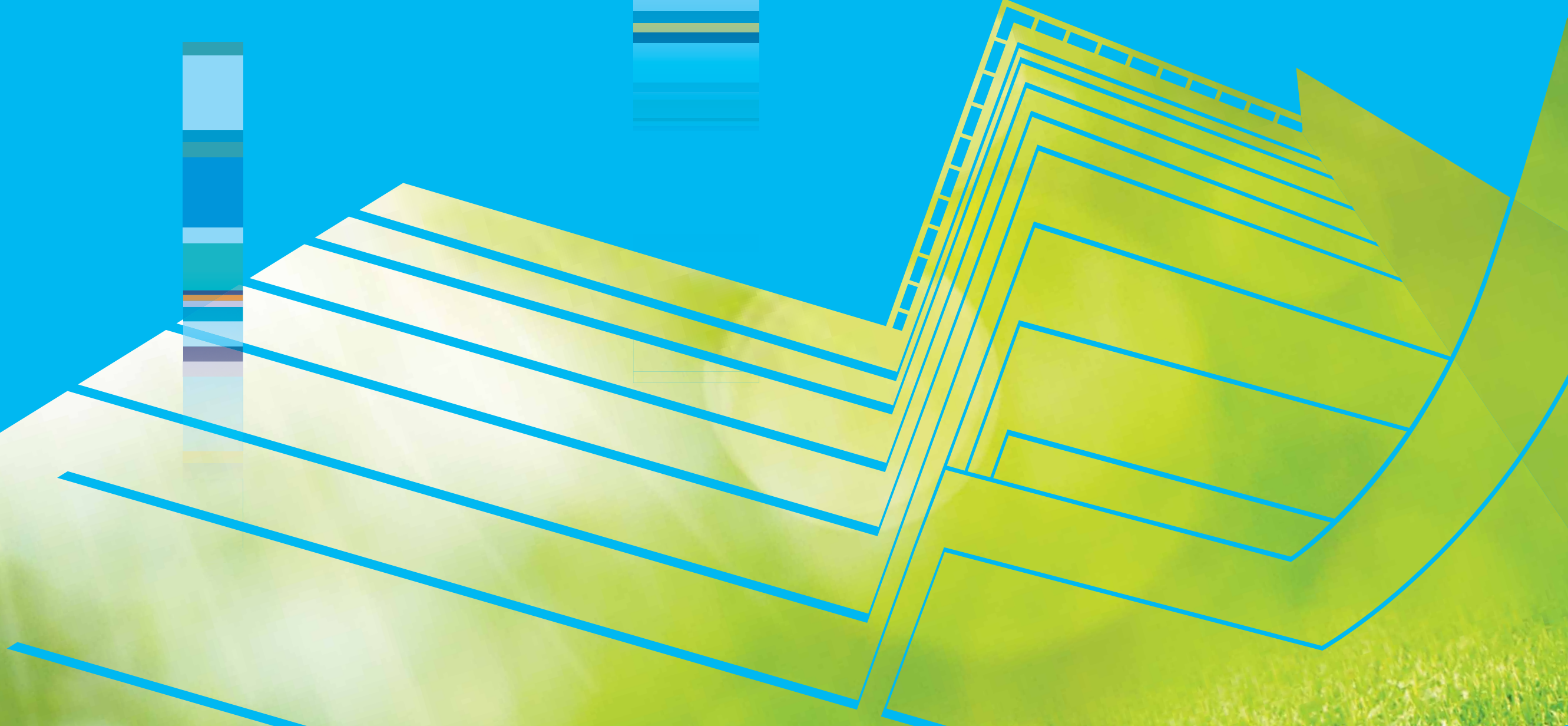
Core Laboratory Team
重點科研設施團隊



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

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 2019, there were approximately 516 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2019年12月，約有516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。



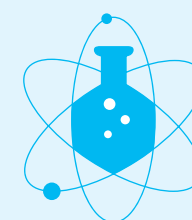
11-Storey



516
Research Personnel



Diseases & Pathobiology



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香港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 overall computing and storage systems, and to refine its system architecture.

The Institute had undertaken a major computing systems and IT infrastructure upgrade during the past year. The major areas for this upgrade planning include:

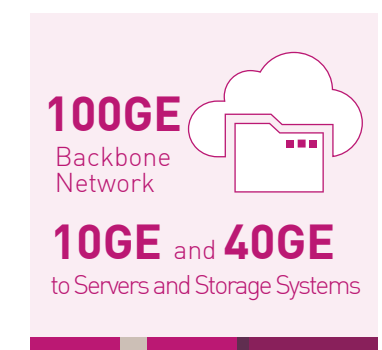
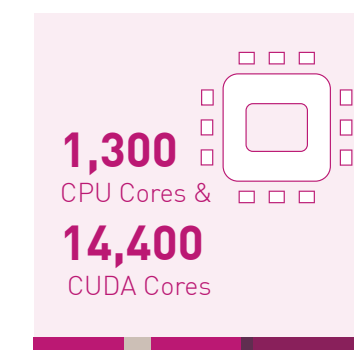
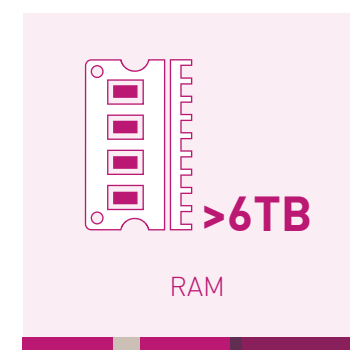
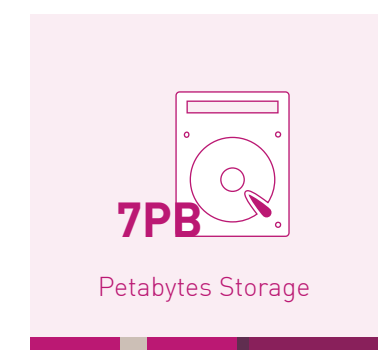
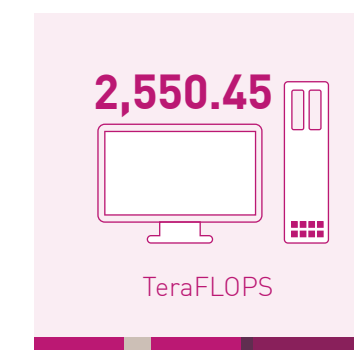
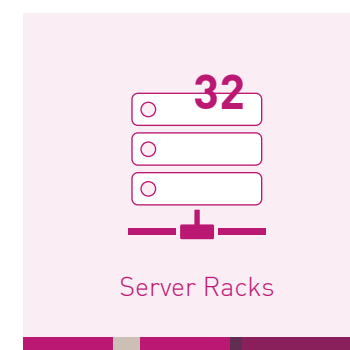
生物醫學計算中心是研究所內的重要設施之一，亦是研究轉譯基因組學的重要設施。

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IT基礎設施及系統建設之基礎上，持續加強其存儲系統和計算系統，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。

在過去一年，研究所正規劃對中心計算機系統、儲存系統和IT基礎設施進行重大升級。這一次中心設施及系統升級規劃的主要領域包括：

- Development of new Data Centre facilities for higher server computing and storage system capacity.
- Deployment of new computing servers, computing architecture, and to increase the computing facilities with new computing servers by more than 1000 cores.
- Deployment of new storage architecture with remote backup, data recovery scheme and additional data security architecture.

- 擴大及發展中心設施、提升中心整體容量以容納更多更高速計算伺服器及高速儲存系統。
- 引入及部署新的更高速的計算伺服器、發展新的計算伺服器架構及計算架構，從而提升中心整體計算伺服器計算能力。規劃中增加新的計算伺服器可為中心帶來多於1000核心的總計算伺服器設施。
- 準備部署具有遠程備份，後備數據恢復方案和強化數據安全架構的新高速存儲架構。



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



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 a variety of functions, including **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**樣本的品質管制**、**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 2100 Bioanalyzer
生物分析儀



■ Invitrogen Qubit 2.0 Fluorometer
螢光定量儀

■ ThermoFisher 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 or shRNA vectors into difficult-to-transfect cell lines and primary cells.

將DNA載體、表達質粒或shRNA載體轉殖至一般較難轉殖的細胞株及初代細胞中。



■ Amaxa Nucleofector II
電穿孔轉殖儀



Bead-based Suspension Analysis
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



■ 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.

分析基因型態、拷貝數變異、基因甲基化及基因表達模組。



■ Life Technology QuantStudio 12K Flex
Real-Time PCR
定量實時聚合酶鏈鎖反應儀



■ Illumina iScan Microarray System
芯片掃描系統

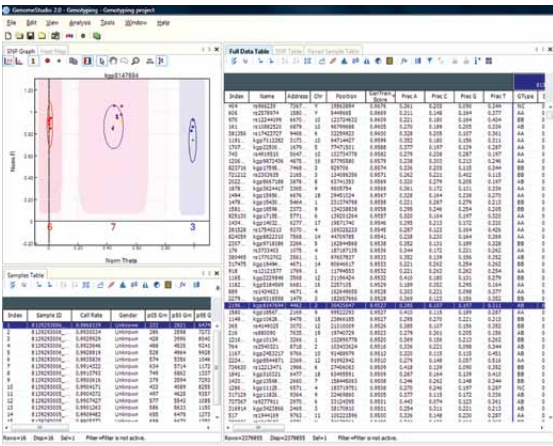


■ Data Analysis 數據分析

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

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設備，**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

Cell Culturing 細胞培養

Cell Expansion & Testing

細胞擴增和測試

Cell Culture Facilities equipped with NSF49 certified Class II Type A2 Biosafety Cabinets, which facilitate the culturing of animal cells, animal cell lines and human cell lines. In view of increasing demand cell culture facilities in recent years, Cell Culture Facilities have been expanded and enhanced in past year. 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標準的第二等級 Type A2 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。



Class II Type A2 Biosafety Cabinet
第二等級 Type A2 生物安全櫃

Cellular Imaging 細胞成像

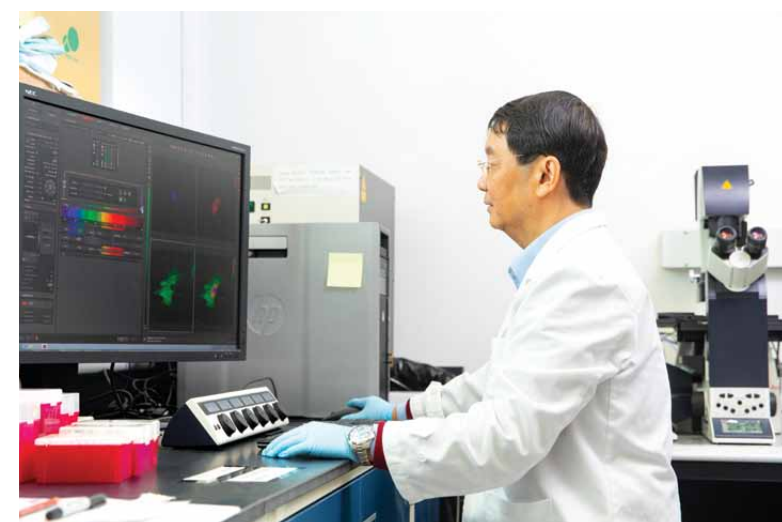
Individual Cell Characterisation & Collection 個體細胞特性分析與收集

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



Leica TCS SP8
共聚焦激光掃描顯微鏡

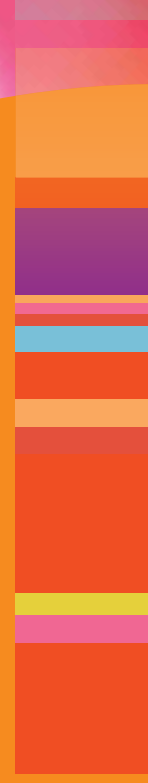
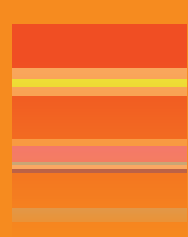
Confocal Laser Scanning Imaging 共聚焦激光掃描顯微技術

To acquire optical sections, high resolution images, three-dimensional images for co-localisation analysis of subcellular structures for cellular research. Live cell imaging function is also available for researchers to track any fast, dynamic process which happens within living cells.

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的三維圖像。本機同時備有活細胞成像功能，令研究員能捕捉發生於活細胞裏快速的動態過程。

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：

8 January 2019 | 2019年 1月8日

Seminar by Professor Junjun Ding, Professor, Zhongshan School of Medicine, Sun Yat-sen University, China on "Epigenetic and 3D Chromatin Regulation of Stem Cell Pluripotency".

丁俊軍教授（中國中山大學中山醫學院教授）舉行研討會，題目為「Epigenetic and 3D Chromatin Regulation of Stem Cell Pluripotency」。



1 February 2019 | 2019年 2月1日

Seminar by Dr. Jian Yan, Assistant Professor, Department of Biomedical Sciences, City University of Hong Kong on "Systematic Analysis of Differential Transcription Factor Binding to Non-Coding Variants in the Human Genome".

嚴健博士（香港城市大學生物醫學系助理教授）舉行研討會，題目為「Systematic Analysis of Differential Transcription Factor Binding to Non-Coding Variants in the Human Genome」。



27 February 2019 | 2019年 2月27日

Seminar by Professor Dave SB Hoon, Director, JWCI Translational Research, Providence Saint John's Health Center, USA on "Utility of Blood CFDNA in Monitoring Patients with Cancer Metastasis and Receiving Checkpoint Inhibitor Immunotherapy".

Dave SB Hoon教授（美國普羅維登斯聖約翰健康中心 JWCI Translational Research，Director）舉行研討會，題目為「Utility of Blood CFDNA in Monitoring Patients with Cancer Metastasis and Receiving Checkpoint Inhibitor Immunotherapy」。



26 March 2019 | 2019年 3月26日

Seminar by Professor Dawn DW Cornelison, Professor, Biological Sciences & Medical Microbiology and Immunology University, USA of Missouri on "A Pillar of the Community (Effect): EphA7 Promotes Myogenic Differentiation via Cell-cell Contact".

Dawn DW Cornelison教授（美國密蘇里大學 Biological Sciences & Medical Microbiology and Immunology 教授）舉行研討會，題目為「A Pillar of the Community (Effect): EphA7 Promotes Myogenic Differentiation via Cell-cell Contact」。



12 June 2019 | 2019年 6月12日

Seminar by Professor Florian Heyd, Professor of RNA Biochemistry, Institute of Chemistry and Biochemistry, Freie Universität Berlin, Canada on "Body Temperature Controlled Kinase Activity: from Rhythmic Alternative Splicing in Mammals to Sex Determination in Reptiles".

Florian Heyd 教授 (德國柏林自由大學 Institute of Chemistry and Biochemistry, Professor of RNA Biochemistry) 舉行研討會, 題目為「Body Temperature Controlled Kinase Activity: from Rhythmic Alternative Splicing in Mammals to Sex Determination in Reptiles」。



22 November 2019 | 2019年 11月22日

Seminar by Professor Andrew P. Feinberg, M.D., M.P.H., Bloomberg Distinguished Professor, Johns Hopkins University School of Medicine, Whiting School of Engineering, and Bloomberg School of Public Health, USA on "The Epigenetic Basis of Common Human Disease".

Andrew P. Feinberg 教授 (美國約翰·霍普金斯大學醫學院 Whiting School of Engineering and Bloomberg School of Public Health, Bloomberg Distinguished Professor) 舉行研討會, 題目為「The Epigenetic Basis of Common Human Disease」。



14 June 2019 | 2019年 6月14日

Seminar by Professor Wen Liu, Professor, Minjiang Scholar, School of Pharmaceutical Sciences, Xiamen University, China on "Function and Molecular Mechanism of Protein Arginine Methyltransferase CARM1 in Breast Carcinogenesis".

劉文教授 (中國廈門大學藥學院「閩江學者」特聘教授) 舉行研討會, 題目為「Function and Molecular Mechanism of Protein Arginine Methyltransferase CARM1 in Breast Carcinogenesis」。



3 December 2019 | 2019年 12月3日

Seminar by Dr. Jian Shu, Helen Hay Whitney Fellow, Eric Lander Lab, Broad Institute of MIT and Harvard; Rudolf Jaenisch Lab, Whitehead Institute, Harvard University, USA on "Reconstructing, Tracing, and Recording Developmental Landscapes and Trajectories from Integrative Analysis of Single-Cell Data".

舒健博士 (美國哈佛大學 Whitehead Institute, Rudolf Jaenisch Lab; Broad Institute of MIT and Harvard, Eric Lander Lab, Helen Hay Whitney Fellow) 舉行研討會, 題目為「Reconstructing, Tracing, and Recording Developmental Landscapes and Trajectories from Integrative Analysis of Single-Cell Data」。



1 August 2019 | 2019年 8月1日

Seminar by Dr. Chris KL Chan, Group Leader, Genome Damage and Stability Centre (GDSC), School of Life Sciences, University of Sussex, United Kingdom on "Towards the Understanding of Faithful Chromosome Segregation".

Chris KL Chan 博士 (英國薩塞克斯大學 School of Life Sciences, Genome Damage and Stability Centre (GDSC), Group Leader) 舉行研討會, 題目為「Towards the Understanding of Faithful Chromosome Segregation」。



RESEARCH ACTIVITIES AND OUTPUTS

科研動態



RESEARCH ACTIVITIES AND OUTPUTS

科研動態

Research Areas and Teams

研究領域隊伍

Research teams within the Institute can be grouped under two main areas, namely, “**Diseases and Pathobiology**” and “**New Technologies**”.

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**」。

Diseases and Pathobiology 疾病及病理生物

Research Area 研究領域	Principal Investigator 首席研究員
Digestive Diseases 消化疾病研究	Jun Yu 于君
Asian Cancers 亞洲癌症研究	Qian Tao 陶謙
	Siu-tim Cheung 張兆恬
Cardiovascular Medicine 心血管疾病研究	Xiaoqiang Yao 姚曉強
	Alex Lee 李沛威
Diabetes and Obesity 糖尿病與肥胖症研究	Juliana Chan 陳重娥
	Ronald Ma 馬青雲
Molecular Microbiology and Emerging Infectious Diseases 分子微生物學及防疫研究	Guoping Zhao 趙國屏
	Shui-shan Lee 李瑞山
	Sunny Wong 黃曦
	Martin Chan 陳子蔚

Diseases and Pathobiology 疾病及病理生物

Research Area 研究領域	Principal Investigator 首席研究員
Inflammatory Diseases 炎症性疾病研究	Hui-yao Lan 藍輝耀
	Erik Fung 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
Nephrology 腎臟疾病研究	Cheuk Chun Szeto 司徒卓俊

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 盧煜明
	Rossa Chiu 趙慧君
	Nelson Tang 鄧亮生
	Allen Chan 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	Gang Li 李剛
	Kathy Lui 呂愛蘭
	Ling Qin 秦嶺
	Oscar Lee 李光申
Genomics and Bioinformatics 基因組學與生物訊息學	Hao Sun 孫昊
	Peiyong Jiang 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 **176** publications from these teams were published.

Among the publications, **79** and **36** 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**176**篇學術論文，當中有**79**及**36**篇分別刊登於影響因子高於4及10的學術刊物。

■ *Peptostreptococcus anaerobius* promotes colorectal carcinogenesis and modulates tumour immunity

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

Journal: *Nature Microbiology*. December 2019.

nature
microbiology

ARTICLES

<https://doi.org/10.1038/s41564-019-0541-3>

Peptostreptococcus anaerobius promotes colorectal carcinogenesis and modulates tumour immunity

Xiaohang Long^{1,2,3}, Chi Chun Wong^{1,2,3}, Li Tong^{1,2,3}, Eagle S. H. Chu^{1,2,3}, Chun Ho Szeto^{1,2,3}, Minne Y. Y. Go^{1,2,3}, Olabisi Oluwabukola Coker^{1,2,3}, Anthony W. H. Chan⁴, Francis K. L. Chan^{1,2,3}, Joseph J. Y. Sung^{1,2,3} and Jun Yu^{1,2,3*}

Emerging evidence implicates a role of the gut microbiota in colorectal cancer (CRC). *Peptostreptococcus anaerobius* (*P. anaerobius*) is an anaerobic bacterium selectively enriched in the faecal and mucosal microbiota from patients with CRC, but its causative role and molecular mechanism in promoting tumorigenesis remain unestablished. We demonstrate that *P. anaerobius* adheres to the CRC mucosa and accelerates CRC development in *Apc*^{Min/+} mice. In vitro assays and transmission electron microscopy revealed that *P. anaerobius* selectively adheres to CRC cell lines (HT-29 and Caco-2) compared to normal colonic epithelial cells (NCM460). We identified a *P. anaerobius* surface protein, putative cell wall binding repeat 2 (PCWBR2), which directly interacts with colonic cell lines via α_2/β_1 integrin, a receptor frequently overexpressed in human CRC tumours and cell lines. Interaction between PCWBR2 and integrin α_2/β_1 induces the activation of the PI3K-Akt pathway in CRC cells via phospho-focal adhesion kinase, leading to increased cell proliferation and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) activation. NF- κ B in turn triggers a pro-inflammatory response as indicated by increased levels of cytokines, such as interleukin-10 and interferon- γ in the tumours of *P. anaerobius*-treated *Apc*^{Min/+} mice. Analyses of tumour-infiltrating immune cell populations in *P. anaerobius*-treated *Apc*^{Min/+} mice revealed significant expansion of myeloid-derived suppressor cells, tumour-associated macrophages and granulocytic tumour-associated neutrophils, which are associated with chronic inflammation and tumour progression. Blockade of integrin α_2/β_1 by RGDS peptide, small interfering RNA or antibodies all impair *P. anaerobius* attachment and abolish *P. anaerobius*-mediated oncogenic response in vitro and in vivo. Collectively, we show that *P. anaerobius* drives CRC via a PCWBR2-integrin α_2/β_1 -PI3K-Akt-NF- κ B signalling axis and identify the PCWBR2-integrin α_2/β_1 axis as a potential therapeutic target for CRC.



Colorectal cancer (CRC) is the number one cancer in Hong Kong. Emerging evidence implicates a role of the gut microbiota in CRC. In this study, Professor Jun Yu and her research team identified a novel anaerobic bacterium *Peptostreptococcus anaerobius* (*P. anaerobius*) enriched in CRC patients as compared to individuals. Next, the team demonstrated that the administration of *P. anaerobius* accelerated CRC development in a genetic mice model of spontaneous CRC (*Apc*^{Min/+} mice), implying that *P. anaerobius* might be a driver of tumorigenesis in the colon. Mechanistic work revealed that *P. anaerobius* could selectively adhere to CRC cell lines compared to normal colonic epithelial cells, and binding of the bacteria to CRC cells involves direct interaction of a *P. anaerobius* surface protein (PCWBR2) with membrane receptors ($\alpha_2\beta_1$ integrin) overexpressed in CRC cells. This interaction in turn activates oncogene PI3K-AKT pathway in CRC cells leading to increased cell growth. *P. anaerobius* colonisation of colon epithelium also promotes inflammation in the tumour microenvironment through the activation of NF- κ B pathway. Blockade of the PCWBR2- $\alpha_2\beta_1$ integrin using RGDS peptide (integrin blocker), small interfering RNA and anti- $\alpha_2\beta_1$ integrin

antibodies all attenuated *P. anaerobius* attachment and abolish *P. anaerobius*-driven colorectal tumorigenesis in mice. Collectively, their studies infer an important role of *P. anaerobius* in CRC and targeting integrin signalling is a therapeutic approach for CRC prevention.

結腸癌是香港發病率最高的癌症類型。近年來研究證實腸道微生物在結腸癌中發揮重要作用。于君教授及其研究團隊研究發現一種新型厭氧菌 *Peptostreptococcus anaerobius* (*P. anaerobius*) 在結腸癌患者糞便樣本中顯著上升。進一步研究發現灌飼 *P. anaerobius* 能加速自發性結腸癌小鼠模型的腸道腫瘤形成，提示 *P. anaerobius* 是結腸腫瘤形成的驅動因素。進一步機理研究發現 *P. anaerobius* 選擇性黏附結腸癌細胞系。 *P. anaerobius* 細菌膜表面蛋白 PCWBR2 能與結腸癌細胞高表達的膜受體 $\alpha_2\beta_1$ 整合素直接相互作用並啟動癌細胞內 PI3K-AKT 信號通路促進癌細胞增殖。 *P. anaerobius* 的定植能啟動癌細胞內 NF- κ B 信號通路促進腫瘤微環境中的炎症反應。靶向阻斷整合素 $\alpha_2\beta_1$ 與 PCWBR2 的結合可以抑制 *P. anaerobius* 對結腸癌細胞的黏附及小鼠結腸腫瘤形成。綜上所述，他們在這項研究中首次揭示了 *P. anaerobius* 促進結腸癌的重要分子機制，整合素信號通路的靶向治療能預防結腸癌的發生。

Methylation analysis of plasma DNA informs etiologies of Epstein-Barr virus-associated diseases

Author(s): Jacky Lam *et al.*

Journal: *Nature Communications*. 2019;10(1).



ARTICLE

<https://doi.org/10.1038/s41467-019-11226-5>

OPEN

Methylation analysis of plasma DNA informs etiologies of Epstein-Barr virus-associated diseases

W.K. Jacky Lam^{1,2,3,4,6}, Peiyong Jiang^{1,2,3,6}, K.C. Allen Chan^{1,2,3,6}, Wenlei Peng^{1,2}, Huimin Shang^{1,2}, Macy M.S. Heung^{1,2}, Suk Hang Cheng^{1,2}, Haiqiang Zhang^{1,2}, O.Y. Olivia Tse^{1,2}, Radha Raghupathy^{3,5}, Brigitte B.Y. Ma^{3,5}, Edwin P. Hui^{3,5}, Anthony T.C. Chan^{3,5}, John K.S. Woo⁴, Rossa W.K. Chiu^{1,2,3} & Y.M. Dennis Lo^{1,2,3}

Epstein-Barr virus (EBV) is associated with a number of diseases, including malignancies. Currently, it is not known whether patients with different EBV-associated diseases have different methylation profiles of circulating EBV DNA. Through whole-genome methylation analysis of plasma samples from patients with nasopharyngeal carcinoma (NPC), EBV-associated lymphoma and infectious mononucleosis, we demonstrate that EBV DNA methylation profiles exhibit a disease-associated pattern. This observation implies a significant potential for the development of methylation analysis of plasma EBV DNA for NPC diagnostics. We further analyse the plasma EBV DNA methylome of NPC and non-NPC subjects from a prospective screening cohort. Plasma EBV DNA fragments demonstrate differential methylation patterns between NPC and non-NPC subjects. Combining such differential methylation patterns with the fractional concentration (count) and size of plasma EBV DNA, population screening of NPC is performed with an improved positive predictive value of 35.1%, compared to a count- and size-based only protocol.

The benefits of screening nasopharyngeal cancer (NPC) with plasma Epstein-Barr (EBV) DNA have recently been validated by Dr. Jacky Lam and his research team in a large-scale prospective study involving more than 20,000 subjects. The current polymerase chain reaction (PCR)-based analysis was shown to be highly sensitive for the detection of plasma EBV DNA from patients with early-stage NPC. In the current study, the team investigated the molecular characteristics of plasma EBV DNA for better differentiation of NPC samples. The team first analysed the methylation profiles of plasma EBV DNA from patients with different EBV-associated diseases and confirmed that plasma EBV DNA methylomes exhibited a disease-associated pattern. Such observation has significant implications in the development

of methylation analysis of plasma EBV DNA for NPC diagnostics. Through the analysis of archived samples from the previous screening cohort, plasma EBV DNA fragments were shown to demonstrate differential methylation patterns between NPC and non-NPC subjects. Their results highlighted a synergistic effect of combining the methylation analysis with the analysis of other molecular characteristics of plasma EBV DNA in the reduction of the false positives. The combined analysis of the three parameters (i.e. methylation, count and size) of plasma EBV DNA yielded a positive predictive value almost 3 times of that of the current PCR-based protocol. This improvement would have a substantial public health impact if a mass screening programme based on this combined analysis of plasma EBV DNA is to be launched in endemic regions. This paper was published in *Nature Communications* and the team has filed a patent application for this technology.

林偉棋醫生及其研究團隊之前進行了一項有超過20,000參加者的大型前瞻性研究，確立了以血漿EB病毒DNA作篩查鼻咽癌的好處。現時以聚合酶鏈式反應為基礎的分析對檢測早期鼻咽癌患者的血漿EB病毒DNA有着很高的靈敏度。在這次研究中，該團隊分析血漿EB病毒DNA的分子特徵，藉此更能區分鼻咽癌的樣本。他們首先從患有不同與EB病毒有關連的疾病的人樣本中，分析血漿EB病毒DNA的甲基化樣式，證實了血漿EB病毒的甲基化有着與疾病關連的樣式。此項結果對於發展以分析血漿EB病毒甲基化作鼻咽癌檢測有着重大的啟示。透過分析之前篩查研究中的樣本，鼻咽癌與非鼻咽癌患者的血漿EB病毒有不同的甲基化樣式。是次研究結果突顯了綜合分析甲基化和其他分子特徵所產生的協同效應，大大減低假陽性的個案。綜合血漿EB病毒DNA的三個指標（甲基化，數量，長短）的分析，所達至的陽性預測值是現時聚合酶鏈式反應分析的差不多3倍。若這個綜合技術應用在鼻咽癌發率較高的地區大型篩查中，將會在改進在公共衛生上帶來重大的影響。本文已刊登於《自然通訊》，該團隊亦為這項技術申請了專利權。



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\$1.23 billion** during this reporting period. In particular, grants under the General Research Fund (GRF) scheme of the Research Grants Council (RGC) of **HK\$32 million** 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十二億三千萬，其中研究資助局的優配研究金共逾港幣三千二百萬，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) (01/01/2017 – 31/12/2019) Elucidation of a Novel Tumor Suppressor Gene Tripartite Motif 67	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
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) (01/01/2019 – 31/12/2021) Combinatorial Blockade of <i>De Novo</i> Cholesterol Biosynthesis and PCSK9 as a Synergistic Therapy for KRAS-Mutant Colorectal Cancer	Jun Yu	971,368
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2019 – 01/12/2021) When Should Low-dose Aspirin be Resumed After Peptic Ulcer Bleeding? A Double-blind, Randomized Controlled Trial	Siew Ng	972,000

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) (01/01/2019 – 31/12/2020) Regulation of Tumor Cell Invasion/metastasis and EMT/stemness by a New Ras Antagonist which is Silenced by CpG Methylation in Esophageal Cancer	Qian Tao	929,280
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2017 – 31/12/2019) TM9SF4 as a Novel Potassium Channel and its Role in Autophagy	Xiaoqiang Yao	1,000,387
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2019 – 30/06/2020) Search for Maturity-Onset Diabetes of the Young in Chinese with Young-Onset Diabetes	Juliana Chan	941,431
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2019 – 31/12/2021) Unraveling the Link between Maternal Hyperglycaemia and Childhood Obesity: Genome-wide Methylation Analysis in a Prospective Cohort of Untreated Gestational Diabetes	Juliana Chan Ronald Ma	970,517
Research Grants Council (RGC) – General Research Fund (GRF) (01/10/2015 – 30/09/2019) Prospective Randomized Trial Comparing Single Loop Duodenojejunal Bypass with Sleeve Gastrectomy Versus Standard Roux-en-Y Gastric Bypass in Patients with Poorly Controlled Type 2 Diabetes Mellitus: From Clinical Outcomes to Hormonal Mechanism	Ronald Ma	1,673,800
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2017 – 30/06/2019) The Impact of Gestational Diabetes Mellitus and Vitamin D Deficiency during Pregnancy on Children’s Cardiometabolic Risk and Methylation	Ronald Ma	998,652
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2019 – 30/06/2021) Spatio-temporal Pattern of Ambient PM2.5 Exposure and the Risk of Tuberculosis Reactivation	Shui-shan Lee	600,000
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2017 – 30/06/2020) Host Interactome of Human Norovirus Structural Proteins	Shui-shan Lee Martin Chan	922,492
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	Shui-shan Lee Martin Chan Sunny Wong	1,132,030

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 – 31/12/2019) Clarifying the Mechanisms of Ribotype 002 Virulence in <i>Clostridium Difficile</i> Infection	Sunny Wong	1,050,589
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) (01/01/2019 – 31/12/2021) Protective Role of Neuropeptide Y (NPY) in Acute Kidney Injury	Hui-yao Lan	831,301
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2019 – 31/12/2021) Regulatory Role and Mechanism of Smad3 in Immunosuppression of Neutrophil Anticancer Activities	Hui-yao Lan	1,151,040
Research Grants Council (RGC) – General Research Fund (GRF) (15/09/2017 – 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) (01/01/2019 – 31/12/2021) Modulating Osteoarthritis Development via Balancing Endogenous Expression of Smad3 and Smad7	Gang Li	953,029
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2019 – 31/12/2021) Genome-wide Computational Identification and <i>in vivo</i> CRISPR Screen of Key Transcription Factors (TFs) and TF Hotspots Governing Muscle Satellite Cell Lineage Progression	Hao Sun	1,136,632
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2019 – 31/12/2021) Mechanistic Investigation of Linc-p27 Function in Skeletal Muscle Satellite Cell and Muscle Regeneration	Hao Sun	970,697
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
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 Hao Sun	922,171

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) (01/01/2018 – 31/12/2020) Functional Dissection of lncRNA SAM in Skeletal Muscle Stem Cells and Muscle Regeneration	Huating Wang Hao Sun	1,232,466
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2019 – 31/12/2021) Elucidation of Post-transcriptional Regulatory Functions of Dhx36 in Skeletal Muscle Stem Cells and Muscle Regeneration	Huating Wang	1,111,376
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2019 – 31/12/2021) Large Scale Interaction Analysis of RNA Binding Proteins/LncRNAs to Identify lncRNA Nuclear Localization Mechanisms	Huating Wang	1,115,175
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) (01/01/2019 – 31/12/2021) A Mechanistic Study of the Therapeutic Effect of Butyrate in Nonalcoholic Steatohepatitis: Involvement of Autophagy	William Wu	971,635
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2019 – 31/12/2021) Reduction of Chronic Postsurgical Pain with Ketamine – The ROCKet Randomized Controlled Trial	William Wu	971,044
Total:		31,991,196

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 second meeting on 29 July 2019 to assess the progress of the project.

2019年7月29日，主題研究計劃科學諮詢委員會舉行第二次會議，評核小組的研究成果。

In the photo, from left seven to right: Professor Allen Chan, Professor Richard M. Myers (Scientific Advisory Board Member), Professor Patrick Tan (Scientific Advisory Board Member), Professor Toshikazu Ushijima (Scientific Advisory Board Member), Professor Dennis Lo, Professor Rossa Chiu, Dr. Diana Han (right seven), Dr. Jacky Lam (right four) and other research team members.

相片中由左七至右為：陳君賜教授，科學諮詢委員會會員Richard M. Myers教授，科學諮詢委員會會員Patrick Tan教授，科學諮詢委員會會員Toshikazu Ushijima教授，盧煜明教授，趙慧君教授，韓小澄醫生（右七），林偉棋醫生（右四）及其他研究團隊成員。



Meeting of the Scientific Advisory Board of Theme-based Research Scheme Project "Plasma DNA as a Platform Technology for Cancer Detection" (29 July 2019)

「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（2019年7月29日）

■ "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 second visit of on-site review on 9 October 2019 to assess the progress of the project.

2019年10月9日，主題研究計劃科學諮詢委員會舉行第二次實地考察，評核小組的研究成果。

In the photo, Professor Peiyong Jiang (left four), from left seven to right: Professor Allen Chan, Professor Rossa Chiu, Professor Roger Reeves (Scientific Advisory Board Member), Professor Dennis Lo, Dr. Diana Han, Dr. Jacky Lam (right four) and other research team members.

相片中，江培勇教授（左四），由左七至右為：陳君賜教授，趙慧君教授，科學諮詢委員會會員Roger Reeves教授，盧煜明教授，韓小澄醫生，林偉棋醫生（右四）及其他研究團隊成員。



Visit of On-site Review of Theme-based Research Scheme Project "Centre for Research into Circulating Fetal Nucleic Acids" [9 October 2019]

「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實地考察（2019年10月9日）

■ "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 fourth meeting on 18 November 2019 to assess the progress of the project.

2019年11月18日，主題研究計劃科學諮詢委員會舉行第四次會議，評核小組的研究成果。

In the photo, Professor Diana W. Bianchi (Scientific Advisory Board Member), Professor Howard S. Cuckle (Scientific Advisory Board Member), Professor Charles Cantor (Scientific Advisory Board Member), Professor Dennis Lo, Professor Rossa Chiu, Professor Allen Chan, Professor Peiyong Jiang, Dr. Jacky Lam and other research team members.

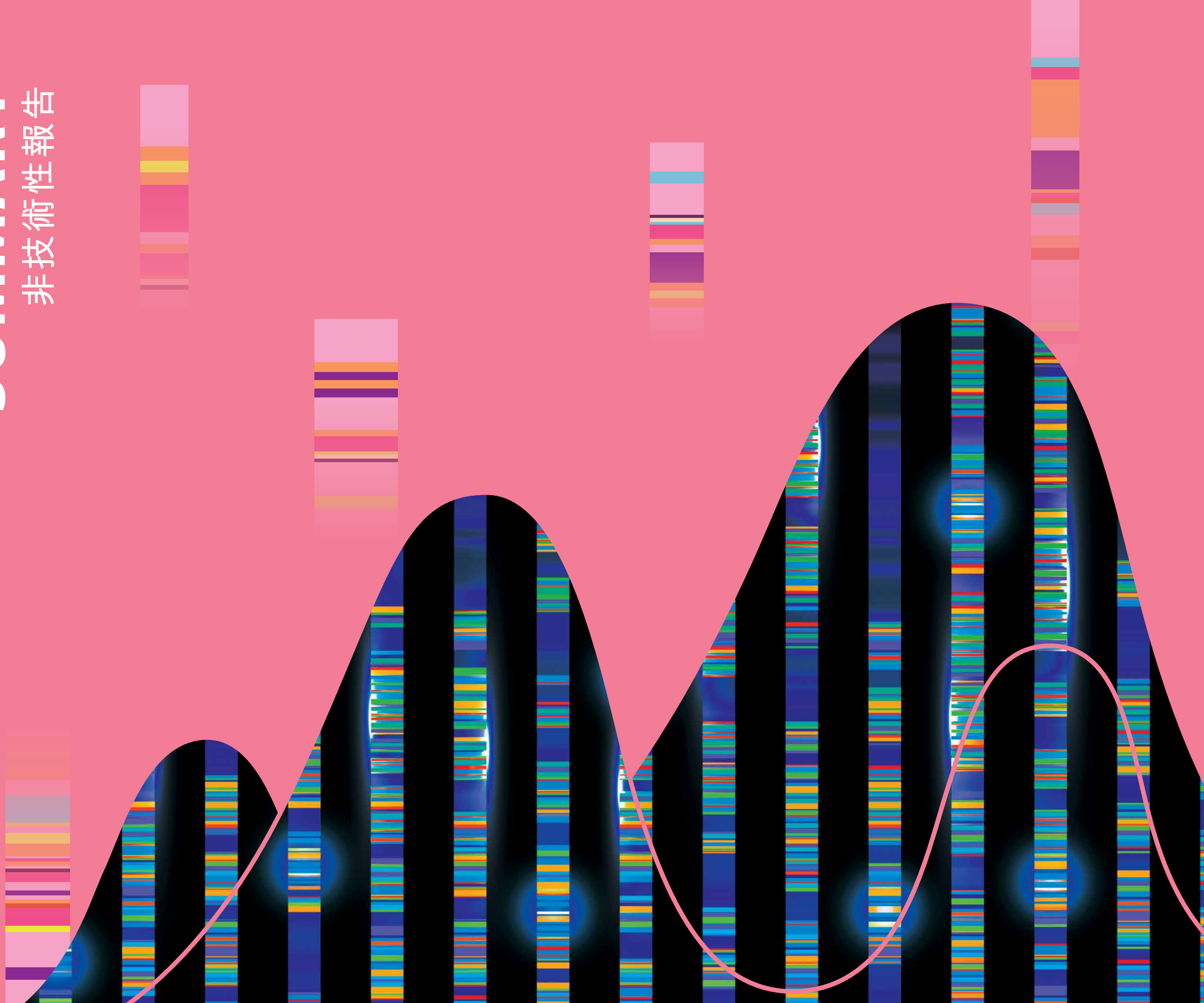
相片中，科學諮詢委員會會員Diana W. Bianchi教授，科學諮詢委員會會員Howard S. Cuckle教授，科學諮詢委員會會員Charles Cantor教授，盧煜明教授，趙慧君教授，陳君賜教授，江培勇教授，林偉棋醫生及其他研究團隊成員。



Meeting of Scientific Advisory Board of Theme-based Research Scheme Project "Centre for Research into Circulating Fetal Nucleic Acids" (18 November 2019)
「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（2019年11月18日）

NON-TECHNICAL SUMMARY

非技術性報告



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NON-TECHNICAL SUMMARY

非技術性報告

01

Digestive Diseases 消化疾病研究



Professor Jun Yu
于君教授

Gastrointestinal (GI) diseases, including GI cancers 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 scientists and clinicians 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; and
- (4) Identification of molecular biomarkers potentially useful for GI cancer diagnosis and prognosis.

消化道疾病如消化道腫瘤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科研人員和醫生組成，團隊的主要工作包括：

- (一) 闡述消化道腫瘤和疾病的分子機制；
- (二) 研究消化道微生態和腫瘤的關係；
- (三) 脂肪性肝病的機制和治療；及
- (四) 開發新的分子標誌物。

02

Molecular Diagnostics 分子診斷學

Professor Dennis Lo, Professor Rossa Chiu and their research team are pioneers in the field of molecular diagnostics. They are experts in translating scientific findings into clinical application and believe that understanding the science behind the biological phenomenon is equally important to its application. In the reporting year, one of the focuses of the research team is to study the biology of circulating nucleic acids and to elucidate how these short DNA fragments are generated as well as their characteristics. With their groundbreaking work in molecular diagnostics, Professor Lo and Professor Chiu have been named the "Top 20 Translational Researchers of 2018" by the prestigious scientific journal *Nature Biotechnology*. They are the only Hong Kong scientists on the list and it is the third consecutive year for Professor Lo to receive this honour.

盧煜明教授、趙慧君教授及他們的研究團隊擅長將科學研究成果轉化為臨床應用，惠及病人，是研究分子診斷學的先驅。他們亦深信鑽研生物現象背後的科學理論跟研究其臨床應用同等重要，二者亦有相輔相成的作用。今年，他們其中一個研究焦點是游離核酸生物學，運用尖端的科技闡析游離DNA碎片如何產生及其特徵。憑著領先創新的研究及對分子診斷學的貢獻，盧教授及趙教授同獲世界權威科學期刊《自然生物科技》(*Nature Biotechnology*) 評為「2018年全球20位頂尖轉化研究科學家」，他們是名單上唯一來自香港的科學家，這亦是盧教授連續第三年獲此殊榮。



Professor Dennis Lo
盧煜明教授

Professor Rossa Chiu
趙慧君教授

Professor Nelson Tang is the principal investigator of the Laboratory for Genetics of Disease Susceptibility. The research team led by Professor Tang is specialised in complex traits and genetic statistics. 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 the 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



Professor Nelson Tang
鄧亮生教授

性狀和GWAS分析，並於最近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信息學課程。

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。當中他是聯合實驗的副主任。最近，團隊發表了一個持續了10年的研究結果，開始了解青少年特發性脊柱側彎的遺傳機制。

cancers by plasma Epstein-Barr virus analysis could lead to significant improvement in treatment outcomes. In 2019, they 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. They are planning to bring this research achievement to clinical service in 2020.

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。該團隊證明通過血漿Epstein-Barr病毒分析篩查鼻咽癌可以顯著改善治療效果。在2019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，因此檢測呈陽性者亦不需要收集額外的血液樣本來確認測試結果。研究團隊計劃在2020年將這項研究成果轉化為臨床服務。



Professor Allen Chan
陳君賜教授

The major research focus of the research team led by **Professor Allen Chan** is to develop new diagnostic approaches based on the analysis of circulating nucleic acids. The team previously showed that the screening for nasopharyngeal

03

Fecal Microbiota Transplantation

腸道微生物移植研究

The team led by **Professor Siew Ng**, consisting of clinicians and scientists, utilises the gut microbiota for the diagnosis and treatment of human diseases including inflammatory bowel disease, obesity, metabolic syndrome, autism, allergy, multidrug resistant infections, and *clostridioides difficile* infections. The team has developed microbial markers to predict disease risk in children and adults. Evolving from fecal microbiota transplantation (FMT), the team is developing next generation probiotics for personalised therapeutics. In 2019, the team was awarded HK\$400M from the Innovation and Technology Commission of the HKSAR (Health@InnoHK) to establish the first Microbiota I-Center (MagIC) at the Hong Kong Science and Technology Park.



Professor Siew Ng
黃秀娟教授

在**黃秀娟教授**的領導下，由臨床醫生和科學家組成的研究小組，致力於利用人類微生物菌群來診斷和治療各種疾病，包括自閉症、過敏症、代謝綜合症、炎症性腸病、多藥耐藥性感染和難辨梭菌感染。該團隊正在開發微生物標記物以預測兒童和成人的患病風險，亦從腸道微生物移植進行演變，研發下一代益生菌為治療之用。今年，該團隊被香港特別行政區創新科技署選中，在香港科學園建立其中一所由創新及科技基金Health@InnoHK撥款的研究中心。

04

Asian Cancers
亞洲癌症研究

Cancer is a gene disease with genetic and epigenetic abnormalities of multiple cancer genes. Epigenetic disruption of critical cancer genes, especially silencing of tumour suppressor genes (TSGs) by promoter CpG methylation, is frequently involved in tumourigenesis, even at the early pathogenic stage of cancers. Characterising the epigenomic abnormalities of tumours leads to the identification of novel TSGs and non-invasive epigenetic biomarkers, as well as the elucidation of molecular pathogenic mechanisms. **Professor Qian Tao**'s laboratory aims to study the epigenome alterations of Hong Kong tumours and identify novel TSGs epigenetically inactivated as specific tumour markers.



Professor Qian Tao
陶謙教授

腫瘤是一種基因疾病，具有多個基因的遺傳或表觀遺傳異常。在腫瘤的發生發展過程中，表觀遺傳異常破壞關鍵性的腫瘤基因，特別是啟動子CpG甲基化沉默失活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。**陶謙教授**的腫瘤表觀遺傳學實驗室旨在通過研究香港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 Siu-tim Cheung
張兆恬教授

Professor Siu-tim Cheung and her team focuses on the investigation of the molecular basis of human cancer, aims to improve treatment strategies and ultimately patient survival. They have 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存活率。該團隊已經解讀了肝癌表達基因譜和癌症轉移的相關基因，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。

05

Cardiovascular Medicine
心血管疾病研究

Professor Xiaoqiang Yao's team is interested in Ca^{2+} signalling, ion channels and other proteins important for cardiovascular function and cancer. The focused areas include vascular tone control, atherosclerosis, mechanosensation and cancer chemoresistance.

姚曉強教授的團隊主要從事鈣信號傳導及離子通道等方面的研究，其重點領域包括心血管功能、動脈粥樣硬化、機械敏感及癌細胞多藥耐藥。



Professor Xiaoqiang Yao
姚曉強教授



Professor Alex Lee
李沛威教授

Professor Alex Lee and his research team focus on clinical application of echocardiography. The team specifically focuses on research and development of advanced imaging techniques such as 3-D echocardiography and 3-D printing in guiding transcatheter cardiac intervention and surgery. They are also interested in discovering novel pathogenic

mechanisms of mitral valve disease using dynamic 3-D echocardiography and strain imaging. Their recent interests have included screening Fabry disease among Chinese patients with left ventricular hypertrophy, diagnosing transthyretin cardiac amyloidosis with strain imaging, and artificial intelligence in echocardiography.

李沛威教授及其研究團隊的研究重點是臨床超聲心動圖。該團隊研發以3-D打印指導經導管心臟介入手術，用動態3-D和應變影像發現二尖瓣病新的致病機制。他們最新的研究包括在左心室肥厚患者中篩查法布瑞氏症、透過應變成像診斷心臟澱粉樣變性和人工智能在超聲心動圖的應用。

06

Diabetes and Obesity

糖尿病與肥胖症研究

Led by a team of physician 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 lifecourse. These include gestational diabetes, childhood obesity, young-onset diabetes, usual-onset diabetes and associated complications. In this overarching programme, 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, innovative technology and holistic care to predict, prevent and control diabetes.



Professor Juliana Chan
陳重娥教授

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，在生命不同階段的成因、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併發症。通過建立隊列、數據生物庫和實驗模型，培訓和機構合作以推進科學知識。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、創新技術和整合管理來預測、預防和控制糖尿病的最終目的。

The research team led by **Professor Ronald Ma** focuses on the causes and consequences of diabetes across the lifecourse, and the identification of molecular biomarkers that would facilitate the diagnosis, stratification and treatment of individuals with diabetes. Their aim is to reveal novel understanding of the underlying pathogenesis of diabetes and its complications, identify biomarkers that can be used clinically, and to translate them to deliver precision medicine for diabetes. In particular, given that more than 60% of the global estimate of people affected by diabetes are from Asia, their studies provide an important Asian perspective to seek the best therapeutic strategies for patients in Asia.



Professor Ronald Ma
馬青雲教授

馬青雲教授帶領的研究團隊側重於糖尿病在整個生命過程中的成因和後果，以及鑑定有助於糖尿病患者的診斷、分類和治療的分子生物標誌物。他們的目標是揭示對糖尿病及其併發症的潛在發病機理的新穎理解，確定可在臨床上使用的生物標誌物，並將其轉化為用於提供糖尿病的精準醫療。鑑於全球估計有60%以上的糖尿病患者來自亞洲，他們的研究更提供了重要的亞洲視角，可以尋找最適合亞洲患者的解決方案。

07

Molecular Microbiology and Emerging Infectious Diseases

分子微生物學及防疫研究

Professor Guoping Zhao is an expert in molecular microbiology and genomics. The team has been focusing on genomics and functional genomics studies to understand the regulatory mechanisms of important bacterial metabolism. Since 2008, they have also been exploring the research of systems and synthetic biology, emphasising technology innovation and application in research and clinic, particularly emphasising genome editing and bioinformatics analysis. Based upon these advanced technology and research strategies, significant progress has been made in revealing the novel mechanisms of physiology and pathology of *Mycobacterium tuberculosis* and other pathogens, particularly regarding persistent infection and drug tolerance.



Professor Guoping Zhao
趙國屏教授

趙國屏教授為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性相關生理病理研究中取得可嘉的成果。



Professor Shui-shan Lee
李瑞山教授

The Emerging Infectious Diseases (EID) Laboratory specialises in the study of infections of public health importance in Hong Kong and around the world. Last year, the research team led by **Professor Shui-shan Lee** has focused on pre-exposure prophylaxis of Human Immunodeficiency Virus (HIV), latent tuberculosis infection and sexual transmission of Hepatitis C virus. 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力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、隱性肺結核感染、丙型肝炎病毒的性傳播等。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。

With the research theme of Molecular Microbiology and Clinical Metagenomics, the team led by **Professor Sunny Wong** focuses on research related to the gut host-microbial interaction in the digestive tract. This host-microbe interface at the gastrointestinal mucosae is now known to be consequential to various bodily physiology, which has opened a new approach to develop innovative diagnostics and therapeutics. Using molecular and bioinformatic techniques, they have worked on the gastrointestinal ecosystem, especially on pertaining to diseases like colorectal cancer and *Clostridioles difficile* infection. Bridging between laboratory and hospital, the team endeavors to bring their 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**帶領的團隊的研究重點為腸道微生物群在健康生理及疾病中的角色。他們致力研究微生物群對於不同生理系統的影響。他們的重點研究在於重要的腸胃科



Professor Sunny Wong
黃曦教授

病，包括大腸癌、腸胃感染如難辨梭菌等。他們希望在腸道微生物群中，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。



Professor Martin Chan
陳子蔚教授

Norovirus is the leading cause of diarrhea in all age groups worldwide in all countries. **Professor Martin Chan** and his team have established a local and global network to monitor norovirus activity and to identify new epidemic and pandemic variants. They were among the first to report two emerging norovirus genotypes which have become epidemic in Asia and part of Europe. Research work from his team suggests Hong Kong may act as an epicentre of new noroviruses. Apart from surveillance work, the team is using a stem cell-derived enteroid model to study the disease-causing mechanism of norovirus by dissecting host factors crucial to virus replication.

諾如病毒是引致全球所有國家不同年齡組群腹瀉的主要成因。**陳子蔚教授**及其團隊已建立起一個本地和全球網絡，用以監察諾如病毒在社區的活躍程度和追蹤病毒的新型變種。他們最先發表兩種在亞洲和歐洲部分地區廣泛傳播的諾如病毒新基因型；另一重大成果為提出香港很可能是新型諾如病毒的發源地。除了病毒監察工作之外，其團隊正利用由幹細胞衍生出的微腸道模型剖析對病毒複製有重要影響的宿主因子，從而打開諾如病毒的致病機制。

08

Inflammatory Diseases 炎症性疾病研究

The past year is favourable to **Professor Hui-yao Lan** and his research team. The study of tumour microenvironment has led to the discovery of a new tumour macrophage-fibroblast phenotype that promotes tumour growth. The team has also studied new immune mechanisms including neuroimmune-related kidney and heart diseases. In addition, the team has made promising progress in translational research including the development of targeted Smad3 therapy for cancer and diabetes by using nanotechnology and Traditional Chinese Medicine.



Professor Hui-yao Lan
藍輝耀教授

藍輝耀教授及其研究團隊在2019年取得了可喜的成果。在腫瘤微環境的研究中發現了一種新的促進腫瘤生長的巨噬細胞-成纖維細胞表型。該團隊還研究了與神經免疫相關的腎臟和心臟疾病的免疫新機制。此外，該團隊在轉化試驗方面取得了突破性的進展，包括使用納米技術和中藥開發靶向Smad3治療癌症和糖尿病。



Professor Erik Fung
馮以文教授

The Laboratory for Heart Failure and Circulation Research is focused on the study of heart failure, frailty and inflammation. **Professor Erik Fung** and his research team use molecular, genetic, clinical and epidemiological methods and tools to advance the understanding of heart failure and its pathophysiology. Recently, the team has used metabolomics to identify a novel methodology to differentiate between cardiac and non-cardiac frailty. They will continue to deepen their understanding using these methods to improve disease risk stratification and complication prediction.

心衰竭及循環系統研究室主要集中於心衰竭、虛弱和發炎的研究。**馮以文教授**及其團隊使用分子學、遺傳學、臨床和流行病學方法，以加深對心衰竭病理的了解。最近，團隊研發了代謝組學分析的新方法來分辨虛弱種類，加深對風險分層和併發症預測的理解。

09

Neuroscience
神經科學

Professor Owen Ko and his team consist 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) Neurovascular and glial dysfunction in the pathogenesis of neurodegenerative diseases; and
- (2) Fundamental principles governing the operation of neural circuits.

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 therapeutics.

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、生物化學和分子生物等多學科技術，圍繞兩個主要的範疇展開研究：

- (一) 神經退化性疾病病理過程中腦血管、膠質細胞功能異常；及
- (二) 大腦神經迴路的運行機制。

他們從系統神經科學層面著力，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，從而揭示神經退化性疾病的病理過程，建立新的診療方法。



Professor Owen Ko
高浩教授

10

Reproduction and Development
生殖與發育研究

Professor Ronald Wang
黃志超教授

Professor Ronald Wang's team focused on research in Reproductive and Development and 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.

黃志超教授及其團隊的研究工作以生殖和發育為主，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、妊娠毒血症、妊娠糖尿病和臍帶血幹細胞的臨床、基礎及遺傳學研究。團隊工作表現傑出，研究成果卓越。

11

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. In 2019, they have obtained substantial external funding support; their work has won 1 national award and they have organised 1 international symposium.

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透過與本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，他們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。在2019年他們獲得了大量政府和企業的研究資金支援，並在研究工作中獲得了一項國家獎，及組織了一次國際學術研討會。



Professor Gang Li
李剛教授



Professor Kathy Lui
呂愛蘭教授

Cardiovascular disease is the leading cause of death worldwide. The team led by **Professor Kathy Lui** has been interested in regenerating the aged or damaged cardiovascular system. They have studied the pathogenesis of cardiovascular diseases and uncovered clinically relevant insights into therapeutic development. Recently, the team studied an unappreciated role of the immune system that directly regulates the development of cardiovascular diseases, repair and regeneration. For instance, they reported that a particular subset of white blood cells called regulatory T-cells regulates the function and regeneration of blood vessels and cardiac myocytes after injury.

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。他們最終還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。



Professor Ling Qin
秦嶺教授

Ageing and increase in life expectancy are 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以及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**率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機構性和功能性的修復，以達到良好的治療效果以及加快康復的速度與質量，並且降低相關的術後併發症和死亡率。



Professor Oscar Lee
李光申教授

The Laboratory for Intelligent Orthopaedic Bio-Engineering Research led by **Professor Oscar Lee**, which consists of orthopaedic surgeons, molecular and cell biologists, bioengineers and computer scientists who collectively develop advanced technologies in regenerative medicine, artificial intelligence and precision medicine. The team works on translational applications of stem cells for degenerative diseases, such as osteoarthritis, osteoporosis, sarcopenia, in elderly patients. Based on molecular and biological approaches and preclinical animal model studies, the team could shed light on the usage and manipulation of stem cells to prevent loss of bones and muscles and the underlying mechanism and ultimately improve patient outcome.

由**李光申教授**帶領的智能骨科醫生工程研究團隊研究主軸為幹細胞治療長者的肌肉骨骼疾病。該團隊應用分子生物學方法和臨床前動物模型研究，以闡明幹細胞治療相關疾病的潛在機制，期望能提升患者的生活品質。

12

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

The 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研究的方法來研究幹細胞的分化過程及其分子機理。



Professor Hao Sun
孫昊教授

In this year, **Professor Peiyong Jiang** and his research team have made a number of achievements in the bioinformatics area. Firstly, the team developed a bioinformatics approach for deciphering the fragmentomics of plasma DNA including plasma DNA topology and end motif, offering a novel means for detection and monitoring of cancers as well as noninvasive prenatal testing. Secondly, they developed a novel method for non-invasive screening of nasopharyngeal carcinoma (NPC) using methylation patterns of plasma Epstein-Barr virus DNA, improving the overall accuracy on a population screening scale. This work has made a step towards the real clinical practice of NPC detection at its early stage. Thirdly, they developed a sophisticated bioinformatics tool to enable an integrative and synergistic analysis of copy number aberrations and methylomic aberrations of urinary DNA, enabling the noninvasive detection of bladder cancer.



Professor Peiyong Jiang
江培勇教授

這一年，**江培勇教授**和他的研究團隊在生物信息學領域取得了一系列的成就。首先，團隊開發了一種生物信息學方法，用於破譯血漿DNA，包括拓撲學和末端模序，為檢測和監測癌症及產前檢測提供了一種新方法。其次，他們開發了一種基於甲基化模式的鼻咽癌非侵入性篩查新方法，提高了人群篩查規模的整體準確性。再者，他們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尿液DNA的拷貝數變異和甲基化組變異，從而實現膀胱癌的無創檢測。

13

Non-coding RNAs 非編碼核糖核苷酸研究

Skeletal muscle has a remarkable ability to regenerate after injury, owing to adult muscle stem cells. These cells are normally in a quiescent stage but can be rapidly activated upon injury, followed by proliferative expansion and differentiation into multinucleated myofiber to repair the damaged muscle tissues. Every phase of stem cell activity is tightly orchestrated by many molecules and signalling pathways both intrinsically from the cell and extrinsically from the niche. The research team led by **Professor Huating Wang** focuses on deciphering both transcriptional and post-transcriptional gene regulatory mechanisms aiming to gain a better understanding of stem cell behaviour in the process of regeneration.

骨骼肌具有強大的再生能力，這是由於成年肌肉幹細胞的存在。這些細胞通常處於靜息狀態期，但是在受傷時可以被快速激活，然後進行增殖性擴張並分化為多核肌纖維，以修復受損的肌肉組織。肌肉幹細胞活動的每個階段都由許多分子和信號通路緊密地協調，這些分子和信號通路既來自細胞，也來自外部。由**王華婷教授**帶領的研究團隊致力於解密轉錄和轉錄後基因調控機制，旨在更好地了解肌肉再生過程中幹細胞的行為。



Professor Huating Wang
王華婷教授

14

Cellular Signalling 細胞訊號轉導

Professor William Wu and his research 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 or cellular processes (e.g. autophagy) of emerging importance, and the use of omics platforms and big data.



Professor William Wu
胡嘉麒教授

胡嘉麒教授及其研究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，發掘與疾病相關的新分子或細胞過程（例如：自噬）。

15

Nephrology 腎臟疾病研究

The research interests of **Professor Cheuk Chun Szeto** and his research team include peritoneal dialysis and urinary biomarker for kidney disease. In peritoneal dialysis, the team focuses on the circulating bacterial and extracellular nucleic acid fragments, peritoneal transport and peritoneal fibrosis, treatment and prevention of peritoneal dialysis related infections, cardiovascular disease and fluid overload, and dialysis adequacy and residual renal function. Their work on urinary biomarker for kidney disease focuses on the exploration of urinary cytokine and transcription factor mRNA, urinary nucleic acid fragments, and urinary podocyte associated molecules for the diagnosis and monitoring of kidney diseases.

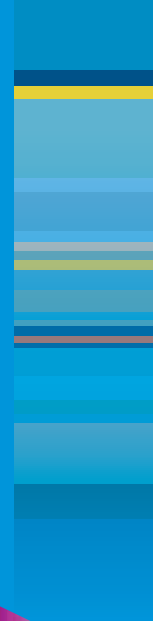
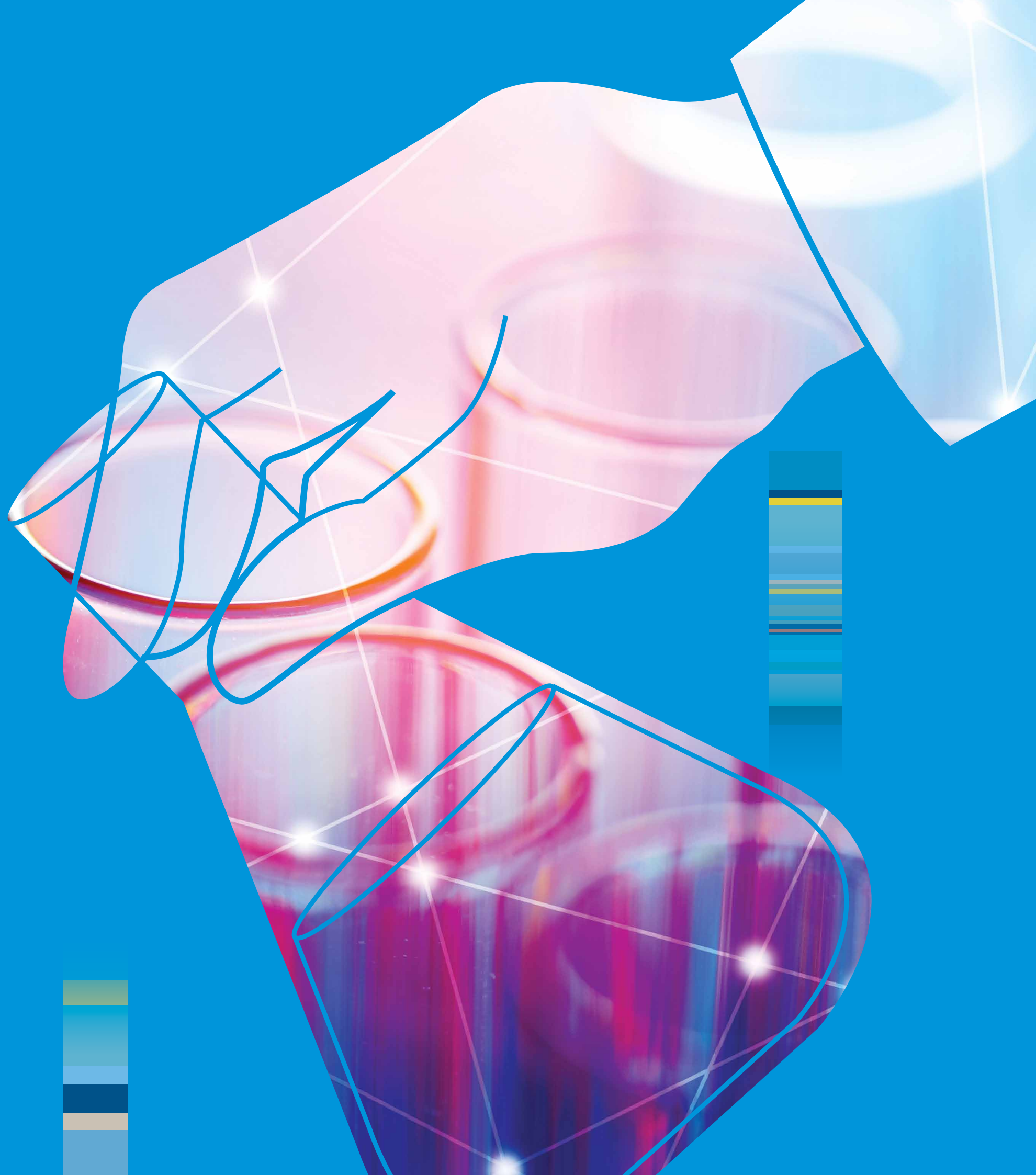
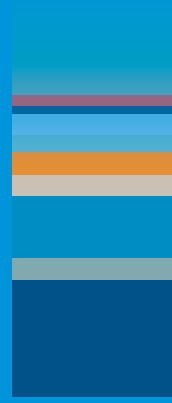


Professor Cheuk Chun Szeto
司徒卓俊教授

司徒卓俊教授及其團隊的研究包括腹膜透析和腎臟疾病的尿液生物標誌物。在腹膜透析中，他們的工作重點是循環中的細菌和細胞外核酸片段、腹膜運輸和腹膜纖維化、以及腹膜透析相關感染的治療和預防；在腎病的尿液生物標誌物方面的重點則在於探索尿液細胞轉錄因子、尿液核酸片段、以及與尿足細胞相關的分子以診斷和監測腎臟疾病。

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

02 Molecular Diagnostics

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

03 Fecal Microbiota Transplantation

■ Professor Siew Ng

04 Asian Cancers

■ Professor Qian Tao
■ Professor Siu-tim Cheung

05 Cardiovascular Medicine

■ Professor Xiaoqiang Yao
■ Professor Alex Lee

06 Diabetes and Obesity

■ Professor Juliana Chan
■ Professor Ronald Ma

07 Molecular Microbiology and Emerging Infectious Diseases

■ Professor Guoping Zhao
■ Professor Shui-shan Lee
■ Professor Sunny Wong
■ Professor Martin Chan

08 Inflammatory Diseases

■ Professor Hui-yao Lan
■ Professor Erik Fung

09 Neuroscience

■ Professor Owen Ko

10 Reproduction and Development

■ Professor Ronald Wang

11 Stem Cells and Tissue Regeneration

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

12 Genomics and Bioinformatics

■ Professor Hao Sun
■ Professor Peiyong Jiang

13 Non-Coding RNAs

■ Professor Huating Wang

14 Cellular Signalling

■ Professor William Wu

15 Nephrology

■ Professor Cheuk Chun Szeto

DIGESTIVE DISEASES



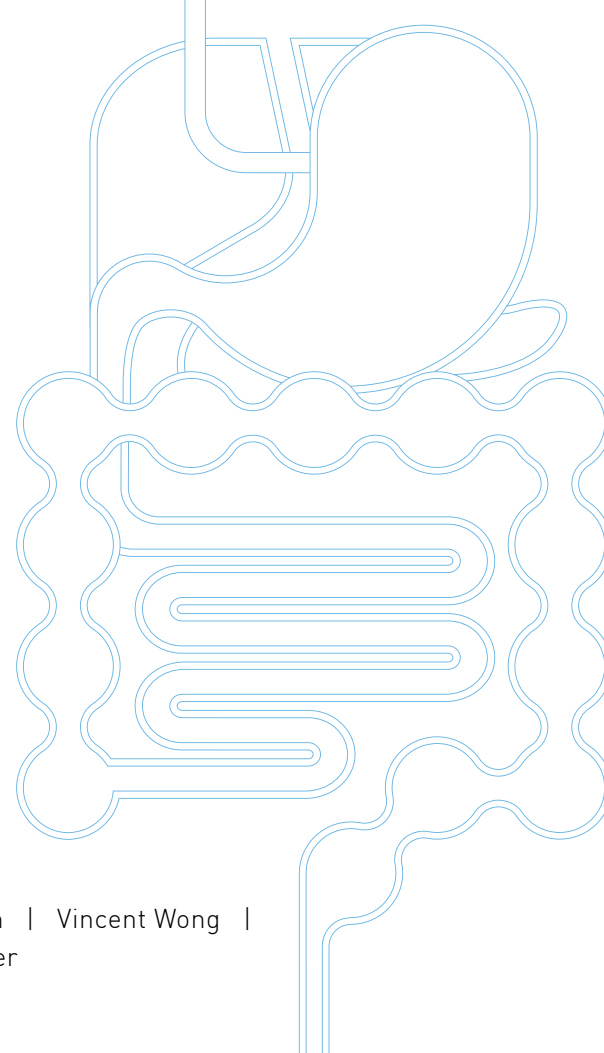
Principal Investigator

Professor Jun Yu



Team

Joseph Sung | Francis Chan | Henry Chan | Vincent Wong |
Dennis Wong | Jessie Liang | Olabisi Coker



Research Progress Summary

Colorectal Cancer:

Gut microbiota:

1. The team led by Professor Jun Yu demonstrated that *Peptostreptococcus anaerobius*, an anaerobic gut bacterium, could adhere to colon mucosa and accelerates CRC development in mice. They further identified that a *P. anaerobius* surface protein, putative cell wall binding repeat 2 (PCWBR2), directly interacts with colonic cell lines via α_2/β_1 integrin. Interaction between PCWBR2 and integrin α_2/β_1 induced the activation of the PI3K-Akt pathway in CRC cells, leading to increased cell proliferation and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) activation. Significant expansion of myeloid-derived suppressor cells, tumour-associated macrophages and granulocytic

tumour-associated neutrophils, which are associated with chronic inflammation and tumour progression were observed in *P. anaerobius*-treated *Apc^{Min/+}* mice. Blockade of integrin α_2/β_1 by RGDS peptide, small interfering RNA or antibodies all impaired *P. anaerobius* attachment and abolished *P. anaerobius*-mediated oncogenic response *in vitro* and *in vivo*. They determined that *P. anaerobius* drives CRC via a PCWBR2-integrin α_2/β_1 -PI3K-Akt-NF- κ B signalling axis and that the PCWBR2-integrin α_2/β_1 axis is a potential therapeutic target for CRC (*Nature Communication* 2019).



2. The team profiled fecal shotgun metagenomic sequences of 184 patients with CRC, 197 patients with adenoma and 204 control subjects from Hong Kong, to elucidate the contribution of enteric gut fungi to CRC. Principal component analysis revealed separate clusters for CRC patients and control, with distinct fungi composition in early-stage and late-stage CRC. Basidiomycota to Ascomycota ratio was higher in CRC with increase in *Malasseziomycetes* and decrease in *Saccharomycetes* and *Pneumocystidomycetes*. Abundances of 14 fungal biomarkers distinguished CRC from controls with an area under the receiver-operating characteristic curve (AUC) of 0.93 which was validated with AUCs of 0.82 in independent Hong Kong validation cohort 1 and 0.74 in a European cohort. These indicated that gut fungi alterations are associated with CRC. They further observed enhanced intrafungal co-occurrence and bacteria–fungi co-exclusive relationships in CRC compared with control; which were validated in independent Hong Kong validation cohort 1 and a European cohort. These results suggested a complex relationship between fungi and bacteria in the gut, in which their antagonistic relationship may contribute to colorectal tumourigenesis [*Gut* 2019].

3. They developed a new method, Bayesian Dirichlet-multinomial regression meta-analysis (BDMMA), to simultaneously model batch effects and detect microbial taxa associated with phenotypes, in microbiome studies. Combining microbial data in meta-analysis is challenging due to the variations between experiments. BDMMA automatically models dependence among microbial taxa and is robust to the high dimensionality of microbiome and their association sparsity. Their method was validated using simulation and real data analysis. They showed that BDMMA can successfully adjust batch effects and substantially reduce false discoveries in microbial meta-analyses [*Bioinformatics* 2019].

4. The team was invited to write a review of their research works and other recent relevant studies about the role of gut microbiome in colorectal neoplasia, including relevant mechanisms in

microbiota-related carcinogenesis, the potential of utilising the microbiota as CRC biomarkers, and the prospect for modulating the microbiota for CRC prevention or treatment. They identified that the modulation of gut microbiota is a promising strategy to enhance treatment efficacy and reduce adverse effects of CRC therapies [*Nature Reviews Gastroenterology & Hepatology* 2019].

Molecular pathogenesis:

1. Using whole-genome methylation analysis, they revealed that Tripartite motif 67 (TRIM67) is a novel tumour suppressor in CRC. TRIM67, was silenced in CRC and its downregulation was associated with poor survival. They generated TRIM67 knockout mice and showed that colon-specific knockout of TRIM67 significantly accelerated CRC development. In terms of its molecular mechanism, RNA-seq showed that anti-tumour effect of TRIM67 was mediated by activation of the p53 signalling pathway. TRIM67 forms a self-amplifying loop with p53 to boost p53-induced cell growth inhibition and apoptosis. Of note, TRIM67 reactivation restored p53 activation and sensitised CRC cells to chemotherapy. TRIM67 thus functions as a tumour suppressor and is a potential target for improving chemotherapy responsiveness [*Clinical Cancer Research* 2019].

2. Whole genome copy number profiling in primary colorectal tumour tissues have unravelled TTPAL as a top amplified gene CRC. They demonstrated that copy number gain of TTPAL leads to gene overexpression in CRC in 2 independent cohorts. They also showed that TTPAL is an oncogene by promoting cell proliferation, migration and invasion *in vitro* and animal models. TTPAL was found to activate activated Wnt/ β -catenin signalling, a key oncogenic pathway in CRC. TTPAL mediates its effect through stabilisation of TRIP6, which in turn, displaced β -catenin from the tumour suppressor MAGI1 via competitive binding. This allows β -catenin to enter the nucleus and promote oncogenic Wnt/ β -catenin. Finally, TTPAL expression also serves as an independent prognostic marker for CRC patients [*Cancer Research* 2019].

Gastric Cancer:

Molecular pathogenesis:

1. Using human genome comparative genomic hybridisation microarray to profile the copy number variations in gastric cancer patients, the team observed frequent amplification of 8q24, in particular for C8orf76, a novel gene with unknown function. C8orf76 is up-regulated in GC and patients with high C8orf76 suffer from poor survival. In GC cell lines, C8orf76 possesses pro-tumourigenic and pro-metastatic functions, and it promotes tumour growth and metastasis in mice models. They revealed that C8orf76 binds to promoter region of lncRNA DUSP5P1 and induces MAPK/ERK cascade to promote gastric tumourigenesis. Collectively, C8orf76 plays pivotal oncogenic role in gastric carcinogenesis and is an independent prognostic factor for GC patients [*Clinical Cancer Research* 2019].

2. To unravel genome-wide signatures in GC, they performed whole genome sequencing in 168 GC patients. Their data demonstrated diverse models of complex structural variations operative in GC, leading to high-level amplification of oncogenes. They identified hotspots of tandem-duplications (TDs) involving well-established cancer genes such as CCND1, ERBB2 and MYC. Importantly, they nominated a novel hotspot involving super-enhancer of ZFP36L2 that is present in ~10% of GC from independent patient cohorts. Functional effects of this novel hotspot were validated using experimental studies. Collectively, their findings suggested that TDs might serve as an important mechanism for cancer gene activation and provide a novel signature for stratification [*Nature Communication* 2019].

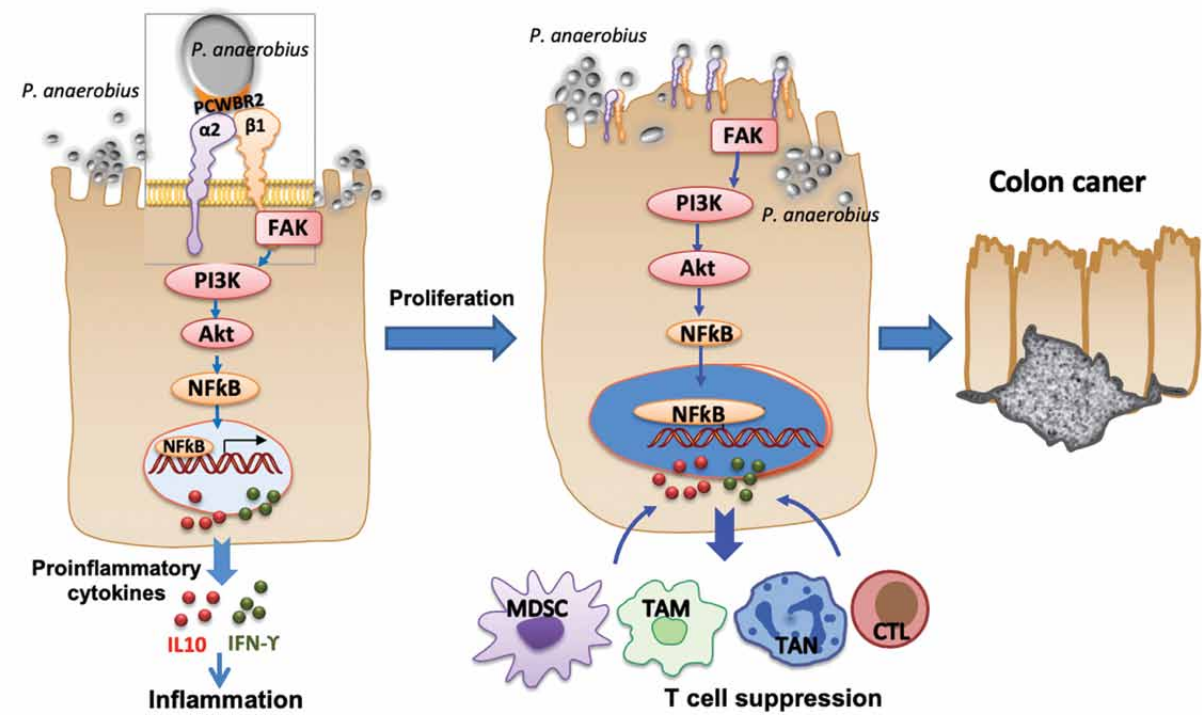
3. Prostaglandin E₂ (PGE₂) is a pro-inflammatory eicosanoid up-regulated in GC, but its role in epigenetic regulation is unknown. The team revealed that PGE₂ up-regulated DNA methylating enzymes in GC cells, leading to genome wide promoter hypermethylation. Consistently, Cox-2 (rate-limiting enzyme for PGE₂ biosynthesis) transgenic expression in mice elevated DNMT expression and DNA methylation. In a patient

cohort of 42 patients with intestinal metaplasia (a precancerous lesion of GC) treated with a COX-2 specific inhibitor Rofecoxib or placebo for 2 years, they found that COX-2 inhibitor down-regulated overall DNA methylation levels (P=0.009). Finally, they demonstrated that pharmacological inhibition of COX-2 and DNMT synergistically inhibited GC growth. This work indicated that PGE₂ induces DNA methylation in GC, and that co-targeting of PGE₂ and DNMT inhibits GC [*Theranostics* 2019].

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

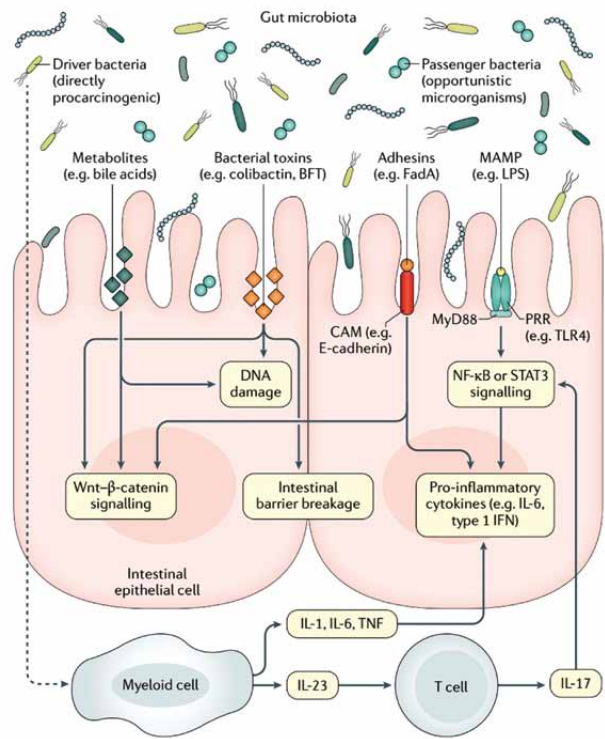
Molecular pathogenesis:

1. The team found that macrophage-specific p38 mitogen-activated protein kinases plays a critical role in pathogenesis of non-alcoholic steatohepatitis (NASH). p38 α was upregulated in the liver tissues of patients with NAFLD. They established macrophage-specific p38 α knockout (p38 $\alpha^{\Delta M\Phi}$) and wild-type (p38 $\alpha^{+/+}$) mice and evaluated its impact on NASH models, including high-fat diet (HFD), high-fat/high-cholesterol diet (HFHC), and methionine-and choline-deficient diet (MCD) models. p38 $\alpha^{\Delta M\Phi}$ mice exhibited less severe steatohepatitis and insulin resistance compared to wild-type mice. Mechanistically, macrophage p38 α promotes steatohepatitis by inducing pro-inflammatory cytokine secretion (CXCL2, IL-1 β , CXCL10 and IL-6) and M1 polarisation, suggesting that macrophage p38 α as a therapeutic target in NASH. Indeed, pharmacological p38 inhibitors suppressed HFHC-induced steatohepatitis. Collectively, specific p38 α inhibition in macrophages by p38 inhibitors might provide a new approach for the treatment of steatohepatitis [*Journal of Hepatology* 2019].



Mechanism of action of a novel oncogenic bacterium, *Peptostreptococcus anaerobius*, in promoting colorectal carcinogenesis, which involves PI3K-NF-KB oncogenic pathway and an immunosuppressive microenvironment.

Source: Long XH, Wong CC, Tong L, Chu ESH, Szeto CH, Go MYY, Coker OO, Chan AWH, Chan FKL, Sung JJY, Yu J. *Peptostreptococcus anaerobius* promotes colorectal carcinogenesis and modulates tumour immunity. *Nature Microbiology*. 2019;4(12):2319-2330. doi:10.1038/s41564-019-0541-3.



Overall mechanisms by which gut microbiota influences colorectal cancer was summarised and their potential clinical applications was reviewed.

Source: Wong SH, Yu J. *Gut microbiota in colorectal cancer: mechanisms of action and clinical applications*. *Nature Reviews Gastroenterology and Hepatology*. 2019;16(11):690-704. doi:10.1038/s41575-019-0209-8.

Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Jun Yu	Science and Technology Collaboration Award, Hebei, China Research Excellence Award 2018-19, CUHK
Chi Chun Wong	Young Investigator Award, Digestive Disease Week 2019, AGA

Fellowships

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

Academic Editorship

Member's Full Name	Details
Joseph Sung	Chief Editor, Journal of Gastroenterology and Hepatology
Jun Yu	Associate Editor, Oncogene Associate Editor, The World Journal of Gastroenterology Associate Editor, Journal of Gastroenterology & Hepatology Associate Editor, Journal of Digestive Disease Editorial Board Member, Gut Editorial Board Member, Journal of Gastroenterology & Hepatology Research Editorial Board Member, Scientific Reports Editorial Board Member, World Journal of Gastrointestinal Pharmacology and Therapeutics Editorial Board Member, Journal of Pathology & Laboratory Medicine Editorial Board Member, Journal of Next Generation Sequencing & Applications Editorial Board Member, Oncogenesis Editorial Board Member, The Open Hepatology Journal Editorial Board Member, Pragmatic and Observational Research Editorial Board Member, ISRN Gastroenterology Editorial Board Member, International Journal of Clinical Medicine Editorial Board Member, Insight Knowledge Editorial Board Member, The Open Gastroenterology Journal Chair, Golden Research Conferences-Translational Cancer Genomics
Francis Chan	Associate Editor, Clinical Gastroenterology and Hepatology Editorial Board Member, Precision and Future Medicine Editorial Board Member, Digestive Endoscopy

Academic Editorship

Member's Full Name	Details
Francis Chan	Editorial Board Member, Digestive & Liver Diseases
	Editorial Board Member, Journal of Digestive Diseases
	Editorial Board Member, Encyclopedia of Gastroenterology
	Editorial Board Member, Elsevier
Vincent Wong	Associate Editor, Clinical Gastroenterology and Hepatology
	Editorial Board Member, PLOS One
	Editorial Board Member, Antiviral Therapy
	Editorial Board Member, Alimentary Pharmacology & Therapeutics
	Editorial Board Member, Journal of Hepatology
	Editorial Board Member, Hepatology
	Editorial Board Member, Hepatology Communications
	Editorial Board Member, JHEP Reports
Henry Chan	Associate Editor, Journal of Hepatology
	Associate Editor, Hepatology International
	Associate Editor, Liver Research
	Associate Editor, Seminars in Liver Research

Reviewer of Journal / Conference

Member's Full Name	Details
Jun Yu	Reviewer, American Journal of Gastroenterology
	Reviewer, American Journal of Pathology
	Reviewer, Annals Oncology
	Reviewer, BMC Cancer
	Reviewer, BMC Gastroenterology
	Reviewer, British Journal of Cancer
	Reviewer, Alimentary Pharmacology & Therapeutics
	Reviewer, Cancer
	Reviewer, Cancer Letters
	Reviewer, Cancer Research
	Reviewer, Carcinogenesis
	Reviewer, Cell Death & Disease
	Reviewer, Clinical Cancer Research
	Reviewer, Clinical Gastroenterology and Hepatology
	Reviewer, Digestion
	Reviewer, Digestive Diseases and Sciences
	Reviewer, eBioMed
	Reviewer, FEBS Letters
	Reviewer, Gastroenterology
	Reviewer, Gut
	Reviewer, Hepatology
	Reviewer, Human Molecular Genetics
	Reviewer, The International Journal of Biochemistry & Cell Biology
	Reviewer, Life Sciences

Reviewer of Journal / Conference

Member's Full Name	Details
Jun Yu	Reviewer, International Journal of Cancer
	Reviewer, International Journal of Oncology
	Reviewer, Journal of Gastroenterology and Hepatology
	Reviewer, The Journal of Hematology & Oncology
	Reviewer, Journal of Hepatology
	Reviewer, Journal of Molecular Medicine
	Reviewer, Journal of Pathology
	Reviewer, Liver International
	Reviewer, Lancet
	Reviewer, Molecular Cancer Research
	Reviewer, Molecular Cancer Therapeutics
	Reviewer, Molecular Carcinogenesis
	Reviewer, Molecular Oncology
	Reviewer, Nature Reviews Gastroeneterology and Hepatology
	Reviewer, New England Journal of Medicine
	Reviewer, Oncogene
	Reviewer, PLOS One
	Reviewer, Scandinavian Journal of Gastroenterology
	Reviewer, Science Translational Medicine
	Reviewer, Theranostics
	Reviewer, Tumor Biology
	Reviewer, Virchows Archiv
	Chair, AGA Abstract Review Committee – Oncology
	Chair, AGA Abstract Review Committee – Microbiome

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

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
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	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 Colorectal Cancer	Science and Technology Program Grant, Shenzhen	01/07/2017	30/06/2020	RMB 2,000,000
Jun Yu	Molecular Pathogenesis of Hepatitis B Associated HCC	Guangdong Natural Scientific Funding	01/05/2018	30/04/2023	RMB 3,000,000
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
Jun Yu	Translational Cancer Genomic	Gordon Research Conference	01/05/2019	30/04/2021	USD 20,000
Jun Yu	Function of the Immune Receptor Regulator DOK1 in Therapy Response of Gastric Cancer	Germany/ Hong Kong Joint Research Scheme 2018/19	01/01/2019	31/12/2020	90,000
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	Fighting Disease Recurrence and Promoting Tissue Repair after Liver Transplantation: Translating Basic Discoveries to Clinical Excellence	Research Grants Council – Theme-based Research Scheme	01/12/2019	30/11/2024	45,000,000

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Jun Yu	Exploiting Stemness as a Cancer Cell Vulnerability Using Hepatocellular Carcinoma (HCC) as a Model System	Research Grants Council – Collaborative Research Fund	01/04/2019	31/03/2022	6,990,790
Jun Yu	Identification and Characterization of Genes and Microenvironment Factors Driving the Metastasis of Upper Gastrointestinal Tract Cancers	Research Grants Council – Collaborative Research Fund	01/07/2019	30/06/2022	4,416,717
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

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Chi Chun Wong	A Novel Epigenetic Therapy for KRAS-mutant Colorectal Cancer	Health and Medical Research Fund – Research Fellowship Scheme	30/09/2019	29/09/2022	1,499,371
Chi Chun Wong	Combinatorial Blockade of De Novo Cholesterol Biosynthesis and PCSK9 as a Synergistic Therapy for KRAS-Mutant Colorectal Cancer	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	971,368
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

Publications

A. Journal Papers

1. Ho IHT, Liu X, Zou Y, Liu T, Hu W, Chan H, Tian Y, Zhang Y, Li Q, Kou S, Chan CS, Gin T, Cheng CHK, Wong SH, Yu J, Zhang L, Wu WKK, Chan MTV. A novel peptide interfering with proBDNF-sortilin interaction alleviates chronic inflammatory pain. *Theranostics*. 2019;9(6):1651-1665. doi:10.7150/thno.29703.

2. Dai Z, Wong SH, Yu J, Wei Y. Batch effects correction for microbiome data with Dirichlet-multinomial regression. *Bioinformatics*. 2019;35(5):807-814. doi:10.1093/bioinformatics/bty729.

3. Wang X, Wu WKK, Gao J, Li Z, Dong B, Lin X, Li Y, Li Y, Gong J, Qi C, Peng Z, Yu J, Shen L. Autophagy inhibition enhances PD-L1 expression in gastric cancer. *Journal of Experimental & Clinical Cancer Research*. 2019;38(1):140. doi:10.1186/s13046-019-1148-5.

4. Wong CC, Li W, Chan B, Yu J. Epigenomic biomarkers for prognostication and diagnosis of gastrointestinal cancers. *Seminars in Cancer Biology*. 2019;55:90-105. doi:10.1016/j.semcancer.2018.04.002 [Review].

5. 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.

6. Yu J, Sung JJY. Differential colorectal cancer genomics between east and west. *Journal of Gastroenterology and Hepatology*. 2019;34(5):811-812. doi:10.1111/jgh.14675 [Editorial].

7. Xing R, Zhou Y, Yu J, Yu Y, Nie Y, Luo W, Yang C, Xiong T, Wu WKK, Li Z, Bing Y, Lin S, Zhang Y, Hu Y, Li L, Han L, Yang C, Huang S, Huang S, Zhou R, Li J, Wu K, Fan D, Tang G, Dou J, Zhu Z, Ji J, Fang X, Lu Y. Whole-genome sequencing reveals novel tandem-duplication hotspots and a prognostic mutational signature in gastric cancer. *Nature Communications*. 2019;10(1):2037. doi:10.1038/s41467-019-09644-6.

8. Wong KC, Chen J, Zhang J, Lin J, Yan S, Zhang S, Li X, Liang C, Peng C, Lin Q, Kwong S, Yu J. Early cancer detection from multianalyte blood test results. *iScience*. 2019;15:332-341. doi:10.1016/j.isci.2019.04.035.

9. Wang X, Liang Q, Zhang L, Gou H, Li Z, Chen H, Dong Y, Ji J, Yu J. C8orf76 promotes gastric tumorigenicity and metastasis by directly inducing lncRNA DUSP5P1 and associates with patient outcomes. *Clinical Cancer Research*. 2019;25(10):3128-3140. doi:10.1158/1078-0432.CCR-18-2804.

10. Wong SH, Kwong TNY, Wu CY, Yu J. Clinical applications of gut microbiota in cancer biology. *Seminars in Cancer Biology*. 2019;55:28-36. doi:10.1016/j.semcancer.2018.05.003 [Review].

11. Chen X, Chan H, Zhang L, Liu X, Ho IHT, Zhang X, Ho J, Hu W, Tian Y, Kou S, Chan CS, Yu J, Wong SH, Gin T, Chan MTV, Sun X, Wu WKK. The phytochemical polydatin ameliorates non-alcoholic steatohepatitis by restoring lysosomal function and autophagic flux. *Journal of Cellular and Molecular Medicine*. 2019;23(6):4290-4300. doi:10.1111/jcmm.14320.

12. Lam SY, Yu J, Peppelenbosch MP. Value of VAV3 methylation in stool DNA might be restricted to Non-Thiopurine-Treated inflammatory bowel disease patients. *Clinical Gastroenterology and Hepatology*. June 2019. doi:10.1016/j.cgh.2019.06.020 [Letter] [Epub ahead of print].

13. Zhang L, Li W, Cao L, Xu J, Qian Y, Chen H, Zhang Y, Kang W, Gou H, Wong CC, Yu J. PKN0X2 suppresses gastric cancer through the transcriptional activation of IGFBP5 and p53. *Oncogene*. 2019;38(23):4590-4604. doi:10.1038/s41388-019-0743-4.

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15. Gou H, Liang JQ, Zhang L, Chen H, Zhang Y, Li R, Wang X, Ji J, Tong JH, To KF, Sung JJY, Chan FKL, Fang JY, Yu J. TTPAL promotes colorectal tumorigenesis by stabilizing TRIP6 to activate Wnt/ β -catenin signaling. *Cancer Research*. 2019;79(13):3332-3346. doi:10.1158/0008-5472.CAN-18-2986.

16. Chen H, Wong CC, Liu D, Go MY, Wu B, Peng S, Kuang M, Wong N, Yu J. APLN promotes hepatocellular carcinoma through activating PI3K/Akt pathway and is a druggable target. *Theranostics*. 2019;9(18):5246-5260. doi:10.7150/thno.34713.

17. Zhang X, Fan L, Wu J, Xu H, Leung WY, Fu K, Wu J, Liu K, Man K, Yang X, Han J, Ren J, Yu J. Macrophage p38 α promotes nutritional steatohepatitis through M1 polarization. *Journal of Hepatology*. 2019;71(1):163-174. doi:10.1016/j.jhep.2019.03.014.

18. Han J, Zhang X, Lau JKC, Fu K, Lau HCH, Xu W, Chu ESH, Lan HY, Yu J. Bone marrow-derived macrophage contributes to fibrosing steatohepatitis through activating hepatic stellate cells. *Journal of Pathology*. 2019;248(4):488-500. doi:10.1002/path.5275.

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21. Dong Y, Zhang Y, Kang W, Wang G, Chen H, Higashimori A, Nakatsu G, Go M, Tong JHM, Zheng S, To KF, Sung JJY, Yang X, Ng SSM, Yu J. VSTM2A suppresses colorectal cancer and antagonizes wnt signaling receptor LRP6. *Theranostics*. 2019;9(22):6517-6531. doi:10.7150/thno.34989.
22. Scott AJ, Alexander JL, Merrifield CA, Cunningham D, Jobin C, Brown R, Alverdy J, O'keefe SJO, Gaskins HR, Teare J, Yu J, Hughes DJ, Verstraelen H, Burton J, O'Toole PWO, Rosenberg DW, Marchesi JR, Kinross JM. International Cancer Microbiome Consortium consensus statement on the role of the human microbiome in carcinogenesis. *Gut*. 2019;68(9):1624-1632. doi:10.1136/gutjnl-2019-318556.
23. Zhang B, Li M-D, Yin R, Liu Y, Yang Y, Mitchell-Richards KA, Nam JH, Li R, Wang L, Iwakiri Y, Chung D, Robert ME, Ehrlich BE, Bennett AM, Yu J, Nathanson MH, Yang X. O-GlcNAc transferase suppresses necroptosis and liver fibrosis. *JCI Insight*. 2019;4(21):e127709. doi:10.1172/jci.insight.127709.
24. Wong SH, Yu J. Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. *Nature Reviews Gastroenterology & Hepatology*. 2019;16(11):690-704. doi:10.1038/s41575-019-0209-8 [Review].
25. Long X, Wong CC, Tong L, Chu ESH, Szeto CH, Go MYY, Coker OO, Chan AWH, Chan FKL, Sung JJY, Yu J. Peptostreptococcus anaerobius promotes colorectal carcinogenesis and modulates tumour immunity. *Nature Microbiology*. December 2019;4(12):2319-2330. doi:10.1038/s41564-019-0541-3 [Epub ahead of print].
26. Wong CC, Kang W, Xu J, Qian Y, Luk STY, Chen H, Li W, Zhao L, Zhang X, Chiu PWY, Ng EKW, Yu J. Prostaglandin E2 induces DNA hypermethylation in gastric cancer *in vitro* and *in vivo*. *Theranostics*. 2019;9(21):6256-6268. doi:10.7150/thno.35766.

B. Patent

1. US Patent:
 - Inventors: Jun Yu, Joseph Sung
 - Title: Biomarker FOXF2 for Gastric Cancer
 - U.S. Non-Provisional Application number US 15/085,658
 - Filed on 30 March 2016 (file no 15/085,658)
 - Patent Granted No: US 10,294,530 B2
 - Date of Patent: 24 May 2019
2. US Patent:
 - Inventors: Jun Yu, Joseph Sung
 - Title: Biomarker RNF6 for Colorectal Cancer
 - Patent Granted No: US 10,457,993 B2
 - Date of Patent: 29 October 2019

3. US Patent:
 - Inventors: Jun Yu, Joseph Sung, Simon Ng, Yujuan Dong
 - Title: A Novel Prognostic Marker for Colorectal Cancer – VSTM2A
 - Patent Granted No: U.S. Patent No. 10,379,124
 - Date of Patent: 13 August 2019
4. US Patent:
 - Inventors: Jun Yu, Joseph Sung, Qiaoyi Liang
 - Title: Tumor Suppressor REC8 as a Biomarker for Gastric Cancer
 - U.S. Provisional Application No. US 15/600,366
 - Filed on 19 May 2017
 - Patent Granted No: U.S. Patent No. 10,364,471
 - Date of Patent: 30 July 2019
5. China PCT:
 - Inventors: Jun Yu, Joseph Sung, Shiyan Wang
 - Title: Biomarker DACT1 for Gastric Cancer
 - Patent Granted No: ZL 201210549153.2
 - Date of Patent: 23 April 2019
6. China PCT:
 - Inventors: Jun Yu, Joseph Sung, Lixia Xu
 - Title: Prognostic Biomarker and Diagnostic Kit For Colorectal Cancer-SLC12A5
 - Patent Granted No: ZL 201510055483.X
 - Date of Patent: 10 May 2019
7. US Patent:
 - Inventors: Simon Ng, Jun Yu, Yujuan Dong
 - Title: A Novel Predictive Biomarker in Patients With Metastatic Colorectal Cancer Receiving Oxaliplatin-Based Chemotherapy – miR-133a
 - Filed on 31 January 2019
8. Hong Kong Patent:
 - Inventors: Jun Yu, Joseph Sung, Qiaoyi Liang
 - Title: Faecal Bacterial Markers for Colorectal Cancer 結腸直腸癌的糞便細菌標誌物
 - Publication Date: 17 May 2019
9. European Patent:
 - Inventors: Jun Yu, Joseph Sung, Qiaoyi Liang
 - Title: Faecal Bacterial Markers for Colorectal Cancer
 - Publication Date: 3 July 2019
10. US Patent:
 - Inventors: Ka Kei Wu, Jun Yu
 - Title: Use of Streptococcus Thermophilus for Treatment and Prevention of Colorectal Cancer
 - Filed on 31 January 2019
11. US Patent:
 - Inventors: Francis Chan, Jun Yu
 - Title: Bacteria Marker for Aspirin Efficacy in Colorectal Cancer
 - U.S. filed No. US 62/925,040 (23 October 2019)

MOLECULAR DIAGNOSTICS

Circulating Fetal Nucleic Acids



Principal Investigator

Professor Dennis Lo | Professor Rossa Chiu



Team

Professor Allen Chan | Mr. Kam Wing Chan | Dr. Rebecca Chan |
Dr. Alice Cheng | Dr. Wanxia Gai | Dr. Diana Han | Dr. Macy Heung |
Miss Daisy Hu | Professor Peiyong Jiang | Ms. Yoyo Jin | Mr. Chris Kum |
Miss Angel Lai | Dr. Jacky Lam | Miss Becky Lau | Ms. Coral Lee |
Mr. Saravanan Ramakrishnan | Dr. Huimin Shang | Dr. Sarah Sin |
Professor Kun Sun | Ms. Patty Tse | Dr. Joaquim Vong | Dr. Ting Ting Xie

Research Progress Summary

Professor Dennis Lo, Professor Rossa Chiu and their research team are pioneers in the field of molecular diagnostics. They are experts in translating scientific findings into clinical application and believe that understanding the science behind the biological phenomenon is equally important to its application. It is known that circulating cell-free DNA (cfDNA) plasma consists of short DNA fragments but the biological processes generating such fragments are not well understood. So, in the reporting year, one of the focuses of the research team is to study the biology of circulating nucleic acids and to elucidate how these short DNA fragments are generated as well as their characteristics.

In 2016 and 2018, Professor Lo, Professor Chiu and their research team have shown the existence of tissue- and tumour-specific preferred end sites in cfDNA, which showed clinical utility in predicting the fetal DNA fractions in maternal plasma and tumour load in hepatocellular carcinoma patients. The finding

demonstrated that cfDNA molecules were not randomly fragmented and possessed information related to their tissues of origin. The pathology leading to death of cells from particular tissue resulted in perturbation in the relative distribution of DNA from the affected tissues in the circulation. Such tissue-of-origin analysis is particularly useful in the development of liquid biopsies for cancer. This year, the research team reported that in open chromatin regions, cfDNA molecules showed characteristic fragmentation patterns reflected by sequencing coverage imbalance and differentially phased fragment end signals. Such cfDNA fragmentation patterns preferentially occurred in tissue-specific open chromatin regions where the corresponding tissues contributed DNA into the plasma. Quantitative analyses of such signals allowed measurement of the relative contributions of various tissues toward the plasma DNA pool. These findings were validated by plasma DNA sequencing data obtained from pregnant women, organ transplantation recipients, and



cancer patients. Orientation-aware plasma DNA fragmentation analysis had potential diagnostic applications in non-invasive prenatal testing, organ transplantation monitoring, and cancer liquid biopsy.

The non-randomness of cfDNA fragmentation prompted the research team to scrutinise what was causing the fragmentation. They had a systematic approach to knockout different nuclease genes. Recently, when DNase I-like 3 (*Dnase1l3*), which was also called DNase gamma, was knocked out, there were changes in the DNA size profiles. DNASE1L3 is a secreted DNASE1-like nuclease capable of digesting DNA in chromatin, and its absence causes anti-DNA responses and autoimmunity in humans and mice. The aberrations in the fragmentation of plasma DNA included an increase in short DNA molecules below 120 bp, which was positively correlated with anti-DNA antibody levels. They also observed an increase in long, multinucleosomal DNA molecules and decreased frequencies of the most common end motifs found in plasma DNA. These aberrations were independent of anti-DNA response, suggesting that they represented a primary effect of DNASE1L3 loss. Interestingly, pregnant *Dnase1l3* ^{-/-} mice carrying *Dnase1l3* ^{+/-} fetuses showed a partial restoration of normal frequencies of plasma DNA end motifs, suggesting that DNASE1L3 from *Dnase1l3*-proficient fetuses could enter maternal systemic circulation and affect both fetal and maternal DNA fragmentation in a systemic as well as local manner. However, the observed shortening of circulating fetal DNA relative to maternal DNA was not affected by the deletion of DNASE1L3. Collectively, the findings demonstrated that DNASE1L3 played a role in circulating plasma DNA homeostasis by enhancing fragmentation and influencing end-motif frequencies. These results support a distinct role of DNASE1L3 as a regulator of the physical form and availability of cell-free DNA and may have important implications for the mechanism whereby this enzyme prevents autoimmunity. This study has thus linked the fields of nuclease biology and circulating nucleic acids and has opened up avenues for future research.

Moreover, it was observed that cfDNA fragments in maternal plasma contained DNA damage and might negatively impact the sensitivity of non-invasive prenatal testing (NIPT). In fact, some of the DNA damages are potentially repairable. The research team explored the possibility to recover those damaged cfDNA molecules. cfDNA was extracted from maternal plasma samples, repaired using PreCR DNA repair mix and sequenced. The results revealed that the size profiles of repaired libraries were altered, with significantly increased long (>250 bp) cfDNA molecules. Single nucleotide polymorphism-based analyses showed that both fetal-derived and maternal-derived cfDNA molecules were enriched by the repair. Fetal DNA fractions in maternal plasma demonstrated a small but consistent (4.8%) increase, which were contributed by a higher increment of long fetal cfDNA molecules. NIPT of five trisomy 21 samples indicated that the Z-score values were improved in all samples. Plasma DNA repair effectively recovered and enriched fetal and maternal long cfDNA molecules in maternal plasma.

Another example of how the understanding of biology facilitated the development of molecular diagnostics was the methylation analysis of plasma Epstein-Barr virus (EBV) DNA. Nasopharyngeal carcinoma (NPC) is highly associated to EBV. In 1999, Professor Lo and his team was the first to develop a molecular test to detect EBV DNA in plasma samples for non-invasive diagnosis of NPC. The test was proved to be useful for early NPC screening in asymptomatic persons as reported in the *New England Journal of Medicine* in 2017. Last year, the test was evolved into a second-generation test with sequencing analysis. EBV DNA methylation is a key epigenetic characteristic for studying EBV biology. Currently, it is not known whether patients with different EBV-associated diseases have different methylation profiles of circulating EBV DNA. Through whole-genome methylation analysis of plasma samples from patients with NPC, EBV-associated lymphoma and infectious mononucleosis, Professor Lo and his team demonstrated that EBV DNA methylation profiles exhibited a disease-associated pattern.

The observation implies a significant potential for the development of methylation analysis of plasma EBV DNA for NPC diagnostics. The research team then further analysed the plasma EBV DNA methylome of NPC and non-NPC subjects from a prospective screening cohort. Plasma EBV DNA fragments demonstrated differential methylation patterns between NPC and non-NPC subjects. Combining such differential methylation patterns with the fractional concentration and size of plasma EBV DNA, population screening of NPC was performed with an improved positive predictive value of 35.1%, compared to a count- and size-based only protocol. The methylation analysis of plasma DNA, which is the third generation of the EBV DNA test, informed the etiologies of EBV-associated diseases.

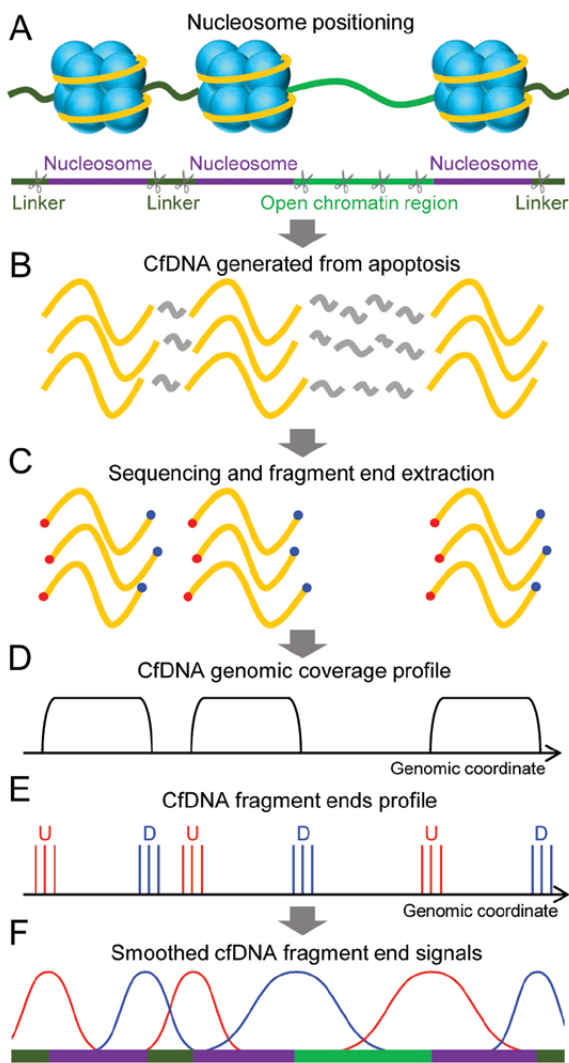
Besides circulating DNA molecules originated from the nucleus, the research team was also interested in extrachromosomal mitochondrial DNA (mtDNA) molecules in plasma. In 2004, Professor Lo and Professor Chiu developed an assay to quantify mitochondrial DNA in the plasma of healthy individuals and to investigate its physical characteristics. This year, with the advanced sequencing technology, the team further investigated the topology of plasma mtDNA and demonstrated the coexistence of both linear and circular mtDNA molecules. They elucidated the topology of plasma mtDNA using restriction enzyme *BfaI* cleavage signatures on mtDNA fragment ends to differentiate linear and circular mtDNA. MtDNA fragments with both ends carrying *BfaI* cleavage signatures were defined as circular-derived mtDNA, whereas those with no cleavage signature or with 1 cleavage signature were defined as linear-derived mtDNA. An independent assay using exonuclease V to remove linear DNA followed by restriction enzyme *MspI* digestion was used for confirming the conclusions based on *BfaI* cleavage analysis. The presence of *BfaI* cleavage signatures on plasma DNA ends in non-hematopoietically and hematopoietically derived DNA molecules were analysed by sequencing plasma DNA from patients with liver transplantation and bone marrow transplantation. In patients with liver transplantation, donor-derived (i.e. liver) mtDNA

molecules were mainly linear (median fraction, 91%; range, 75%-97%), whereas recipient-derived (i.e. hematopoietic) mtDNA molecules were mainly circular (median fraction, 88%; range, 77%-93%). The proportion of linear mtDNA was well correlated with liver DNA contribution in the plasma DNA pool ($r = 0.83$; P value = 0.0008). Consistent data were obtained from a bone marrow transplantation recipient in whom the donor-derived (i.e. hematopoietic) mtDNA molecules were predominantly circular. The findings illustrated that linear and circular mtDNA molecules coexisted in plasma and they might have different tissue origins.

In addition to plasma, urine is another ideal medium for non-invasive diagnosis. Previous efforts in urine-based detection of bladder cancer focused on targeted approaches that are predicated on the tumour expressing specific aberrations. In the recent study, the team aimed to noninvasively detect bladder cancer by the genome-wide assessment of methylomic and copy number aberrations (CNAs). They also investigated the size of tumour cfDNA fragments. Shallow-depth paired-end genome-wide bisulfite sequencing of urinary cfDNA was done for 46 bladder cancer patients and 39 cancer-free controls with hematuria. Methylomic and copy number approaches were synergistically combined to detect bladder cancer with a sensitivity of 93.5% and a specificity of 95.8%. The prevalence of methylomic and CNAs reflected disease stage and tumour size. Sampling over multiple time points could assess residual disease and changes in tumour load. Muscle-invasive bladder cancer was associated with a higher proportion of long cfDNA, as well as longer cfDNA fragments originating from genomic regions enriched for tumour DNA. The essence of the study was that bladder cancer could be detected non-invasively in urinary cfDNA by methylomic and copy number analysis without previous knowledge or assumptions of specific aberrations. Such analysis could be used as a liquid biopsy to aid diagnosis and for potential longitudinal monitoring of tumour load. Further understanding of the differential size and fragmentation of cfDNA could improve the detection of bladder cancer.

Cell-free DNA is a class of biomarkers with many current and potential future diagnostic applications. Studying the biology of cfDNA laid a solid foundation for the development of molecular diagnostics. In the reporting period, the team published a total of 10 peer-reviewed articles and reviews in international journals. With their groundbreaking work in molecular diagnostics,

Professor Dennis Lo and Professor Rossa Chiu put Hong Kong on the world map of outstanding translational researchers. They have been named the “Top 20 Translational Researchers of 2018” by the prestigious scientific journal *Nature Biotechnology*. They are the only Hong Kong scientists on the list and it is the third consecutive year for Professor Lo to receive this honour.



Conceptual framework of cell-free DNA (cfDNA) fragmentation analysis.

(A) Illustration of nucleosomes with wrapped DNA (yellow line), linkers (brown line), and open chromatin regions (green line). An abstraction of nucleosome positioning and illustration of cutting events (scissors) during apoptosis were also provided.

(B) Illustration of cfDNA generated from apoptotic DNA fragmentation. DNA wrapped around the nucleosomes is preserved, and that in the linkers and open chromatin regions will be cleaved into small pieces (gray line) that cannot be sequenced efficiently.

(C) Illustration of the sequenced reads and extraction of the ends. Red and blue represent upstream (U) and downstream (D) fragment ends, respectively.

(D) Genomic coverage.

(E) U and D end profiles of cfDNA in relation to the reference genome.

(F) Smoothed cfDNA end signals and deduced nucleosome positioning. Purple, brown, and green lines represent nucleosomes, linkers, and open chromatin regions, respectively.

Source: Sun K, Jiang PY, Cheng SH, Cheng THT, Wong J, Wong VWS, Ng SSM, Ma BBY, Leung TY, Chan SL, Mok TSK, Lai PBS, Chan HLY, Sun H, Chan KCA, Chiu RWK, Lo YMD. Orientation-aware plasma cell-free DNA fragmentation analysis in open chromatin regions informs tissue of origin. *Genome Research*. 2019;29(3):418-427. doi:10.1101/gr.242719.118.

Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Dennis Lo	國家教育部2018年度高等學校科學研究優秀成果獎「技術發明獎二等獎」
	Senior Fellow of PHG Foundation
	The German Society of Clinical Chemistry and Laboratory Medicine (DGKL) Biochemical Analysis Prize 2019
	Nature Biotechnology Top 20 Translational Researchers of 2018
	Fudan-Zhongzhi Science Award, Fudan University and Zhongzhi Enterprise Group
Rossa Chiu	Nature Biotechnology Top 20 Translational Researchers of 2018

Fellowships

Member's Full Name	Details
Dennis Lo	Hong Kong Academy of Medicine Honorary Fellowship

Academic Editorship

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

Reviewer of Journal / Conference

Member's Full Name	Details
Dennis Lo	Reviewer, Hong Kong Journal of Radiology
Rossa Chiu	Reviewer, Clinical Chemistry
	Reviewer, Clinical Chemistry and Laboratory Medicine
	Reviewer, American Journal of Obstetrics and Gynecology
	Reviewer, Obstetrics and Gynecology
	Reviewer, Prenatal Diagnosis
	Reviewer, The Journal of Obstetrics and Gynaecology Research
	Reviewer, Annals of Hematology

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Dennis Lo Rossa Chiu	Plasma DNA as a Platform Technology for Cancer Detection	The Chinese University of Hong Kong Focused Innovations Scheme C	01/12/2016	30/11/2021	2,093,500
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
Dennis Lo Rossa Chiu	Cirina Contract Research	Cirina Limited	01/09/2017	31/08/2021	136,500,000
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	Centre for Research into Circulating Fetal Nucleic Acids	The Chinese University of Hong Kong Focused Innovations Scheme C	01/01/2016	31/12/2020	5,217,900

Publications

A. Journal Papers

- Ma MJL, Zhang H, Jiang P, Sin STK, Lam WKJ, Cheng SH, Lee WS, Gai W, Tse OYO, Peng W, Wong J, Raghupathy R, Wong RSM, Sahota D, Leung TY, Chan KCA, Chiu RWK, Lo DYM. Topologic analysis of plasma mitochondrial DNA reveals the coexistence of both linear and circular molecules. *Clinical Chemistry*. 2019;65(9):1161-1170. doi:10.1373/clinchem.2019.308122.
- Jiang P, Chan KCA, Lo YMD. Liver-derived cell-free nucleic acids in plasma: Biology and applications in liquid biopsies. *Journal of Hepatology*. 2019;71(2):409-421. doi:10.1016/j.jhep.2019.04.003 [Review].
- Cheng THT, Jiang P, Teoh JYC, Heung MMS, Tam JCW, Sun X, Lee WS, Ni M, Chan RCK, Ng CF, Chan KCA, Chiu RWK, Lo YMD. Noninvasive detection of bladder cancer by shallow-depth genome-wide bisulfite sequencing of urinary cell-free DNA for methylation and copy number profiling. *Clinical Chemistry*. 2019;65(7):927-936. doi:10.1373/clinchem.2018.301341.
- Lam WKJ, Jiang P, Chan KCA, Peng W, Shang H, Heung MMS, Cheng SH, Zhang H, Tse OYO, Raghupathy R, Ma BBY, Hui EP, Chan ATC, Woo JKS, Chiu RWK, Lo YMD. Methylation analysis of plasma DNA informs etiologies of Epstein-Barr virus-associated diseases. *Nature Communications*. 2019;10(1):3256. doi:10.1038/s41467-019-11226-5.
- King AD, Woo JKS, Ai QY, Chan JSM, Lam WKJ, Tse IOL, Bhatia KS, Zee BCY, Hui EP, Ma BBY, Chiu RWK, van Hasselt AC, Chan ATC, Lo YMD, Chan KCA . Complementary roles of MRI and endoscopic examination in the early detection of nasopharyngeal carcinoma. *Annals of Oncology*. 2019;30(6):977-982. doi:10.1093/annonc/mdz106.
- Lam WKJ, Chan KCA, Lo YMD. Plasma Epstein-Barr virus DNA as an archetypal circulating tumour DNA marker. *Journal of Pathology*. 2019;247(5):641-649. doi:10.1002/path.5249 [Review].
- Sun K, Jiang P, Cheng SH, Cheng THT, Wong J, Wong VWS, Ng SSM, Ma BBY, Leung TY, Chan SL, Mok TSK, Lai PBS, Chan HLY, Sun H, Chan KCA, Chiu RWK, Lo YMD. Orientation-aware plasma cell-free DNA fragmentation analysis in open chromatin regions informs tissue of origin. *Genome Research*. 2019;29(3):418-427. doi:10.1101/gr.242719.118.
- Chiu RWK. Circulating microRNAs: in a class of their own. *Clinical Chemistry*. 2020; 66(1):257-258. doi: 10.1373/clinchem.2018.301051 (Epub in 2019) [Review].
- Vong JSL, Jiang P, Cheng SH, Lee WS, Tsang JCH, Leung TY, Chan KCA, Chiu RWK, Lo YMD. Enrichment of fetal and maternal long cell-free DNA fragments from maternal plasma following DNA repair. *Prenatal Diagnosis*. 2019;39(2):88-99. doi:10.1002/pd.5406.
- Serpas L, Chan RWY, Jiang P, Ni M, Sun K, Rashidfarrokhi A, Soni C, Sisirak V, Lee WS, Cheng SH, Peng w, Chan KCA, Chiu RWK, Reizis B, Lo YMD. Dnase1l3 deletion causes aberrations in length and end-motif frequencies in plasma DNA. *Proceedings of the National Academy of Sciences of the United States of America*. 2019;116(2):641-649. doi:10.1073/pnas.1815031116.

MOLECULAR DIAGNOSTICS

Genetics of Disease Susceptibility



Principal Investigator

Professor Nelson Tang



Team

Raphael Chan | Helen Chiu | Linda Lam | Ting Fan Leung |
Suk Ling Ma | Xiaoqiang Yao

Research Progress Summary

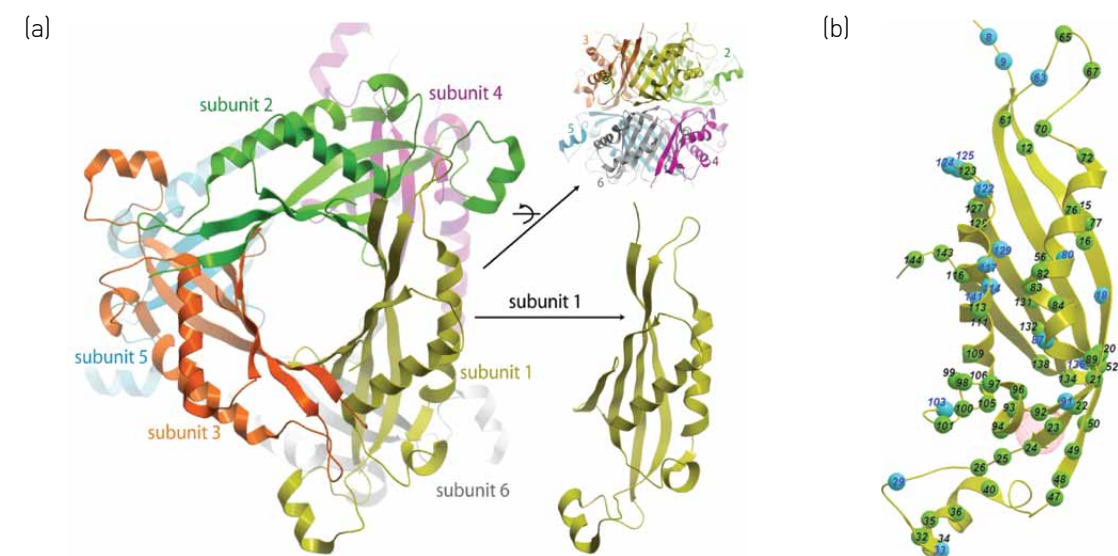
Research Directions

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 the 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 ageing (including bone and

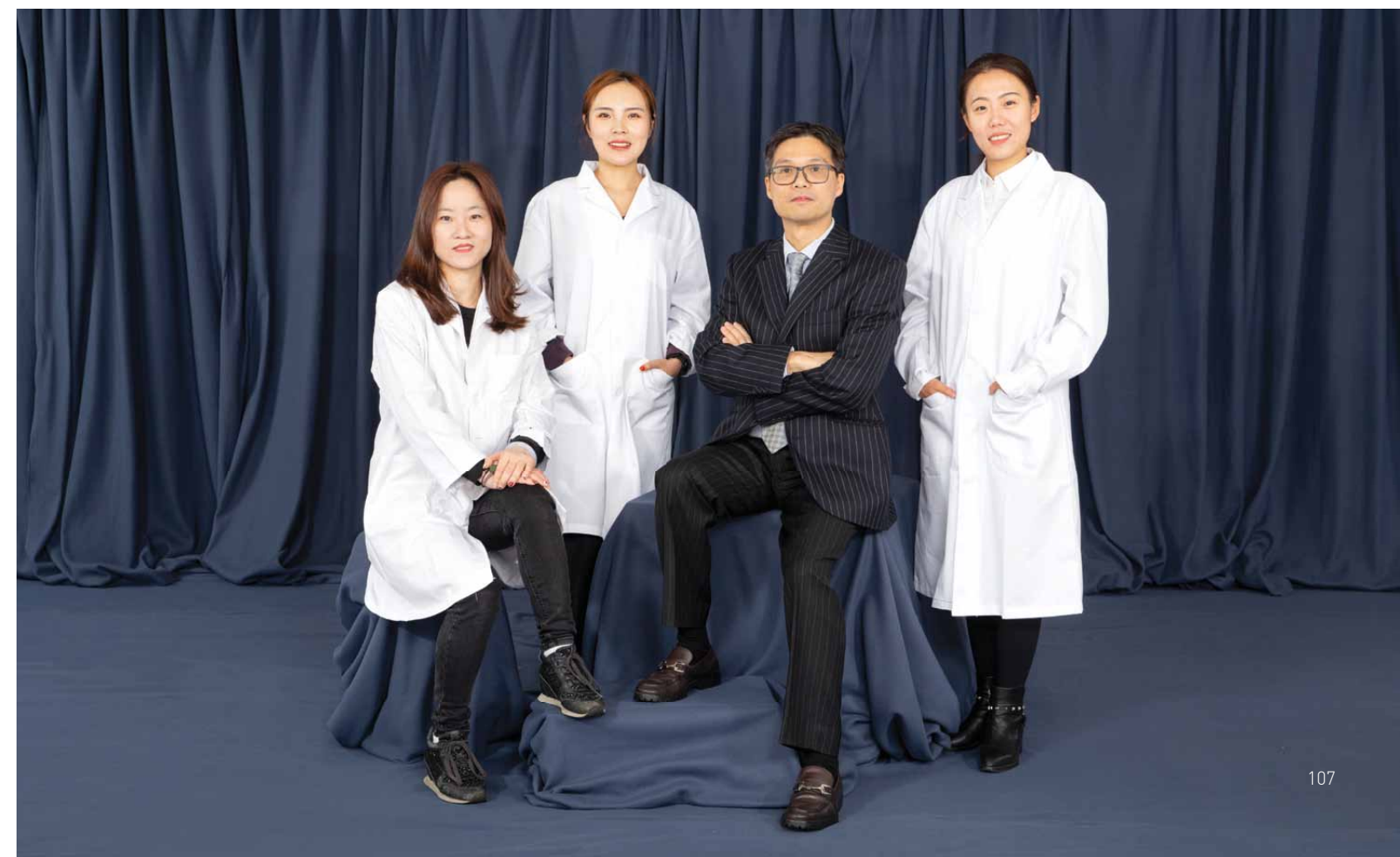
other phenotypes), breast cancer, and genetic susceptibility to adolescent idiopathic scoliosis and tuberculosis. With the advance in sequencing and other technology, the team acquires biological data in an unprecedented volume nowadays. The analysis and statistical method become limiting factors in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



(a) Ribbon diagram of human 6-pyruvoyl-tetrahydropterin synthase (PTPS) structure illustrating the homo-hexameric assembly. The six subunits are coloured distinctly. The protein structure of human enzyme is used to evaluate the effect of mutations found in patients.

(b) Clustering of human 6-pyruvoyl-tetrahydropterin synthase (PTPS) missense variants. The positions of amino acid variants in one PTPS protomer are indicated by spheres and numbered according to their residue number. Mutation sites with uncertain in-silico classification are shown in cyan spheres; the remainder are shown in green spheres. The active site divalent metal ion is shown in the red sphere.

Source: Muniz JRC, Szeto NW sum, Frise R, Lee WH, Wang X, Thony B, Himmelreich N, Blau N, Hsiao KJ, Liu TT, Gileadi O, Oppermann U, Delft FV, Yue WW, Tang NLS. Role of protein structure in variant annotation: structural insight of mutations causing 6-pyruvoyl-tetrahydropterin synthase deficiency. *Pathology*. 2019;51(3):274-280. doi:10.1016/j.pathol.2018.11.011.



■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Nelson Tang	Bronze Prize, The 47 th International Exhibition of Inventions of Geneva

Academic Editorship

Member's Full Name	Details
Nelson Tang	Editorial Board Member, Frontiers in Genetic Disorders
	Editorial Board Member, Frontiers in Pediatrics
	Editorial Board Member, Journal of Pediatric Biochemistry (Official Journal of the World Society of Child Science)
	Editorial Board Member, Genes - Open Access Journal of Genetics & Genomics

Academic Editorship

Member's Full Name	Details
Nelson Tang	Reviewer, Hong Kong Medical Journal
	Reviewer, Scientific Reports
	Reviewer, Pathology
	Reviewer, New England Journal of Medicine
	Reviewer, Journal of Clinical Laboratory Analysis

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Nelson Tang	Prediction of Clinical Outcomes by Determining the Kinetics of Serum Proadrenomedullin, Procalcitonin, and C-Reactive Protein in Adult Patients with Bloodstream Infections	CUHK Research Committee – Direct Grant	30/6/2019	29/06/2020	149,775
Nelson Tang	Expression and Functional Characterization of LBX1 in Adolescent Idiopathic Scoliosis	The National Natural Science Foundation of China – Research Grant Council 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	RMB 300,000
Nelson Tang	Mitochondrial Heteroplasmy and Cognitive Decline	CUHK Research Committee – Direct Grant	29/06/2017	28/04/2019	69,650

■ Publications

A. Journal Papers

1. Li L, Chan SL, Mo F, Hui EP, Koh J, Chan AKC, Tang NLS, Chu CM, Hui J, Lee KF, Yu S, Yeo W. Status of inflammation in relation to health related quality of life in hepatocellular carcinoma patients. *Quality of Life Research*. 2019;28(9):2597-2607. doi:10.1007/s11136-019-02190-0.
2. Styrkarsdottir U, Stefansson OA, Gunnarsdottir K, Thorleifsson G, Lund SH, Stefansdottir L, Juliusson K, Agustsdottir AB, Zink F, Halldorsson GH, Ivarsdottir EV, Benonisdottir S, Jonsson H, Gylfason A, Norland K, Trajanoska K, Boer CG, Southam L, Leung JSC, Tang NLS, Kwok TCY, Lee JSW, Ho SC, Byrjalsen I, Center JR, Lee SH, Koh JM, Lohmander LS, Ho-Pham LT, Nguyen TV, Eisman JA, Woo J, Leung PC, Loughlin J, Zeggini E, Christiansen C, Rivadeneira F, van Meurs J, Uitterlinden AG, Mogensen B, Jonsson H, Ingvarsson T, Sigurdsson G, Benediktsson R, Sulem P, Jonsdottir I, Masson G, Holm H, Norddahl GL, Thorsteinsdottir U, Gudbjartsson DF, Stefansson K. GWAS of bone size yields twelve loci that also affect height, BMD, osteoarthritis or fractures. *Nature Communications*. 2019;10(1):2054. doi:10.1038/s41467-019-09860-0.
3. Li L, Mo F, Hui EP, Chan SL, Koh J, Tang NLS, Yu SCH, Yeo W. The association of liver function and quality of life of patients with liver cancer. *BMC Gastroenterology*. 2019;19(1):66. doi:10.1186/s12876-019-0984-2.
4. Li L, Chan SL, Mo F, Hui EP, Koh J, Chan AKC, Tang NLS, Lee KF, Lai PBS, Yu SCH, Yeo W. Correlations of health-related quality of life with serum inflammatory indicators IL-8 and mBI in patients with hepatocellular carcinoma. *Cancer Management and Research*. 2019;11:2719-2727. doi:10.2147/CMAR.S178482.
5. Muniz JRC, Szeto NWS, Frise R, Lee WH, Wang X, Thony B, Himmelreich N, Blau N, Hsiao KJ, Liu TT, Gileadi O, Oppermann U, Delft FV, Yue WW, Tang NLS. Role of protein structure in variant annotation: structural insight of mutations causing 6-pyruvoyl-tetrahydropterin synthase deficiency. *Pathology*. 2019;51(3):274-280. doi:10.1016/j.pathol.2018.11.011.
6. Man GCW, Tang NLS, Chan TF, Lam TP, Li JW, Ng BKW, Zhu Z, Qiu Y, Cheng JCY. Replication study for the association of GWAS-associated loci with adolescent idiopathic scoliosis susceptibility and curve progression in a chinese population. *Spine (Phila Pa 1976)*. 2019;44(7):464-471. doi:10.1097/BRS.0000000000002866.
7. Tang NLS, Wang X, Chang KC, Chan C, Szeto NW, Huang D, Wu J, Lui GCY, Leung CC, Hui M. Genetic susceptibility to tuberculosis: interaction between HLA-DQA1 and age of onset. *Infection Genetics and Evolution*. 2019;68:98-104. doi:10.1016/j.meegid.2018.12.014.
8. Sheng F, Xia C, Xu L, Qin X, Tang NLS, Qiu Y, Cheng JCY, Zhu Z. New evidence supporting the role of FBN1 in the development of adolescent idiopathic scoliosis. *Spine (Phila Pa 1976)*. 2019;44(4):E225-E232. doi:10.1097/BRS.0000000000002809.
9. Ma SL, Tang NLS, Wat KHY, Tang JHY, Lau KH, Law CB, Chiu J, Tam CCW, Poon TK, Lin KL, Kng CPL, Long HL, Chan TY, Chan WC, Lam LCW. Effect of CYP2D6 and CYP3A4 genotypes on the efficacy of cholinesterase inhibitors in southern chinese patients with Alzheimer’s disease. *American Journal of Alzheimers Disease and Other Dementias*. 2019;34(5):302-307. doi:10.1177/1533317519848237.

MOLECULAR DIAGNOSTICS

Plasma Nucleic Acids Research



Principal Investigator

Professor Allen Chan



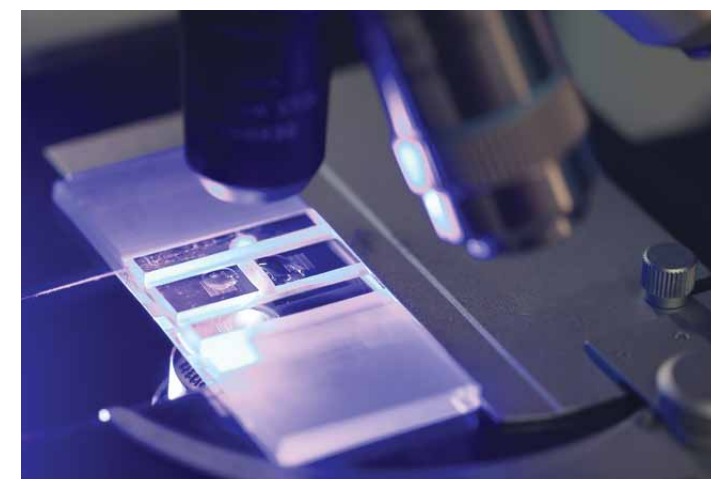
Team

Jacky Lam | Irene Tse | Wanxia Gai | Maggie Li | Amy Fung Chu Tsang
Vivien Lin | Patrick Lee

Research Progress Summary

Professor Allen Chan and his research 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. The 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-up study can address the optimal interval for NPC screening and if those non-cancer individuals with detectable plasma EBV DNA would have an increased risk of developing NPC in the future. Professor Chan was bestowed with the Inaugural Lo Ying Shek Chi Wai Foundation Meritorious Research Award in 2019.





Professor Allen Chan receiving the Inaugural Lo Ying Shek Chi Wai Foundation Meritorious Research Award from Dr. Archie Lo.

Source: Lo Ying Shek Chi Wai Foundation

Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Allen Chan	Inaugural Lo Ying Shek Chi Wai Scholar

Academic Editorship

Member's Full Name	Details
Allen Chan	Expert Review, Molecular Diagnostics

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

Publications

A. Journal Papers

1. Lam WKJ, Jiang P, Chan KCA, Peng W, Shang H, Heung MMS, Cheng SH, Zhang H, Tse OYO, Raghupathy R, Ma BBY, Hui EP, Chan ATC, Woo JKS, Chiu RWK, Lo YMD. Methylation analysis of plasma DNA informs etiologies of Epstein-Barr virus-associated diseases. *Nature Communications*. 2019;10(1):3256. doi:10.1038/s41467-019-11226-5.

2. Jiang P, Chan KCA, Lo YMD. Liver-derived cell-free nucleic acids in plasma: Biology and applications in liquid biopsies. *Journal of Hepatology*. 2019;71(2):409-421. doi:10.1016/j.jhep.2019.04.003 [Review].

3. King AD, Woo JKS, Ai QY, Chan JSM, Lam WKJ, Tse IOL, Bhatia KS, Zee BCY, Hui EP, Ma BBY, Chiu RWK, van Hasselt AC, Chan ATC, Lo YMD, Chan KCA. Complementary roles of MRI and endoscopic examination in the early detection of nasopharyngeal carcinoma. *Annals of Oncology*. 2019;30(6):977-982. doi:10.1093/annonc/mdz106.

4. Lam WKJ, Chan KCA, Lo YMD. Plasma Epstein-Barr virus DNA as an archetypal circulating tumour DNA marker. *Journal of Pathology*. 2019;247(5):641-649. doi:10.1002/path.5249 [Review].

5. Cheng THT, Jiang P, Teoh JYC, Heung MMS, Tam JCW, Sun X, Lee WS, Ni M, Chan RCK, Ng CF, Chan KCA, Chiu RWK, Lo YMD. Noninvasive detection of bladder cancer by shallow-depth genome-wide bisulfite sequencing of urinary cell-free DNA for methylation and copy number profiling. *Clinical Chemistry*. 2019;65(7):927-936. doi:10.1373/clinchem.2018.301341.

FECAL MICROBIOTA TRANSPLANTATION



Principal Investigator

Professor Siew Ng



Team

Tao Zuo | Arthur Chung | Qin Liu | Zhilu Xu |
CP Cheung | Whitney Tang | Mandy Lee | Clinical FMT team

Research Progress Summary

2019 has been a productive year for the project team led by Professor Siew Ng. The project team was successfully awarded a grant amounting to HK400M by the Innovation and Technology Commission of the HKSAR to establish a Health@InnoHK Research Centre at the Hong Kong Science Park – The Microbiota I-Center (MagIC). The MagIC centre will develop effective and accessible microbiome medicine to improve human health with a focus on knowledge transfer and entrepreneurship mentoring. The MagIC centre will partner with leading microbiota experts from the University of Chicago. A CUHK-UChicago Joint Microbiome Symposium was held in December 2019 at the University of Chicago Francis Rose Yuen Campus in Hong Kong to discuss innovations and discoveries in microbiome medicine.

In the same year, Professor Ng's team led a "Frontiers in Fecal Microbiota Transplant (FMT)" with 14 experts from 7 countries in Asia-Pacific to define future directions of FMT. The resulting joint document was endorsed by the Asia-Pacific Association of Gastroenterology (APAGE) and the Asia-Pacific Society for Digestive Endoscopy (APSDE) and published in the prestigious journal *Gut*. The team has also developed the first and most comprehensive longitudinal Fecal Microbiota Transplantation Registry in Asia to aid the development of personalised gut microbiota-based therapy and safety surveillance. To date, the project team is the only provider of FMT service to the local health authority in Hong Kong for the treatment of recurrent *Clostridioides difficile* infections. In 2019, Professor Siew Ng and Professor Francis Chan co-founded a microbiome





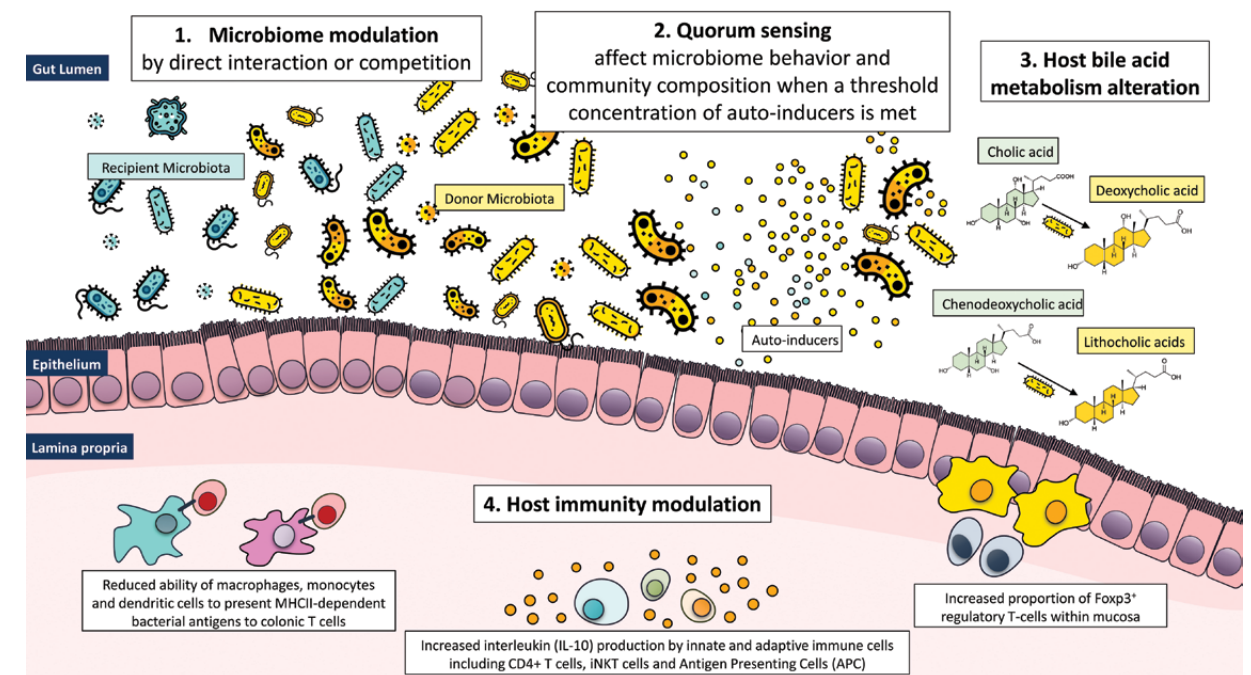
startup, Geniebiome, with the mission to target and fix the gut microbiome using the latest unique metagenomic datasets. The team had filed applications for several microbiome related patents.

In terms of research collaboration, the team has established a strong network of hospitals in the Greater Bay Area (Hong Kong and its neighbouring cities in southern China) to develop a first of its kind long-term cohort of 100,000 mothers and babies with the aim of using “microbiome medicine” to improve health of the next generation. This comprehensive, longitudinal cohort will generate not only an enormous repertoire of clinical dataset and biological specimens, but also will attract world-renowned institutions and pharmaceutical companies to invest in Hong Kong. In a recent multi-center (Beijing, Xiangshan, Hong Kong) study, the project team has demonstrated that ulcerative colitis is characterised by substantial alterations of the mucosa gut virome. This knowledge advances the understanding of the pathogenesis of



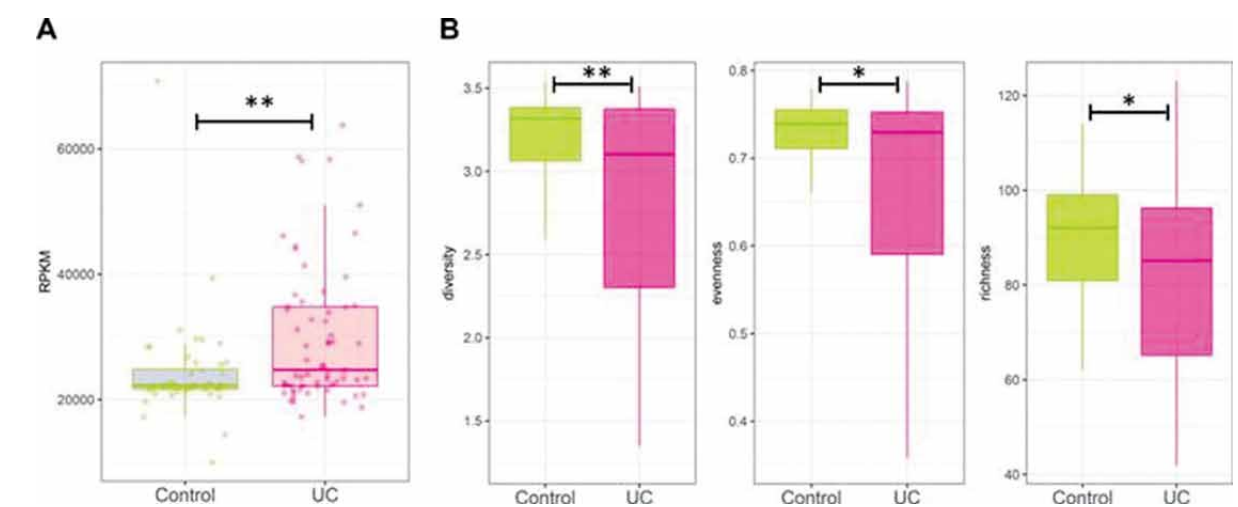
inflammatory bowel disease and the findings were published in *Gut*. This paper was selected by the Editor-in-Chief as a *Gut* video abstract both on its website and social media including YouTube (<https://youtu.be/despjZ-yKb0>).

In summary, 2019 has been a productive year for the research team. Professor Ng has received a number of accolades in the same year including the Croucher Senior Medical Research Fellowship in recognition of her excellent achievements in scientific research in medicine, Sir Francis Avery Jones Visiting Professorship, UK and Joanna and David Sachar Visiting Professorship, USA.



Potential mechanisms of faecal microbiota transplantation (FMT). Potential mechanisms of FMT include direct interaction or competition between donor and recipient gut microbiota to achieve homeostasis, effect of donor microbiota on the host immunity and effect of microbiota on modulating host metabolism and physiology.

Source: SC Ng, MA Kamm, YK Yeoh, PKS Chan, T Zuo, W Tang, A Sood, A Andoh, N Ohmiya, Y Zhou, CJ Ooi, V Mahachai, CY Wu, F Zhang, K Sugano, FKL Chan. *Scientific frontiers in faecal microbiota transplantation: joint document of Asia-Pacific Association of Gastroenterology (APAGE) and Asia-Pacific Society for Digestive Endoscopy (APSDE)*. *Gut*. 2020;69(1):83-91. doi:10.1136/gutjnl-2019-319407.



Mucosal virome alterations in abundance and diversity in UC.

Source: T Zuo, XJ Lu, Y Zhang, CP Cheung, S Lam, F Zhang, W Tang, JYL Ching, R Zhao, PKS Chan, JJY Sung, J Yu, FKL Chan, Q Cao, JQ Sheng, SC Ng. *Gut*. 2019;68(7):1169-1179. doi:10.1136/gutjnl-2018-318131.

■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Siew Ng	2019 Croucher Senior Medical Research Fellowships Award, Croucher Foundation, Hong Kong
	Sir Francis Avery Jones Visiting Professorship and Award, St Mark's Hospital, London, UK
	Joanna and David B. Sachar M.D. International Award and Visiting Professorship in Inflammatory Bowel Disease, The Icahn School of Medicine, Mount Sinai, USA
Qin Liu	Early Career Investigator Award, Digestive Disease Week. San Diego, USA

Fellowships

Member's Full Name	Details
Qin Liu	Postdoctoral Fellowship Research Award, The Chinese University of Hong Kong, Hong Kong

Academic Editorship

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

Reviewer of Journal / Conference

Member's Full Name	Details
Siew Ng	Abstract Reviewer, Digestive Disease Week, 2019, Washington, United States
	Invited Reviewer, Gastroenterology
	Invited Reviewer, Gut
	Invited Reviewer, Nature Review Gastroenterology & Hepatology
	Invited Reviewer, American Journal of Gastroenterology
	Invited Reviewer, Clinical Gastroenterology and Hepatology
	Invited Reviewer, Alimentary Pharmacology and Therapeutics
	Invited Reviewer, Gastrointestinal Endoscopy
	Invited Reviewer, Journal of Crohn's and Colitis
	Invited Reviewer, Inflammatory Bowel Disease
	Invited Reviewer, Journal of Gastroenterology and Hepatology
	Invited Reviewer, World Journal of Gastroenterology
	Invited Reviewer, Digestive Diseases and Sciences
	Invited Reviewer, BMC Gastroenterology
	Invited Reviewer, European Journal of Gastroenterology and Hepatology
	Invited Reviewer, Journal of Gastroenterology

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Siew Ng	Health@InnoHK	Innovation and Technology Commission	01/10/2019	30/09/2024	400,000,000
Siew Ng	When Should Low-dose Aspirin be Resumed After Peptic Ulcer Bleeding? A Double-blind, Randomized Controlled Trial	Research Grant Council – General Research Fund	01/01/2019	31/12/2021	972,000
Siew Ng	A Randomised, Placebo-controlled Study on Fecal Microbiota Transplantation for Patients with Irritable Bowel Syndrome with Fecal and Mucosal Microbiota Assessment (FMT-IBS Study)	Food and Health Bureau – Health and Medical Research Fund	01/06/2019	31/05/2021	1,301,112

Publications

A. Journal Papers

1. Ng SC, Kamm MA, Yeoh YK, Chan PKS, Zuo T, Tang W, Sood A, Andoh A, Ohmiya N, Zhou Y, Ooi CJ, Mahachai V, Wu CY, Zhang F, Sugano K, Chan FKL. Scientific frontiers in faecal microbiota transplantation: joint document of Asia-Pacific Association of Gastroenterology (APAGE) and Asia-Pacific Society for Digestive Endoscopy (APSDE). *Gut*. 2020;69(1):83-91. doi:10.1136/gutjnl-2019-319407 [Epub in 2019].
2. Zuo T, Lu XJ, Zhang Y, Cheung CP, Lam S, Zhang F, Tang W, Ching JYL, Zhao R, Chan PKS, Sung JJY, Yu J, Chan FLS, Cao Q, Sheng JQ, Ng SC. Gut mucosal virome alterations in ulcerative colitis. *Gut*. 2019;68(7):1169-1179. doi:10.1136/gutjnl-2018-318131.
3. Ng SC, Kyaw MH, Suen BY, Tse YKM, Wong MCS, Hui AJ, Tak HY, Lau JYW, Sung JJY, Chan FKL. Prospective colonoscopic study to investigate risk of colorectal neoplasms in first-degree relatives of patients with non-advanced adenomas. *Gut*. 2020;69(2):304-310. doi: 10.1136/gutjnl-2018-318117 [Epub in 2019].
4. Chan FKL, Kyaw MH, Hsiang JC, Suen BY, Kee KM, Tse YK, Ching JYL, Cheong PK, Ng D, Lam K, Lo A, Lee V, Ng SC. Risk of postpolypectomy bleeding with uninterrupted clopidogrel therapy in an industry-independent, double-blind, randomized trial. *Gastroenterology*. 2019;156(4):918-925.e1. doi:10.1053/j.gastro.2018.10.036.
5. Lai CY, Sung J, Cheng F, Tang W, Wong SH, Chan PKS, Kamm MA, Sung JJY, Kaplan G, Chan FKL, Ng SC. Systematic review with meta-analysis: review of donor features, procedures and outcomes in 168 clinical studies of faecal microbiota transplantation. *Alimentary Pharmacology and Therapeutics*. 2019;49(4):354-363. doi:10.1111/apt.15116.
6. Ng SC, Ananthakrishnan AN. New approaches along the IBD course: diet, tight control and stem cells. *Nature Reviews Gastroenterology & Hepatology*. 2019;16(2):82-84. doi:10.1038/s41575-018-0088-4 [Editorial].
7. Chan JSH, Chao ACW, Cheung VCH, Wong SSK, Tang W, Wu JCY, Chan HLY, Chan FKL, Sung JJY, Ng SC. Gastrointestinal disease burden and mortality: A public hospital-based study from 2005 to 2014. *Journal of Gastroenterology and Hepatology*. 2019;34(1):124-131. doi:10.1111/jgh.14377.

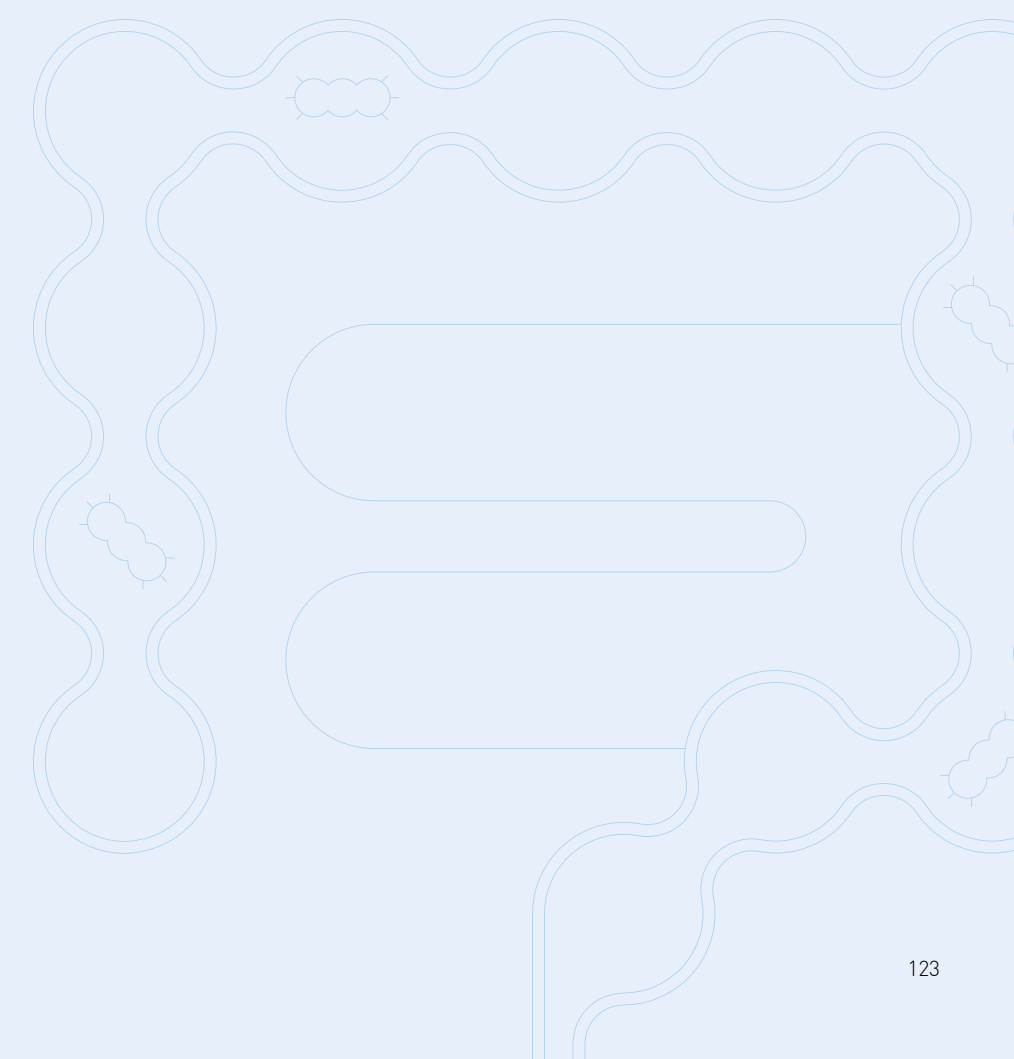
B. Conference Papers

1. Zhang JW, Berendsen E, Hoedt EC, Liu Q, Xu ZL, Zhang F, Hamilton AL, Wilson-O'Brien A, Ching JY, Sung JJ, Kamm MA, Morrison M, Yu J, Ng SC. Proteus is a key candidate in the pathogenesis of crohn's disease: mucosa, stool genomics and functional analysis: the enigma study, *Gastroenterology*. 05, 2019. 156. p. S50-S50. In: *Digestive Disease Week 2019*. San Diego, USA. 2019 May 18-21.
2. Zuo T, Lu XJ, Cheung CP, Lam S, Zhang F, Tang W, Ching JY, Zhao RS, Chan PK, Sung JJ, Yu J, Chan FK, Sheng JQ, Ng SC. Increased bacteriophage abundance and loss of viral-bacterial interactions in the mucosa of ulcerative colitis: key to pathogenesis? *Gastroenterology*. 05, 2019. 156. p. S49-S49. In: *Digestive Disease Week 2019*. San Diego, USA. 2019 May 18-21.
3. Xu ZL, Yang KL, Zhang JW, Zuo T, Chevarin C, Chu LC, Chan FK, Sung JJ, Yu J, Barnich N, Wong SH, Ng SC. Adherent-invasive escherichia coli in inflammatory bowel disease impacts fecal microbiota transplantation efficacy by hindering engraftment of beneficial bacteria, *Gastroenterology*. 05, 2019. 156. p. S1147-S1147. In: *Digestive Disease Week 2019*. San Diego, USA. 2019 May 18-21.

4. Mak WY, Tang W, Chan FK, Leung WK, Li MK, Lo FH, Ng CKM, Sze SF, Leung CM, Tsang S, Shan EHS, Chan KH, Lam BCY, Hui AJ, Chow WH, Sung JJ, Ng SC. Can we stop anti-tumour necrosis factor (anti-Tnf) in patients with perianal crohn's disease? Results from a population-based study., *Gastroenterology*. 05, 2019. 156. p. S886-S886. In: *Digestive Disease Week 2019*. San Diego, USA. 2019 May 18-21.
5. Zhang F, Yeoh YK, Cheng F, Zuo T, Tang W, Cheung K, Yang KL, Liu Q, Cheung CP, Chow CM, Chan FK, Li CK, PK Chan, Ng SC. Rapid and durable engraftment of donor fungi and bacteria after successful fecal microbiota transplantation in acute graft-versus-host disease: intensive serial metagenomics study, *Gastroenterology*. 05, 2019. 156. p. S1157-S1158. In: *Digestive Disease Week 2019*. San Diego, USA. 2019 May 18-21.
6. Liu Q, Yang KL, Xu ZL, Zuo T, Tang W, Zhang F, Lau LHS, Lui RN, Wong R, Chin ML, Chan PK, Chan FK, Lui GC, Ng SC. Donor fungi and bacteria engraftment after successful eradication of carbapenem-resistant enterobacteriaceae with fecal microbiota transplantation: serial fecal metagenomics analysis, *Gastroenterology*. 05, 2019. 156. p. S131-S131. In: *Digestive Disease Week 2019*. San Diego, USA. 2019 May 18-21.
7. Mak WY, Tang W, Lam TO, Chan FK, Sung JJ, Ng SC. Risk of infections and hospitalisations in inflammatory bowel disease and other immune-mediated diseases on thiopurine therapy: a population-based study, *Gastroenterology*. 05, 2019. 156. p. S663-S663. In: *Digestive Disease Week 2019*. San Diego, USA. 2019 May 18-21.
8. Laube R, Yau YY, Selinger CP, Thomas A, Ahuja V, Alharbi O, Banerjee R, Chuah SW, Hilmi I, Mao R, Ng SC, Ong DE, Seow CH, Wei SC, Leong RW. Knowledge and attitudes towards pregnancy in females with inflammatory bowel disease? an international, multi-centre study, *Gastroenterology*. 05, 2019. 156. p. S1131-S1131. In: *Digestive Disease Week 2019*. San Diego, USA. 2019 May 18-21.
9. King JA, Jeong J, Underwood FE, Quan J, Panaccione N, Windsor JW, Coward S, deBruyn J, Ronksley P, Shaheen AA, Quan HD, Godley J, van Zanten SV, Lebowhl B, Ng SC, Kaplan G. Incidence of celiac disease is increasing over time: a systematic review and meta-analysis, *Gastroenterology*. 05, 2019. 156. p. S918-S918. In: *Digestive Disease Week 2019*. San Diego, USA. 2019 May 18-21.
10. Singh S, Underwood FE, Loftus EV, Dulai PS, Ghosh S, Sandborn WJ, Ng SC, Kaplan G. Worldwide incidence of older-onset inflammatory bowel diseases in the 21st century: a systematic review of population-based studies, *Gastroenterology*. 05, 2019. 156. p. S394-S395. In: *Digestive Disease Week 2019*. San Diego, USA. 2019 May 18-21.
11. Berendsen E, Hoedt EC, Teh JJ, Zhang JW, Zhang F, Liu Q, Hamilton AL, Wilson-O'Brien A, Ching JY, Sung JJ, Yu J, Ng SC, Kamm MA, Morrison M. Characterization of crohn's disease mucosa-associated microbiota by a novel combination of microbe culture and metagenomic sequencing (Mc-Mgs). The Enigma Study, *Gastroenterology*. 05, 2019. 156. p. S1152-S1152. In: *Digestive Disease Week 2019*. San Diego, USA. 2019 May 18-21.

12. Berendsen E, Hoedt EC, Teh JJ, Zhang JW, Zhang F, Liu Q, Hamilton AL, Wilson-O'Brien A, Ching JY, Sung JJ, Yu J, Ng SC, Kamm MA, Morrison M. Urease-positive proteobacteria in crohn's disease identified by novel ex-vivo mucosal microbe culture combined with metgenomic sequencing (Mc-Mgs). The Enigma Study, Gastroenterology. 05, 2019. 156. p. S1146-S1146. In: *Digestive Disease Week 2019*. San Diego, USA. 2019 May 18-21.
13. Gearry RB, McCombie A, Vatn MH, Rubin DT, Steinwurz F, Loftus EV, Kruis W, Tysk C, Colombel JF, Ng SC, Van Assche GA, Bernstein CN. What are the most challenging aspects of IBD? An international survey of gastroenterologists comparing western and non-western countries, Gastroenterology. 05, 2019. 156. p. S1134-S1134. In: *Digestive Disease Week 2019*. San Diego, USA. 2019 May 18-21.
14. Hart A, Ng SC, Ghosh S, Watkins J, Fullarton J, Paridaens K. A national, retrospective, observational study on the use of 5-aminosalicylates (5-asa) in Crohn's disease (Cd), Gastroenterology. 05, 2019. 156. p. S1128-S1129. In: *Digestive Disease Week 2019*. San Diego, USA. 2019 May 18-21.
15. Mak WY, Tang W, Chan FKL, Leung WK, Li MKK, Lo FH, Ng CKM, Sze ASF, Leung CM, Tsang SWC, Shan EHS, Chan KH, Lam BCY, Hui AJ, Chow WH, Sung JJY, Ng SC. Stopping anti-tumour necrosis factor (TNF) therapy in patients with perianal Crohn's disease: Results from a population-based study, Journal of Crohn's & Colitis. 03, 2019. 13. p. S431-S431. In: *Congress of European Crohn's and Colitis Organisation 2019*. Copenhagen, Denmark. 2019 March 6-9.
16. Zhang J, Berendsen E, Hoedt E, Liu Q, Zhang F, Xu Z, Hamilton A, Brien AWO, Ching J, Sung JJ, Kamm MA, Morrison M, Yu J, SC Ng. Proteus is a key candidate in the pathogenesis of Crohn's disease: mucosa, stool genomics and functional analysis: the ENIGMA study, Journal of Crohn's & Colitis. 03, 2019. 13. p. S541-S541. In: *Congress of European Crohn's and Colitis Organisation 2019*. Copenhagen, Denmark. 2019 March 6-9.
17. Loayza JJJ, Berendsen EM, Teh JJ, Hoedt EC, Zhang J, Liu Q, Hamilton AL, Wilson-O'Brien A, Trakman GL, Lin W, Tang W, Ching J, Or LMH, Sung JJ, Yu J, Ng SC, Kamm MA, Morrison M. The common food additives sodium sulfite and polysorbate 80 have a profound inhibitory effect on the commensal, anti-inflammatory bacterium *Faecalibacterium prausnitzii*: the ENIGMA study, Journal of Crohn's & Colitis. 03, 2019. 13. p. S542-S543. In: *Congress of European Crohn's and Colitis Organisation 2019*. Copenhagen, Denmark. 2019 March 6-9.
18. Hart A, Ng SC, Ghosh S, Watkins J, Fullarton J, Paridaens K. A national, retrospective, observational study on the use of 5-aminosalicylates (5-ASA) in Crohn's disease (CD), Journal of Crohn's & Colitis. 03, 2019. 13. p. S398-S399. In: *Congress of European Crohn's and Colitis Organisation 2019*. Copenhagen, Denmark. 2019 March 6-9.
19. Berendsen EM, Hoedt EC, Teh JJ, Zhang J, Zhang F, Liu Q, Hamilton AL, Wilson-O'Brien A, Ching J, Sung JJ, Yu J, Ng SC, Kamm MA, Morrison M. Characterisation of Crohn's disease mucosa-associated microbiota by a novel combination of microbe culture and metagenomic sequencing (MC-MGS): the ENIGMA study, Journal of Crohn's & Colitis. 03, 2019. 13. p. S550-S550. In: *Congress of European Crohn's and Colitis Organisation 2019*. Copenhagen, Denmark. 2019 March 6-9.
20. Trakman G, Lin WYY, Wilson-O'brien A, Ching J, Tang W, Orr L, Stanley A, Hamilton AL, Morrison M, Yu J, Sung JJ, Ng SC, Kamm MA. Development and validation of tools to assess food additive intake: the ENIGMA study, Journal of Crohn's & Colitis. 03, 2019. 13. p. S507-S507. In: *Congress of European Crohn's and Colitis Organisation 2019*. Copenhagen, Denmark. 2019 March 6-9.

21. Xu Z, Yang K, Zhang J, Zuo T, Chevarin C, Wong SH, Chan FK, Sung JJ, Yu J, Barnich N, SC Ng. Adherent-invasive *Escherichia coli* in inflammatory bowel disease impacts faecal microbiota transplantation efficacy by hindering engraftment of beneficial bacteria, Journal of Crohn's & Colitis. 03, 2019. 13. p. S539-S539. In: *Congress of European Crohn's and Colitis Organisation 2019*. Copenhagen, Denmark. 2019 March 6-9.
22. Berendsen EM, Hoedt EC, Teh JJ, Zhang J, Zhang F, Liu Q, Hamilton AL, Ching J, Sung JJ, Yu J, Ng SC, Kamm MA, Morrison M. Urease-positive proteobacteria in Crohn's disease identified by novel ex vivo mucosal microbe culture combined with metagenomic sequencing (MC-MGS): the ENIGMA study, Journal of Crohn's & Colitis. 03, 2019. 13. p. S548-S549. In: *Congress of European Crohn's and Colitis Organisation 2019*. Copenhagen, Denmark. 2019 March 6-9.
23. Kotze PG, Underwood F, Damiao AO, Ferraz J, Saad-Hossne R, Toro M, Vergara BMI, Bosques-Padilla F, Teixeira F, Julian-Banos F, Simian D, Ghosh S, Panaccione R, Ng SC, Kaplan G. The Progression of Inflammatory Bowel Disease Throughout Latin America: A Systematic Review, Inflammatory Bowel Diseases. 02, 2019. 25. p. S51-S51. In: *Crohn's and Colitis Congress 2019*. Las Vegas, USA. 2019 February 7-9.
24. Kotze PG, Underwood F, Damiao AO, Ferraz J, Saad-Hossne R, Toro M, Vergara BMI, Bosques-Padilla F, Teixeira F, Julian-Banos F, Simian D, Ghosh S, Panaccione R, Ng SC, Kaplan G. The Progression of Inflammatory Bowel Disease Throughout Latin America: A Systematic Review, Gastroenterology. 02, 2019. 156. p. S401-S402. In: *Crohn's and Colitis Congress 2019*. Las Vegas, USA. 2019 February 7-9.



ASIAN CANCERS

Cancer Epigenetics



Principal Investigator

Professor Qian Tao



Team

Dr. Lili Li | Dr. Shuang Tong | Dr. Lixin Wang | Tao Ding | Shujun Feng |
Junyu Zhu | Yingjun Zhang | Jun Zhou | Miyu Terashima



Research Progress Summary

Professor Qian Tao and his research team work on the epigenome alterations of Hong Kong tumours and identify novel tumour suppression genes (TSGs) epigenetically inactivated. The team specifically studies the epigenetic disruption of cell signalling regulation through silencing signalling TSGs by promoter CpG methylation in tumourigenesis. They have characterised an epigenetically inactivated, tumour suppressive Ras GTPase-activating protein (RasGAP) - *RAS45*, which antagonises Ras signalling perturbation in carcinomas. Aberrant RAS activation is common in human cancers with even a few mutations of Ras, indicating alternative regulation leading to RAS signalling activation other than genetic mutations. They identified a Ras

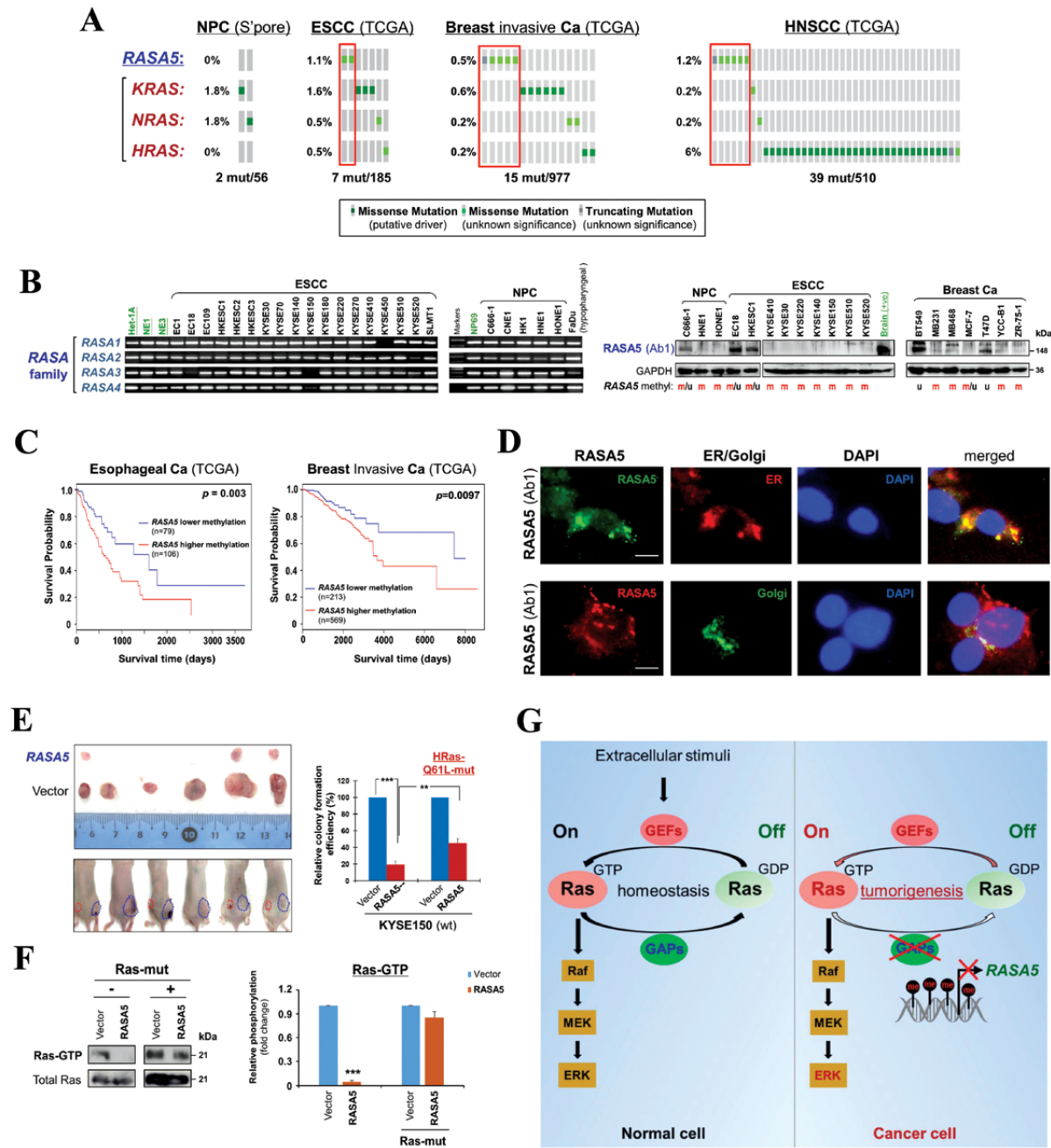
GTPase-activating protein gene *RAS45*, located at a common 6p21.3 deletion, methylated and downregulated in several carcinomas, while its homologous RASA family members (*RASA1-4*) were broadly expressed and only occasionally downregulated in tumours, indicating that *RAS45* has a special and important role in tumourigenesis among the RASA family. Unlike other RASA members like *RASA1*, mutations are rare for *RAS45*, while its promoter CpG methylation is frequently present in cancer cell lines and primary carcinomas of esophageal, nasopharyngeal, breast, lung, gastric and colon, and associated with patient poor survival. They further found that *RAS45* inhibited tumour cell migration/invasion and growth in the mouse model, thus as a *bona fide* tumour



suppressor. *RAS45* suppressed RAS signalling, depending on its RasGAP catalytic activity, which could be counteracted by oncogenic HRas Q61L mutant. Meanwhile, *RAS45* knockdown enhanced Ras signalling to promote tumour

cell growth. *RAS45* also inhibited epithelial-mesenchymal transition (EMT) through regulating actin remodelling in cells. Thus, their study characterised a novel tumour suppressive role of *RAS45*, in addition to its known functions in neuro cell development and regulation. Epigenetic inactivation of *RAS45* contributing to hyperactive RAS signalling might have an important role in Ras-driven oncogenesis, particularly in carcinomas with few oncogenic Ras mutations.

Meanwhile, the team also identified the epigenetic disruption of other TSGs by promoter CpG methylation, including ZBTB28, ZFP82 and SOX7, contributing to multiple tumourigeneses and also as potential epigenetic biomarkers.



Novel tumour suppressive role of the Ras GTPase-activating protein RASA5 to Ras signalling perturbation in human carcinomas.

Source: Professor Qian Tao

Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Qian Tao	Second Prize, Chongqing Science and Technology Award 2019

Fellowships

Member's Full Name	Details
Shuang Tong	Postdoctoral Fellowship of Research Committee Research Fellowship Scheme (RFS) 2019/20, The Chinese University of Hong Kong

Academic Editorship

Member's Full Name	Details
Qian Tao	Vice-President, The Epigenetics Society
	Editorial Board Member / Academic Editor, Clinical Epigenetics
	Editorial Board Member / Academic Editor, Epigenomes
	Editorial Board Member / Academic Editor, Cancer Communications
	Editorial Board Member / Academic Editor, Epigenetic Diagnosis & Therapy
	Editorial Board Member / Academic Editor, PLOS One
	Editorial Board Member / Academic Editor, Journal of Clinical Epigenetics
	Reviewer, 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)
	Panel member and reviewer, 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)
	Reviewer, Grants of Children's Cancer and Leukaemia Group (CCLG), UK
	Scientific Reviewer, Research Fund of the Food and Health Bureau, Hong Kong
	Reviewer, Guangdong Science and Technology Department (廣東省基礎與應用基礎研究項目評審專家)
	Reviewer, Multi-Year Research Grant (MYRG), University of Macau, Macau
	Advisor Committee, Basic Research in Shenzhen (深圳市基礎研究專家諮詢委員會)
	Science and Technology Advisor Committee for Shenzhen (深圳市科技專家委員會)
	Academic Advisor, State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Hospital, Guangdong, China
	Academic Advisor, Key Laboratory of Biotherapy of Zhejiang Province, Zhejiang University, China
	Academic Advisor, Key Laboratory of MOE, Cancer Research Institute, Central South University, Hunan, China
	Overseas Board Member, Oncology Section/ China Association of Pathophysiology
	Visiting Chair Professor, National Research Center, Centre for Urologic Oncology of China/Beijing, Peking University 1 st Hospital & Institute of Urology, Beijing, China
	Visiting Professor, State Key Laboratory of Oncology in South China, The Cancer Institute, Sun Yat-sen University (SYSU) and SYSU Affiliated Zhongshan Hospital, Guangdong, China
	Visiting Professor, Hunan Yale (XiangYa) School of Medicine, Central South University, Changsha, China

Reviewer of Journal / Conference

Member's Full Name	Details
Qian Tao	Reviewer, Nature Communications
	Reviewer, Blood, Cancer Research
	Reviewer, Lancet
	Reviewer, Cell Death and Differentiation
	Reviewer, Journal of Pathology
	Reviewer, Oncogene
	Reviewer, Nucleic Acids Research
	Reviewer, Epigenetics
	Reviewer, Clinical Epigenetics

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Qian Tao	Regulation of Tumor Cell Invasion/Metastasis and EMT/Stemness by a New Ras Antagonist which is Silenced by CpG Methylation in Esophageal Cancer	Research Grants Council – General Research Fund	01/01/2019	31/12/2020	929,280
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	National Natural Science Foundation of China	01/2016	12/2019	RMB 570,000
Qian Tao	Epigenetic Disruption of Wnt/β-catenin Signaling Pathway in the Development, Invasion and Metastasis of Breast Cancer	National Natural Sciences Foundation of China – International Cooperation and Exchange	01/2015	12/2019	RMB 2,850,000
Qian Tao	From Basic Science to Clinical Application-Molecular Study of Common Tumors Prevalent in South China	Chinese Ministry of Science and Technology – National Key Research and Development Program	07/2018	06/2020	1,173,250

Publications

A. Journal Papers

- Li L, Fan Y, Huang X, Luo J, Zhong L, Shu XS, Lu L, Xiang T, Chan ATC, Yeo W, Chen C, Chan WY, Hugarir RL, Tao Q. Tumor suppression of ras GTPase-activating protein R4SA5 through antagonizing ras signaling perturbation in carcinomas. *iScience*. 2019;21:1-18. doi:10.1016/j.isci.2019.10.007.
- Xiang T, Tang J, Li L, Peng W, Du Z, Wang X, Li Q, Xu H, Xiong L, Xu C, Le X, Wei X, Yu F, Li S, Xiao Q, Luo B, Xiang X, Huang A, Lin Y, Ren G, Tao Q. Tumor suppressive BTB/POZ zinc-finger protein ZBTB28 inhibits oncogenic BCL6/ZBTB27 signaling to maintain p53 transcription in multiple carcinogenesis. *Theranostics*. 2019;9(26):8182-8195. doi:10.7150/thno.34983.
- Wu Y, Qin J, Li F, Yang C, Li Z, Zhou Z, Zhang H, Li Y, Wang X, Liu R, Tao Q, Chen W, Chen C. USP3 promotes breast cancer cell proliferation by deubiquitinating KLF5. *Journal of Biological Chemistry*. 2019;294(47):17837-17847. doi:10.1074/jbc.RA119.009102.
- Mohamed G, Talima S, Li L, Wei W, Rudzki Z, Allam RM, Simmons W, Tao Q, Murray PG. Low expression and promoter hypermethylation of the tumour suppressor SLIT2, are associated with adverse patient outcomes in diffuse large B cell lymphoma. *Pathology & Oncology Research*. 2019;25(3):1223-1231. doi:10.1007/s12253-019-00600-9.
- 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-κB 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 Journal*. 2019;33(1):254-263. doi:10.1096/fj.201701453RR.

B. Book Chapter

- Li L, Tao Q. Chapter of Epigenetic biomarkers. *Cancer Epigenetics*. 2019. China: China Science Publishing.
- Tao Q, Liu W, Li L. Chapter of Cancer Epigenetics. *National postgraduate textbook 5th edition Oncology*. 2019. China: People's Medical Publishing House.

C. Patent

- Tao Q, Li L. Tumor Suppressor TET1 and Uses Thereof. United States of America, US20190167708.

ASIAN CANCERS

Biomarkers and
Targeted Therapeutics



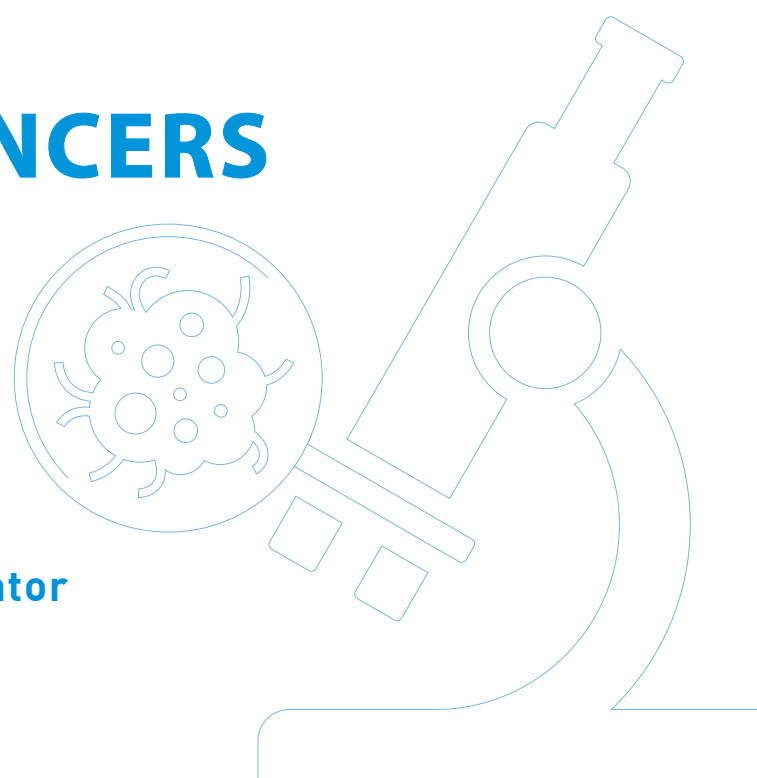
Principal Investigator

Professor Siu-tim Cheung



Team

Carol Lee | Shin Yee Hui | Philip Yeung | Jett Au |
Elaine Or | Elaine Siu | Linda Ng | Peter Li | Iris Xu

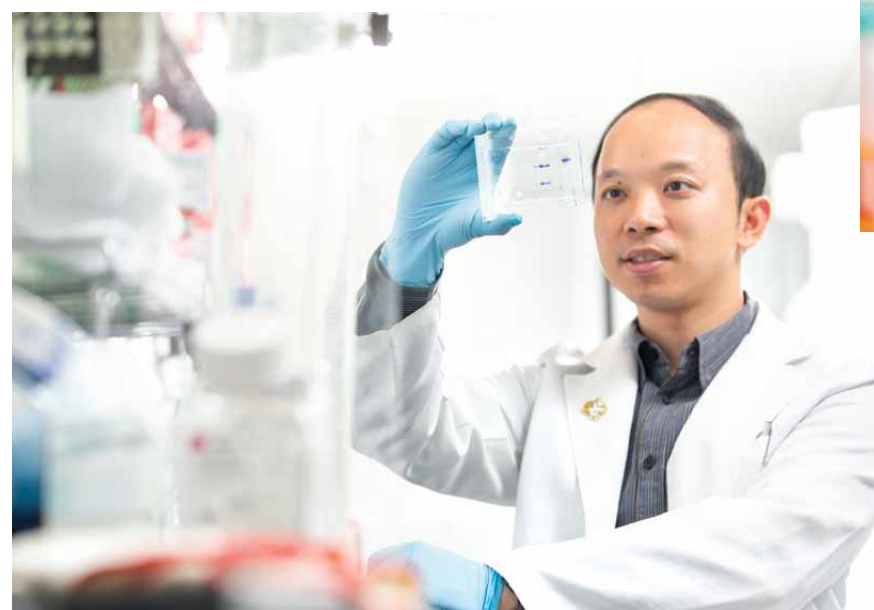


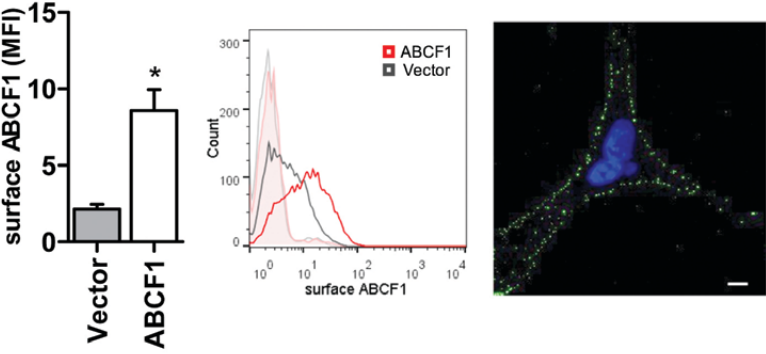
Research Progress Summary

ATP-binding cassette (ABC) transporters mediate multidrug resistance and cancer stem cell properties in various cancer models. Nonetheless, their biological significance in human cancers, especially in liver cancer, remains unclear. Recently, the team led by Professor Siu-tim Cheung has revealed the function of ABCF1 in liver cancer and its potential as a therapeutic target. ABCF1 was highly expressed in fetal mouse livers but not in normal adult livers. ABCF1 expression was upregulated in liver cancer. These results demonstrated that ABCF1

functions as a hepatic oncofetal protein. They further demonstrated an elevated ABCF1 expression in hepatocellular carcinoma (HCC) cells upon acquiring chemoresistance. Suppression of ABCF1 by siRNA sensitised both parental cells and chemoresistant cells to chemotherapeutic agents. Reversely, ABCF1 overexpression promoted chemoresistance and drug efflux. In addition, overexpression of ABCF1 enhanced migration, spheroid and colony formation and epithelial-mesenchymal transition (EMT) induction. RNA sequencing

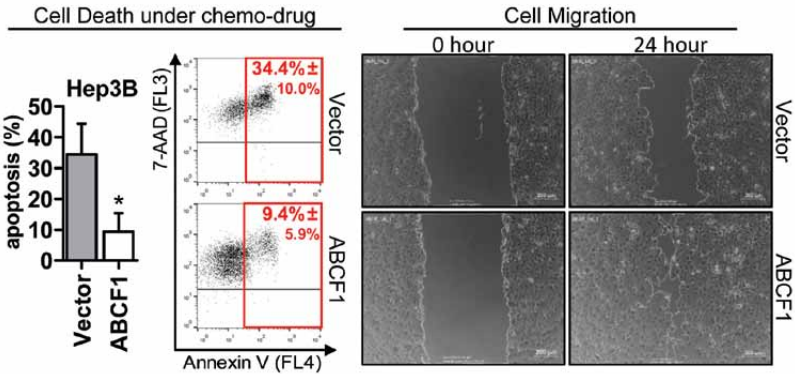
analysis revealed EMT inducers HIF1 α /IL8 and Sox4 as potential mediators for the oncogenic effect of ABCF1 in HCC progression. In summary, the team has demonstrated that ABCF1 as a novel therapeutic target for the treatment of liver cancer.





Expression of drug transporter ABCF1 on cancer cell surface.

Source: Fung SW, Cheung PF, Yip CW, Ng LW, Cheung TT, Chong CC, Lee C, Lai PB, Chan AW, Tsao GS, Wong CH, Chan SL, Lo KW, Cheung ST. The ATP-binding cassette transporter ABCF1 is a hepatic oncofetal protein that promotes chemoresistance, EMT and cancer stemness in hepatocellular carcinoma. *Cancer Letters*. 2019;457:98-109. doi:10.1016/j.canlet.2019.05.010.



ABCF1 augmented chemo-resistance and aggressive cancer feature.

Source: Fung SW, Cheung PF, Yip CW, Ng LW, Cheung TT, Chong CC, Lee C, Lai PB, Chan AW, Tsao GS, Wong CH, Chan SL, Lo KW, Cheung ST. The ATP-binding cassette transporter ABCF1 is a hepatic oncofetal protein that promotes chemoresistance, EMT and cancer stemness in hepatocellular carcinoma. *Cancer Letters*. 2019;457:98-109. doi:10.1016/j.canlet.2019.05.010.

Research and Scholarship

Academic Editorship

Member's Full Name	Details
Siu-tim Cheung	Molecular Carcinogenesis, Associate Editor

Reviewer of Journal / Conference

Member's Full Name	Details
Siu-tim Cheung	Reviewer, Hepatology
	Reviewer, Cancers
	Reviewer, BMC Cancer

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 Research Fellowship Scheme	01/04/2018	30/09/2020	981,720
Siu-tim Cheung	Inflammatory Factor Interleukin-8 Impairs Natural Killer Cell Function in Liver Cancer: Translational Studies to Develop Therapeutic Approaches	The Terry Fox Foundation	01/07/2017	30/06/2020	1,100,000
Siu-tim Cheung	Molecular Targets to Enhance Natural Killer Cell Cytotoxic Activity Against Hepatocellular Carcinoma	CUHK Research Committee – Direct Grant	01/06/2019	01/06/2020	105,000

Publications

A. Journal Papers

- Fung SW, Cheung PF, Yip CW, Ng LW, Cheung TT, Chong CC, Lee C, Lai PB, Chan AW, Tsao GS, Wong CH, Chan SL, Lo KW, Cheung ST. The ATP-binding cassette transporter ABCF1 is a hepatic oncofetal protein that promotes chemoresistance, EMT and cancer stemness in hepatocellular carcinoma. *Cancer Letters*. 2019;457:98-109. doi:10.1016/j.canlet.2019.05.010.
- Lee C, Cheung ST. STAT3: An emerging therapeutic target for hepatocellular carcinoma. *Cancers (Basel)*. 2019;11(11):1646. doi:10.3390/cancers11111646 (Review).

CARDIOVASCULAR MEDICINE

Vascular Medicine –
Basic Research



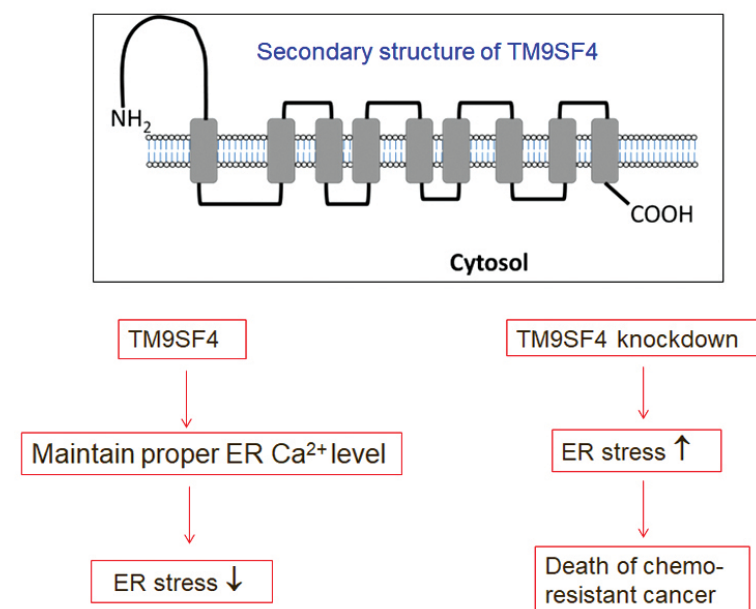
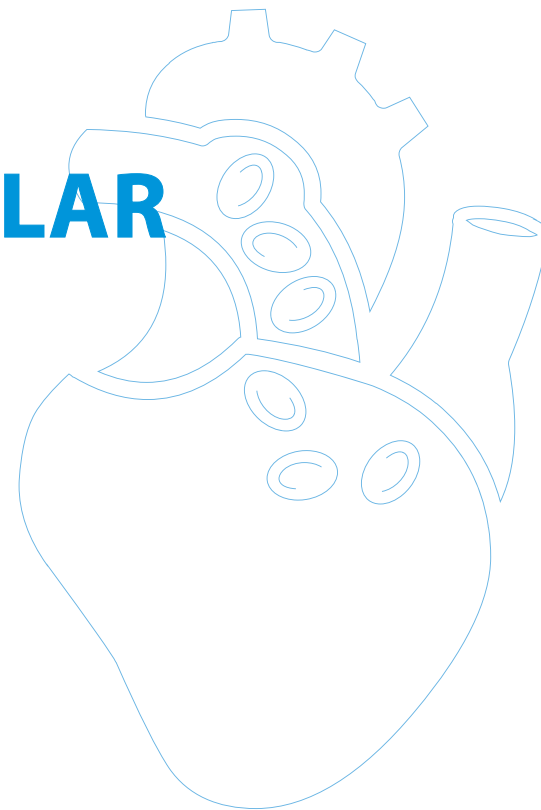
Principal Investigator

Professor Xiaoqiang Yao



Team

Zhaoyue Meng | Fan Ying | Duan Zhuo | Hongyan Yu | Mingxu Xie |
Libo Yu | Yunting Zhang | Jingxuan Li | Xiao Li | Ishan Lakhni |
Chun-yin Lo | Chiu-lam Tsang | Him Cheung | Wai-ho Chan



Schematic Figure showing the secondary structure and function of a novel protein TM9SF4. Knockdown of TM9SF4 kills the chemoresistant breast cancer cells.

Source: Zhu Y, Xie M, Meng Z, Leung LK, Chan FL, Hu X, Chi K, Liu CL, Yao X. Knockdown of TM9SF4 boosts ER stress to trigger cell death of chemoresistant breast cancer cells. *Oncogene*. 2019;38(29):5778-5791. doi:10.1038/s41388-019-0846-y.

Research Progress Summary

Drug resistance is one of the major obstacles to breast cancer therapy. However, the mechanisms of how cancer cells develop chemoresistance are still not fully understood. In the present study, the team led by Professor Xiaoqiang Yao found a critical role of

novel protein TM9SF4 in adriamycin (ADM)-resistant breast cancer cells MCF-7. Knockdown of this protein effectively killed the chemoresistant breast cancer cells. The research highlights a possible strategy of targeting TM9SF4 to overcome breast cancer chemoresistance.



■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Mingxu Xie	1 st Prize of Young Investigator Award (Oral Presentation), 23 rd Scientific Meeting of Hong Kong Institute of Cardiovascular Sciences and Medicine, Hong Kong

Academic Editorship

Member's Full Name	Details
Xiaoqiang Yao	Editor, Scientific Reports
	Editor, Frontiers in Pharmacology
	Editor, World Journal of Pharmacology
	Editor, World Journal of Hypertension
	Editor, Archives of Stem Cell Research
	Editor, Journal of Cancer Sciences

Reviewer of Journal / Conference

Member's Full Name	Details
Xiaoqiang Yao	Reviewer, Circulation Research
	Reviewer, Cell Report
	Reviewer, Cardiovascular Research
	Reviewer, Journal of Biological Chemistry
	Reviewer, Journal of Physiology
	Reviewer, American Journal of Physiology
	Reviewer, British Journal of Pharmacology
	Reviewer, Chemistry & Biology
	Reviewer, Journal of Cellular Physiology
	Reviewer, European Journal of Physiology
	Reviewer, Cell Proliferation
	Reviewer, Scientific Reports
	Symposium Organizer and Section Chair, 9 th FAOPS Congress (Federation of Asian and Oceanian Physiological Society), Kobe, Japan
	Organising Committee, 7 th International Ion Channel Conference, Hangzhou, China
	Organising Committee, 5 th China Wine City International Cardiovascular Congress, Luzhou, China

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Xiaoqiang Yao	Active Immunization with TRPM2 Peptide Antigens as a Potential Treatment Strategy for Atherosclerotic Progression in a Mouse Model	Innovation and Technology Commission – Innovation and Technology Fund	01/01/2019	31/07/2020	1,400,000
Xiaoqiang Yao	Targeting TRPM2 as a Potential Therapeutic Strategy for Spontaneous Atherosclerosis	Food and Health Bureau – Health and Medical Research Fund	01/09/2019	31/08/2022	1,181,050
Xiaoqiang Yao	TM9SF4 as a Novel Potassium Channel and its Role in Autophagy	Research Grants Council – General Research Fund	01/01/2017	31/12/2019	1,000,387
Xiaoqiang Yao	Centre for Organelle Biogenesis and Function	Research Grants Council – Area of Excellence	01/01/2014	31/12/2021	47,250,000
Xiaoqiang Yao	Plant Bioreactor for Pharmaceutical Proteins	Research Grants Council – Research Impact Fund	01/06/2019	31/05/2024	5,000,000

■ Publications

A. Journal Papers

1. Zhu Y, Xie M, Meng Z, Leung LK, Chan FL, Hu X, Chi K, Liu CL, Yao X. Knockdown of TM9SF4 boosts ER stress to trigger cell death of chemoresistant breast cancer cells. *Oncogene*. 2019;38(29):5778-5791. doi:10.1038/s41388-019-0846-y.
2. 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.

CARDIOVASCULAR MEDICINE

Heart Diseases –
Cardiac Imaging and Intervention



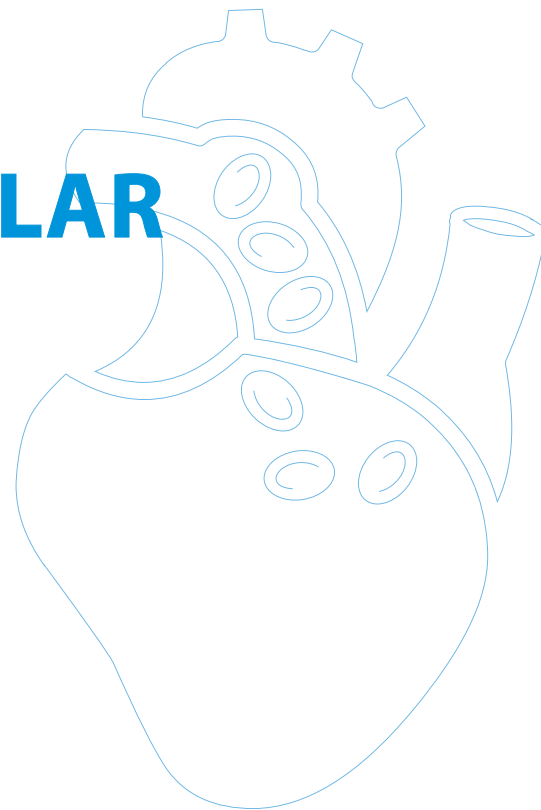
Principal Investigator

Professor Alex Lee



Team

Randolph Wong | Yiting Fan | Kevin Kam | Kent So | Ada Yu |
Josie Chow | Xueting Wang | Kandy Li | Tsz-ngai Chan



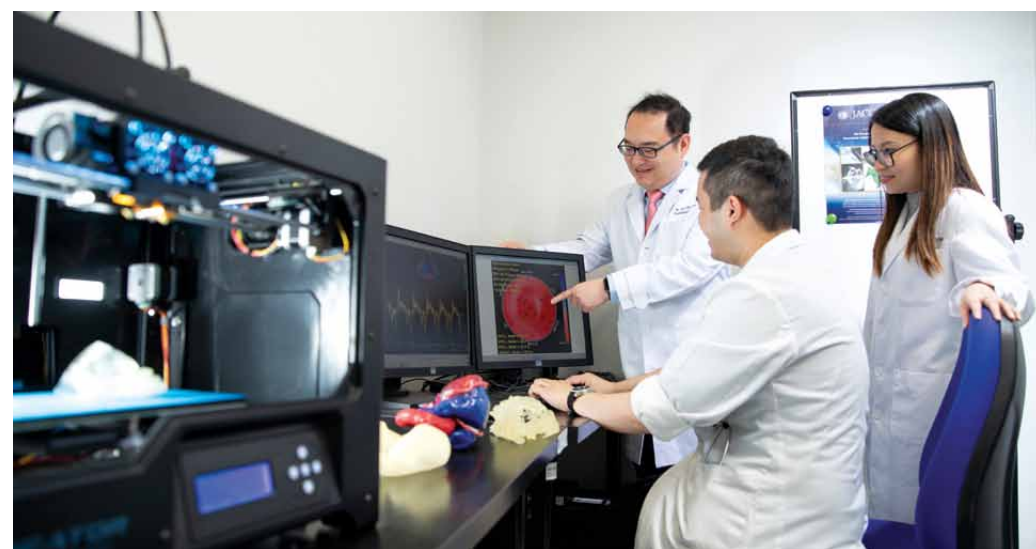
imaging from over 6 countries/regions. The first CU Echo PRO course on 3D echocardiography was held in November, attracting 31 attendees.

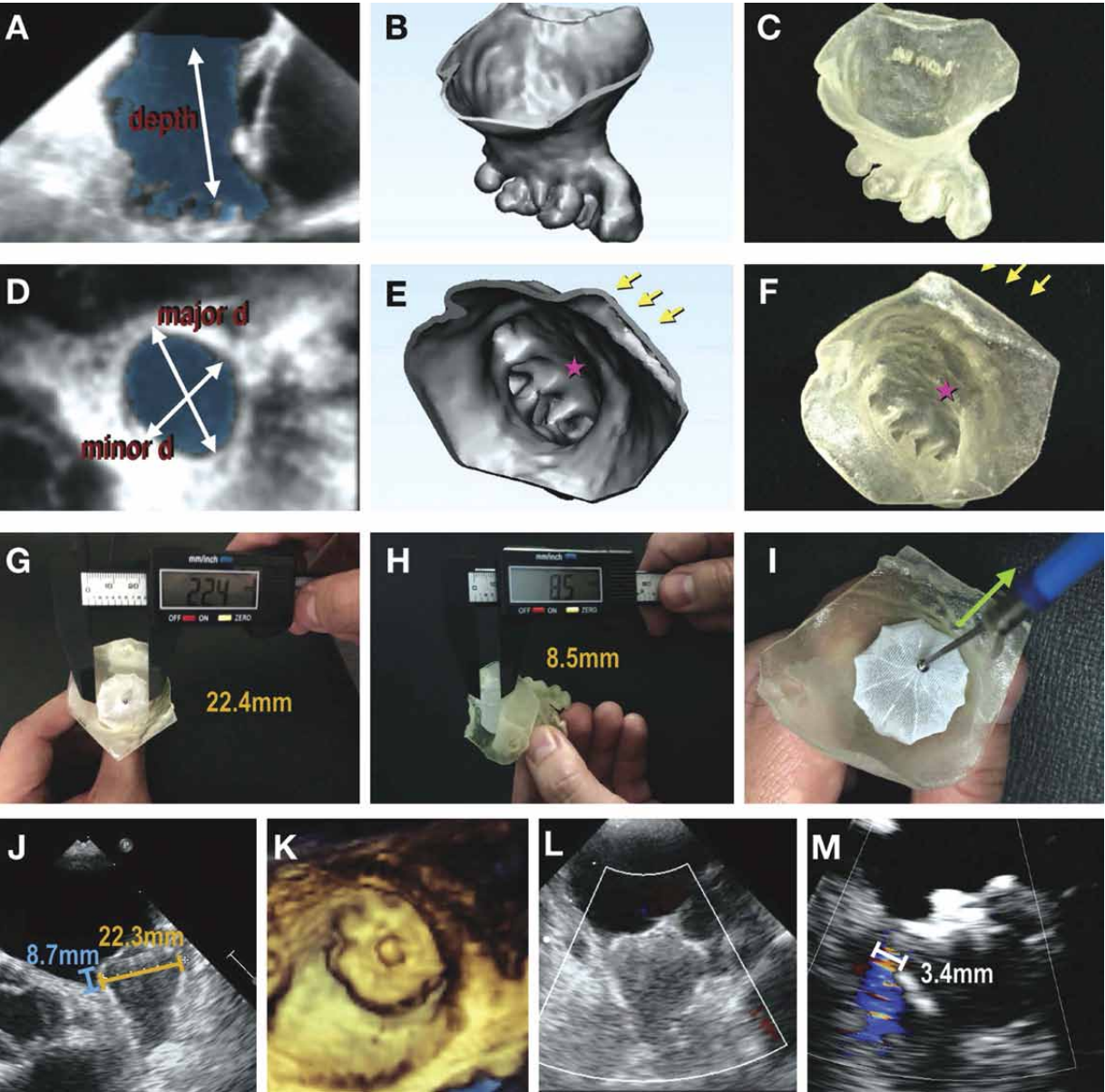
The team has established a new academic partnership with the University of Padua in research on valvular heart disease, specifically in defining the mechanism of arrhythmias associated with mitral valve prolapse and mitral annular disjunction. A memorandum of understanding has been signed between the department of medicine/cardiology between the two universities. Their collaboration with the MIDA group on the outcome study of patients with mitral regurgitation has continued. They have established a new collaboration with the University of Alberta in Fabry disease high risk screening among patients with hypertrophic cardiomyopathy. They are leading the MIDA group and the University of Alberta in preparing 2 research manuscripts.

Research Progress Summary

In 2019, the Health and Medical Research Fund (HMRF) supported the multicentre clinical trial on 3D printing for structural heart intervention is underway with good recruitment progress. This project has generated publications in the *Journal of American Society of Echocardiography* and *JACC Cardiovascular Intervention*. The team led by Professor Alex Lee has worked on procedural simulation

with patient-specific 3D-printed aortic root models for TAVI planning has won the high-score abstract in PCR Tokyo Valves. They have successfully organised the “ECHO guidance for screening and interventions in Structural Heart Diseases” intensive training workshops in 2019, with excellent feedback from the 33 attendees who are leading experts in interventional cardiology and cardiac





Echocardiography-based 3D printing of patient-specific models. (A–F) From 3D TEE image to 3D physical model. (A, D) Segmentation of LAA (shaded area) on 3D TEE data. The major and minor ostial diameters and depth of the LAA are measured. (B, E) Digital object created. (C, F) Three-dimensional-printed physical model made of tissue-mimicking material. (A–C) Long-axis views and (D–F) short-axis views demonstrating oval shape of the ostium. Arrows denote pulmonary vein ridge; stars denote appendicular trabeculations. (G–I) Device sizing in 3D model. (G) Device compression and (H) protrusion in 3D model measured using a digital caliper. Note the device-related deformation of the 3D-printed models, with the oval ostium becoming rounded after the deployment of a round WATCHMAN device. (I) Tug test for stability. (J) Device compression and protrusion measured in clinical procedure. (K) Three-dimensional TEE en face view of final device position. (L) Colour Doppler assessment showing no peridevice leak. (M) In another case, colour Doppler assessment revealed residual leak with a jet width of 3.4 mm.

Source: Fan YT, Yang F, Cheung GSH, Chan AKY, Wang DD, Lam YY, Chow MCK, Leong MCW, Kam KKH, So KCY, Tse G, Qiao ZQ, He B, Kwok KW, Lee APW. Device sizing guided by echocardiography-based three-dimensional printing is associated with superior outcome after percutaneous left atrial appendage occlusion. *Journal of The American Society of Echocardiography*. 2019;32(6):708-719.e1. doi:10.1016/j.echo.2019.02.003.

■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Alex Lee	High Scoring Abstract titled "Avoiding coronary occlusion in TAVI: the role of procedural simulation with patient-specific 3D-printed aortic root models", PCR Tokyo Valves, Tokyo, Japan

Fellowships

Member's Full Name	Details
Yiting Fan	Faculty Postdoctoral Fellowship Scheme, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong
	Research Fellowship in Mayo Clinic, Rochester, USA

Academic Editorship

Member's Full Name	Details
Alex Lee	Editor, Gavin Journal of Cardiology and Cardiovascular Diseases
	Editor, Journal of Clinical and Interventional Cardiology

Reviewer of Journal / Conference

Member's Full Name	Details
Alex Lee	Reviewer, Circulation Cardiovascular Imaging
	Reviewer, Heart
	Reviewer, PLOS One
	Reviewer, Current Cardiology Reviews
	Reviewer, Echocardiography
	Reviewer, International Journal of Imaging Systems and Technology
	Reviewer, Cardiovascular Ultrasound
	Reviewer, American Journal of Cardiology
	Reviewer, The Journal of Thoracic Disease
	Reviewer of Conference, Abstract Grader for European Society of Cardiology Annual Scientific Congress

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Alex Lee	A Randomized Parallel-Group, Placebo-Controlled, Double-Blind, Event-Driven, Multi-Center Pivotal Phase III Clinical Outcome Trial of Efficacy and Safety of the Oral sGC Stimulator Vericiguat in Subjects with Heart Failure with Reduced Ejection Fraction	Merck Sharp & Dohme Corp.	05/01/2017	05/05/2020	825,987
Alex Lee	Resolution of Left Atrial Thrombus with Dabigatran in Patients with Nonvalvular Atrial Fibrillation: A Pilot Transesophageal Echocardiographic Study	Boehringer Ingelheim (Hong Kong) Ltd.	01/04/2017	30/12/2019	282,353
Alex Lee	Myocardial Mechanics in Heart Failure with Reduced Ejection Fraction Assessed by Novel Speckle Tracking Echocardiography	Novartis Pharmaceuticals (HK) Ltd.	01/07/2017	30/06/2019	413,494
Alex Lee	Prevalence of Fabry Disease Among Chinese Patients With Left Ventricular Hypertrophy in Hong Kong	Sanofi-Aventis Hong Kong Ltd.	01/09/2017	31/10/2020	743,400
Alex Lee	Non-interventional Study on Edoxaban Treatment in Routine Clinical Practice for Patients with Non Valvular Atrial Fibrillation (ETNA-AF-Hong Kong)	Daiichi Sankyo Hong Kong Ltd.	29/09/2017	30/09/2021	176,772
Alex Lee	3D Printing Technology for Planning Left Atrial Appendage Occlusion: A Randomised Trial	Food and Health Bureau – Health and Medical Research Fund	01/05/2018	30/04/2021	1,191,977
Alex Lee	3D Printed Simulation Platforms for Mitral Valve Repair Procedures	CUHK Research Committee – Direct Grant	30/06/2018	29/06/2019	71,000
Alex Lee	Echo Guidance for Screening and Interventions in Structural Heart Diseases	Abbott Medical (Hong Kong) Ltd.	15/09/2018	30/04/2019	250,000

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Alex Lee	A Multinational, Multicenter Study to Assess the Effects of Oral Sildenafil on Mortality in Adults with Pulmonary Arterial Hypertension (PAH)	Pfizer Inc.	25/10/2018	31/08/2023	2,399,028
Alex Lee	Heart Failure Study	Novartis Pharmaceuticals (HK) Ltd.	01/02/2019	31/07/2020	433,626
Alex Lee	Automatic Retinal Image Analysis (ARIA) to Predict Coronary Artery Disease in HIV-infected Individuals	Centre for Health Protection AIDS Trust Fund	04/2019	03/2021	560,462

Publications

A. Journal Papers

1. Woo J, Yang X, Tin Lui L, Li Q, Fai Cheng K, Fan Y, Yau F, Lee APW, Lee JSW and Fung E. Utility of the FRAIL questionnaire in detecting heart failure with preserved ejection fraction. *Journal of Nutrition Health & Aging*. 2019;23(4):373-377. doi:10.1007/s12603-019-1158-1.
2. So CY, Fan Y, Wu EB and Lee AP. 3D printing in transcatheter aortic valve implantation: anticipating coronary obstruction in high risk aortic root anatomy. *EuroIntervention*. 2019. doi:10.4244/EIJ-D-19-00609 [Epub ahead of print].



DIABETES AND OBESITY



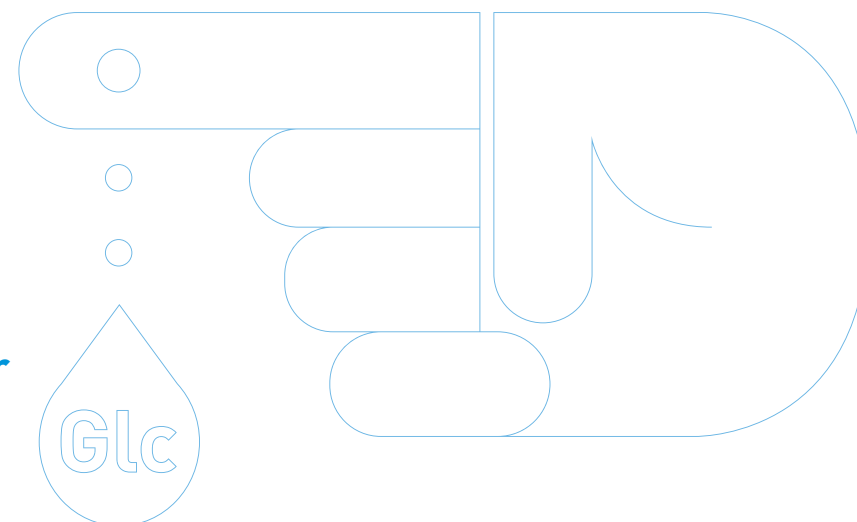
Principal Investigator

Professor Juliana Chan



Team

Ronald Ma | Alice Kong | Andrea Luk | Elaine Chow | Wing Yee So | Risa Ozaki |
 Kitty Cheung | Cadmon Lim | Baoqi Fan | Guozhi Jiang | Dandan Mao |
 Claudia Tam | Raymond Wan | Hongjiang Wu | Aimin Yang | Arthur Chung |
 Eric Lau | Heung Man Lee | Calvin Ke | Huanyi Cao | Feifei Cheng |
 Lorena Cheung | Chenzhao Ding | James Ling | Lee Ling Lim | Clara Lo |
 Noel Ng | Sylvia Qiu | Kwun Kiu Wong | Kit Ying Tsoi | Xing Ming |
 Wei Wei Zeng | Ming C Leung | Hou Yong



Research Progress Summary

In 2019, the research team led by Professor Juliana Chan continues with its overarching strategy of using big data, experimental studies and interventional programmes to unravel the causes, trajectories and consequences of diabetes and its complications, focusing on genotype-phenotype-treatment-outcome interactions. Supported by major grant bodies including the Research Grants Council (RGC), the Innovation and Technology Commission (ITC), the Health and Medical Research Fund (HMRF), National Science Foundation of China – National Health and Medical Research Council of Australia Joint Research Scheme (NSFC-NHMRC), the National Institutes of Health (NIH), industry, donations, proceedings from conferences and professional courses, they have nurtured a team of young physicians, healthcare professionals, scientists, technologists and analysts to discover and apply new knowledge in the field of diabetes, endocrinology and clinical pharmacology.

Genomic and Genetics in Diabetes

The team has successfully delivered the 4-year Theme-based Research Scheme (TRS) where they established the 12-Centre Hong Kong Diabetes Biobank (HKDB) to discover the genetic regulation of diabetic complications. Together with the Hong Kong Diabetes Register (HKDR), the team has now created a unique resource of biosamples of over 30,000 patients with diabetes followed up since 1995. With the availability of genome-wide microarray data in over 20,000 patients, they have established strong partnerships with leading groups in USA, UK and Australia to contribute to the discovery and validation of biomarkers for both type 1 (T1D) and type 2 diabetes (T2D). In a proof-of-concept randomised clinical trial (RCT), they have used genetic information to enhance usual care in patients with diabetes. Through this RGC-TRS, the team becomes one of the key partners in the International Type 2 Diabetes



Genetics Consortium and Accelerating Medicines Partnership Type 2 Diabetes Knowledge Portal, funded by the Foundation of NIH (FNIH) with industrial support. Through this consortium, they have contributed to the global knowledge of genetic association of diabetes and its related traits and complications. Using zebrafish in an experimental model, they have successfully confirmed the deleterious effects of a loci first discovered in the patients with young-onset diabetes (YOD) on pancreatic islet development. Meanwhile, they continue to work with local and overseas biologists and data scientists to use methylome, transcriptome, proteome and phenome data to perform complex analysis and develop risk scores to predict and classify diabetes as well as discover new biology.

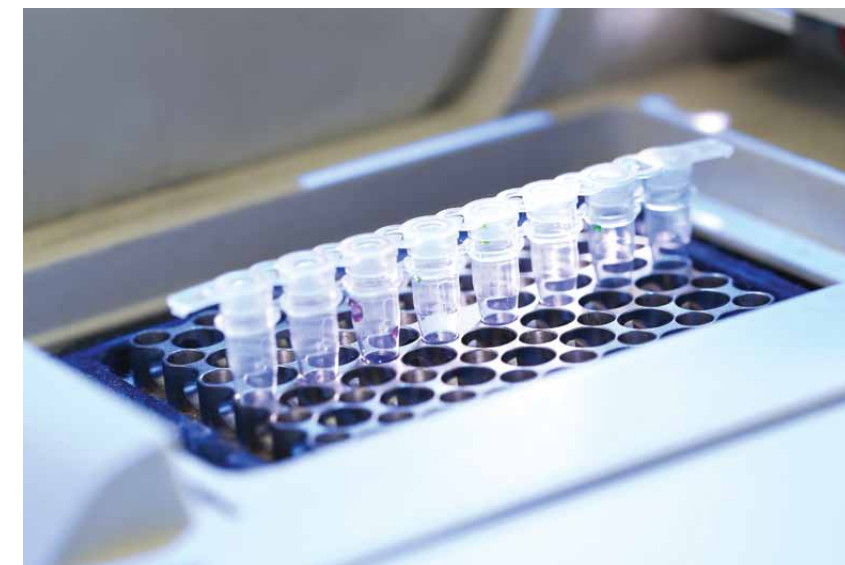
Supported by a major grant awarded by a top pharmaceutical company, the team shall apply whole genome sequencing to a subset of patients with diabetic kidney disease. In this project, they will leverage upon the capacity of academia and industry to use state-of-the-art analytical tools and experimental platforms to discover druggable pathways and select safe and feasible drug targets for developing novel compounds in diabetic kidney disease. In 2019, coordinated

by Professor Ronald Ma, they were awarded a RGC-Research Impact Fund to take the TRS forward which includes the analysis of metabolites in these biosamples, experimental studies on candidate pathways and a multicenter RCT to use available genetic information to empower both patients and care teams to improve outcomes.

On a translational front, Professor Juliana Chan has been commissioned by the Food and Health Bureau (FHB) to lead a project to discover novel biogenetic markers and sequences in familial YOD as well as conduct a 3-year RCT to explore the impacts of using autoimmune, common and rare genetic variants along with e-care to intensify and individualise management in YOD (PRISM: Precision Medicine to Redefine Insulin Secretion and Monogenic Diabetes in Chinese Patients with Young-onset Diabetes).

Disease Mechanisms

In collaboration with basic scientists from the School of Biomedical Science, Professor Alice Kong is supervising several postgraduate students who have discovered common pathways implicated in beta-cell biology and fatty liver. Supported by the ITC, she and her



team have discovered novel micro-RNAs associated with liver cancer in diabetes and are now working with cancer biologists to elucidate their functional significance. Through her coordinating efforts in bariatric surgery project, the team has successfully used transcriptome data from the surgical samples of adipose tissues and discovered an epigenetic network implicated in obesity associated with T2D. Meanwhile, supported by microbiologists and obstetricians, Professor Juliana Chan and her postdoctoral fellow have discovered novel mechanisms of the diabetes-cancer link and the potential anti-cancer and anti-diabetic effects of Traditional Chinese Medicine (TCM).

Health Informatics and Analytics

In addition to being the medical director of the Phase 1 Clinical Trial Centre (P1CTC), Professor Andrea Luk, supported by RGC, is developing a panel of genetic variants of MODY (maturity onset diabetes of the young) for disease classification. In another RGC grant, she has reported the high frequency of autoantibodies and its association with responsiveness to insulin treatment in YOD. In the PRISM project, she will examine the role of autoimmunity in adult-onset T2D by measuring autoantibodies in all 6,000 patients with T2D in the HKDR. Meanwhile, using the Hong Kong

Diabetes Surveillance Database (HKDSD) consisting of data from 0.8 million people with diabetes registered in the Hospital Authority Clinical Management System, she has synthesised new evidence and reported the 50-70% decline in death rates amongst people with diabetes, albeit not in young people who had 8-fold increased risk of death compared to their peers without diabetes. In these young patients, she has reported the huge burden of hospitalisation in YOD especially due to mental illness. Furthermore, she has reported the overall declining incidence of diabetes but a rising trend in the young population. These epidemiological data reiterates the strategic nature of the PRISM project which aims to redefine diabetes for precision care in YOD. Supported by a HMRF grant, she is developing a Chinese Diabetes Outcome Model to simulate multiple events in people with T2D over a 15-year horizon for quantifying the impact of progression and intervention of T2D in order to inform policies and practices.

New Technology and Therapeutics

Dr. Elaine Chow, the clinical pharmacologist in Professor Juliana Chan's team with interest in endocrinology, has successfully developed the continuous glucose/insulin infusion techniques at the P1CTC to standardise hyper, normo and hypoglycemic conditions for evaluation of





beta-cell function and performance of various technologies. Using this technique, she has successfully confirmed the accuracy of an innovative 28-day continuous glucose monitoring system (CGMS) developed by a local biotech company based on a unique technology licensed in from Europe. Supported by the ITC, she will be leading a multicenter RCT including two institutions in Greater Bay Area to evaluate this CGMS for registration in China to be followed by large scale clinical trials. Currently, she is working with biotech companies in Hong Kong and China to explore the pharmacokinetic and pharmacodynamic effects of new compounds and formulations for blood glucose lowering. Based on the positive results of their mechanistic studies of using TCM to improve beta-cell function and fatty liver and supported by a CUHK strategic grant, Professor Juliana Chan is working with the CUHK School of Chinese Medicine and P1CTC to conduct dose-finding experiments of a novel TCM formulation for prevention of diabetes in high risk individuals.

As a team of physician scientists, the various PIs are running multiple phase 2-4 clinical trials of innovative compounds at the National Medical Products Administration (NMPA) accredited Clinical Trial Unit, supported by multinational companies. In anticipation of the growing burden of YOD, the team has sent fellows to overseas

institutions to learn new technology in glucose sensing and insulin delivery system and set up strategic partnerships with top universities in Australia and China for collaborative projects. Working with a leading company from Sweden which focuses on using high quality food and beverages to improve nutrition, they are embarking upon mechanistic studies and RCTs to explore their blood-glucose lowering effects in people at high risk for developing diabetes and adolescents, focusing on early detection and prevention of diabetes.

Knowledge transfer

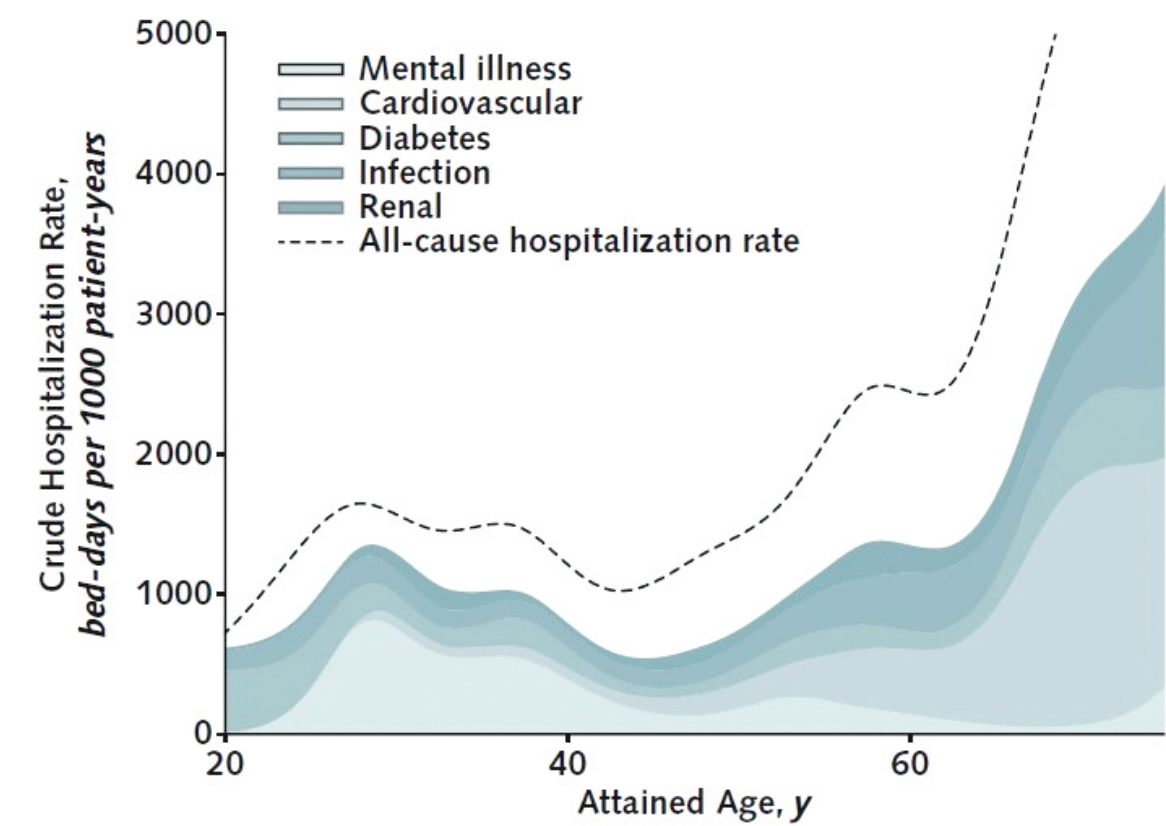
As an International Diabetes Federation (IDF) Centre of Education and IDF Center of Excellence in Diabetes Care, the team continues to share its translational research and practices with local and overseas visitors and institutions. In 2019, they have graduated postgraduate students and recruited new postdoctoral fellows for knowledge transfer and capacity building. Apart from exposing them to integrated research, education and care programme, through their supervisors, they have also received training in top institutions in UK, USA and Australia to learn new laboratory and analytical skills in pursuit of using precision medicine to predict, prevent and personalise diabetes care.

Several of the PIs are members of steering committees of international projects in epidemiology and clinical trials in the field of diabetes and related fields. Apart from serving on FHB and HA committees on diabetes, NCD and drug utilisation, most of the PIs are members of grant review committees of ITC, RGC and HMRF. In a knowledge transfer project, they have established the Asia Diabetes Foundation (ADF), governed by the CUHK Foundation, to develop and use the web-based Joint Asia Diabetes Evaluation (JADE) platform to establish a regional register for translation and discovery of knowledge. Working in concert with ADF and supported by industrial grants, they have used real-world evidence to evaluate the usage and impacts of common drugs such as lipid regulating drugs, insulin and metformin in Asian patients with T2D, while implementing pragmatic large scale intervention programmes of using data-driven integrated care to improve outcomes in low and middle income countries.

Awards and recognitions

In recognition of the impacts of 3 decades of research, the data-driven integrated care model was selected as one of the 13 impact stories by the CUHK for submission to RGC Research Assessment Exercise in 2020. In June 2019 in San Francisco, USA, Professor Juliana Chan received the Harold Rifkin Award for International Service for a Cause in Diabetes bestowed by the American Diabetes Association. In December 2019, at the World Diabetes Congress held in Busan, Korea, she delivered the IDF Award Lecture in Epidemiology and Public Health. Other major awards include the Harry Keen Memorial Award received by Professor Andrea Luk, bestowed by the International Diabetes Epidemiology Group (IDEG) for young research leaders in the field of diabetes epidemiology and Croucher Senior Research Fellowship received by Professor Ronald Ma in recognition of his research excellence in the field of genomics and genetics of diabetes.





Crude hospitalisation rates (bed-days per 1000patient-years) for selected principal diagnoses, by attained age, among persons with young-onset type 2 diabetes in the registry cohort.

Source: Ke C, Lau E, Shah BR, Stukel TA, Ma RC, So WY, Kong AP, Chow E, Clarke P, Goggins W, Chan JCN, Luk A. Excess Burden of Mental Illness and Hospitalization in Young-Onset Type 2 Diabetes. *Annals of Internal Medicine*. 2019;170(3):145. doi:10.7326/M18-1900.

Research and Scholarship

Research Awards and Recognitions

Member’s Full Name	Details
Juliana Chan	Harold Rifkin Award for Distinguished International Service in the Cause of Diabetes, American Diabetes Association (ADA), San Francisco, USA
	International Diabetes Federation Award Lecture (Epidemiology and Public Health) entitled: Diabetes – where public and personal health meet, World Diabetes Congress, Busan, Korea
Ronald Ma	2019 Croucher Senior Research Fellowship, Croucher Foundation, Hong Kong
Andrea Luk	2019 Harry Keen Award Lecture, International Diabetes Epidemiology Group
Elaine Chow	Hong Kong College of Physicians Young Investigator’s Research Grant
Feifei Cheng	Best Poster Presentation, the 16 th Symposium of the International Diabetes Epidemiology Group (IDEG), Seoul, Korea.
	European Association for Study of Diabetes (EASD) Travel Grant
Lee-ling Lim	Early Career Travel Award, ENDO 2019, the USA Endocrine Society, New Orleans, Louisiana, USA
	Outstanding Abstract Award, the USA Endocrine Society at the ENDO 2019, New Orleans, Louisiana, USA
	Travel Grant, the 55 th Annual Meeting of EASD, the European Association for the Study of Diabetes (EASD), Barcelona, Spain
	IDF Grant Programme, IDF World Diabetes Congress, Busan, Korea
Xing Ming	Travel Grant, European Association for the Study of Diabetes (EASD), the 55 th Annual Meeting of EASD, Barcelona, Spain

Academic Editorship and Reviews

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

Journal / Conference Reviews

Member’s Full Name	Details
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	Identifying the Epigenomic Fingerprint of Coronary Heart Disease in Chinese Adults with Type 2 Diabetes	National Science Foundation of China – National Health and Medical Research Council of Australia Joint Research Scheme	2016	2020	RMB 3,500,000
Juliana Chan Ronald Ma	Using Whole Genome Sequencing, Computational Biology and Functional Analysis to Discover Biological Pathways Implicated in Diabetic Kidney Disease	AstraZeneca	2019	2021	USD 1,150,000
Juliana Chan Andrea Luk	Precision Medicine to Redefine Insulin Secretion and Monogenic Diabetes (PRISM) in Chinese Patients with Young-onset Diabetes	Food and Health Bureau – Health and Medical Research Fund Commissioned	2019	2024	8,457,718
Juliana Chan Elaine Chow	Real-World Evidence on the Effects of Metformin on Clinical Outcomes in Patients with Type 2 Diabetes at Different Stages of Chronic Kidney Disease (CKD)	Merck (Germany) via Asia Diabetes Foundation	2019	2021	1,265,000
Juliana Chan	Transforming Diabetes Care: From Research to Practice to Community	CUHK Research Committee – One-off Project Impact Enhancement Fund	2019	2020	500,000
Juliana Chan	Using Modern and Traditional Technologies to Redefine and Prevent Young-onset Diabetes	CUHK Funding for Research Sustainability of Major RGC Funding Schemes	2019	2022	500,000
Juliana Chan	Self-managing Healthy Eating & Active Lifestyle For impeding 3-Highs (high blood glucose, high blood pressure and high cholesterol) Mobile Application (SHEALF3 APP) (renamed as Citybite APP)	Innovation and Technology Commission – Innovation and Technology Fund for Better Living via Asia Diabetes Foundation	2018	2022	4,247,006
Ronald Ma Juliana Chan	Translating Multi-omic Discoveries to Transform Diabetes Care and Reduce Diabetic Complications	Research Grants Council Impact Research Fund with CUHK Matching Fund	2019	2023	8,400,000

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Ronald Ma	Unraveling the Link between Maternal Hyperglycaemia and Childhood Obesity: Genome-wide Methylation Analysis in a Prospective Cohort of Untreated Gestational Diabetes	Research Grants Council – General Research Fund	2019	2021	970,517
Ronald Ma	Precision Medicine in Diabetes	CUHK – Shanghai Jiao Tong University Joint Research Fund	2018	2020	2,000,000
Ronald Ma	Validation of Novel Protein Markers for the Prediction of Diabetic Kidney Disease	CUHK – Technology and Business Development Fund	2018	2019	100,000
Claudia Tam	Early Growth Genetics and Cardiometabolic Risk in Chinese Adolescents	Food and Health Bureau – Health and Medical Research Fund	2018	2020	1,200,000
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	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
Andrea Luk	Search for Maturity-onset Diabetes of the Young in Chinese with Young-onset Diabetes	Research Grants Council – General Research Fund	2019	2020	941,431
Elaine Chow	Effectiveness and Safety Study of the Percutaneous Optical Fibre Glucose Sensor (FiberSense) for Home Use in Diabetic and Prediabetic Individuals	Innovation and Technology Commission – University Industrial Collaboration Programme	2017	2020	2,422,061
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

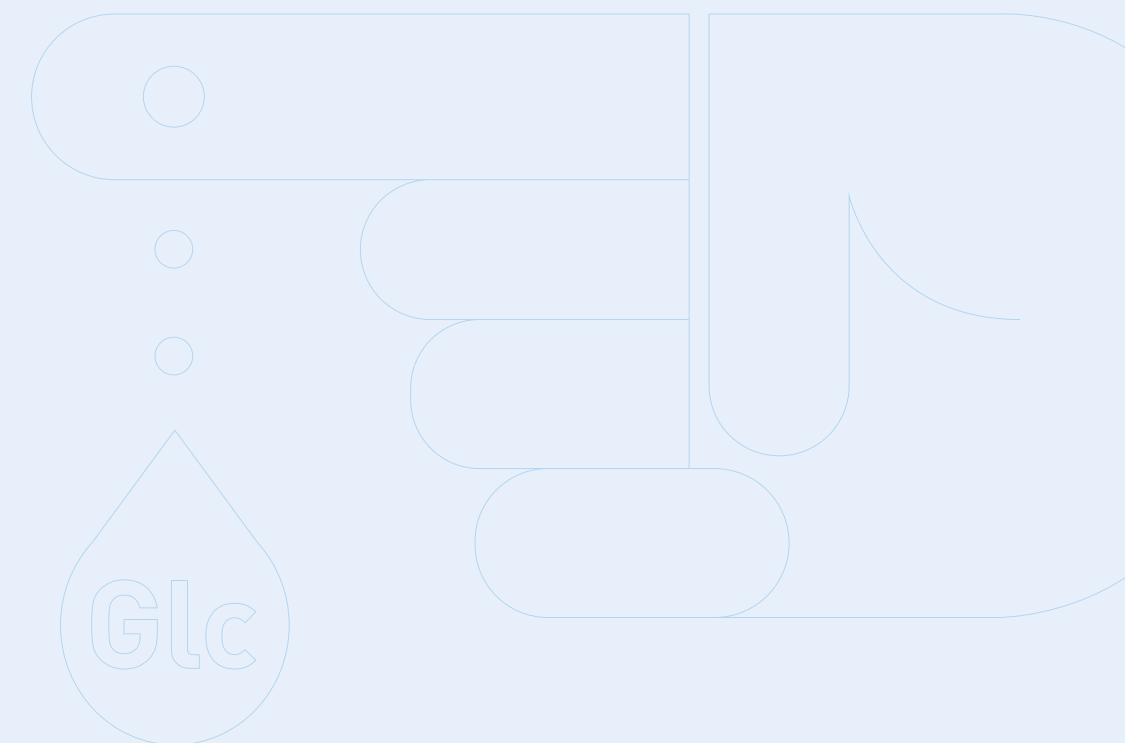
Publications

A. Journal Papers

1. Ng NYH, Jiang G, Cheung LP, Zhang Y, Tam CHT, Luk AOY, Quan J, Lau ESH, Yau TTL, Chan MHM, Ho CS, Lim CKP, Ozaki R, Huang J, Liu KH, Tam WH, Sahota DS, Chu WCW, Goggins W, Woo J, Li TC, Chow CC, Chan JCN, Ma RCW. Progression of glucose intolerance and cardiometabolic risk factors over a decade in Chinese women with polycystic ovary syndrome: A case-control study. *PLOS Medicine*. 2019;16(10):e1002953. doi:10.1371/journal.pmed.1002953.
2. Chan JCN, Lim LL, Luk AOY, Ozaki R, Kong APS, Ma RCW, So WY, Lo SV. From Hong Kong diabetes register to JADE program to RAMP-DM for data-driven actions. *Diabetes Care*. 2019;42(11):2022-2031. doi:10.2337/dci19-0003.
3. Lim LL, Chan JCN. Sodium-glucose co-transporter-2 inhibitors: Know the patient and the drugs. *Hong Kong Medical Journal*. 2019;25(4):268-270. doi:10.12809/hkmj195089 (Editorial).
4. Flannick J, Mercader JM, Fuchsberger C, Udler MS, Mahajan A, Wessel J, ... , So WY, Soberón X, Stringham HM, Strom TM, Tam CHT, ... , Chan JCN, ... , Ma RCW, et al. Exome sequencing of 20,791 cases of type 2 diabetes and 24,440 controls. *Nature*. 2019;570(7759):71-76. doi:10.1038/s41586-019-1231-2.
5. Lim LL, Tse G, Choi KC, Zhang J, Luk AOY, Chow E, Ma RCW, Chan MHM, Wing YK, Kong APS, Chan JCN. Temporal changes in obesity and sleep habits in Hong Kong Chinese school children: a prospective study. *Scientific Reports*. 2019;9(1):5881. doi:10.1038/s41598-019-42346-z.
6. Luk AOY, Lau ESH, Lim C, Kong APS, Chow E, Ma RCW, Chan JCN. Diabetes-related complications and mortality in patients with young-onset latent autoimmune diabetes: A 14-year analysis of the prospective Hong Kong Diabetes register. *Diabetes Care*. 2019;42(6):1042-1050. doi:10.2337/dc18-1796.
7. Ding C, Zhang J, Lau ESH, Luk AOY, So WY, Ma RCW, Choi KC, Chan JCN, Wing YK, Kong APS. Gender differences in the associations between insomnia and glycemic control in patients with type 2 diabetes: A cross-sectional study. *Sleep*. 2019;42(4):zsz014. doi:10.1093/sleep/zsz014.
8. Wong PW, Lee HM, Lau ESH, Lim C, Ma RCW, Kong APS, Chan JCN, Luk AOY. Interactive effects of testosterone and the androgen receptor CAG repeat length polymorphism on cardiovascular-renal events and mortality in men with diabetes. *Diabetes-metabolism Research and Reviews*. 2019;35(1):e3081. doi:10.1002/dmrr.3081.
9. Huo X, Li J, Cao YF, Li SN, Shao P, Leng J, Li W, Liu J, Yang K, Ma RC, Hu G, Fang ZZ, Yang X. Trimethylamine N-oxide metabolites in early pregnancy and risk of gestational diabetes: A nested case-control study. *Journal of Clinical Endocrinology & Metabolism*. 2019;104(11):5529-5539. doi:10.1210/jc.2019-00710.

B. Poster Presentation / Oral Presentation

1. Lim LL, Lee HM, Lau ESH, Luk A, Chow E, Ma RCW, Chan JCN, Kong APS. Association between serum branched-chain amino acids and cancer risk: the Hong Kong Diabetes Register (HKDR). In: *ENDO 2019, The Endocrine Society Annual Meeting*. New Orleans, Louisiana, USA. March 23-26, 2019.
2. Lim LL, Lau ESH, Lee HM, Tam CH, Lim CKP, Luk A, Chow E, Ma RCW, Chan JCN, Kong APS. Association of serum branched-chain amino acids with kidney function decline in type 2 diabetes: the Hong Kong Diabetes Register. In: *79th Scientific Sessions of American Diabetes Association*. San Francisco, California, USA. June 7-11, 2019.
3. Lim LL, Lee HM, Lau E, Luk A, Chow E, Ma R, Chan JCN, Kong APS. Association between serum branched-chain amino acids and cancer risk: the Hong Kong Diabetes Register (HKDR). In: *55th Annual Meeting of the European Association for the Study of Diabetes*. Barcelona, Spain. September 16-20, 2019.
4. Ming X, Tian XY, Chung ACK, Lee HM, Schoonjans K, Auwerx J, Chan JCN, Kong APS. Sirtuin 3 (Sirt3) impairs glucose stimulated insulin secretion (GSIS) in pancreatic beta cells. In: *55th Annual Meeting of the European Association for the Study of Diabetes*. Barcelona, Spain. September 16-20, 2019.



DIABETES AND OBESITY



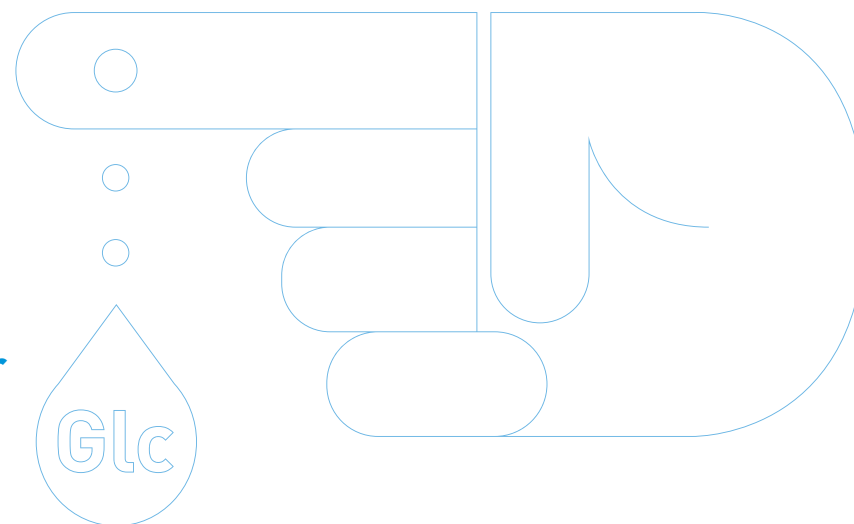
Principal Investigator

Professor Ronald Ma



Team

Andrea Luk | Risa Ozaki | Wing Yee So | Cadmon Lim | Heung Man Lee
 Claudia Tam | Raymond Wang | Guozhi Jiang | Vince Chan | Yong Hou |
 Charmaine Lee | Baoqi Fan | Noel Ng | Clara Lo | Kit Ying Tsoi |
 Feifei Cheng | Kwun Kiu Wong | Qiao Jin | Chuiguo Huang | Fei Xie



Research Progress Summary

Epidemiology of Diabetes and Diabetes complications in Asians

The research team led by Professor Ronald Ma has continued to generate novel insights on the epidemiology of diabetes and diabetic complications in Asians, to help inform the formulation of strategies and policies to address this important public health burden. Supported by the Research Grants Council Theme-based Research Scheme (TRS) on Diabetes Complications (PC: Professor Ronald Ma), they have charted the natural history of diabetic kidney disease and the progressive decline in renal function using various novel analytic approaches, including latent trajectory analysis. This work has highlighted the heterogeneity of decline in renal function, and identified subgroups at particular risk of renal dysfunction. They are currently using various omics approaches to identify predisposing factors and markers associated with rapid renal function decline and the development of diabetic kidney disease.

Earlier work has also highlighted the burden of young-onset diabetes. In work supported by the Research Grants Council General Research Fund, the research team has completed one of the longest follow-up studies to investigate the impact of Polycystic Ovary Syndrome (PCOS) on the development of glucose intolerance and diabetes among young women. This study, which charted the progression of dysglycaemia and cardiometabolic risk factors over a decade among Chinese women with PCOS, as well as women not affected by the condition, highlighted the marked increased risk of diabetes in women with PCOS. Furthermore, the onset of diabetes is much earlier in these women, highlighting the potential contribution of PCOS to young onset diabetes. Initial results from this study have already influenced the development of recommendations for diabetes screening in international guidelines on the management of PCOS.

Genetics of Diabetes and Gestational diabetes

Work from the research team has contributed significantly to advance the understanding of the genetic basis of type 2 diabetes. Together with colleagues across Asia, they have completed one of the largest genome-wide association studies (GWAS) for type 2 diabetes, and identified more than 50 novel loci for type 2 diabetes. This study has considerably expanded the number of genetic loci associated with type 2 diabetes in Asians, and would form the basis of future translation towards clinical prediction and care. They are currently investigating the role of these markers in the development of glucose intolerance and other metabolic abnormalities among adolescents and children.

In a project supported by Research Grants Council General Research Fund, Dr. Andrea Luk is leading an analysis to identify monogenic forms of diabetes among the research team's cohort of patients with young-onset diabetes. This work will provide complementary information



on rare genetic variation that contributes to the heritability of diabetes in Asians, and help to advance precision medicine in diabetes.

Gestational diabetes has become a common major complication of pregnancy, and has long-term adverse effects for the mother and offspring. In collaboration with Professor Xilin Yang from Tianjin Medical University, China, they have conducted a meta-analysis of genome-wide association study to identify novel genetic variants associated with gestational diabetes in the Chinese population.

Long-term consequences of gestational diabetes and related biomarkers

In a long-term collaborative study together with Professor Wing Hung Tam from the Department of Obstetrics and Gynaecology, the research team has investigated the long-term health impact of gestational diabetes. This includes the long-term follow-up of a GDM mother-offspring cohort for more than 2 decades to follow their long-term progression to metabolic abnormalities as well as diabetes, and the multi-centre Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Follow Up Study. The latter has highlighted the long-term risk of diabetes among women with gestational diabetes, as well as the independent association between maternal GDM and offspring adiposity. In order to unravel the link between maternal hyperglycaemia and offspring metabolic abnormalities, in work supported by the Research Grants Council, they are applying epigenomic profiling to identify potential methylation changes to offspring DNA following exposure to maternal hyperglycaemia.

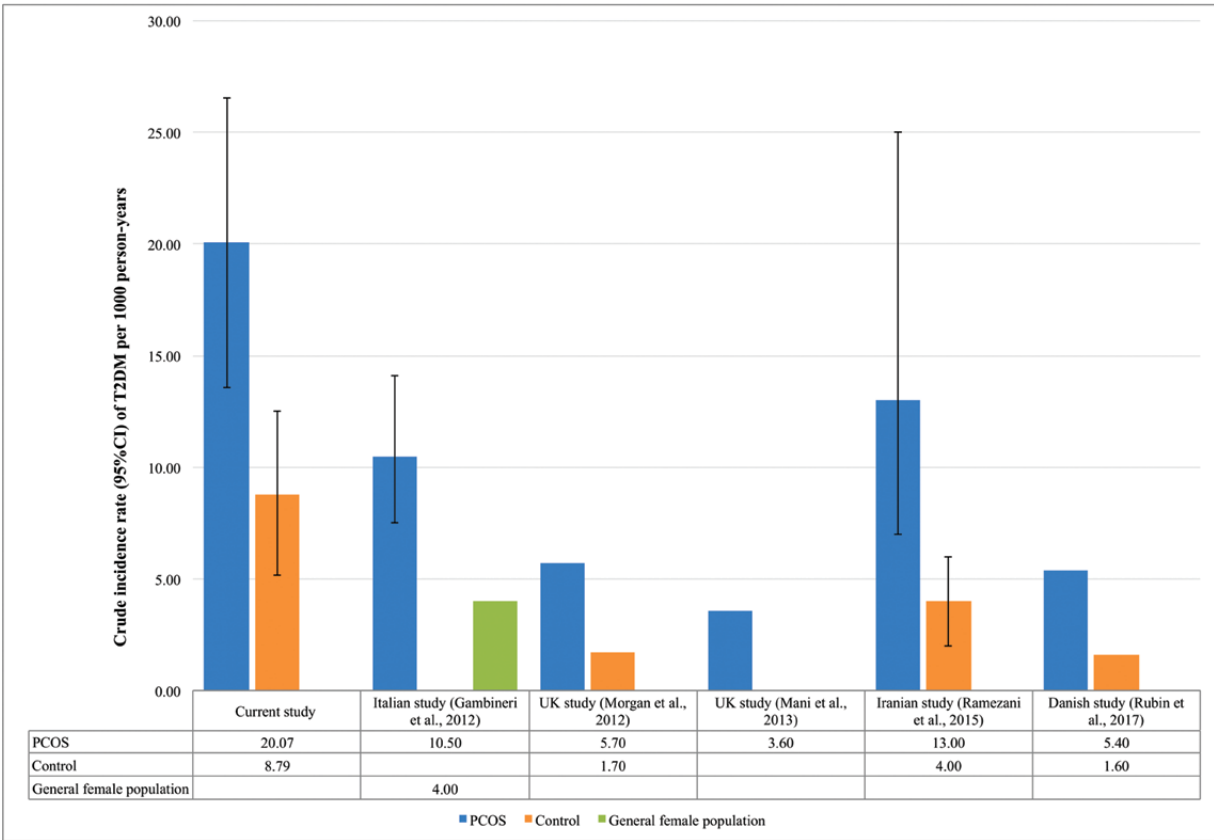
Genetic and novel biomarkers of diabetes complications

In work supported by the Research Grants Council Theme-based Research Scheme, the research team has completed one of the largest genome-wide association studies for diabetes complications globally, and identified a number of genomic regions associated with diabetic kidney disease in Asians. In addition, through the TRS, they have established the multi-centre

Hong Kong Diabetes Biobank (HKDB), which forms a unique dataset with detailed clinical phenotyping, multi-omics profiling and long-term follow-up which would serve to advance future epidemiology research as well as biomarker discovery. Ongoing work includes investigating the biological mechanisms whereby the new genes impact on the development of diabetes complications, with views to develop novel treatments to target diabetes complications. They have also obtained support from the Research Grants Council Research Impact Fund to continue their work on biomarkers for diabetes complications, and will expand that effort to incorporate metabolomic profiling to integrate into their multi-omics analyses to obtain a better picture of key disease pathways.

Precision Medicine in Diabetes

Through support from the Research Grants Council Research Impact Fund and the Croucher Foundation, they aim to bring some of the discoveries generated from their work to translate to the bedside to impact on clinical care. This includes incorporating their biomarkers into clinical management of patients with diabetes, development of various polygenic risk scores, as well as pharmacogenomics studies to stratify patients based on treatment response for better selection of glucose-lowering and other treatments. Much of their research is highly multidisciplinary and collaborative, with ongoing collaborations with more than 20 research groups across the world.



Comparison of crude incidence rate (95% confidence interval) of Type 2 diabetes per 1000 person-years in the study of Chinese PCOS women compared to other major published studies.

Source: Ng NYH, Jiang GZ, Cheung LP, Zhang YY, Tam CHT, Luk AOY, Quan JC, Lau ESH, Yau TTL, Chan MHM, Ho CS, Lim CKP, Ozaki R, Huang J, Liu KH, Tam WH, Sahota DS, Chu WCW, Goggins W, Woo J, Li TC, Chow CC, Chan JCN, Ma RCW. Progression of glucose intolerance and cardiometabolic risk factors over a decade in Chinese women with polycystic ovary syndrome: A case-control study. PLOS Medicine. 2019;16(10):e1002953. doi:10.1371/journal.pmed.1002953.

Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Ronald Ma	2019 Croucher Senior Research Fellow, Croucher Foundation, Hong Kong
	Key Reviewer 2018-2019, Diabetologia
	Member of Lancet Clinical Commission on Diabetes
	Executive Board Member, Asian Association for the Study of Diabetes (AASD)
Andrea Luk	Harry Keen Memorial Award, 16 th Symposium of the International Diabetes Epidemiology Group (IDEG)
	Co-lead, Epidemiology section, and Member, Lancet Clinical Commission on Diabetes

Research Awards and Recognitions

Member's Full Name	Details
Feifei Cheung	Selected Participant of the 2019 Cambridge Diabetes Seminar (CDS2019)
	Bursary, 16 th Symposium of the International Diabetes Epidemiology Group (IDEG), 29 November - 2 December 2019, Seoul, Korea
	Outstanding Mini-Oral Presentation, 16 th Symposium of the International Diabetes Epidemiology Group (IDEG), 2 December 2019, Seoul, Korea
	European Association for the Study of Diabetes (EASD) Travel Grant, 2019
Fei Xie	Croucher Foundation Scholarship, Croucher Foundation, Hong Kong
	NDM Prize Studentship, Nuffield Department of Medicine, University of Oxford

Fellowships

Member's Full Name	Details
Ronald Ma	Croucher Senior Medical Research Fellowship (2019/2020)

Academic Editorship

Member's Full Name	Details
Ronald Ma	Regional Editor, Diabetic Medicine
	Assistant Editor, Journal of Diabetes Investigation
	Member of Editorial Board, PLOS Medicine
	Member of Editorial Board, Obesity Reviews
	Member of Editorial Board, Nutrition, Metabolism and Cardiovascular Diseases
Andrea Luk	Associate Editor, Diabetic Medicine

Reviewer of Journal / Conference

Member's Full Name	Details
Ronald Ma	Reviewer, PLOS Medicine
	Reviewer, Diabetes Care
	Reviewer, Diabetologia
	Reviewer, Diabetes
	Reviewer, Diabetic Medicine
	Reviewer, Epigenetics
	Reviewer, Clinical Chemistry
	Reviewer, Obesity Reviews
	Reviewer, International Journal of Obesity
	Reviewer, Metabolism
	Reviewer, Nature Reviews Nephrology
	Reviewer, Nephrology Dialysis Transplantation
	Reviewer, Gastroenterology
	Reviewer, Molecular Genetics and Genomics
	Reviewer, BMC Medical Genomics
	Reviewer, Stream Lead Diabetes and Woman World Diabetes Congress 2019 Seoul Korea
	Reviewer, Board member, Worldwide Initiative for Diabetes Education (WorldWIDE Diabetes)

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Ronald Ma	Translating Multi-omic Discoveries to Transform Diabetes Care and Reduce Diabetic Complications	Research Grants Council – Research Impact Fund	02/05/2019	30/04/2024	8,400,000
Ronald Ma	Translating Multi-omic Discoveries to Transform Diabetes Care and Reduce Diabetic Complications	Research Committee – Research Impact Matching Fund	01/05/2019	30/04/2024	3,401,550
Ronald Ma	Translating Multi-omic Discoveries to Transform Diabetes Care and Reduce Diabetic Complications	Research Committee – Funding for Research Sustainability of Major Research Grants Council Funding Schemes	27/05/2019	30/04/2024	500,000
Ronald Ma	Unraveling the Link between Maternal Hyperglycaemia and Childhood Obesity: Genome-wide Methylation Analysis in A Prospective Cohort of Untreated Gestational Diabetes	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	970,517
Ronald Ma	Validation of Novel Protein Markers for the Prediction of Diabetic Kidney Disease	CUHK Technology and Business Development Fund (TBF18MED010)	30/06/2018	29/06/2019	100,000
Ronald Ma	Precision Medicine in Diabetes	CUHK – Shanghai Jiao Tong University Joint Research Fund	01/02/2018	31/01/2020	2,000,000
Ronald Ma	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 (Ref. 15162161)	01/04/2018	31/03/2021	1,197,580
Ronald Ma	The Impact of Gestational Diabetes Mellitus and Vitamin D Deficiency during Pregnancy on Children's Cardiometabolic Risk and Methylation	Research Grants Council – General Research Fund	01/01/2017	30/06/2019	998,652

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Ronald Ma	Prospective Randomized Trial Comparing Single Loop Duodenojejunal Bypass with Sleeve Gastrectomy Versus Standard Roux-en-Y Gastric Bypass in Patients with Poorly Controlled Type 2 Diabetes Mellitus: From Clinical Outcomes to Hormonal Mechanism	Research Grants Council – General Research Fund	01/10/2015	30/09/2019	1,673,800
Ronald Ma	Effect of GLP-1 Receptor Agonist Exenatide on Endothelial Dysfunction Associated with Hyperhomocysteinemia in Type 2 Diabetes	Food and Health Bureau – Health and Medical Research Fund	01/06/2018	31/05/2020	947,616
Ronald Ma	Biomarkers for Risk and Outcomes of Type 2 Diabetes: A Discovery and Validation Approach in Australian and Chinese Subjects	National Science Foundation of China – National Health and Medical Research Council of Australia Joint Research Scheme (APP1113592)	01/01/2016	31/12/2020	AUD 599,489
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	04/01/2016	31/07/2021	1,413,250
Ronald Ma	Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Assess Cardiovascular Outcomes Following Treatment with Ertugliflozin (MK-8835/PF-04971729) in Subjects with Type 2 Diabetes Mellitus and Established Vascular Disease, the Vertis CV Study (MD16819)	Merck Sharp & Dohme (Asia) Ltd	28/02/2017	02/07/2024	2,345,800

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Ronald Ma	A Phase 3b, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of TRC101 in Delaying Chronic Kidney Disease Progression in Subjects with Metabolic Acidosis (MD18893)	Tricida, Inc.	01/04/2019	31/12/2024	1,605,460
Ronald Ma	PIONEER 12 China Multi-regional Clinical Trial: Efficacy and Safety of Oral Semaglutide Versus Sitagliptin in Subjects with Type 2 Diabetes Mellitus Treated with Metformin	Novo Nordisk Hong Kong Limited	01/08/2019	13/09/2021	2,332,500
Ronald Ma	Semaglutide Cardiovascular Outcomes Trial in Patients with Type 2 Diabetes (SOUL)	Novo Nordisk Hong Kong Limited	29/08/2019	29/07/2024	9,424,000
Andrea Luk	Search for Maturity-Onset Diabetes of the Young in Chinese with Young-Onset Diabetes	Research Grants Council General – Research Fund	01/01/2019	30/06/2020	941,431
Andrea Luk	A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter, Event-driven Phase III Study to Investigate the Efficacy and Safety of Finerenone, in Addition to Standard of Care, on the Progression of Kidney Disease in Subjects with Type 2 D	Bayer Healthcare Limited	04/01/2016	31/05/2020	1,515,750
Tam Ha Ting	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

Publications

A. Journal Papers

1. Chan JC, Lim LL, Luk AO, Ozaki R, Kong AP, Ma RC, So WY, Lo SV. From Hong Kong Diabetes Register to JADE program to RAMP-DM for data-driven actions. *Diabetes Care*. 2019;42(11):2022-2031. doi:10.2337/dci19-0003.
2. Luk AOY, Lau ESH, Lim C, Kong APS, Chow E, Ma RCW, Chan JCN. Diabetes-related complications and mortality in patients with young-onset latent autoimmune diabetes: A 14-year analysis of the prospective Hong Kong Diabetes Register. *Diabetes Care*. 2019;42(6):1042-1050. doi:10.2337/dc18-1796.
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11. Zhang YY, Tang PM, Tang PC, Xiao J, Huang XR, Yu C, Ma RCW, Lan HY. LRNA9884, a novel Smad3-dependent long noncoding RNA, promotes diabetic kidney injury in db / db mice via enhancing MCP-1-dependent renal inflammation. *Diabetes*. 2019;68(7):1485-1498. doi:10.2337/db18-1075.

B. Conference Papers / Abstract

1. Ma RC, Jin N, Luk CW, Lee HM, Lim CK, So WY, Chan RCK, Lan HY, Ng CF, Chan JC, Chan TF, Szeto CC, TRANSCEND Consortium. RNA-Sequencing of laser-microdissected glomeruli and tubules reveal differentially expressed genes in diabetic kidney disease. In: *79th Scientific Sessions of American Diabetes Association*. San Francisco, USA. 2019 June 7-11. (Abstract).
2. Tam CH, Mao MD, Yuen LY, Ma RC, Tam WH. Determine the optimal gestational weight gain for Chinese population from the HAPO study cohort. In: *10th International DIP Symposium on Diabetes, Hypertension, Metabolic Syndrome & Pregnancy*. Florence, Italy. 2019 May 29 - June 1 (Abstract).
3. Mao D, Yuen LY, Ho CS, Wang CC, Tam HT, Sahota DS, Ozaki R, Chan MH, Lao TT, Ma RC, Tam WH. The associations of in utero vitamin D status with offspring's arterial stiffness in adolescence - follow up of HAPO study cohort. In: *10th International DIP Symposium on Diabetes, Hypertension, Metabolic Syndrome & Pregnancy*. Florence, Italy. 2019 May 29 - June 1 (Abstract).
4. Tam CH, Huo X, Yuen LY, Wang Y, Ozaki R, Liang Y, Ng ACW, Li J, Lim CK, Hang L, Li AM, Liu J, Chan JC, Tam WH, Yang X, Ma RC. Meta-analysis of genome-wide association studies identifies novel genetic variants associated with offspring birthweight in Chinese women. In: *10th International DIP Symposium on Diabetes, Hypertension, Metabolic Syndrome & Pregnancy*. Florence, Italy. 2019 May 29 - June 1 (Abstract).
5. Cheng F, Ng A, Luk AO, Jiang G, Lim CK, Joglekar M, Jenkins AJ, Chan JC, Hardikar A, Ma RC. The relationship between telomere length and diabetic kidney disease - The Hong Kong Diabetes Register. In: *55th European Association for the Study of Diabetes Annual Meeting*. Barcelona, Spain. 2019 September 17-20 (Abstract).
6. Cheng F, Ng AC, Luk AO, Tam CH, Lim CK, Joglekar M, Jenkins AJ, Chan JC, Hardikar A, Ma RC. The relationship between telomere length and coronary heart disease in Type 2 Diabetes - The Hong Kong Diabetes Register. In: *International Diabetes Federation Congress 2019*. Busan, Korea. 2019 December 2-6 (Abstract).
7. Fan B, Lau ES, Tam CH, Jiang G, Lee HM, Lim CK, HKDR TRS Study Group, Kong AP, Ozaki R, Chow CC, So WY, Chan JC, Ma RC, Luk AO. Bilirubin may be protective but not causal for progression of renal and cardiovascular disease in type 2 diabetes: Hong Kong Diabetes Register. In: *International Diabetes Federation Congress 2019*. Busan, Korea. 2019 December 2-6 (Abstract).
8. Chan M, Lee N, Ma RC, Graham C, PKS Chan. Genetic susceptibility of Hong Kong Ethnic Chinese to Severe Influenza and RSV infections. In: *Health Research Symposium 2019 - Genomics and Big Data in Health and Disease*. Hong Kong, China. 2019 June 12.

C. Book / Book Chapter

1. O'Brien EC, Tsoi KY, Ma RCW, Hanson MA, Hod M, McAuliffe FM. Nutrition through the life cycle: Pregnancy. In: *Encyclopedia of Food Security and Sustainability*. Elsevier; 2018:49-74. doi:10.1016/B978-0-08-100596-5.21912-4.

MOLECULAR MICROBIOLOGY AND EMERGING INFECTIOUS DISEASES

Molecular Microbiology –
Clinical Microbial Genomics



Principal Investigator

Professor Guoping Zhao



Team

Channy Wei



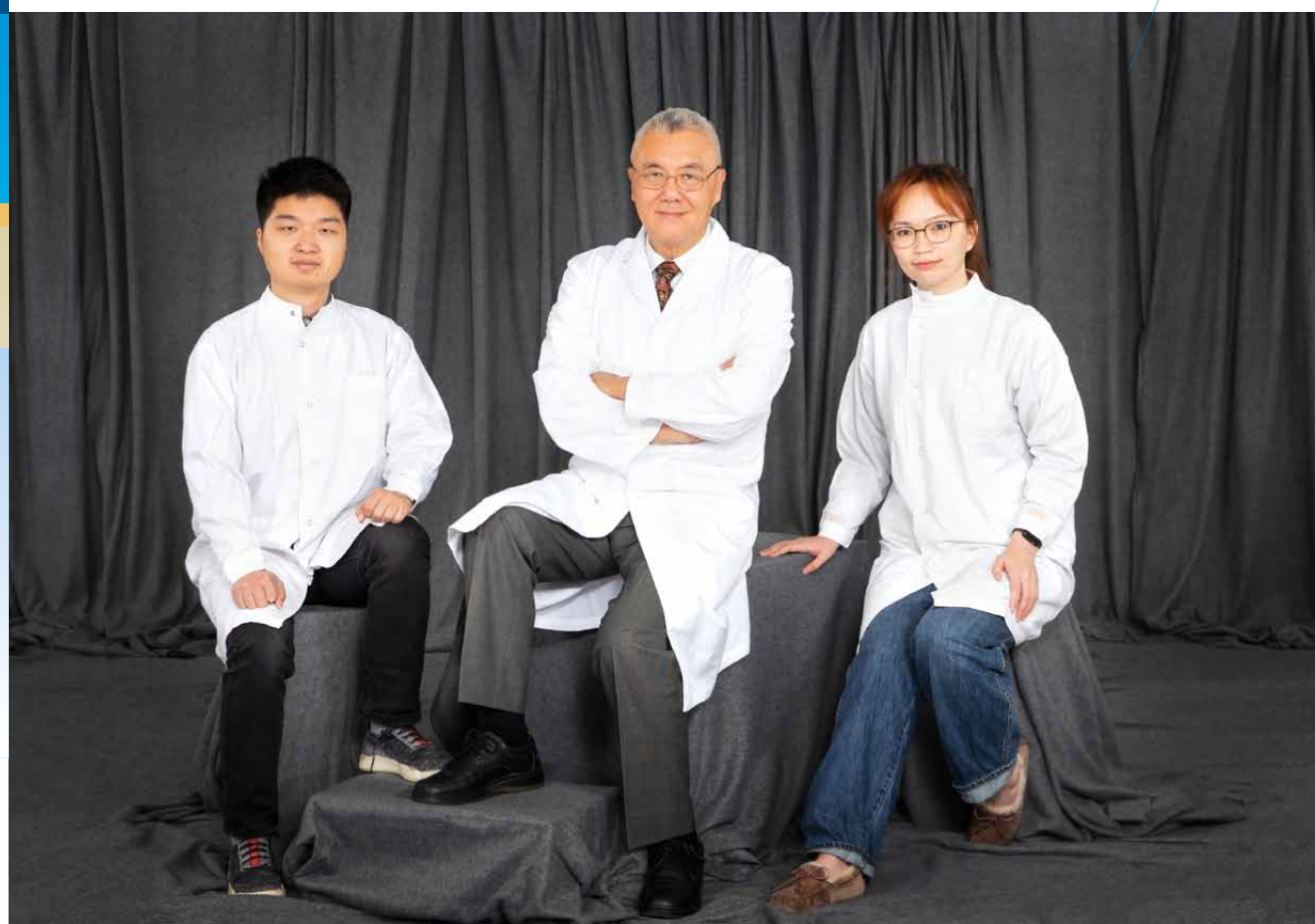
Research Progress Summary

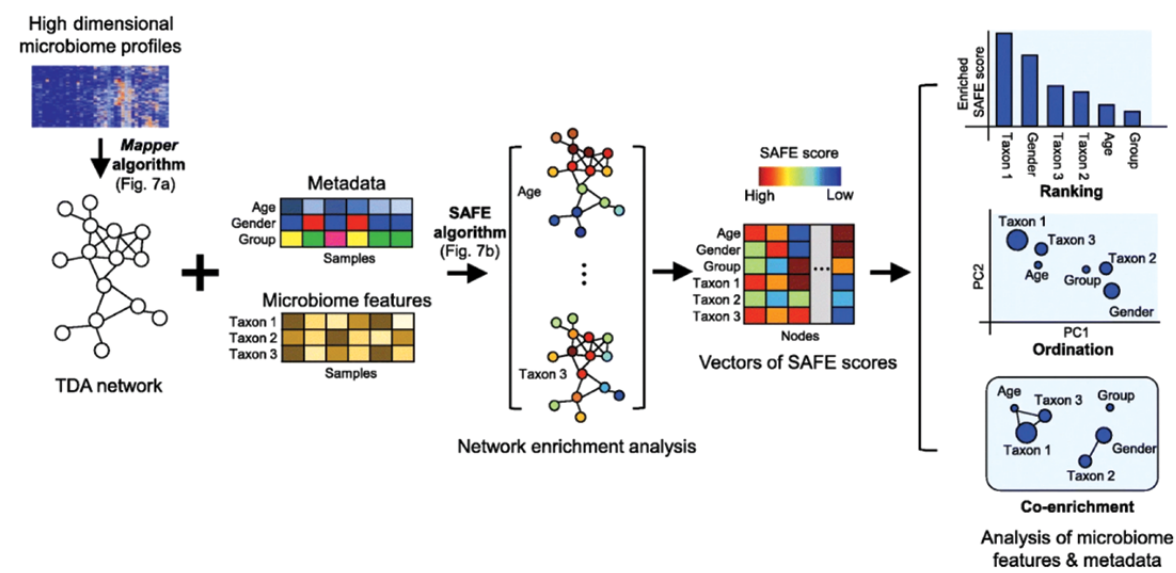
The team led by Professor Guoping Zhao has been exploring on comparative analysis of the population-level human microbiome and developing new bioinformatical methods for microbiome-wide association study (MWAS). To untangle the complex variations of the human microbiome associated with large-scale host phenotypes or environment types, the team developed tmap – an integrative framework based on topological data analysis for population-scale microbiome stratification and association studies (*Genome Biology* 20, 293, 2019). The performance of tmap is clearly superior over the most commonly used methods shown by applications to several population-scale microbiomes research projects revealing microbiome-associated host or environmental features and in understanding the systematic interrelations among their association patterns.

Professor Guoping Zhao has been studying the genomics of *Mycobacterium tuberculosis* (Mtb) since 2008 via sequencing the genome of the classical avirulent strain H37Ra (*PLOS One* 3(6): e2375). The 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 Pathogens* 9: e1003814, 2013). They 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) (*Proceedings of the National Academy of Sciences of the United States of America* 115(9), 2210–2215, 2018).

They have been exploring the microbial systems and synthetic biology study since 2008. The team's decade's effort was rewarded by three significant breakthroughs in 2018. They were actively involved in the Yeast genome editing and reconstruction project (*Nature* 560, 331–335) and facilitated the efforts in the identification of a novel ornithine-ammonia cycle in nitrogen fixation cyanobacteria based on metabolic flux technology (*Nature Chemical Biology* 14, 575–581). Based on revealing the trans-cleavage activity of Cas12a (*Cell Research* 28, 491–493), the team developed a novel nucleic acid detection system – HOLMES (*Cell Discovery* 4, 20).





Overview of tmap workflow for integrative microbiome data analysis.

Source: Liao TH, Wei YC, Luo MJ, Zhao GP, Zhou HK. Tmap: An integrative framework based on topological data analysis for population-scale microbiome stratification and association studies. *Genome Biology*. 2019;20(1). doi:10.1186/s13059-019-1871-4.

Research and Scholarship

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
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
Guoping Zhao	結核分枝桿菌持留菌基因組維護機制研究	國家自然科學基金委員會	01/01/2019	31/12/2023	RMB 2,970,000

Publications

A. Journal Papers

1. Liao T, Wei Y, Luo M, Zhao GP, Zhao H. Tmap: an integrative framework based on topological data analysis for population-scale microbiome stratification and association studies. *Genome Biology*. 2019; 20:293. doi:10.1186/s13059-019-1871-4.

2. Li SY, Cheng QX, Wang JM, Li XY, Zhang ZL, Gao S, Cao RB, Zhao GP, Wang J. Author Correction: CRISPR-Cas12a-assisted nucleic acid detection [Cell Discovery, (2018), 4, 1, (20), 10.1038/s41421-018-0028-z]. *Cell Discovery*. 2019;5(1):1-1. doi:10.1038/s41421-019-0083-0 [Supplementary information].

MOLECULAR MICROBIOLOGY AND EMERGING INFECTIOUS DISEASES

Emerging Infectious Diseases



Principal Investigator

Professor Shui-shan Lee



Team

Dr. Denise Chan | Dr. Kai-man Kam | Dr. Grace Lui |
Dr. Martin Chan | 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 led by Professor Shui-shan Lee have varied from year to year, with an emphasis on conditions of concern. On an ongoing basis, the team examines the transmission dynamics of human immunodeficiency virus (HIV) and other emerging infections, manages clinical cohorts, explores HIV comorbidities, conducts analyses on outbreaks and maps the geographic distribution of emerging infections. For the year in 2019, the highlights were HIV pre-exposure prophylaxis; sexual transmission of hepatitis C virus (HCV); and latent tuberculosis infection.

HIV Pre-exposure Prophylaxis

Internationally, pre-exposure prophylaxis (PrEP) is currently one of the most

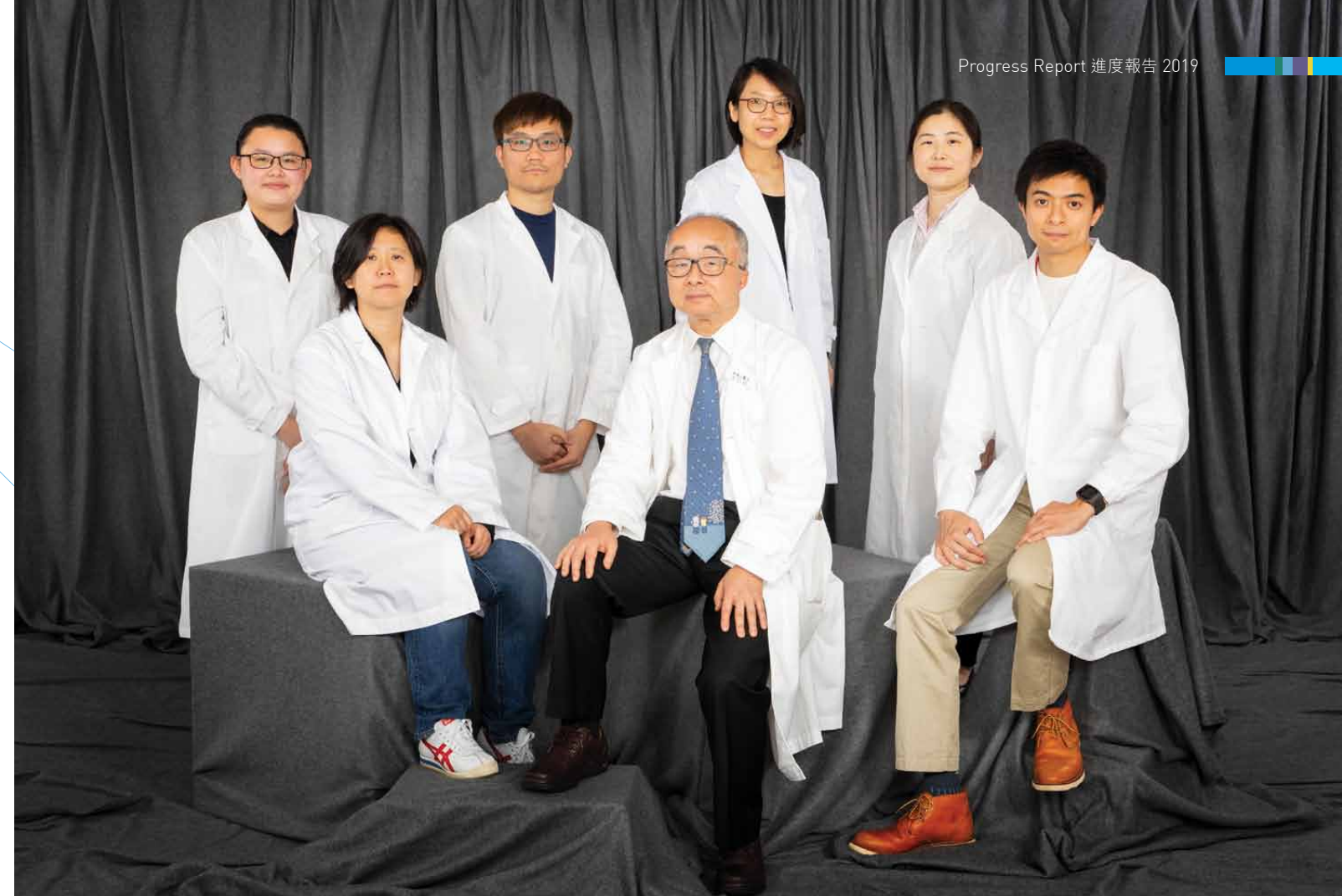
important means of preventing HIV transmission in the community. While the prescription of daily or event-based co-formulated tenofovir disoproxil fumarate / emtricitabine (TDF/FTC) is the standard, uptake has so far been slow with less than 0.4 million people globally having accessed PrEP. The team pioneered Hong Kong's first clinical trials on PrEP since 2017. 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 2019, about 200 men who have sex with men (MSM) with high risk sexual behaviours have enrolled in the studies, providing useful data for informing public health policy. 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 published as research manuscripts. Their 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 the Health and Medical Research Fund of the Hong Kong SAR Government.

HCV Co-infection in People Living with HIV

Sexual transmission of HCV was previously thought to be exceedingly uncommon. In the past decade, HCV outbreaks were repeatedly reported among men who have sex with men (MSM) as a result of virus exposure through unprotected anal sex. Following the research team's report in 2015 of the emergence of a monophyletic genotype 3a

cluster in Hong Kong, an ongoing epidemiologic study is conducted through the establishment of a cohort comprising about 100 HIV infected MSM. The monophyletic cluster has given way to a more diverse pattern of further dissemination with the inclusion of genotype 1b. Their analyses confirmed that there was no spilling over of infection from injection drug users whose HCV prevalence had been high at 80% locally. Collaboration has been built with researchers from 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 genetically closely related to the Hong Kong cluster. With the support of the Health and Medical Research Fund, the team is beginning a new follow-up epidemiologic study with the incorporation of Next Generation Sequencing.



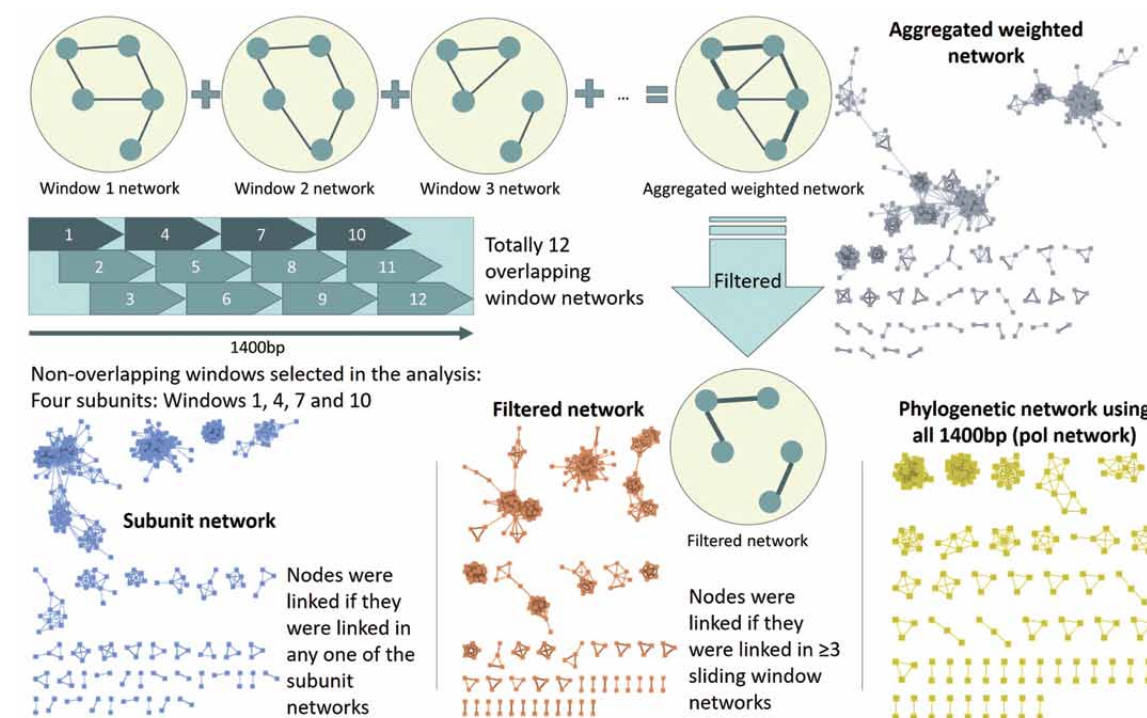
Latent Tuberculosis Infection and Reactivation

Hong Kong is classified as an intermediate endemicity area for tuberculosis (TB) infection with thousands of disease cases reported per year. Reactivation of latent TB infection (LTBI) accounts for a majority of the reported cases which occur as a result of compromised immunity. Screening for LTBI is recommended in the clinical management of HIV infection because of the risk of predisposing to TB reactivation. The research team conducted a longitudinal study on 2719 HIV patients over a 15 years' period. The results showed that antiretroviral therapy with immune reconstitution is associated with a reduction of the risk of reactivation. Baseline LTBI testing is found to be an important strategy for identifying individual at higher risk of reactivation who would benefit for treatment. In a cost-effectiveness analysis study, their results showed that a strategy of baseline LTBI testing followed by up to 3 subsequent annual tests could avert a similar proportion of new TB infections while incurring a lower cost compared with annually repeated testing. These results

suggested that less intense subsequent LTBI testing strategy should be considered for HIV infected persons in the local setting. In Hong Kong, a majority of TB reactivation occurs among elderly population. Apart from host factors, environmental influence is a newly discovered dimension deserving public health attention. In collaboration with the University of Science and Technology, and the Department of Health TB and Chest Service, the team is working on the association between TB reactivation and ambient PM2.5, the results of which would be important for informing strategy for reducing TB burden in the community.

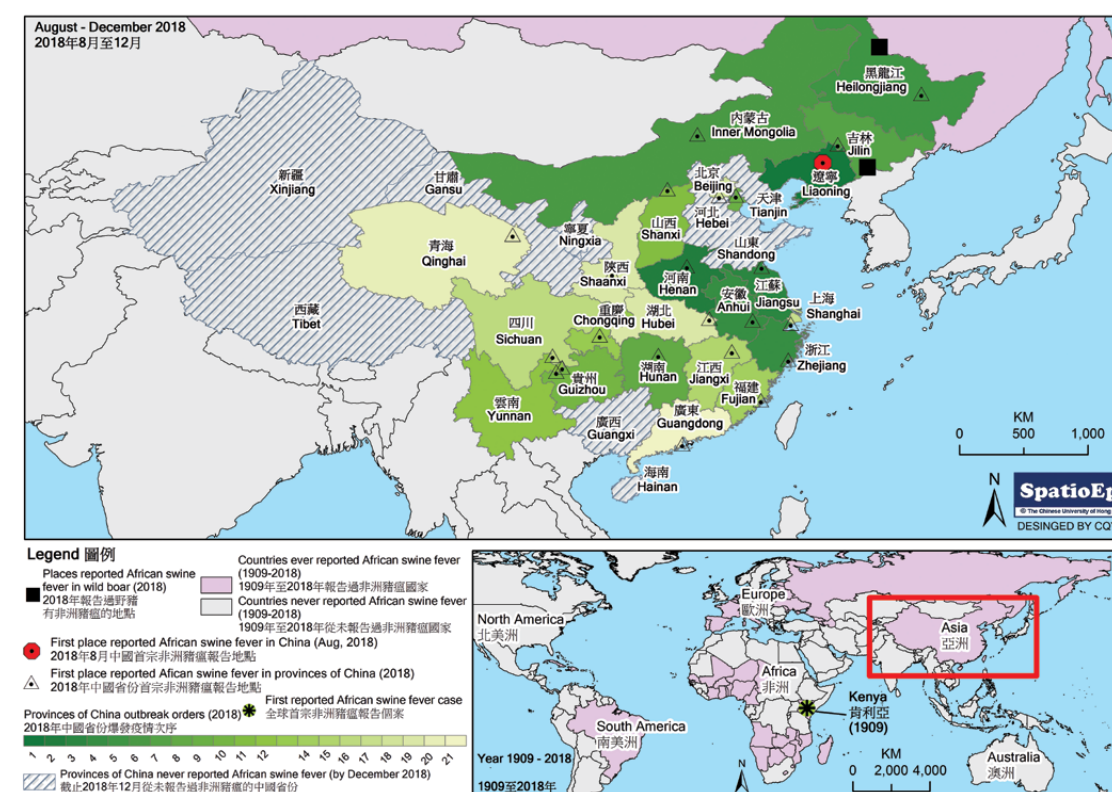
Mapping of Diseases

Since a decade ago, the research team has been generating maps on various diseases to highlight their public health implications with a local and global perspective. Through the team's Public Health Mapping website (www.SpatioEpi.com), the distribution of infectious diseases of public health importance are displayed for the information of not just professional but members of the public. In 2019, maps on influenza, measles, hepatitis B, HIV and African Swine Fever were shown. The website has attracted viewers from over 100 countries/cities, and is a general education reference for secondary school students in Hong Kong.



HIV transmission network – HIV sequences of 1400bp were cropped into 300bp bins with a 100bp sliding window. For each window, genetic distance was calculated and those with <1.5% distance were considered linked. Final genetic network was constructed from those links presented in at least 3 overlapping window networks and was compared with a non-overlapping window network and a 1-window 1400bp network.

Source: Professor Shui-shan Lee



Mapping of Africa Swine Fever outbreak, an emerging zoonotic infection in 2019.

Source: Professor Shui-shan Lee

■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Shui-shan Lee	Daniel Yu Research Professor of Infectious Diseases
Tsz-ho Kwan	Teaching Assistant Award, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong

Academic Editorship

Member's Full Name	Details
Shui-shan Lee	Editor, International Journal of Infectious Diseases
	Academic Editor, Medicine (Baltimore)
	Assistant Editor, Addiction
Ngai-sze Wong	Academic Editor, PLOS One
Martin Chan	Associate Editor, BMC Infectious Diseases
	Member, Editorial Board, Journal of Virological Methods
	Member, Editorial Board, Scientific Reports (Microbiology)

Academic Editorship

Member's Full Name	Details
Shui-shan Lee	Manuscript Reviewer, International Journal of Infectious Diseases
	Manuscript Reviewer, Journal of Viral Hepatitis
	Manuscript Reviewer, International Journal of Drug Policy
	Manuscript Reviewer, Infection, Disease & Health
	Manuscript Reviewer, Harm Reduction Journal
	Grant Reviewer, Gilead Sciences Research Scholars Program in HIV Asia
Ngai-sze Wong	Manuscript Reviewer, Journal of the International AIDS Society
	Manuscript Reviewer, BMC Infectious Diseases
	Manuscript Reviewer, Scientific Reports
	Manuscript Reviewer, International Journal of Geographical Information Science
	Manuscript Reviewer, AIDS Research and Therapy
Martin Chan	Manuscript Reviewer, Annals of Internal Medicine
	Manuscript Reviewer, Infection, Genetics and Evolution
	Manuscript Reviewer, Applied and Environmental Microbiology
	Manuscript Reviewer, Journal of Medical Virology
	Manuscript Reviewer, Journal of Virological Methods
	Manuscript Reviewer, Emerging Infectious Diseases
	Manuscript Reviewer, Influenza and Other Respiratory Viruses
	Manuscript Reviewer, BMC Infectious Diseases
	Manuscript Reviewer, Clinical Microbiology and Infection

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Shui-shan Lee	Characterization of the Pattern and Trends of HIV Spread among Newly Diagnosed Patients in Hong Kong	Council for the AIDS Trust Fund	01/07/2016	31/12/2019	1,300,127
Shui-shan Lee	Exploration of the Harm Reduction Effects of Methadone Treatment in Hong Kong	Council for the AIDS Trust Fund	01/07/2017	30/06/2019	462,326
Shui-shan Lee	Impacts of Change from Permanent to Time-limited Deferral of Men Who Have Sex with Men From Blood Donation in Hong Kong	Council for the AIDS Trust Fund	01/06/2017	31/05/2020	178,307
Shui-shan Lee	Operability of a Pilot Incentivised PrEP Programme for MSM in Hong Kong	Council for the AIDS Trust Fund	01/09/2017	31/08/2020	2,931,337
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	Time Associated Evolvment 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	30/06/2020	345,549
Shui-shan Lee	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	31/05/2021	1,196,480
Shui-shan Lee	Spatio-temporal Pattern of Ambient PM2.5 Exposure and the Risk of Tuberculosis Reactivation	Research Grants Council – General Research Fund	01/01/2019	30/06/2021	600,000
Shui-shan Lee	Potentiating Host Immunity for HIV-1 Functional Cure	Research Grants Council – Theme-based Research Scheme	01/01/2019	31/12/2024	4,325,556

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Shui-shan Lee	Regular Self-sampled STI/HIV Testing and Its Association with Infection Risks in Men Who Have Sex with Men	Council for the AIDS Trust Fund	01/07/2019	30/06/2021	1,481,811
Shui-shan Lee	Molecular Differentiation of HIV and HCV Transmission Networks in HIV/HCV Co-infected Men Who Have Sex with Men In Hong Kong	Food and Health Bureau – Health and Medical Research Fund	01/10/2019	30/09/2021	1,097,688
Ngai-sze Wong	Re-examining the Cost-effectiveness of Annual Latent TB Infection Retesting for Reducing the Risk of TB Reactivation among HIV Diagnosed Patients in the HAART Era in Hong Kong	Council for the AIDS Trust Fund	01/09/2017	28/02/2019	343,368
Ngai-sze Wong	Perception of PrEP Use and Its Monitoring Mechanism in MSM – A Qualitative Study	Council for the AIDS Trust Fund	01/08/2019	31/07/2020	337,769
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 Programmes on Control of Infectious Diseases (Phase III)	01/11/2018	21/12/2019	305,376
Grace Lui	Virokinetics and Its Influencing Factors in RSV Lower Respiratory Tract Infections in Adults	Food and Health Bureau – Health and Medical Research Fund Commissioned Programmes on Control of Infectious Diseases (Phase III)	15/01/2015	31/12/2019	364,836
Grace 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 Lui	Outcomes of Carbapenem-resistant Enterobacteriaceae Infections in Hong Kong	Food and Health Bureau – Health and Medical Research Fund Commissioned Programmes on Control of Infectious Diseases (Phase III)	01/12/2018	30/11/2019	333,528

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Grace Lui	Optimisation 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 Lui	Lifestyle Modification Programme for HIV-infected Individuals with Non-alcoholic Fatty Liver Disease: A Randomisation Controlled Trial	Food and Health Bureau – Health and Medical Research Fund	01/04/2019	31/03/2020	1,481,206
Grace Lui	Automatic Retinal Image Analysis (ARIA) to Predict Coronary Artery Disease in HIV-infected Individuals	Council for the AIDS Trust Fund	01/04/2019	31/03/2021	1,029,120
Grace Lui	Contribution of Physical, Psychological and Socioeconomic Factors to Frailty and Quality of Life in Chinese People Living with HIV and Comorbidities	Council for the AIDS Trust Fund	01/04/2019	30/09/2020	560,462
Grace 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	1,184,189
Denise Chan	A Modelling Study for Assessing the Effect of Expedited 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	160,785
Denise Chan	Seroepidemiology Study of Dengue Infection among Healthy Adults in Hong Kong	Food and Health Bureau – Health and Medical Research Fund Commissioned Programmes on Control of Infectious Diseases (Phase III)	01/12/2018	30/11/2019	283,000
Denise Chan	Acceptability of STI Test by Post in Hong Kong	Food and Health Bureau – Health and Medical Research Fund Commissioned Programmes on Control of Infectious Diseases (CHP)	24/08/2018	23/08/2019	443,405

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Martin Chan	Characteristics and Clinical Relevance of Microbiome Changes in Severe Influenza and Respiratory Syncytial Virus Infection	Food and Health Bureau – Health and Medical Research Fund Commissioned Programmes on Control of Infectious Diseases (Phase III)	01/01/2016	30/06/2019	329,793
Martin Chan	Use of Next-generation Sequencing to Identify New Intestinal Viruses Associated with Unexplained Acute Gastroenteritis	Food and Health Bureau – Health and Medical Research Fund Commissioned Programmes on Control of Infectious Diseases (Phase III)	01/07/2017	31/06/2019	392,761
Martin Chan	Discovery of Novel/Unrecognised Viruses Associated with Unexplained Acute Syndromes in Immunocompromised Patients	Food and Health Bureau – Health and Medical Research Fund Commissioned Programmes on Control of Infectious Diseases (Phase III)	01/07/2017	30/06/2019	329,793
Martin Chan	Identification of Novel/Unrecognised Viruses Associated with Unexplained Severe Acute Respiratory Illnesses	Food and Health Bureau – Health and Medical Research Fund Commissioned Programmes on Control of Infectious Diseases (Phase III)	01/01/2017	30/06/2019	329,793
Martin Chan	Host Interactome of Human Norovirus Structural Proteins	Research Grants Council – General Research Fund	01/01/2017	30/06/2020	922,492
Martin Chan	Glycan Array-based High-throughput Screening for Carbohydrate Binding Profile of Emerging Norovirus Genotypes	CUHK Faculty of Medicine – Medicine Panel Internal Review Scheme	01/10/2017	30/09/2019	30,000
Martin Chan	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
Martin Chan	Generation of Host Genetic Factor Information Known to Associate with Hospitalized Severe Influenza	Food and Health Bureau – Health and Medical Research Fund Commissioned Programmes for Influenza Research	01/09/2019	31/08/2022	955,432

Publications

A. Journal Papers

1. 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*. 2019;102(3):337-342. doi:10.1016/j.jhin.2018.11.017.
2. Kwan TH, Wong NS, Lee SS. Participation pattern of methadone users and its association with social connection and HIV status: Analyses of electronic health records data. *PLOS One*. 2019;14(5):e0216727. doi:10.1371/journal.pone.0216727.
3. Kwan TH, Lee SS. Bridging awareness and acceptance of pre-exposure prophylaxis among men who have sex with men and the need for targeting chemsex and HIV testing: Cross-sectional survey. *JMIR Public Health and Surveillance*. 2019 Jul 3;5(3):e13083. doi: 10.2196/13083.
4. Lee SS, Crofts N, Hung CC. Macro-efforts for the micro-elimination of hepatitis C targeting people who inject drugs. *International Journal of Infectious Diseases*. 2019;85:141-142. doi:10.1016/j.ijid.2019.06.003 (Editorial).
5. Wong NS, Leung CC, Chan KCW, Chan WK, Lin AWC, Lee SS. A longitudinal study on latent TB infection screening and its association with TB incidence in HIV patients. *Scientific Reports*. 2019;9(1):10093. doi:10.1038/s41598-019-46570-5.
6. Wong NS, Chan KCW, Wong BCK, Leung CC, Chan WK, Lin AWC, Lui GCY, Mitchell KM, Lee SS. Latent tuberculosis infection testing strategies for HIV-positive individuals in Hong Kong. *JAMA Network Open*. 2019;2(9):e1910960. doi:10.1001/jamanetworkopen.2019.10960.
7. Li KK, Chan MWH, Lee SS, Kwok KO. The mediating roles of social benefits and social influence on the relationships between collectivism, power distance, and influenza vaccination among Hong Kong nurses: A cross-sectional study. *International Journal of Nursing Studies*. 2019;99:103359. doi:10.1016/j.ijnurstu.2019.05.007.
8. Lee SS, Kwan TH, Wong NS, Lee KCK, Chan DPC, Lam TTN, Lui GCY. Piloting a partially self-financed mode of human immunodeficiency virus pre-exposure prophylaxis delivery for men who have sex with men in Hong Kong. *Hong Kong Medical Journal*. 2019;5:382-91. doi:10.12809/hkmj198030.
9. Wong NS, Kwan TH, Lee KCK, Lau JYC, Lee SS. Delineation of chemsex patterns of men who have sex with men in association with their sexual networks and linkage to HIV prevention. *International Journal of Drug Policy*. 2019;75:102591. doi:10.1016/j.drugpo.2019.10.015.
10. Lui GCY, Wong NS, Wong RYK, Tse YK, Wong VWS, Leung CC, Chan HLY, Wong GLH. Antiviral therapy for hepatitis B prevents liver injury in patients with tuberculosis and hepatitis B co-infection. *Clinical Infectious Diseases*. 2019;70(4):660-666. doi:10.1093/cid/ciz241.
11. Leung AKC, Leung AAM, Wong AHC, Sergi CM, Kam JKM. Giardiasis: An overview. *Recent Patents on Inflammation & Allergy Drug Discovery*. 2019;13(2):134-143. doi:10.2174/1872213X13666190618124901 (Review).
12. Kam JKM, Wong LK, Fu KCW. Creation of sexually transmitted diseases education program for young adults in rural cambodia. *Frontiers in Public Health*. 2019;7:50. doi:10.3389/fpubh.2019.00050.

B. Conference Posters / Presentations

1. Poon CM, Ho KM, Kwan CK, Wong NS, Lau LHW, Ye C, Lee SS. History of sexually transmitted infection before HIV diagnosis among attendees of STI clinics in Hong Kong. [abstract 78] In: *4th Asia Pacific Conference on AIDS and co-infections*. Hong Kong, China. 2019 June 27-29.
2. Kwan TH, Lui GCY, Lee KCK, Wong NS, Chan DCP, Lee SS. Practical perspective of the use of point-of-care testing for supporting the delivery of HIV pre-exposure prophylaxis. [abstract 1] In: *4th Asia Pacific Conference on AIDS and co-infections*. Hong Kong, China. 2019 June 27-29.
3. Kwan TH, Wong NS, Lui GCY, Chan KCK, Tsang OTY, Leung WS, Ho KM, Lee MP, Lam W, Chan S, Chan DCP, Lee SS. Genetic connectedness by segment of HIV sequence and its association with sex-networking profiles. [abstract 74] In: *4th Asia Pacific Conference on AIDS and co-infections*. Hong Kong, China. 2019 June 27-29.
4. Lee SS, Wong NS, Kwan TH, Lau J, Lau LHW, Chan TCP, Poon CM. HIV/STI testing among men who have sex with men in Hong Kong. [abstract 73] In: *4th Asia Pacific Conference on AIDS and co-infections*. Hong Kong, China. 2019 June 27-29.
5. Chan DPC, Chan TCM, Lee SS. Variability of plasma level of integrase inhibitors in virologically suppressed HIV-infected patients. [abstract 68] In: *4th Asia Pacific Conference on AIDS and co-infections*. Hong Kong, China. 2019 June 27-29.
6. Kwan TH, Lui GCY, Lee KCK, Wong NS, Chan DPC, Lee SS. High acceptability of a partially self-financed pre-exposure prophylaxis delivery model among men who have sex with men in Hong Kong. [abstract 81] In: *4th Asia Pacific Conference on AIDS and co-infections*. Hong Kong, China. 2019 June 27-29.
7. Kwan TH, Lee SS. Genetic variability and its effect on genetic network construction. In: *Infection 2019*. Hong Kong, China. 2019 June 10-12.
8. Lau HE, Wong NG, Lee SS. Influenza vaccine hesitancy among nursing professionals in Hong Kong. In: *Infection 2019*. Hong Kong, China. 2019 June 10-12.
9. Kwan TH, Lui GCY, Lee KCK, Wong NS, Chan DPC, Lee SS. A questionnaire-based scale for assessing adherence of men who have sex with men to pre-exposure prophylaxis. [WEPEC497] In: *10th IAS Conference on HIV Science (IAS 2019)*. Mexico City, Mexico. 2019 July 21-24.
10. Kwan TH, Lui GCY, Lee KCK, Lam TTN, Wong NS, Lam CY, Chan DPC, Lee SS. HIV prevention in men who have sex with men as inferred from their adherence to daily versus event-driven pre-exposure prophylaxis: cross-over clinical trial. [WEPEC496] In: *10th IAS Conference on HIV Science (IAS 2019)*. Mexico City, Mexico. 2019 July 21-24.
11. Kwan TH, Lui GCY, Lee KCK, Lam TTN, Wong NS, Lam CY, Chan DPC, Lee SS. Temporal dynamics of sexual behaviour among MSM on sequential daily and event-driven PrEP: Results from a crossover study. [WEPEC394] In: *10th IAS Conference on HIV Science (IAS 2019)*. Mexico City, Mexico. 2019 July 21-24.
12. Kwan TH, Wong NS, Lui GCY, Chan KCW, Tsang OTY, Leung WS, Ho KM, Lee MP, Lam W, Chan SN, Chan DPC, Lee SS. Individual and dyadic determinants for the growth of HIV genetic network. In: *24th International Bioinformatics Workshop on Virus Evolution and Molecular Epidemiology*. Hong Kong China. 2019 August 4-9.

13. Chan CP, Wong NS, Lee SS. Estimated vaccination coverage of vaccine-preventable diseases among nurses in Hong Kong. In: *Hong Kong College of Community Medicine Annual Scientific Meeting*. Hong Kong, China. 2019 September 28.
14. Lau LHW, Wong NS, Lee SS. Acceptability of biannual influenza vaccination schedule among health care professionals in Hong Kong. In: *Hong Kong College of Community Medicine Annual Scientific Meeting*. Hong Kong, China. 2019 September 28.
15. Kwan TH, Wong NS, Lui GCY, Chan KCW, Tsang OTY, Leung WS, Ho KM, MP Lee, Lam W, Chan SN, Chan DPC, To SWC, Yam WC, Lee SS. HIV transmission links between past and newly diagnosed infections: A molecular epidemiology study. [abstract] In: *Lancet CAMS Health Conference 2019*. Chengdu, China. 2019 October 19-20.
16. Lau JYC, Wong NS, Lee K, Lee SS. Perception of condom use in the era of pre-exposure prophylaxis (PrEP): A qualitative analysis. [PE30/20] In: *17th European AIDS Conference*. Basel, Switzerland. 2019 November 6-9.
17. Lau JYC, Wong NS, Lee K, Lee SS. Users' perspective of an ideal service model for delivering pre-exposure prophylaxis (PrEP) to men who have sex with men. [PE28/9] In: *17th European AIDS Conference*. Basel, Switzerland. 2019 November 6-9.
18. Wong NS, Chan K, Chan WK, Lin A, Leung CC, Lee SS. Association between immunological status and TB disease development in HIV-infected individuals with LTBI. [PE35/6] In: *17th European AIDS Conference*. Basel, Switzerland. 2019 November 6-9.
19. Wong NS. 愛滋病毒感染者的定期潛伏性結核感染篩查策略. In: 粵港澳大灣區結核病控制學術研討會 (*Tuberculosis Symposium*). Hong Kong, China. 2019 June 22.
20. Wong NS. Should repeat LTBI screening be performed in HIV patients. In: *Infection 2019*. Hong Kong, China. 2019 June 11.
21. Kam KM, Chan CP, Kwok KO, Wei VWI, Lee SS. *In vitro* activity of delamanid against wild type clinical strains of Mycobacterium tuberculosis strains in Hong Kong. In: *4th International Interscience Conference on Infection and Chemotherapy (ICIC) & 12th International Symposium on Antimicrobial Agents and Resistance (ISAAR)*. Gyeongju, Korea. 2019 September 26-28.

C. Others

1. Wong NS. Re-visiting the LTBI testing strategies among HIV-infected individuals in Hong Kong. In: *44th Scientific Committee on AIDS and STI (SCAS)*. Hong Kong, China. 2019 May 28.

MOLECULAR MICROBIOLOGY AND EMERGING INFECTIOUS DISEASES

Molecular Microbiology –
Clinical Meta-genomics



Principal Investigator

Professor Sunny Wong



Team

Thomas Kwong | Chun-kit Choi | Jing Zhu | Emily Kong | Jason Kang |
Shirley Zhang | Duncan Lai | Tai-cheong Chow | Cosmos Guo

Research Progress Summary

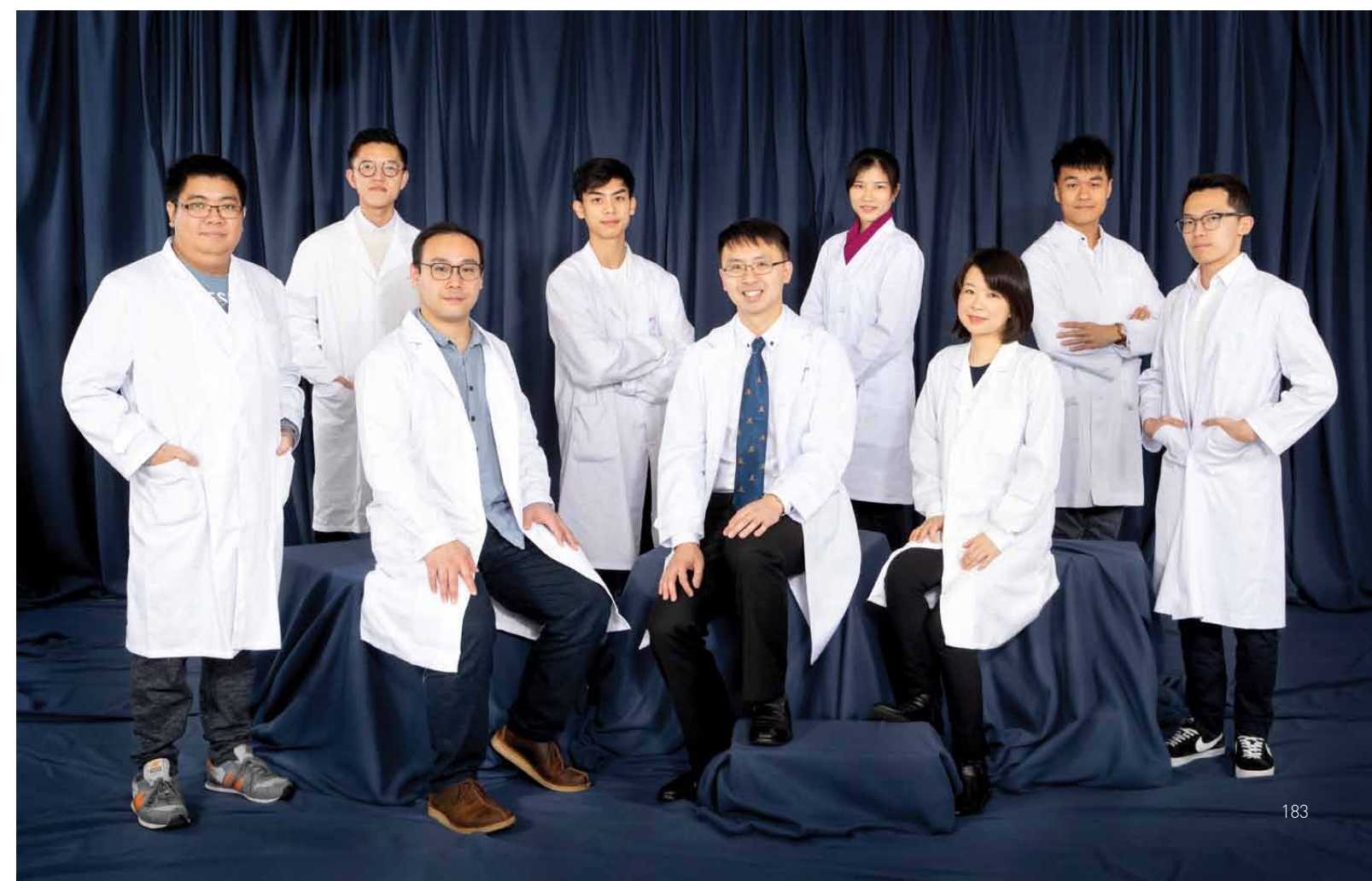
The major research focus of the research team led by Professor Sunny Wong is to investigate the gut host-microbe relationships in the context of digestive diseases, particularly gastrointestinal cancers and infections. Building upon their previous works (Wong SH *et al*, *Gastroenterology* 2017) (Dai Z *et al*, *Microbiome* 2018), they have continued to deepen their research into the genomic and metagenomic landscape of cancers (Wong and Wu, *Seminars in Cancer Biology* 2019). These include collaborative works to further investigate the colorectal cancer microbiota, developing novel bioinformatic methods (Dai Z *et al*, *Bioinformatics* 2019) and revealing new important microbial components in its carcinogenesis (Coker OO *et al*, *Gut* 2019). Furthermore, they have much interest in translating these

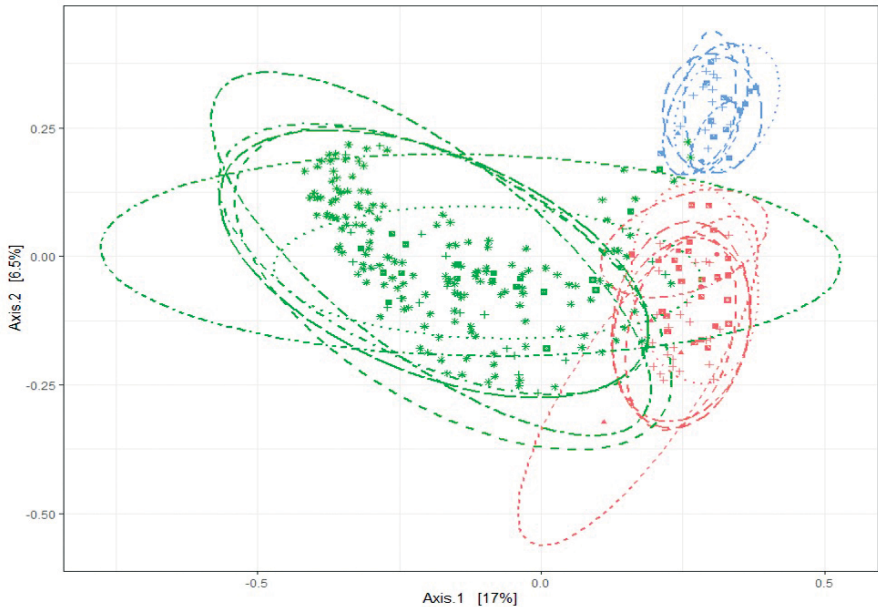
genomic findings into applications, such as biomarkers for enhancing early diagnosis and novel therapeutic options for cancer (Wong SH *et al*, *Seminars in Cancer Biology* 2019) (Wong and Yu, *Nature Reviews Gastroenterology & Hepatology* 2019).

Moreover, their continuing works in gastrointestinal infections have also borne fruits in 2019. Following their works on the local epidemiology of *Clostridioides difficile* (Ho J *et al*, *Emerging Infectious Diseases* 2017) (Chow VC *et al*, *Scientific Reports* 2017), they have continued to study and explore novel ways of its diagnosis and treatment, such as using fluorescent magnetic microrobots for toxin detection (Zhang Y *et al*, *Science Advances* 2019) or using fecal transplantation as a novel therapy for recurrent cases (Lui RN *et al*, *Hong Kong Medical Journal*

2019). Currently, they are prospectively collecting clinical samples for further works in its molecular epidemiology and disease mechanisms.

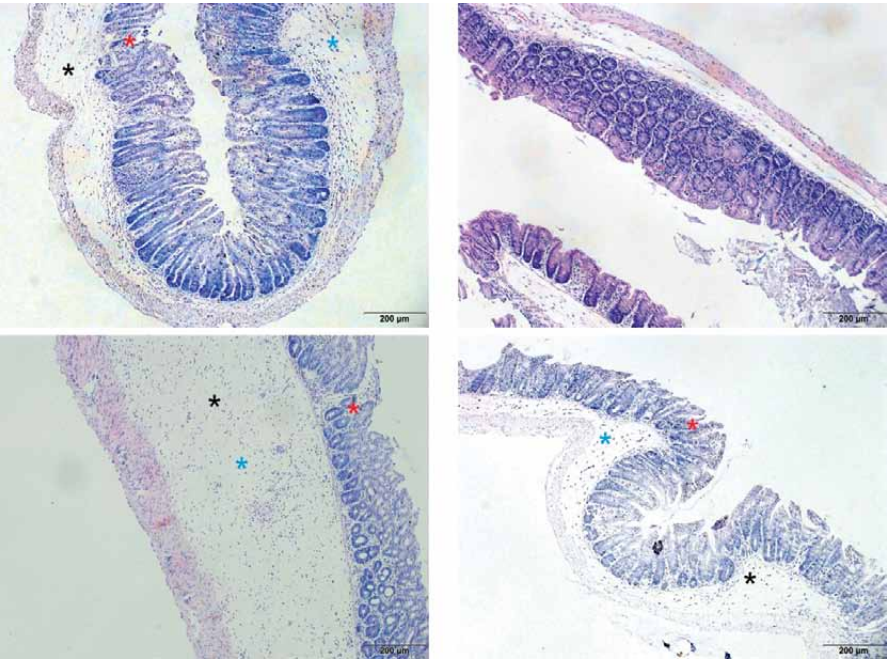
The team has been an active player for dissemination of scientific knowledge in 2019. Members of the research team have presented at international conferences, including the United States Digestive Disease Week, the Taiwan Digestive Disease Week, and other international meetings. These translational 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.





Multi-dimensional scaling (MDS) plot showing the microbiota diversity of different colonic samples in patients with or without cancer.

Source: Professor Sunny Wong



Histology of mice infected with different strains of *Clostridioides difficile* in animal model. Asterisks indicate areas of inflammatory infiltration and epithelial tissue damage.

Source: Professor Sunny Wong

■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Sunny Wong	Excellent Young Scientists Fund, National Natural Science Foundation of China
Chun-kit Choi	Top Prize, Hong Kong Medical and Healthcare Device Industries Association Student Research Awards
	Champion, HKIE Materials Division: Best Paper on Materials 2019
	Poster Presentation Award 2019, Plasmonically-Powered Processes Conference, Gordon Research Conference

Academic Editorship

Member's Full Name	Details
Sunny Wong	Associate Editor, Journal of Gastroenterology and Hepatology
	Editorial Board Member, Gut
	Editorial Board Member, Scientific Reports

Reviewer of Journal / Conference

Member's Full Name	Details
Sunny Wong	Grant Reviewer, Singapore National Medical Research Council
	Grant Reviewer, Swiss National Science Foundation
	Grant Reviewer, National Science Foundation (US)

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 Syndrom	Council for the AIDS Trust Fund	01/04/2018	31/03/2019	453,735
Sunny Wong	Clarifying the Mechanisms of Ribotype 002 Virulence in Clostridium Difficile Infection	Research Grant Council – General Research Fund/ Early Career Scheme	01/01/2017	31/12/2019	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 Grant Council – General Research Fund	01/01/2018	31/12/2020	1,132,030
Sunny Wong	Development of Novel Polymer-based Oral Sequestrants for Treatment of Cardiometabolic Diseases	Innovation and Technology Commission – Innovation and Technology Fund	01/02/2019	31/01/2021	4,459,700

Publications

A. Journal Papers

1. Wong SH, Yu J. Gut microbiota in colorectal cancer: Mechanisms of action and clinical applications. *Nature Reviews Gastroenterology & Hepatology*. 2019;16(11):690-704. doi:10.1038/s41575-019-0209-8 (Review).
2. Wong SH, Kwong TNY, Wu CY, Yu J. Clinical applications of gut microbiota in cancer biology. *Seminars in Cancer Biology*. 2019;55:28-36. doi:10.1016/j.semcancer.2018.05.003 (Review).
3. Wong SH, Wu WKK. Cancer genomics: From benchtop to bedside. *Seminars in Cancer Biology*. 2019;55:iii-iv. doi:10.1016/j.semcancer.2019.03.001 [Editorial].
4. Dai Z, Wong SH, Yu J, Wei Y. Batch effects correction for microbiome data with Dirichlet-multinomial regression. *Bioinformatics*. 2019;35(5):807-814. doi:10.1093/bioinformatics/bty729.
5. 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.
6. Wang S, Huang J, Li C, Zhao L, Wong CC, Zhai J, Zhou Y, Deng W, Zeng Y, Gao S, Zhang Y, Wang G, Guan XY, Wei H, Wong SH, He HH, Shay JW, Yu J. MAP9 loss triggers chromosomal instability, initiates colorectal tumorigenesis, and is associated with poor survival of patients with colorectal cancer. *Clinical Cancer Research*. 2019;26(3):746-757. doi:10.1158/1078-0432.CCR-19-1611 [Epub in 2019].
7. Hu W, Chan H, Lu L, Wong KT, Wong SH, Li MX, Xiao ZG, Cho CH, Gin T, Chan MTV, Wu WKK, Zhang L. Autophagy in intracellular bacterial infection. *Seminars in Cell & Developmental Biology*. 2019; 101:41-50. doi: 10.1016/j.semcdb.2019.07.014 [Epub in 2019] (Review).
8. Ho IHT, Liu X, Zou Y, Liu T, Hu W, Chan H, Tian Y, Zhang Y, Li Q, Kou S, Chan CS, Gin T, Cheng CHK, Wong SH, Yu J, Zhang L, Wu WKK, Chan MTV. A novel peptide interfering with proBDNF-sortilin interaction alleviates chronic inflammatory pain. *Theranostics*. 2019;9(6):1651-1665. doi:10.7150/thno.29703.
9. Chen X, Chan H, Zhang L, Liu X, Ho IHT, Zhang X, Ho J, Hu W, Tian Y, Kou S, Chan CS, Yu J, Wong SH, Gin T, Chan MTV, Sun X, Wu WKK. The phytochemical polydatin ameliorates non-alcoholic steatohepatitis by restoring lysosomal function and autophagic flux. *Journal of Cellular Molecular Medicine*. 2019;23(6):4290-4300. doi:10.1111/jcmm.14320.
10. Zhang Y, Zhang L, Yang L, Vong CI, Chan KF, Wu WKK, Kwong TNY, Lo NWS, Ip M, Wong SH, Sung JJY, Chiu PWY, Zhang L. Real-time tracking of fluorescent magnetic spore-based microrobots for remote detection of C. diff toxins. *Science Advances*. 2019;5(1):eaau9650. doi:10.1126/sciadv.aau9650.
11. Wong J, Chopra J, Chiang LLW, Liu T, Ho J, Wu WKK, Tse G, Wong SH. The role of connexins in gastrointestinal diseases. *Journal of Molecular Biology*. 2019;431(4):643-652. doi:10.1016/j.jmb.2019.01.007 (Review).
12. Lai CY, Sung J, Cheng F, Tang W, Wong SH, Chan PKS, Kamm MA, Sung JJY, Kaplan G, Chan FKL, Ng SC. Systematic review with meta-analysis: Review of donor features, procedures and outcomes in 168 clinical studies of faecal microbiota transplantation. *Alimentary Pharmacology & Therapeutics*. 2019;49(4):354-363. doi:10.1111/apt.15116.
13. Degenhardt F, Wendorff M, Wittig M, Ellinghaus E, Datta LW, Schembri J, Ng SC, Rosati E, Hübenthal M, Ellinghaus D, Jung ES, Lieb W, Abedian S, Malekzadeh R, Cheon JH, Ellul P, Sood A, Midha V, Thelma BK, Wong SH, Schreiber S, Yamazaki K, Kubo M, Boucher G, Rioux JD, 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*. 2019;28(12):20782092. doi:10.1093/hmg/ddy443.



MOLECULAR MICROBIOLOGY AND EMERGING INFECTIOUS DISEASES

Emerging Infectious Diseases – Enteric Infections



Principal Investigator

Professor Martin Chan



Team

Erin Tse | Jenny Chan | Miko Zhang | Paul Lau

Research Progress Summary

Professor Martin Chan and his team focus on studying molecular epidemiology and pathogenesis of human norovirus. This virus is the leading cause of acute gastroenteritis, accounting for 18% of all-cause diarrhea in all age groups worldwide. In 2015, the World Health Organization (WHO) report on the global burden of foodborne

illnesses, norovirus was, to the surprise of many, ranked the first as the key global cause of foodborne diarrhoeal diseases, surpassing all bacteria combined. Norovirus is without doubt a clinically important pathogen of public health impact. Since 2012, the research team has established a laboratory-based surveillance system in hospitalised patients in Hong Kong to untangle norovirus genotype distribution and to monitor the emergence of novel strains. They were among the first to report the emergence of two new norovirus genotypes, GII.17 in 2014 and GII.2 in 2016, that caused widespread outbreaks in Asia and part of Europe. They had completed



an international study of 13 countries from five continents to investigate the global spread of norovirus GII.17. Phylogeographic and haplotype network analyses suggested that Hong Kong may act as an epicentre of new noroviruses. Recently, they have identified a potential new norovirus pandemic variant, GII.4 HK, that was named after Hong Kong. Considering the strategic role of Hong Kong in global norovirus transmission, the group was invited by the National Calicivirus Laboratory of the US CDC in 2018 to join NoroSurv, which is a global pediatric norovirus surveillance network for young children. This network aims to guide norovirus vaccine strain selection in the future. Apart from virus surveillance, they are also actively using the stem cell-derived organoid model to dissect the disease-causing mechanism of norovirus. Their long-term goal is to develop into a world-leading laboratory for norovirus surveillance and pathogenesis to reduce the disease burden of viral gastroenteritis.



Small intestinal organoid culture grown on three-dimensional matrix.

Source: Professor Martin Chan

■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Jenny Chan	International Student Travel Grant, 7 th International Calicivirus Conference, 13-17 October 2019, Sydney, Australia

Academic Editorship

Member's Full Name	Details
Martin Chan	Associate Editor, BMC Infectious Diseases
	Member, Editorial Board, Journal of Virological Methods
	Member, Editorial Board, Scientific Reports (Microbiology)

Reviewer of Journal / Conference

Member's Full Name	Details
Martin Chan	Reviewer, Annals of Internal Medicine
	Reviewer, Infection, Genetics and Evolution
	Reviewer, Applied and Environmental Microbiology
	Reviewer, Journal of Medical Virology
	Reviewer, Journal of Virological Methods
	Reviewer, Emerging Infectious Diseases
	Reviewer, Influenza and Other Respiratory Viruses
	Reviewer, BMC Infectious Diseases
	Reviewer, Clinical Microbiology and Infection

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Martin Chan	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
Martin Chan	Host Interactome of Human Norovirus Structural Proteins	Research Grants Council – General Research Fund	01/01/2017	30/06/2020	922,492
Martin Chan	Generation of Host Genetic Factor Information Known to Associate with Hospitalized Severe Influenza	Food and Health Bureau – Health and Medical Research Fund (Commissioned)	01/09/2019	31/08/2022	955,432
Martin Chan	Glycan Array-based High-throughput Screening for Carbohydrate Binding Profile of Emerging Norovirus Genotypes	CUHK Faculty of Medicine – Medicine Panel Internal Review Scheme	01/10/2017	30/09/2019	30,000
Martin Chan	Use of Next-generation Sequencing to Identify New Intestinal Viruses Associated with Unexplained Acute Gastroenteritis	Food and Health Bureau – Health and Medical Research Fund (commissioned)	01/07/2017	31/06/2019	392,761

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Martin Chan	Discovery of Novel/Unrecognized Viruses Associated with Unexplained Acute Syndromes in Immunocompromised Patients	Food and Health Bureau – Health and Medical Research Fund (Commissioned)	01/07/2017	30/06/2019	329,793
Martin Chan	Identification of Novel/Unrecognized Viruses Associated with Unexplained Severe Acute Respiratory Illnesses	Food and Health Bureau – Health and Medical Research Fund (Commissioned)	01/01/2017	30/06/2019	329,793
Martin Chan	Characteristics and Clinical Relevance of Microbiome Changes in Severe Influenza and Respiratory Syncytial Virus Infection	Food and Health Bureau – Health and Medical Research Fund (Commissioned)	01/01/2016	30/06/2019	329,793

■ Publications

A. Journal Papers

1. Chhabra P, de Graaf M, Parra GI, Chan MC, Green KY, Martella V, Wang Q, White PA, Katayama K, Vennema H, Koopmans MP, Vinjé J. Updated classification of norovirus genogroups and genotypes. *Journal of General Virology*. 2019;100(10):1393-1406. doi:10.1099/jgv.0.001318.

B. Conference Papers / Oral Presentation / Poster Presentation

1. Chan MC, Zhang LY, Guo LT, Chan PK. Metagenomic identification and winter seasonality of picobirnavirus in stool of hospitalized patients with acute gastroenteritis. In: *22nd European Society for Clinical Virology Annual Meeting*. Copenhagen, Denmark. 2019 September 11-14.
2. Chan MC, Mohammad KN, Zhang LY, Lam WL, Cheng FW, Chan PK. Detection of human pegivirus in blood of immunocompromised children with acute myeloid leukemia. In: *67th Annual Meeting of the Japanese Society for Virology*. Tokyo, Japan. 2019 October 29-31.
3. Chan JC, Mohammad KN, Zhang LY, Wong SH, Chan MC. Norovirus-induced immune response in human intestinal enteroids. In: *7th International Calicivirus Conference*. Sydney, Australia. 2019 October 13-17.
4. Chan MC. Rise of non-GII.4 capsids and GII.P16 polymerase in norovirus gastroenteritis. In: *7th International Calicivirus Conference*. Sydney, Australia. 2019 October 13-17. (Invited State-of-the-art talk)

C. Book Chapter

1. Chan MC and Chan JC. Human organoids: Past, present, and future. In: A. Chan (Ed.), *Biotechnology in Hong Kong Volume IV*(pp. 15-27). New York: United States-China Intellectual Property Institute Inc.

INFLAMMATORY DISEASES



Principal Investigator

Professor Hui-yao Lan



Team

Xiaoru Lan | Guangyu Lian | Thomas Mak | Biao Wei | Choilai Chung |
Yuyan Qin | Huijun He | Jiaoyi Chen | Yueyu Gu | Junzhe Chen |
Qixia Shen | Honglian Wang | Zhongjing Hu | Liying Liang | Ruizhi Tan |
Wenbiao Wang | Wenqian Xu



has also received support from RGC high Impact Research Fund. Thus, they are continuous to research on the new mechanisms of TGF- β /Smad3 signalling in diabetic complications, tissue fibrosis and tumour microenvironment. Third, with the support by RGC CRF grant, their research development into study the specific role of macrophage TLR4 in crescentic glomerulonephritis has made a great progress with several novel findings that deletion of TLR4 from macrophages resulted in the shift from inflammatory macrophages to the anti-inflammatory macrophages and importantly, the Th1 and Th17 T cells to Treg cells. Such important

Research Progress Summary

The research team led by Professor Hui-yao Lan has a very successful year in 2019 in research development. First, they have developed a new research area to explore the neuroimmune mechanisms in acute kidney and heart diseases by identifying a new neuron peptide-producing immune cell (CD68+NPY+). Their preliminary results demonstrated that this new cell type plays a critical role in protection against acute kidney and heart diseases. Importantly, they have also found that NPY may be a novel therapeutic agent for both acute kidney disease and heart disease. This new finding has resulted in one Research Grants Council (RGC) Collaborative Research Fund (CRF) grant support. Second, their research project on the role of Smad3 in diabetic kidney disease has been funded by the Hong Kong Health and Medical Research Fund and the development of new nanoSmad3



findings have encouraged collaboration with the kidney transplantation team from the Zhejiang University.

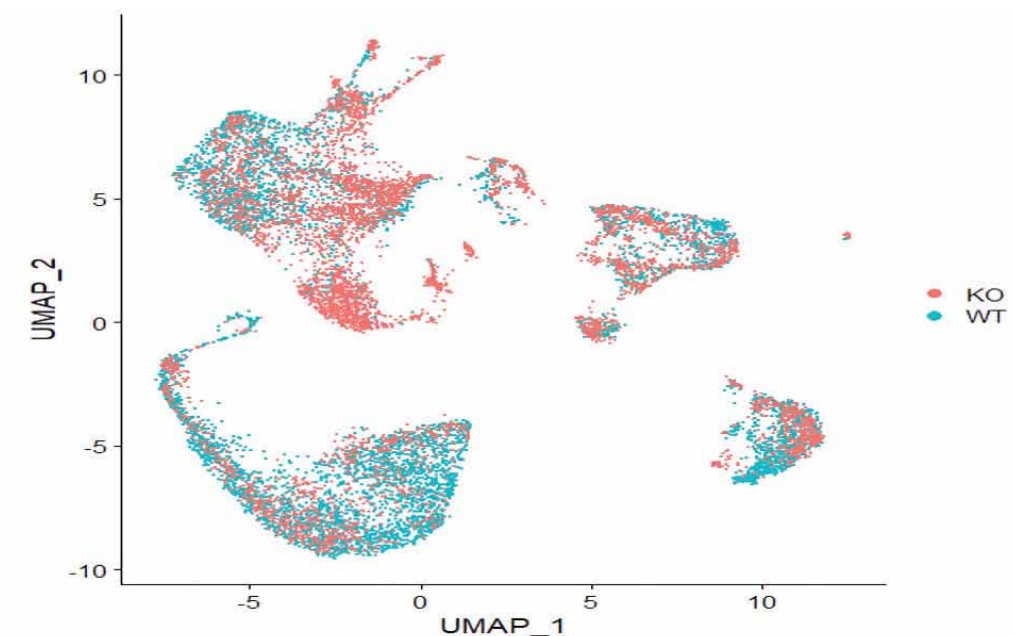
The team is also working hard to develop new drugs including Smad3 targeted nanomedicines and novel Smad3 inhibitors as anticancer drugs and immunotherapy for diabetes in animal experimental models. These translational research projects will continue to be the research direction of the team in the next few years.

Collaborations are always important. Under the Greater Bay Area policies, the team has been successfully awarded a Joint Laboratory with the Guangdong People's Hospital "The Guangdong-Hong Kong Joint Laboratory for Immune and Genetic Kidney Disease" by Guangdong Provincial ST. In addition, in collaboration with BGI Shenzhen, an advanced technology by using

Single Cell RNA Sequencing has been widely used in their research approaches.

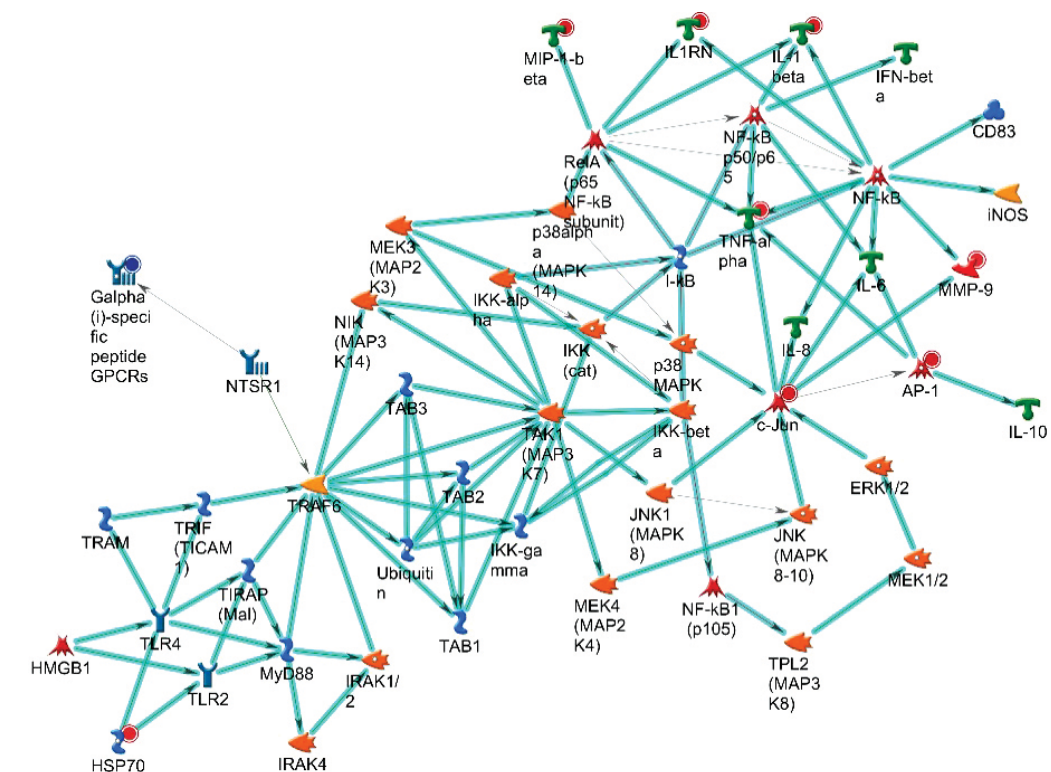
In the past year, team members have been awarded at the international, regional and local academic conferences which improved their academic standards and enhanced the reputation of The Chinese University of Hong Kong. Research training is another goal for their team. Over the past year, 2 PhD students, 7 post-doctoral fellows (2 from Hong Kong-China Scholar programme) have been trained in their laboratory. Based on the excellent progress of all research projects, the team released 15 peer-reviewed papers in 2019.

In summary, 2019 was a year worthy of the team's respect, and they look forward to achieving even greater goals in 2020.



10X genomics single cell sequencing integrated analysis in Seurat v3.5.1 for transcriptome profiles from two groups of transgenic mice with experimental crescentic glomerulonephritis.

Source: Professor Hui-yao Lan



MetaCore analytical suite illustrated a Toll Like Receptor 4 downstream signalling enriched network reconstructed with pro-inflammatory macrophage-dependent differentially expressed genes in mouse crescentic glomerulonephritis.

Source: Professor Hui-yao Lan

■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Honglian Wang	Young Investigators Oral Presentation Award, Diabetic & Cardiovascular Risk Factors - East Meet West symposium, 28-29 September 2019
Thomas Mak	Outstanding Oral Presentation-2 nd Prize, Annual Scientific Meeting, The Institute of Cardiovascular Science & Medicine of Hong Kong, 9 November 2019
Jinhong Li	The Outstanding Scientific Presentation Award and Travel Grant Award, ERA-EDTA, 13-16 June 2019
Hui-yao Lan	Consultant of Guangdong, Hong Kong and Macao Medical Health and Pathology Alliance Committee. 2019-2022
	Expert Consultation on Hygiene and Health Cooperation in Guangdong, Hong Kong and Macau Greater Bay Area. 2018-2021
	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
	Vice Chairperson of 2 nd Board of Specialty Committee of Immunology of TCM of World Federation of Chinese Medicine Societies. 2018-2023

Academic Editorship

Member's Full Name	Details
Hui-yao Lan	Editor, Clinical and Experimental Pharmacology and Physiology
	Associate Editor, Journal of Clinical and Molecular Medicine (JCMM)
	Associate Editor, Frontiers in Psychology

Reviewer of Journal / Conference

Member's Full Name	Details
Hui-yao Lan	Reviewer, Journal of American Society of Nephrology (JASN)
	Reviewer, Molecular Therapy
	Reviewer, Scientific Reports
	Reviewer, Kidney Disease

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Hui-yao Lan	Protective Role of Neuropeptide Y (NPY) in Acute Kidney Injury	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	831,301
Hui-yao Lan	Translating Multi-omic Discoveries to Transform Diabetes Care and Reduce Diabetic Complications	Research Grants Council – Research Impact Fund	01/03/2019	28/02/2024	11,980,232
Hui-yao Lan	Prevention and Treatment of Type 2 Diabetes and Diabetic Complications by Targeting Smad3 with a Smad3 Inhibitor SIS3	Food and Health Bureau – Health and Medical Research Fund	01/04/2019	31/03/2022	1,500,000
Hui-yao Lan	Terminal Shortening Triggers the Molecular Regulation Mechanism of Neutrophil Capture in Acute Kidney Injury	Research Grants Council – Collaborative Research Fund	01/01/2019	31/12/2020	RMB 500,000
Hui-yao Lan	Development of a Novel Virus-free Anticancer Gene Therapy: USMB-shMincle	Innovation and Technology Commission – Innovation and Technology Fund	01/01/2019	30/06/2020	1,391,500
Hui-yao Lan	Regulatory Role and Mechanism of Smad3 in Immunosuppression of Neutrophil Anticancer Activities	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	1,151,040
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
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	Mechanism of Renal Inflammation: Role of Toll-like Receptor 4	Research Grants Council –Collaborative Research Fund	30/06/2017	29/06/2020	7,518,927

Publications

A. Journal Papers

1. Wang H, Sheng J, He H, Chen X, Li J, Tan R, Wang L, Lan HY. A simple and highly purified method for isolation of glomeruli from the mouse kidney. *American Journal of Physiology-Renal Physiology*. 2019;317(5):F1217-F1223. doi:10.1152/ajprenal.00293.2019.
2. Xu BH, Sheng J, You YK, Huang XR, Ma RCW, Wang Q, Lan HY. Deletion of Smad3 prevents renal fibrosis and inflammation in type 2 diabetic nephropathy. *Metabolism*. 2019;103:154013. doi:10.1016/j.metabol.2019.154013 [Epub in 2019].
3. Yang Q, Ren GL, Wei B, Jin J, Huang XR, Shao W, Li J, Meng XM, Lan HY. Conditional knockout of TGF- β RII/Smad2 signals protects against acute renal injury by alleviating cell necroptosis, apoptosis and inflammation. *Theranostics*. 2019;9(26):8277-8293. doi:10.7150/thno.35686.
4. Tan RZ, Wang C, Deng C, Zhong X, Yan Y, Luo Y, Lan HY, He T, Wang L. Quercetin protects against cisplatin-induced acute kidney injury by inhibiting Mincle/Syk/NF- κ B signaling maintained macrophage inflammation. *Phytotherapy Research*. 2020;34(1):139-152. doi:10.1002/ptr.6507.
5. Li J, Yang KY, Tam RCY, Chan VW, Lan HY, Hori S, Zhou B, Lui KO. Regulatory T-cells regulate neonatal heart regeneration by potentiating cardiomyocyte proliferation in a paracrine manner. *Theranostics*. 2019;9(15):4324-4341. doi:10.7150/thno.32734.
6. You YK, Luo Q, Wu WF, Zhang JJ, Zhu HJ, Lao L, Lan HY, Chen HY, Cheng YX. Petchiether A attenuates obstructive nephropathy by suppressing TGF- β /Smad3 and NF- κ B signalling. *Journal of Cellular And Molecular Medicine*. 2019;23(8):5576-5587. doi:10.1111/jcmm.14454.
7. Zhang YY, Tang PM, Tang PC, Xiao J, Huang XR, Yu C, Ma RCW, Lan HY. LRNA9884, a novel Smad3-dependent long noncoding RNA, promotes diabetic kidney injury in db/db mice via enhancing MCP-1-dependent renal inflammation. *Diabetes*. 2019;68(7):1485-1498. doi:10.2337/db18-1075.
8. Li JH, Tang Y, Lv J, Wang XH, Yang H, Tang PMK, Huang XR, He ZJ, Zhou ZJ, Huang QY, Klug J, Meinhardt A, Fingerle-Rowson G, Xu AP, Zheng ZH, Lan HY. Macrophage migration inhibitory factor promotes renal injury induced by ischemic reperfusion. *Journal of Cellular and Molecular Medicine*. 2019;23(6):3867-3877. doi:10.1111/jcmm.14234.
9. Tang TT, Lv LL, Lan HY, Liu BC. Extracellular vesicles: Opportunities and challenges for the treatment of renal diseases. *Frontiers in Physiology*. 2019;10(MAR). doi:10.3389/fphys.2019.00226 [Review].
10. Tang PM, Nikolic-Paterson DJ, Lan HY. Macrophages: Versatile players in renal inflammation and fibrosis. *Nature Reviews Nephrology*. 2019;15(3):144-158. doi:10.1038/s41581-019-0110-2 [Review].
11. Zhang J, Lan HY, Wan S. Letter by Zhang *et al* regarding article, "Heart failure stimulates tumor growth by circulating factors." *Circulation*. 2019;139(5):718-719. doi:10.1161/CIRCULATIONAHA.118.037275 [Letter].
12. Tan RZ, Liu J, Zhang YY, Wang HL, Li JC, Liu YH, Zhong X, Zhang YW, Yan Y, Lan HY, Wang L. Curcumin relieved cisplatin-induced kidney inflammation through inhibiting Mincle-maintained M1 macrophage phenotype. *Phytomedicine*. 2019;52:284-294. doi:10.1016/j.phymed.2018.09.210.

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 RNA polymerase II subunit 5-mediating protein causes myocardial dysfunction and heart failure. *Cardiovascular Research*. 2019;115(11):1617-1628. doi:10.1093/cvr/cvy307.
14. 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 HY, Tsui SKW, Fan X, Szeto CC, So WY, Chan JCN, Ma RCH, for the Hong Kong Diabetes Register TRS Study Group. 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.

B. Conference Papers

1. Li JH, Zhu WJ, Yang H, Tang P, Hong L, Huang XR, Xu AP, Zheng ZH, Lan HY. A negative regulatory role of Smad3 in B cell activation in lupus nephritis via the E4BP4-Mincle-Syk dependent mechanism. In: *World Congress of Nephrology*. Melbourne, Australia. 2019 April 12-15.
2. Yang F, Huang XR, Yiu WH, Tang SCW, Lan HY. Deficiency of myeloid specific toll-like receptor 4 protects against crescentic glomerulonephritis via inhibition of macrophage-mediated immune response and macrophage-myofibroblast-mediated fibrosis. In: *World Congress of Nephrology*. Melbourne, Australia. 2019 April 12-15.
3. Huang XR, Yang F, Yiu WH, Tang SCW, Lan HY. Loss of toll-like receptor 4 in macrophage inhibits renal fibrosis by mitigating TGF β /Smad3 signaling via the bambi-dependent mechanism in obstructive nephropathy. In: *World Congress of Nephrology*. Melbourne, Australia. 2019 April 12-15.
4. Tang PMK, Zhang Y, Hung JSC, Huang XiaoR, Lan HY. A novel DPP4/CD32b/NF-kappa B circuit is essential for CRP-driven type-2 diabetic nephropathy. In: *World Congress of Nephrology*. Melbourne, Australia. 2019 April 12-15.
5. He HJ, Wang HL, Huang XR, Lan HY. Hepatic steatosis in type 2 diabetic mice is improved by targeting Smad3 with a Smad3 inhibitor SIS3. In: *21st Diabetes and Cardiovascular Risk Factors – East Meets West Symposium*. Hong Kong, China. 2019 September 28–29.
6. Wang HL He HJ, Huang XR, Lan HY. Smad3 deficiency promotes β cell proliferation and ameliorates diabetes by targeting E2F3, a key regulator for G1/S entry. In: *21st Diabetes and Cardiovascular Risk Factors – East Meets West Symposium*. Hong Kong, China. 2019 September 28–29.
7. Gu YY, Liu X, Huang XR, Lan HY. The protective effects of quercetin on diabetic nephropathy by balancing the TGF- β /Smad signaling pathway. In: *21st Diabetes and Cardiovascular Risk Factors – East Meets West Symposium*. Hong Kong, China. 2019 September 28–29.

C. Book Chapter

1. Meng XM, Mak TS, Lan HY. Macrophages in renal fibrosis. *Advances in Experimental Medicine and Biology*. 2019:285-303. doi:10.1007/978-981-13-8871-2_13.

INFLAMMATORY DISEASES



Principal Investigator

Professor Erik Fung



Team

Leong Ting Lui | King Fai Cheng | Samantha Leung |
Behzad Nasiri Ahmadabadi | Alex Fung | Xiaobo Yang | Suyi Xie |
Hangqi Luo | Donghao Guo | Yanny Wong

Research Progress Summary

The Third Asia Pacific Advanced Heart Failure Forum (APAHFF) was successfully held in Macau on 14 December 2019. The Forum was opened by Professor Jackie Taylor, President of the Royal College of Physicians and Surgeons of Glasgow (UK), and the Keynote Lecture was delivered by Professor Marc Alan Pfeffer, the Victor Dzau Professor of Medicine, Harvard Medical School, USA. APAHFF 2019 also marks the inauguration of the Asian CardioGeriatric Association, an interest group established to advanced geriatric cardiology care, management and research. APAHFF continues to be a premiere regional meeting for heart failure specialists,

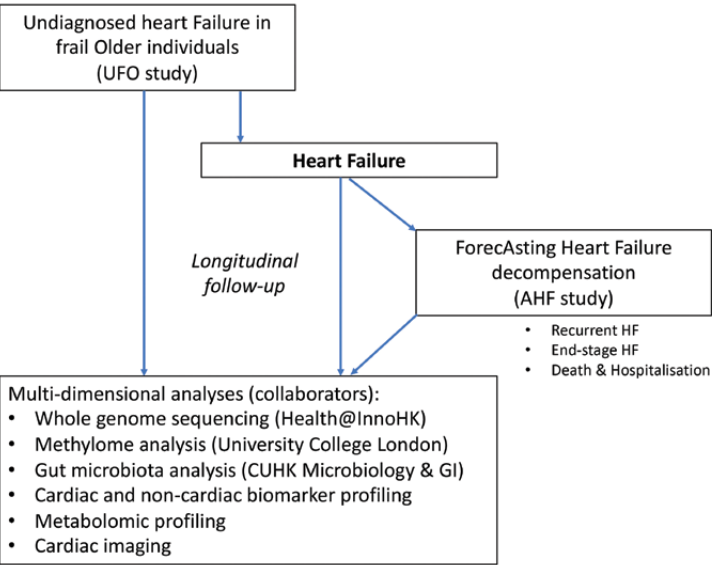
ranging from cardiologists, cardiac surgeons, intensivists, geriatricians, internists, palliative physicians, nurses to others with an interest in advanced cardiovascular disease. The platform was enabled research networks to be established. Through APAHFF, Professor Erik Fung has been able to foster research collaborations with researchers at Royal Papworth Hospital (Cambridge, UK), Brigham and Women's Hospital (Boston, USA), University of New South Wales (Australia), Chiba University Hospital (Japan), National Heart Centre Singapore (Singapore), and Taipei Veterans General Hospital (Taiwan ROC). There are plans to potentially establish

a Joint Meeting with the Heart Failure Society of America in the near future.

For local collaborations, Professor Fung is continuing research activity at NTEC hospitals (Shatin Hospital, Alice Ho Miu Ling Nethersole Hospital and Tai Po Hospital) where community-living elderly and heart failure patients are being recruited. He will deepen collaborations with Nightingale Health, a Finnish metabolomics company.

Professor Fung is currently in the process of completing a patent application related to biomarker-guided metabolomic profiling to distinguish between cardiac and non-cardiac frailty.





Research Focus Areas of the Laboratory Heart Failure + Circulation Research (LHFCR) at LiHS.

Source: Professor Erik Fung

Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Qi Li	Poster presenter, European Society of Cardiology (ESC) Heart Failure 2019 – 6 th World Congress on Acute Heart Failure, Athens, Greece, 25–28 May 2019. (Poster P1716)
Xiaobo Yang	Poster presentation, ESC Heart Failure 2019 – 6 th World Congress on Acute Heart Failure, Athens, Greece, 25–28 May 2019. (Poster P2074)
Erik Fung	ESC Heart Failure 2019 – 6 th World Congress on Acute Heart Failure, Athens, Greece, 25–28 May 2019. (Poster P2073) 2019 Canadian Cardiovascular Congress, Montréal, Quebec, Canada, 24–27 October 2019. (ePoster Session 4, 102)
Xiaobo Yang	Poster presentation, ESC Asia, Singapore, 8–10 November 2019. (Poster P39)

Fellowships

Member's Full Name	Details
Erik Fung	European Certification (life-time), Heart Failure Association of the European Society of Cardiology

Academic Editorship

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

Reviewer of Journal / Conference

Member's Full Name	Details
Erik Fung	Journal Reviewer, Heart Asia (BMJ Publishing)
	Journal Reviewer, IEEE Access
	Journal Reviewer, Nephrology
	Journal Reviewer, Scientific Reports
	Journal Reviewer, Clinical Science (London, England)
	Journal Reviewer, European Journal of Emergency Medicine
	Journal Reviewer, Asia-Pacific Journal of Sports Medicine, Arthroscopy, Rehabilitation and Technology

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Erik Fung	VerlCiguaT Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA)	Merck Sharp & Dohme Corp.	01/01/2017	01/01/2020	825,987
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 Ltd.	01/06/2017	01/06/2021	79,591
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 (HARE 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 Inc.	01/01/2019	31/12/2023	2,399,028
Erik Fung	Tracking Longitudinal Changes in Serum Metabolomics Profile and Cardiac Function in an Established Longitudinal Cohort of Community-living Older Adults: a UFO Sub-study	CUHK Research Committee – Direct Grant	01/06/2019	01/06/2020	105,000
Erik Fung	Epidemiology and Temporal Trends of Myocarditis at Tertiary Referral Hospitals in Hong Kong and Taipei	CUHK Taiwan Collaboration Fund	01/07/2019	01/04/2020	14,000

Publications

A. Journal Papers

- 1. Woo J, Yang X, Lui LT, Li Q, Cheng KF, Lee APW, Lee JSW, Fung E. Utility of the FRAIL questionnaire in detecting heart failure with preserved ejection fraction. *The Journal of Nutrition, Health and Aging*. 2019;23(4):373-377. doi:10.1007/s12603-019-1158-1.
- 2. Teekakirikul P, Zhu W, Huang HC, Fung E. Hypertrophic Cardiomyopathy: An overview of genetics and management. *Biomolecules*. 2019;9(12):878. doi:10.3390/biom9120878 [Review].

B. Conference Papers

- 1. Fung E, Yang X, Lui LT, Li Q, Cheng KF, Sahota D, Fan Y, Lee JSW, Lee APW, Hui E, Woo J. Frailty, diastolic dysfunction and latent heart failure in the community-living elderly in Hong Kong: cross-sectional findings from the UFO study. *Journal of the American College of Cardiology*. 2019;73:1873. doi: 10.1016/S0735-1097(19)32479-9.
- 2. Kam KKH, Yu A, Fung E, Lee APW. Optimising heart failure care by Multi-disciplinary Heart Failure Clinic (MHFC). *Heart Asia*. 2019;11(Suppl 1):A2.
- 3. Lee APW, Kam KKH, Fung E, Chow J, Fan Y, Teekakirikul P, Wong K, Chan JYS, Chan D, Sheng B. Fabry disease in East Asia. *Heart Asia*. 2019;11(Suppl 1):A13.
- 4. Fung E. CardioMEMSTM in VAD patients. *Heart Asia*. 2019;11(Suppl 1):A11.
- 5. Fung E, Yang X, Li Q, Cheng KF, Liu S, Yau F, Sahota D, Fan Y, Lee APW, Lui LT, Woo J. Sarcopenia and cardiac dysfunction in community-living older adults. *European Journal of Heart Failure*. 2019;21, S1.
- 6. Li Q, Lui LT, Yang X, Liu S, Cheng KF, Lupón J, Bayés-Genís A, Sahota D, Woo J, Fung E. Association analysis of N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) and growth differentiation factor 15 (GDF-15) in cardiac and non-cardiac frailty. *European Journal of Heart Failure*. 2019;21, S1.
- 7. Yang X, Lui LT, Li Q, Cheng KF, Liu S, Yau F, Fan Y, Lee APW, Woo J, Fung E. Sarcopenia and reduced physical fitness are associated with cardiac dysfunction in community-living older adults. *European Journal of Heart Failure*. 2019;21, S1.
- 8. Ho C, Fung E, Tam LS. Analysis of survival associated with pulmonary arterial hypertension in patients with systemic lupus erythematosus. *Annals of the Rheumatic Diseases*. 2019;78: Suppl 2, 410
- 9. Yang X, Lui LT, Li Q, Cheng KF, Liu S, Yau F, Sahota D, Fan Y, Lee APW, Woo J, Fung E. Cross-sectional analysis of 6-minute walk distance and diastolic function in a Hong Kong cohort of community-living older adults. *European Journal of Heart Failure*. 2019;41: Suppl 1, P39.

C. Intellectual Property and Patents

- 1. Transcatheter self-expandable tricuspid valve replacement system. CUHK/Ref: 17/MED/765; US Provisional Application No. 62/886,245 filed on 13 August 2019.

D. Invited Oral Presentations

- 1. HFpEF, HFmrEF, HFrEF: How are they different? *Heart Failure Conference, Management Society for Healthcare Professionals*. Hong Kong, China. 2019 March 23-24.
- 2. Challenging cases in end-stage heart failure. British Medical Association (Hong Kong Branch) *Therapeutics Course on the Care for Serious Illness and Advanced Disease*: Heart. China Building, Central, Hong Kong, China. 2019 May 6.
- 3. Hypertension and heart failure. *Symposium on Better Self-Management of Blood Pressure – The Global Engagement of May Measurement Month*. Prince of Wales Hospital Auditorium, Shatin, Hong Kong, China. 2019 May 31.
- 4. When the right heart goes wrong. *Medical Grand Rounds*, CUHK. Prince of Wales Hospital, Hong Kong, China. 2019 June 19.



NEUROSCIENCE



Principal Investigator

Professor Owen Ko



Team

Danny Chan | Leo Yan | Jenny Zhang | Hei Ming Lai | Junzhe Huang |
Kuan Jung Wu | Becky Yung | Samuel Sy | Richard Li | Caroline Chen |
Yanling Jin | Fiona Fan | Yumi Tang

Research Progress Summary

Molecular Genetics and Glial Dysfunction in Neurological Diseases

The fundamental mechanism for maintaining central nervous system homeostasis is accomplished by the cohesive functioning of different cells, including vascular cells (e.g. endothelial cell, smooth muscle cell and pericyte) and glial cells (e.g. astrocyte, microglia and oligodendrocyte). Each of the brain cell types serves its specific yet intertwined physiological roles. Over the past decades, accumulating evidence points to causal roles of vascular and glial cell dysfunction in various neurodegenerative diseases. Professor Owen Ko and his research team

have adopted a multimodal approach combining molecular assays, *in vivo* functional and structural imaging, as well as single-cell transcriptomic profiling to uncover how ageing and neurodegenerative disease-related genetic mutations in Asian populations culminate in neurovascular, glial and neuronal dysfunction.

Recently, their work revealed endothelial cell subtype-dependent transcriptomic changes in the aged mouse brain, encompassing important functional pathways impacting blood-brain barrier (BBB) regulation, immune/cytokine signalling, energy metabolism and Alzheimer's disease (AD)-pathogenesis

especially in the capillary endothelium (Zhao L and Li Z *et al.*, manuscript under review; preprint: *bioRxiv*, 2019 Oct 10;800318). Importantly, they also discovered key expression changes with significant functional implications at the BBB that generalise to human aged subjects and AD patients. They went on to demonstrate a practical pharmacological approach for reversing ageing-associated changes, whereby treatment with glucagon-like peptide 1 receptor (GLP-1R) agonist can strongly reverse BBB leakage and the differential expressions in aged brain endothelium. This applies to genes mediating important BBB functions and those that exhibit concordant expressions changes in human aged or AD brains. Their study thus offers novel insights into neurovascular ageing, neurodegenerative diseases and therapeutics development.

They have presented this work at two conferences, including the Society for Neuroscience Annual Meeting 2019. They are

currently extending the approach to other neurovascular and glial cells, in both ageing and disease models.

Neural Circuits Underlying 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, larval zebrafish can already perform an incredible repertoire of innate behaviours including chemosensory behaviour, alongside phototaxis, oculomotor and optokinetic responses, prey capture and various escape responses. 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



brainwide activities mediating sensorimotor transformation with cellular resolution. They are interested in fundamental questions of how neural circuits in the brain process survival-relevant sensory cues to drive motor response. They have thus constructed an integrated microfluidics-behavioural and brainwide imaging system, to precisely manipulate the sensory environment of zebrafish larvae while performing volumetric whole-brain imaging of neuronal activities.

In both vertebrates and invertebrates, sensory organs often come in pairs with lateral anatomical locations. Despite well-known chemosensory avoidance behaviours in various



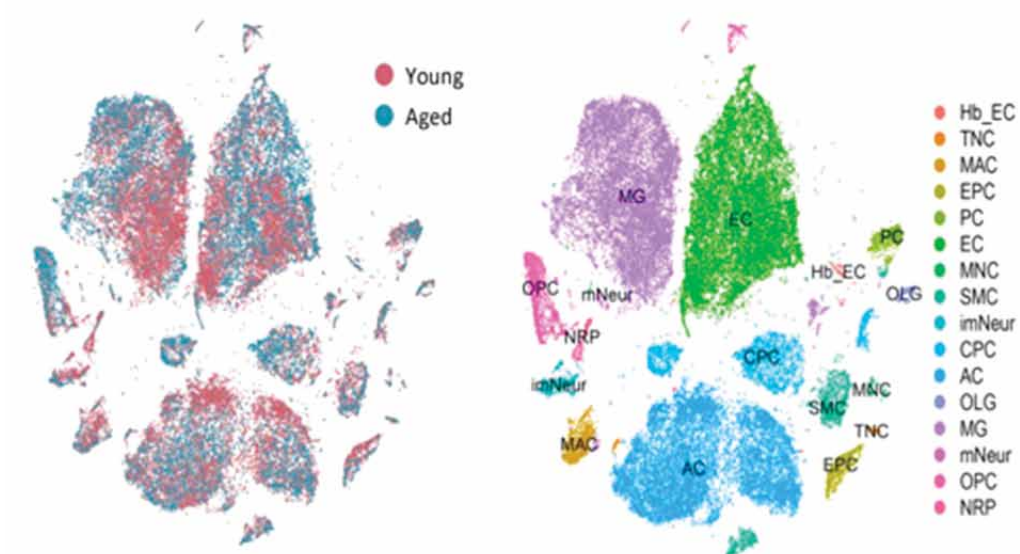
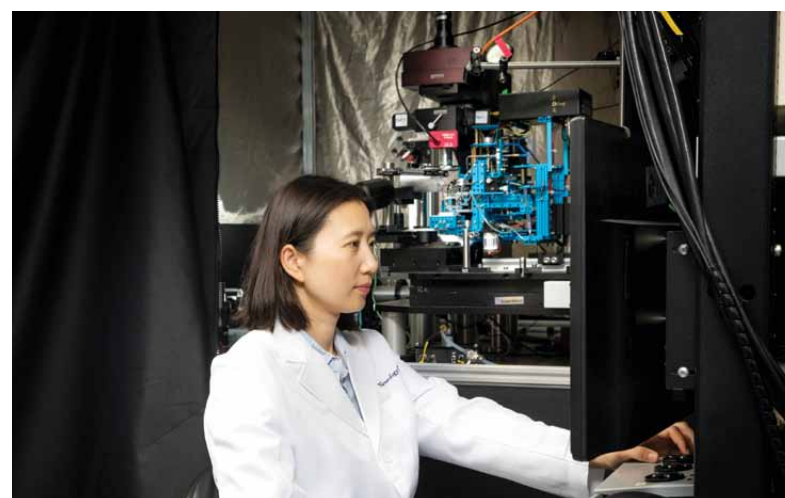
species, how bilateral olfactory inputs are integrated to guide these behaviours remains unknown. Utilising the system, in their recent work (Sy SKH *et al.*, manuscript in preparation), they uncovered navigational strategies that larval zebrafish employs to efficiently escape noxious chemical zones, a behaviour that requires bilateral olfactory input. By brainwide neuronal activity imaging, they found that a distributed neural representation characterised by a dichotomy of on / off responses, continua of left/right input selectivity and summation linearity emerge in the early olfactory pathway and diverse forebrain regions. These results revealed the neural basis of paired sensory organ input integration that drives downstream

sensorimotor transformation. This work has also been presented at the Society for Neuroscience Annual Meeting 2019 and will be submitted for publication soon.

ii. *Mus musculus* (Mouse)

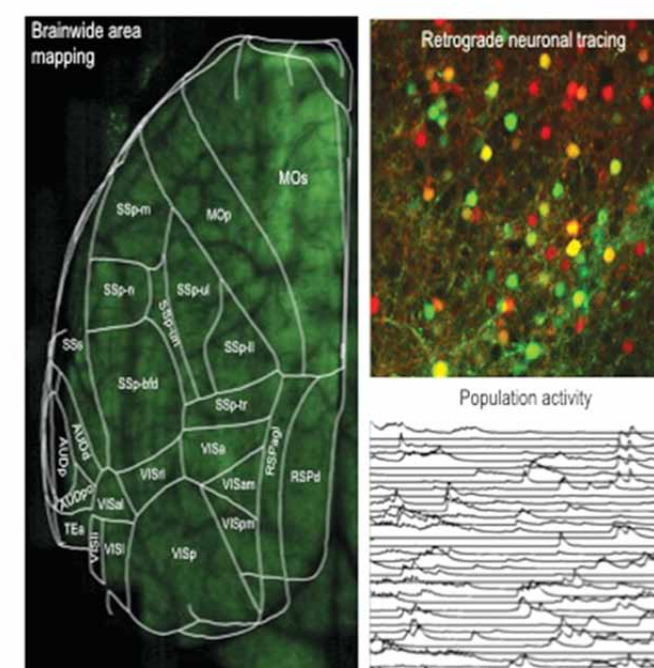
To survive in the wild, animals must be able to associate sensory cues with the need to perform corresponding motor responses. These processes involve coordinated neural activity and signal flow across primary sensory, association and motor areas. Often, sensorimotor tasks also necessitate the acquisition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

In their lab, they have developed fully automated behavioural and stimulation platforms on which mice learn to execute complex forelimb motor and general locomotor tasks in response to visual cues, while neuronal activities are recorded from different cortical areas by multiphoton microscopy. Combined with circuit tracing techniques, they are currently studying the rules governing the encoding of distinct task-related information along pathways connecting higher visual areas to association and motor areas.



tSNE-visualisation of single-cell transcriptomes. **Left panel:** single-cell transcriptomes from young adult (brown, 3 months old) and aged mouse brains (blue, 18 months old). **Right panel:** clustering of single-cell transcriptomes, revealing major brain vascular and glial cell types, including endothelial cell (EC), pericyte (PC), astrocyte (AC), microglia (MG) and oligodendrocyte (OLG).

Source: Professor Owen Ko



Techniques for studying neural circuits. **Left panel:** identification of cortical areas by automated *ex vivo* imaging of mouse brain, image registration and anatomical reconstruction. **Right upper panel:** cortical neurons imaged *in vivo* under two-photon microscopy labelled by fluorescent proteins via rAAV2 transfection, showing neurons with single- (red or green) or dual-target area projections (yellow). **Right lower panel:** activities of a neuronal population during a sensorimotor behavioural task extracted from *in vivo* two-photon calcium imaging.

Source: Professor Owen Ko

■ Research and Scholarship

Fellowships

Member's Full Name	Details
Owen Ko	Member, Nexus of Rare Neurodegenerative Diseases (NRND)
	Member, Society for Neuroscience (SfN)
	Member, Hong Kong Epigenomics Project (EpiHK)

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Owen Ko	Cellular Mechanisms of Synaptic Functions and Plasticity in Health and Neurodegenerative Diseases	University Grants Committee – Areas of Excellence Scheme	01/07/2017	31/05/2025	77,516,000
Owen Ko	Design and Characterization of Novel MRI Contrast Agents for Alzheimer's Disease	Videns Incorporation Ltd.	01/02/2019	30/06/2021	2,560,000
Owen Ko	Faculty Innovation Award (Clinical Lecturer Scheme)	CUHK Faculty of Medicine	01/10/2017	30/09/2020	750,000
Owen Ko	Nanorobots Swarm for Stroke Treatment: Pilot Study	CUHK Research Committee – Funding for Research Sustainability of Major RGC Funding Schemes	01/06/2019	31/05/2021	625,000
Owen Ko	High-content Screening of Small Molecules for Inhibiting Microglia Phagocytotic Clearance of Inhibitory Synapses in the Management of Chronic Pain	CUHK Research Committee – Funding for Research Sustainability of Major RGC Funding Schemes	15/05/2019	14/05/2021	625,000

■ Publications

A. Journal Papers

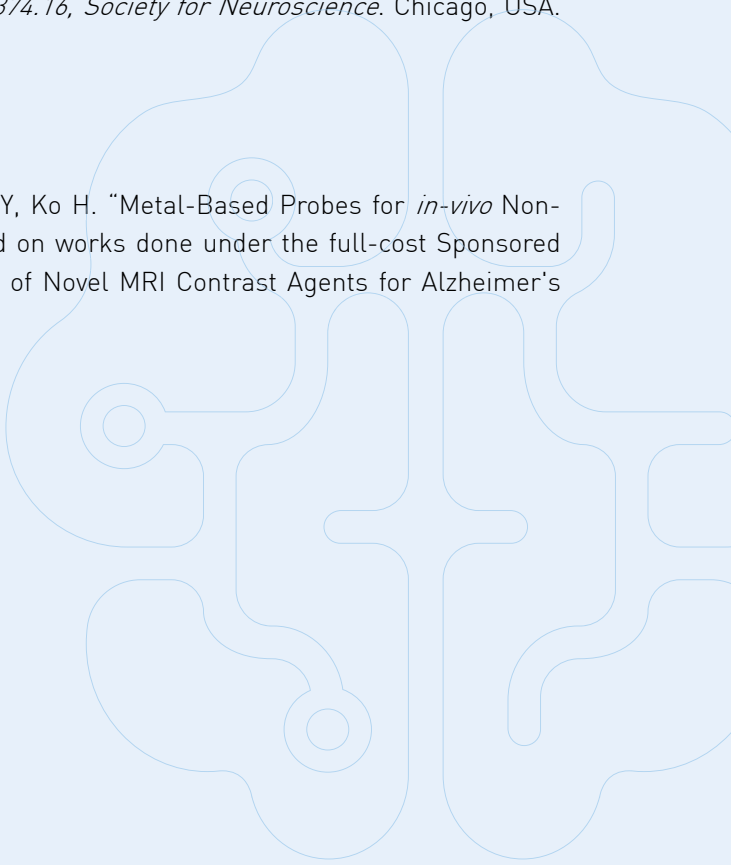
1. Zhao L, Li Z, L Vong JS, Chen X, Lai HM, Yan LYC, Huang J, Sy SKH, Tian X, Huang Y, Chan EYE, So HC, Ng WL, Tang Y, Lin WJ, Mok VCT, Ko H. Zonation-dependent single-endothelial cell transcriptomic changes in the aged brain. *bioRxiv*. 2019 Oct 10 doi:10.1101/800318 (Epub ahead of print).
2. Kang D, Wong A, Fu J, Qun X, Liu W, Wang Z, Lin S, Kwan P, Lo E, Au LWC, Ko H, Lau AYL, Leung TWH, Abrigo J, Chu WCW, Mok VCT, Lam BYK. Can transcranial Doppler ultrasound be used for screening cerebral small vessel diseases in the community? *Journal of Neurological Sciences*. 2019;406:116439. doi:10.1016/j.jns.2019.116439.
3. Lam BYK, Leung KT, Yiu B, Zhao L, Biesbroek JM, Au L, Tang Y, Wang K, Fan Y, Fu JH, Xu Q, Song H, Tian X, Chu WCW, Abrigo J, Shi L, Ko H, Lau A, Duering M, Wong A, Mok VCT. Peak width of skeletonized mean diffusivity and its association with age-related cognitive alterations and vascular risk factors. *Alzheimer's Dementia: Diagnosis, Assessment & Disease Monitoring*. 2019;11:721-729. doi:10.1016/j.dadm.2019.09.003.

B. Conference Papers

1. Sy SKH, Chan DCW, Lai HM, Li Z, Choi JCH, Mok VCT, Ko H. Towards characterizing brain-wide neural circuitry dynamics underlying chemosensory avoidance in larval zebrafish. In: *Neuroscience Meeting Planner 2019 Program No. 663.21, Society for Neuroscience*. Chicago, USA. 2019 October 19–23.
2. Zhao L, Li Z, Vong JSL, Chen X, Lai HM, Huang J, Sy SKH, Tian X, Huang Y, Chan HYE, So HC, Ng WL, Tang Y, Lin WJ, Mok VCT, Ko H. Single-cell analysis of aged brain vasculature reveals capillary endothelium as locus of neurodegeneration implicated gene changes and therapeutic target. In: *Neuroscience Meeting Planner 2019 Program No. 374.16, Society for Neuroscience*. Chicago, USA. 2019 October 19–23.

C. Provisional Patent

1. Ng WL, Huang J, Yan YCL, Wu KJ, Poon CSD, Li HY, Ko H. "Metal-Based Probes for *in-vivo* Non-Invasive Detection of Amyloid Plaques." (filed based on works done under the full-cost Sponsored Research Agreement "Design and Characterization of Novel MRI Contrast Agents for Alzheimer's Disease").



REPRODUCTION AND DEVELOPMENT



Principal Investigator

Professor Ronald Wang



Team

Hui Xu | Nina Chu | Simon Cui | Linda Wu | Alan Chan | Ricky Wu |
Zinnat Hasina | Ying He | Melody Mao | Yi Song | Kennes Hung |
Rachel Zhang | Alice Lin | Scoot Lin | Tan Zhou Yu Rong | Sophia |
Jerry Huang | Ya Ting Gao

Research Progress Summary

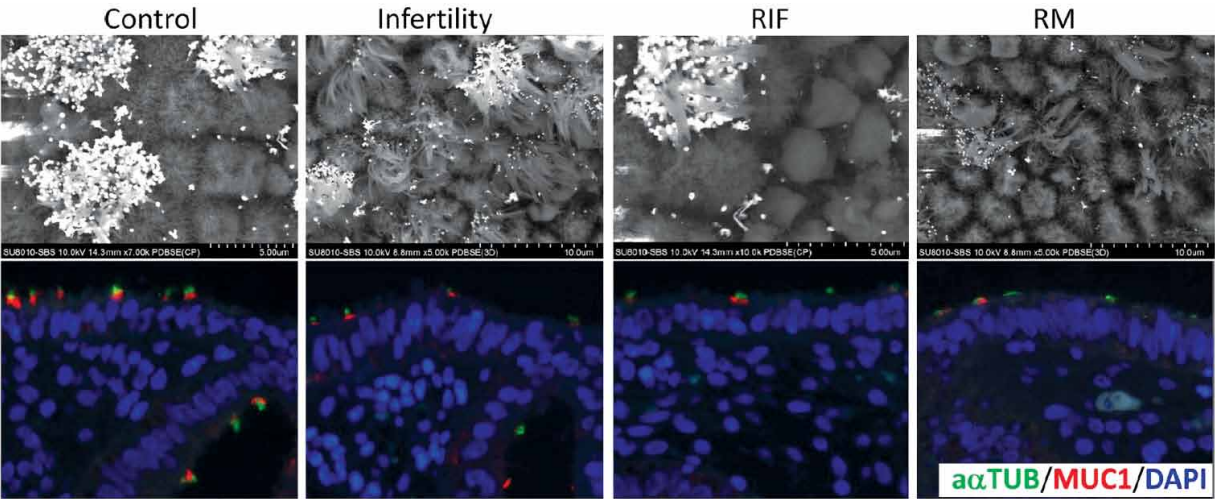
Professor Ronald Wang and his team from the Department of Obstetrics & Gynaecology focus on the field of Reproduction and Development. The team covered a wide spectrum of clinical, basic and genetic studies of female and male reproduction, and embryo and fetal development in human and mice. For reproduction, 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 neural stem cell regeneration, abnormal neurodevelopmental mechanism (e.g. cerebellar ataxia, Down's syndrome), embryopathy in maternal disease (e.g. pregestational and gestational diabetes),

placental function (e.g. fetal growth restriction, preterm birth, preeclampsia, hormonal expression), cord blood stem cells (e.g. mononuclear cells for neonatal cerebral ischemia and anaemia), drug safety during pregnancy (e.g. melamine, Chinese herbal medicine), etc.

In 2019, the team has published 1 review, 16 papers and 1 book chapter (12 LiHS acknowledged, 6 Health and Medical Research Fund / last / corresponding author) and obtained 10 research grants (4 as PI including 1 Health and Medical Research Fund (HMRF) and 1 Direct Grant; and 6 as Co-I including 2 General Research Fund (GRF), 4 HMRF and 1 Shenzhen Innovation and Technology Fund (SZ-ITF).

Currently, the team consists of 9 PhD students (7 as principal supervisor; 2 as co-supervisor), 3 of them will submit their thesis in 2020.





Localisation and expression of Mucin 1 (MUC1) in luminal epithelial cells. Representative scanning immunoelectron microscopy of MUC1 localisation (upper panel) and modified double immunofluorescence of MUC1 expressed ciliated cells (lower panel) on LH+7 day endometrium among control receptive (Control), Infertility, recurrent implantation failure (RIF), and recurrent miscarriage (RM).

Source: Wu FR, Mao D, Liu YY, Chen XY, Xu H, Li TC, Wang CC. Localization of Mucin 1 in endometrial luminal epithelium and its expression in women with reproductive failure during implantation window. *Journal of Molecular Histology*. 2019;50(6):563-572. doi:10.1007/s10735-019-09848-6.

■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Ronald Wang	Outbound Research Mobility Scheme for 2019-20. Internationalization Faculty Mobility Schemes. The Chinese University of Hong Kong, Hong Kong. Karolinska Institutet, Sweden, 17-24 August 2017
Kennes Hung	CUHK-Karolinska Institutet PhD Student Exchange Programme for 2018-19 to undertake a research attachment at the Department of Medical Biochemistry and Biophysics in Karolinska Institutet, Sweden, March - August 2019

Fellowships

Member's Full Name	Details
Ronald Wang	Professor (Distinguished), Jiangxi University of Traditional Chinese Medicine, Nanchang
Simon Cui	University Postdoctoral Fellowship, The Chinese University of Hong Kong
Linda Wu	Faculty Postdoctoral Fellowship, The Chinese University of Hong Kong

Reviewer of Journal / Conference

Member's Full Name	Details
Ronald Wang	Reviewer, International Immunopharmacology
	Reviewer, Proceedings of the National Academy of Sciences of the United States of America
	Reviewer, Science of the Total Environment
	Reviewer, Public Health Nutrition
	Reviewer, Gynecological Endocrinology
	Reviewer, Cancers
	Reviewer, Reproductive BioMedicine Online
	Reviewer, Endocrine Journal
	Reviewer, American Journal of Reproductive Immunology
	Reviewer, Reproductive BioMedicine Online
	Reviewer, Neurotoxicology
	Reviewer, Clinical Chemistry
	Reviewer, Journal of Assisted Reproduction and Genetics
	Reviewer, Evidence-Based Complementary and Alternative Medicine
	Reviewer, British Medical Journal
	Reviewer, Frontiers in Genetics
	Reviewer, Clinical Endocrinology
	Reviewer, Integrative Medicine
	Reviewer, Gynecological Endocrinology
	Reviewer, Journal of Pathology
	Reviewer, Diabetes, Obesity and Metabolism
	Reviewer, Cancers
	Reviewer, European Journal of Obstetrics & Gynecology and Reproductive Biology
	Reviewer, FASEB Journal
	Reviewer, Reproductive BioMedicine Online
	Reviewer, Scientific Reports
	Reviewer, Journal of Diabetes Investigation

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Ronald Wang KSW Hung	An <i>in silico</i> (PharmMapper and Microarray) Approach to Identify Drug Targets of EGCG and Pro-EGCG in Treating Endometriosis	The Obstetrical and Gynaecological Society of Hong Kong – Hong Kong Obstetrical and Gynaecological Trust Fund	01/08/2019	31/07/2020	30,000
Ronald Wang Y He H Xu	Therapeutic Mechanism of Sunitinib Inhibiting Myeloid-derived Suppressor Cells for a Novel Treatment of Endometriosis	The Obstetrical and Gynaecological Society of Hong Kong – Hong Kong Obstetrical and Gynaecological Trust Fund	01/08/2019	31/07/2020	50,000

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Ronald Wang RZ Zhang	Whole Genome DNA Methylation and Transcriptome Sequencing to Reveal Epigenetic Regulations of Endometrium Receptivity in Women with Reproductive Failure – a Pilot Study	CUHK Research Committee – Direct Grant	30/06/2019	29/06/2020	105,000
Ronald Wang	A Metabolomic Approach to Redefine Diagnostic Criteria and Classification of Polycystic Ovary Syndrome	Food and Health Bureau – Health and Medical Research Fund	01/04/2019	31/03/2021	1,499,999
Ronald Wang	Evaluation of Aspirin Non-responsiveness in Preeclampsia Prevention: a Pharmacometabolomics Approach (06171046)	Food and Health Bureau – Health and Medical Research Fund	01/08/2019	31/01/2021	989,600
Ronald Wang	Do Endometrial Leucocytes and Angiogenesis in the Peri-implantation Period Predict Hypertensive Disorders in the Subsequent Pregnancy? (06170186)	Food and Health Bureau – Health and Medical Research Fund	01/08/2019	31/01/2021	477,196
Ronald Wang	A Double Blinded, Randomized Placebo Controlled Trial on Effect of Traditional Chinese Medicine Formula WuziYanzong Pill on Improving Semen Qualities in Men with Sub-optimal Parameters	Food and Health Bureau – Health and Medical Research Fund	01/05/2019	30/04/2022	1,114,156

3. Law TSM, Wu FR, Xu H, Wang CC, Li TC. Endometrium imaging using real-time rotational optical coherence tomography imaging system. *Medicine (Baltimore)*. 2019;98(44):e17738. doi:10.1097/MD.00000000000017738.

4. Cui L, Chen YS, Liu F, Luo YH, Fan Y, Xu GF, Zhou B, Li P, Pan XY, Wang CC. EDNRB isoform 3 confers Temozolomide resistance in A375 melanoma cells by modulating membrane potential, reactive oxygen species and mitochondrial Ca2+. *Cancer Management and Research*. 2019;Volume 11:7353-7367. doi:10.2147/CMAR.S208604.

5. Li L, Tang LY, Liang B, Wang RY, Sun QH, Lau CBS, Leung PC, Fritsche E, Liebsch M, Seiler A, Spielmann H, Wang CC. Evaluation of *in vitro* embryotoxicity tests for Chinese herbal medicines. *Reproductive Toxicology*. 2019;89:45-53. doi:10.1016/j.reprotox.2019.06.001.

6. Chen J, Deng Y, Ao LF, Song Y, Xu Y, Wang CC, Choy KW, Chung TKH, Du Q, Sui Y, Yang T, Yang J, Tang T. The high-risk HPV oncogene E7 upregulates miR-182 expression through the TGF-β/Smad pathway in cervical cancer. *Cancer Letter*. 2019;460:75-85. doi:10.1016/j.canlet.2019.06.015.

7. Chen FY, Zhou JJ, Li YY, Zhao Y, Cap Y, Wang LJ, Zhang ZK, Zhang BT, Wang CC, Wu ZG, Wong CCL, Sun H, Wang HT. YY1 regulates skeletal muscle regeneration through controlling metabolic reprogramming of satellite cells. *EMBO Journal*. 2019;38(10):e99727. doi:10.15252/embj.201899727.

8. Wu L, Wang CC. Genetic variants in promoter regions associated with type 2 diabetes mellitus: A large-scale meta-analysis and subgroup analysis. *Journal of Cellular Biochemistry*. 2019;120(8):13012-13025. doi:10.1002/jcb.28572.

9. Law TSM, Cheung WC, Wu FR, Zhang RZ, Chung JPW, Wang CC, Chen XY, Li TC. Endometrial vascularization characterized by optical coherence tomography and immunohistochemistry in women undergoing *in vitro* fertilization-embryo transfer treatment. *Medicina (B Aires)*. 2019;55(4):81. doi:10.3390/medicina55040081.

10. Ling L, Wu T, To KKW, Cheung KW, Lui KO, Niu M, Lam KS, Wang CC, Li J, Wang H, Yuen KY, Chen Z. Vedolizumab-mediated integrin α4β7 blockade does not control HIV-1SF162 rebound after combination antiretroviral therapy interruption in humanized mice. *AIDS*. 2019;33(4):F1-F12. doi:10.1097/QAD.0000000000002149.

11. Cui L, Zhou F, Chen C, Wang CC. Overexpression of CCDC69 activates p14ARF/MDM2/p53 pathway and confers cisplatin sensitivity. *Journal of Ovarian Research*. 2019;12(1):4. doi:10.1186/s13048-019-0479-3.

12. Zhang T, Chen XY, Wang CC, Li TC, Kim JK. Intrauterine infusion of human chorionic gonadotropin before embryo transfer in IVF/ET cycle: The critical review. *American Journal of Reproductive Immunology*. 2019;81(2):e13077. doi:10.1111/aji.13077 (Review).

B. Patents

1. 李天照，黃志超，宋李烟，梁為亮，李百靈，高峻。一種OCT探頭驅動裝置和OCT檢測設置(SIPO 201820311468.6)。

Publications

A. Journal Papers

1. Wu FR, Mao D, Liu YY, Chen XY, Xu H, Li TC, Wang CC. Localization of Mucin 1 in endometrial luminal epithelium and its expression in women with reproductive failure during implantation window. *Journal of Molecular Histology*. 2019;50(6):563-572. doi:10.1007/s10735-019-09848-6.

2. Li J, Wu Q, Wang CC, Wang R, Ng EHY, Liu JP, Mol BWJ, Wu XK, Li WT, PCOSA Study Group. Endocrine characteristics, body mass index and metabolic syndrome in women with polycystic ovary syndrome. *Reproductive Biomedicine Online*. 2019;39(5):868-876. doi:10.1016/j.rbmo.2019.06.014.

STEM CELLS AND TISSUE REGENERATION

Adult Stem Cell Biology and Applications



Principal Investigator

Professor Gang Li



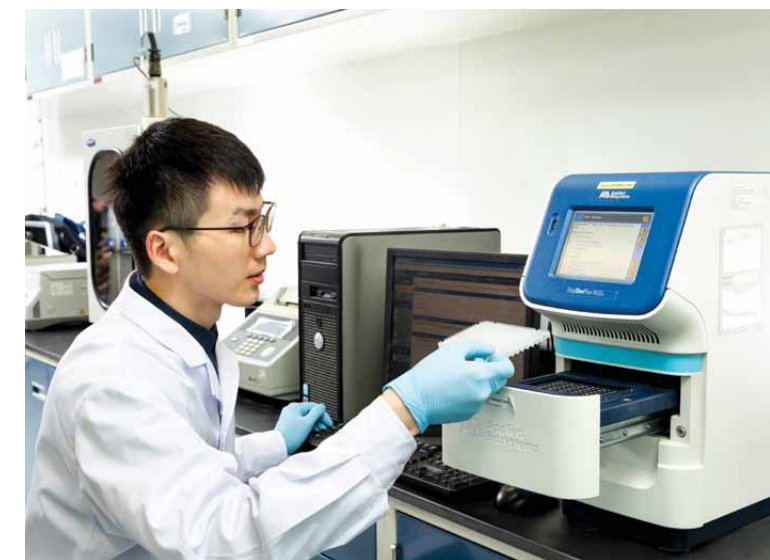
Team

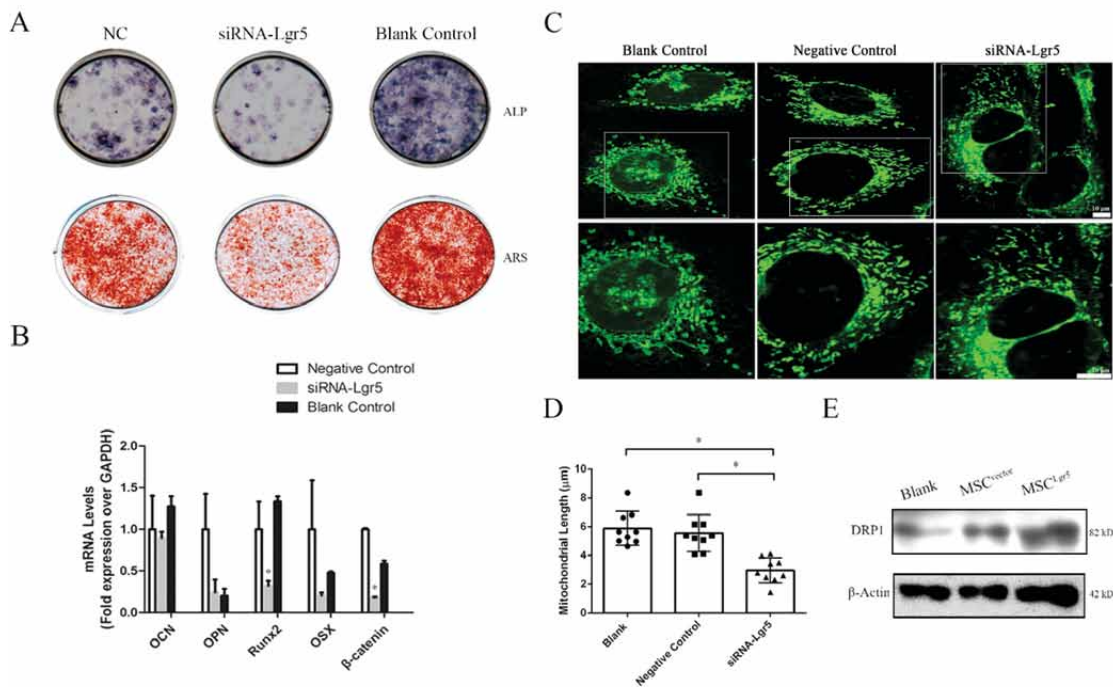
Wayne Lee | Sien Lin | Meiling Zhu | Lu Feng | Bin Wang | Yan Wang |
Weiping Lin | Yujia Wang | Yucong Li | Qi Pan | Haixing Wang |
Xiaoting Zhang | Yuan Li | Zhengmeng Yang | Shanshan Bai | Jessica Lo |
Pong U King | Yongkang Yang | Lingchi Kong | Tszlam Yiu

Research Progress Summary

In 2019, the research team led by Professor Gang Li has 19 members (1 Research Associate Professor, 4 Postdoctoral Fellows, 2 Research Associates, 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) novel therapy strategies for diabetic foot ulcers treatment; (4) industry and Hong Kong Government contract research works on pre-clinical studies of biological compounds and biophysical stimulations; (5) engaging in international collaborations and educational programmes. These projects

progress as planned, with production of more than 17 peer-reviewed publications and over HK\$7 million research grants secured by the team in 2019. In 2019, Professor Li has also successfully organised the 9th CUHK International Symposium. 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 2019, 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 also serves as the council member of 4 prestigious national research societies, and editorial board member for 4 international journals. He also actively engaged in knowledge transfer and provided advice / consultation service for Hong Kong Science Park, local and international healthcare related industries.





Inhibition of Lgr5 expression by siRNA transfection suppressed osteogenic differentiation of murine peripheral blood-derived mesenchymal stem cells (mPB-MSCs). A. Effects of Lgr5 silence on alkaline phosphatase activity at day 5 and calcium deposition at day 7 after osteogenic induction in mPB-MSCs, determined by alkaline phosphatase (ALP) staining (BCIP / NBT liquid substrate system) or Alizarin Red S (ARS) staining respectively. B. Gene expression levels of osteogenic-associated markers were examined by qRT-PCR among negative control, siRNA-Lgr5-transfection, and blank control groups after 7-day-osteogenic induction. C. Detection of β-catenin expression among negative control, siRNA-Lgr5-transfection, and blank control groups by Western blot after 7-day-osteogenic induction. D. Mitochondrial morphology imaging after 24-h-osteogenic induction under confocal microscope using Mito-tracker green. Scale bar, 10 μm. Mitochondrial branch lengths were analysed by ImageJ. n=9, *: P< 0.05. E. Western blot analysis of DRP1 protein expression.

Source: Lin WP, Xu LL, Pan Q, Lin SE, Feng L, Wang B, Chen SX, Li Y, Wang HX, Li YC, Wang Y, Lee WYW, Sun D, Li G. Lgr5-overexpressing mesenchymal stem cells augment fracture healing through regulation of Wnt/ERK signaling pathways and mitochondrial dynamics. *FASEB Journal*. 2019;33(7):8565-8577. doi:10.1096/fj.201900082RR.

Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Gang Li	「骨與關節多組織損傷創新模型構建及分子治療的基礎研究」中國生物材料學會科學技術獎三等獎。(2019年5月)

Fellowships

Member's Full Name	Details
Gang Li	Distinguished Tang Aoqing Guest Professorship, Jilin University, China
	Adjunct Professor, Australian Regenerative Medicine Institute (ARMI), Monash University, Australia
	Visiting Professor, Department of Orthopaedic Surgery and Traumatology, University of Malaya, Malaysia
	Visiting Professor, Guang Dong Medical College, Dongguan, China
	Visiting Professor, Xijing Orthopaedic Hospital, The Air Force Medical University, Xian, China

Fellowships

Member's Full Name	Details
Gang Li	Visiting Professor, Shenzhen Baoan People's Hospital, Shenzhen, China
	Visiting Professor, China Medical University, Shenyang, China
	Visiting Professor, South Eastern University Medical School, Nanjing, China
	General Secretary, Division of Limb Deformity Correction and Reconstruction, Chinese Association of Orthopaedic Surgeons
	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)

Academic Editorship

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

Grants and Consultancy

Member's Full Name	Details
Gang Li	Reviewer, Biomaterials
	Reviewer, Stem Cell
	Reviewer, Stem Cells Research and Therapy
	Reviewer, Journal of Physiology
	Reviewer, Journal of Chemical Engineering

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Gang Li	Modulating Osteoarthritis Development via Balancing Endogenous Expression of Smad3 and Smad7	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	953,029
Gang Li	Effects of Danshen and Jixuecao Extracts on Glucocorticoid Induced Bone Loss and Growth Suppression	Food and Health Bureau – Health and Medical Research Fund	01/07/2019	30/06/2022	1,495,584
Gang Li	Exploiting the True Joint Progenitor Cell for Articular Cartilage Repair	Research Grants Council – Collaborative Research Fund	01/06/2019	31/05/2022	7,370,000
Gang Li	Biomaterials-mediated Bone Formation and Consolidation in Distraction Osteogenesis	Research Grants Council – General Research Fund	15/09/2017	14/09/2020	1,098,710

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Gang Li	PEMF Effects on MSCs Chondrogenic Differentiation and Cartilage Lesion Repair	Orthofix Company	31/12/2017	31/12/2019	2,478,510
Gang Li	Development of Bio-scaffold Encapsulating Human Fetal Mesenchymal Stem Cells Secretion for Promoting Difficult Skin Wound Healing	Innovation and Technology Commission – Innovation and Technology Fund	01/03/2017	30/06/2019	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 and Technology Commission – Internship Programme	01/03/2017	30/06/2019	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
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	Bioactive Components in Fetal Skeletal Muscle for Sarcopenia	Innovation and Technology Commission – Innovation and Technology Fund	01/01/2019	31/12/2020	1,768,700

Publications

A. Journal Papers

1. Wen G, Xu J, Wu T, Zhang S, Chai Y, Kang Q, Li G. Functionalized polycaprolactone/hydroxyapatite composite microspheres for promoting bone consolidation in a rat distraction osteogenesis model. *Journal of Orthopaedic Research*. 2020;38(5):961-971. doi:10.1002/jor.24542 [Epub in 2019].

2. Shi J, Liu F, Zhang Y, Lian A, Han X, Zuo K, Liu M, Zheng T, Zou F, Liu X, Jin MH, Mu Y, Li G, Liu JY. NANOG attenuates hair follicle-derived mesenchymal stem cell senescence by upregulating PBX1 and activating AKT signaling. *Oxidative Medicine and Cellular Longevity*. 2019;2019:4286213. doi:10.1155/2019/4286213.

3. Jiang Y, Liu F, Zou F, Zhang Y, Wang B, Zhang Y, Lian A, Han X, Liu Z, Liu X, Jin M, Wang D, Li G, Liu J. PBX homeobox 1 enhances hair follicle mesenchymal stem cell proliferation and reprogramming through activation of the AKT/glycogen synthase kinase signaling pathway and suppression of apoptosis. *Stem Cell Research & Therapy*. 2019;10(1):268. doi:10.1186/s13287-019-1382-y.

4. Xu L, Lin W, Wen L, Li G. Lgr5 in cancer biology: Functional identification of Lgr5 in cancer progression and potential opportunities for novel therapy. *Stem Cell Research & Therapy*. 2019;10(1):219. doi:10.1186/s13287-019-1288-8.

5. Huang JP, Wang HX, Huang ML, Zong ZX, Wu X, Xu JB, Lan HY, Zheng JC, Zhang XT, Lee YW, Wei B, Cui L, Li G, Lin SE. Asiatic acid attenuates bone loss by regulating osteoclastic differentiation. *Calcified Tissue International*. 2019;105(5):531-545. doi:10.1007/s00223-019-00596-z.

6. Zhou J, So KK, LI YY, Li Y, Yuan J, Ding YZ, Chen FY, Huang Y, Liu J, Lee W, Li G, Ju ZY, Sun H, Wang HT. Elevated H3K27ac in aged skeletal muscle leads to increase in extracellular matrix and fibrogenic conversion of muscle satellite cells. *Aging Cell*. 2019;18(5). doi:10.1111/ace1.12996.

7. Lin WP, Huang LF, Li Y, Fang B, Li G, Chen LL, Xu LL. Mesenchymal stem cells and cancer: Clinical challenges and opportunities. *BioMed Research International*. 2019;2019:2820853. doi:10.1155/2019/2820853 [Review].

8. Chen X, Li R, Wong DX, Wei K, Cui M, Chen H, Jiang Y, Yang B, Zhao P, Xu J, Chen H, Yin C, Lin S, Lee WYW, Jing Y, Li Z, Yang Z, Xia J, Chen G, Li G, Bian L. Conformational manipulation of scale-up prepared single-chain polymeric nanogels for multiscale regulation of cells. *Nature Communications*. 2019;10(1):2705. doi:10.1038/s41467-019-10640-z.

9. Lin WP, Xu LL, Pa Q, Lin SE, Feng L, Wang B, Chen SX, Li Y, Wang HX, Li YC, Wang Y, Lee WYW, Sun D, Li G. Lgr5-overexpressing mesenchymal stem cells augment fracture healing through regulation of Wnt/ERK signaling pathways and mitochondrial dynamics. *FASEB Journal*. 2019;33(7):8565-8577. doi:10.1096/fj.201900082RR.

10. Kang H, Yang BG, Zhang KY, Pan Q, Yuan WH, Li G, Bian LM. Immunoregulation of macrophages by dynamic ligand presentation via ligand-cation coordination. *Nature Communications*. 2019;10(1):1696. doi:10.1038/s41467-019-09733-6.

11. Kang H, Wong SHD, Pan Q, Li G, Bian L. Anisotropic ligand nanogeometry modulates the adhesion and polarization state of macrophages. *Nano Letters*. 2019;19(3):1963-1975. doi:10.1021/acs.nanolett.8b05150 [Letter].

12. Lin WP, Xu LL, Lin SE, Shi L, Lee WYW, Wang B, Pan Q, Li G. Characterisation of multipotent stem cells from human peripheral blood using an improved protocol. *Journal of Orthopaedic Translation*. 2019;19:18-28. doi:10.1016/j.jot.2019.02.003.

13. Lin W, Xu L, Li G. A novel protocol for isolation and culture of multipotent progenitor cells from human urine. *Journal of Orthopaedic Translation*. 2019;19:12-17. doi:10.1016/j.jot.2019.02.005.

14. Xu LL, E SM, Lin S, Hou YH, Lin WP, He W, Wang HB, Li G. Sox11-modified mesenchymal stem cells accelerate cartilage defect repair in SD rats. *Cell & Tissue Research*. 2019;376(2):247-255. doi:10.1007/s00441-018-02979-4.

15. Liu Y, Feng L, Xu J, Yang Z, Wu T, Zhang J, Shi L, Zhu D, Zhang J, Li G. MiR-378a suppresses tenogenic differentiation and tendon repair by targeting at TGF-β2. *Stem Cell Research & Therapy*. 2019;10(1):108. doi:10.1186/s13287-019-1216-y.

16. Lin SE, Cui L, Chen GH, Huang JP, Yang YH, Zou KJ, Lai YX, Wang XL, Zuo LY, Wu T, Cheng JCY, Li G, Wei B, Lee WYW. PLGA/β-TCP composite scaffold incorporating salvianolic 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.

STEM CELLS AND TISSUE REGENERATION

Immune and Regenerative Medicine



Principal Investigator

Professor Kathy Lui



Team

Vicken Chan | Kevin Yang | Cai Liang | Xisheng Li | Di Liu | Zhangjing Ma |
Peng Ye | Kathleen Chan | Danny Leung | Tiffany Fung

Research Progress Summary

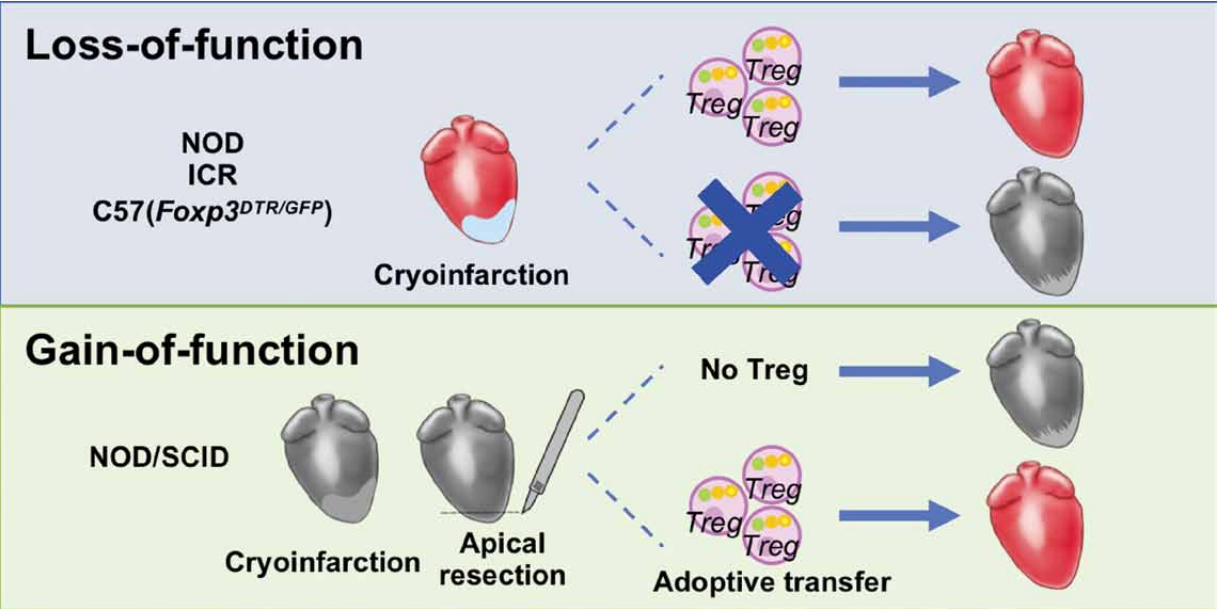
During the past years, Professor Kathy Lui and her team have been studying the pathogenesis of cardiovascular complications associated with diabetes; and developing new strategies including human pluripotent stem cells, therapeutic modified mRNAs, monoclonal antibodies and temporal yet precise lineage-tracing 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 the 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) and directly regulate neonatal cardiomyocyte proliferation and regeneration (Li J *et al.*, *Theranostics*, 2019). On the other hand, they have also uncovered that the plasticity of CD8+ T cells regulate vascular regeneration in type-2 diabetes (Liang C *et al.*, *Theranostics*, in press). Taken together, there is an unappreciated role of immune cells in the regulation of regeneration of cardiovascular cells. The team believes that tipping the balance of immunity could give clinically relevant insights into novel therapeutics targeting cardiovascular diseases.





A graphical summary demonstrating how regulatory T-cells regulate mouse heart regeneration using both gain- and loss-of-function experiments.

Source: Li J, Yang KY, Tam RC, Chan VW, Lan HY, Hori S, Zhou B, Lui KO. Regulatory T-cells regulate neonatal heart regeneration by potentiating cardiomyocyte proliferation in a paracrine manner. *Theranostics*. 2019;9(15):4324-4341. doi:10.7150/thno.32734.

■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Kathy Lui	Founding Member, Young Academy of Sciences of Hong Kong
	National Natural Science Foundation of China Excellent Young Scientists Fund (Macau & Hong Kong)

Fellowships

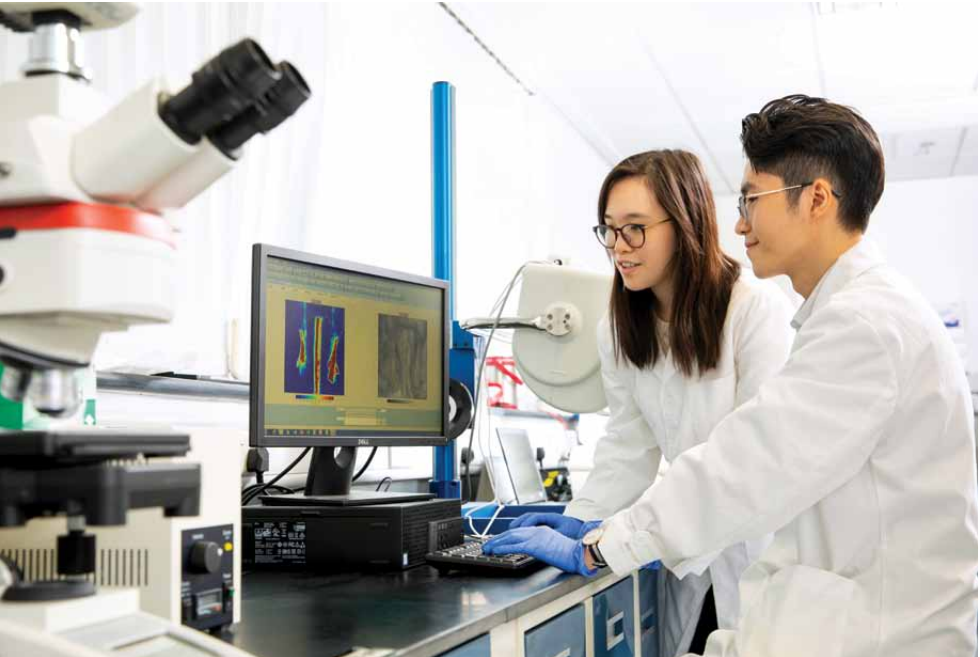
Member's Full Name	Details
Kevin Yang	Research Fellowship Scheme, Research Committee, The Chinese University of Hong Kong
Cai Liang	Faculty Postdoctoral Fellowship, Faculty of Medicine, The Chinese University of Hong Kong

Academic Editorship

Member's Full Name	Details
Kathy Lui	Associate Editor, Journal of Immunology and Regenerative Medicine
	Associate Editor, Stem Journal
	Editorial Board Member, Scientific Reports
	Editorial Board Member, Current Stem Cell Research & Therapy

Reviewer of Journal / Conference

Member's Full Name	Details
Kathy Lui	Reviewer, Genome Medicine
	Reviewer, Cellular and Molecular Immunology
	Reviewer, Canadian Journal of Cardiology
	Reviewer, Stem Cells
	Reviewer, Science China Life Sciences
	Reviewer, International Journal of Nanomedicine
	Reviewer, Cell Proliferation
	Reviewer, The Journal of Biochemical Chemistry
	Reviewer, Development
	Reviewer, International Journal of Molecular Sciences
	Reviewer, Journal of Cardiovascular Development and Disease
	Reviewer, Stem Cell Reports
	Reviewer, Oncotarget
	Reviewer, Frontiers in Endocrinology
	Reviewer, Stem Cell Research and Therapy
	Reviewer, Current Stem Cell Research and Therapy
	Reviewer, Cells
	Reviewer, Journal of Cellular and Molecular Medicine



Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Kathy Lui	A Multi-disciplinary Study on the Beneficial Effects of PPAR δ in Physical Exercise against Diabetic Vascular Complications: Cellular Crosstalk and Energy Metabolism	Research Grants Council – Collaborative Research Fund	30/06/2017	29/06/2020	6,817,834
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	Modelling Human Congenital Heart Disease in Diabetes Using the ISL1-Cre Lineage Tracing Human Pluripotent Stem Cells	CUHK Faculty of Medicine – Faculty Innovation Award	01/01/2017	31/12/2021	2,500,000
Kathy Lui	Joint R&D of Magnesium-based Orthopaedic Implants	Research Grants Council – Collaborative Research Fund	01/04/2018	31/03/2021	5,545,807
Kathy Lui	Immune Regulation of Tissue Regeneration: from Mechanistic to Potential Clinical Implications	CUHK Research Committee – Research Sustainability of Major Research Grants Council Funding Schemes	01/06/2019	31/05/2021	625,000
Kathy Lui	Unraveling the Impact of Hyperglycemia on Human Second Heart Field Development	University Grants Committee – Research Matching Grant Scheme (RMGS)	01/07/2019	30/06/2020	500,000
Kathy Lui	Paracrine Regulation of Human Pancreatic Beta-like Cell Maturation by RARRES2	CUHK Research Committee – Direct Grant	01/07/2018	29/06/2020	104,814

Publications

A. Journal Papers

1. He L, Lui KO, Zhou B. The formation of coronary vessels in cardiac development and disease. *Cold Spring Harbor Perspectives in Biology*. 2020;12(5):a037168. doi:10.1101/cshperspect.a037168 (Perspective) [Epub in 2019].
2. Li J, Yang KY, Tam RC, Chan VW, Lan HY, Hori S, Zhou B, Lui KO. Regulatory T-cells regulate neonatal heart regeneration by potentiating cardiomyocyte proliferation in a paracrine manner. *Theranostics*. 2019;9(15):4324-4341. doi:10.7150/thno.32734.
3. Li Y, Lv Z, He L, Huang X, Zhang S, Zhao H, Pu W, Li Y, Yu W, Zhang L, Liu X, Liu K, Tang J, Tian X, Wang QD, Lui KO, Zhou B. Genetic tracing identifies early segregation of the cardiomyocyte and nonmyocyte lineages. *Circulation Research*. 2019;125(3):343-355. doi:10.1161/circresaha.119.315280.
4. Ling L, Wu T, To KK, Cheung KW, Lui KO, Niu M, Lam K, Wang C, Li J, Wang H, Yuen KY, Chen Z. Vedolizumab-mediated integrin $\alpha4\beta7$ blockade does not control HIV-1SF162 rebound after combination antiretroviral therapy interruption in humanized mice. *AIDS*. 2019;33(4):F1-F12. doi:10.1097/qad.0000000000002149.
5. Han X, Wang Y, Pu W, Huang X, Qiu L, Li Y, Yu W, Zhao H, Liu X, He L, Zhang L, Ji Y, Lu J, Lui KO, Zhou B. Lineage tracing reveals the bipotency of SOX9+ hepatocytes during liver regeneration. *Stem Cell Reports*. 2019;12(3):624-638. doi:10.1016/j.stemcr.2019.01.010.
6. Zhao Y, Feng Z, Zhang Y, Sun Y, Chen Y, Liu X, Li S, Zhou T, Chen L, Wei Y, Ma D, Lui KO, Ying H, Chen Y, Ding Q. Gain-of-function mutations of SLC16A11 contribute to the pathogenesis of type 2 diabetes. *Cell Reports*. 2019;26(4):884-892.e4. doi:10.1016/j.celrep.2018.12.100.
7. Leung CS, Li J, Xu F, Wong AS, Lui KO. Ectopic expression of recipient CD47 inhibits mouse macrophage-mediated immune rejection against human stem cell transplants. *The FASEB Journal*. 2019;33(1):484-493. doi:10.1096/fj.201800449r.



STEM CELLS AND TISSUE 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 | Wenxuan Tong | Jiali Wang |
Jiankun Xu | Hao Yao | Ri Zhang | Nianye Zheng | Lizhen Zheng |
Liangbin Zhou | Li Zou | Haiyue Zu | Zhi Yao | Liang Chang |
Meiling Huang | Xueting Yi | Yue Wu

Research Progress Summary

Professor Ling Qin and the team focus on the research and development of innovative orthopaedic implants and drugs, supplements and drugs for external use for prevention and treatment of musculoskeletal disorders and injuries with limited healing potential, including patients with impaired healing

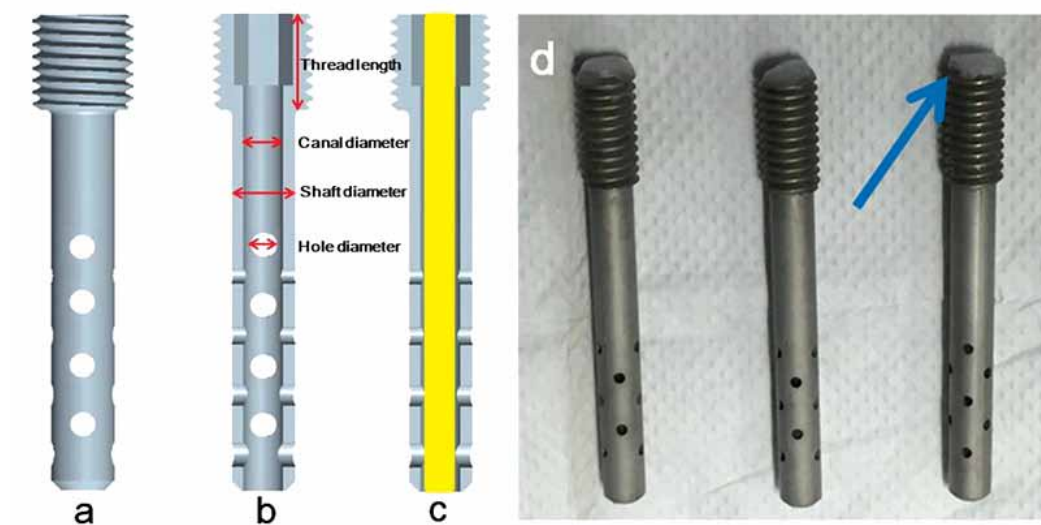
capacity, large bone defects, large wound and healing at different tissue types such as the bone-tendon/bone-cartilage interface. He has been developing innovative biomedical and tissue engineering products, clinical indication-orientated treatment regimens and protocols that utilise stem cells, bioactive 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 investigated different pure Mg and Mg-based alloys to clinical implantations for different clinical purposes. One innovative implant is pure Mg cannulated stents which have modified current commercially available implants to incorporate Mg components to prevent collapse of femoral head and enhance bone healing of osteonecrosis. This biodegradable Mg cannulated stent with injection of bone cement containing Mg ion is believed to be one of the potential therapeutic strategies to avoid the incidence of femoral head collapse and simultaneously promote bone regeneration and angiogenesis of osteonecrosis. 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.



Schematic diagram for illustration of the structure and mechanism of the cannulated Mg stents.

- (a). The computer aided design (CAD) graph of the cannulated Mg stent.
- (b). The inside structure of the cannulated Mg stent.
- (c). The yellow filling represents the cement containing Mg.
- (d). When the cement has been injected, it would come out from the very top of the cannulated Mg stent (pointed with the blue arrow).

Source: Mr. Wing Ho Chau and Dr. Haiyue Zu



Illustrations showing combine cannulated Mg stents with bone cement injection for ONFH treatment.

- (a) X ray showed that Mg stent insert into the targeting necrotic lesion.
- (b) With bone cement filling via our designed canal.

Source: Dr. Haiyue Zu

■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
賴毓霄，李龍，秦嶺，王新巒，張鵬	中國專利獎銀獎
Wei Hsin Liao, Chunhao Zhong, Xuan Zhao, Ling Qin, Sheung Wai Law	47 th International Exhibition of Inventions of Geneva Silver Prize
Li Zou	Third Young Investigator Prize – the 4 th International Chinese Musculoskeletal Research Conference
	Talent Development Scholarship – Hong Kong Special Administrative Region Government Scholarship Fund
Xiaodan Chen	Third Young Investigator Prize – the 4 th International Chinese Musculoskeletal Research Conference
Ling Qin	2020 Berton Rahn Research Award (AO Foundation, Switzerland)

Academic Editorship

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

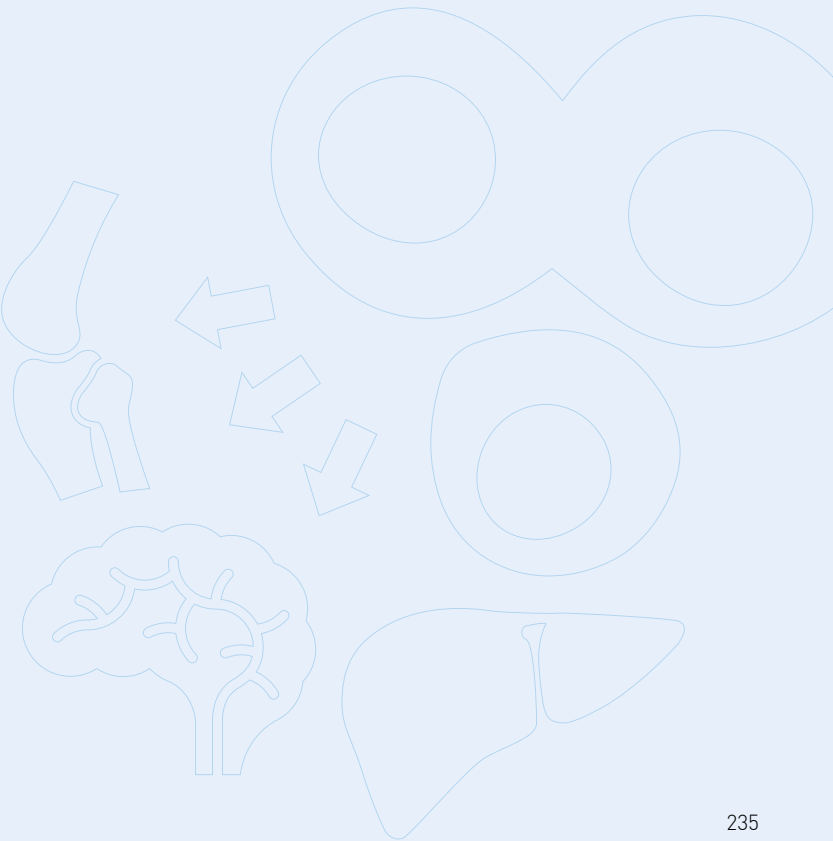
Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Ling Qin	Further Development and Translation of Innovative Titanium-Magnesium Plate-screw Hybrid Fixation System for Osteoporotic Fracture Fixation and Healing Enhancement	Innovation and Technology Commission – Innovation and Technology Support Programme	01/01/2019	31/12/2022	2,469,000
Ling Qin	Further Development and Translation of Innovative Titanium-Magnesium Plate-screw Hybrid Fixation System for Osteoporotic Fracture Fixation and Healing Enhancement	Innovation and Technology Commission – Postdoctoral Hub	13/09/2019	31/12/2020	523,000

■ Publications

A. Journal Papers

1. Yu W, Li R, Long J, Chen P, Hou AY, Li L, Sun X, Zheng GQ, Meng HY, Wang Y, Wang AY, Sui X, Guo QY, Tao S, Peng J, Qin L, Lu SB, Lai YX. 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.
2. Tian L, Deng N, Ngai T, C Wu, Huang L, YC Yuan, 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).
3. Tong WX, Zeng YL, Chow HK, Yeung W, Xu JK, Deng YJ, Chen SH, Zhao H, Zhang XL, Ho KW, Qin L, Mak KL. Wnt16 attenuates osteoarthritis progression through a PCP/JNK-mTORC1-PTHrP cascade. *Annals of the Rheumatic Diseases*. 2019;78(4):551-561. doi:10.1136/annrheumdis-2018-214200.
4. Feng Q, Xu JK, Zhang KY, Yao H, Zheng NY, Zheng LZ, Wang JL, Wei KC, Xiao XF, Qin L, Bian LM. Dynamic and cell-infiltratable hydrogels as injectable carrier of therapeutic cells and drugs for treating challenging bone defects. *ACS Central Science*. 2019;5(3):440-450. doi:10.1021/acscentsci.8b00764.
5. Chow DH, Zheng L, Tian L, Ho KS, Qin L, Guo X. Application of ultrasound accelerates the decalcification process of bone matrix without affecting histological and immunohistochemical analysis. *Journal of Orthopaedic Translation*. 2019;17:112-120. doi:10.1016/j.jot.2018.08.001.
6. Li S, Qiu J, Qin L, Peng P, Li C, Mao J, Fang G, Chen Z, Lin S, Fu Y, Cai W, Ding Y. NOD2 negatively regulated titanium particle-induced osteolysis in mice. *Biomaterials Science*. 2019;7(7):2702-2715. doi:10.1039/c9bm00306a.



STEM CELLS AND TISSUE REGENERATION

Intelligent Orthopaedic Bio-Engineering Research



Principal Investigator

Professor Oscar Lee



Team

Chien-wei Lee | Carol Lau | Zoey Lin | Tina Cheng | Jason Wan |
Rita Shin | Belle Wang | Amanda Wang | Shawn Zhu | Allen Hsiao |
Stella Cheung | Kwan Yau Law

Research Progress Summary

The Laboratory for Intelligent Orthopaedic Bio-Engineering Research consists of Orthopaedic surgeons, molecular and cell biologists, bioengineers and computer scientists who collectively develop advanced technologies in regenerative medicine. Professor Oscar Lee and his research team have investigated the pathophysiology of musculoskeletal diseases, such as bone tumours and ageing-related conditions including osteoporosis, sarcopenia and frailty. The team also dedicates to develop potential therapeutic approaches for the above mentioned problems. Besides, they study the possibility of using extraction from traditional Chinese medicine to improve osteoporosis and reduce the incidence of osteoporotic

fractures in elderly populations. They have established solid intra-departmental and inter-departmental research collaborations in CUHK, and even collaborations between universities in and outside of Hong Kong. For instance, Professor Lee and Dr. Carol Lau, in collaboration with Professor Jianfang Wang of Department of Physics and Professor Christopher Cheng of School of Biomedical Sciences, establish a non-destructive chemical analysis protocol using Raman Spectroscopic to rapidly and accurately assess the degree of malignancy in osteosarcoma. They will further combine AI technology for developing a confident classification model in terms of the clinical application. Professor Lee and Professor Chien-wei Lee cooperate

with Professor Changshun Shao from Institutes for Translational Medicine, Soochow University, for the National Natural Science Foundation of China (NSFC) and the Research Grants Council (RGC) of Hong Kong Joint Research Scheme proposal, which focuses on "Development of novel stem cell-based immunotherapeutics for systemic lupus erythematosus". What is more, Professor Oscar Lee and Professor Chien-wei Lee extended their research interests

to discover the hepatogenic potential of Mesenchymal Stem Cells (MSCs) and focus on developing MSC-based therapies on obesity-related nonalcoholic fatty liver disease. They have also coordinated a research project, recruited scientists from CUHK, HKU and Oslo University Hospital, to study the "Development of Novel Treatment" for Non-Alcoholic Fatty Liver Disease, and applied for the Research Grant Council - Theme-based Research Grant.

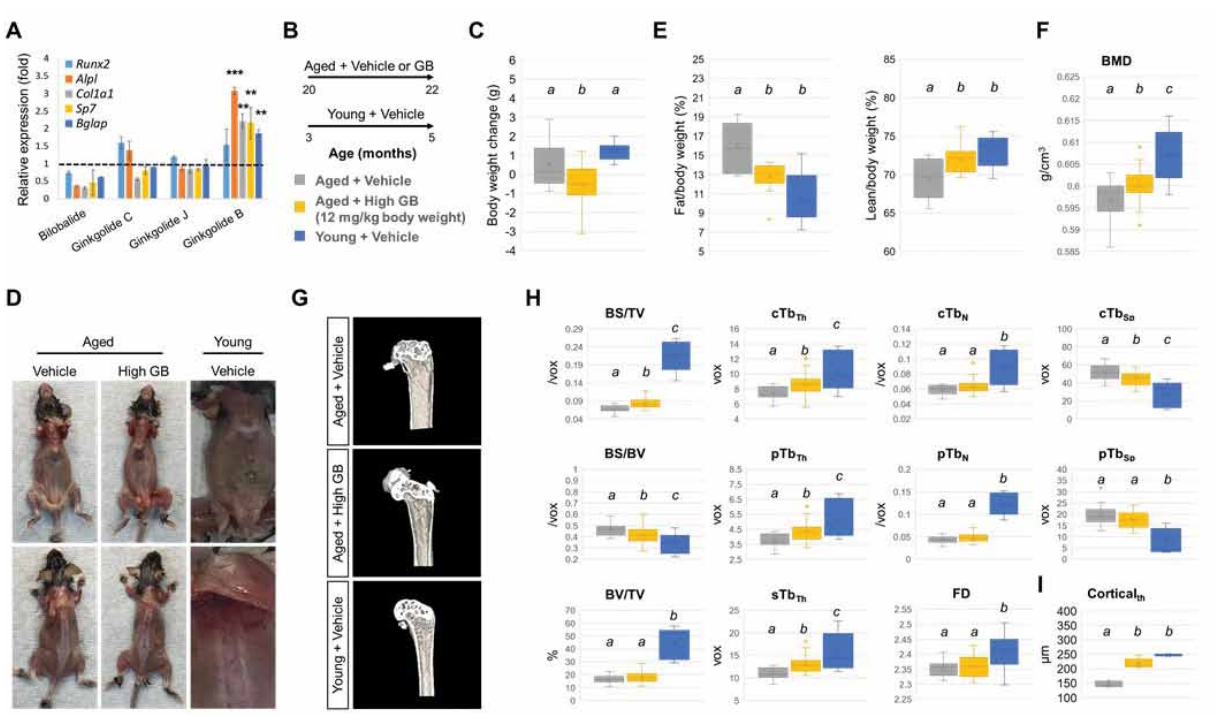
Professor Oscar Lee and his research team have intensively joined several international / local conferences to showcase their research results. Professor Oscar Lee was invited by Academician Yingze Zhang from the Chinese Academy of Engineering to give a talk on "Biological reconstruction after wide resection of malignant bone tumours" during 第一屆河北省骨腫瘤學術會議/疑難病例MDT病例討論會暨第二屆石家莊市骨腫瘤學術會議 in January. Professor Chien-wei Lee, Dr. Carol Lau and Miss Rita Shin attended the Orthopaedic Research Society (ORS) 2019 Annual Meeting in February, to present their research results titled "Therapeutic Potentials of Ginkgo Biloba Extract in Osteoporosis Treatment",



“Simvastatin Induces Anti-Tumour Effect in Giant Cell Tumour of Bone through Differentiation Promotion”, and “Effects of Dexamethasone on Osteocyte Formation of Mesenchymal Stromal Cells”, respectively. In March, Professor Oscar Lee attended 兒童肝移植和術後恢復及移植後幹細胞參與治療等相關課題會談 and discussed about the collaboration on “Treatment of malignant musculoskeletal tumours in children”. Later on, Professor Oscar Lee presented the latest finding on “Treatment of Spinocerebellar Ataxia with Allogenic Mesenchymal Stem Cells” during the 25th Annual Meeting of the International Society for Cellular Therapy held in Melbourne, Australia in May, and he also served as a Review Committee / Organiser of the conference. Then, Professor Lee was invited by The Guanghua School of Stomatology, Hospital of Stomatology, SUN Yat-sen University as a Keynote speaker and gave a talk on “Mesenchymal Stem Cells and Skeletal Tissue Engineering” during 2019 中國生物醫學工程學會組織工程與再生醫學分會學術研討會 in July. Professor Oscar Lee also paid a few visits to the Institute of Engineering in Medicine, University of California San Diego to discuss research progress on “Novel bioengineering and technological approaches to solve two major health problems” collaborative project during this year. The team also attended the 39th Annual Congress of the Hong Kong Orthopaedic Association in November and presented 3 podium talks and 4 posters.

Furthermore, Professor Oscar Lee and Professor Chien-wei Lee, as faculties of the Institute for Tissue Engineering and Regenerative Medicine, devoted themselves to bridge translation barriers and promote clinical translation of biomedical research in multidisciplinary approaches, and also to build up collaborations across the Great Bay Area. Professor Oscar Lee presented a lecture in “MSCs for Liver Diseases: From Bench to Bedside” during the 10th iTERM Lunchtime Seminar in April. Professor Oscar Lee was invited to 廣東省醫學會第七次細胞治療學術會議 and gave a lecture on the topic: “Research and Translational Application of Mesenchymal Stem Cells” in August. Professor Chien-wei Lee also presented “Mesenchymal

stem cell-based therapy for non-alcoholic fatty liver disease” during the School of Biomedical Sciences (SBS) Research Day 2019 in May. Moreover, Professor Chien-wei Lee attended the International Chinese Musculoskeletal Research Conference in Shenzhen, Guangdong, to present the study result on “Ginkgo biloba extract rebalances bone remodeling and ameliorates osteoporosis *in vivo*”, and visited The Chinese University of Hong Kong, Shenzhen for possible collaboration opportunities. Both professors also brought academic exchanges between Hong Kong and Taiwan. Professor Oscar Lee attended the 2019 International Summit for Shock Wave, CAOS and Regeneration Medicine in Taiwan and gave a speech on “Cell Therapy for Osteoarthritis” in September. He was invited as an Expert Panel / Speaker in “Taiwan’s next step on Regenerative medicine: Stem cell” Forum during Futex Taipei 2019 in December. Professor Chien-wei Lee also led most of the group members to attend the Abcam Epigenetics Conference and 14th Asia Epigenome Meeting (AEM) / 3rd Taipei Epigenetics and Chromatin Meeting (TECM) on 16-18 of October with the support of CUHK Taiwan Collaboration fund. During their visit, Professor Chien-wei Lee has also discussed with Professor Li-jung Juan (Genomic Research Center, Academia Sinica, Taiwan) and Professor Chih-yu Yang (Institute of Clinical Medicine, National Yang-Ming University), to share research ideas on epigenetic manipulation of mesenchymal stem cells in order to treat liver diseases and application of cell therapy on chronic kidney diseases.



Ginkgolide B ameliorates for ageing-related osteoporosis.

Oral gavage of ginkgolide B, an unique component of Ginkgo biloba extract, for two months reduces body weight and increases the bone mineral density in aged mice.

(A) qRT-PCR of osteogenic-specific genes in MSC-derived osteoblasts after different Ginkgo biloba extractions treatment for 48 hours.

(B) Experimental design for animal study.

(C-E) Change of body weight (C) and representative photographs of mice (D) and Body composition (E) after ginkgolide B administration to aged mice for 2 months.

(F) Bone mineral density (BMD) of proximal femur.

(G) Representative μ CT images of proximal femur.

(H) Quantification of μ CT-derived proximal femur morphological parameters.

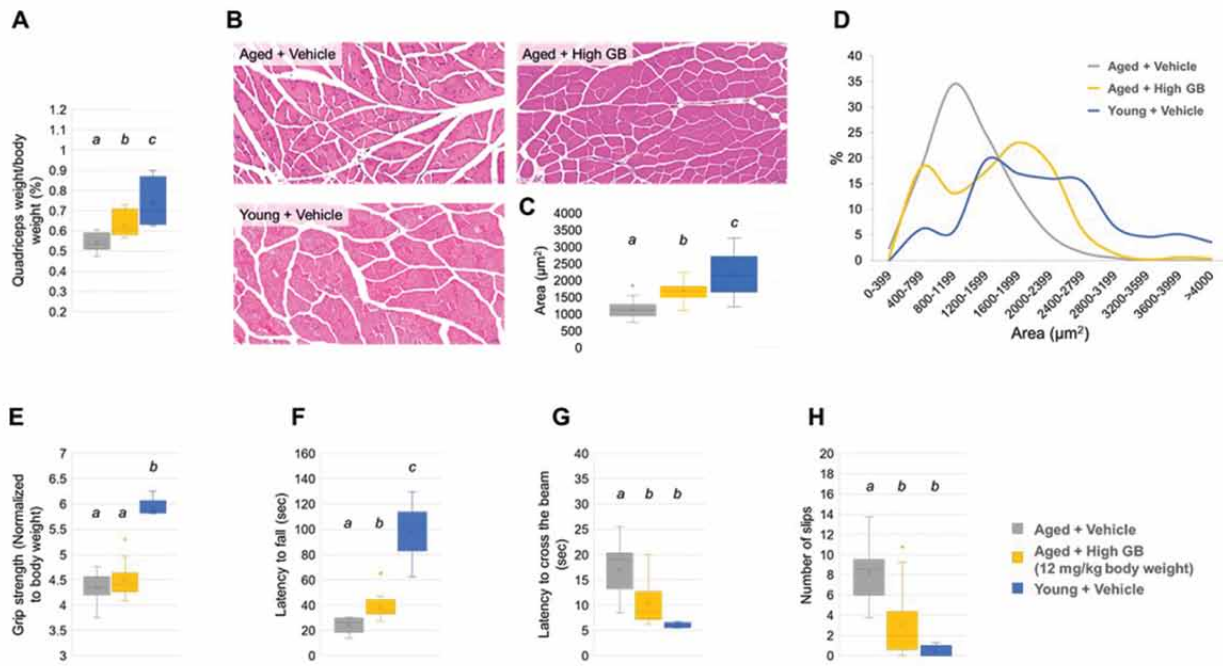
(I) Quantification of cortical thickness from HE staining of femur.

BS, Bone surface area; BV, Bone volume; TV, Tissue volume; BS/TV, Bone surface density; BS/BV, Bone specific surface; BV/TV, Percentage bone volume; cTbTh, pTbTh and sTbTh, Trabecular thickness (cylinder, plate, and sphere types); cTbN and pTbN, Trabecular number (cylinder and plate types); cTbSp and pTbSp, Trabecular separation (cylinder and plate types); FD, Fractal dimension; CorticalTh, Cortical thickness.

For panel A, statistical analyses are performed using Student’s paired t-test. For comparison to vehicle control group, with significance set at $P < 0.05$. (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$).

For panel C-F and H, statistical analyses are performed using Tukey’s multiple comparison test. Means not share any letter are significantly different ($p < 0.05$).

Source: Professor Oscar Lee



Ginkgolide B ameliorates ageing-related sarcopenia.

Oral gavage of ginkgolide B increases muscle mass and functions in aged mice.

(A) Quadriceps weight-to-body weight. (Aged + Vehicle, n = 14; Aged + High GB, n = 19; Young + Vehicle, n = 10).

(B) Representative HE staining of quadriceps. Scale bar, 100 μ m.

(C-D) Quantification (C) and distribution (D) of myofiber cross-sectional area are measured from 30 images from 3 mice each group.

(E-H) Muscle function was measured by grip strength (E), rotarod (F) and balance beam assay (G-H).

For panel A, C, E-H statistical analyses are performed using Tukey's multiple comparison test. Means not share any letter are significantly different ($p < 0.05$).

Source: Professor Oscar Lee

Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Oscar Lee	MWLC Associate Member of Karolinska Institute's Ming Wai Lau Centre for Reparative Medicine, (since 1 September 2019)

Fellowships

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

Fellowships

Member's Full Name	Details
Oscar Lee	Reviewer, Gastroenterology
	Reviewer, Stem Cells
	Reviewer, Hepatology
	Reviewer, Orthopaedic Research Society 2019 Annual Meeting
Chien-wei Lee	Reviewer, Cytotherapy
	Reviewer, Stem Cell Research & Therapy

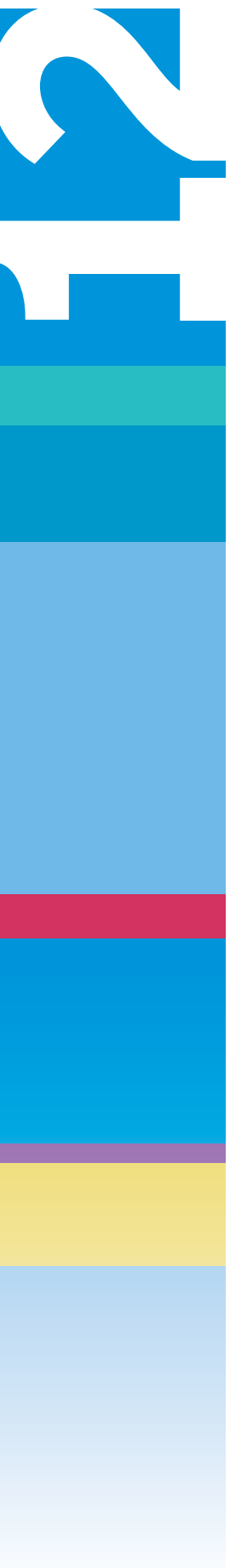
Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Oscar Lee	Treatment of Obesity-Induced Nonalcoholic Fatty Liver Disease with Exosomes from Mesenchymal Stem Cells	Karolinska Institute	01/09/2019	31/08/2020	525,000
Chien-wei Lee Oscar Lee	Development of a Disease-in-a-dish Model Mimicking De Novo Lipogenesis-mediated Fatty Liver	CUHK Research Committee – Direct Grant	30/06/2019	29/06/2020	150,000
Chien-wei Lee	Participate in the Joint AEM / TECM Conference and Identify Potential Collaborative Opportunities from NYMU and Academia Sinica in Taiwan	CUHK Taiwan Collaboration Fund	15/10/2019	18/10/2019	21,000

Publications

A. Journal Papers

- Xu HT, Lee CW, Li MY, Wang YF, Yung SHP, Lee KSO. The shift in macrophages polarization after tendon injury: A systematic review. *Journal of Orthopaedic Translation*. 2019. doi:10.1016/j.jot.2019.11.009.
- Lau CPY, Fung CSH, Wong KC, Wang B, Huang L, Lee OK, Kumta SM. Simvastatin possesses antitumor and differentiation-promoting properties that affect stromal cells in giant cell tumor of bone. *Journal of Orthopaedic Research*. 2020;38(2):297-310. doi:10.1002/jor.24456 [Epub ahead of print].



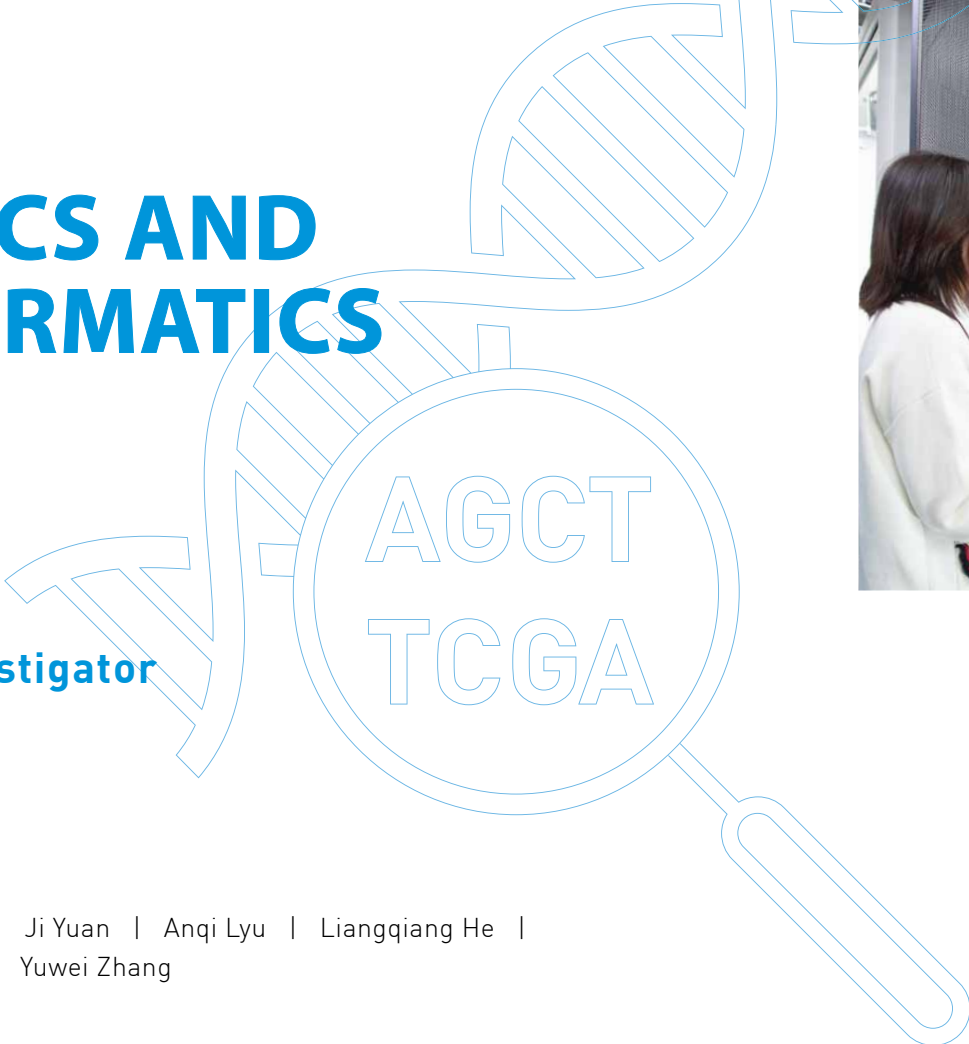
GENOMICS AND BIOINFORMATICS

Principal Investigator

Professor Hao Sun

Team

Yile Huang | Yingzhe Ding | Ji Yuan | Anqi Lyu | Liangqiang He | Zhiming He | Yulong Qiao | Yuwei Zhang



Research and Scholarship

Fellowships

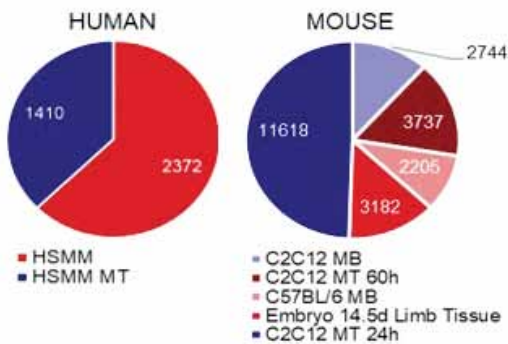
Member's Full Name	Details
Liangqiang He	Postdoctoral Fellowship, Faculty of Medicine, The Chinese University of Hong Kong

Academic Editorship and Reviews

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

Research Progress Summary

In the reporting period, Professor Hao Sun and his team are funded by 13 different grants from Research Grants Council – General Research Fund, National Natural Science Foundation of China/Research Grants Council Joint Research Scheme, Food and Health Bureau-Health and Medical Research Fund, and Research Grants Council – Theme-based Research Scheme, for studying of transcriptional regulation mechanisms in muscle stem cells as well as next generation data analysis for plasma DNA/RNA sequencing. The team also published 7 papers on *Nature Methods*, *Nature Communications*, and *Bioinformatics et al.*



Distribution of Transcription Factor binding hotspots in different cell types in SkmDB.

Source: Yuan J, Zhou JJ, Wang HT, 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.



Journal / Conference Reviews

Member's Full Name	Details
Hao Sun	Reviewer, Bioinformatics
	Reviewer, Clinical Biochemistry
	Reviewer, Clinical Chemistry
	Reviewer, Databases
	Reviewer, Scientific Reports
	Reviewer, EMBO Journal

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Hao Sun	Study on the Mechanism Underlying BMAL1/CLOCK-mediated Regulation of Human Stem Cell Homeostasis and Aging	National Natural Science Foundation of China/Research Grants Council – Joint Research Scheme 2018/19	01/01/2019	31/12/2022	1,166,714
Hao Sun	Genome-wide Computational Identification and <i>in vivo</i> CRISPR Screen of Key Transcription Factors (TFs) and TF Hotspots Governing Muscle Satellite Cell Lineage Progression	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	1,136,632
Hao Sun	Mechanistic Investigation of Linc-p27 Function in Skeletal Muscle Satellite Cell and Muscle Regeneration	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	970,697
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	CUHK Research Committee – Direct Grant	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	CUHK 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 Theme-based Research Scheme	01/12/2016	30/11/2021	4,444,000

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
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	Mechanistic Investigation of Linc-p27 Function in Skeletal Muscle Satellite Cell and Muscle Regeneration	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	970,697
Hao Sun	Investigate the Role of Satellite Cell Derived M-CSF in Regulating Macrophage Function during Skeletal Muscle Regeneration	Research Grants Council /Procore-HK Joint Research Scheme	01/01/2018	31/12/2019	86,400
Hao Sun	To Investigate Long Noncoding RNA (lncRNA) Nuclear Localisation Mechanism by Genome-wide Analysis of lncRNA and RNA Binding Protein Interactions	CUHK Research Committee – Direct Grant	30/06/2019	29/06/2020	94,800

Publications

A. Journal Papers

1. Sun K, Jiang P, Cheng SH, Cheng THT, Wong J, Wong VWS, Ng SSM, Ma BBY, Leung TY, Chan SL, Mok TSK, Lai PBS, Chan HLY, Sun H, Chan KCA, Chiu RWK and Lo YMD. Orientation-aware plasma cell-free DNA fragmentation analysis in open chromatin regions informs tissue of origin. *Genome Research*. 2019;29(3):418-427. doi:10.1101/gr.242719.118.

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.

3. Zhou J, So KK, Li Y, Li Y, Yuan J, Ding Y, Chen F, Huang Y, Liu J, Lee W, Li G, Ju Z, Sun H, Wang H. Elevated H3K27ac in aged skeletal muscle leads to increase in extracellular matrix and fibrogenic conversion of muscle satellite cells. *Aging Cell*. 2019;18(5):e12996. doi:10.1111/ace1.12996.

4. Chen F, Zhou J, Li Y, Zhao Y, Yuan J, Cao Y, Wang L, Zhang Z, Zhang B, Wang CC, Cheung TH, Wu Z, Wong CC, Sun H, Wang H. YY1 regulates skeletal muscle regeneration through controlling metabolic reprogramming of satellite cells. *EMBO Journal*. 2019 May 15;38(10). doi:10.15252/embj.201899727.

5. Yu Zhao, Jiajian Zhou, Liangqiang He, Yuying Li, Jie Yuan, Kun Sun, Xiaona Chen, Xichen Bao, Miguel A. Esteban, Hao Sun, Wang H. MyoD induced enhancer RNA interacts with hnRNPL to activate target gene transcription during myogenic differentiation. *Nature Communications*. 2019;10(1):5787. doi:10.1038/s41467-019-13598-0.

GENOMICS AND BIOINFORMATICS



Principal Investigator

Professor Peiyong Jiang

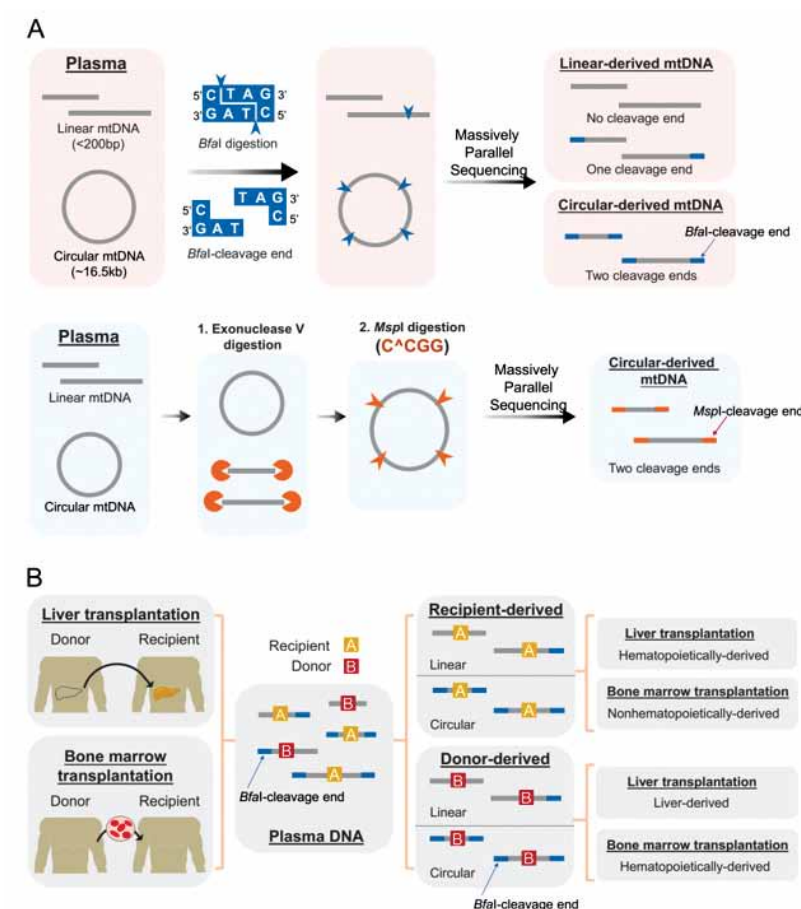


Team

Xingqian Li | Meng Ni | Olivia Tse | Daisy Gao | Coral Lee |
Ze Zhou | Haiqiang Zhang | Lu Ji | Wenlei Peng | Xi Hu | Silvia Deng |
Harry Chan | Liangbo Huang

Research Progress Summary

In this academic year, Professor Peiyong Jiang and his research team have made several important achievements in the bioinformatics area. Cell-free DNA fragmentation is a nonrandom process. The team developed a bioinformatics approach for profiling the landscape of plasma DNA end motifs, providing new means for cancer detection and noninvasive prenatal testing. This analysis further revealed the biological linkage between nucleases and plasma DNA generation. On the other hand, they took advantage of the methylation patterns of plasma EBV DNA to develop a novel bioinformatics platform for non-invasive screening of nasopharyngeal carcinoma (NPC) at its early stage. Moreover, they developed a sophisticated bioinformatics platform to enable an integrative and synergistic analysis of urinary DNA for detecting patients with bladder cancer.



Schematic illustration of the principles of topologic analysis of mtDNA.

Source: Ma MJL, Zhang HA, Jiang PY, Sin STK, Lam WKJ, Cheng SH, Lee WS, Gai WX, Tse OYO, Peng WL, Wong J, Raghupathy R, Wong RSM, Sahota D, Leung TY, Chan KCA, Chiu RWK, Lo YMD. Topologic analysis of plasma mitochondrial DNA reveals the coexistence of both linear and circular molecules. *Clinical Chemistry*. 2019;65(9):1161-1170. doi:10.1373/clinchem.2019.308122.





■ 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 Commission – 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 Grant Council – General Research Fund	01/12/2018	30/11/2020	739,525

■ Publications

A. Journal Papers

1. Lam WKJ, Jiang P, Chan KCA, Peng W, Shang H, Heung MMS, Cheng SH, Zhang H, Tse OYO, Raghupathy R, Ma BBY, Hui EP, Chan ATC, Woo JKS, Chiu RWK, Lo YMD. Methylation analysis of plasma DNA informs etiologies of Epstein-Barr virus-associated diseases. *Nature Communications*. 2019;10(1):3256. doi:10.1038/s41467-019-11226-5.
2. Ma MJL, Zhang H, Jiang P, Sin STK, Lam WKJ, Cheng SH, Lee WS, Gai W, Tse OYO, Peng W, Wong J, Raghupathy R, Wong RSM, Sahota D, Leung TY, Chan KCA, Chiu RWK, Lo DYM. Topologic analysis of plasma mitochondrial DNA reveals the coexistence of both linear and circular molecules. *Clinical Chemistry*. 2019;65(9):1161-1170. doi:10.1373/clinchem.2019.308122.
3. Jiang P, Chan KCA, Lo YMD. Liver-derived cell-free nucleic acids in plasma: Biology and applications in liquid biopsies. *Journal of Hepatology*. 2019;71(2):409-421. doi:10.1016/j.jhep.2019.04.003 [Review].
4. Cheng THT, Jiang P, Teoh JYC, Heung MMS, Tam JCW, Sun X, Lee WS, Ni M, Chan RCK, Ng CF, Chan KCA, Chiu RWK, Lo YMD. Noninvasive detection of bladder cancer by shallow-depth genome-wide bisulfite sequencing of urinary cell-free DNA for methylation and copy number profiling. *Clinical Chemistry*. 2019;65(7):927-936. doi:10.1373/clinchem.2018.301341.
5. Gabbett MT, Laporte J, Sekar R, Nandini A, McGrath P, Lead MN, Sapkota Yadav, Jiang P, Zhang H, Burgess T, Montgomery GW, Chiu RWK, Fisk NM. Molecular support for heterogonesis resulting in sesquizygotic twinning. *New England Journal of Medicine*. 2019;380(9):842-849. doi:10.1056/NEJMoa1701313 [Brief Report].
6. Sun K, Jiang P, Cheng SH, Cheng THT, Wong J, Wong WWS, Ng SSM, Ma BBY, Leung TY, Chan SL, Mok TSK, Lai PBS, Chan HLY, Sun H, Chan KCA, Chiu RWK, Lo YMD. Orientation-aware plasma cell-free DNA fragmentation analysis in open chromatin regions informs tissue of origin. *Genome Research*. 2019;29(3):418-427. doi:10.1101/gr.242719.118.
7. Serpas L, Chan RWY, Jiang P, Ni M, Sun K, Rashidfarrokhi A, Soni C, Sisirak V, Lee WS, Cheng SH, Peng W, Chan KCA, Chiu RWK, Reizis B, Lo YMD. Dnase1l3 deletion causes aberrations in length and end-motif frequencies in plasma DNA. *Proceedings of the National Academy of Sciences of the United States of America*. 2019;116(2):641-649. doi:10.1073/pnas.1815031116.
8. Vong JSL, Jiang P, Cheng SH, Lee WS, Tsang JCH, Leung TY, Chan KCA, Chiu RWK, Lo YMD. Enrichment of fetal and maternal long cell-free DNA fragments from maternal plasma following DNA repair. *Prenatal Diagnosis*. 2019;39(2):88-99. doi:10.1002/pd.5406.

B. Book Chapter

1. Ni M, Peng XL, Jiang P. Bioinformatics pipeline for accurate quantification of fetal DNA fraction in maternal plasma. *Methods in Molecular Biology*. 2019;1909:177-180. doi: 10.1007/978-1-4939-8973-7_13.

NON-CODING RNAs



Principal Investigator

Professor Huating Wang



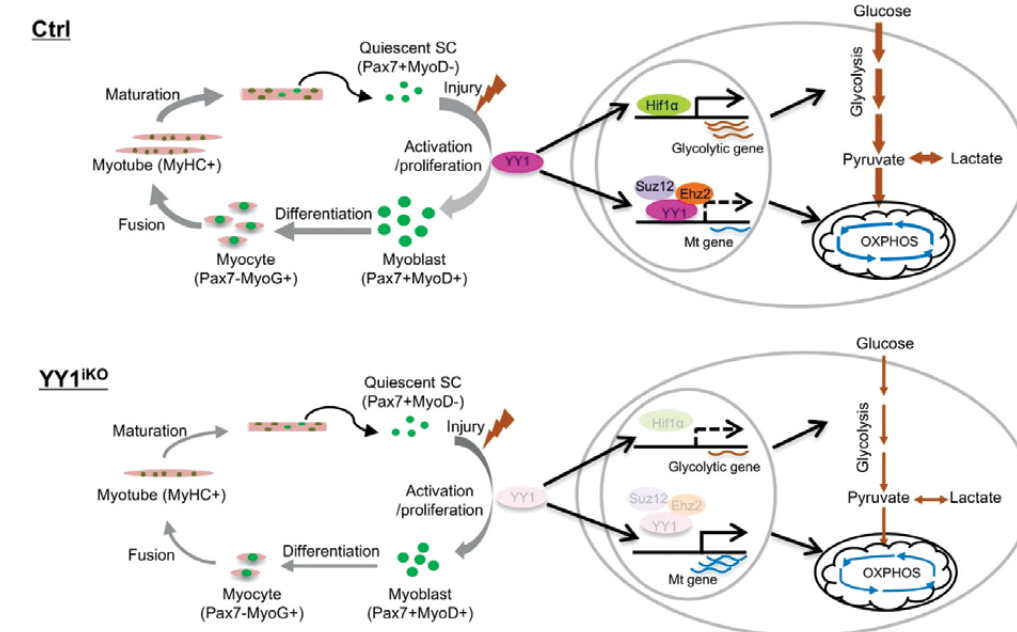
Team

Xiaona Chen | Yu Zhao | Liangqiang He | Yuying Li | Suyang Zhang |
Guang Xue | Yang Li | Zhiming He | Yulong Qiao

Research Progress Summary

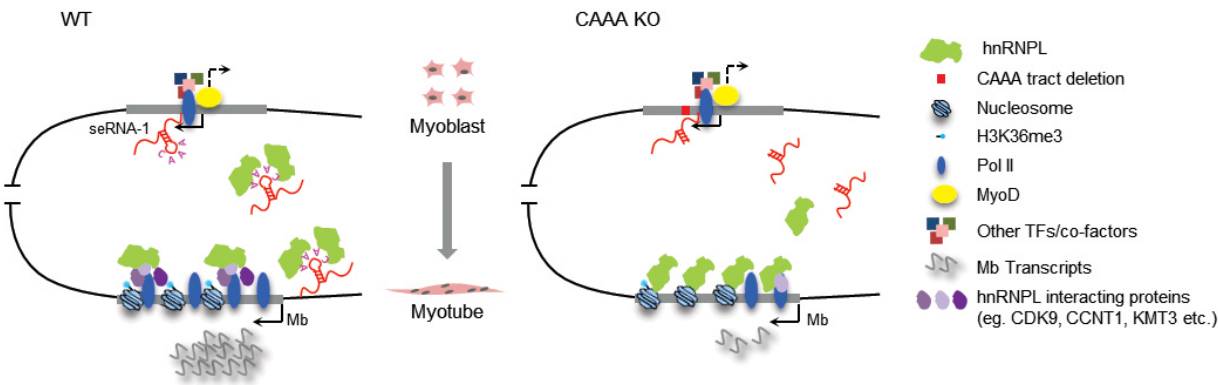
During the past year, the team led by Professor Huating Wang continued the work on gene regulatory mechanisms centred on transcription factors (TFs) and RNA binding proteins (RBPs) in skeletal muscle stem cells and muscle regeneration. Specifically, they have been focusing on the following projects:

- (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 muscle stem cell lineage progression as well as sarcopenia, a muscle weakening condition associated with ageing; and
- (4) to define and characterise TFs governing the early activation of muscle stem cells.



Schematic model of the role of YY1 during adult muscle regeneration.

Source: Chen FY, Zhou JJ, Li YY, Zhao Y, Yuan J, Cao Y, Wang LJ, Zhang ZK, Zhang BT, Wang CC, Cheung TH, Wu ZG, Wong CCL, Sun H, Wang HT. YY 1 regulates skeletal muscle regeneration through controlling metabolic reprogramming of satellite cells. *EMBO Journal*. 2019;38(10). doi:10.15252/emboj.201899727.



Schematic model of the eRNA regulation and function in myoblast differentiation.

Source: Zhao Y, Zhou JJ, He LQ, Li YY, Yuan J, Sun K, Chen XN, Bao XC, Esteban MA, Sun H, Wang HT. MyoD induced enhancer RNA interacts with hnRNPL to activate target gene transcription during myogenic differentiation. *Nature Communications*. 2019;10(1). doi:10.1038/s41467-019-13598-0.

Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Guang Xue	Best Talk Award, 9 th CUHK International Symposium on Stem Cell Biology & Regenerative Medicine, Hong Kong
Yuying Li	Best Talk Award, 5 th China Muscle Society Symposium, Hong Kong University of Science and Technology, Hong Kong
Xiaona Chen	廣東省自然科學基金面上項目

Fellowships

Member's Full Name	Details
Yu Zhao	Postdoctoral Fellowship, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong
Yuying Li	Postdoctoral Fellowship, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong
Liangqiang He	Postdoctoral Fellowship, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong

Reviewer of Journal / Conference

Member's Full Name	Details
Huating Wang	Reviewer, Nucleic Acid Research
	Reviewer, Cell Research
	Reviewer, Journal of Clinical Investigation
	Reviewer, Journal of Orthopedics

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Huating Wang	Elucidation of Post-transcriptional Regulatory Functions of Dhx36 in Skeletal Muscle Stem Cells and Muscle Regeneration	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	1,111,376
Huating Wang	Large Scale Interaction Analysis of RNA Binding Proteins/LncRNAs to Identify lncRNA Nuclear Localization Mechanisms	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	1,115,175
Huating Wang	長鏈非編碼RNA Linc-Cdkn1b 對骨骼肌幹細胞及肌肉再生的調控及其分子機制研究	National Natural Science Foundation of China	01/01/2018	31/12/2021	RMB 600,000
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	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 Satelll ite Cell and Muscle Regeneration	CUHK Research Committee – Direct Grant	30/06/2018	29/06/2019	71,000

Publications

A. Journal Papers

1. Zhao Y, Zhou J, He L, Li Y, Yuan J, Sun K, Chen X, Bao X, Esteban MA, Sun H, Wang H. MyoD induced enhancer RNA interacts with hnRNPL to activate target gene transcription during myogenic differentiation. *Nature Communications*. 2019;10(1):5787. doi:10.1038/s41467-019-13598-0.
2. Zhou J, So KK, Li Y, Li Y, Yuan J, Ding Y, Chen F, Huang Y, Liu J, Lee W, Li G, Ju Z, Sun H, Wang H. Elevated H3K27ac in aged skeletal muscle leads to increase in extracellular matrix and fibrogenic conversion of muscle satellite cells. *Aging Cell*. 2019;18(5):e12996. doi:10.1111/ace1.12996.
3. Chen F, Zhou J, Li Y, Zhao Y, Yuan J, Cao Y, Wang L, Zhang Z, Zhang B, Wang CC, Cheung TH, Wu Z, Wong CCL, Sun H, Wang H. YY 1 regulates skeletal muscle regeneration through controlling metabolic reprogramming of satellite cells. *EMBO Journal*. 2019;38(10):e99727. doi:10.15252/emboj.201899727.

CELLULAR SIGNALLING



Principal Investigator

Professor William Wu



Team

Tony Gin | Matthew Chan | Lin Zhang | Xiaodong Liu | Wei Hu | Idy Ho |
Dan Huang | Lhotse Ng | Yan Wang | Qing Li | Hung Chan |
Xiansong Wang | Judeng Zeng | Yidan Zou | Wenyi Zhu | Yingzhi Liu |
TP Tam | Wenye Xu | Ling Lin | Zheng Huang | Yanjun Jiang

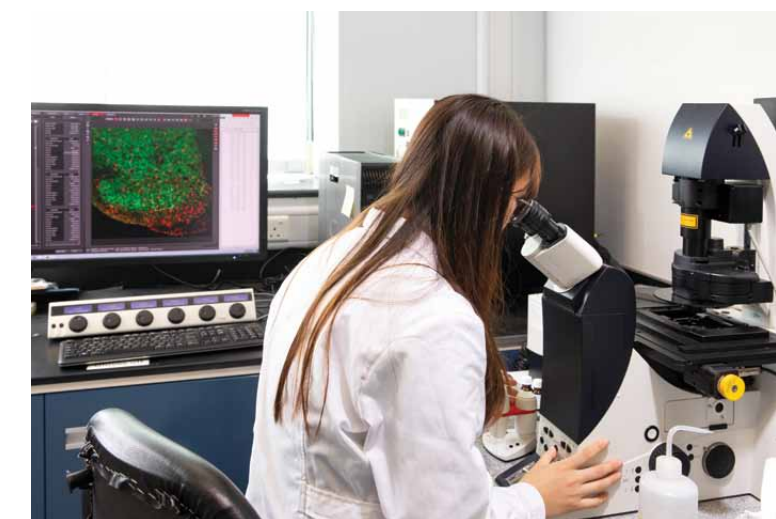
Research Progress Summary

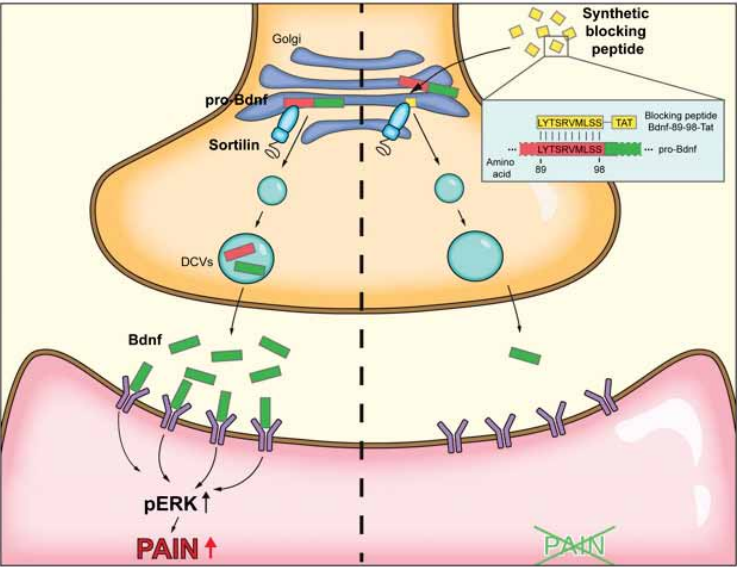
Autophagy – The team led by Professor William Wu discovered that *Helicobacter pylori* could invade into the gastric epithelium where it became sequestered and survived in autophagosomes with impaired lysosomal acidification. Vitamin D3 activated the PDIA3-STAT3-MCOLN3-lysosomal Ca^{2+} cascade to normalise lysosomal acidification (*Autophagy*, 2019). In nutritional steatohepatitis, they found that the phytochemical polydatin protected against hepatic lipid accumulation and alleviated inflammation and hepatocyte damage by upregulating the expression and activity of TFEB, a known master regulator of lysosomal function (*Journal of Cellular and Molecular Medicine*, 2019).

Pain Mechanism – They found that sortilin-mediated secretion of brain-derived neurotrophic factor (BDNF) from dorsal root ganglia neurons contributed to the development

and persistence of inflammatory pain. The team also devised a peptide to interfere with sortilin-BDNF interaction, which might serve as a novel therapeutic approach for chronic inflammatory pain (*Theranostics*, 2019).

Cancer – They re-analysed The Cancer Genome Atlas (TCGA) dataset and identified new genetic features associated with altered survival in patients with pancreatic ductal adenocarcinoma (*Seminars in Cancer Biology*, 2019). In colorectal cancer, they found that the traditional Chinese Medicine compound bufalin prevented tumour formation in two murine models via inhibition of oncogenic NF- κ B and PI3K/Akt pathways (*Cancer Prevention Research (Phila)*, 2019) whereas tissue expression of eukaryotic elongation factor-2 kinases served as an independent prognostic factor (*BMC Cancer*, 2019).





A novel peptide interfering with proBDNF-sortilin interaction alleviates chronic inflammatory pain.

Source: Ho IHT, Liu XD, Zou YD, Liu TA, Hu W, Chan H, Tian YY, Zhang YC, Li Q, Kou SL, Chan CS, Gin T, Cheng CHK, Wong SH, Yu J, Zhang L, Wu WKK, Chan MTV. (2019). A Novel Peptide Interfering with proBDNF-Sortilin Interaction Alleviates Chronic Inflammatory Pain. *Theranostics*, 9(6), 1651-1665. doi.10.7150/thno.29703.

■ Research and Scholarship

Fellowships

Member's Full Name	Details
William Wu	Fellow of Royal College of Physicians and Surgeons of Glasgow, UK

Academic Editorship

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

Reviewer of Journal / Conference

Member's Full Name	Details
William Wu	Ad hoc Reviewer, Oncogene

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
William Wu	A Mechanistic Study on the Influence of Cancers on Human Genome Evolution	Shenzhen Science, Technology and Innovation Commission – Shenzhen Science and Technology Programme	18/03/2019	31/03/2022	RMB 3,000,000
William Wu	A Mechanistic Study of the Therapeutic Effect of Butyrate in Nonalcoholic Steatohepatitis: Involvement of Autophagy	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	971,635

Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
William Wu	Molecular Characterization of the Ubiquitin-proteasome System as a Host Defense Mechanism against Intracellular <i>Helicobacter pylori</i> Infection	The TUYF Charitable Trust	01/09/2019	31/08/2022	2,851,800
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	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
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
Tony Gin	Reduction of Chronic Postsurgical Pain with Ketamine – The ROCKet Randomized Controlled Trial	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	971,044
Matthew Chan	Pharmacokinetics of Oseltamivir in Critically Ill Patients with Severe Influenza	Food and Health Bureau – Commissioned Research on Control of Infectious Diseases (Phase III)	01/04/2015	30/09/2019	290,000
Lin Zhang	A Mechanistic Study of the Therapeutic Effect of Butyrate in <i>Helicobacter Pylori</i> Colonization and its Associated Gastritis: Involvement of Autophagic-lysosomal Pathway	National Natural Science Foundation of China	01/01/2019	31/12/2022	RMB 580,000
Lin Zhang	Effects of Ketamine and Cannabis on Antimicrobial Peptide Expression and Infection Susceptibility	Narcotics Division, Security Bureau – Beat Drugs Fund	01/08/2019	31/07/2022	2,684,140
Lin Zhang	Elucidation of the Role of Cathelicidin in Protection against Against Multi-drug Resistant <i>Acinetobacter Baumannii</i> Associated Pneumonia	Food and Health Bureau – Health and Medical Research Fund	20/09/2019	19/09/2022	1,499,800
Lin Zhang	Activating Mucolipin for Restoring Lysosomal Function in the Control of <i>Helicobacter Pylori</i> Colonization	Food and Health Bureau – Health and Medical Research Fund	01/09/2017	31/08/2019	1,198,360

Publications

A. Journal Papers

1. Ho IHT, Liu X, Zou Y, Liu T, Hu W, Chan H, Tian Y, Zhang Y, Li Q, Kou S, Chan CS, Gin T, Cheng C, Wong SH, Yu J, Zhang L, Wu WKK, Chan MTV. A novel peptide interfering with proBDNF-sortilin interaction alleviates chronic inflammatory pain. *Theranostics*. 2019;9(6):1651-1665. doi:10.7150/thno.29703.

2. Ho J, Li X, Zhang L, Liang Y, Hu W, Yau JCW, Chan H, Gin T, Chan MTV, Tse G, Wu WKK. Translational genomics in pancreatic ductal adenocarcinoma: A review with re-analysis of TCGA dataset. *Seminars in Cancer Biology*. 2019;55:70-77. doi:10.1016/j.semcancer.2018.04.004 (Review).

3. Wong SH, Wu WKK. Cancer genomics: From benchtop to bedside. *Seminars in Cancer Biology*. 2019;55:iii-iv. doi:10.1016/j.semcancer.2019.03.001 (Editorial).

4. Hu W, Zhang L, Li MX, Shen J, Liu XD, Xiao ZG, Wu DL, Ho IHT, Wu JCY, Cheung CKY, Zhang YC, Lau AHY, Ashktorab H, Smoot DT, Fang EF, Chan MTV, Gin T, Gong W, Wu WKK, Cho CH. Vitamin D3 activates the autolysosomal degradation function against *Helicobacter pylori* through the PDIA3 receptor in gastric epithelial cells. *Autophagy*. 2019;15(4):707-725. doi:10.1080/15548627.2018.1557835.

5. Li Z, Li X, Chen X, Li S, Ho IHT, Liu X, Chan MTV, Wu WKK. Emerging roles of long non-coding RNAs in neuropathic pain. *Cell Proliferation*. 2019;52(1). doi:10.1111/cpr.12528 (Review).

6. Li Z, Chen X, Xu D, Li S, Chan MTV, Wu WKK. Circular RNAs in nucleus pulposus cell function and intervertebral disc degeneration. *Cell Proliferation*. 2019;52(6):e12704. doi:10.1111/cpr.12704 (Review).

7. Chen X, Chan H, Zhang L, Liu X, Ho IHT, Zhang X, Ho J, Hu W, Tian Y, Kou S, Chan CS, Yu J, Wong SH, Gin T, Chan MTV, Sun X, Wu WKK. The phytochemical polydatin ameliorates non-alcoholic steatohepatitis by restoring lysosomal function and autophagic flux. *Journal of Cellular and Molecular Medicine*. 2019;23(6):4290-4300. doi:10.1111/jcmm.14320.

8. Sun X, Ng TTH, Sham KKY, Zhang L, Chan MTV, Wu WKK, Cheng CHK. Bufalin, a traditional Chinese medicine compound, prevents tumor formation in two murine models of colorectal cancer. *Cancer Prevention Research (Phila)*. 2019;12(10):653-666. doi:10.1158/1940-6207.CAPR-19-0134.

9. Ng TH, Sham KKY, Xie CM, Ng SSM, To KF, Tong JHM, Liu WYZ, Zhang L, Chan MTV, Wu WKK, Cheng CHK. Eukaryotic elongation factor-2 kinase expression is an independent prognostic factor in colorectal cancer. *BMC Cancer*. 2019;19(1):649. doi:10.1186/s12885-019-5873-0.

10. Coker OO, Nakatsu G, Dai Z, Wu WKK, Chen Z, Ng SC, Wong SH, 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.

11. Xing R, Zhou Y, Yu J, Yu Y, Nie YZ, Luo W, Yang C, Xiong T, Wu WKK, Li Z, Bing Y, Lin S, Zhang Y, Hu Y, Li L, Han L, Yang C, Huang S, Huang, S, Zhou R, Li J, Wu K, Fan D, Tang G, Zou J, Zhu Z, Ji J, Fang X, Lu Y. Whole-genome sequencing reveals novel tandem-duplication hotspots and a prognostic mutational signature in gastric cancer. *Nature Communications*. 2019;10(1):2037. doi:10.1038/s41467-019-09644-6.

12. Zhang Y, Zhang L, Yang L, Vong CI, Chan KF, Wu WKK, Kwong TNY, Lo NWS, Ip M, Wong SH, Sung JJY, Chiu PWY, Zhang L. Real-time tracking of fluorescent magnetic spore-based microrobots for remote detection of *C. diff* toxins. *Science Advances*. 2019;5(1):eaau9650. doi:10.1126/sciadv.aau9650.

13. Li Z, Li X, Bi J, Chan MTV, Wu WKK, Shen J. Melatonin protected against the detrimental effects of microRNA-363 in a rat model of vitamin A-associated congenital spinal deformities: Involvement of Notch signaling. *Journal of Pineal Research*. 2019;66(3):e12558. doi:10.1111/jpi.12558.

14. Zeng J deng, Wu WKK, Wang H yun, Li X xing. Serine and one-carbon metabolism, a bridge that links mTOR signaling and DNA methylation in cancer. *Pharmacological Research*. 2019;149:104352. doi:10.1016/j.phrs.2019.104352 (Review).

15. Li Z, Ho IHT, Li X, Xu D, Wu WKK, Chan MTV Li S, Liu X. Long non-coding RNAs in the spinal cord injury: Novel spotlight. *Journal of Cellular and Molecular Medicine*. 2019;23(8):4883-4890. doi:10.1111/jcmm.14422 (Review).

16. Li Z, Ma J, Li X, Chan MTV, Wu WKK, Wu Z, Shen J. Aberrantly expressed long non-coding RNAs in air pollution-induced congenital defects. *Journal of Cellular and Molecular Medicine*. 2019;23(11):7717-7725. doi:10.1111/jcmm.14645.

17. Li Z, Ma J, Bi J, Guo H, Chan MTV, Wu WKK, Wu Z, Shen J. MicroRNA signature of air pollution exposure-induced congenital defects. *Journal of Cellular Physiology*. 2019;234(10):17896-17904. doi:10.1002/jcp.28422.

18. Konstantatos AH, Zhong T, Paul E, Tsang S, Tian S, Liu M, Liang Y, Tian Y, Qiao S, Wu WKK, Chan MTV. Effect of cultural background and healthcare environment on postoperative opioid requirement. *Canadian Journal of Anesthesia*. 2019;66(3):309-317. doi:10.1007/s12630-018-01267-7.

19. Li Z, Ma J, Shen J, Chan MTV, Wu WKK, Wu Z. Differentially expressed circular RNAs in air pollution-exposed rat embryos. *Environmental Science and Pollution Research*. 2019;26(33):34421-34429. doi:10.1007/s11356-019-06489-w.

20. Sun R, Xia X, Chong KC, Zee BCY, Wu WKK, Wang MH. Wtest: An integrated R package for genetic epistasis testing. *BMC Medical Genomics*. 2019;12 (Suppl 9):180. doi:10.1186/s12920-019-0638-9.

21. Ren Z, Li Z, Li S, Sheng L, Xu D, Chen X, Wu WKK, Chan MTV, Ho J. Local infiltration with cocktail analgesics during 2 level lumbar spinal fusion surgery: Study protocol of a randomized controlled trial. *Medicine (Baltimore)*. 2019;98(19):e15526. doi:10.1097/MD.00000000000015526 (Study Protocol).

22. Ng C, Li H, Wu WKK, Wong SH, Yu J. Genomics and metagenomics of colorectal cancer. *Journal of Gastrointestinal Oncology*. 2019;10(6):1164-1170. doi:10.21037/jgo.2019.06.04 (Review).

23. Kwong TNY, Wu WKK, Wong SH. Reply. *Gastroenterology*. 2019;156(1):292. doi:10.1053/j.gastro.2018.11.047 (Correspondence).

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NEPHROLOGY

Biomarker and Translational Research



Principal Investigator

Professor Cheuk Chun Szeto



Team

Peter Poon | Ka Bik Lai | Cathy Luk | Pascal Wei | Phyllis Cheng |
Bonnie Kwan | Jack Ng | Winston Fung | Gordon Chan

Research Progress Summary

Current research activities concentrate on laboratory study of peritoneal dialysis and glomerulonephritis, notably IgA nephropathy. In addition, the research team led by Professor Cheuk Chun Szeto has a final phase of securing financial and technical support for the territory-wide research project on autosomal dominant polycystic kidney disease.

An effort made to attract private funds for research

The team received various donations supporting laboratory research during this period. In addition, they have been actively exploring various funding sources from overseas non-profit making establishments.



Inter-institutional collaboration

The team has numerous collaborations with academic institutes and pharmaceutical companies. Here are a few recently completed or on-going collaboration with international and regional organisations:

1. with Professor Chris McIntyre, Division of Nephrology, Schulich School of Medicine and Dentistry, University of Western Ontario, Canada on Endotoxemia in chronic kidney disease;
2. with Professor Stanley Fan, Barts Health NHS Trust, London, United Kingdom on Polymerase Chain Reaction/Electrospray Ionisation-Mass

Spectrometry (PCR/ESI-MS) for rapid bacterial identification in peritoneal dialysis effluent;

3. with Dr. Daniel March, Department of Infection, Immunity & Inflammation, University of Leicester, United Kingdom on Endotoxemia and cardiovascular disease in dialysis patients; and
4. with Professor Christoph Aufricht, Medical University of Vienna, Austria on Alanyl-Glutamine in Peritoneal Dialysis Fluids Improves Peritoneal Health and Systemic Inflammation.



Promotion of research collaboration

The team is actively exploring opportunities to collaborate with industrial and biotechnological establishments in the field of peritoneal dialysis for product development and validation.

Ongoing and upcoming collaborative work with biotechnological establishments include:

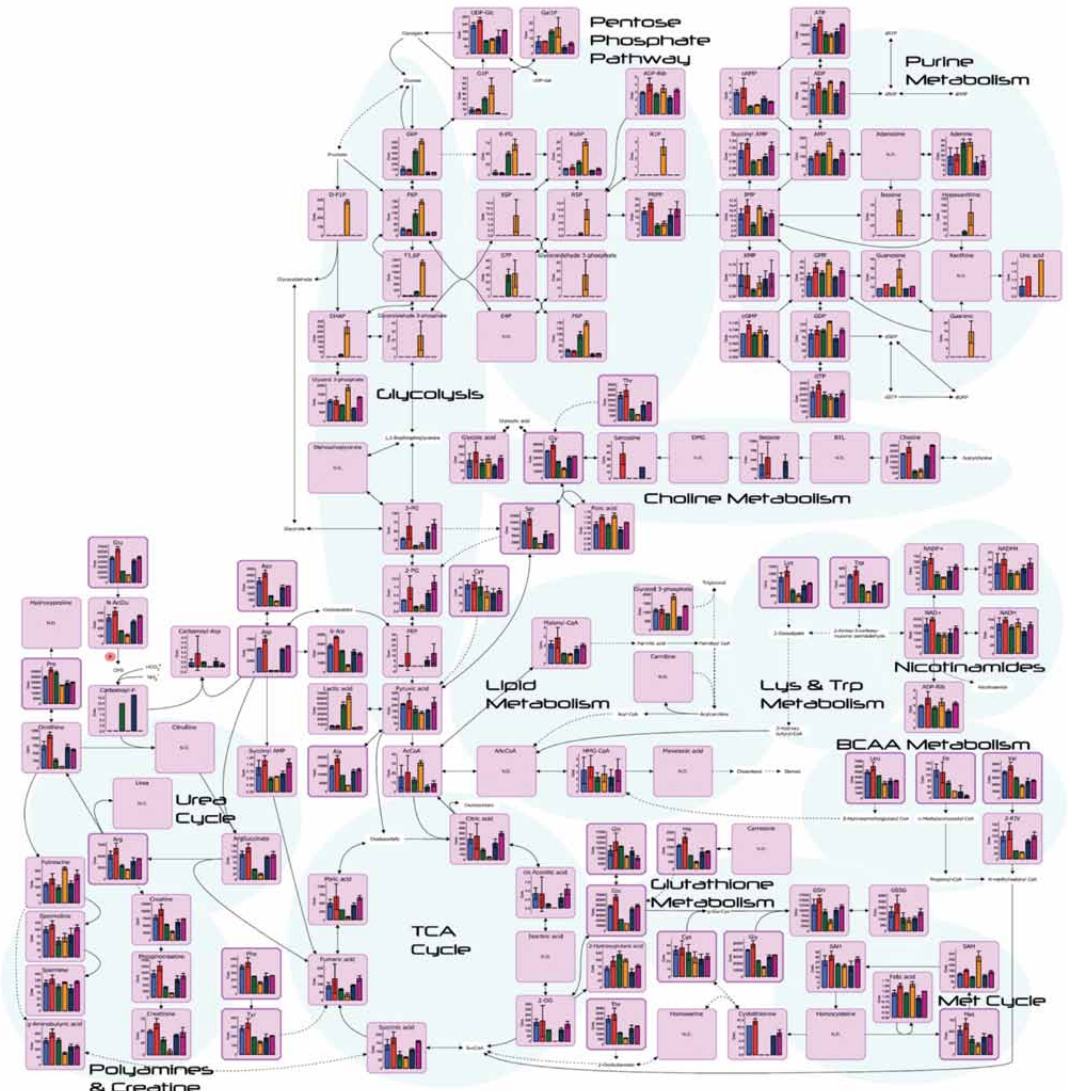
1. with Retrophin® and George Clinical, San Diego, California, USA on A Randomised, Multicenter, Double-Blind, Parallel-Group, Active-Control Study of the Efficacy and Safety of Sparsentan for the Treatment of Immunoglobulin A Nephropathy

2. with Omeros, Seattle, USA on A Phase 2 Study to Evaluate the Safety and Effect on Proteinuria of OMS721 in Subjects with IgA Nephropathy, Lupus Nephritis, Membranous Nephropathy, or C3 Glomerulopathy including Dense Deposit Disease;

3. with Gilead Sciences, Inc. and George Clinical, Foster City, California, USA on: A Phase 3, Randomised, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study Evaluating the Efficacy and Safety of Selonsertib in Subjects with Moderate to Advanced Diabetic Kidney Disease

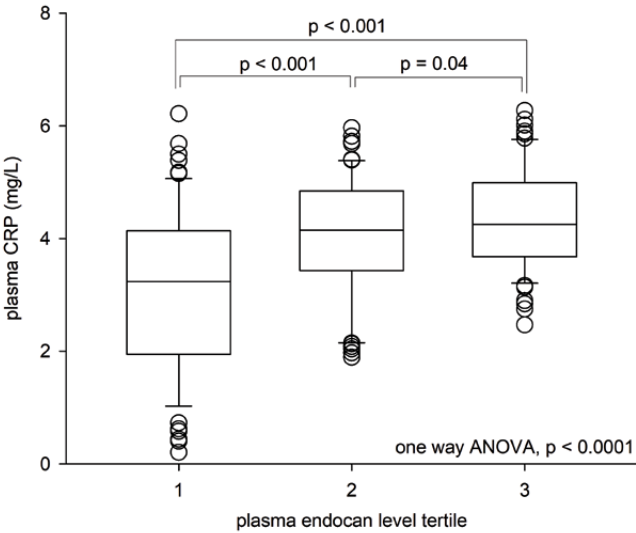
4. with Zytotec GmbH, Germany on: Alanyl-Glutamine in Peritoneal Dialysis Fluids Improves Peritoneal Health and Systemic Inflammation; and

5. with liberDi, The Trendlines Group, Israel on: The liberDi dialysis system.



Metabolomic changes of human proximal tubular cell line in high glucose environment.

Source: Wei PZ, Fung, WWS, Ng JKC, Lai KB, Luk CCW, Chow KM, Li PKT, Szeto CC. Metabolomic changes of human proximal tubular cell line in high glucose environment. Scientific Reports. 2019;9(1). doi:10.1038/s41598-019-53214-1.



The relation between serum endocan tertile groups and serum C-reactive protein (CRP) level.

Source: Poon PYK, Ng JKC, Fung WWS, Chow KM, Ching-Ha Kwan B, Li PKT, Szeto CC. Relationship between plasma endocan level and clinical outcome of chinese peritoneal dialysis patients. Kidney & Blood Pressure Research. 2019;44(5):1259-1270. doi:10.1159/000502961.

■ Research and Scholarship

Research Awards and Recognitions

Member's Full Name	Details
Cheuk Chun Szeto	Keynote Lecture titled "Messengers from the kidney" at Hong Kong Society of Nephrology Annual Scientific Meeting

Academic Editorship

Member's Full Name	Details
Cheuk Chun Szeto	Deputy Editor, Nephrology
	Associate Editor, Peritoneal Dialysis International
	Theme Editor (Peritoneal Dialysis), Clinical Kidney Journal
	Editorial Board, Clinical Journal of American Society of Nephrology

Reviewer of Journal / Conference

Member's Full Name	Details
Cheuk Chun Szeto	Member of Scientific Committee and Coordinator of Abstract Review Committee, American Society of Nephrology Renal Week 2019, Washington, D.C., USA
	Member of Scientific Committee, 10 th Asia Pacific Chapter Meeting of the International Society for Peritoneal Dialysis, Nagoya, Japan

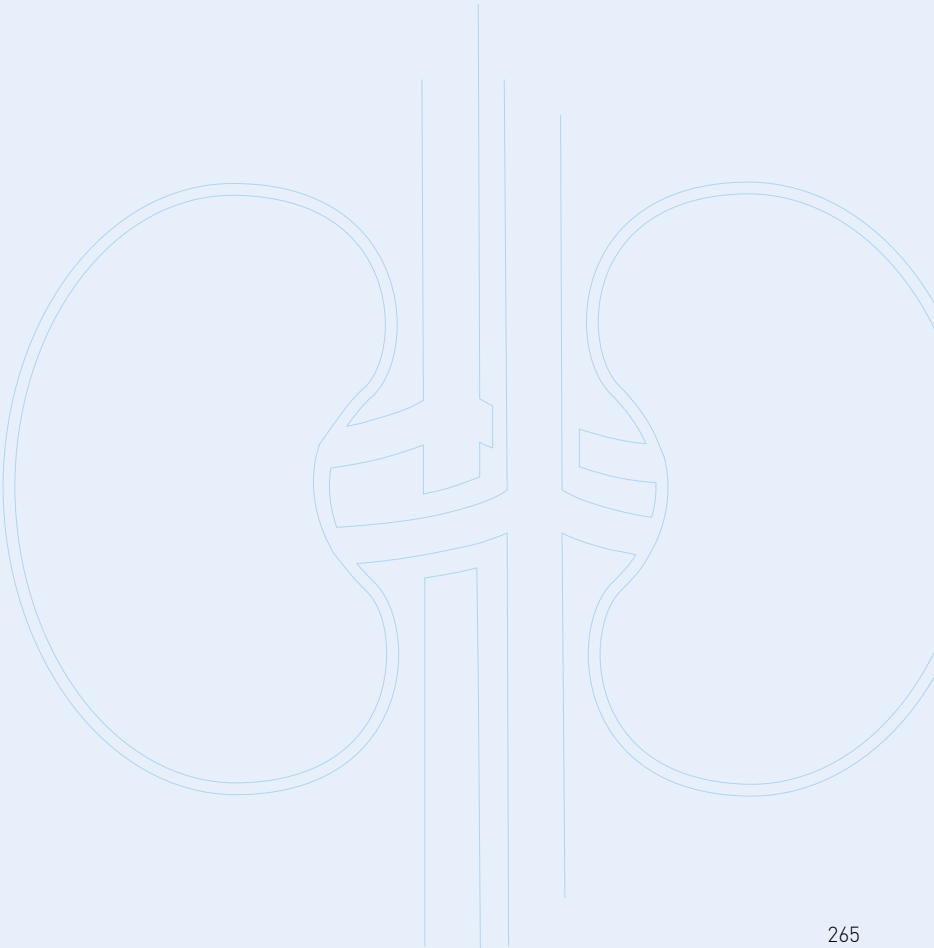
Grants and Consultancy

Name	Project Title	Funding Source	Start Date	End Date	Amount (HK\$)
Cheuk Chun Szeto Winston Fung	A Longitudinal Observational Cohort of Autosomal Dominant Polycystic Kidney Disease Patients in Hong Kong: The Establishment of a Disease Data Registry	Hong Kong Society of Nephrology 35 th Anniversary Research Grant	01/11/2018	30/11/2023	500,000
Cheuk Chun Szeto Winston Fung	The Effect of Nonsteroidal Anti-inflammatory Drugs on Intraperitoneal Cytokine Levels and the Concomitant Alterations in Peritoneal Transport Characteristics in Peritoneal Dialysis Patients	Hong Kong College of Physicians Young Investigator Grant	01/10/2019	01/10/2021	50,000

■ Publications

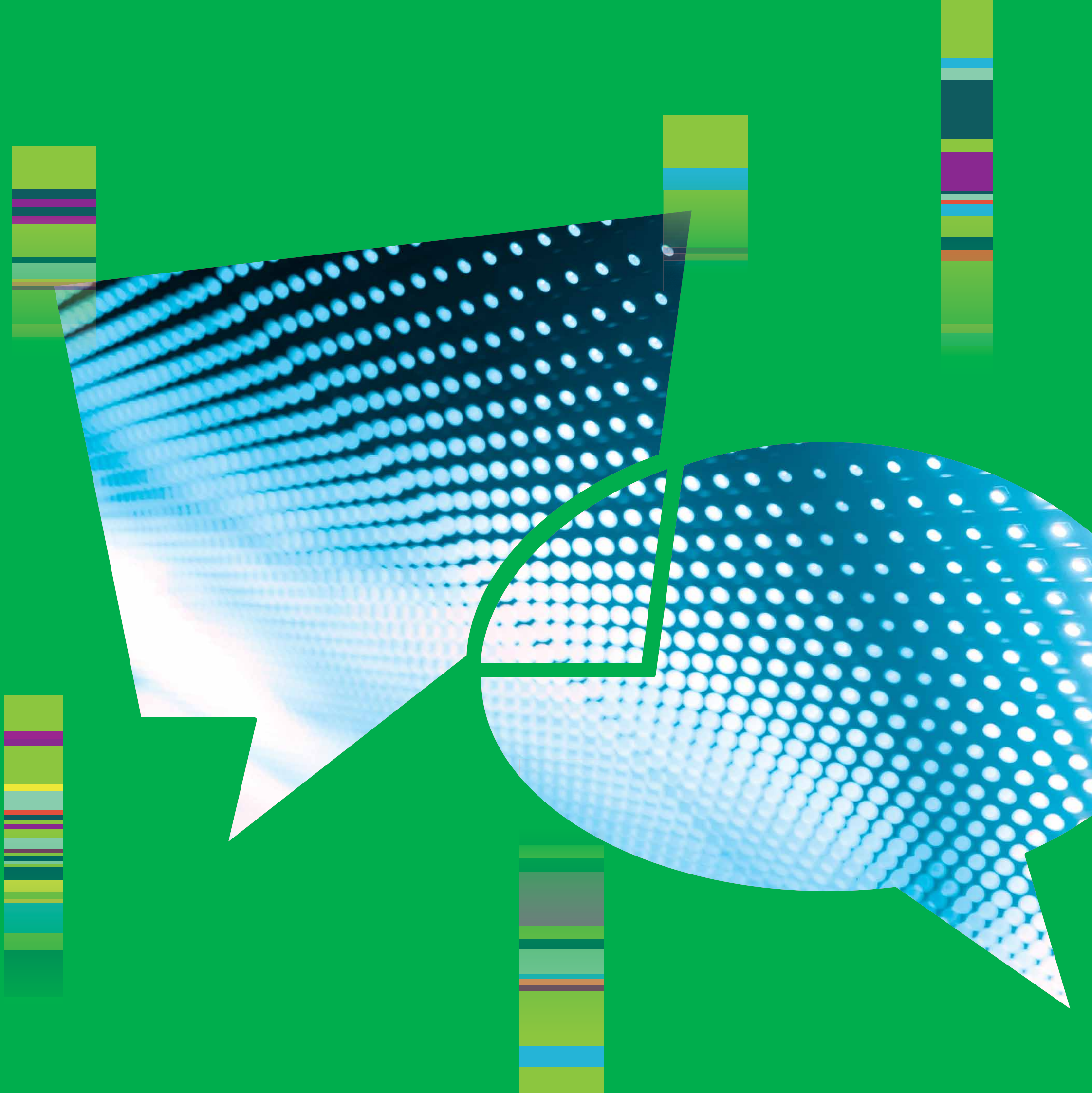
A. Journal Papers

- Wei PZ, Fung WW, Ng JK, Lai KB, Luk CC, Chow KM, Li PK, Szeto CC. Metabolomic changes of human proximal tubular cell line in high glucose environment. *Scientific Reports*. 2019;9(1):16617. doi:10.1038/s41598-019-53214-1.
- Poon PY, Ng JK, Fung WW, Chow KM, Kwan BC, Li PK, Szeto CC. Relationship between plasma endocan level and clinical outcome of chinese peritoneal dialysis patients. *Kidney & Blood Pressure Research*. 2019;44(5):1259-1270. doi:10.1159/000502961.



INTERVIEWS OF PRINCIPAL INVESTIGATORS

與首席研究員對話



INTERVIEWS OF PRINCIPAL INVESTIGATORS

與首席研究員對話

Interview with Professor Ronald Ma

馬青雲教授

Professor Ronald Ma completed his endocrinology fellowship training in the Prince of Wales Hospital, after finishing his medical training at the University of Cambridge, United Kingdom in 1997. He was awarded the Croucher Foundation Fellowship and furthered his research training at the Joslin Diabetes Centre in the Harvard Medical School between 2001 and 2003. Professor Ma joined the Department of Medicine and Therapeutics of The Chinese University of Hong Kong in 2008 and become a world renowned expert in epidemiology and genetics of diabetic. He has published more than 300 journal articles and book chapters.



Having completed medical training at the University of Cambridge and hospitals in London for around 10 years, why did you decide to return to Hong Kong?

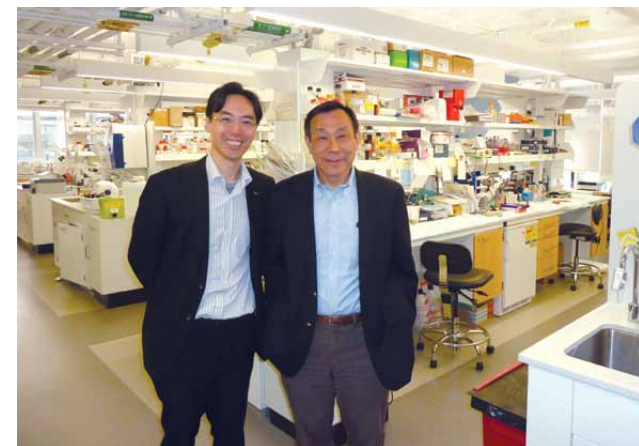
I had finished my internal medicine training at that stage, and was at a career crossroads. I was contemplating whether to apply to commence specialist training in the United Kingdom, or to undertake a research fellowship there. It so happened that I returned to Hong Kong in the summer of 1997 around the time of the handover, and the thought of moving back to Hong Kong then entered my mind. The Hong Kong Hospital Authority was inviting applications from overseas medical graduates at the time, and I submitted my application, was fortunate to be offered the opportunity to work at the Prince of Wales Hospital (PWH), so I jumped at that opportunity and moved back to Hong Kong

within 3 months and began my career in Hong Kong at the Prince of Wales Hospital.



Professor Ma was delivering a talk on "Diabetes in Asia" at the World Diabetes Congress.

You completed the endocrinology fellowship training in Hong Kong, and then you were awarded the Croucher Foundation Fellowship and furthered your research interest at the Joslin Diabetes Centre in Harvard Medical School. When did you first start your interest in diabetes? Why are you so interested in diabetes?



Professor Ma was re-visiting the laboratory of his mentor Dr. George King at Joslin Diabetes Centre.

Diabetes is a condition that I first heard about as a young child, but knew relatively little about it, other than that it can have devastating consequences if not well managed. When I was undertaking my internal medicine training in London, I was particularly interested in the epidemiology and prevention of cardiovascular diseases and I actually thought I may want to be a cardiologist. But it was really through my first rotation at the Prince of Wales Hospital, where I was fortunate to learn from Professor Clive Cockram and the endocrine team, that I became very interested in diabetes and endocrine disorders. I realised that in managing patients with diabetes, I also play an important role in cardiovascular prevention, by optimising risk factors to lower cardiovascular risk in patients with diabetes. After completion of my endocrine training at PWH, I decided to embark on research in diabetes, as it was becoming increasingly common, yet had lots of interesting

unanswered questions. My research fellowship at the Joslin Diabetes Center, Harvard Medical School, was focused on studying the molecular mechanisms of diabetes vascular complications, under the mentorship of Dr. George King. I used different animal models and cell culture models to see how diabetes caused vascular complications such as heart disease. This was an invaluable opportunity for me and gave me very good training in the approach to research, a solid foundation in molecular biology and insights into the study of diabetes complications. Joslin is one of the premier diabetes research centres in the world, and I was also fortunate to be exposed to many exciting research areas in diabetes during my time there. One of my current research focuses relates to biomarkers for diabetes complications, and this reflects the profound impact my time at Joslin has on my academic development and interests in diabetes.



Professor Ma and his project team members at a research retreat for their Theme-based Research Scheme project on diabetes complications.

Diabetes is usually considered as a disease of affluence. Why is that and how changes in lifestyle contribute to the prevalence of diabetes, and how is diabetes related to endocrinology and metabolism?

While diabetes was traditionally considered disease of affluence, that is no longer true and in fact in many parts of the world, it is the socially less privileged who are now most at risk of diabetes. This is due to the fact that obesity is one of the main risk factors for diabetes, in particular to type 2 diabetes. Whilst obesity may be related to affluence and excess caloric intake in the past, obesity is now increasingly linked with social deprivation and being from disadvantaged backgrounds, with unhealthy lifestyles and dietary patterns. But diabetes and obesity are much more complex than just unhealthy lifestyles. It is increasingly appreciated that different early life factors can also influence the later risk of diabetes in adults. This is another important area that I am undertaking research in.

Diabetes, a condition with chronic elevation of blood glucose, is closely linked to endocrinology and metabolism.

One of the most important hormones in the body is insulin, which regulates glucose metabolism. Problems with insulin production or its actions can therefore lead to diabetes. For example, in type 1 diabetes, there is a lack of insulin due to destruction of the insulin-producing cells in our body by the immune system. On the other hand, in type 2 diabetes, different factors including aging, obesity, or lack of exercise or sleep, can make insulin less effective, and when the insulin-producing cells cannot compensate for the decrease of insulin activity, then there would be elevated glucose levels and diabetes. As you can see, diabetes is intriguingly linked to hormones and metabolism.



Professor Ma and his team members and collaborators at World Diabetes Congress.

Research focus on the discovery of novel biomarkers for predicting diabetes and diabetic complication in the Chinese population, major ethnic groups inside and outside Asia. What are the major differences you have spotted among research of diabetes in various regions?

Asians including Chinese have a slightly different pattern of diabetes when compared with the west. Chinese develop diabetes at a much lower level of obesity, suggesting that other mechanisms are important in contributing to diabetes risk in the Chinese population. In large scale genetic studies that we have undertaken, we have identified different genetic markers that are associated with the risk of diabetes in Asians, and many of these relate to genes related to insulin secretion, suggesting that this may be particularly important in the development of diabetes among Asians. We have also identified

some genetic changes in important genes for insulin production whereby these changes appear unique to the Asian population that the genes do not occur or less frequently present in Europeans. Another important difference is the pattern of diabetes complications. Asians appear not to have as high a risk of cardiovascular complications compared to patients in Europe or in the US, though we seem to have higher risk of kidney complications. That is why we have focused much of our effort into identifying biomarkers for predicting diabetic kidney complications in Asians.



Professor Ma with his medical and nursing colleagues of the Diabetes Mellitus and Endocrine Centre at Prince of Wales Hospital.

Would you mind introducing to us the development of genetic variant association and precision medicine in diabetes? Can you share with us the latest trend in diabetes research?

Studying the genetics of a disease is the key to improving our understanding of its pathogenesis. Some of our discoveries point towards disease-causing mutations, which can shed light on novel genes implicated in diabetes and diabetic complications, and provide new targets for developing treatments. More often, we may identify common genetic variants that are

associated with the disease, and they may alter disease risk through more subtle alteration in the regulation of gene expression. We are currently developing ways to translate these disease markers to help predict risk in clinical practice. In addition to predicting disease risk, we are also studying the interactions between different treatments and our biomarkers to understand how best we can develop guidelines to guide treatment based on biomarkers to provide a more tailored treatment plan. And I think this underpins the principle of precision medicine where we are trying to tailor patient needs according to their underlying biology.

How do you see the research environment in Hong Kong on genomics and bioinformatics? Are they going to be the trend of research in the near future?

I think this is an exciting time to be a researcher in Hong Kong. There is also increasing interest and support towards the development of genomics and genomic medicine in Hong Kong. Given our rapidly increasing knowledge of genome and functional implications of different genetic changes, the availability of more efficient and cheaper way to identify the genotype or sequence individuals, I think genomic medicine

is very much here to stay and turn into more important area in clinical medicine. Given the excellent medical infra-structure, I think Hong Kong has many strengths for the development of genomic medicine, both locally, as well as within the Greater Bay Area. I believe there will be a lot of future development on genomics and bioinformatics in Hong Kong.



Professor Ma and fellow members of the FIGO Pregnancy and NCD Committee at the World Diabetes Congress 2019.

You are committee member of many international and local organisations with both clinical and academic roles. Can you share with us some insights on how to maintain excellent performance in various aspects in your busy life?

This remains a challenge and I am constantly learning how to best juggle my different roles. I guess I am keen to contribute as much as I can to education, research and clinical care in medicine and my chosen field of diabetes and endocrinology. For example, having a good understanding of the underlying factors that lead to diabetes, as well as the consequences of diabetes, I feel compelled to contribute to the fight against diabetes. That is the reason I have been involved in different NGOs and professional

organisations including Diabetes Hongkong (DHK), Youth Diabetes Action (YDA), International Diabetes Federation (IDF), International Diabetes Epidemiology Group (IDEG), Asian Association for the Study of Diabetes (AASD), and others, and to join local efforts to reduce sugar intake among our youth. Learning to be more efficient, and to solicit help and support when needed, are important to be able to undertake all these responsibilities. I have to confess that there is much I need to learn to improve in this area.



Professor Ma was working with Professor Wing Hung Tam and Professor Boyd Metzger on studies in gestational diabetes in the HAPO study.

As a successful clinician as well as a scientist, what advice would you like to give to the younger generations who are interested in research or to pursue a career in medical science?

Keeping a youthful outlook and do not be afraid of entering unfamiliar territory or learning new things. Maintain the hunger to learn and be challenged. Don't be afraid to seek your own path and answers. I recently gave a talk to our medical students at our weekly medical grand rounds entitled "50% of what you are taught at medical school may be wrong", and I used that opportunity to reflect on how much knowledge

and research in diabetes has advanced over the last 2 decades, and how several traditional dogmas have now been proven wrong and replaced with new paradigms. I hope our medical students and future doctors will appreciate the importance of lifelong learning, and hopefully a few of them might even be inspired to pursue medical research!

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

I hope that our work in biomarkers in diabetes will lead to changes in the way we manage people with diabetes, whereby we can have more individualised treatment plans and strategies, where we will no longer apply the "one-size fits all" approach, but instead, select the best treatment strategies and algorithms for our patients based on their biological makeup, rather like what we now see in cancer treatment. That would then allow us to provide the best treatment, at the right time, for each of our patients. Being able to deliver that, and make that standard practice in diabetes care, would be a great challenge, but one worth striving for.



Professor Ma and his research team was able to start and co-host the first Gordon Research Conference on Epigenomics of Diabetes and Metabolic Diseases in Hong Kong.

Interviews with Professor Cheuk Chun Szeto

司徒卓俊教授

Professor Szeto graduated from the Faculty of Medicine of The Chinese University of Hong Kong in 1991. He joined CUHK as an Associate Professor in 1999 and obtained his Doctor of Medicine in 2001. His research interests include peritoneal dialysis, urinary biomarkers for kidney diseases and treatment of glomerular diseases. Professor Szeto is currently the Chairman of the Best Practice Recommendation Committee (of the Asia Pacific Society) and also co-editor of the Clinical Practice Guidelines for Renal Service Hong Kong. He is very enthusiastic in promoting professional standards or best practices of nephrology.



Among so many specialties in internal medicine, what makes you choose to pursue nephrology studies as your lifetime career? When did you start your interest in nephrology?

“ If you want a simple answer, it is because there was a training post when I finished basic medical training. The two very senior consultants at that time in nephrology were very supportive and helped me a lot in learning various aspects in this subject. They also had very much facilitation on my interest in the field and that's why I chose nephrology as the specialty. When I started the training and learnt more about

nephrology, I come to realise that there were actually a lot of interesting and challenging cases. Renal medicine is a very fine balance between mental exercise and a lot of hand-on procedures. So you have to rely on your manual skills as well as your intellect capability to master the subject. So it is a very nice balance of every aspect. ”



Professor CC Szeto had Division Lunch gathering in June 2019.

You are currently the Chairman of the Best Practice Recommendations Committee of the Asian Pacific Society of Nephrology, the Secretary of Credentialing Committee of the Hong Kong College of Physicians and a co-editor of the Clinical Practice Guidelines for Renal Service Hong Kong. You are very enthusiastic in promoting professional standard or best practices of nephrology. Would you mind explaining more on this specific aspect within medical field?

“ There are two levels of clinical research or clinical medicine. On one hand, there are scientific advances that we want to do to learn more about the subject, understand more about the disease and develop more new therapy. In addition, there is a layer of how we can promote or standardise the treatment of our patient. This is what we call evidence-based medical practice that we have to make sure the routine daily practice by every doctor is up to certain standard and the care between physicians, even between different countries should be standardised. Therefore, I put quite a bit of effort to contribute to this aspect and sitting in different committees.

These committees try to ensure the standard of practice within Hong Kong and in addition within the Asia Pacific countries. Drawing guidelines and ensuring the guidelines are really executed so that the basic medical research can be put forward into actual daily care of the patients. ”



Professor CC Szeto was meeting Professor Ronald Ma (left) and Professor Sydney Tang (right) before the plenary lecture of World Congress of Nephrology 2019 at Melbourne, Australia.

You received the John Maher Award from the International Society for Peritoneal Dialysis (ISPD) in 2012 for the preparation of the latest guidelines in the treatment and prevention of peritoneal dialysis related infection published in 2011. Would you share with us more about the development and progress in setting the guidelines?

“ To begin with the John Maher Award by International Society for Peritoneal Dialysis (ISPD) was given to me as a recognition of not only my own work but the work of our whole team on the research in the peritoneal dialysis related infections particularly peritonitis. We did quite a bit of work in understanding the clinical behaviour, natural history, response to treatment, risk of relapse, the behaviour of different organisms and spectrum of resistance in our local population which is quite representative to the global dialysis committee. On the other hand, we also have local advantage because of the local policy we have a lot of these patients. Hong Kong is a very good place to perform research in this area. In addition to giving award to us, our research results were also substantially incorporated into ISPD

guideline on the treatment of peritoneal dialysis related infections.

Your question says that we were largely responsible to prepare the guideline published in 2011. In fact, we had updated set of guidelines published in 2017. In this aspect, the knowledge over the past fifteen or twenty years in this field has expanded a lot so that our work is increasingly recognised and could be incorporated into the guideline.

As previous question says understanding the disease by research is one thing we are heavily working on. Putting forward guidelines so that the level of care could be improved and standardised across different countries. ”

In 2016, you have received the State Scientific and Technological Progress Award First-class Award by the Ministry of Health, China, for your work on IgA nephropathy. Can you tell us more on your research work?

The collaborative research was with another large group of Peking University from Beijing. The background idea and the huge research project is on exploration of the various novel therapeutic strategy of IgA nephropathy which is the most common primary glomerulonephritis around the world including Hong Kong and China. The original research led by the Peking group focused on the treatment and particularly on novel herbal remedy or traditional Chinese medicine treatment for this disease. But our group was invited to take part in several specific aspects of IgA nephropathy. First is the assessment of the natural history of patient IgA nephropathy particularly in subgroup of patients who present with isolated microscopic hematuria and very

minimal proteinuria. That is a very specific subgroup which we did quite a bit of work to understand the behaviour, the clinical variety and the prognosis at this condition. And in addition, as part of this project, we also had another prospective study to see the response to treatment from these specific groups with only a little bit of hematuria and no proteinuria. And a large aspect that we contribute to this project is our group was actively working on urine biomarkers. For this project we work on urinary microRNA and messenger RNA as a prognostic biomarker for risk stratification for IgA nephropathy. So we contribute to this entire project in two different parts and we are quite fortunate that our work is being recognised.



Professor CC Szeto and team members had poster presentation at the American Society of Nephrology Renal Week 2018 at Chicago; (from left to right) Dr. Agnes Choy, Dr. Winston Fung, Professor CC Szeto, and Dr. Gordon Chan.

Professor CC Szeto gave plenary lecture at the Hong Kong Society of Nephrology Annual Scientific Meeting on 29 September 2019; (from left to right) Dr. Sing-leung Lui, Professor CC Szeto, Dr. Yuk-lun Cheng, and Dr. Matthew Tong.



Patients suffering from nephrological diseases usually complain about decrease in quality of life due to frequent and time-consuming dialysis. How can patients benefit from the latest development in the field?

Actually it is not an easy objective to achieve. We have a few strategies to help patients in that sense. First, we have quite a lot of research on pre-dialysis chronic kidney disease. The ultimate aim is actually to prevent patients from going into dialysis by reducing the rate of progression of patients from having chronic kidney disease to dialysis dependent renal failure. We all know that dialysis is no good for the quality of life, so if we can do something to prevent them from progressing to needing dialysis, then that will help the patients. And the other aspect is that we had done quite a lot of research on peritoneal dialysis and peritonitis. Another aim for us is to do research and help to reduce the complications of patients on dialysis, which can improve their survival. And more importantly, by reducing the

complication we can improve their quality of life. Say for example, for peritoneal dialysis patients having peritonitis, even though the patient may not die, is a very important burden to their quality of life and cause a lot of symptoms affecting their normal life. So by preventing or improving the treatment of peritonitis, we can improve their quality of life. We also have some research on advanced dialysis technology. By improving the technology, say how we perform dialysis may also reduce the burden of dialysis to the patients. So that we can improve their quality of life. That is not related to the complication of dialysis. Just in the way of how the dialysis is performed. If we can simplify and improve the technology, also improve the quality of life of our patients.



Professor CC Szeto with a group of Hong Kong nephrologists at a dinner symposium during the International Society for Peritoneal Dialysis Asia Pacific Chapter 2009 meeting at Nagoya, Japan.

Dialysis is associated with high risk of infections and complications in laymen's perspective. What is the actual risk level of the procedure, and how does research in the field improve the treatment?

For dialysis patients, the overall mortality each year is around 10-12%. If you specifically talk about peritonitis related to peritoneal dialysis, the current figure is around 0.5 episode per patient year on dialysis. In other words, for every patient on average after being treated for 24 months you will expect 1 episode of peritonitis. That obviously has a high variability. Some of our patients were on dialysis for 8-10 years without a single episode of dialysis. We also have patients after 6 months of dialysis already had 3-4 episodes. It really varies a lot. So 1 episode in 24 months is really an average.

But research from our group, on one hand we improve the treatment regime of these patients to enhance their treatment response rate and reduce the rate of having relapsing or repeated peritonitis episode. In addition to peritonitis, we also did quite a bit of work on cardiovascular disease in dialysis patients which is another major cause of death. By understanding more about how we treat cardiovascular disease in dialysis patients then we can also improve their well-being and also improve the survival of these patients.



Apart from research work, you have also taken up a lot of external roles or duties. How do you manage your time to also publish over 400 peer publication over the year?

“ I use the electronic version of the bullet journal system to prioritise my daily work, and I hold a weekly “one-man” project meeting every Saturday morning to go through the progress of every project at hand. I start my day early and spend 45 minutes every morning to work on the most important but not urgent project (usually for writing paper or grant proposal), and I only check my emails twice a day – that saves a lot of time. ”



Professor CC Szeto had dinner with team members during World Congress of Nephrology 2019 at Melbourne, Australia; (from left to right) Dr. Tiffany Yau, Dr. Jack Ng, Dr. Winston Fung, Professor CC Szeto, and Dr. Gordon Chan.

Being the management levels and members of a lot of international organisations and societies, how do you describe the differences in research directions of nephrology in various countries?

“ If you want a simple answer, then I must say the world is flat and the whole nephrology circle across the world in a sense that is very united. And we communicate a lot and the research directions for various countries are quite united particularly over the past few years. The major interest around the world is chronic kidney disease in general and particularly diabetic kidney disease. Of course if you go to specific regions then each individual country has its own research edge and tendency to work on

some particular areas. Say for example, electrolyte and acid base disorder is mostly done by American nephrologists. On the other hand, for experimental glomerulonephritis or animal research, although the American do a lot, nowadays the Japanese and the Chinese researchers appear to have the most contribution. For genetic disease or pathological studies, then I must say our European colleagues are doing a better job. ”



Professor CC Szeto was celebrating 40th anniversary of the Hong Kong Society of Nephrology, with Professor Hui-Yao Lan (left) and Dr. Andrew Wong (middle).

As a successful clinician as well as a scientist, what advice would you like to give to the younger generations who are interested in research or to pursue a career in medical science?

“ If you want a short answer, then just learn from your peers. There are always very brilliant people around whom we could always learn somethings from. On the other hand, a very pragmatic advice is that we should not be very over-ambitious. What I mean is to be trained up as a good clinician is one aspect. To be trained up as good scientist is quite a different thing.

My humble opinion is that it would be better idea to be competent with one thing before learning and take up the other. In other words, you either train to be a competent clinician and then gradually move forward to expand the interest to research. Unless you are exceptionally talented, it is quite impossible to learn to be both at the same time. ”



Professor CC Szeto at the Nephrology specialty board, Hong Kong College of Physician in June 2018.

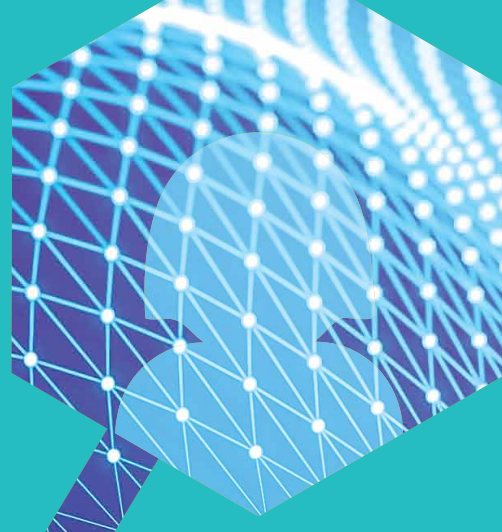
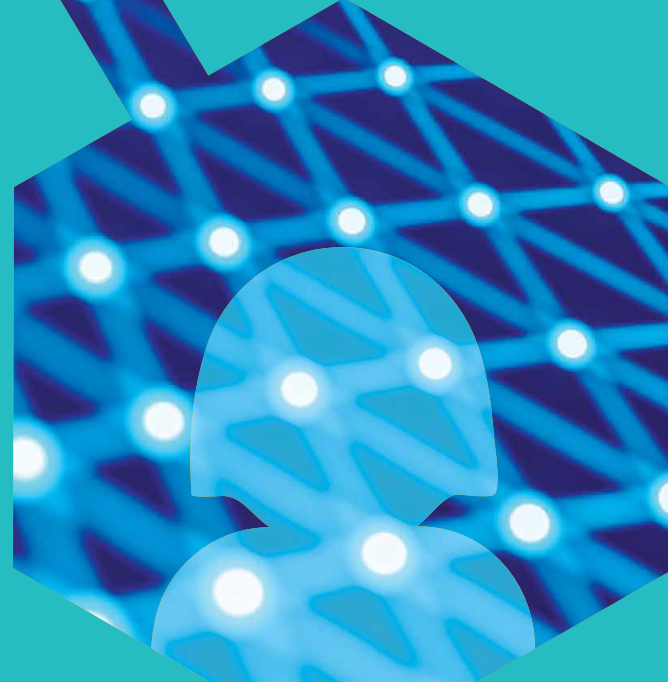
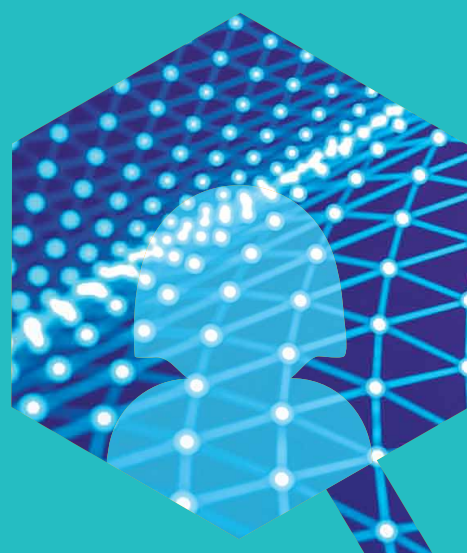
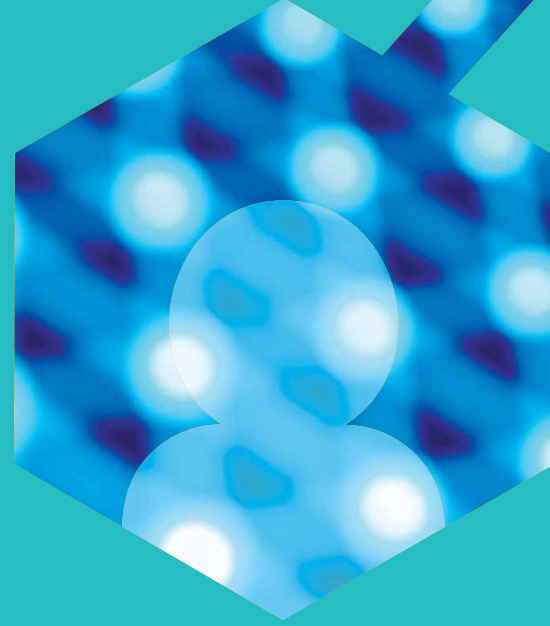
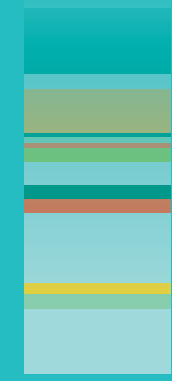
Being a new Principal Investigator of the Institute, what are your visions and goals, say in 5 years' time?

“ Our work on nucleic acids and bacterial fragments has an increasing international recognition. We plan to extend our work to non-coding RNAs and archaeobacterial fragments, which are neglected field of research. Second, we will apply our established

technique to diabetic kidney disease (DKD), which is now a worldwide epidemic. We will focus on mitochondrial DNA fragment as a biomarker of DKD and explore metabolic disturbances and mitochondrial dysfunction in DKD. ”

FROM SCIENCE TO IMPACTS

從科學到影響



FROM SCIENCE TO IMPACTS

從科學到影響

Interview with Professor Allen Chan and Dr. Jacky Lam

陳君賜教授、林偉棋醫生



The translation of scientific discoveries from bench to bedside requires multiple studies in order to realise the benefits to patients and generate the most impact to the society. Following the seminal study on the use of circulating Epstein-Barr Virus (EBV) DNA analysis in blood plasma for screening nasopharyngeal carcinoma (NPC), which was selected as one of the ten most notable articles of the New England Journal of Medicine in 2017, Professor Allen Chan, Dr Jacky Lam and their team have further investigated the molecular characteristics of circulating EBV DNA with the focus on the viral DNA methylation in various

EBV-associated human diseases. NPC remains to be one of the most common cancers in Hong Kong. Professor Chan, Dr Lam and the team, through the analysis of the molecular characteristics of plasma EBV DNA, have further lowered the false positive rate of NPC screening from 5% at the beginning, to 0.3% in the recently published study. All these efforts from the team would make a population wide screening more cost-effective as fewer confirmatory tests including endoscopy and MRI would be required for tested positive individuals. The findings would also illuminate the screening of other virus-associated cancers.

Epstein-Barr virus (EBV) is a member of the herpesvirus family and EBV infections are very common that we may have probably contracted the virus without even noticing it. How does EBV affect our health?

J: It is estimated that over 90% of the worldwide population has been infected by the Epstein-Barr virus (EBV). The health effect of EBV infection on human varies a lot. For most of the time, the virus remains in the human body in a latent state of infection and the infected individuals would remain asymptomatic. Some individuals would develop a benign disease called infectious mononucleosis in which patients experience

symptoms such as fever, fatigue and sore throat and the symptoms are self-limiting.

On the other hand, EBV is believed to play an oncogenic role in certain types of cancer. NPC is one example. Previous studies have shown that EBV DNA is virtually present in all the NPC cancer cells. In addition, some types of lymphoma are also found to be EBV-associated.



Professor Chan, Dr. Lam and members of their research team.

Methylation analysis of plasma DNA plays a main role in your study. Can you explain to us what DNA methylation is? What are the functions and mechanisms of DNA methylation and how DNA methylations work in our body?

J: DNA methylation is an epigenetic process by which methyl groups are added to the nucleotides of DNA. Through the epigenetic modification of the chemical structures of the nucleotides, gene functions, in particular transcription, could be controlled.

A: In general, all cells in the human body share the same genome. In different organs, cells would 'switch on' specific genes that regulate the synthesis of proteins to perform certain cell functions. DNA methylation is one of the mechanisms which regulate cell functions by controlling the expression of different genes. Very broadly, one gene would be 'switched off' or not expressed when the promotor region of the gene is being methylated. DNA methylation is essential for normal development and is associated with a number of key physiological processes.

Why would you decide to look deeper into the circulating EBV DNA methylation patterns? Can you tell us more about the process and your major finding in the study?

A: In the prospective study mentioned before, we used a polymerase chain reaction (PCR)-based assay to analyse circulating EBV DNA from screening participants. This method detects if EBV DNA is present in the blood of tested subjects. In approximately 5% of subjects without NPC, low levels of EBV DNA would be present and this represents false-positives. Tested subjects with positive test results would require further confirmatory tests including nasal endoscopy and MRI.

With our knowledge that the consequences of EBV infection could be so different among individuals, our research team began to ask if EBV adopts different DNA methylation profiles in different EBV-associated diseases. Assuming that EBV would 'switch on' a specific set of genes for a particular disease, each disease would have its own EBV DNA methylation pattern. By analysing the circulating EBV DNA methylation patterns, we may be able to tell if the subject develops a specific EBV-associated disease. The finding of this study proves that our hypothesis is correct.

J: In the study, we have analysed three types of EBV-associated diseases in our study, namely infectious mononucleosis, EBV-associated lymphoma and nasopharyngeal carcinoma. Targeted bisulfite sequencing was used to capture and analyse the circulating EBV DNA methylation patterns in the plasma of subjects. EBV DNA in plasma was first enriched to increase the quantity of viral DNA that could be used in the analysis. Then, the methylation status across the whole EBV genome was revealed down to single nucleotide resolution, i.e. the methylation state of every CpG site was studied.

The results revealed that, for each EBV-associated disease, there is a distinctive circulating EBV DNA methylation pattern.

Professor Chan, Dr. Lam discussed research works with team members.



Your team has previously described the count- and size-based analysis of plasma EBV DNA and demonstrated the improvement in the diagnostic performance of NPC screening test. How would these three types of analysis work together? What are the mechanisms behind?

J: In the original clinical study published in the *New England Journal of Medicine*¹ in 2017, the detection of EBV DNA in blood was performed using a PCR assay. EBV DNA was present in 5% of all screening subjects with a single time-point analysis. In order to lower the false positive rate, a second analysis was conducted for EBV-positive subjects 4 weeks after the first analysis. Subjects who were found to be EBV-positive in two consecutive analyses would be referred to endoscopic examination and magnetic resonance imaging (MRI). The false positive rate was lowered to 1.5% with such arrangement.

This two time-point testing arrangement, however, could pose a logistical challenge in the real-life clinical setting. At the same time, our team started to explore the molecular characteristics of plasma EBV DNA between NPC patients and non-NPC subjects (false positives). We discovered that there existed a difference in both the quantitative and size profiles of plasma

EBV DNA between NPC and non-NPC subjects with the use of next-generation sequencing. By combining the count- and size-based analysis of plasma EBV DNA, the team managed to reduce the false positive rate to 0.7%. More importantly, this improvement could be achieved by a single time-point analysis. The enhancement would facilitate a wide adoption of a screening program. The finding was published in the *Proceedings of the National Academy of Sciences of the United States of America*² in 2018.

In this study, with the realisation of the disease-associated patterns of plasma EBV DNA methylation profiles, we further discovered that patients with NPC and non-NPC subjects exhibited different plasma EBV DNA methylation patterns. Now, with the incorporation of EBV DNA methylation analysis to the count- and size-based analyses, the false positive rate can be further reduced to 0.3%.

¹ Chan KCA, Woo JKS, King A, Zee BCY, Lam WKJ, Chan SL, Chu SWI, Mak C, Tse IOL, Leung SYM, Chan G, Hui EP, Ma BBY, Chiu RWK, Leung SF, van Hasselt AC, Chan ATC, Lo YMD. Analysis of Plasma Epstein-Barr Virus DNA to Screen for Nasopharyngeal Cancer. *New England Journal of Medicine*. 2017;377(6):513-522. doi:10.1056/nejmoa1701717.

² 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.

What are the potential public health impacts of enhanced NPC screening in endemic regions?

A: The substantial reduction in false positive rate from 5% (using only the PCR analysis) to 0.3% (combined count-, size- and methylation-based analysis of plasma EBV DNA) would mean a lot to any healthcare system, in terms of resources. Take Hong Kong as an example, if there is a population-wide NPC

screening in Hong Kong and 1 million people are to be screened, the number of subjects who would be referred to endoscopic examination and MRI would be reduced from 50,000 (5% of the population) to 3,000 (0.3% of the population). The reduction would have an implication on the healthcare resource allocation.



Professor Chan and Dr. Lam holding health talks in community for potential subjects.



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

In your opinion, how would you think about a population-wide NPC screening in Hong Kong? Is it necessary and do we have the potential to do so?

A: Yes, I do believe that there is a potential to conduct a population-wide NPC screening in Hong Kong. Hong Kong has a relative high incidence rate of NPC, which is over 1% for the local male population.

The clinical benefit of early cancer detection of NPC through screening has been demonstrated in our prospective clinical study. With screening, around 70% of patients were identified to have stage 1 or 2 cancer, whereas more than 80% of patients were diagnosed with late-stage (stage 3 or 4) disease without NPC screening. In addition,

there was a survival benefit among NPC patients identified by screening compared to those symptomatic patients from a historical cohort.

The enhancements in the performance of NPC screening tests would lead to reduction of false positive rate and potentially the overall screening cost. Considering the financial conditions of Hong Kong and the relatively high incidence of nasopharyngeal cancer, it seems reasonable to conduct population-wide NPC screening, in particular for high risk group of male between age 35 and 65.

What's next? What would be your team's future direction in the next few years?

A: The approach described in our current study can be applied to other virus-associated cancers such as head, neck cancer and cervical

cancer. Certainly this would be another direction that the team will work on.

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Address 地址 Li Ka Shing Medical Sciences Building,
The Chinese University of Hong Kong, Prince of Wales Hospital,
Shatin, New Territories, HKSAR, 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

Tel 電話 [852] 3763 6003
Fax 傳真 [852] 3763 6333
Home Page 網址 www.lihs.cuhk.edu.hk

Photography 攝影 Mr. Gary Mak, Mad Production
Design 設計 Mr. Leo Lei, Ms. Cary Mak, Matisse Design Limited

Production 印刷 Matisse Design Limited

Print Run 版次 July 2020 | 2020年7月

Quantity 印數 500 Copies | 500本