CU Medicine

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

LI KA SHING INSTITUTE OF HEALTH SCIENCES
香港中文大學 李嘉誠健康科學研究所

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 香港中文大學李嘉誠醫學大樓




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# PROGRESS REPORT

LI KA SHING INSTITUTE OF HEALTH SCIENCES
JANUARY - DECEMBER 2017

李嘉誠健康科學研究所進度報告
2017年1月-12月

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# EXECUTIVE SUMMARY
# 報告摘要

Since our last annual progress report, the Principal Investigators at the Institute have made notable advances 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 am most honoured to receive an Outstanding Achievements Award during the 11th annual WuXi Pharma Tech Life Science and Chemistry Awards ceremony, which was supported by the Ministry of Science & Technology. Professor Jun Yu also received a Scholar Award during the same ceremony. The awards ceremony was held on 9 December 2017 at the Diaoyutai State Guesthouse in Beijing. Professor Qide Han, Honorary Vice-Chairman of the Awards Committee and Vice-Chairman of the 12th National Committee of the Chinese People's Political Consultative Conference, presented the awards to the award-winning scientists.

The Sing Tao News Corporation Limited founded the Leader of the Year Awards since 1994 to acknowledge the outstanding leaders for their contributions to Hong Kong and for serving as an inspiration to the younger generation. This year, Professor Rossa Chiu and myself were named as one of the Leaders of the Year 2017, in the Commerce & Industry / Finance category, for our work on cancer screening and non-invasive prenatal testing.

I am also most delighted to note that Professor Siew Ng, working in the exciting emerging field of fecal microbiota transplantation, was awarded the Sir David Todd Lectureship by the Hong Kong College of Physicians.



On the scientific front, our various Principal Investigators have achieved remarkable progress in their respective research areas in 2017. In particular, Professor Allen Chan and colleagues, completed a large-scale prospective study involving over 20,000 subjects for the feasibility of screening nasopharyngeal carcinoma (NPC) using circulating DNA analysis in human plasma. This work has demonstrated a remarkable ability to detect this potentially fatal cancer during the early stages and a dramatic improvement in survival following cancer detection when compared with unscreened subjects. This work was published in the *New England Journal of Medicine* and was chosen by this journal as one of the "Ten Notable Articles in 2017". This achievement has also been recorded in the Calendar of Events of the 2017 Hong Kong Yearbook published by the Hong Kong SAR Government.

**Dennis Lo**
**盧煜明**

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

Concerning the biology of NPC, Professor Kwok-wai Lo and Professor Ka-fai To have performed whole-exome and whole-genome sequencing on over 100 NPC cases, which provides the most comprehensive view of NPC genomics to date. The groundbreaking findings, which were published in the *Nature Communications*, would facilitate the development of personalised medicine for NPC patients.

Professor Siew Ng has conducted a systematic review of all population-based studies reporting the incidence or prevalence of inflammatory bowel diseases (IBD) since 1990. This is the most comprehensive and up-to-date global overview of the incidence and prevalence of IBD in the 21st century. The valuable findings have been published in the *Lancet*, which provide important pointers for future research for elucidating environmental risk factors and potential strategies for intervention for IBD.

Our research team working on inflammatory diseases led by Professor Hui-yao Lan, has uncovered the mechanism as to how cancer cells utilise a transforming growth factor-beta (TGF-β1) protein to circumvent the frontline of our immune system against cancer. This work may contribute to the development Smad3-targeted anticancer therapy in the future.

I am also very pleased to report that through the work of our circulating nucleic acids group, I was named as one of the "Top 20 Translational Researchers of 2016" by the authoritative scientific journal *Nature Biotechnology*. I am encouraged by this award and pleased to note the scientific, healthcare and commercial impact generated by this body of work.

As always, we are looking forward to what science has in store for our investigators in the coming year.

過去一年，研究所各首席研究員繼續推動各範疇的科研研究，堅守研究所宗旨，竭力將科研發展轉化成臨床應用，惠及病人及醫療保健行業。多位首席研究員於去年獲得國內及國際獎項，表揚其卓越科研成就及貢獻。

本人及于君教授有幸在第十一屆經國家科技部批准成立的「藥明康德生命化學研究獎」中，分別獲頒「傑出成就獎」及「學者獎」。該頒獎典禮於2017年12月9日假北京釣魚台國賓館舉行，由評審委員會名譽副主席、第十二屆全國政協副主席韓啟德院士頒獎。

星島報業集團自1994年起，每年均舉辦「傑出領袖選舉」，旨在表揚優秀領袖對香港的貢獻及對年輕一代的啟迪。本人與趙慧君教授榮獲「2017年傑出領袖選舉」工商/金融組別獎項，以作為對我們癌症篩查及產前無創診斷技術研究工作的肯定。

此外，致力研究腸道微生物移植這項新興技術的黃秀娟教授，亦獲本年度香港內科醫學院頒授達安輝爵士教授講師。

在科研發展方面，研究所各首席研究員在2017年於多個範疇均取得卓越成果。陳君賜教授帶領的研究團隊完成了一個囊括2萬多名志願者的大規模癌症篩查研究項目，檢視利用分析血漿內DNA以診斷鼻咽癌的可行性。此研究有助於更早階段確診鼻咽癌，而通過篩查發現鼻咽癌的患者治療效果及存活率明顯較未接受鼻咽癌篩查的患者大為提高。有關研究成果已於《新英格蘭醫學雜誌》發表，並被該期刊評選為「2017年度十大最矚目文章」之一。這項榮譽亦被記錄於香港特區政府出版的2017年香港年鑑。



致力研究鼻咽癌的杜家輝教授及羅國煒教授為100多個鼻咽癌病例進行了全外顯子組和全基因組測序，提供至今最全面的鼻咽癌基因組圖譜。此突破性發現獲刊載於期刊《自然通訊》，有望幫助開發鼻咽癌病人的個人化治療。

黃秀娟教授以人口統計為基礎，蒐集了自1990年以來有關炎症性腸病的患病率及發病率的數據並進行系統性回顧研究，是21世紀中對炎症性腸病最全面及最貼近現況的全域概覽。這些珍貴的數據在期刊《刺針》發表，揭示未來研究應循環境風險因素及預防炎症性腸病的干預措施方向發展。

由藍輝耀教授帶領的炎症性疾病研究團隊於癌症相關研究中發現癌細胞如何利用自身產生的轉化生長因子（TGF-β1）蛋白去逃避人體第一道免疫抗癌防線，此研究結果有助發展既安全又有效的Smad3標靶腫瘤免疫治療。

另外，就著血漿核酸研究團隊的研究成果，本人獲權威科學期刊《自然－生物科技》選為「2016年全球20位頂尖轉化研究科學家」之一，深受鼓舞的同時也樂見研究成果對科研、醫療保健及商業領域帶來影響。

在2018年，我們一如以往殷切地期待科學為研究員提供更多驚喜。

# GOVERNANCE AND ADMINISTRATION
# 管治與行政


Dr. Frieda Law


Prof. Francis Chan


Prof. Hsiang-fu Kung


Prof. Joseph Lau


Prof. Wai-yee Chan


Prof. Guoping Zhao


Prof. Dennis Lo


Prof. Hui-yao Lan

## 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 eleventh meeting of the Steering Committee was held on 12 December 2017 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2017年12月12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

**Prof. Francis Chan**
**陳家亮教授**

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

### Members
### 成員

**Dr. Frieda Law**
**羅敏潔醫生**

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

**Prof. Dennis Lo**
**盧煜明教授**

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

**Prof. Hui-yao Lan**
**藍輝耀教授**

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

**Prof. Hsiang-fu Kung**
**孔祥復教授**

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

**Prof. Joseph Lau**
**劉允怡教授**

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

**Prof. Guoping Zhao**
**趙國屏教授**

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

**Prof. Wai-yee Chan**
**陳偉儀教授**

Director, School of Biomedical Sciences, CUHK
Professor of Biomedical Sciences, CUHK
香港中文大學生物醫學學院院長
香港中文大學生物醫學講座教授

### Secretary
### 秘書

**Ms. Cecilia Leung**
**梁欣欣女士**

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

# The Eleventh Meeting of the Steering Committee

*(12 December 2017)*

# 第十一次督導委員會會議

*(2017年12月12日)*



# LiHS Office
# 研究所辦公室

As of December 2017, a total of 13 staff members in the LiHS Office were in post, including administrative, scientific, research, technical and supporting 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 Cell Therapy Laboratory, the Molecular Biology Core Facilities, and the Cell Biology Core Facilities.

截至2017年12月底，研究所辦公室共已聘任13名僱員，包括行政、科學、研究、技術及支援人員，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、細胞治療實驗室、分子生物學重點科研設施和細胞生物學重點科研設施。



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



Core Laboratory Team
重點科研設施團隊



# THE LI KA SHING MEDICAL SCIENCES BUILDING
# 李嘉誠醫學大樓

The Li Ka Shing Institute of Health Sciences was housed inside the 11-storey Li Ka Shing Medical Sciences Building. As of December 2017, there were approximately 511 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-notched research scientists in order to enhance our competitiveness in research.

*11-*
Storey

*511*
Research Personnel

Diseases & Pathobiology

New Technologies

Multi-disciplinary
Research Laboratories











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2017年12月，約有511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。

# RESEARCH FACILITIES
# 研究設施

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

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






## Biomedical Computer Centre
## 生物醫學計算中心

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

To cater for growing research needs on Next Generation Sequencing (NGS) and data analysis, the Centre has greatly enhanced its storage systems and computing systems after enhancing the Centre's network infrastructure and bandwidth.

**生物醫學計算中心**是研究所內的重要設施之一，亦是研究轉譯基因組學的重要一環。

為滿足次世代排序（NGS）和數據分析方面日益增長的研究需要，在加強中心的網絡基礎設施和帶寬之基礎上，中心於去年大大加強了其存儲系統和計算系統，大幅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。

**32**
**Server Racks**

**>6TB**
**RAM**

**1,344 CPU Cores**
**& 14,400 CUDA Cores**

**6PB**
**Petabytes Storage**

**2,550.45**
**TeraFLOPS**

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

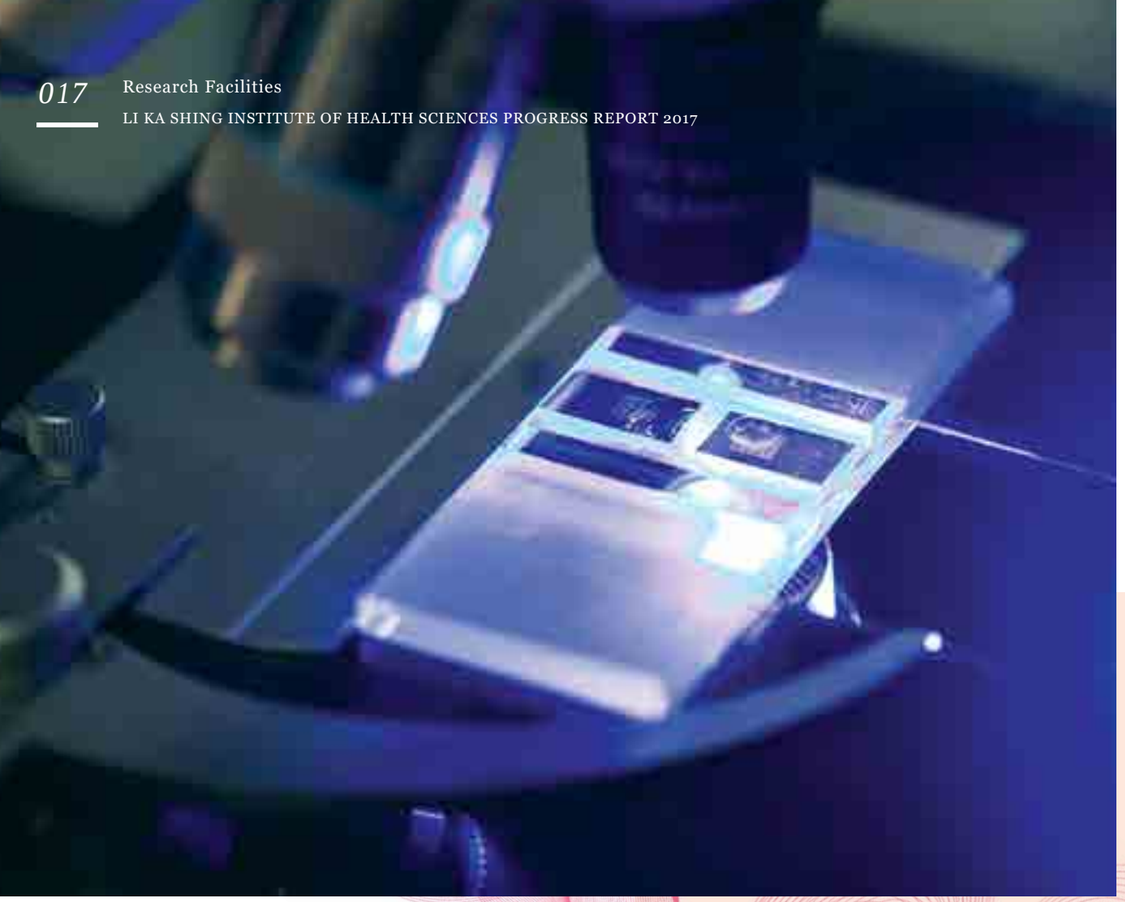
- Enhanced network performance by establishing a 10Gb Dense Wavelength Division Multiplexing (DWDM) local network circuit to connect to CUHK Campus and Science Demilitarised Zone (DMZ).
  建立10Gb本地密集波分復（DWDM）系統網絡連接中大校園和科學週邊網路（DMZ），增強網絡穩定性與傳輸性能。

- Enhanced and expanded Tier 1 storage systems performance and capacity with a 18GB Read/Write I/O throughput and 3.1PB storage space Lustre file and storage system.
  整合及應用具18GB讀寫輸入/輸出（I/O）吞吐量和3.1PB容量的Lustre文件和存儲系統，增強和擴展第1層存儲系統的性能和容量。

- Expanded the Tier 2 and Tier 3 storage by a new and high-speed storage system with 1.4PB capacity.
  應用1.4PB容量高速存儲系統，擴展第二層和第三層存儲器整體容量。

- Strengthened the Centre's computing power with 8 units of dual socket Broadwell servers that all equip with 16 cores 2.6GHz Intel Xeon E5-2697A v4, and 256GB RAM, providing additional 2,496 TeraFLOPS computational power to the existing computing clusters.
  增配8台服務器以增強中心的綜合計算能力。所有新服務器都配備16核、時脈速度2.6GHz的英特爾Xeon E5-2697A v4、及256GB內存，為現有的計算集群提供額外的2,496 TeraFLOPS計算能力。

- Established and integrated new computing capability on big data analysis and cloud environment for new NGS software and tools.
  為新的NGS軟件和工具建立和整合具大數據分析及雲環境處理效能的新工作環境及計算能力。



## 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
- Cell Therapy Laboratory.
  細胞治療實驗室



# 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 Assessment
## 樣本品質鑒定

**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片段的長短、數量和質量，以備後續實驗使用。



Agilent Bioanalyzer
生物分析儀



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



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

## Transfection
## 基因轉染

### Electroporation
### 電脈衝穿孔

To transfect any DNA vectors (expression plasmids, shRNA vectors) into difficult-to-transfect cell lines and primary cell.
將DNA載體（表達質體或shRNA載體）轉染成細胞株及初代細胞。

Amaxa Nucleofector II
電穿孔轉殖儀







Affymetrix Microarray System
微陣列分析儀

## Molecular Analysis
## 分子分析

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

To analyse genotyping, copy number variation, DNA methylation and gene expression profiling.
分析基因型態、拷貝數變異、基因甲基化及基因表現模組。



Illumina iScan Microarray System
芯片掃描系統



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



### Bead-based Suspension
### 磁珠懸浮偵測

To quantify up to 100 analytes in a single sample (i.e. a flexible multiplex immunoassay system which uses colour-coded bead sets).
利用多重抗體陣列系統對樣本進行定量分析，可同時處理單一樣本內高達100種分析物。

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



## Data Analysis
## 數據分析

### Data Analysis Workstation
### 數據分析工作平台

To analyse data generated by microarray analysis (i.e. an integrated and comprehensive data analysis tool)
對微陣列數據進行綜合分析。

GenomeStudio

Transcriptome Analysis Console
轉錄組分析控制台

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

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

**細胞生物學重點科研設施**為研究員提供全面的研究設備，篩擇和培育細胞，及提供細胞成像。

## Cell Selection
## 細胞篩選

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

To characterise and collect cells of interest as the cells pass through the sample stream and are interrogated by laser beam.
以雷射激光照射流動中的細胞，分類並收集目標細胞。





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



## Cell Culturing
## 細胞培養

**Cell Culture Facilities** equipped with NSF49 certified Biosafety Cabinets, which facilitate the culturing of animal cells, animal cell lines and human cell lines. In view of increasing demand 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標準的生物安全櫃，可供研究員培育動物細胞、動物細胞株及人類細胞株。為配合日益增長的需求，研究所於去年擴充細胞培育設施，設施容量倍增後，有助提升研究效率並有利於研究與細胞相關的項目。

## Cellular Imaging
## 細胞成像

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

To acquire optical sections, high resolution images, three-dimensional images for co-localisation analysis of subcellular structures, and dynamic processes for cellular research.
用於採集高分辨率圖像，包括用於亞細胞結構的共定位分析和細胞研究的動態過程的三維圖像。



Leica TCS SP8



# Cell Therapy Laboratory
# 細胞治療實驗室

The **Cell Therapy Laboratory** allows researchers to conduct a wide range of cell-based therapeutics researches using human mesenchymal stem cells in disorders including osteoarthritis, chronic wound, brain injury, vascular diseases and cancer.

The laboratory is qualified for Purification, Expansion, Reprogramming and Differentiation of human stem cells for cell therapies.

研究員可於**細胞治療實驗室**進行多種細胞實驗，利用人類間質幹細胞尋求各種疾病的治療方法，如骨骼關節炎、慢性傷口、腦損傷、血管疾病及癌症。

實驗室為細胞療法提供淨化、擴增、重編及人類幹細胞分化培殖服務。





It composes of:
實驗室包括：

- 2 ISO 14644-1 Class 7 Clean Room Suites
  兩間符合ISO14644-1等級7標準的無塵室
- 1 Preparation Room
  一間製劑室
- 1 Quality Control Area
  一個品質控制區
- **Cell Therapy Laboratory** with ISO 14644-1 Class 7 Certification, which facilitates the culturing of human stem cells.
  **細胞治療實驗室**符合ISO14644-1等級7的標準，協助培育人類幹細胞。





# RESEARCH ACTIVITIES AND OUTPUTS
# 科研動態



## Research Areas and Teams
## 研究領域及隊伍

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

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

### Diseases and Pathobiology
### 疾病及病理生物

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

### New Technologies
### 創新技術

| Research Area 研究領域 | Principal Investigator | 首席研究員 |
|---|---|---|
| Molecular Diagnostics<br>分子診斷學 | Dennis Lo<br>Rossa Chiu<br>Allen Chan<br>Nelson Tang<br>Timothy Cheng | 盧煜明<br>趙慧君<br>陳君賜<br>鄧亮生<br>鄭華哲 |
| Fecal Microbiota Transplantation<br>腸道微生物移植研究 | Siew Ng | 黃秀娟 |
| Stem Cells and Tissue Regeneration<br>幹細胞及組織再生研究 | Gang Li<br>Kathy Lui<br>Ling Qin | 李剛<br>呂愛蘭<br>秦嶺 |
| Genomics and Bioinformatics<br>基因組學與生物訊息學 | Hao Sun<br>Peiyong Jiang | 孫昊<br>江培勇 |
| Non-coding RNAs<br>非編碼核糖核苷酸研究 | Huating Wang | 王華婷 |
| Cellular Signalling<br>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 **167** publications from these teams were published. Among the publications, **92** and **25** 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**167**篇學術論文，當中有**92**及**25**篇分別刊登於影響分子高於**4**及**10**的學術刊物。

## Analysis of Plasma Epstein–Barr Virus DNA to Screen for Nasopharyngeal Cancer

### Author(s)

Allen Chan, Rossa Chiu, Dennis Lo *et al.*

### Journal

*New England Journal of Medicine* 2017; 377(6): 513-522


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 10, 2017 VOL. 377 NO. 6

Analysis of Plasma Epstein–Barr Virus DNA to Screen for Nasopharyngeal Cancer

K.C. Allen Chan, F.R.C.P.A., John K.S. Woo, F.R.C.S., Ann King, F.R.C.R., Benny C.Y. Zee, Ph.D., W.K. Jacky Lam, F.R.C.S., Stephen L. Chan, F.R.C.P., Sam W.I. Chiu, B.Sc., Constance Mak, B.S.N., Irene O.L. Tse, B.N., Samantha Y.M. Leung, B.N., Gloria Chan, R.N., Edwin P. Hui, F.R.C.P., Brigette B.Y. Ma, M.D., Rossa W.K. Chiu, F.R.C.P.A., Sing-Fai Leung, F.R.C.R., Andrew C. van Hasselt, F.R.C.S., Anthony T.C. Chan, F.R.C.P., and Y.M. Dennis Lo, F.R.S.



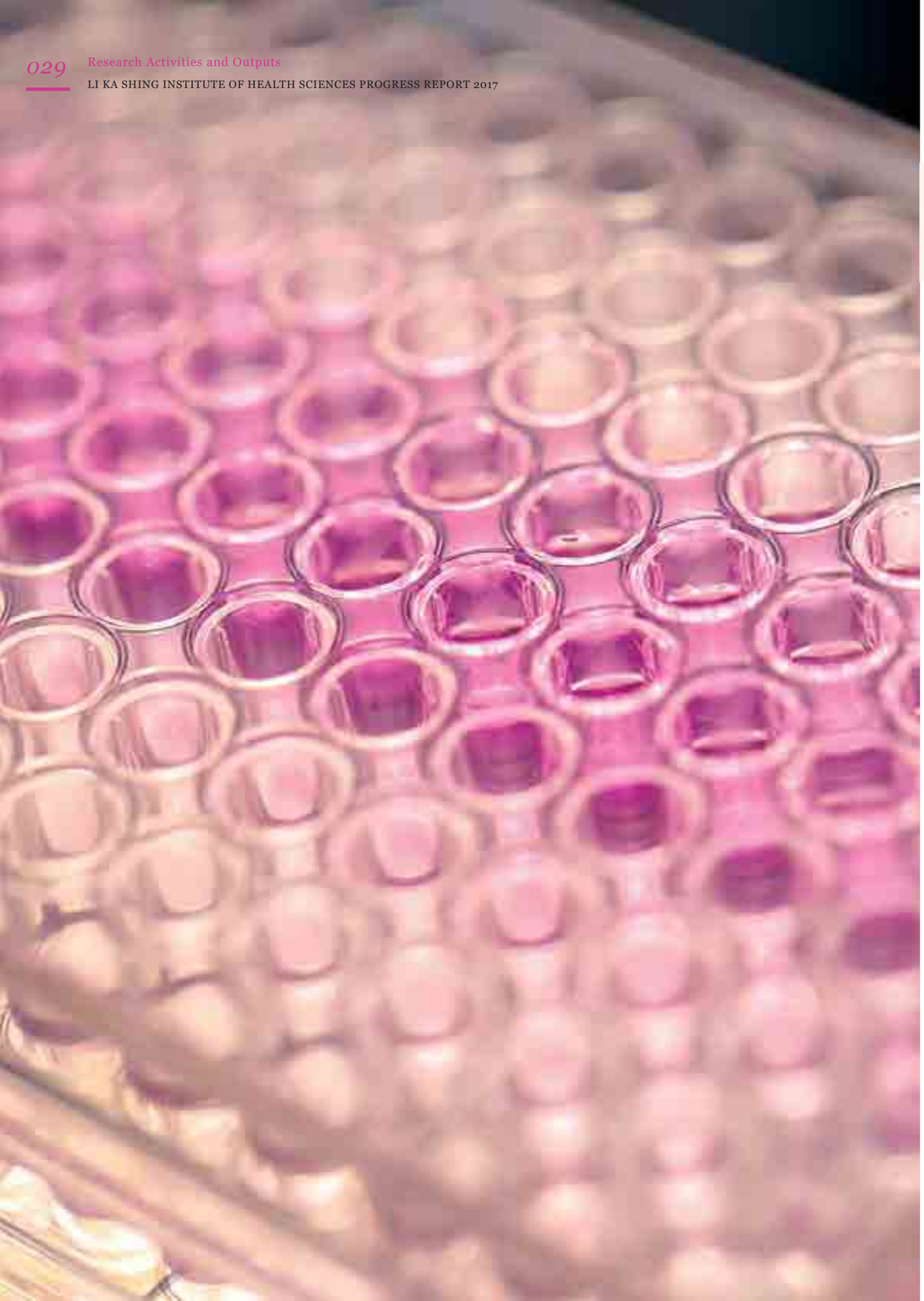
### Introduction

For cancer patients, the extent of disease at diagnosis is the most important factor determining the treatment outcomes. Patients with early-stage cancers generally have much better long-term survival and fewer treatment-associated complications compared with those with advanced cancers. Using nasopharyngeal cancer as a model, the team investigated the potential application of circulating tumour DNA analysis in blood plasma for the screening of early cancers in asymptomatic individuals. From 2013 to 2016, the team recruited over 20,000 apparently healthy volunteers to this study and all of them did not have any symptoms of nasopharyngeal cancer. These participants were screened for nasopharyngeal carcinoma using a DNA-based blood test. Individuals with a positive test result were further investigated with nasal endoscopy and MRI. Through this arrangement, 34 participants were identified as having nasopharyngeal cancer. Compared with the historical data reported in the Hong Kong Cancer Registry 2013, patients identified through this screening programme had significantly earlier stage distribution. Remarkably, 16 (47%) of the 34 patients had stage I cancer. In 2013, only 4.6% of all nasopharyngeal cancer patients in Hong Kong had stage I disease. Because of the shifting of cancers to earlier stage, patients identified by screening had much better treatment outcome. The probability of disease progression and death was reduced by 90% in patients identified by screening compared with those who had not undergone screening.

This large-scale prospective study provides the first conclusive evidence that circulating DNA analysis is useful for the screening of early asymptomatic cancers which can lead to substantial improvement in treatment outcomes. This technology can be potentially applied for the detection of virtually all types of cancers. The significance of this study is highlighted by it being selected as one of the "Ten Notable Articles in 2017" by the *New England Journal of Medicine*, the most prestigious medical journal in the world. This has also been recorded in the Calendar of Events of the 2017 Hong Kong Yearbook.

腫瘤細胞影響的範圍是決定癌症治療效果的最重要因素。一般而言，相對於晚期癌症患者，早期患者有較高的存活率，出現治療相關併發症的機會亦較少。然而由於大部分的早期癌症並沒有任何病徵，因此很多癌症病人確診的時候已經到達比較後期。以鼻咽癌為示範，研究團隊利用血漿中腫瘤DNA分析，用以篩查早期無病徵的癌症的可行性。從2013年到2016年，團隊為2萬多名無鼻咽癌病徵的志願者進行血漿鼻咽癌DNA分析，以篩選鼻咽癌。測試結果呈陽性的參加者會接受鼻咽內視鏡及磁力共振掃描檢查，以確定是否患有鼻咽癌。通過這種安排，34名參加者被確診患有鼻咽癌。與2013年香港癌症資料統計中心的數據相比，通過本篩查計劃確定的患者有明顯較早分期。在34名確診鼻咽癌患者中，有16名（47%）確診第一期。相對2013年，全港所有鼻咽癌患者中只有4.6%確診為第一期。由於能及早發現癌症，通過篩查發現鼻咽癌的患者治療效果明顯較好。與未接受篩查的患者相比，他們的疾病進展或死亡概率降低了百分之九十。

這項大規模的前瞻性研究首次提供了確鑿的證據證明能夠利用血漿DNA分析篩查出早期無症狀的癌症，由此顯著改善治療的結果。這項技術將來有機會應用於檢測鼻咽癌以外的其他癌症。這項研究被世界上最負盛名的《新英格蘭醫學雜誌》評選為「2017年度十大最矚目文章」之一。這項榮譽亦已被記錄在2017年香港年鑑中。





# Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies

**Author(s)**

Siew Ng *et al.*

**Journal**

*Lancet* 2017; 390: 2769-78

**Introduction**

Articles

**Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies**

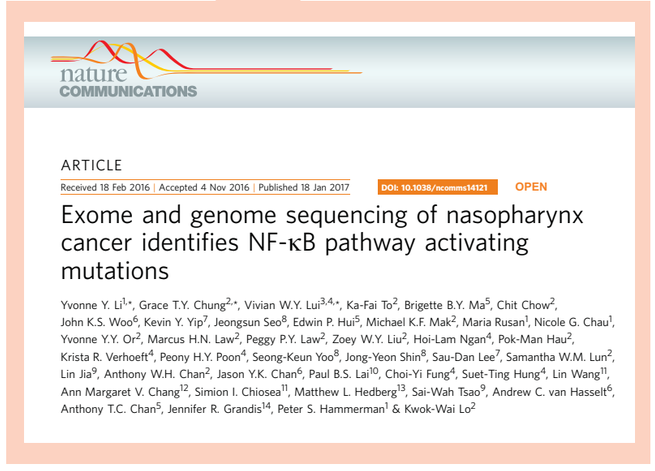
*Siew C Ng*, Hai Yun Shi, Nima Hamidi, Fox E Underwood, Whitney Tang, Eric I Benchimol, Remo Panaccione, Subrata Ghosh, Justin C Y Wu, Francis K L Chan, Joseph J Y Sung, Gilaad G Kaplan**

Inflammatory bowel diseases (IBD), consisting of Crohn's disease and ulcerative colitis, are modern diseases of modern times. The team conducted a systematic review of all population-based studies reporting the incidence or prevalence of IBD since 1990. This is the most comprehensive and up-to-date global overview of the incidence and prevalence of IBD in the 21st century. For the last century, IBD has been a challenge for patients and the medical community in the Western world. This paper, published in the *Lancet*, showed that countries outside the Western world may now be facing the same pattern of increasing IBD rates. Over the past 100 years, the incidence of IBD in Western countries has climbed and then plateaued. The research shows that countries outside the Western world now appear to be in the first stage of this sequence. At the turn of the 21st century, IBD became a global disease with accelerating incidence in newly industrialised countries of Asia, South America, the Middle East, and Africa whose societies have become more westernised. Over the past generation, newly industrialised countries have experienced greater urbanisation with populations moving from rural areas to densely populated cities. Prevalence of IBD in newly industrialised countries is expected to climb. The data emphasises the need for research into prevention of IBD and innovations in health-care systems to manage this complex and costly disease worldwide, by clinicians and health policy makers. Future research should focus on identifying environmental risk factors observed during the early stages of industrialisation in order to target intervention that helps to prevent IBD.

炎症性腸病包括克隆氏症及潰瘍性結腸炎，這都是現今世代出現的新時代疾病。研究團隊以人口統計為基礎，蒐集了自1990年以來有關炎症性腸病的患病率及發病率進行了系統性回顧研究。這是在21世紀中一項對炎症性腸病最全面及最新的全域概覽。於上個世紀，炎症性腸病已成為西方國家患者和醫學界的挑戰。在《刺針》發表的這篇文章中，團隊指出西方世界以外的國家，現在可能面臨著同樣持續上升的發病率。在過去一百年間，炎症性腸病發病率在西方國家已攀升至頂點，然後開始平穩。是次研究指出，西方國家以外的地區現在似乎處於同一序列的第一個階段。在現今21世紀，炎症性腸病成為了全球性疾病，其發病率在新興工業化國家如亞洲、南美洲、中東及非洲，這些都是較為西化的社會加速上升。在過去的一代，新興工業化國家經歷了更大的城市化，人口從農村地區遷移到人口稠密的城市。炎症性腸病的患病率並預期在這些國家會繼續攀升。

文章中的數據強調，有需要由臨床醫生和衛生政策制定者研究預防炎症性腸病及保健系統的創新，以助管理及治療這一全球性既複雜又昂貴的疾病。未來的研究，應該優先考慮確定在早期工業化階段所觀察到的環境風險因素，以針對有助於預防炎症性腸病的干預措施。

# Exome and genome sequencing of nasopharynx cancer identifies NF-κB pathway activating mutations


nature COMMUNICATIONS

ARTICLE

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Exome and genome sequencing of nasopharynx cancer identifies NF-κB pathway activating mutations

Yvonne Y. Li[1,*], Grace T.Y. Chung[2,*], Vivian W.Y. Lui[3,4,*], Ka-Fai To[2], Brigette B.Y. Ma[5], Chit Chow[2], John K.S. Woo[6], Kevin Y. Yip[7], Jeongsun Seo[8], Edwin P. Hui[5], Michael K.F. Mak[2], Maria Rusan[1], Nicole G. Chau[1], Yvonne Y.Y. Or[2], Marcus H.N. Law[2], Peggy P.Y. Law[2], Zoey W.Y. Liu[2], Hoi-Lam Ngan[4], Pok-Man Hau[2], Krista R. Verhoeft[4], Peony H.Y. Poon[4], Seong-Keun Yoo[8], Jong-Yeon Shin[8], Sau-Dan Lee[7], Samantha W.M. Lun[2], Lin Jia[9], Anthony W.H. Chan[2], Jason Y.K. Chan[6], Paul B.S. Lai[10], Choi-Yi Fung[4], Suet-Ting Hung[4], Lin Wang[11], Ann Margaret V. Chang[12], Simion I. Chiosea[11], Matthew L. Hedberg[13], Sai-Wah Tsao[9], Andrew C. van Hasselt[6], Anthony T.C. Chan[5], Jennifer R. Grandis[14], Peter S. Hammerman[1] & Kwok-Wai Lo[2]

## Author(s)

Kwok-wai Lo, Ka-fai To *et al.*

## Journal

*Nature Communications* 2017; 8:14121

## Introduction

Nasopharyngeal carcinoma (NPC) is a common type of cancer in Hong Kong and in other parts of Southern China. It is one of the most aggressive head and neck cancers characterised by Epstein-Barr virus (EBV) infection. To determine the genomic landscape of NPC, the research team performed whole-exome and whole-genome sequencing on over 100 EBV-positive NPC cases in 2015-2016. With the largest cohort of cases, the study provides the most comprehensive view of NPC genomics. Importantly, it identified several novel and key genomic events that promote NPC cell growth including the prevalence inactivating mutation of regulatory proteins of the inflammation NF-κB pathway and MHC class I molecules. The groundbreaking findings will facilitate the development of personalised medicine for NPC patients.

鼻咽癌是香港和南中國常見的癌症。它是一種與Epstein-Barr病毒（EBV）感染有關的侵襲性頭頸部腫瘤。研究團隊在2015至2016年對100多例EBV陽性的鼻咽癌病例進行了全外顯子組和全基因組測序以確定鼻咽癌基因組景觀。通過研究大量的病例，團隊成功全面拆解鼻咽癌基因組圖譜。他們更發現多個促進鼻咽癌生長的關鍵基因變異，包括NF-κB通路調節蛋白和主要組織相容性複合體（MHC）分子的失活突變。是次突破性的發現將有助於為鼻咽癌病人開發個人化治療。



# Smad3 promotes cancer progression by inhibiting E4BP4-mediated NK cell development


nature COMMUNICATIONS

ARTICLE

Received 29 Jul 2015 | Accepted 23 Jan 2017 | Published 6 Mar 2017 DOI: 10.1038/ncomms14677 OPEN

Smad3 promotes cancer progression by inhibiting E4BP4-mediated NK cell development

Patrick Ming-Kuen Tang[1,2,*], Shuang Zhou[2,3,4,*], Xiao-Ming Meng[2,*], Qing-Ming Wang[2], Chun-Jie Li[2], Guang-Yu Lian[2], Xiao-Ru Huang[2], Yong-Jiang Tang[2], Xin-Yuan Guan[5], Bryan Ping-Yen Yan[2], Ka-Fai To[1] & Hui-Yao Lan[1,2]

## Author(s)

Hui-yao Lan *et al.*

## Journal

*Nature Communications* 2017; 8:14677

## Introduction

Tumour immunity is a determinant factor of cancer progression. The team's recent study uncovered the mechanism as to how cancer cells utilise a transforming growth factor-beta (TGF-β1) protein to circumvent the frontline of our immune system against cancer. Based on this discovery, a new immunotherapy for cancer by targeting TGF-β/Smad3 signalling was developed.

The research team found that cancer cells can produce abundant TGF-β1 to activate its downstream biomolecule Smad3 to suppress the host immunity against cancer and therefore promote tumour growth and metastasis. Disrupted Smad3 in mice largely promoted the host innate immunity with a 10-fold increase in nature killer (NK) cells and their cancer-killing activities in the tumour microenvironment. Further studies identified that Smad3 is a key checkpoint for TGF-β1 mediated immunosuppression in the tumour microenvironment. Smad3 can directly inhibit a master gene called E4BP4 to suppress NK cell production and functions. Thus, removal of Smad3 can restore the NK cell development and tumour-killing activities.

This discovery has resulted in a pre-clinical work of Smad3-targeted anticancer therapy. In two syngeneic mouse tumour models of invasive lung carcinoma and melanoma, treatment with a Smad3 inhibitor can effectively suppress cancer progression by increasing NK cell production and other anticancer activities in the tumour microenvironment. This new finding may lead to the development of a Smad3-targeted immunotherapy for cancer clinically.

機體免疫力的下降是導致癌腫瘤進展的主要因素。這篇文章成功揭示了癌細胞如何利用自身產生轉化生長因子（TGF-β1）蛋白逃脱人體第一道免疫抗癌防線 — 自然殺傷細胞（NK）的機制，並據此找到恢復和促進機體抗癌的免疫治療新方案。

研究團隊發現癌細胞能夠通過大量產生轉化生長因子蛋白去激活腫瘤微環境（泛指腫瘤組織中的非癌部分）的生物分子信號Smad3蛋白而抑制機體抗癌免疫力，促進癌細胞的生長和轉移。通過實驗性肺癌及黑色素腫瘤，發現除去Smad3的腫瘤微環境中，NK細胞數目增加了10倍之多，帶瘤小鼠的抗癌能力亦大幅提升，存活率達100%。證明Smad3是TGF-β1抑制機體腫瘤免疫和促進癌細胞生長和轉移的關鍵蛋白。研究進一步發現，Smad3蛋白是通過直接抑制轉錄因子E4BP4而阻止NK細胞的發育和抗癌功能。因此，團隊開始進行Smad3標靶抗癌治療的臨床前研究。結果顯示Smad3標靶治療不但增加了腫瘤微環境中的NK細胞數目，亦同時減低了其他有利癌細胞生長的因素，因而大幅抑制癌症進展，效果顯著，有望發展為既安全又有效的標靶腫瘤免疫治療。

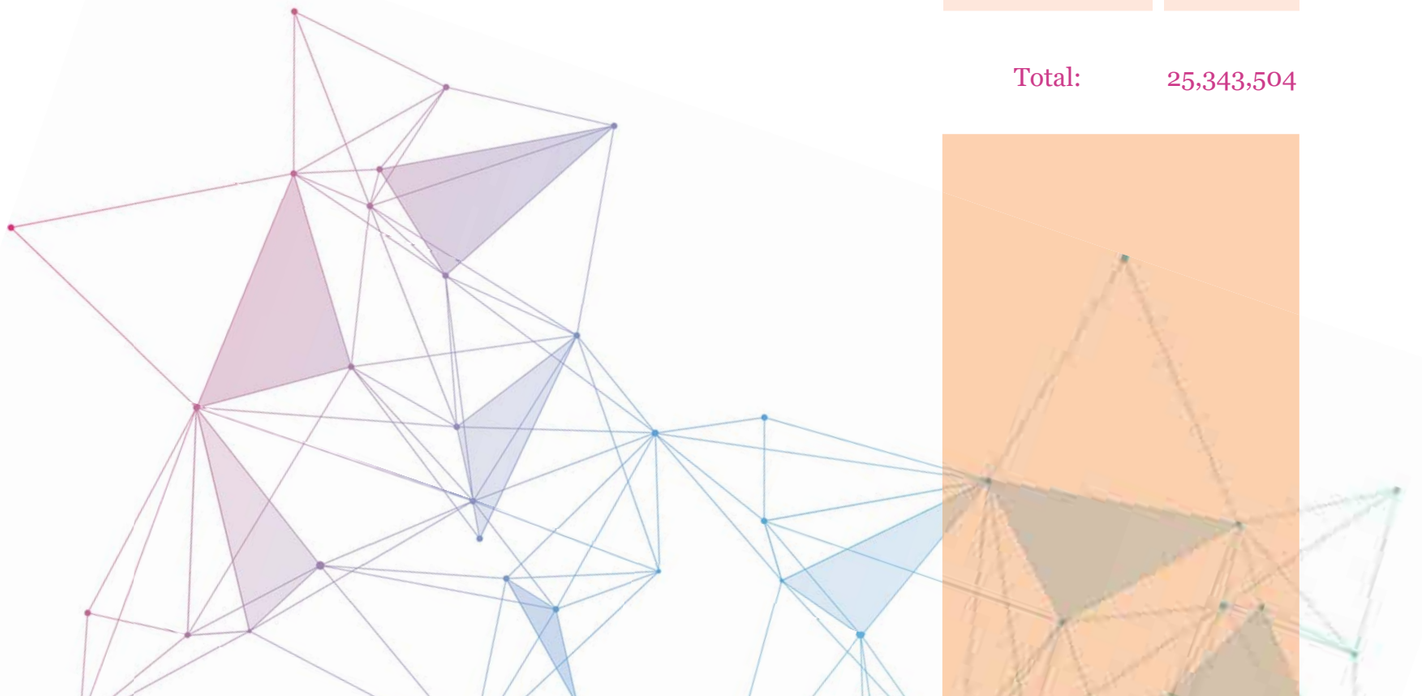
# Grants
# 補助金及其他資助

Our Principal Investigators and their teams affiliated to the Institute have received grants of over **HK$391M** during this reporting period. In particular, grants under the General Research Fund (GRF) scheme of the Research Grants Council (RGC) of **HK$25M** 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**港幣三億九千一百萬**，其中研究資助局的優配研究金共佔**港幣二千五百萬**，獲資助研究項目的詳情如下：

| Project Title 研究題目 | Principal Investigator 研究所項目負責人 | Amount (HK$) |
|---|---|---|
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/01/2016 – 31/06/2017)<br>Using C-peptide, anti-glutamic acid decarboxylase antibodies and body mass index to identify patients with young-onset type 2 diabetes for early insulin therapy | Juliana Chan | 600,000 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/01/2016 – 31/12/2017)<br>Progression of glucose intolerance, cardio-metabolic risk factors and subclinical atherosclerosis in Chinese women with Polycystic Ovary Syndrome | Juliana Chan | 600,000 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(15/09/2017 – 25/09/2020)<br>Biomaterials-mediated bone formation and consolidation in distraction osteogenesis | Gang Li | 1,098,710 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/01/2016 – 31/12/2018)<br>Is Smad7 a potential therapeutic target for preventing osteoporotic bone loss? | Gang Li | 821,097 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/01/2016 – 31/12/2018)<br>Identification and functional characterization of super enhancer associated RNAs (seRNAs) in skeletal myogenesis using integrated genomic approach | Hao Sun | 1,228,445 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/01/2015 – 31/12/2017)<br>Integrating large intergenic noncoding RNAs into Pax7 mediated regulatory circuitry in muscle satellite cells | Hao Sun | 623,277 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/01/2015 – 31/12/2018)<br>Functional characterization of YY1 in skeletal muscle stem cells and muscle regeneration | Huating Wang | 1,182,869 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/01/2014 – 31/12/2017)<br>Functional characterization of Malat1 in skeletal muscle stem cells and muscle regeneration | Huating Wang | 1,086,500 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/01/2016 – 31/12/2019)<br>Mechanistic Exploration of Super-enhancer Associated seRNA Function in Skeletal Muscle Cells | Huating Wang | 922,171 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/01/2016 – 31/12/2018)<br>Role of a Newly Identified Long Noncoding RNA in Sarcopenia | Huating Wang | 1,009,452 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/01/2016 – 31/12/2018)<br>Is there a Link between Systemic Muscle Mass, Muscle Strength, Serum and Muscle Expression of Myokines and LBX1 with Bone Mineral Density and Bone Quality in Adolescent Idiopathic Scoliosis? | Huating Wang | 593,675 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/01/2016 – 31/12/2018)<br>Role of a novel lncRNA np_5318 in kidney disease | Hui-yao Lan | 1,088,569 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/01/2017 – 31/12/2019)<br>Elucidation of a novel tumor suppressor gene tripartite motif 67 (TRIM67) in colorectal cancer | Jun Yu | 1,154,550 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/01/2016 – 31/12/2018)<br>Functional characterization of squalene epoxidase in promoting fatty liver disease-associated liver cancer | Jun Yu | 1,141,432 |

| Project Title 研究題目 | Principal Investigator 研究所項目負責人 | Amount (HK$) |
|---|---|---|
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/10/2015 – 30/09/2018)<br>PGE2-induced DNA methylation in gastric cancer: mechanisms and therapeutic implications | Jun Yu | 852,552 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/09/2016 – 31/08/2018)<br>Target Inhibition of ATM-mediated Homologous Recombination Repair by Epstein-Barr Virus miRBARTs in Nasopharyngeal Carcinoma: Molecular Mechanisms and Clinical Implications | Ka-fai To | 811,383 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/01/2016 – 31/12/2018)<br>Study on the role of Esptein-Barr Virus (EBV)- encoded microRNAs in controlling DNA damage repairs in EBV-associated nasopharyngeal carcinoma | Ka-fai To | 1,187,649 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/01/2017 – 31/12/2018)<br>Unraveling the impact of hyperglycemia on survival and cell fate commitment of the human multipotent ISL1+ heart progenitors | Kathy Lui | 902,460 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/01/2015 – 31/12/2017)<br>An Innovative Intramedullary Nail Containing Biodegradable Osteogenic Magnesium (Mg) Designed for Fracture Repair Enhancement-From Mechanisms to Translation | Ling Qin | 647,399 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/01/2017 – 31/12/2019)<br>An Innovative Bio-intramedullary Nail with Osteogenic Mg-ions for Accelerating Bone Defect Repair – A Proof-of-Concept Study | Ling Qin | 929,880 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/09/2016 – 19/01/2018)<br>The impact of gestational diabetes mellitus and vitamin D deficiency during pregnancy on children's cardiometabolic risk and methylation | Ronald Wang | 998,652 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/10/2017 – 30/09/2020)<br>Association of Retinoid Deficiency With Inborn Nephron Deficit in Offspring Exposed to Maternal Diabetes | Ronald Wang | 1,212,780 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/01/2016 – 31/12/2017)<br>Application of a Diffusion Model for Characterizing HIV Transmission Dynamics in Men-having-sex-with-men (MSM) in Hong Kong | Shui-shan Lee | 547,036 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/01/2015 – 31/12/2017)<br>Vascular Events in Surgery Patients Cohort Evaluation (VISION) – Cardiac Surgery Study | William Wu | 1,051,942 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/01/2017 – 31/12/2019)<br>TM9SF4 as a novel K+ channel and its role in autophagy | Xiaoqiang Yao | 1,000,387 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/01/2017 – 31/12/2019)<br>Targeting TFEB to reverse endothelial dysfunction in diabetic mice through induction of autophagy | Yu Huang | 1,317,102 |
| **Research Grants Council (RGC) – General Research Fund (GRF)**<br>(01/06/2016 – 30/05/2018)<br>Phenolic-type Reactive Carbonyl Scavengers as Inhibitors against the Formation of Advanced Glycation End Products (AGEs) and AGEs-induced Endothelial Dysfunction, Cell Apoptosis and Inflammation | Yu Huang | 733,535 |
| | Total: | 25,343,504 |



# Theme-based Research Scheme
# 主題研究計劃

In 2015, the University Grants Committee (UGC) selected "Centre for Research into Circulating Fetal Nucleic Acids" led by Professor Dennis Lo as one of the Theme-based Research Scheme projects. The project was progressing smoothly during the reporting period. The Scientific Advisory Board of the Theme-based Research Scheme project conducted its second meeting on 30 August 2017 to assess the progress of the project.

2015年，由盧煜明教授率領的「母體血漿胎兒核酸研究中心」獲得大學教育資助委員會的主題研究計劃撥款資助，並於過去一年順利進行研究。2017年8月30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。



Meeting of the Scientific Advisory Board of Theme-based Research Scheme Project "Centre for Research into Circulating Fetal Nucleic Acids" (30 August 2017)
「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（2017年8月30日）

(In the photo, from left to right: Professor Hao Sun, Professor Allen Chan, Professor Dennis Lo, Professor Howard S. Cuckle (Scientific Advisory Board Member), Professor Charles Cantor (Scientific Advisory Board Member), Professor Rossa Chiu)
（相片中由左至右為：孫昊教授，陳君賜教授，盧煜明教授，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，趙慧君教授）

# 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：



**Date**

7 March 2017

**Seminar**

Seminar by Dr. Jian Han, Faculty Investigator, HudsonAlpha Institute for Biotechnology, Alabama, USA, on “Towards the Ultimate Diagnostics: NGS of Immune Repertoire, Method and Applications”.

韓健博士（美國亞拉巴馬州HudsonAlpha Institute for Biotechnology研究員）舉行研討會，題目為「Towards the Ultimate Diagnostics: NGS of Immune Repertoire, Method and Applications」（2017年3月7日）。

**Date**

16 June 2017

**Seminar**

Seminar by Professor Mone Zaidi, Professor of Medicine and of Structural and Chemical Biology, Icahn School of Medicine at Mount Sinai, New York, USA, on “Can We Treat Obesity and Osteoporosis With A Single Drug?”.

Mone Zaidi教授（美國紐約Icahn School of Medicine at Mount Sinai，Professor of Medicine and of Structural and Chemical Biology）舉行研討會，題目為「Can We Treat Obesity and Osteoporosis With A Single Drug?」（2017年6月16日）。





**Date**

24 June 2017

**Seminar**

Organised by The Hong Kong Down Syndrome Association, and co-organised by the Faculty of Medicine and the Institute, “The Hong Kong Down Syndrome Association 30th Anniversary Symposium - Innovation, Insights & Intervention” aims to enhance public awareness on Down’s Syndrome from the perspectives of medical research, healthcare services, early education and experiences sharing.

由香港唐氏綜合症協會主辦及香港中文大學醫學院與本研究所協辦之「香港唐氏綜合症協會三十周年研討會 — 創新、創見、創將來」，旨在從醫學研究、醫療服務、早期教育及照顧歷程的分享等不同角度，提升公眾對唐氏綜合症的認知（2017年6月24日）。






**Date**

4 July 2017

**Seminar**

Seminar by Professor Xiang Gao, Director of Model Animal Research Centre, The National Resource Centre for Mutant Mice of China, Nanjing University, China, on “Disease models, what are we looking for today?”

高翔教授（中國南京大學動物模式研究所所長）舉行研討會，題目為「Disease models, what are we looking for today?」（2017年7月4日）。



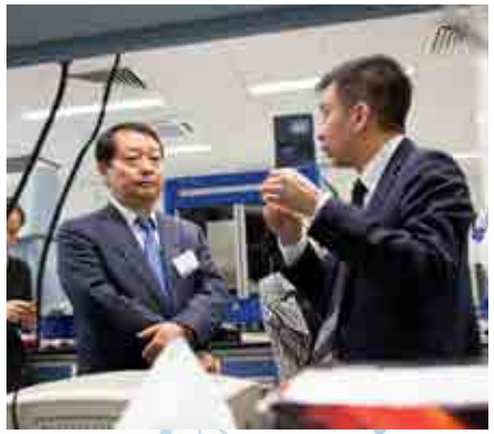
**Date**

25 September 2017

**Visit**

Visit by Dr. Wei Huang, Vice Minister of the Ministry of Science and Technology of China. The delegations visited the Institute, State Key Laboratory of Oncology in South China, and State Key Laboratory of Digestive Disease. Prof. Jun Yu and Prof. Allen Chan introduced the latest development in Partner Laboratories in CUHK.

中國國家科學技術部黃衛副部長及代表團到訪研究所，並參觀華南腫瘤學國家重點實驗室及消化疾病研究國家重點實驗室（香港中文大學夥伴實驗室）。于君教授和陳君賜教授向訪問團介紹香港中文大學夥伴實驗室的最新研究發展（2017年9月25日）。





**Date**

14 December 2017

**Seminar**

Seminar by Professor Sunney Xie, Mallinckrodt Professor of Chemistry and Chemical Biology, Department of Chemistry and Chemical Biology, Harvard University, USA, on “Life at the Single Molecule Level”.

謝曉亮教授（美國哈佛大學化學及化學生物系，Mallinckrodt化學及化學生物教授）舉行研討會，題目為「Life at the Single Molecule Level」。（2017年12月14日）



# Scientific Exchange
## 學術交流

The 2017 East-West Alliance (EWA) Global Symposium was held at University of Oxford, United Kingdom from 11 to 14 September 2017. Professor Ronald Ma and Professor Peiyong Jiang from the Faculty of Medicine attended this meeting on behalf of The Chinese University of Hong Kong. The EWA is a global network of universities and medical schools that are supported by the Li Ka Shing Foundation. The Alliance aims to foster knowledge exchange and collaboration among leading medical institutions on high-impact research and educational projects. The theme of the 2017 EWA Global Symposium was “*Big Data in Health*”.

2017年度東西方聯盟國際高峰會於2017年9月11日至14日期間假英國牛津大學舉行，醫學院馬青雲教授及江培勇教授代表香港中文大學出席是次會議。「東西方聯盟」由13所獲李嘉誠基金會捐助的國際頂尖學府及醫學院組成，藉構建跨機構學術交流的平台，促進醫學研究及教育發展。本年度高峰會的主題為「*Big Data in Health*」。




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



Professor Ronald Ma and Professor Peiyong Jiang at The 2017 East-West Alliance (EWA) Global Symposium
馬青雲教授及江培勇教授代表香港中文大學醫學院參加2017年度東西方聯盟國際高峰會

# APPENDIX
# 附錄

## Reports on Research Activities
## 科研活動報告

01
Digestive Diseases
消化疾病研究

02
Molecular Diagnostics
分子診斷學

06
Diabetes and Obesity
糖尿病與肥胖症研究

07
Emerging Infectious Diseases
防疫研究

09
Inflammatory Diseases
炎症性疾病研究

11
Reproduction and Development
生殖與發育研究



03
Fecal Microbiota Transplantation
腸道微生物移植研究

04
Asian Cancers
亞洲癌症研究

05
Vascular Medicine
血管疾病研究

08
Molecular Microbiology
分子微生物學研究

10
Neuroscience
神經科學

12
Stem Cells and Tissue Regeneration
幹細胞及組織再生研究

13
Genomics and Bioinformatics
基因組學與生物訊息學

14
Non-coding RNAs
非編碼核糖核苷酸研究

15
Cellular Signalling
細胞訊號轉導

# NON-TECHNICAL SUMMARY
# 非技術性報告

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

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

## 01
## Digestive Diseases
## 消化疾病研究

Gastrointestinal (GI) diseases, including GI cancers (stomach, liver and colorectal), non-alcoholic fatty liver disease (NAFLD) and liver fibrosis, are the major diseases in Hong Kong and they cause significant morbidity and mortality. The multidisciplinary team of physicians and scientists led by **Professor Jun Yu** specialises in GI diseases research. Their work includes 1) elucidation of molecular mechanisms underlying the pathogenesis of GI cancers, NAFLD and liver fibrosis via the use of next generation sequencing approaches and animal models; 2) identification of molecular biomarkers potentially useful for GI disease diagnosis, prognosis and treatment; and 3) unravelling the role of gut microbiota in the development of GI diseases.

消化道疾病如消化道（胃腸肝）腫瘤、非酒精性脂肪肝和肝纖維化是香港常見的疾病。**于君教授**帶領的研究團隊由消化疾病醫生和研究專家組成，團隊的主要工作包括（1）闡述相關分子機制；（2）開發新的診斷、預後標誌物及治療靶點；（3）研究消化道菌群和疾病的關係。



Professor Jun Yu
于君教授



## 02
## Molecular Diagnostics
## 分子診斷學



Professor Dennis Lo
盧煜明教授

2017 has been a remarkably productive year for **Professor Dennis Lo**, **Professor Rossa Chiu** and their research team. The project team was successfully awarded another HK$44M Theme-based Research Scheme grant from the Research Grants Council and dedicated to exploring "Plasma DNA as a Platform Technology for Cancer Detection". In terms of knowledge transfer, a contract research agreement has been established between the CUHK project team and Cirina, a Hong Kong-based biotechnology startup company, to facilitate continued technology transfer and translation of the team's research output on cancer diagnostics, especially on identification of early stage cancer. As for research output, the team completed a number of landmark studies. Their publication of the prospective trial on using plasma Epstein-Barr virus DNA to screen for nasopharyngeal carcinoma among asymptomatic individuals in the eminent medical journal, *New England Journal of Medicine*, was selected as one of the 10 most notable articles in 2017. Moreover, their development on single-cell transcriptomic analysis allowed better interpretation of plasma RNA profiles to achieve higher disease specificity. Also, the team has overcome a key bottleneck in noninvasive prenatal diagnosis of fetal monogenic diseases, for example haemophilia, by adopting a novel technology, linked-read sequencing. The progression has made the impossible possible. This year, Prof. Lo has received a number of accolades. In particular, Prof. Lo was bestowed the Life Science Prize of the prestigious Future Science Prize.



Professor Rossa Chiu
趙慧君教授

二零一七年對**盧煜明教授**、**趙慧君教授**及他們所領導的研究團隊來說是高效能的豐收年。團隊貫徹一貫的研究方針，致力發展、開拓「血漿DNA作為檢測癌症之平台技術」，成功獲得大學資助委員會主題研究計劃四千四百萬港元的研究款項，並與一家本港初創企業思為諾簽訂研究合作協議以促進持續研究及知識轉移，從而將研究成果轉化為可實踐的癌症診斷，尤其是將科技應用於識別早期癌症方面。過去一年，團隊的研究計劃都成為個別範疇的里程碑，特別是一項在未有病徵前透過分析血漿EB病毒（Epstein-Barr virus）DNA便能有效地及早診斷鼻咽癌的研究計劃，最近出版並榮獲全球頂尖醫學期刊《新英格蘭醫學雜誌》（*The New England Journal of Medicine*）選為「2017年度十大最受矚目研究文章」。除此以外，團隊利用單細胞轉錄組學分析令血漿RNA的數據面貌闡釋更全面，同時，亦以血友病為例，運用嶄新的序列連結定序技術突破了一直以來產前胎兒單基因疾病診斷的瓶頸，為無創產前測試寫下新的一頁。盧教授團隊的研究成果化不可能成為可能，今年，盧教授榮膺多項殊榮，並獲頒有「中國諾貝爾獎」之稱的「未來科學大獎 — 生命科學獎」。

The research focus of **Professor Allen Chan**'s team is to develop new diagnostic approaches based on the analysis of circulating cell-free nucleic acids. In 2017, the team has completed a cancer screening project, with over 20,000 subjects screened for nasopharyngeal cancer using plasma Epstein-Barr virus (EBV) DNA analysis. 34 cases of nasopharyngeal cancers were detected and they have significantly earlier stage distribution and superior progression-free survival compared with historical cohorts. This study was published in the *New England Journal of Medicine* and the article was selected as one of the ten notable articles published in 2017.

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。在2017年，團隊完成了一項癌症篩查研究項目，利用血漿中的人類疱疹病毒第四型（EBV）DNA分析，為超過20,000名無症狀的香港市民進行鼻咽癌篩查，其中34名參加者通過團隊的癌症篩查計劃被確診患有鼻咽癌。與歷史數據相比，這34名鼻咽癌患者的癌症分期顯著較早期。透過跟進他們治療後的疾病進展，團隊證實他們的無進展生存期顯著較好，復發及死亡率降低了90%。本研究發表在《新英格蘭醫學雜誌》上，並被選為「2017年度十大最受矚目研究文章」。



Professor Allen Chan
陳君賜教授



**Professor Nelson Tang** is the principal investigator of the Laboratory for Genetics of Disease Susceptibility. The research team led by Prof. Tang specialises in genetics of complex traits and statistical analysis. The team's 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. Prof. Tang is also teaching a bioinformatics course in the Faculty of Engineering.

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

**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。團隊的研究涵蓋遺傳關聯研究，表達數量性狀和全基因組關聯分析（GWAS），最近亦獲得了一項專利用於基因表達分析。鄧教授也在工程學院教授生物訊息學課程。

研究小組長期與國際研究人員合作，包括中國科學院昆明動物研究所。鄧教授是該聯合實驗室的副主任。最近，團隊發表了十年努力研究的成果，助大眾了解青少年特發性脊柱側彎的遺傳機制。



Professor Nelson Tang
鄧亮生教授

**Dr. Timothy Cheng**'s research is focused on the analysis of cell-free nucleic acids in plasma and urine.

**鄭華哲醫生**的研究重點是分析血漿和尿液中的無細胞核酸。



Dr. Timothy Cheng
鄭華哲醫生



Professor Siew Ng
黃秀娟教授

# 03

## Fecal Microbiota Transplantation
## 腸道微生物移植研究

The team led by **Professor Siew Ng**, consisting of both clinicians and scientists, centres on faecal microbiota transplantation (FMT) for the treatment of various diseases, including inflammatory bowel disease, *Clostridium difficile* infections and obesity. The team's work aims to untangle the relationship between gut microbiota and human host in health and disease. This year, they are the first to pioneer novel methods and compositions – 'Dark Matters' of gut microbiome - virome and fungome, useful for more effective FMT treatment. These findings have compelling implications on personalised approach to microbiota modulation as therapeutics. With their distinguished achievements, Prof. Ng has won prestigious awards and grants.

**黃秀娟教授**帶領的研究團隊由醫生和科學家組成，主要研究以腸道微生物移植來治療各種疾病，包括炎症性腸病、難辨梭菌感染和肥胖。他們的研究目的是要剖析腸道微生物與人類宿主的健康或疾病之間的關係。今年，他們成為首個率先利用創新技術找出能提高腸道微生物移植療效的微生物成份 — 腸道中的「暗物質」— 病毒組與真菌組。這些發現對於日後發展因人制宜的微生物調整有非常重要的啟示。研究團隊卓越的表現及研究成果為黃教授贏得傑出的獎項及著名的基金資助。





Professor Nathalie Wong
王昭春教授

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

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



Professor Ka-fai To
杜家輝教授

# 04

## Asian Cancers
## 亞洲癌症研究



Professor Kwok-wai Lo
羅國煒教授



Epigenetic alterations including promoter CpG methylation, as hallmarks of human cancers, are critically involved in cancer initiation and progression, with the same pathogenic consequence as genetic mutations. Abnormal promoter methylation silences important tumour suppressor genes (TSGs), resulting in aberrant host gene expression program to initiate and promote tumourigenesis. Importantly, epigenetic changes occur in the early stage of tumour pathogenesis. The Cancer Epigenetics Laboratory led by **Professor Qian Tao** aims to characterise the genome-wide CpG methylation changes (methylome) of common tumours in Hong Kong, identify novel TSGs silenced by promoter methylation, characterise their biological functions and molecular mechanisms, and finally develop non-invasive epigenetic biomarkers for cancer diagnosis.

表觀遺傳學改變包括啟動子CpG甲基化作為癌症的標誌，對癌症的發生發展起著重要的作用，其影響與基因突變後果相同。異常的啟動子甲基化使得重要的抑癌基因（TSG）沉默失活，導致異常的基因表達程序而啟動或促進腫瘤發生。重要的是，表觀遺傳學改變發生在腫瘤發病的早期階段。由**陶謙教授**帶領的腫瘤表觀遺傳學實驗室旨在闡明香港常見腫瘤的表觀遺傳組學改變，鑒定由啟動子甲基化沉默的新抑癌基因，研究其生物學功能和分子機制，以及最終開發非侵入性的表觀遺傳生物標誌物。

Professor Qian Tao
陶謙教授



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

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

Professor Siu Tim Cheung
張兆恬教授



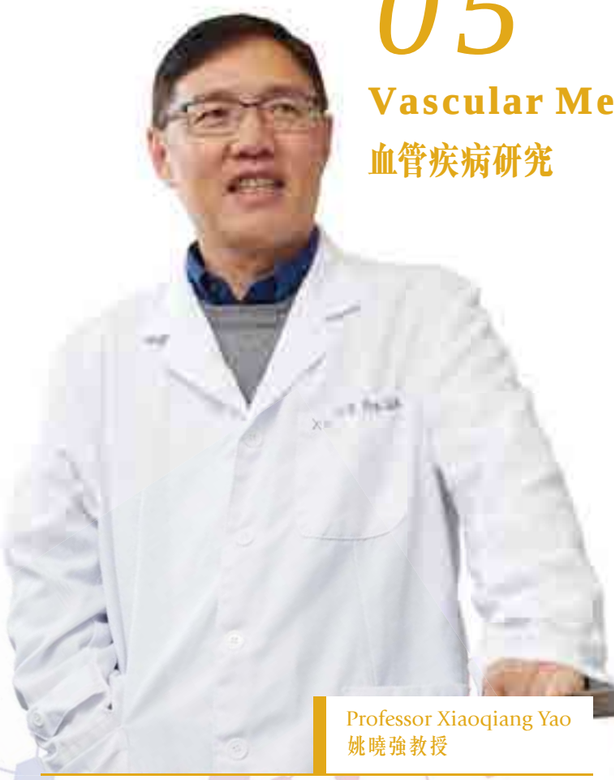
Dilated cardiomyopathy (DCM) is cardiac disease characterised by increased left ventricular chamber volume and decreased systolic function. In the present study, **Professor Xiaoqiang Yao**'s team generated DCM patient-specific human induced-pluripotent stem cells-derived cardiomyocytes. With the use of this disease model, the team demonstrated that an abnormal TRPV4-mediated $Ca^{2+}$ signalling contributes to the DCM disease progression.

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

擴張型心肌病病人（DCM）心臟擴大，左心室收縮功能下降。**姚曉強教授**從DCM患者中誘導產生多能幹細胞，並由此分化產生DCM患者特異性的心肌細胞。研究團隊使用這種疾病模型證明了TRPV4的異常會引發DCM疾病。

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

# 05
## Vascular Medicine
## 血管疾病研究



Professor Xiaoqiang Yao
姚曉強教授



Professor Yu Huang
黃聿教授



**Professor Gary Tse**'s team focuses on conducting meaningful translational research in understanding the pathology of atrial and ventricular arrhythmias, which are important conditions leading to thromboembolic events and sudden cardiac death, respectively. His team has unraveled the novel mechanisms by which immunosuppressive, anti-lipidemic and anti-diabetic medications exert protective effects against atrial fibrillation (Liu,..., Tse, Li and Liu, *Cardiovasc Ther*. 2017; 35(5)). Using a combination of genetic, pharmacological, biochemical and imaging approaches, the team has identified their mechanisms of action, of which reductions in oxidative stress and prevention of mitochondrial dysfunction are critical to achieve reverse remodelling of the atria (Zhang,...Tse, Li and Liu, *J Am Heart Assoc*. 2017; 6(5). pii: e005945).

**謝家偉教授**及其團隊的研究重點是透過轉化型研究去理解涉及心房及心室心律不正的原因，這些疾病是導致血栓栓塞和心臟猝死的關鍵。研究團隊展示了免疫抑制劑、抗血脂藥物及抗糖尿病藥物，是對心房顫動具有保護作用之新機制（Liu,..., Tse, Li and Liu, *Cardiovasc Ther*. 2017; 35(5)）。他們以糅合了遺傳學、藥理學、生物化學和造影的方法，確定其機制是透過減少氧化壓力和預防線粒體功能障礙，對心房的逆向重塑是至關鍵重要的（Zhang,...Tse, Li and Liu, *J Am Heart Assoc*. 2017; 6(5). pii: e005945）。

Professor Gary Tse
謝家偉教授



# 06
# Diabetes and Obesity
# 糖尿病與肥胖症研究



Professor Juliana Chan
陳重娥教授

The research portfolio of the research team led by **Professor Juliana Chan** covers the investigation of causes, trajectories and consequences of diabetes across different stages of the life course, including gestational diabetes, young-onset diabetes, diabetes and its associated complications. Through a series of collaborative inter-linking projects and training of students and fellows, the research team has established cohorts, databases, biobanks and experimental models to advance scientific knowledge. The team has also translated this whole set of knowledge into technologies, prototypes and services through public-private-partnerships in pursuit of the team's ultimate goal of using genomic medicine and holistic care to predict, prevent and control diabetes.

由**陳重娥教授**帶領的研究團隊探討糖尿病在生命歷程的成因、發展和結果；當中包括妊娠糖尿病、早發性糖尿病、糖尿病及其併發症。通過一系列互聯項目合作研究，研究團隊分析隊列數據，建立資料庫、生物樣本庫和實驗模型，並培育學生和研究員推進科學知識。研究團隊亦透過公私型合作將整套知識轉化為技術、原型和服務，以追求他們使用基因組醫學和整全護理來預測、預防和管理糖尿病的最終目標。



Professor Shui-shan Lee
李瑞山教授

# 07
## Emerging Infectious Diseases
## 防疫研究

The Emerging Infectious Diseases (EID) Laboratory specialises in the study of infections of public health importance in Hong Kong and around the world. In the past one year, the research team led by **Professor Shui-shan Lee** has focused on HIV treatment outcome, hepatitis C transmission and the emergence of vectorborne infections including zika and dengue. 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，團隊過去一年重點探討愛滋病毒治療效益、丙型肝炎擴散及包括寨卡和登革熱等媒介傳播感染。團隊以跨領域研究，探討感染的傳播動力，並推算未來趨勢。項目涉及實驗室、臨床和社區研究。





Professor Guoping Zhao
趙國屏教授

# 08
## Molecular Microbiology
## 分子微生物學研究

**Professor Guoping Zhao** is an expert of molecular microbiology and genomics. The research team led by Prof. Zhao has been focusing on pathogenesis and persistence of important bacterial pathogens, e.g., *Mycobacterium tuberculosis* (*Mtb*). Besides the team's recent achievements in the characterisation of *Mtb* MazG as a 5-OH-dCTP-specific housecleaning enzyme involving in persistent infection and drug tolerance, mycobacterial nitrogen metabolism and alternative functions of molybdenum cofactor (MoCo) biosynthesis genes are the two new foci of the laboratory. Meanwhile, in-depth characterisation of Beijing lineage *Mtb* unique chromosomal RD has been another major research direction since the complete sequencing of 5 genomes of clinical isolates were finished.

**趙國屏教授**是分子微生物學及基因組學專家。由趙教授帶領的團隊發現*Mtb* MazG為5-OH-dCTP特異性水解酶，與持續性感染和藥物耐受相關。團隊亦研究與*Mtb*持續感染相關的硝酸鹽代謝與MoCo合成多拷貝基因，基於全基因組測序及比較研究，鑒定北京型菌株特有RD區域。



Professor Sunny Wong
黃曦教授

The main research interest of the Clinical Meta-genomics team is to understand the gut host-microbial interaction and explore it for clinical translation. Using meta-genomic and bioinformatic techniques, the team led by **Professor Sunny Wong** has worked on the digestive tract as an intricate ecosystem between the host and the gut microbiota. This interaction has been recently found to be consequential to various systems, including the alimentary, metabolic, cardiovascular and neurological physiology. This has opened a new approach to develop innovative diagnostics and therapeutics. The focus on the research team has been on gastrointestinal diseases, including colorectal cancer, *Clostridium difficile* and other gastrointestinal infections. Bridging between laboratory and hospital, the team endeavors to bring the scientific discoveries to clinical translation, and to improve human health through developing innovative diagnostics and therapeutics out of the gut microbiota.

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。透過基因排序、生物訊息科技及功能性實驗，他們致力研究微生物群對於不同生理系統的影響。團隊的重點研究在於重要的腸胃科病，包括大腸癌、腸胃感染如難辨梭菌等，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。

# 09

## Inflammatory Diseases
## 炎症性疾病研究



Professor Hui-yao Lan
藍輝耀教授

The year 2017 was again a fruitful year for the research team led by **Professor Hui-yao Lan**. The team produced excellent research outputs, including many successful research grants, scientific publications, student training, and research awards. The research team continued to work on new mechanisms of tissue scarring and identified a new role for Smad3 in kidney diseases and cancer. Moreover, the team has published their findings in the study of tumour microenvironments on high impact scientific journal *Nature Communications*, which further developed into novel anticancer immunotherapies using genetically modified natural killer (NK) cells and traditional Chinese medicine.

過去一年由**藍輝耀教授**所帶領的研究團隊在科研基金、論文發表、培養科研人才和學生等各方面都取得豐碩成果。研究團隊繼續致力於研究組織硬化和腫瘤微環境，並領先發現Smad3在腎病及癌症上扮演的新角色。團隊的研究成果已於具影響力的科學期刊《自然通訊》發表，並轉化為與中藥結合的全新腫瘤免疫療法。



Professor Erik Fung
馮以文教授

**Professor Erik Fung**'s research team focuses on mechanisms of heart failure (HF) and circulatory disorders. The team uses epidemiological, clinical and basic science information and tools to query and formulate questions with potential impact on clinical and public health outcomes. They address these questions in studies, including one such initiative as the Undiagnosed heart Failure in frail Older individuals (UFO) study in collaboration with the CUHK Jockey Club Institute of Ageing. The study aims to elucidate the scale of latent HF in elderly with frailty, the role of cardiac screening in uncovering HF and advanced cardiac disease, and novel subphenotypes in HF and frailty.

**馮以文教授**帶領的研究團隊專注研究心臟衰竭（心衰）和循環系統疾病的機制。團隊透過利用流行病學、臨床醫學和基礎科學，來提出和建構對臨床和公共衛生發展具影響力的問題。研究團隊在研究中針對了這些問題，其中包括與香港中文大學賽馬會老年學研究所合作的「虛弱老年人士中未經診斷的心臟衰竭研究」（簡稱UFO）。該研究旨在闡明在虛弱老年人中，潛伏性心衰的程度、心臟檢查對發現心衰和晚期心臟病中的作用，以及心衰和虛弱性的關係。



# 10

## Neuroscience
## 神經科學



Dr. Owen Ko
高浩醫生

After initial phase of building up the lab and recruitment, **Dr. Owen Ko** and his team has now established in the laboratory two-photon fluorescence excitation microscopy with integrated animal behavioural platform for *in vivo* imaging of neuronal network structure and activity, intrinsic-signal optical imaging macroscope for localisation of brain regions participating in specific sensory processing tasks (e.g. visual scenes) and light-sheet fluorescence microscope for zebrafish larva whole-brain imaging of neuronal structure and activity, in addition to standard chemical and biological assays.

Employing the platforms established, the team now focuses on two research themes:

1. Neural circuitry underlying sensory perception and behaviour;
2. Neurodegenerative diseases.

On the basic science aspect, the team seeks to uncover principles of neural circuitry operation that allow mice and zebrafish to perform sensory perception and innate behaviours. On the applied arm, the team's main goal is to develop new diagnostic tools for improving accuracies of neurodegenerative diseases diagnoses.

經過了最初的實驗室建立和人才招聘階段，**高浩醫生**及其團隊目前已經建立了：

1. 雙光子螢光顯微鏡和動物行為學實驗平台，可以用於活體成像進行神經網絡結構和功能的研究；
2. 內源信號光學信號宏觀顯微鏡，用於定位與處理特定感覺功能相關的腦區域；
3. 層光螢光顯微鏡，可用於斑馬魚幼體的全腦結構和功能的成像；
4. 常規生物化學實驗設備。

通過已經建立的平台，團隊目前主要關注兩個研究方向：

1. 與感覺接受和行為活動相關的神經環路；
2. 神經退行性疾病。

在基礎科學的研究領域，團隊研究小鼠和斑馬魚感官認知和先天行為相關的神經環路運作機制。在轉化應用領域，團隊的主要目標是建立可以提高現有神經退行性疾病診斷準確性的新型診斷工具。

# 11

## Reproduction and Development
## 生殖與發育研究

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

這是**黃志超教授**加入研究所的第二年，研究工作主要以生殖和發育為主。黃教授及其團隊積極參與子宮內膜異位症、生殖失敗、子宮內膜成像、子宮內膜癌、妊娠糖尿病和臍帶血幹細胞的臨床、基礎及遺傳學研究。團隊工作進展良好，研究成果卓越。



Professor Ronald Wang
黃志超教授





Professor Gang Li
李剛教授

Mesenchymal stem cells (MSCs) are adult stem cells and the key components for tissue regeneration in adulthood. MSCs are also key seeding cells for tissue engineering applications in the treatment of numerous degenerative diseases and post-traumatic injuries. 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 initiated two local clinical trials using MSCs on cartilage repair in wrist and knee and organised an international symposium. With these, they hope to make contribution to the development of MSCs therapy in Hong Kong.

間充質幹細胞（MSCs）是成體幹細胞，也是成年期組織再生的關鍵成分。間充質幹細胞亦是組織工程應用的關鍵種子細胞，用於治療許多退化性疾病和創傷後損傷。由**李剛教授**所帶領的團隊研究工作集中在間充質幹細胞在骨、軟骨和肌腱修復中的生物學和應用，並與本地和國際臨床醫生和科學家密切合作。在過去的一年裡，團隊啟動了兩個本地臨床試驗，使用間充質幹細胞進行腕及膝關節軟骨修復，並組織了一次國際研討會。有了這些，他們希望對間充質幹細胞治療在香港的應用發展作出貢獻。

# 12

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

During the past year, the team led by **Professor Kathy Lui** has been studying the pathogenesis of cardiovascular complications associated with diabetes; and developing new strategies including human pluripotent stem cells, modified mRNAs, monoclonal antibodies and temporal lineage-tracing mouse models with the hope to improve cardiovascular function and promote cardiovascular regeneration under hyperglycemic condition. In particular, the team is interested in the role of adaptive immunity in the pathogenesis and repair of the cardiovascular system.

在過去一年中，由**呂愛蘭教授**帶領的團隊繼續研究與糖尿病相關的心血管併發症的發病機制，並開發使用人類多能幹細胞、修飾的mRNA、單克隆抗體和時間譜系追踪小鼠模型來驅動心血管再生，希望在高血糖條件下改善心血管功能。研究團隊對免疫系統在心血管系統發病機制和修復中的作用尤其感興趣。



Professor Kathy Lui
呂愛蘭教授



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, their 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. The team's research and development strategy is to facilitate both anatomical and functional restoration to achieve good treatment outcomes and early rehabilitation, as well as reduce its associated morbidity and mortality.

Professor Ling Qin
秦嶺教授

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、其家庭和社會帶來了巨大的經濟和醫療負擔。因此，現有的外科干預方式是有迫切需要改良的。由**秦嶺教授**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、具有生物活性和可生物降解特質的材料/內置物、內源性和外源性的生長因數、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。研究團隊亦致力改善結構和功能恢復，以達到良好的治療效果及提早康復，並且降低相關的術後併發症和死亡率。



Bioinformatics is a modern field of science which lies at the crossroads of multiple disciplines including Biology, Computing and Mathematics. It is developing rapidly and has become a crucial area of research in Biomedical Sciences following the establishment of Next-generation Sequencing (NGS). The research team led by **Professor Hao Sun** has committed to use integrative genomic approaches to study the transcriptional regulation mechanism during different stages of stem cell development, as well as developing computational approaches for sequencing based disease diagnosis.

生物資訊學是一門正在迅速興起的邊緣學科，它位於生物、電腦、數學等多個領域的交叉點上。隨著第二代基因測序技術的出現，生物資訊學已經成為生物醫學研究的重要領域。由**孫昊教授**所領導的生物資訊學研究小組致力運用基因組學的研究的方法來研究幹細胞的分化過程及其分子機理。

# 13
# Genomics and Bioinformatics
# 基因組學與生物訊息學





Professor Hao Sun
孫昊教授

Professor Peiyong Jiang
江培勇教授

In this year, **Professor Peiyong Jiang** and his team have made a number of achievements. First, the team has developed a bioinformatics approach for urinary cell-free DNA analysis, revealing its origin and fragmentation patterns. Second, they have developed a novel method for non-invasive fetal chromosomal examination using maternal plasma DNA, which obviates the requirement of a control group, thus improving the accuracy and reducing the cost. Third, the team has developed a sophisticated bioinformatics tool to enable integrative and synergistic analysis regarding single-cell and cell-free plasma RNA transcriptomics.

這一年，**江培勇教授**和他的團隊取得了一系列的成就，包括：1）開發了尿液游離DNA的生物訊息分析手段，揭露了尿液游離DNA的來源和片段化模式；2）開發了可以用於胎兒染色體異常無創檢測的新方法，此方法不需要對照樣本從而提高準確度和降低成本；3）開發了可以全面和協同分析單細胞和血漿游離RNA的生物訊息學軟件。

# 14

## Non-coding RNAs
## 非編碼核糖核苷酸研究

Transcription regulation is the premier mechanism underlying differential gene activity in animal development and disease. Transcription factors (TFs) shape the precise gene expression pattern required for a cell to perform its unique functions by binding cis-acting regulatory elements known as enhancers and by recruiting coactivators and RNA polymerase II (RNA Pol II) to target genes. DNA high throughput sequencing technologies have enabled the identification of putative mammalian enhancers on a broad scale based on their enrichment of histone modifications of mono-methylation of histone H3 at lysine 4 (H3K4me1) and acetylation of histone H3 at lysine 27 (H3K27ac), and the binding of coactivators such as p300. In 2017, the team led by **Professor Huating Wang** continued on the functional investigation of enhancers in skeletal muscle stem cells, muscle regeneration and muscle related diseases. The team believes their efforts will lead to enhanced understanding of transcriptional regulatory mechanisms underlying normal developmental processes as well as human diseases, which will eventually result in the development of novel therapeutic approaches.



Professor Huating Wang
王華婷教授

轉錄調控是在動物發育和疾病中影響基因表達的重要機制。增強子能吸引轉錄因子（TFs）、共激活因子（coactivators）和RNA聚合酶II（RNA Pol II）連接到目標基因上，並激活目標基因的表達。透過高通量DNA測序配合增強子標記如組蛋白H3K27ac和H3K4me1、以及共激活因子p300，由**王華婷教授**率領的研究團隊成功找出動物基因組內的增強子。在2017年裡，研究組繼續研究轉錄因子和增強子在骨骼肌幹細胞、骨骼肌再生和骨骼肌相關疾病中的功能。他們透過研究發掘正常發育和非正常疾病中有關增強子的分子機理，從而為新的醫用治療提供理論基礎。





Professor William Wu
胡嘉麒教授

**Professor William Wu** and his team are devoted to the pursuit of excellence in research on cellular signalling in diseases of public-health significance, including sepsis, infection, cancer and chronic pain. They are particularly interested in molecules (e.g. host defence peptides, non-coding RNAs) or cellular processes (e.g. autophagy) of emerging importance and the use of omics platforms and big data.

**胡嘉麒教授**及其團隊致力於開展與公眾健康密切相關的前沿性科學研究，包括敗血症、感染、癌症與慢性疼痛研究。通過研究細胞信號轉導及基因組學平台和大數據，發掘與疾病相關的新分子（如宿主防禦肽、非編碼RNAs）或細胞過程（如自噬）。

# 15

## Cellular Signalling
## 細胞訊號轉導

# Technical Reports on Research Programmes
# 研究項目：技術性報告

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# 01
# DIGESTIVE DISEASES



## Principal Investigator

Professor Jun Yu (Department of Medicine & Therapeutics, Institute of Digestive Diseases)

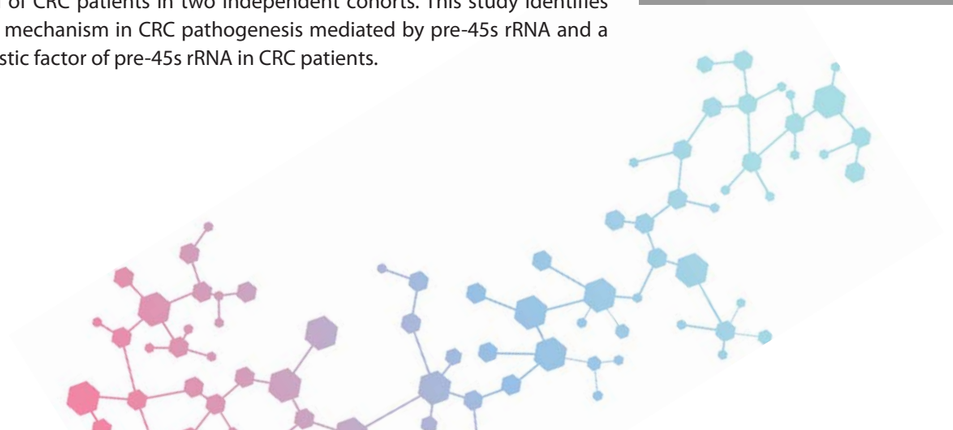
## Team

Joseph JY Sung, Francis KL Chan, Henry LY Chan, Justin CY Wu, Vincent WS Wong, Siew C Ng, Dennis CC Wong, Jessie Q Liang (Medicine & Therapeutics, Institute of Digestive Disease); Enders KW Ng, James YW Lau, Simon SM Ng, Philip WY Chiu (Surgery, Institute of Digestive Disease)

## Research Progress Summary

A. Molecular Pathogenesis and Biomarkers in Colorectal Cancer (CRC)

1. The mechanism of the abnormally high rate of cell metabolism in cancer cells is elusive. The team revealed that enhanced precursor 45s ribosomal RNA (pre-45srRNA) is one of the core mechanisms in promoting the pathogenesis of CRC. Knockdown of pre-45s rRNA inhibits G1/S cell-cycle transition by stabilising p53 through inducing murine double minute 2 and ribosomal protein L11 interaction. High rate of cancer cell metabolism triggers the passive release of calcium ion from endoplasmic reticulum to the cytoplasm, which activates the signalling cascade of calcium/calmodulin-dependent protein kinase II, ribosomal S6 kinase (S6K) and ribosomal S6K (CaMKII-S6K-UBF). The activated UBF subsequently increases expression of pre-45s rRNA. Moreover, the high expression level of pre-45s rRNA is associated with poor survival of CRC patients in two independent cohorts. This study identifies a novel mechanism in CRC pathogenesis mediated by pre-45s rRNA and a prognostic factor of pre-45s rRNA in CRC patients.



2. Following identification of potential bacteria associated with CRC by metagenome sequencing analysis, the team evaluated the utility of fecal bacterial marker candidates, including *Fusobacterium nucleatum* (Fn), *Bacteroides clarus* (Bc), *Roseburia intestinalis* (Ri), *Clostridium hathewayi* (Ch), and one undefined species (labeled as m7), using targeted qPCR for CRC diagnosis. Fn performed well in discriminating CRC from controls. A simple linear combination of four bacteria (Fn + Ch + m7-Bc) showed an improved diagnostic ability compared with Fn alone, which is further improved by combining with fecal immunochemical testing.

B. Molecular Pathogenesis in Gastric Cancer

1. The team identified the sodium channel subunit SCNN1B as a candidate biomarker in gastric cancer. SCNN1B mRNA expression was silenced commonly by promoter hypermethylation in gastric cancer. SCNN1B interacted with the endoplasmic reticulum chaperone, GRP78, and induced its degradation via polyubiquitination, triggering the unfolded protein response (UPR) via activation of PERK, ATF4, XBP1s, and C/EBP homologous protein and leading in turn to caspase-dependent apoptosis. Of note, high expression of SCNN1B was an independent prognostic factor for longer survival in gastric cancer patients, especially those with late-stage disease.

2. The team found that REC8 meiotic recombination protein (REC8) was preferentially methylated in gastric cancer using promoter methylation array, and further elucidated the epigenetic alteration and biological function of REC8 in gastric cancer. REC8 significantly suppressed cell viability, clonogenicity and cell cycle progression; it induced apoptosis and inhibited migration of gastric cancer cells, and it suppressed tumourigenicity in nude mice. The tumour-suppressive effect of REC8 is mediated at least in part by the downregulation of genes involved in cell growth (G6PD, SLC2A1, etc), and the upregulation of apoptosis/migration inhibitors (GADD45G and LDHA) and tumour suppressors (PinX1, IGFBP3 and ETS2). Multivariate analysis revealed that promoter methylation of REC8 was an independent risk factor for poor survival of gastric cancer patients.

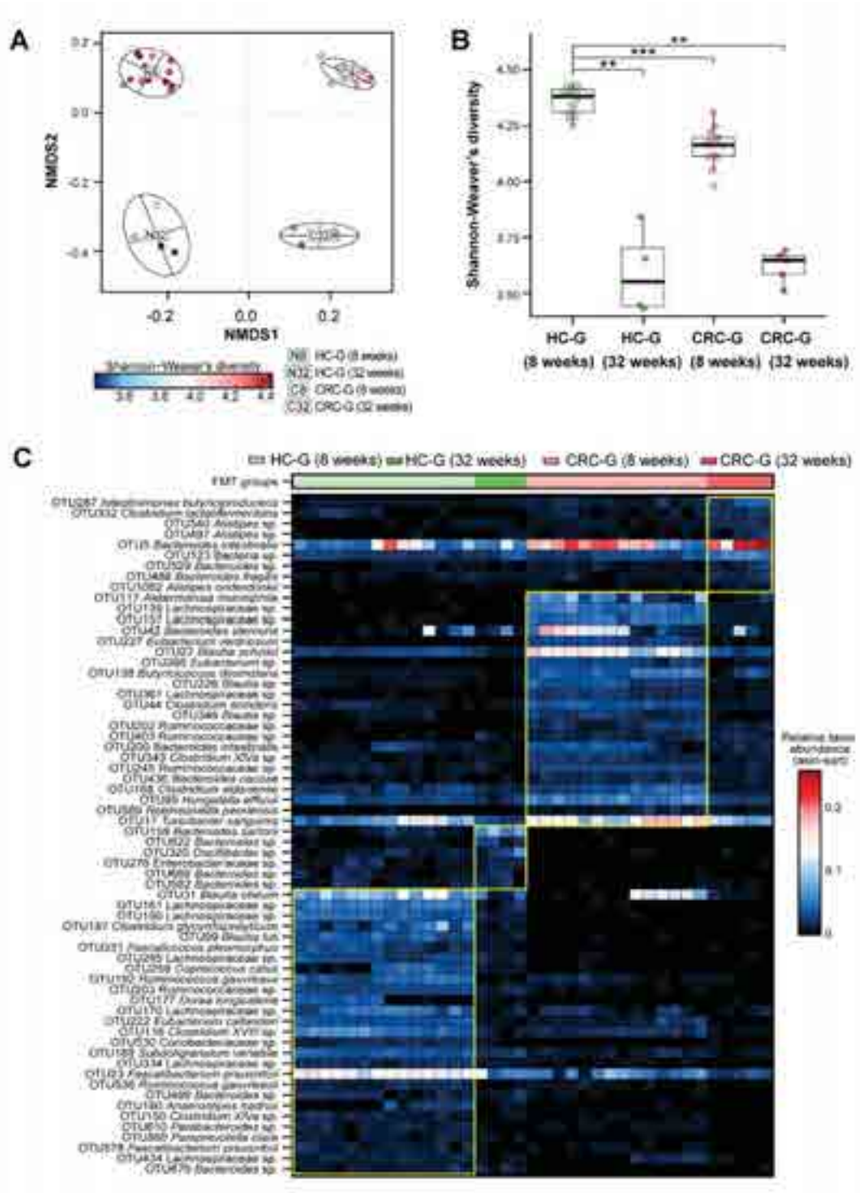
3. IGF2BP2 lists in the top rank up-regulated genes in gastric cancer, but its functional role is unclear. The team investigated the biological function of IGF2BP2 in gastric cancer. IGF2BP3 exerted oncogenic role in gastric tumourigenesis by regulating cell proliferation and invasion. Apart from copy number gain, the team confirmed the activation of IGF2BP3 was partly due to the silence of miR-34a in gastric cancer. Moreover, the up-regulated IGF2BP3 expression was associated with poor survival in patients with gastric cancer.

C. Non-Alcoholic Fatty Liver Disease (NAFLD) and hepatocellular carcinoma (HCC)

1. O-GlcNAc transferase (OGT) is a unique glycosyltransferase involved in metabolic reprogramming. The team elucidated the functional role of OGT in NAFLD-associated HCC. OGT plays a role in cancer by promoting tumour growth and metastasis in both cell models and animal models. OGT plays an oncogenic role in NAFLD-HCC through regulating palmitic acid and inducing endoplasmic reticulum stress, consequently activating oncogenic JNK/c-jun/AP-1 and NF-κB cascades.

2. The team investigated the regulatory effect of CXCL10, a crucial pro-inflammatory factor in chronic hepatitis, on the autophagosome-lysosome system during NAFLD development. Upregulated CXCL10 in steatohepatitis impairs autophagic flux by reducing autolysosome formation, thereby inhibiting autophagic protein degradation and the accumulation of ubiquitinated proteins, leading to the development of steatohepatitis.






Gut microbiota in AOM mice after stool gavage. (A) Nonmetric multidimensional scaling (NMDS) ordination analysis of bacterial OTU community distance based on Bray-Curtis dissimilarity metrics of relative abundance profiles (HC-A, n = 12; CRC-A, n = 11). Data points are grouped by 95% confidence ellipses and color-coded by the magnitude of alpha index. (B) Comparison of Chao1 community richness between HC-A and CRC-A groups. The richness indexes were compared using the Wilcoxon rank-sum test. (C) Relative abundance heat-map of differentially enriched bacterial OTUs in AOM mice receiving CRC and healthy control stool. OTUs with false discovery rate ≤ .05, and average robust fold enrichment of ≥ 4 coupled with fold depletion of ≤ 1 are reported. ***P < .001.

Source: Wong SH, Zhao LY, Zhang X, Nakatsu G, Han JQ, Xu WQ, Xiao X, Kwong TNY, Tsoi H, Wu WKK, Zeng BH, Chan FKL, Sung JJY, Wei H, Yu J. Gavage of Fecal Samples From Patients With Colorectal Cancer Promotes Intestinal Carcinogenesis in Germ-Free and Conventional Mice. *Gastroenterology*. 2017;153(6):1621-33. Doi: https://doi.org/10.1053/j.gastro.2017.08.022

3. The regulator of mitochondrial dysfunction in the pathogenesis of non-alcoholic steatohepatitis (NASH) is still largely unclear. CXCR3 is an essential pro-inflammatory factor in chronic liver diseases. The team explored the significance of CXCR3 in regulating mitochondrial function during NASH development in animal models and cultured hepatocytes. CXCR3 induces mitochondrial dysfunction, which contributes to the pathogenesis of steatohepatitis. Pharmacologic blockade of CXCR3 prevents mitochondrial dysfunction and restores the severity of steatohepatitis, indicating a potential clinical impact for controlling the disease.

4. Cyclooxygenase (COX)-2 is known to be upregulated in HCC, but its direct causative effect in spontaneous HCC formation remains unknown. The team thus investigated the role and molecular pathogenesis of COX-2 in HCC by using liver-specific COX-2 transgenic mice. The team demonstrated for the first time that enhanced COX-2 expression in hepatocytes is sufficient to induce HCC through inducing promoter hypermethylation by reducing TET1, silencing tumour-suppressive genes and activating key oncogenic pathways. Inhibition of COX-2 represents a mechanism-based target for HCC prevention.

D. Microbiota in Gastrointestinal Diseases

1. The team investigated whether stool from patients with CRC could directly induce colorectal carcinogenesis by gavaging stool samples from patients with CRC and healthy individuals to germ-free mice and conventional mice with azoxymethane. Stool from patients with CRC increased the numbers of polyps, levels of intestinal dysplasia and proliferation, markers of inflammation, and proportions of Th1 and Th17 cells in colon, compared with stool from individuals without CRC. This study provides evidence that the faecal microbiota from patients with CRC can promote tumourigenesis.

2. The team further investigated whether *P. anaerobius*, identified to be enriched in CRC by metagenome sequencing, contributes to colon tumour formation in mice and its possible mechanisms of carcinogenesis. *P. anaerobius* increased colon dysplasia in a mouse model of CRC. *P. anaerobius* interacted with TLR2 and TLR4 on colon cells to increase levels of reactive oxidative species, which promotes cholesterol synthesis and cell proliferation.

3. The team characterised the microbial changes associated with histological stages of gastric tumourigenesis, including superficial gastritis, atrophic gastritis, intestinal metaplasia and gastric cancer, using 16S rRNA gene analysis. In addition to microbial compositional changes, differences in bacterial interactions across stages of gastric carcinogenesis were identified. The significant enrichments and network centralities suggest potentially important roles of *P. stomatis*, *D. pneumosintes*, *S. exigua*, *P. micra* and *S. anginosus* in gastric cancer progression.



4. Non-steroidal anti-inflammatory drugs (NSAIDs) can cause significant small bowel injuries. The role of gut microbiota in this NSAID-induced enteropathy is poorly understood. The team studied the dynamic changes in gut microbiota following indomethacin administration in mice, and investigated the effects of these adaptive changes on subsequent NSAID-induced enteropathy. After indomethacin treatment, significant adaptive changes in gut microbiota were observed, including increased abundance of Firmicutes and decreased abundance in that of Bacteroidetes. Depletion of gut microbiota with antibiotics led to a significantly higher mortality in mice compared to controls. Mice pre-transplanted with adaptively changed microbiota showed less small bowel injury and lower levels of pro-inflammatory cytokines when exposed to indomethacin.

E. Inflammatory Bowel Disease (IBD)

1. The team conducted a systematic review of population-based studies to assess the changing incidence and prevalence of IBD around the world, involving data from 119 studies of incidence and 69 studies of prevalence. The results showed that, at the turn of the 21st century, IBD has become a global disease with accelerating incidence in newly industrialised countries whose societies have become more westernised. Although incidence is stabilising in western countries, burden remains high as prevalence surpasses 0.3%. These data highlight the need for research into prevention of IBD and innovations in health-care systems to manage this complex and costly disease.

2. Studies on cancer risk in IBD have yielded inconsistent results. The team conducted a population-based study to determine the risk of cancer in 2,621 Chinese patients with Crohn's disease (CD) and ulcerative colitis (UC). The results showed that Chinese patients with CD are at an increased risk of anorectal cancers and hematological cancers compared with the general population. A higher risk of nonmelanoma skin cancer was also observed in CD and UC. Therefore, cancer surveillance in IBD patients should be considered.

3. Endoscopic and histological healing are associated with improved clinical outcomes in UC. The team investigated the predictive value of faecal immunochemical test (FIT) for endoscopic and histological healing in UC. Quantitative FIT and faecal calprotectin (FC) were measured in 140 consecutive UC patients who underwent colonoscopy. FIT < 50 ng/ml predicted endoscopic healing with a sensitivity, specificity, and positive predictive value [PPV] of 72%, 68%, and 82%, respectively, and for histological healing with a sensitivity, specificity, and PPV of 73-75%, 67%, and 78-80%, respectively. FIT represents a promising non-invasive tool for monitoring mucosal healing in UC.

4. Mucosal healing is the goal for UC therapy, but it needs to be confirmed via colonoscopy. Colon capsule endoscopy (CCE) is a noninvasive technique for colon investigation. The team investigated the accuracy of second-generation CCE (CCE-2) in assessing mucosal lesions and disease activity in 150 UC patients. The sensitivity and specificity of CCE-2 in detecting postinflammatory polyps were 100% and 91%, respectively. CCE-2 was better tolerated and preferred by patients than was colonoscopy. CCE-2 represents a well-tolerated and reliable tool for disease monitoring in UC.

## Recognitions

Awards and Fellowships

| Member's Full Name | Details |
|---|---|
| Joseph Sung, Jun Yu, Francis Chan, et al. | Second-class State Natural Science Award 2016, China |
| Joseph Sung, Jun Yu, et al. | State Scientific & Technological Progress Award 2016, China |
| Jun Yu | 藥明康德生命化學研究獎學者獎2017 |
| Jun Yu | 2017 American Gastroenterology Association (AGA) Council Oncology Research Mentor Award |
| Vincent Wai-sun Wong | Research Excellence Award, Food and Health Bureau, Hong Kong SAR Government, 2017 |
| Siew Ng | Sir David Todd Lectureship |
| Siew Ng | Outstanding Fellow of the Faculty of Medicine, CUHK |
| Jessie Liang | The Health and Medical Research Fund Research Fellowship |



Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Jun Yu | Elucidation of a novel tumor suppressor gene tripartite motif 67 (TRIM67) in colorectal cancer | Research Grants Council – General Research Fund | 01/01/2017 | 31/12/2019 | 1,154,550 |
| Jun Yu Siew Ng (Co-PIs) | The ENIGMA Studies – Eastern Inflammatory Bowel Disease Gut Microbiota | The Leona M. & Harry B. Helmsley Charitable Trust Grant, USA | 01/03/2017 | 29/02/2020 | US$ 1,828,104/ HK$ 14,259,211 |
| Jun Yu | Croucher Senior Research Fellowship | Croucher Foundation | 01/03/2017 | 29/02/2020 | 865,842 |
| Jun Yu | Study on the relationship between gut microbial dysbiosis and colorectal cancer | Science and Technology Program Grant, Shenzhen | 01/07/2017 | 30/06/2020 | RMB 2,000,000 |
| Siew Ng | PACIfIC: Prevalence, characteristics and genetics of adherent-invasive Escherichia coli in Crohn's disease patients: comparative study between France and Hong Kong | ANR/RGC Joint Research Scheme | 01/02/2018 | 31/01/2022 | 2,611,942 |
| Siew Ng | A Step-Forward for Blending Learning: Mobile Micro-Module Flipped Classroom Courseware in Clinical Year Studies | Micro-Module Courseware Development Grant | 01/12/2017 | 31/08/2018 | 100,000 |
| Jessie Liang | Establishing a best panel of stool-based detection for non-invasive colorectal neoplasm screening | Food and Health Bureau – The Health and Medical Research Fund Research Fellowship Scheme | 01/10/2017 | 30/09/2019 | 1,187,488 |

## Publications

A. Journal Papers

1. Brim H, Yooseph S, Lee E, Sherif ZA, Abbas M, Laiyemo AO, Varma S, Torralba M, Dowd SE, Nelson KE, Pathmasiri W, Sumner S, de Vos W, Liang Q, Yu J, Zoetendal E, Ashktorab H. A Microbiomic Analysis in African Americans with Colonic Lesions Reveals Streptococcus sp.VT162 as a Marker of Neoplastic Transformation. *Genes*. 2017; 8(11):314.

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7. Kaplan GG, Ng SC. Understanding and Preventing the Global Increase of Inflammatory Bowel Disease. *Gastroenterology*. 2017; 152(2):313-21.

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10. Li XN, Wong CC, Tang Z, Wu JL, Li SF, Qian Y, Xu JY, Yang ZY, Shen Y, Yu J, Cai ZW. Determination of amino acids in colon cancer cells by using UHPLC-MS/MS and [U-C-13(5)]-glutamine as the isotope tracer. *Talanta*. 2017; 162:285-92.

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# 02
# MOLECULAR DIAGNOSTICS

*(Circulating Fetal Nucleic Acids)*

## Principal Investigators

Professor Dennis Lo and Professor Rossa Chiu

## Team

Prof. Allen Chan, Mr. Kam Wing Chan, Dr. Lisa Chan, Dr. Rebecca Chan, Dr. Alice Cheng, Ms. Eunice Chiu, Dr. Wanxia Gai, Dr. Macy Heung, Miss Winnie Hui, Prof. Peiyong Jiang, Ms. Yoyo Jin, Mr. Chris Kum, Dr. Jacky Lam, Ms. Coral Lee, Ms. Elena Lo, Dr. Huimin Shang, Prof. Hao Sun, Dr. Kun Sun, Dr. Jason Tsang, Ms. Patty Tse, Dr. Yu Kwan Tong, Dr. Joaquim Vong



## Research Progress Summary

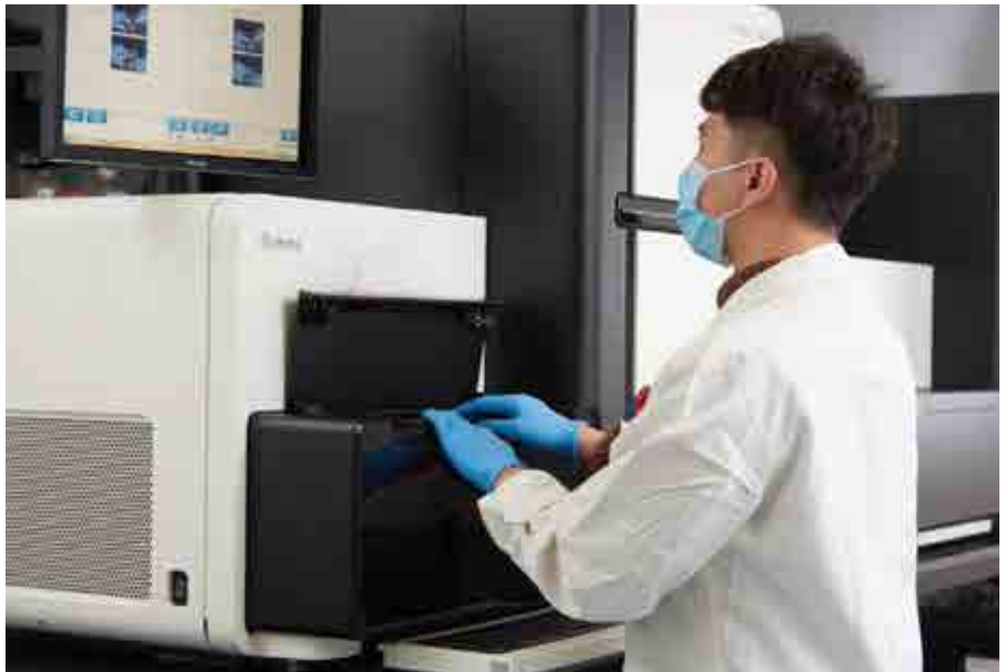
2017 has been a remarkably productive year for the project team. The project team was successfully awarded another Theme-based Research Scheme grant from the Research Grants Council amounting to HK$44M and dedicated to exploring "Plasma DNA as a Platform Technology for Cancer Detection". The project team will be conducting this project alongside another Theme-based Research Scheme grant amounting to HK$48M on "Centre for Research into Circulating Fetal Nucleic Acids". In terms of knowledge transfer, Cirina, a biotechnology startup company at the Hong Kong Science Park that was founded by Professors Dennis Lo, Rossa Chiu and Allen Chan, merged with a US company based at Menlo Park, California, GRAIL. The merged entity would devote its combined talent pool and resources to developing strategies for the identification of early stage cancers. A contract research agreement has been established between the CUHK project team and Cirina to facilitate continued technology transfer and translation of the research output generated by the team on cancer diagnostics.



In terms of research output, the team has completed and published a number of landmark studies, each having a significant impact on the respective fields. Among these studies, the most notable one would be the publication of the prospective trial on using plasma Epstein-Barr virus DNA to screen for nasopharyngeal carcinoma (NPC) among asymptomatic individuals. The test achieved 97.1% sensitivity and 98.6% specificity in identifying NPC. About 70% of the cases detected by screening were of early stage. This compared favourably with a historical population cohort that did not have screening. Only 20% of the unscreened cohort was of early stage. NPC patients detected by screening had 10 times better prognosis than the unscreened cohort. This study was the first demonstration of a blood test based on circulating tumour-derived DNA analysis achieving effective early cancer detection with demonstrable downstaging of presentation and improvement in prognosis in a prospective trial. The study was published in the eminent medical journal, *New England Journal of Medicine* (Chan et al., 2017; 377: 513-22). The journal has further selected this article as one of the 10 most notable articles in 2017 (http://www.nejm.org/nejm-special?promo=ONFKNA16&query=ppc&utm_source=google&utm_medium=cpc&utm_campaign=na17&gclid=EAIaIQobChMIw-_enLmq2AIVXIGzCh253A3TEAAYASACEgI0VfD_BwE).

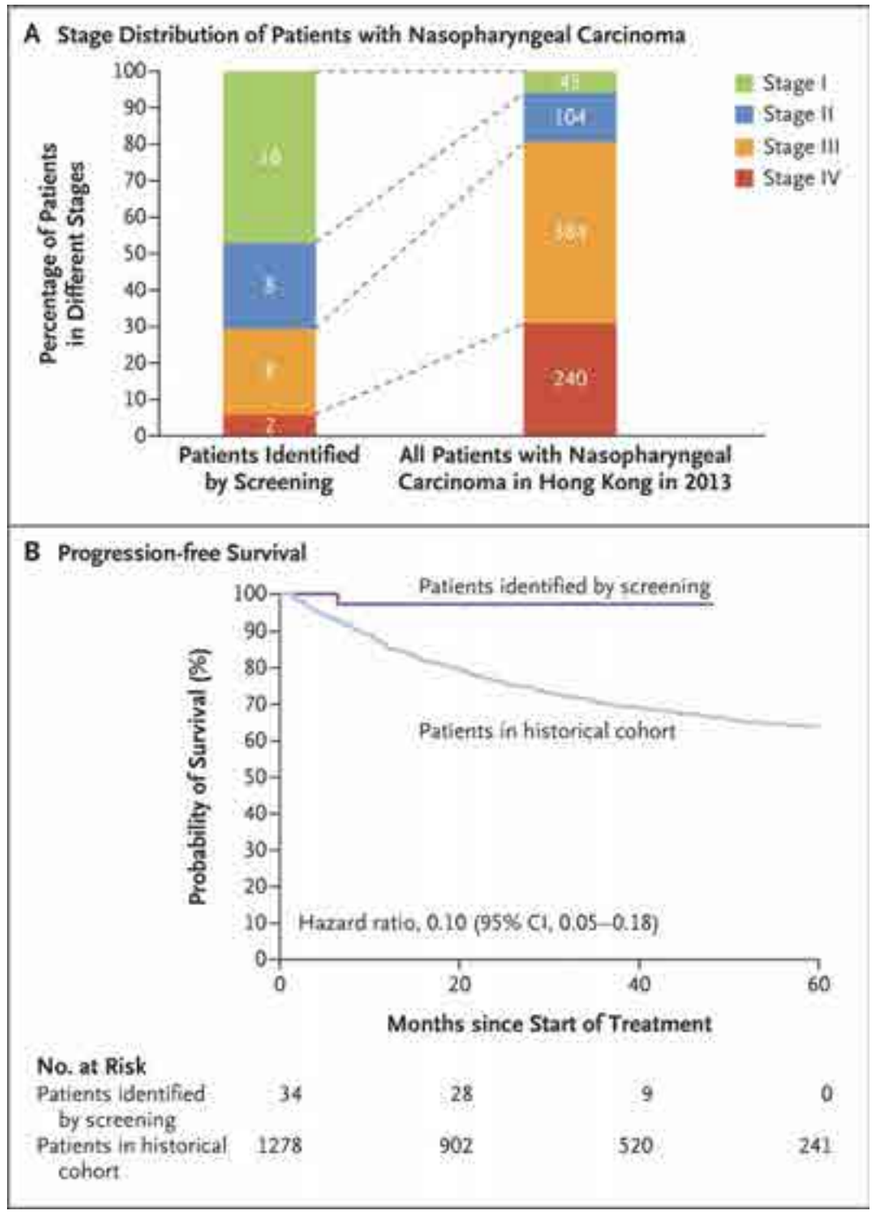


The project team has successfully established a platform for single-cell sorting followed by single-cell transcriptomic analysis. The team applied this platform to placental cell analysis (Tsang et al., *Proc Natl Acad Sci U S A* 114: E7786-95). The RNA expression profiles of the different placental cell types were delineated. They then analysed plasma of pregnant women to identify groups of RNA that belonged to the various placental cell lineages. The information allowed better interpretation of plasma RNA profiles to achieved higher disease specificity.



Stage Distribution and Progression-free Survival among the Participants with Nasopharyngeal Carcinoma Identified by Screening. Panel A shows the distribution of disease stage among the 34 participants with nasopharyngeal carcinoma. The stage distribution in all the patients with nasopharyngeal carcinoma in Hong Kong in 2013 according to the Hong Kong Cancer Registry is shown as a comparison. The number of cases for each stage is shown. Panel B shows the rate of progression-free survival among the participants as compared with 1278 age- and sex-matched patients in a historical cohort in Hong Kong. CI denotes confidence interval.

Source: 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):513-22. Doi: 10.1056/NEJMoa1701717



The project team has developed a number of new applications to overcome various bottlenecks in current molecular diagnostic schemes. For example, in a new study, the team has achieved the non-invasive prenatal diagnosis (NIPD) of most mutation types causing haemophilia A and B. Inversion within intron 22 of Factor 8 gene is the most common mutation resulting in haemophilia A. However, the non-invasive prenatal detection of this mutation had been challenging because cell-free fetal DNA exist as short fragments while the inversion straddles a much larger genomic region with variable breakpoints observed in different individuals. In their study (Hudecova et al., *Blood* 2017; 130: 340-7), relative haplotype dosage (RHDO) analysis of maternal plasma DNA was adopted to achieve assessment of whether the fetus has inherited the inversion mutation. In RHDO analysis, the team search for statistical evidence supporting the over-representation of plasma DNA molecules originating from either maternal chromosome X haplotypes in carrier women pregnant with a male fetus. The over-represented haplotype would be the one inherited by the male fetus. The publication of their study was accompanied by an editorial commentary (Ragni Blood 2017; 130: 240-1) that indicated the new findings rendered the clinical implementation of NIPD of the haemophilias clinically feasible.

Regarding the NIPD of fetal monogenic diseases, the team have overcome a key bottleneck that had been limiting the expanded adoption of NIPD. RHDO analysis is one of strategies that allowed effective NIPD of monogenic diseases. However, RHDO is dependent on knowing the parental haplotype information. Parental haplotypes could be determined by analysing DNA from probands. However, this approach would limit NIPD to at-risk pregnancies where DNA samples from probands were available. In their new study (Hui et al., Clinical Chemistry 2017; 63: 513-24), linked-read sequencing was adopted to achieve direct haplotyping of parental DNA. Consequently, NIPD could be opened up to pregnancies at-risk for a variety of monogenic diseases, including those without proband DNA. The team believe that the new approach would allow much wider clinical adoption of NIPD.

The project team has also developed a refined protocol to improve the specificity for the non-invasive screening of fetal subchromosomal aneuploidies (Yu et al., Clinical Chemistry 2017; 63: 495-502). This protocol has been adopted in some commercial laboratories.

On the other hand, the project team has shown that erythroid derived DNA is presented at surprisingly high concentrations in human plasma. Levels of plasma erythroid DNA also reflected the erythropoietic activity in the bone marrow. The team has shown in a proof-of-principle study that there may be clinical value in assessing bone marrow activity through a blood test.

In summary, 2017 has been a productive year for the research team. Prof. Dennis Lo has received a number of accolades in the same year. In particular, Prof. Lo was bestowed the Life Science Prize of the prestigious Future Science Prize.



## Recognitions

Awards and Fellowships

| Member's Full Name | Details |
|---|---|
| Dennis Lo | The Society for Maternal – Fetal Medicine (SMFM) 2017 Honorary Member |
| Dennis Lo | 2016 Future Science Prize – Life Science Prize |
| Dennis Lo | 2017 International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Distinguished Clinical Chemist Award |
| Dennis Lo | Top 20 Translational Researchers of 2016 recognised by Nature Biotechnology |
| Dennis Lo | WuXi PharmaTech Life Science and Chemistry Awards – Outstanding Achievements Award |



Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Dennis Lo | Plasma DNA as a Platform Technology for Cancer Detection | Research Grants Council – Theme-based Research Scheme | 01/12/2016 | 30/11/2021 | HKD 40,000,000 from RGC; HKD 4,444,000 matching from CUHK |
| Dennis Lo<br>Rossa Chiu | Cirina Contract Research Agreement | | | | |





## Publications

A. Journal Papers

1. Cheng TH, Lui KO, Peng XL, Cheng SH, Jiang P, Chan KC, Chiu RW and Lo YM. DNase1 Does Not Appear to Play a Major Role in the Fragmentation of Plasma DNA in a Knockout Mouse Model. *Clinical Chemistry*. 2018; 64(2):406-8. [Epub ahead of print]

2. Tsang JCH, Vong JSL, Ji L, Poon LCY, Jiang P, Lui KO, Ni YB, To KF, Cheng YKY, Chiu RWK and Lo YMD. Integrative single-cell and cell-free plasma RNA transcriptomics elucidates placental cellular dynamics. *Proceedings of the National Academy Sciences of the United States of America*. 2017; 114: E7786-95.

3. Chan KC, Woo JK, King A, Zee BC, Lam WK, Chan SL, Chu SW, Mak C, Tse IO, Leung SY, Chan G, Hui EP, Ma BB, Chiu RW, Leung SF, van Hasselt AC, Chan AT and Lo YM. Analysis of Plasma Epstein - Barr virus DNA to Screen for Nasopharyngeal Cancer. *New England Journal of Medicine*. 2017; 377: 513-22.

4. Lam WK, Gai W, Sun K, Wong RS, Chan RW, Jiang P, Chan NPH, Hui WW, Chan AW, Szeto CC, Ng SC, Law MF, Chan KC, Chiu RW and Lo YM. DNA of Erythroid Origin Is Present in Human Plasma and Informs the Types of Anemia. *Clinical Chemistry*. 2017; 63: 1614-23.

5. Hudecova I, Jiang P, Davies J, Lo YM, Kadir RA and Chiu RW. Noninvasive detection of F8 int22h-related inversions and sequence variants in maternal plasma of hemophilia carriers. *Blood*. 2017; 130: 340-7.

6. Vong JS, Tsang JC, Jiang P, Lee WS, Leung TY, Chan KC, Chiu RW and Lo YM. Single-Stranded DNA Library Preparation Preferentially Enriches Short Maternal DNA in Maternal Plasma. *Clinical Chemistry*. 2017; 63: 1031-7.

7. Cheng TH, Jiang P, Tam JC, Sun X, Lee WS, Yu SC, Teoh JY, Chiu PK, Ng CF, Chow KM, Szeto CC, Chan KC, Chiu RW and Lo YM. Genomewide bisulfite sequencing reveals the origin and time-dependent fragmentation of urinary cfDNA. *Clinical Biochemistry*. 2017; 50: 496-501.

8. Sun K, Chan KC, Hudecova I, Chiu RW, Lo YM and Jiang P. COFFEE: control-free noninvasive fetal chromosomal examination using maternal plasma DNA. *Prenatal Diagnosis*. 2017; 37: 336-40.

9. Jiang P, Tong YK, Sun K, Cheng SH, Leung TY, Chan KC, Chiu RW and Lo YM. Gestational Age Assessment by Methylation and Size Profiling of Maternal Plasma DNA: A Feasibility Study. *Clinical Chemistry*. 2017; 63: 606-8. (Letter to the Editor)

10. Yu SC, Jiang P, Chan KC, Faas BH, Choy KW, Leung WC, Leung TY, Lo YM and Chiu RW. Combined Count- and Size-Based Analysis of Maternal Plasma DNA for Noninvasive Prenatal Detection of Fetal Subchromosomal Aberrations Facilitates Elucidation of the Fetal and / or Maternal Origin of the Aberrations. *Clinical Chemistry*. 2017; 63: 495-502.

11. Hui WW, Jiang P, Tong YK, Lee WS, Cheng YK, New MI, Kadir RA, Chan KC, Leung TY, Lo YM and Chiu RW. Universal Haplotype-Based Noninvasive Prenatal Testing for Single Gene Diseases. *Clinical Chemistry*. 2017; 63: 513-24.

# 02
# MOLECULAR DIAGNOSTICS

*(Genetics of Disease Susceptibility)*

## Principal Investigator

Professor Nelson Tang

## Team

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

## Research Progress Summary

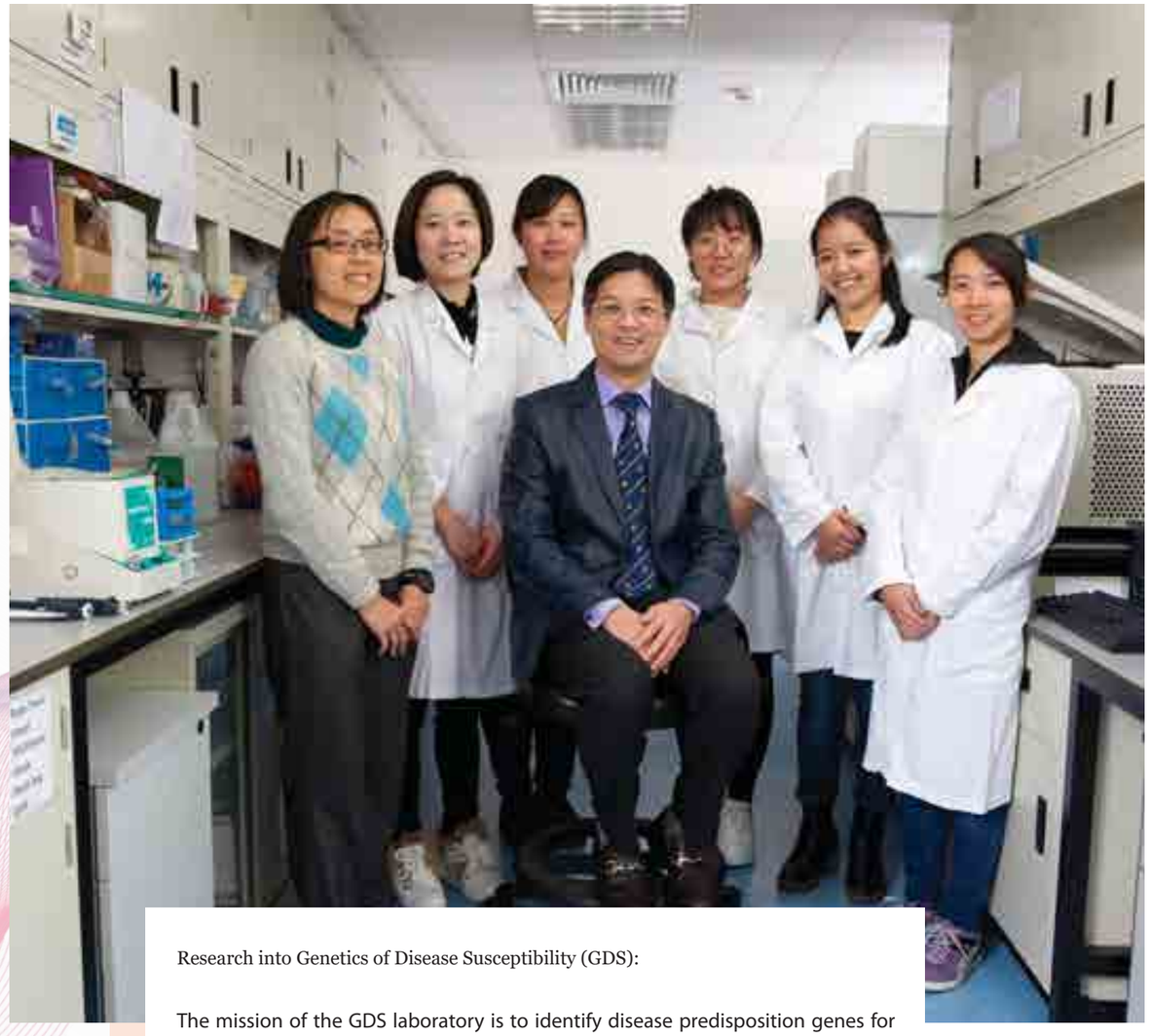
Research directions

1. Genetics of complex traits: to identify prevalent genetic variants causing common diseases in Han Chinese;

2. Statistical genetics and computational statistical analysis of big genetic and biological datasets.

3. Analysis of variation of the transcriptome using latest technology of next generation sequencing.





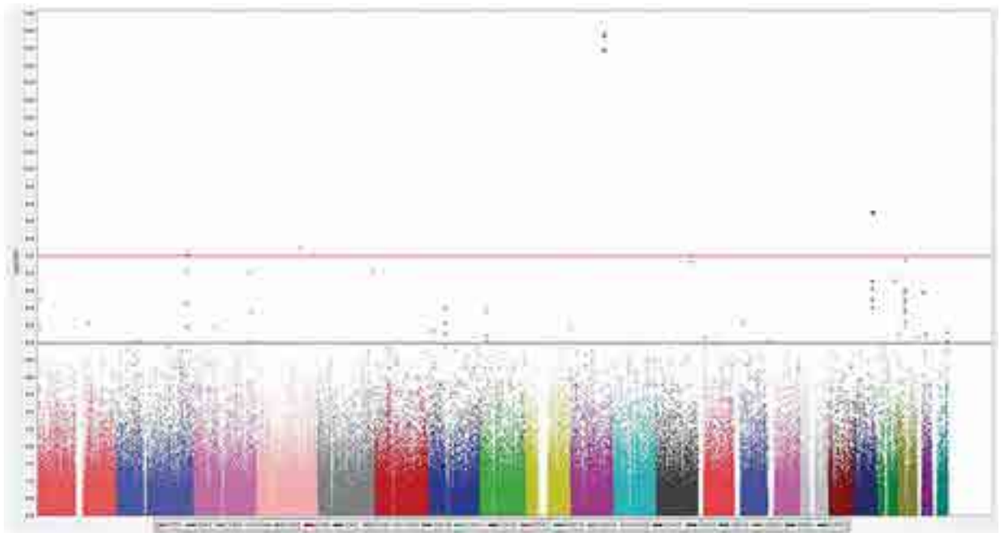
Research into Genetics of Disease Susceptibility (GDS):

The mission of the GDS laboratory is to identify disease predisposition genes for common diseases, also known as complex traits. The research team 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 phentoypes), breast cancer, and genetic susceptibility to adolescent idiopathic scoliosis tuberculosis. With the advance in sequencing and other technology, the team acquires biological data in an unprecedented volume nowadays. The analysis and statistic method become limiting factor in handling such huge volume of data.

## Recognitions

Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Nelson Tang | Genetic Studies of Tuberculosis: In-depth Study of Recently GWAS Identified Loci in Chinese Patients | Food and Health Bureau – Health and Medical Research Fund | 01/07/2015 | 31/12/2017 | 987,414 |
| Nelson Tang | CUHK Jockey Club Institute of Ageing – Research Initiatives | Vice-Chancellor's One-off Discretionary Fund | 01/01/2016 | 31/12/2019 | 200,000 |
| Nelson Tang | Genetics of Idiopathic Scoliosis | CUHK Research Committee – Direct Grants | 01/06/2016 | 31/05/2017 | 50,000 |
| Nelson Tang (Co-I) | Mitochondrial Heteroplasmy and Cognitive Decline | CUHK Research Committee – Direct Grants | 29/07/2017 | 28/06/2018 | 69,650 |
| Nelson Tang (Co-I) | Expression and Functional Characterization of LBX1 in Adolescent Idiopathic Scoliosis | NSFC / RGC Joint Research Scheme | 01/01/2017 | 31/12/2020 | 1,045,271 |
| Nelson Tang (Co-I) | Relationship between Chronic Inflammation and Vitamin D Level to Prevalent and Incident Frailty in Older Adults | Food and Health Bureau – Health and Medical Research Fund | 12/03/2015 | 11/03/2017 | 996,108 |
| Nelson Tang (Co-I) | An Integrated Trans-omics Approach to Diabetic Cardio-renal Complications: From Novel Discoveries to Personalized Medicine (Project Coordinator: Professor Ronald Ma) | Research Grants Council – Theme-based Research Scheme | 01/01/2014 | 31/12/2018 | 47,000,000 |
| Nelson Tang (Co-I) | CUHK – CAS KIZ Joint Laboratory of Bioresources and Molecular Research in Common Diseases | CUHK Research Committee's One-off Funding for joint / lab and collaboration | 01/07/2015 | 30/06/2017 | 1,000,000 |



The Manhattan plot showing negative log10-transformed P values in the discovery stage (1456 cases and 2104 controls). The blue line represents the threshold of the suggestive whole-genome significance (P < 1.0 × 10<sup>−5</sup>). The red line represents the threshold of genome-wide significance threshold (P < 1.0 × 10<sup>−8</sup>).

Source: Zhu ZZ, Xu LL, Tang NLS, Qin XD, Feng ZH, Sun WX, Zhu WG, Shi BL, Liu P, Mao SH, Qiao J, Liu Z, Sun X, Li FC, Cheng JCY, Qiu Y. Genome-wide association study identifies novel susceptible loci and highlights Wnt/beta-catenin pathway in the development of adolescent idiopathic scoliosis. *Human Molecular Genetics*. 2017; 26(8):1577-83. Doi: 10.1093/hmg/ddx045

## Publications

A. Journal Papers

1. Styrkarsdottir U, Helgason H, Sigurdsson A, Norddahl GL, Agustsdottir AB, Reynard LN, Villalvilla A, Halldorsson GH, Jonasdottir A, Magnusdottir A, Oddson A, Sulem G, Zink F, Sveinbjornsson G, Helgason A, Johannsdottir HS, Helgadottir A, Stefansson H, Gretarsdottir S, Rafnar T, Almdahl IS, Braekhus A, Fladby T, Selbaek G, Hosseinpanah F, Azizi F, Koh JM, Tang NLS, Daneshpour MS, Mayordomo JI, Welt C, Braund PS, Samani NJ, Kiemeney LA, Lohmander LS, Christiansen C, Andreassen OA, Magnusson O, Masson G, Kong A, Jonsdottir I, Gudbjartsson D, Sulem P, Jonsson H, Loughlin J, Ingvarsson T, Thorsteinsdottir U, Stefansson K, Consortium A. Whole-genome sequencing identifies rare genotypes in COMP and CHADL associated with high risk of hip osteoarthritis. *Nature Genetics*. 2017; 49(5):801-5. (Letter)

2. Xu LL, Xia C, Qin XD, Sun WX, Tang NLS, Qiu Y, Cheng JCY, Zhu ZZ. Genetic variant of BNC2 gene is functionally associated with adolescent idiopathic scoliosis in Chinese population. *Molecular Genetics and Genomics*. 2017; 292(4):789-94.

3. Yeo W, Mo FK, Pang E, Suen JJ, Koh J, Loong HH, Yip CC, Ng RY, Yip CH, Tang NL, Liem GS. Profiles of lipids, blood pressure and weight changes among premenopausal Chinese breast cancer patients after adjuvant chemotherapy. *BMC Womens Health*. 2017; 17:55.



4. Wang ZM, Fang HY, Tang NLS, Deng MH. VCNet: vector-based gene co-expression network construction and its application to RNA-seq data. *Bioinformatics*. 2017; 33(14):2173-81.

5. Zhu ZZ, Xu LL, Tang NLS, Qin XD, Feng ZH, Sun WX, Zhu WG, Shi BL, Liu P, Mao SH, Qiao J, Liu Z, Sun X, Li FC, Cheng JCY, Qiu Y. Genome-wide association study identifies novel susceptible loci and highlights Wnt/beta-catenin pathway in the development of adolescent idiopathic scoliosis. *Human Molecular Genetics*. 2017; 26(8):1577-83.

6. Zhang YF, Wang H, Cheng Q, Qin L, Tang NLS, Leung PC, Kwok TCY. The relationship between angiotensin-converting enzyme (ACE) insertion (I)/deletion (D) polymorphism, serum ACE activity and bone mineral density (BMD) in older Chinese. *Journal of the Renin-Angiotensin-Aldosterone System*. 2017; 18(1):1-7.

7. Li L, Mo FKF, Chan SL, Hui EP, Tang NSL, Koh J, Leung LKS, Poon ANY, Hui J, Chu CM, Lee KF, Ma BBY, Lai PBS, Chan ATC, Yu SCH, Yeo W. Prognostic values of EORTC QLQ-C30 and QLQ-HCC18 index-scores in patients with hepatocellular carcinoma – clinical application of health-related quality-of-life data. *BMC Cancer*. 2017; 17:8.



B. Conference Papers

1. Ingvarsson T, Styrkarsdottir U, Helgason H et al. Whole Genome Sequencing Finds Rare High-Risk Genotypes For Hip Osteoarthritis In The Comp And Chadl Genes. In: *World Congress of the Osteoarthritis-Research-Society-International (OARSI) on Osteoarthritis*; Las Vegas, USA; 2017 Apr 27-30.

2. Man GC, Tang NL, Lee WY, Zhang J, Ng BK, Xu L, Yong Q, Cheng JC. Expression of LBX1 in muscle and bone of adolescent idiopathic scoliosis in Chinese. In: Orthopaedic Research Society (ORS) 2017 *Annual Meeting*; San Diego, California, USA; 2017 Mar 19-22.

3. Man GC, Tang NL, Chan TF, Ng BK, Xu L, Lam TP, Zhu ZZ, Qiu Y, Cheng JC, Lee WY. GWAS-associated Single Nucleotide Polymorphisms are associated with Curve Progression in Adolescent Idiopathic Scoliosis? In: *52nd Scoliosis Research Society Annual Meeting & Course*; Philadelphia, USA; 2017 Sep 6-9.

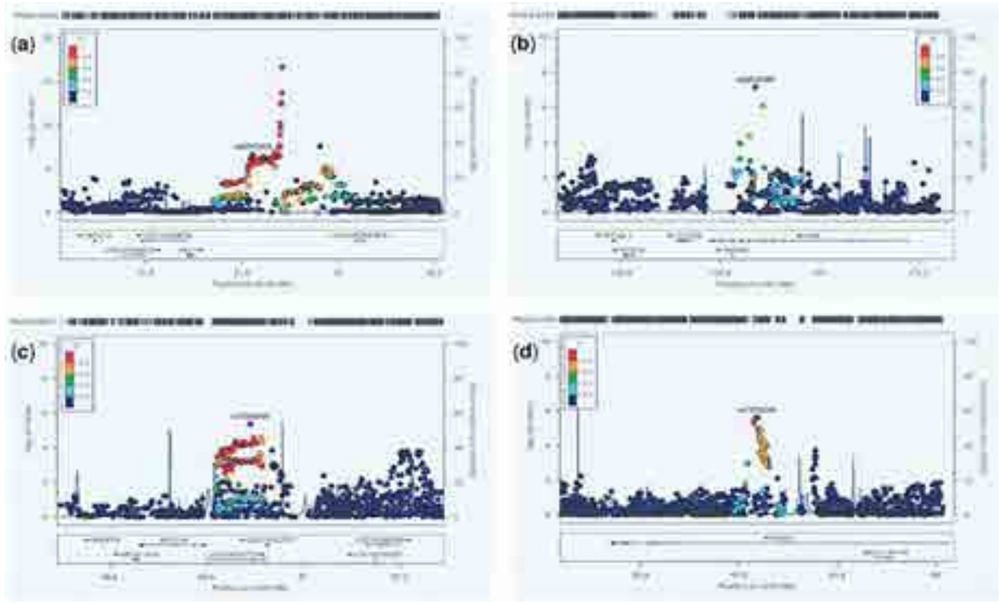
4. Lam TP, Yip BH, Yu FW, Tam EM, Man GC, Lee WY, Tang NL, To KK, Lee KW, Ng BK, Qiu Y, Cheng JC. Using Calcium and Vitamin D Supplementation for Control of Curve Progression in Adolescent Idiopathic Scoliosis – An In-depth Analysis of a Randomized, Double-blinded, Placebo-controlled Trial. In: *15th International Phillip Zorab Symposium 2017*; London, United Kingdom; 2017 Jun 15-16.

5. Man GC, Tang NL, Chan TF, Lam TP, Qiu Y, Cheng JC. Validation of Genome-wide Association Studies–associated Variants and Its Association with Curve Progression in Chinese Adolescent Idiopathic Scoliosis Patients. In: *Hong Kong Orthopaedic Association 37th Annual Congress 2017*; Hong Kong; 2017 Nov 4-5.

C. Others

1. Patents grant – USA US 9589099 B2 (Date of Grant: 7 Mar 2017)
"Determination of gene expression levels of a cell type"






Regional association plots of the 4 susceptible loci associated with AIS. Each plot represents –log 10 (P value) against the chromosome positions for SNPs in the specific region, together with the positions and orientations of genes. The strongest association signal observed in the discovery stage is indicated by a purple diamond, and the other SNPs are colored according to LD with the proxy SNP. The blue line represents the recombination rate. (A) 20p11.22,(B) 3q26.2, (C) 2p14, (D) 3p14.1.

Source: Zhu ZZ, Xu LL, Tang NLS, Qin XD, Feng ZH, Sun WX, Zhu WG, Shi BL, Liu P, Mao SH, Qiao J, Liu Z, Sun X, Li FC, Cheng JCY, Qiu Y. Genome-wide association study identifies novel susceptible loci and highlights Wnt/beta-catenin pathway in the development of adolescent idiopathic scoliosis. *Human Molecular Genetics*. 2017; 26(8):1577-83. Doi: 10.1093/hmg/ddx045

# 02
# MOLECULAR DIAGNOSTICS

*(Plasma Nucleic Acids Research)*

## Principal Investigator

Professor Allen Chan

## Team

Wai-kei Lam, Hiu-ki Chan, Kin-fung Tin, Pak-hang Lee, Gurung Bijay Jang, Wai-lam Kwok, Chi-leung Lam, Wai-lin Chan, Oi-lin Tse, Zi-jun Maggie Li, Fung-chu Tsang, Wai-sum Ruby Cheng, Chun-man Wong, Fung-shan Wong, Weng-in Chu

## Research Progress Summary

Since 2013, Professor Allen Chan and his team have screened over 20,000 asymptomatic subjects for nasopharyngeal carcinoma (NPC) using liquid biopsy. 34 cases of NPC were detected through this screening programme. The cases identified by screening had significantly earlier stage distribution compared with historical cohorts. Remarkably, over 50% of the cases were of stage I disease. Because of early detection, cases identified through screening had 90% reduction in disease progression and mortality after treatment. This study has demonstrated for the first time that a small tumour would release a substantially large amount of DNA into the circulation to detection through circulating tumoural DNA analysis and provides important scientific grounds to support the potential use of "liquid biopsy" for early cancer screening. The result of this study was published in the *New England Journal of Medicine* and this article was selected as one of the ten notable research outputs published in the journal in 2017.



## Recognitions

Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | 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. 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):513-22.

2. Lam WKJ, Gai W, Sun K, Wong RSM, Chan RWY, Jiang P, Chan NPH, Hui WWI, Chan AWH, Szeto CC, Ng SC, Law MF, Chan KCA, Chiu RWK, Lo YMD. DNA of Erythroid Origin Is Present in Human Plasma and Informs the Types of Anemia. *Clinical Chemistry*. 2017;63(10):1614-23.

3. Tsang JCH, Chan KCA. Quality Materials for Quality Assurance in the Analysis of Liquid Biopsy Samples. *Clinical Chemistry*. 2017;63(9):1431-2.

4. Payne DA, Baluchova K, Peoc'h KH, van Schaik RHN, Chan KCA, Maekawa M, Mamotte C, Russomando G, Rousseau F, Ahmad-Nejad P; IFCC Committee for Molecular Diagnostics (C-MD). Pre-examination factors affecting molecular diagnostic test results and interpretation: A case-based approach. *International Journal of Clinical Chemistry*. 2017; 467:59-69.

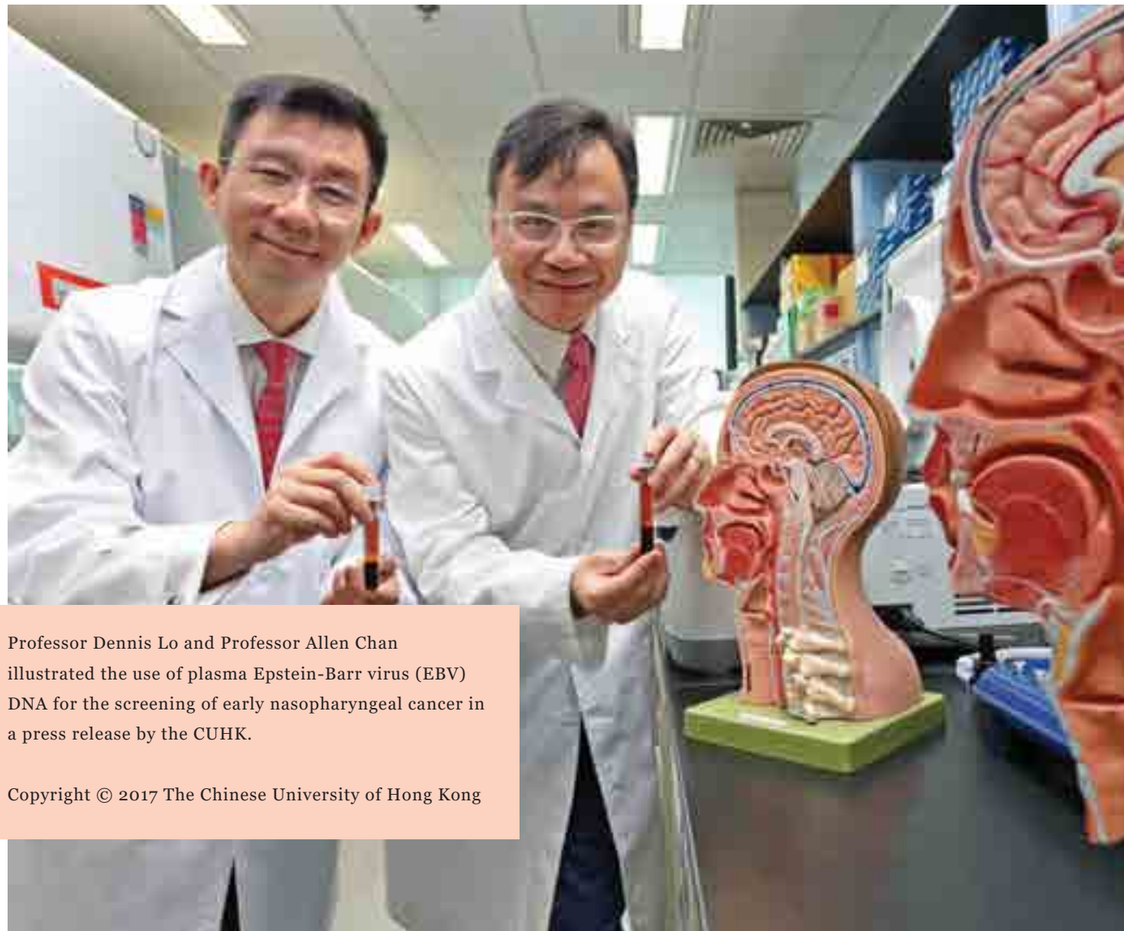
5. King A, Wong LYS, Law BKH, Bhatia KS, Woo JKS, Ai QY, Tan TY, Goh J, Chuah KL, Mo FKF, Chan KCA, Chan ATC, Vlantis AC. MR Imaging Criteria for the Detection of Nasopharyngeal Carcinoma: Discrimination of Early-Stage Primary Tumors from Benign Hyperplasia. *American Journal of Neuroradiology*. 2017; doi: 10.3174/ajnr.A5493. [Epub ahead of print]






The study on nasopharyngeal cancer screening is selected as one of the ten notable publications in 2017 by the *New England Journal of Medicine*.

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Professor Dennis Lo and Professor Allen Chan illustrated the use of plasma Epstein-Barr virus (EBV) DNA for the screening of early nasopharyngeal cancer in a press release by the CUHK.

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# 02
# MOLECULAR DIAGNOSTICS

## Principal Investigator



Dr. Timothy Cheng

## Research Progress Summary

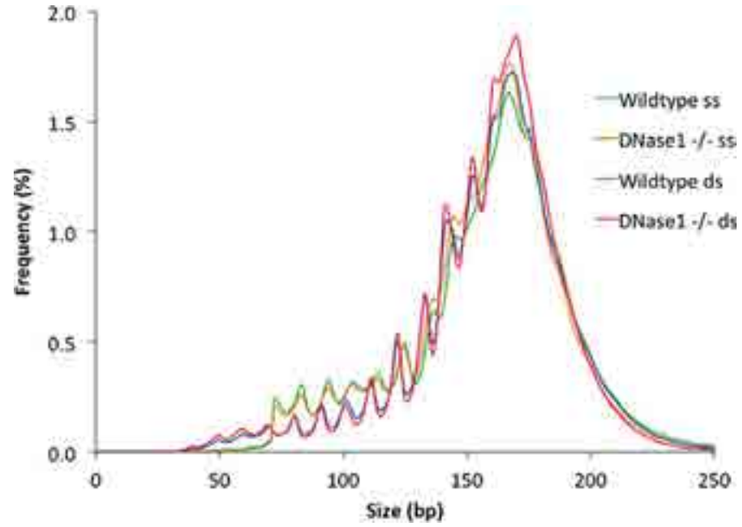
Cell-free DNA in the plasma and urine is fragmented from genomic DNA to lengths of 200 bp and below. The mechanism of the fragmentation in the systemic circulation and in the urinary system is not well characterised. Dr. Timothy Cheng's research aims to elucidate the mechanism by which fragmentation occurs, and to study how physiological and pathological conditions might impact cell-free DNA fragmentation.

## Publications

A. Journal Papers

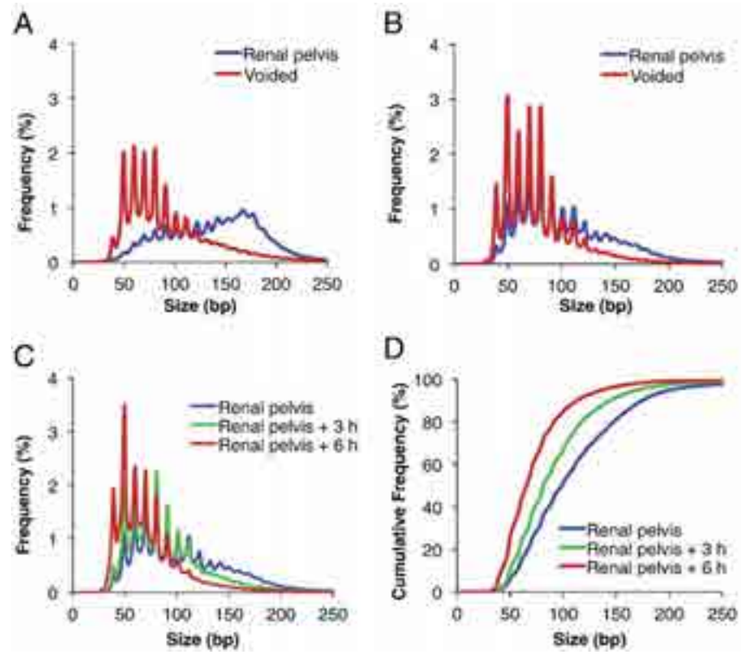
1. Cheng TH, Jiang PY, Tam JC, Sun X, Lee WS, Yu SC, Teoh JY, Chiu PK, Ng CF, Chow KM, Szeto CC, Chan KC, Chiu RW, Lo YM. Genomewide bisulfite sequencing reveals the origin and time-dependent fragmentation of urinary cfDNA. *Clinical Biochemistry*. 2017; 50(9):496-501.

2. Cheng TH, Lui KO, Peng XL, Cheng SH, Jiang P, Chan KC, Chiu RW, Lo YM. DNase1 Does Not Appear to Play a Major Role in the Fragmentation of Plasma DNA in a Knockout Mouse Model. *Clinical Chemistry*. 2018; 64(2):406–8. [Epub ahead of print]




The size of cell-free DNA in DNase1 knockout mice and wildtype mice using single-strand and double-strand library preparation protocols. The constitutional knockout of DNase1 does not appear to have a large effect on cell-free DNA fragment size.

Source: Cheng TH, Lui KO, Peng XL, Cheng SH, Jiang P, Chan KC, Chiu RW, Lo YM. DNase1 Does Not Appear to Play a Major Role in the Fragmentation of Plasma DNA in a Knockout Mouse Model. *Clinical Chemistry*. 2018; 64(2):406–8. Doi: 10.1373/clinchem.2017.280446




Cell-free DNA fragment size in the urinary system. Cell-free DNA is longer in the renal pelvis compared to voided urine. Urinary cell-free DNA undergoes a time-dependent fragmentation at 37 °C.

Source: Cheng TH, Jiang PY, Tam JC, Sun X, Lee WS, Yu SC, Teoh JY, Chiu PK, Ng CF, Chow KM, Szeto CC, Chan KC, Chiu RW, Lo YM. Genomewide bisulfite sequencing reveals the origin and time-dependent fragmentation of urinary cfDNA. *Clinical Biochemistry*. 2017; 50(9):496-501. Doi: https://doi.org/10.1016/j.clinbiochem.2017.02.017

# 03
# FECAL MICROBIOTA TRANSPLANTATION

## Principal Investigator

Professor Siew Ng

## Team

Laboratory of Fecal Microbiota Transplantation (FMT)

## Research Progress Summary

In the reporting year, Professor Siew Ng and her collaborators were awarded a grant from the Helmsley Foundation in the US, which led to their work on the identification of a specific bacterial genus *Proteus spp*. that is associated with, and predictive of Crohn's disease and disease recurrence. No causative organism has been identified to date that has such strong positive associations with Crohn's disease as their preliminary findings. This novel finding has led them to hypothesise that a *Proteus spp*. identified to species or strain level may target key molecules of genetic and epigenetic pathways that contribute to disease pathogenesis. In addition, their work on adherent-invasive *E. coli* strains showed that this organism has virulent factors and may play an important role in disease development. These findings will open avenues for treatment targets and prevention of Crohn's disease.

In the same year, Professor Ng's team was amongst the first teams in Hong Kong to conduct studies in FMT in treating *Clostridium difficile* infection, and their current work of FMT has expanded to clinical trials and translational laboratory research in other diseases, including obesity, inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). The team has created a longitudinal FMT registry in Asia – the Asia-Pacific FMT registry. The elucidation of the role of gut microbiome, including bacteriome, virome and fungome in health and disease as well as in FMT therapy will substantially aid in the development of personalised gut microbiota-based therapy and enhanced efficacy of FMT. The group was also the first to show that both the gut virome and fungome impact on FMT efficacy, whereby high donor virome richness and the presence of low abundance of fungi, especially *candida albicans*, in stool of donor or recipient are associated with favourable FMT outcomes. These novel findings highlight the importance of optimal and targeted donor selection, recipient stratification and donor-recipient matching in FMT practice. The team's work not only exerted profound impact on the understanding of "dark matters" of the microbiome but also had compelling implications for FMT in treatment of other human diseases.



In summary, Professor Ng's team has identified novel microorganisms which may potentially contribute to the pathogenesis of Crohn's disease. The team's discoveries of specific donor virome / fungome profile predicting FMT response have uncovered the understanding of the importance of other "neglected" compositions of the microbiome. In the reporting period, the team has published over 10 peer-reviewed articles and reviews in international journals and was invited to give talks in several local and international conferences.

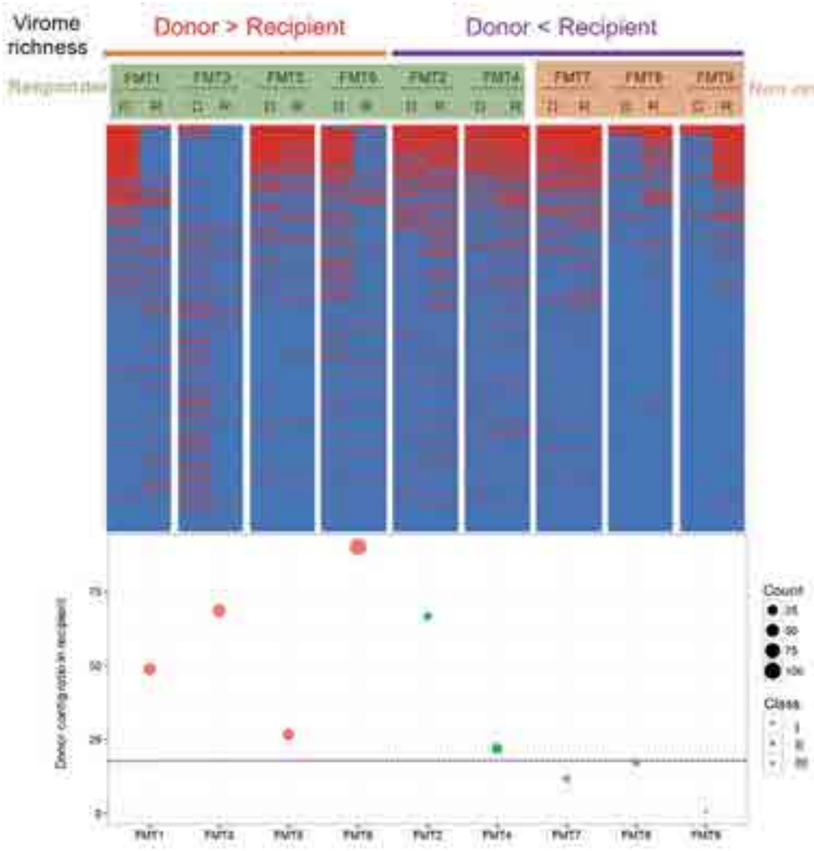
## Recognitions

Awards and Fellowships

| Member's Full Name | Details |
|---|---|
| Siew Ng | Sir David Todd Lectureship |
| Siew Ng | Outstanding Fellow of the Faculty of Medicine, CUHK |
| Tao Zuo | Early Career Investigator, American Gastroenterological Association |
| Tao Zuo | Research Fellowship Scheme, CUHK |

Donor-recipient virome richness discrepancy and colonization ratio of donor-derived viruses are associated with treatment outcome in Fecal Microbiota Transplantation (FMT)

Source: Zuo T, Wong SH, Lam K, et al Bacteriophage transfer during faecal microbiota transplantation in Clostridium difficile infection is associated with treatment outcome. *Gut*. 2018;67:634-643. Doi: http://dx.doi.org/10.1136/gutjnl-2017-313952




Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Siew Ng | Microbiome and Inflammatory Bowel Disease | Vice-Chancellor Discretionary Fund (3rd Round) | 01/01/2018 | 31/12/2022 | 5,000,000 |
| Siew Ng | PACIfIC: Prevalence, characteristics and genetics of adherent-invasive Escherichia coli in Crohn's disease patients: comparative study between France and Hong Kong | Research Grants Council – ANR/RGC Joint Research Scheme | 01/02/2018 | 31/01/2022 | 2,611,942 |
| Siew Ng | A Step-Forward for Blending Learning: Mobile Micro-Module Flipped Classroom Courseware in Clinical Year Studies | Micro-Module Courseware Development Grant | 01/12/2017 | 31/08/2018 | 100,000 |
| Siew Ng | The ENIGMA studies – Eastern Inflammatory Bowel Disease Gut Microbiota | The Leona M. & Harry B. Helmsley Charitable Trust | 01/03/2017 | 29/02/2020 | 14,259,211 |
| Siew Ng | Gastrointestinal Diseases and Cancer Research | ANR/RGC Joint Research Scheme | 01/02/2018 | 31/01/2022 | 2,611,942 |






Prof. Joseph J.Y. Sung and Prof. Siew Chien Ng talk about the incidence of Crohn's disease in Hong Kong and Australia with Prof. Michael Kamm, Professor of Gastroenterology from St. Vincent Hospital and the University of Melbourne, via video calling.

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## Publications

A. Journal Papers

1. Hooi J, Lai W, Ng W, Suen M, Underwood F, Tanyingoh D, Malfertheiner P, Graham D, Wong V, Wu J, Chan F, Sung J, Kaplan G, Ng S. Global Prevalence of *Helicobacter pylori* Infection: Systematic Review and Meta-Analysis. *Gastroenterology*. 2017;153(2):420-29.

2. Kaplan G, Ng S. Understanding and Preventing the Global Increase of Inflammatory Bowel Disease. *Gastroenterology*. 2017;152(2):313-21.e2.

3. Lam W, Gai W, Sun K, Wong R, Chan R, Jiang P, Chan N, Hui W, Chan A, Szeto C, Ng S, Law M, Chan K, Chiu R, Lo Y. DNA of Erythroid Origin Is Present in Human Plasma and Informs the Types of Anemia. *Clinical Chemistry*. 2017; 63(10):1614-23.

4. Liang Q, Chiu J, Chen Y, Huang Y, Higashimori A, Fang J, Brim H, Ashktorab H, Ng S, Ng S, Zheng S, Chan F, Sung J, Yu J. Fecal Bacteria Act as Novel Biomarkers for Noninvasive Diagnosis of Colorectal Cancer. *Clinical Cancer Research*. 2017; 23(8):2061-70.

5. Ng S, Shi H, Hamidi N, Underwood F, Tang W, Benchimol E, Panaccione R, Ghosh S, Wu J, Chan F, Sung J, Kaplan G. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *The Lancet*. 2017; 390(10114):2769-78.

6. So J, Tang W, Leung W, Li M, Lo F, Wong M, Sze A, Leung C, Tsang S, Shan E, Chan K, Lam B, Hui A, Chow W, Lam T, Lam V, Lee T, Lo H, Tang C, Wong C, Wu J, Chan F, Sung J, Harbord M, Ng S. Cancer Risk in 2621 Chinese Patients with Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*. 2017; 23(11):2061-8.

7. Tsoi H, Chu E, Zhang X, Sheng J, Nakatsu G, Ng S, Chan A, Chan F, Sung J, Yu J. Peptostreptococcus anaerobius Induces Intracellular Cholesterol Biosynthesis in Colon Cells to Induce Proliferation and Causes Dysplasia in Mice. *Gastroenterology*. 2017; 152(6):1419-33.e5.

8. Tsoi H, Lam K, Dong Y, Zhang X, Lee C, Zhang J, Ng S, Ng S, Zheng S, Chen Y, Fang J, Yu J. Pre-45s rRNA promotes colon cancer and is associated with poor survival of CRC patients. *Oncogene*. 2017; 36(44):6109-18.

9. Wong S, Kwong T, Chow T, Luk A, Dai R, Nakatsu G, Lam T, Zhang L, Wu J, Chan F, Ng S, Wong M, Ng S, Wu W, Yu J, Sung J. Quantitation of faecal Fusobacterium improves faecal immunochemical test in detecting advanced colorectal neoplasia. *Gut*. 2017; 66(8):1441-8.

10. Yu J, Feng Q, Wong S, Zhang D, Liang Q, Qin Y, Tang L, Zhao H, Stenvang J, Li Y, Wang X, Xu X, Chen N, Wu W, Al-Aama J, Nielsen H, Kiilerich P, Jensen B, Yau T, Lan Z, Jia H, Li J, Xiao L, Lam T, Ng S, Cheng A, Wong V, Chan F, Xu X, Yang H, Madsen L, Datz C, Tilg H, Wang J, Brünner N, Kristiansen K, Arumugam M, Sung J, Wang J. Metagenomic analysis of faecal microbiome as a tool towards targeted non-invasive biomarkers for colorectal cancer. *Gut*. 2017; 66(1):70-8.

B. Books / Book Chapters

1. Ng, SC. Fibrostenotic Inflammatory Bowel Disease (published by Springer)

C. Conference Papers

1. Chan F, Otani K, Higashimori A, Kee C, Ching J, Tse Y, Tang R, Lo A, Chan H, Lam L, Lui R, Arakawa T, Ng S, Fujiwara Y, Wu J, Watanabe T. A Double-Blind, Randomized Trial of Misoprostol for Healing of Small Bowel Bleeding Ulcers in Patients on Continuous Aspirin. *Gastroenterology*. 2017;152(5):S149.

2. Chan TT, Lau L, Tang W, Chan FKL, Leung WK, Li MKK . . . Ng SC. Cardiovascular accident risks in 2143 patients with inflammatory bowel diseases: Results from a territory-wide study in Hong Kong. *Journal of Gastroenterology and Hepatology*. 2017;32(S3).

3. Ho T, Chu E, Zhang X, Sheng J, Nakatsu D, Ng S, Chan A, Chan F, Sung J, Yu J. Peptostreptococcus Anaerobius Induces Intracellular Cholesterol Biosynthesis in Colon Cells to Induce Proliferation and Causes Dysplasia in Mice. *Gastroenterology*. 2017;152(5):S1010.

4. Ng S, Ip M, Tam L, Hung E, Tang W, Cheung K, Li A, Lui G, Lee N, Wu J, Chan F, Sung J. Frequent Conversion of Tuberculosis Screening Test During Anti-Tumour Necrosis Factor Therapy in Chinese Patients with Inflammatory Bowel Disease: A Prospective Study with 3 Years Follow-Up. *Gastroenterology*. 2017;152(5):S387.

5. Ng S, Kyaw M, Wong J, Suen B, Tse Y, Ching J, Wu J, Chan F, Lau J, Sung J. Risk of Colorectal Neoplasms in First-Degree Relatives of Individuals with Non-Advanced Adenomas: A Cross-Sectional Study. *Gastroenterology*. 2017;152(5):S537-8.

6. Ng S, Palo W, Blake A, Rana-Khan Q, Bhayat F. Vedolizumab Clinical and Post-Marketing Safety Experience of Opportunistic Infections. *Gastroenterology*. 2017;152(5):S575-6.

7. Ng S, Palo W, Blake A, Rana-Khan Q, Bhayat F. Vedolizumab clinical and post-marketing safety experience of opportunistic infections. *Journal of Crohn's and Colitis*. 2017;11(suppl_1):S41.

8. Ng S, Shi H, Hamidi N, Underwood F, Tang W, Benchimol E, Wu J, Chan F, Sung J, Kaplan G. The Worldwide Incidence and Prevalence of Inflammatory Bowel Disease in the 21st Century: A Systematic Review of Population-Based Studies. *Gastroenterology*. 2017;152(5):S970-1.

9. Ng W, Hooi J, Lai L, Suen M, Underwood F, Tanyingoh D, Graham D, Wu J, Wong V, Chan F, Sung J, Kaplan G, Ng S. The Global Prevalence of *Helicobacter Pylori* : A Systematic Review and Meta-Analysis of Population-Based Studies from 1970 to 2016. *Gastroenterology*. 2017;152(5):S182.

10. Shi H, Chan F, Chan A, Higashimori A, Kyaw M, Ching J, Luk A, Wu J, Sung J, Ng S. Fecal Immunochemical Test Predicts Histological Healing in Ulcerative Colitis: A Prospective Study Using the Geboes Score and Nancy Index. *Gastroenterology*. 2017;152(5):S209.

11. Shi H, Levy A, Trivedi H, Chan F, Ng S, Ananthakrishnan A. Ethnicity is Associated with Phenotype and Outcomes in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis of Population-Based Studies. *Gastroenterology*. 2017;152(5):S974.





12. So J, Tang W, Chan F, Leung W, Li M, Leung C, Lao W, Ng C, Lo F, Sze S, Hui Y, Tsang S, Shan E, Loo C, Chan K, Hui A, Chow W, Wu J, Sung J, Ng S. 5-Aminosalicylic Acid and Statin use are Associated with Reduced Risk of Cancers in Patients with Inflammatory Bowel Disease: A Population-Based Cohort Study. *Gastroenterology*. 2017;152(5):S373.

13. Wong J, Wong M, Ching J, Chan V, Ng S, Tang R, Kyaw M, Wong S, Lau J, Wu J, Chan F, Sung J. Adenoma Detection Rate among Colonoscopy for Positive Screening Fit is Higher than for Direct Screening Colonoscopy: A Call for Differential ADR Targets. *Gastroenterology*. 2017;152(5):S217-8.

14. Wong S, Tang W, Li A, Sung J, Ng S. Risk of Tuberculosis in Inflammatory Bowel Disease and Other Autoimmune Patients on Biologic Therapy: A Population-Based Study of 2,579 Patients. *Gastroenterology*. 2017;152(5):S781.

15. Zuo T, Wong S, Lam L, Lui R, Cheung K, Tang W, Ching J, Wu J, Chan F, Yu J, Sung J, Ng S. Bacteriophage Transfer during Fecal Microbiota Transplantation is Associated with Treatment Response in *Clostridium Difficile* Infection. *Gastroenterology*. 2017;152(5):S140-1.

# 04

# ASIAN CANCERS

*(Integrated Genome Research)*

## Principal Investigators

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

## Research Progress Summary

Nasopharyngeal carcinoma (NPC)

By whole-genome sequencing, the research team has built up comprehensive genomic landscapes of ~80 NPCs including established cell lines, xenografts and microdissected clinical specimens. With the transcriptome data, integrative informatics analysis was conducted to discover somatic alterations in both coding and noncoding regions (e.g. promoters, enhancers). In addition to the frequent mutated NF-κB regulators reported in the team's recent whole-exome sequencing study, the team has uncovered multiple novel somatic changes TGFβ-SMADs, ROBO-SLIT and NOTCH pathways that play roles in the tumourigenesis of EBV-associated NPC. The EBV transcriptome study has also demonstrated distinct transcription patterns of EBV-encoded microRNAs, (miR-BARTs), lytic genes and unique transcripts in NPC xenografts and clinical specimens. Functional study further revealed that multiple miR-BARTs negatively regulate the expression of a key DNA double-strand breaks (DSBs) repair gene, ATM, thereby controlling DNA damage repairs and inhibiting Zta-induced lytic reactivation. As an EBV-encoded oncoprotein, LMP1 plays a significant role in the development of NPC by virtue of its ability to engage multiple signalling pathways and cellular targets. In recent study, the team uncovered a novel function of LMP1 in activation of SREBP1 activity and enhancement of FASN expression, thereby promoting *de novo* lipogenesis. The LMP1-mediated lipogenesis promotes tumour cell growth and contribute to the EBV-driven NPC pathogenesis. The therapeutic potential of utilising lipogenesis inhibitors in the treatment of locally advanced or metastatic tumours was proven in both *in vitro* and *in vivo* NPC models.





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

Gastric cancer

TEA domain (TEAD) transcription factors are key components of the Hippo-YAP1 signalling pathway. The team found TEAD1 and TEAD4 are oncogenic factors in gastric tumourigenesis whose aberrant activation are, in part, mediated by the silence of miR-377-3p, miR-1343-3p and miR-4269. Downregulation of miR-4269 was associated with poor disease-specific survival and showed a negative correlation with TEAD4. IGF2BP3 ranked the number 1 of the up-regulated genes by expression microarray analysis in gastric cancer cell lines. The up-regulated IGF2BP3 expression was associated with poor disease specific survival. IGF2BP3 knockdown significantly inhibited cell proliferation and invasion. Apart from copy number gain, IGF2BP3 has been confirmed to be negatively regulated by tumour-suppressive miRNA, namely miR-34a. The expression of miR-34a showed negative correlation with IGF2BP3 mRNA expression in primary GC samples and more importantly, re-overexpression of IGF2BP3 rescued the inhibitory effect of miR-34a. The team compressively revealed the oncogenic role of IGF2BP3 in gastric tumourigenesis and confirmed its activation is partly due to the silence of miR-34a.





Liver cancer

Concurrent fatty liver in hepatitis B virus (HBV)-infected patients without significant alcohol intake is a frequent and increasingly alarming problem because of the non-alcoholic fatty liver disease pandemic. The risk of HBV-related hepatocellular carcinoma (HCC) development was increased by concomitant obesity and diabetes. The team evaluated the prevalence of concurrent histologically proven fatty liver and its association with subsequent HCC development and examined nine polymorphisms on six non-alcoholic fatty liver disease-related candidate genes (ADIPOQ, APOC3, GCKR, LEPR, PNPLA3, and PPARG). The team found concurrent fatty liver is common in HBV-infected patients and an independent risk factor potentiating HBV-associated HCC development by 7.3-fold. The risk of HBV-related HCC is increased by APOC3 gene polymorphism.

The albumin-bilirubin (ALBI) grade is a recently emerging alternative of the Child-Pugh (CP) grade. The Cancer of the Liver Italian Program (CLIP) has been demonstrated to be a useful prognostic model for hepatocellular carcinoma (HCC) in large prospective cohorts. The team investigated the feasibility of substituting the CP grade by the ALBI grade in the CLIP system and compared the prognostic performance with other existing staging systems. The team demonstrated the ALBI grade performed as well as the CP grade when integrating into the CLIP system. ALBI-CLIP and CP-CLIP systems are the most accurate prognostic models among 11 existing staging systems.

In the past year, the research team led by Professor Nathalie Wong has initiated studies on the tumour microenvironment (TME) of hepatocellular carcinoma (HCC). Cancer immunotherapy has revolutionised the treatment landscape and survival prospects of patients. Checkpoint blockades have shown high reactivity across many cancer types but the therapeutic benefit is often limited to a subset of patients in each cancer entity. The presence of CD8+ cytotoxic T cells within TME is a strong indicator for clinical benefits in response to checkpoint inhibitions. However, the precise mechanism underscoring cytokine/chemokine expressions and T cell exclusion remain incompletely understood. Recent evidence from Prof. Wong's team showed that a number of tumour-intrinsic oncogene pathways are involved in T cell exclusion and consequentially immune evasion. In HCC, the team showed that tumour-intrinsic Wnt/β-catenin and PTEN/PI3K signalling pathways control expression of chemoattractants and influence T cells, and other immune cells, migration into tumour site. The team's recent work on TME of HCC has resulted in an RGC Collaborative Research Fund in the 2017/18 exercise.

## Recognitions

Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Nathalie Wong | Regulation and Mechanism of Tumor-intrinsic Oncogene Pathways in Mediating an Immune Suppressed Microenvironment in Hepatocellular Carcinoma | Research Grants Council – Collaborative Research Fund | 30/06/2018 | 29/06/2021 | 7,544,147 |
| Ka-fai To | Target Inhibition of ATM-mediated Homologous Recombination Repair by Epstein-Barr Virus miRBARTs in Nasopharyngeal Carcinoma: Molecular Mechanisms and Clinical Implications | Research Grants Council – General Research Fund | 01/09/2016 | 31/08/2018 | 811,383 |
| Ka-fai To | Study on the role of Esptein-Barr Virus (EBV)- encoded microRNAs in controlling DNA damage repairs in EBV-associated nasopharyngeal carcinoma | Research Grants Council – General Research Fund | 01/01/2016 | 31/12/2018 | 1,187,649 |
| Kwok-wai Lo | Systematic Development of Molecular Targets for Nasopharyngeal Carcinoma | Research Grants Council – Theme-based Research Scheme | 01/01/2014 | 31/12/2018 | 55,610,000 |
| Nathalie Wong | Establishment of Third Generation Sequencing Core Facility | Research Grants Council – Collaborative Research Fund Equipment Grant | 01/06/2017 | 31/05/2020 | 3,222,257 |
| Ka-fai To, Nathalie Wong | Functional Liver Cancer Epigenomics: Exploiting Epigenetic Vulnerabilities for Therapeutics | Research Grants Council – Collaborative Research Fund | 01/06/2015 | 31/05/2018 | 7,418,375 |





## Publications

A. Journal Papers

1. Chan AW, Wong GL, Chan HY, Tong JH, Yu YH, Choi PC, Chan HL, To KF, Wong VW. Concurrent fatty liver increases risk of hepatocellular carcinoma among patients with chronic hepatitis B. *Journal of Gastroenterology and Hepatology*. 2017; 32(3):667-76.

2. Chan AW, Chong CC, Mo FK, Wong J, Yeo W, Johnson PJ, Yu S, Lai PB, Chan AT, To KF, Chan SL. Incorporating albumin-bilirubin grade into the cancer of the liver Italian program system for hepatocellular carcinoma. *Journal of Gastroenterology and Hepatology*. 2017; 32(1):221-8.

3. Zhou Y, Huang T, Zhang J, Wong CC, Zhang B, Dong Y, Wu F, Tong JHM, Wu WK, Cheng AS, Yu J, Kang W, To KF. TEAD1/4 exerts oncogenic role and is negatively regulated by miR-4269 in gastric tumourigenesis. *Oncogene*. 2017; 36(47):6518-30.

4. Zhou Y, Huang T, Siu HL, Wong CC, Dong Y, Wu F, Zhang B, Wu WK, Cheng AS, Yu J, To KF, Kang W. IGF2BP3 functions as a potential oncogene and is a crucial target of miR-34a in gastric carcinogenesis. *Molecular Cancer*. 2017; 16(1):77.

5. Zhang L, Zhou Y, Huang T, Cheng AS, Yu J, Kang W, To KF. The Interplay of LncRNA-H19 and Its Binding Partners in Physiological Process and Gastric Carcinogenesis. *International Journal of Molecular Sciences*. 2017; 18(2). pii: E450. (Review)

6. Zhang J, Huang T, Zhou Y, Cheng AS, Yu J, To KF, Kang W. The oncogenic role of Epstein-Barr virus-encoded microRNAs in Epstein-Barr virus-associated gastric carcinoma. *Journal of Cellular and Molecular Medicine*. 2018; 22(1): 38-45. [Epub ahead of print] (Review)

7. Chong CC, Chan AW, Wong J, Chu CM, Chan SL, Lee KF, Yu SC, To KF, Johnson P, Lai PB. Albumin-bilirubin grade predicts the outcomes of liver resection versus radiofrequency ablation for very early / early stage of hepatocellular carcinoma. *Surgeon*. pii: S1479-666X(17)30112-9. [Epub ahead of print]

8. Lung RW, Hau PM, Yu KH, Yip KY, Tong JH, Chak WP, Chan AW, Lam KH, Lo AK, Tin EK, Chau SL, Pang JC, Kwan JS, Busson P, Young LS, Yap LF, Tsao SW, To KF, Lo KW. EBV-encoded miRNAs target ATM-mediated response in nasopharyngeal carcinoma. *Journal of Pathology*. 2018; 244(4):394-407. [Epub ahead of print]

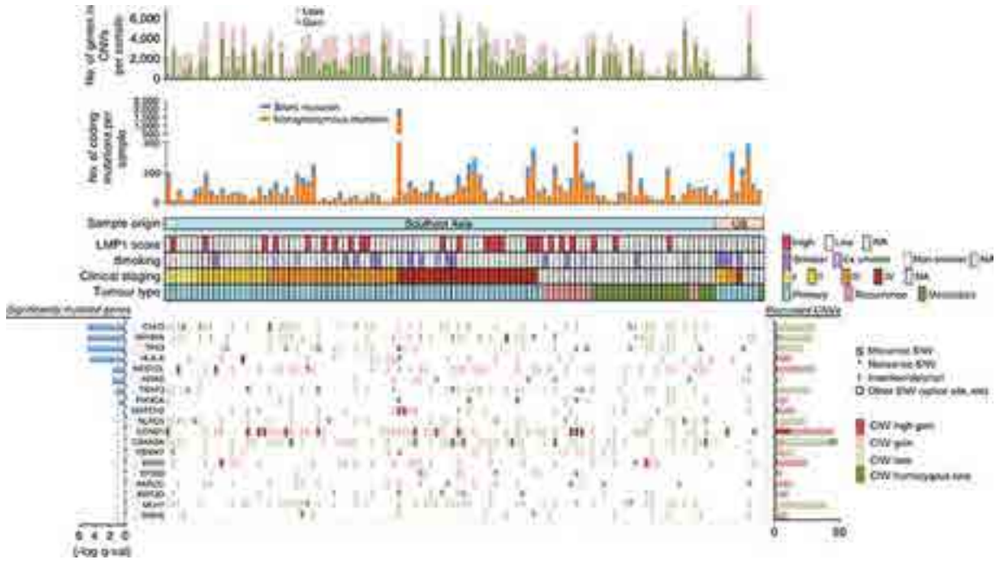
9. Lo AK, Dawson CW, Young LS, Lo KW. The role of metabolic reprogramming in γ-herpesvirus-associated oncogenesis. *International Journal of Cancer*. 2017; 141(8):1512-21.

10. Lee HM, Lo KW, Wei W, Tsao SW, Chung GT, Ibrahim MH, Dawson CW, Murray PG, Paterson IC, Yap LF. Oncogenic S1P signalling in EBV-associated nasopharyngeal carcinoma activates AKT and promotes cell migration through S1P receptor 3. *Journal of Pathology*. 2017; 242(1):62-72.

11. Chak WP, Lung RW, Tong JH, Chan SY, Lun SW, Tsao SW, Lo KW, To KF. Downregulation of long non-coding RNA MEG3 in nasopharyngeal carcinoma. *Molecular Carcinogenesis*. 2017; 56(3):1041-54.

12. Li YY, Chung GT, Lui VW, TO KF, Ma BB, Chow C, Woo JK, Yip KY, Seo JS, Hui EP, Mak MK, Rusan M, Chau NG, Or YY, Law MH, Law PP, Liu ZW, Ngan HL, Hau PM, Verhoeft KR, Poon PH, Yoo SK, Shin JY, Lee SD, Lun SW, Jia L, Chan AW, Chan JY, Lai PB, Fung CY, Hung ST, Wang L, Chang AM, Chiosea SI, Hedberg ML, Tsao SW, van Hasselt AC, Chan AT, Grandis JR, Hammerman PS, Lo KW. Exome and genome sequencing of nasopharynx cancer identifies NF-κB pathway activating mutations. *Nature Communications*. 2017; 8:14121.






The genomic landscape of NPC. For each patient (each column), recurrently altered genes (rows) with mutations and CNVs are shown.

Significantly mutated genes (identified using the MutSigCV 2.0 algorithm; q00.1, left panel) are ordered by q value, with additional genes near significance are also shown. Recurrent gene copy changes across the patients are summarized on the right panel. For each patient, the number of mutations and CNVs are shown on the top panels, as well as the sample origin, latent-membrane protein 1 (LMP1) expression, smoking status, clinical staging and tumour type.

Source: Li YY, Chung GT, Lui VW, TO KF, Ma BB, Chow C, Woo JK, Yip KY, Seo JS, Hui EP, Mak MK, Rusan M, Chau NG, Or YY, Law MH, Law PP, Liu ZW, Ngan HL, Hau PM, Verhoeft KR, Poon PH, Yoo SK, Shin JY, Lee SD, Lun SW, Jia L, Chan AW, Chan JY, Lai PB, Fung CY, Hung ST, Wang L, Chang AM, Chiosea SI, Hedberg ML, Tsao SW, van Hasselt AC, Chan AT, Grandis JR, Hammerman PS, Lo KW. Exome and genome sequencing of nasopharynx cancer identifies NF-κB pathway activating mutations. *Nature Communications*. 2017; 8:14121. Doi: https://doi.org/10.1038/ncomms14121

# 04

# ASIAN CANCERS

*(Cancer Epigenetics)*

## Principal Investigator

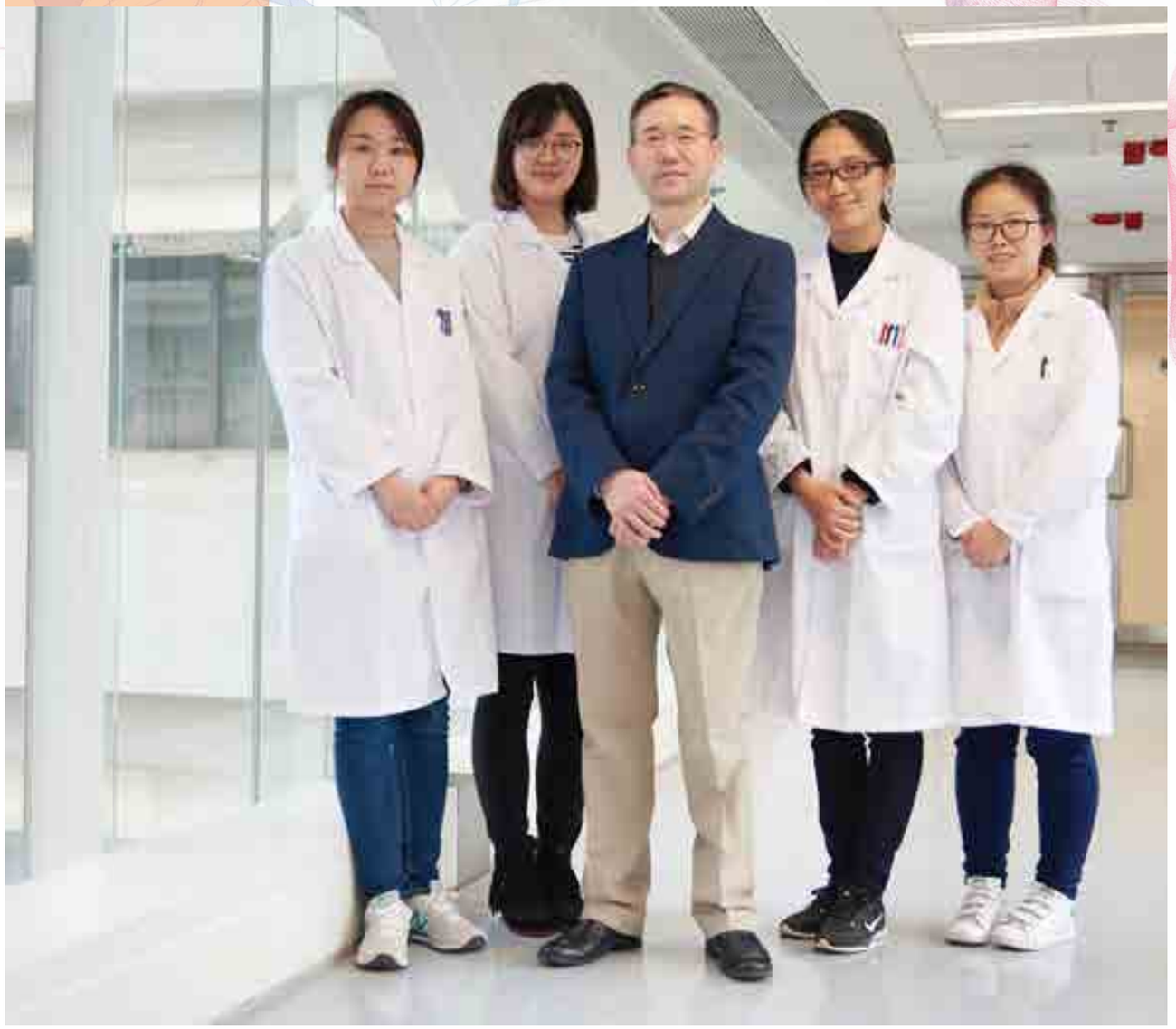
Professor Qian Tao

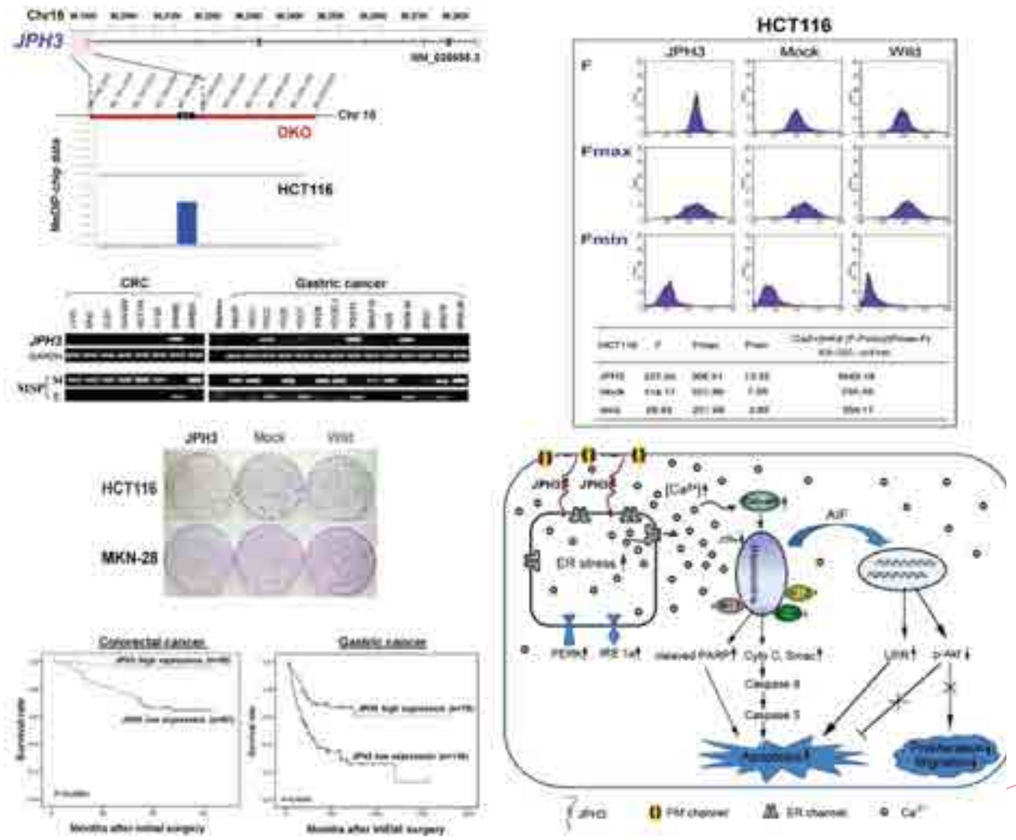
## Research Progress Summary

Through epigenomic study of a colon cancer cell line pair (HCT116 and DKO), the team identified JPH3 as a methylated novel tumour suppressor gene (TSG) candidate at 16q24. JPH3 expression at the RNA level was found to be frequently silenced or reduced in colorectal and gastric cancers due to its promoter CpG methylation, which is associated with tumour progression and poor survival of digestive cancer patients. Ectopic expression of JPH3 inhibited tumour cell growth *in vitro* and *in vivo*. JPH3 expression upregulated the cytosolic Ca2+ levels, and unfolded protein response gene expression upon endoplasmic reticulum stress. JPH3 also induced calpain activation and subsequent mitochondrial membrane depolarisation and cell apoptosis. Thus, JPH3 was identified as a novel TSG methylated in colorectal and gastric tumours which promotes mitochondrial-mediated apoptosis, also as a potential metastasis and survival biomarker for digestive cancers.

Through cancer methylome study, the team also identified BCLB as a methylated gene in HCC. BCLB was methylated in all tumour cell lines with silenced or reduced expression. BCLB was further found to be silenced in 55.2% of HCC samples, while 91.4% of paired non-tumour tissues showed high BCLB expression. BCLB protein expression was significantly correlated with HBV status, AFP, tumour size, and TNM stage. The overall survival and disease-free survival rate of HCC patients with positive BCLB expression were both significantly higher than those with negative BCLB expression. Ectopic expression of BCLB in HCC cells inhibited cell growth *in vitro* and *in vivo*. Mechanistic study showed that BCLB expression was a starvation stress sensor inducing apoptosis and autophagy simultaneously in HCC cells through the adenosine monophosphate-activated protein kinase AMPK-mTOR signalling cascade. Thus, epigenetic suppression of BCLB expression is involved in HCC development, which might have therapeutic implications for HCC patients.








Epigenomic and functional characterisation of Junctophilin 3 (JPH3) as a novel tumour suppressor being frequently inactivated by promoter CpG methylation in digestive cancers

Source: Hu X, Kuang Y, Li L, Tang H, Shi Q, Shu X, Zhang Y, Chan F, Tao Q, He C. Epigenomic and Functional Characterization of Junctophilin 3 (JPH3) as a Novel Tumor Suppressor Being Frequently Inactivated by Promoter CpG Methylation in Digestive Cancers. *Theranostics*. 2017; 7(7):2150-63. Doi: 10.7150/thno.18185



## Recognitions

Awards and Fellowships

| Member's Full Name | Details |
|---|---|
| Qian Tao | 深圳市科技創新委員會　2017年度國家級科技項目獎先進個人 |

Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Qian Tao | Genome-wide Study of CpG Methylation of EB Virus-associated Nasal Lymphoma Identifies Disrupted Transcription Program Derived from Silencing of Tumor Suppressor PAX5 | Food and Health Bureau – Health and Medical Research Fund | 01/09/2017 | 31/08/2019 | 1,015,032 |
| Qian Tao | Mechanism Study of a New RhoA-signaling Antagonist in Esophageal Cancer Pathogenesis | The National Natural Science Foundation of China | 01/2016 | 12/2019 | RMB 570,000 |
| Qian Tao (Co-PI) | Systematic Development of Molecular Targets for Nasopharyngeal | Research Grants Council – Theme-based Research Scheme | 01/2014 | 12/2018 | 55,610,000 |
| Qian Tao (Co-PI) | Innovation Platform of Oncology Pathogenesis and Targeted Therapy in Guangdong and Hong Kong | Guangdong and Hong Kong Joint Innovation Areas | 06/2015 | 08/2018 | RMB 2,000,000 |
| Qian Tao (Co-PI) | Epigenetic Disruption of Wnt/β-catenin Signaling Pathway in the Development, Invasion and Metastasis of Breast Cancer | International Cooperation and Exchange of the National Natural Science Foundation of China | 01/2015 | 12/2019 | RMB 2,850,000 |
| Lili Li (PI) | Functional and Mechanic Studies of a Novel Tumor Suppressor ROR2 Frequently Methylated in Common Carcinomas and Involved in Epithelial Mesenchymal Transition | The National Natural Science Foundation of China | 01/2014 | 12/2017 | RMB 700,000 |





## Publications

A. Journal Papers

1. Hu X, Kuang Y, Li L, Tang H, Shi Q, Shu X, Zhang Y, Chan F, Tao Q, He C. Epigenomic and Functional Characterization of Junctophilin 3 (JPH3) as a Novel Tumor Suppressor Being Frequently Inactivated by Promoter CpG Methylation in Digestive Cancers. *Theranostics*. 2017; 7(7):2150-63.

2. Liu X, Hu X, Kuang Y, Yan P, Li L, Li C, Tao Q, Cai X. BCLB, methylated in hepatocellular carcinoma, is a starvation stress sensor that induces apoptosis and autophagy through the AMPK-mTOR signaling cascade. *Cancer Letters*. 2017; 395:63-71.

3. Luo X, Xiong X, Shao Q, Xiang T, Li L, Yin X, Li X, Tao Q, Ren G. The tumor suppressor interferon regulatory factor 8 inhibits β-catenin signaling in breast cancers, but is frequently silenced by promoter methylation. *Oncotarget*. 2017; 8(30):48875-88.

4. Mu J, Hui T, Shao B, Li L, Du Z, Lu L, Ye L, Li S, Li Q, Xiao Q, Qiu Z, Zhang Y, Fan J, Ren G, Tao Q, Xiang T. Dickkopf-related protein 2 induces G0/G1 arrest and apoptosis through suppressing Wnt/β-catenin signaling and is frequently methylated in breast cancer. *Oncotarget*. 2017; 8(24):39443-59.

5. Shao B, Feng Y, Zhang H, Yu F, Li Q, Tan C, Xu H, Ying J, Li L, Yang D, Peng W, Tang J, Li S, Ren G, Tao Q, Xiang T. The 3p14.2 tumour suppressor ADAMTS9 is inactivated by promoter CpG methylation and inhibits tumour cell growth in breast cancer. *Journal of Cellular and Molecular Medicine*. 2018; 22(2):1257-71. [Epub ahead of print]



# 04

# ASIAN CANCERS

*(Biomarkers and Targeted Therapeutics)*

## Principal Investigator

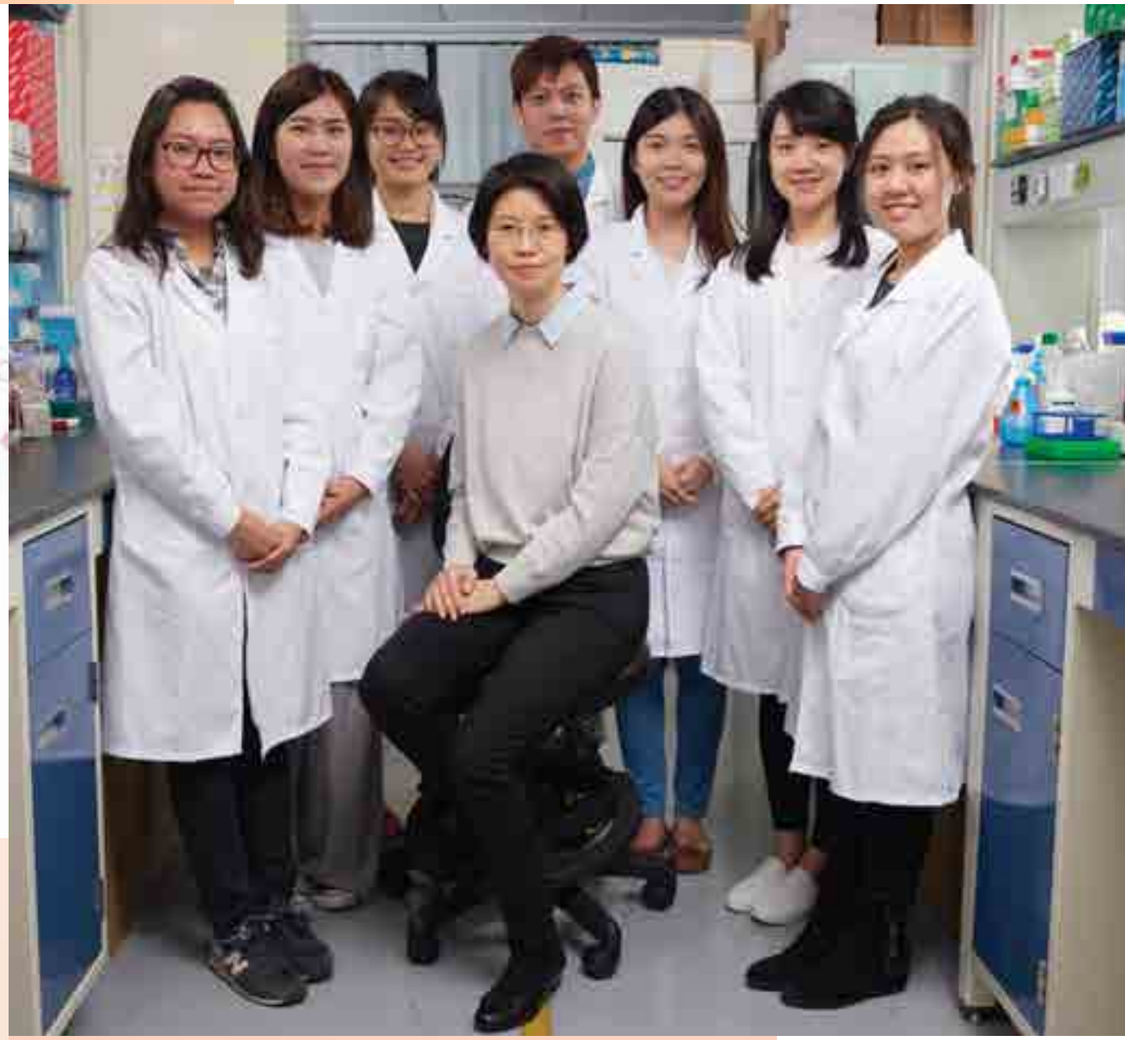
Professor Siu Tim Cheung

## Team

Linda WC Ng, Katie SW Fung, Marcus HN Law, Elaine HL Siu, Alyssa MT Liu, Carol Lee, Shin Yee Hui

## Research Progress Summary

Granulin-epithelin precursor (GEP) is a secretory growth factor, which has been demonstrated to control cancer growth, invasion, drug resistance and immune escape. The team's previous studies and others also demonstrated its potential as target for cancer treatment. Comprehensive characterisation of GEP partner on cancer cells is warranted. The team led by Professor Siu-tim Cheung has examined the membrane fractions of liver cancer cells for capturing binding partner with the specific monoclonal antibody against GEP. The team identified the GEP-binding protein as 78-kDa glucose-regulated protein (GRP78, also named heat shock 70-kDa protein 5, HSPA5). This interaction was validated in independent liver cancer cell lines. Increased GRP78 mRNA levels were demonstrated in primary liver cancer tissues compared with the paralleled liver tissues. GRP78 and GEP transcript levels were significantly correlated in patient's samples and the proteins were also detectable on the plasma membrane and cytoplasm of liver cancer cells. In summary, GRP78 and GEP are interacting protein partners in liver cancer cells and may play a role in cancer progression in liver cancer.



## Recognitions

Awards and Fellowships

| Member's Full Name | Details |
|---|---|
| Siu Tim Cheung, Phyllis F.Y. Cheung, Katie S.W. Fung, Charing C.N. Chong, Stephen L. Chan, Tan To Cheung, Paul B.S. Lai, George G. Chen, George S.W. Tsao, Anthony W.H. Chan | Best Poster Award, Health Research Symposium 2017 by Food and Health Bureau, Hong Kong (Project entitled "Drug Transporter Expressions Associate with Drug Resistance and Poor Prognosis in Liver Cancer Patients") |

Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Stephen Chan (PI), Siu Tim Cheung (PI) | 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 |





## Publications

A. Journal Papers

1. Yip CW, Lam CY, Poon, TC, Cheung TT, Cheung PF, Fung SW, Wang XQ, Leung IC, Ng LW, Lo CM, Tsao SW, Cheung ST. Granulin-epithelin precursor interacts with 78-kDa glucose-regulated protein in hepatocellular carcinoma. *BMC Cancer*. 2017; 17(1): 409.

B. Conference Papers

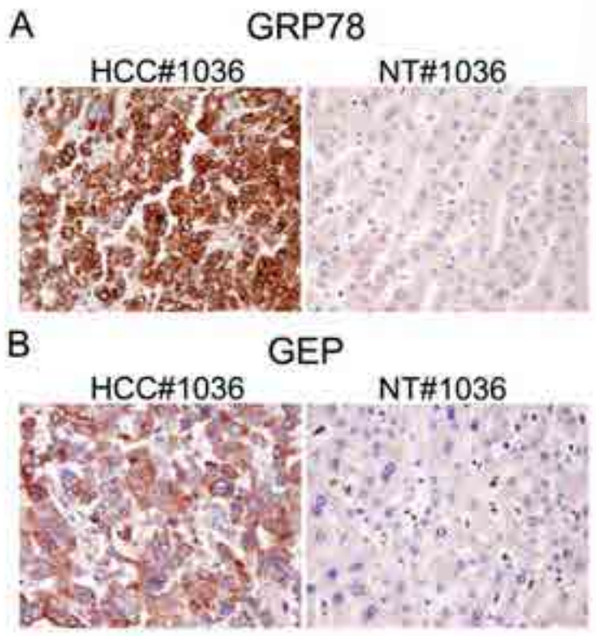
1. Cheung ST, Cheung PFY, Chong CCN, Chan AWH, Chan SL. Natural killer cell anergy in liver cancer patients and potential of adoptive cell transfer. In: *Third CRI-CIMT-EATI-AACR International Cancer Immunotherapy Conference: Translating Science into Survival*; Mainz, Germany; 2017 Sep 6-9.

2. Fung SW, Cheung PFY, Yip CW, Ng WC, Cheung TT, Chong CCN, Tsao GSW, Cheung ST. Expression of ATP-binding cassette transporter ABCF1 in fetal liver and liver cancer associated with stem cell markers and chemo-resistance. In: *HK Inter-University Postgraduate Symposium in Biomedical Sciences*; Hong Kong; 2017 Jun 16.

C. Others

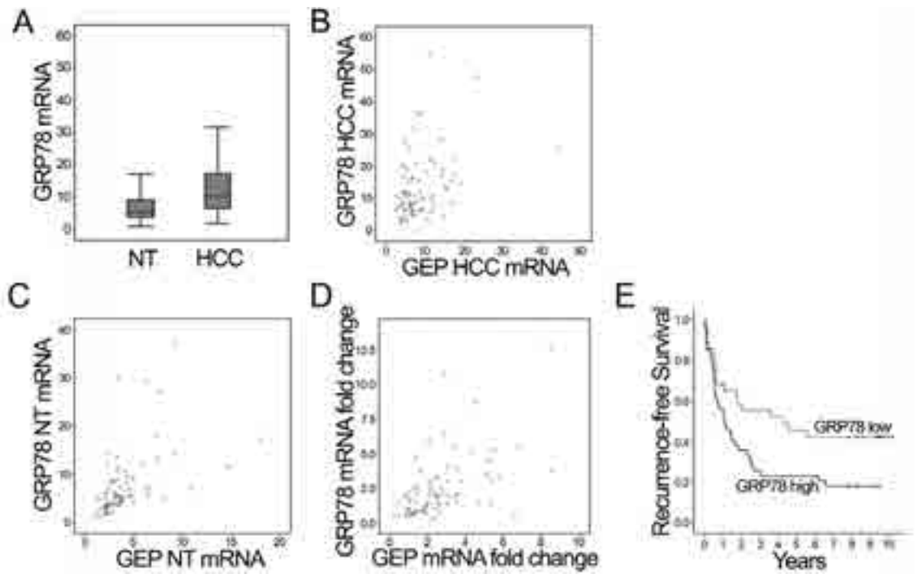
1. Invited Lectures:
Translational medicine in surgery. *The 20th Chinese University of Hong Kong Surgical Symposium*. October 14, 2017. Hong Kong.

2. Growth factor signaling in HCC. *The 26th Annual Conference of the Asian Pacific Association for the Study of the Liver (APASL)*. February 15-19, 2017. Shanghai, China.




Elevated expression of GRP78 and GEP protein in clinical samples by immunohistochemistry.

Source: Yip CW, Lam CY, Poon, TC, Cheung TT, Cheung PF, Fung SW, Wang XQ, Leung IC, Ng LW, Lo CM, Tsao SW, Cheung ST. Granulin-epithelin precursor interacts with 78-kDa glucose-regulated protein in hepatocellular carcinoma. *BMC Cancer*. 2017; 17(1): 409. Doi: 10.1186/s12885-017-3399-x.




Upregulation of transcript levels of GRP78 associated with GEP levels and recurrence-free survival of the patients.

Source: Yip CW, Lam CY, Poon, TC, Cheung TT, Cheung PF, Fung SW, Wang XQ, Leung IC, Ng LW, Lo CM, Tsao SW, Cheung ST. Granulin-epithelin precursor interacts with 78-kDa glucose-regulated protein in hepatocellular carcinoma. *BMC Cancer*. 2017; 17(1): 409. Doi: 10.1186/s12885-017-3399-x.

# 05
# VASCULAR MEDICINE

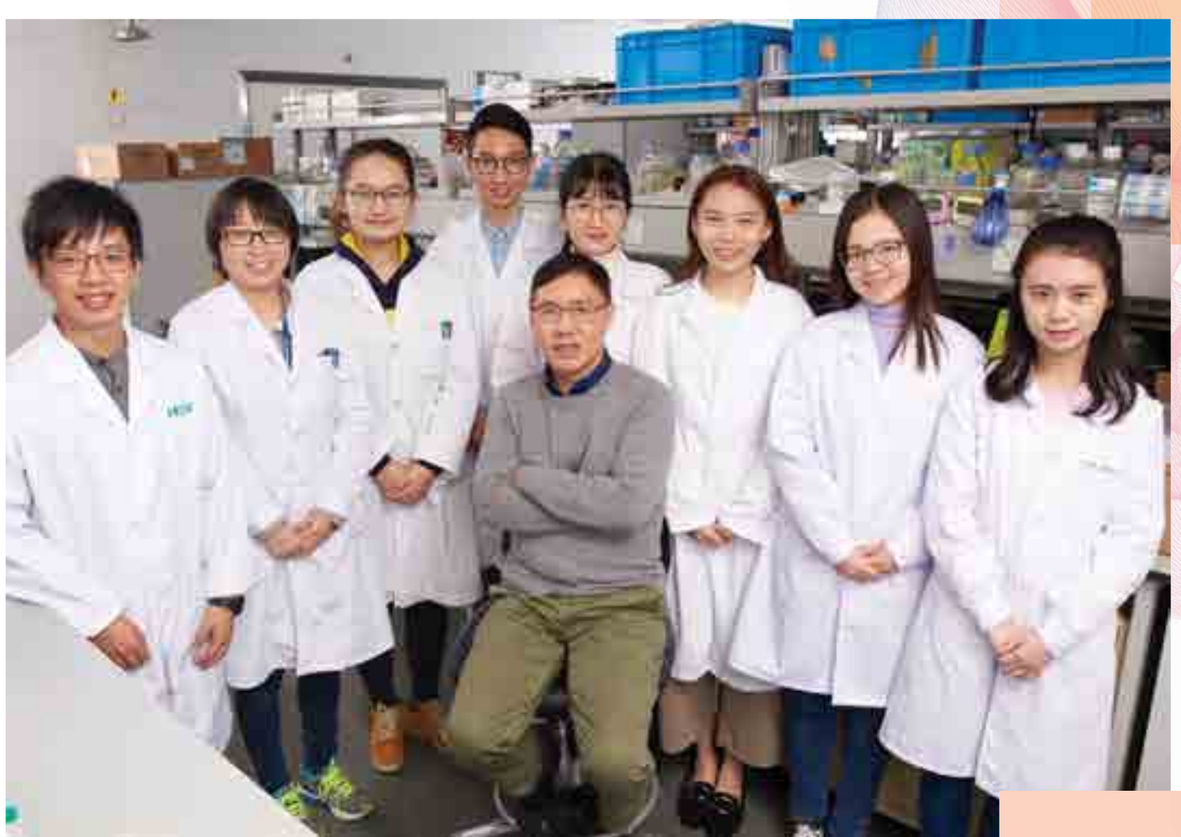
*(Basic Research)*

## Principal Investigators

Professor Xiaoqiang Yao, Professor Yu Huang

## Research Progress Summary

The team led by Professor Xiaoqiang Yao had novel findings that TRPV4 contributes to the dilated cardiomyopathy using iPSC-derived cardiomyocytes from patients. He also found that the active ingredient of Chinese Medicine Gastrodin (天麻) can inhibit cardiac hypertrophy via its action on store-operated $Ca^{2+}$ entry. Furthermore, he found that HADC inhibitors can act through L-type Ca channels to induce vascular dilation.







Professor Yu Huang's team has provided new evidence on the molecular mechanisms underlying protection of endothelial cell function exerted by running exercise in diabetic mice and highlighted the importance of inhibiting AMPK-PPARdelta-ER stress against endothelial dysfunction in diabetes. His team also revealed a significant role of microRNA 29a in the development of diabetic endothelial dysfunction. These studies further confirm the pathological role of increased oxidative stress in the vascular wall in diabetic vasculopathy.

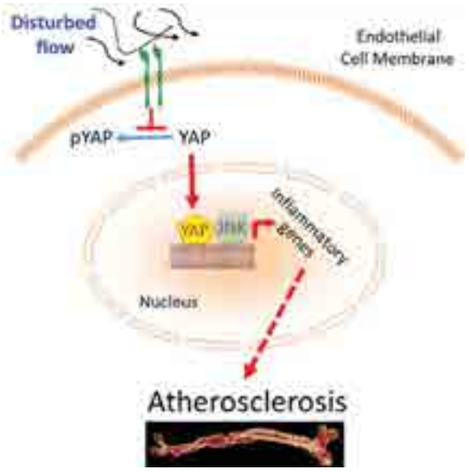
## Recognitions

Awards and Fellowships

| Member's Full Name | Details |
|---|---|
| Yu Huang | Research Excellence Award 2016-2017 by CUHK |

Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Yu Huang | Targeting YAP/ TAZ activation to ameliorates endothelial dysfunction in diabetic mice | Research Grants Council – General Research Fund | 2018 | 2020 | 1,126,512 |
| Yu Huang | Novel lipid-lowering-independent benefits of statins against vascular dysfunction in metabolic syndrome | Food and Health Bureau – Health and Medical Research Fund | 2017 | 2019 | 1,199,176 |
| Yu Huang | A multi-disciplinary study on the beneficial effects of PPARD in physical exercise against diabetic vascular complications: cellular crosstalk and energy metabolism | Research Grants Council – Collaborative Research Fund | 2017 | 2020 | 6,817,834 |




Mechanical stimulation on vascular endothelial cells brought by disturbed flood flow promotes nuclear translocation of Yap, the effect of the Hippo pathway, leading to increased expression of genes that induce vascular inflammation and development of atherosclerosis in the lumen of arteries.

Source: Prof. Yu Huang



## Publications

A. Journal Papers

1. Cheang WS, Wong WT, Zhao L, Xu J, Wang L, Lau CW, Chen ZY, Ma RCW, Xu AM, Wang NP, Tian XY, Huang Y. PPAR delta Is Required for Exercise to Attenuate Endoplasmic Reticulum Stress and Endothelial Dysfunction in Diabetic Mice. *Diabetes*. 2017; 66(2):519-28.

2. Huo M, Huang Y, Qu D, Zhang H, Wong WT, Chawla A, Huang Y, Tian XY. Myeloid Bmal1 deletion increases monocyte recruitment and worsens atherosclerosis. *FASEB Journal*. 2017;31(3): 1097-106.

3. Ling WC, Liu J, Lau CW, Murugan DD, Mustafa MR, Huang Y. Treatment with salvianolic acid B restores endothelial function in angiotensin II-induced hypertensive mice. *Biochemical Pharmacology*. 2017; 136:76-85.

4. Lu J, Lee Y, Ran X, Lai W, Li R, Keung W, Tse K, Tse H, Yao X. An abnormal TRPV4-related cytosolic Ca 2+ rise in response to uniaxial stretch in induced pluripotent stem cells-derived cardiomyocytes from dilated cardiomyopathy patients. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*. 2017;1863(11): 2964-72.

5. Qin L, Wong SHS, Sun FH, Huang Y, Sheridan S, Sit CHP. Effects of Alpha-Lactalbumin or Whey Protein Isolate on Muscle Damage, Muscle Pain, and Mood States Following Prolonged Strenuous Endurance Exercise. *Frontiers in Physiology*. 2017; 8: Article 754.

6. Yang JY, Wang Y, Zhou T, Wong LY, Tian XY, Hong XY, Lai WH, Au KW, Wei R, Liu YQ, Cheng LH, Liang GC, Huang ZJ, Fan WX, Zhao P, Wang XW, Ibanez DP, Luo ZW, Li YY, Zhong XF, Chen SH, Wang DY, Li L, Lai LX, Qin BM, Bao XC, Hutchins AP, Siu CW, Huang Y, Esteban MA, Tse HF. Generation of Human Liver Chimeric Mice with Hepatocytes from Familial Hypercholesterolemia Induced Pluripotent Stem Cells. *Stem Cell Reports*. 2017; 8(3):605-18.

7. Zheng C, Lo C, Meng Z, Li Z, Zhong M, Zhang P, Lu J, Yang Z, Yan F, Zhang Y, Huang Y, Yao X. Gastrodin Inhibits Store-Operated Ca2+ Entry and Alleviates Cardiac Hypertrophy. *Frontiers in Pharmacology*. 2017; 8:222.

8. Zheng C, Zhong M, Qi Z, Shen F, Zhao Q, Wu L, Huang Y, Tsang S, Yao X. Histone Deacetylase Inhibitors Relax Mouse Aorta Partly through Their Inhibitory Action on L-Type Ca 2+ Channels. *Journal of Pharmacology and Experimental Therapeutics*. 2017; 363(2):211-20.

# 05
# VASCULAR MEDICINE

## Principal Investigator

Professor Gary Tse

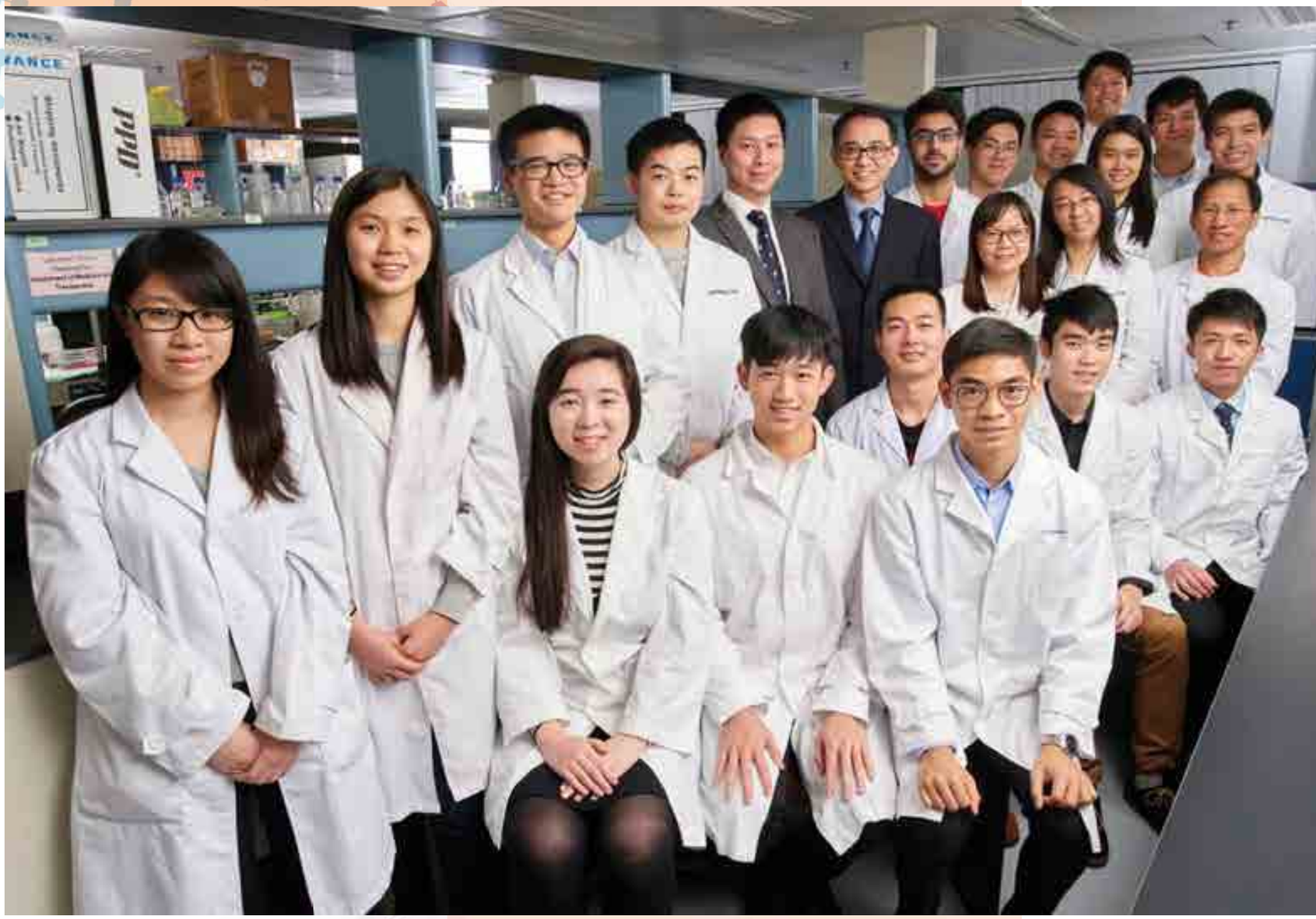
## Team

Sabrina So, Lorraine Chiang, Francis Chen, Ken Wong, Gary Tse, Jack Wong, Jeremy Liu, Dominic Lau, Ricko Wong, Calista Chan, Enpei Zhang, Thompson Kot, Ishan Lakhani, Christina Leung, Yan Yee Ting, Henry Wong, Elizabeth Ng, Walter Wan, Ming Zhaung Chen, Timothy Tipoe, Kevin Ho, Sunny Tsang

## Research Progress Summary

Professor Gary Tse's team has elucidated the relative contributions of gap junction and sodium channel function to cardiac conduction (Tse et al., *Mol Med Rep*. 2016 Nov;14(5):4069-74), and the relationship between conduction (Tse et al., *J Physiol Sci*. 2012 Mar;62(2):79-92), repolarisation, their heterogeneities, and dynamic substrates of electrical restitution (Tse et al., *Oncotarget*, 2017, 8(49):85341-52) to atrial and ventricular arrhythmogenicity (Tse et al., *PLOS One*. 2016 Feb 12;11(2):e0148858) using Langendorff model systems (reviewed in Yeo,...and Tse, J Basic *Clin Physiol Pharmacol*. 2017 May 1;28(3):191-200). Of note, his group was the first to validate the use of the S1S2 protocol against the gold standard of dynamic pacing for assessing electrical restitution in the mouse (Tse et al., *Biomed Rep*. 2016 Jun;4(6):673-80). Recently, the team have focused on the roles of oxidative stress in mediating endoplasmic reticulum stress and mitochondrial dysfunction and how these relate to atrial fibrillation (reviewed in Tse et al., *Front Physiol*. 2016 Aug 3;7:313).







Using insights from their pre-clinical programme, they have identified key electrocardiographic (ECG) predictors that can aid risk stratification in stroke. For example, they validated that atrial remodelling can be detected using the ECG and P-wave parameters reflecting atrial electrical dysfunction can predict future onset and recurrence of atrial fibrillation (AF) (Tse et al., *Int J Cardiol*. 2017), and more importantly stroke events independently of AF (He, Tse et al., *Stroke*. 2017 Aug;48(8): 2066-72). Moreover, they have identified ECG predictors for ventricular arrhythmic and sudden cardiac death events in congenital ion channelopathies such as Brugada (Tse et al., *Front Physiol*. 2016 Oct 18;7:467) and Long QT syndromes (Tse et al., *Int J Cardiol Heart Vasc*. 2016 Nov 26;14:8-13), and more prevalent conditions of ischemic heart disease and myocardial infarction. These include fragmentation of the QRS complex (Meng et al., *Front Physiol*. 2017 Sep 12;8:678) and prolonged Tpeak-Tend intervals (Tse et al. *Heart Rhythm*. 2017 Aug;14(8): 1131-37), reflecting increased dispersion of conduction velocities and excerbated transmural or global repolarization gradients, respectively (reviewed in Tse and Yan, *Europace*. 2017 May 1;19(5): 712-21). Together with their clinical colleagues in Mainland, Europe and Canada, they discovered that abnormal unipolar voltage mapping detected at the free wall of the right ventricular outflow tract can be used to predict ventricular fibrillation inducibility in Brugada syndrome (Letsas…Tse… Brugada, *Circulation: Arrhythmia and Electrophysiology*, 2018, in press).



## Recognitions

Awards and Fellowships

| Member's Full Name | Details |
|---|---|
| Gary Tse | Fellow of American College of Epidemiology (FACE) |
| Gary Tse | Fellow of Academy of Translational Medicine Professionals (FAcadTM) |
| Gary Tse | Fellow of Royal College of Physicians and Surgeons of Glasgow (FRCP) |
| Gary Tse | Fellow of American College of Cardiology (FACC) |
| Gary Tse | Croucher Foundation Clinical Assistant Professorship in Medicine and Therapeutics |
| Tong Liu, Gary Tse | Xanthine oxidase inhibitor allopurinol prevents oxidative stress-mediated atrial remodeling in alloxan-induced diabetes rabbits. American College of Cardiology Asia Pacific Congress 2017. **Best Poster Award** |

Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Gary Tse | Aliskiren and Endothelial Function | CUHK Research Committee – Direct Grant | 26/06/2017 | 25/06/2018 | 150,000 |
| Gary Tse | Clinical Assistant Professorship in Medicine and Therapeutics | The Croucher Foundation | 12/09/2016 | 11/09/2020 | 2,000,000 |
| Jack Wing Tak Wong (PI), Gary Tse (Co-I) | Engineering Microenvironments with Human Induced Pluripotent Stem Cell-derived Neural Progenitor Cells for Disease Modeling, Drug Screening, and Cell-based Therapy | Faculty of Science, CUHK (Major Research Area 2 Translational Biomedicine Research Incentive Scheme) | 01/06/2017 | 31/05/2018 | 200,000 |
| Jack Wing Tak Wong (PI), Gary Tse (Co-I) | Cardiovascular Calcium Signaling Pathway: Role in Health and Disease | National Natural Science Foundation of China (NSFC) / Research Grants Council (RGC) Joint Research Scheme | 01/05/2017 | 09/12/2017 | 250,000 |

## Publications

A. Journal Papers

1. Tse G, Wu W, Gong M, Bazoukis G, Wong W, Wong S, Lampropoulos K, Baranchuk A, Tse L, Xia Y, Li G, Wong M, Chan Y, Mu N, Dong M, Liu T. Patent foramen ovale closure versus medical therapy for stroke prevention: A systematic review and meta-analysis of randomized controlled trials. *F1000Research*. 2017; 6:2178. (Review)

2. Lampropoulos K, Bakalakos A, Bazoukis G, Saplaouras A, Sakellaropoulou A, Anagnostou A, Tse G, Tsamatsoulis M, Charitos C. A "tilt" toward cinefluoroscopy. *Clinical Case Reports*. 2017; 6(1):242-3. (Clinical Video)

3. Li K, Bazoukis G, Liu T, Li G, Wu W, Wong S, Wong W, Chan Y, Wong M, Wassilew K, Vassiliou V, Tse G. Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) in clinical practice. *Journal of Arrhythmia*. 2017; 34(1):11-22. (Review)

4. Tse G, Wong CW, Gong M, et al. Meta-analysis of T-wave indices for risk stratification in myocardial infarction. *Journal of Geriatric Cardiology* : JGC. 2017;14(12):776-9. (Letter)

5. Liu T, Yang Y, Gong M, Li H, Liang X, Zhang Z, Yuan M, Zhang Y, Jiao Z, Tse G, Li G. Rapamycin attenuates atrial fibrosis in 5/6 nephrectomized rats by inhibiting mammalian target of rapamycin and profibrotic signaling. *International Journal of Heart Rhythm*. 2017; 2(2):81.

6. Bayoumy A, Gong M-Q, Christien Li KH, et al. Spontaneous type 1 pattern, ventricular arrhythmias and sudden cardiac death in Brugada Syndrome: an updated systematic review and meta-analysis. *Journal of Geriatric Cardiology* : JGC. 2017; 14(10):639-43. (Letter)

7. Lampropoulos K, Bazoukis G, Kolyviras A, Tse G, Saplaouras A, Iliopoulos T. Pancreatitis and myocarditis coexistence due to infection by Coxsackie B1 and B4 viruses. *Clinical Case Reports*. 2017; 6(1):23-6. (Case Report)

8. Li Z, Yang B, Weng X, Tse G, Chan M, Wu W. Emerging roles of MicroRNAs in osteonecrosis of the femoral head. *Cell Proliferation*. 2017; 51(1):e12405. (Review)

9. Li Z, Li X, Jiang C, Qian W, Tse G, Chan M, Wu W. Long non-coding RNAs in rheumatoid arthritis. *Cell Proliferation*. 2017; 51(1):e12404. (Review)

10. Ho J, He W, Chan M, Tse G, Liu T, Wong S, Leung C, Wong W, Tsang S, Zhang L, Chan R, Gin T, Leung J, Lau B, Wu W, Ngai S. Eosinophilia and clinical outcome of chronic obstructive pulmonary disease: a meta-analysis. *Scientific Reports*. 2017; 7(1):13451.

11. Letsas K, Asvestas D, Baranchuk A, Liu T, Georgopoulos S, Efremidis M, Korantzopoulos P, Bazoukis G, Tse G, Sideris A, Takagi M, Ehrlich J. Prognosis, risk stratification, and management of asymptomatic individuals with Brugada syndrome: A systematic review. *Pacing and Clinical Electrophysiology*. 2017; 40(12):1332-45. (Review)

12. Lampropoulos K, Giannoulis E, Bazoukis G, Tse G, Triantafyllou E, Triantafyllou A. Reversible Stress Cardiomyopathy Secondary to Aneurysmal Subarachnoid Hemorrhage: A Case Report. *The Journal of Emergency Medicine*. 2017; 53(6):e129-31. (Clinical Communications)

13. Suo Y, Zhang Y, Wang Y, Yuan M, Kariyawasam S, Tse G, Liu T, Fu H, Li G. Renin–angiotensin system inhibition is associated with reduced risk of left atrial appendage thrombosis formation in patients with atrial fibrillation. *Cardiology Journal*. 2017. [Epub ahead of print]



14. Sun M, Feng W, Wang F, Li P, Li Z, Li M, Tse G, Vlaanderen J, Vermeulen R, Tse L. Meta-analysis on shift work and risks of specific obesity types. *Obesity Reviews*. 2017;19(1):28-40.

15. Meng L, Letsas K, Baranchuk A, Shao Q, Tse G, Zhang N, Zhang Z, Hu D, Li G, Liu T. Meta-analysis of Fragmented QRS as an Electrocardiographic Predictor for Arrhythmic Events in Patients with Brugada Syndrome. *Frontiers in Physiology*. 2017; 8:678.

16. Ho J, Dai R, Kwong T, Wang X, Zhang L, Ip M, Chan R, Hawkey P, Lam K, Wong M, Tse G, Chan M, Chan F, Yu J, Ng S, Lee N, Wu J, Sung J, Wu W, Wong S. Disease Burden of *Clostridium difficile* Infections in Adults, Hong Kong, China, 2006–2014. *Emerging Infectious Diseases*. 2017; 23(10):1671-9.

17. Tse G, Liu T, Li G, Tak Wong W, Chin Pang Chan G, Chan Y, Yan B. Implantation of the Micra leadless pacemaker in a patient with a low body mass index of 16. *Oxford Medical Case Reports*. 2017; 2017(9):omx051. (Case Report)

18. Tse G, Gong M, Wong C, Chan C, Georgopoulos S, Chan Y, Yan B, Li G, Whittaker P, Ciobanu A, Ali-Hasan-Al-Saegh S, Wong S, Wu W, Bazoukis G, Lampropoulos K, Wong W, Tse L, Baranchuk A, Letsas K, Liu T. Total cosine R-to-T for predicting ventricular arrhythmic and mortality outcomes: A systematic review and meta-analysis. *Annals of Noninvasive Electrocardiology*. 2017; 23(2):e12495.

19. Tse G, Lip G, Liu T. The CHADS 2 and CHA 2 DS 2 -VASc scores for predicting healthcare utilization and outcomes: Observations on the Appropriate Use and Misuse of Risk scores. *International Journal of Cardiology*. 2017; 245:181-2.

20. Lampropoulos K, Megalou A, Bazoukis G, Tse G, Manolis A. Pre-loading therapy with statins in patients with angina and acute coronary syndromes undergoing PCI. *Journal of Interventional Cardiology*. 2017; 30(6):507-13.

21. Chen FM, Tse G, Ma S, Sayed N, Wong WT. Getting to the Heart of the Matter: A Perspective on Cardiomyocyte Biology. *Annals of Vascular Medicine and Research*. 2017; 4(5):1067. (Editorial)

22. Tse G, Liu T, Li G, Keung W, Yeo J, Chan Y, Yan B, Chan Y, Wong S, Li R, Zhao J, Wu W, Wong W. Effects of pharmacological gap junction and sodium channel blockade on S1S2 restitution properties in Langendorff-perfused mouse hearts. *Oncotarget*. 2017; 8(49): 85341-52.

23. He J, Tse G, Korantzopoulos P, Letsas K, Ali-Hasan-Al-Saegh S, Kamel H, Li G, Lip G, Liu T. P-Wave Indices and Risk of Ischemic Stroke. *Stroke*. 2017; 48(8):2066-72.

24. Liu C, Liu R, Fu H, Li J, Wang X, Cheng L, Korantzopoulos P, Tse G, Li G, Liu T. Pioglitazone attenuates atrial remodeling and vulnerability to atrial fibrillation in alloxan-induced diabetic rabbits. *Cardiovascular Therapeutics*. 2017; 35(5):e12284.

25. Zhang N, Liu T, Tse G, Yu S, Fu H, Xu G, Zhou C, Zhang C, Li G. Brugada phenocopy in a patient with acute pulmonary embolism presenting with recurrent syncope. *Oxford Medical Case Reports*. 2017; 2017(5):omx014. (Case Report)

26. Zhang N, Tse G, Liang X, Li G, Liu T. Telomere length: A newly marker for predicting atrial fibrillation?. *International Journal of Cardiology*. 2017; 239:21. (Letter)

27. Tse G, Gong M, Wong W, Georgopoulos S, Letsas K, Vassiliou V, Chan Y, Yan B, Wong S, Wu W, Ciobanu A, Li G, Shenthar J, Saguner A, Ali-Hasan-Al-Saegh S, Bhardwaj A, Sawant A, Whittaker P, Xia Y, Yan G, Liu T. The T peak – T end interval as an electrocardiographic risk marker of arrhythmic and mortality outcomes: A systematic review and meta-analysis. *Heart Rhythm*. 2017;14(8):1131-7.

28. Zhang X, Zhang Z, Zhao Y, Jiang N, Qiu J, Yang Y, Li J, Liang X, Wang X, Tse G, Li G, Liu T. Alogliptin, a Dipeptidyl Peptidase-4 Inhibitor, Alleviates Atrial Remodeling and Improves Mitochondrial Function and Biogenesis in Diabetic Rabbits. *Journal of the American Heart Association*. 2017; 6(5):e005945.

29. Weymann A, Ali-Hasan-Al-Saegh S, Sabashnikov A, Popov A, Mirhosseini S, Liu T, Lotfaliani M, Sá M, Baker W, Yavuz S, Zeriouh M, Jang J, Dehghan H, Meng L, Testa L, D\'Ascenzo F, Benedetto U, Tse G, Nombela-Franco L, Dohmen P, Deshmukh A, Linde C, Biondi-Zoccai G, Stone G, Calkins H, Surgery and Cardiology-Group [IMCSC-Group] I. Prediction of New-Onset and Recurrent Atrial Fibrillation by Complete Blood Count Tests: A Comprehensive Systematic Review with Meta-Analysis. *Medical Science Monitor Basic Research*. 2017; 23:179-222. (Meta-analysis)

30. Zhang Z, Zhang X, Korantzopoulos P, Letsas K, Tse G, Gong M, Meng L, Li G, Liu T. Thiazolidinedione use and atrial fibrillation in diabetic patients: a meta-analysis. *BMC Cardiovascular Disorders*. 2017; 17(1):96.

31. Qiu J, Zhao J, Li J, Liang X, Yang Y, Zhang Z, Zhang X, Fu H, Korantzopoulos P, Tse G, Liu T, Li G. Apocynin attenuates left ventricular remodeling in diabetic rabbits. *Oncotarget*. 2017; 8(24):38482-90.

32. Yan B, Chan C, Li C, To O, Lai W, Tse G, Poh Y, Poh M. Resting and Postexercise Heart Rate Detection From Fingertip and Facial Photoplethysmography Using a Smartphone Camera: A Validation Study. *JMIR Mhealth Uhealth*. 2017;5(3):e33.

33. Lee Y, Laxton V, Lin H, Chan Y, Fitzgerald-Smith S, To T, Yan B, Liu T, Tse G. Animal models of atherosclerosis. *Biomedical Reports*. 2017;6(3):259-66. (Review).

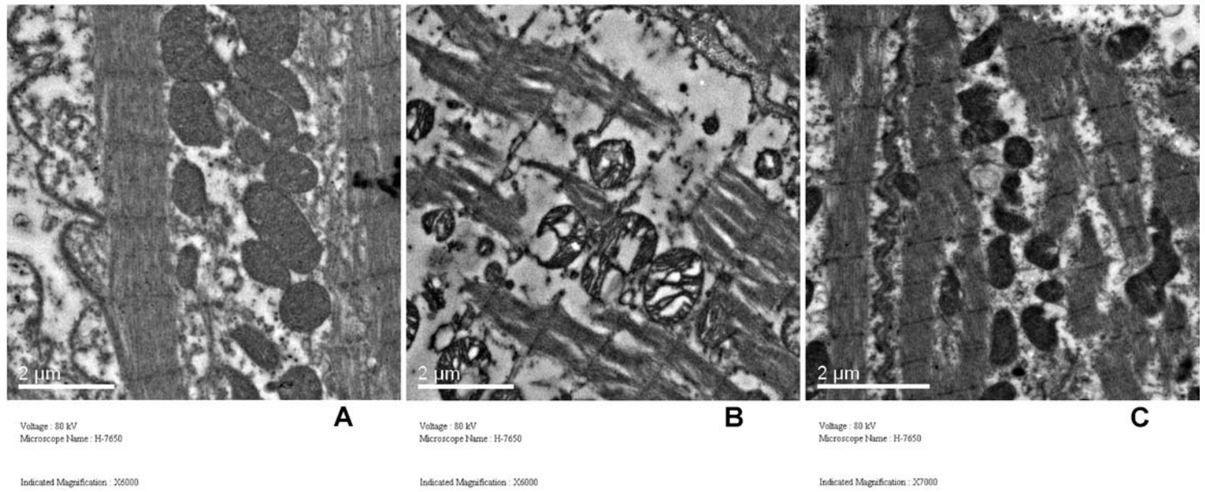
34. Qi W, Zhang N, Korantzopoulos P, Letsas K, Cheng M, Di F, Tse G, Liu T, Li G. Serum glycated hemoglobin level as a predictor of atrial fibrillation: A systematic review with meta-analysis and meta-regression. *PLoS ONE*. 2017;12(3):e0170955.

35. Tse G, Liu T, Li K, Laxton V, Wong A, Chan Y, Keung W, Chan C, Li R. Tachycardia-bradycardia syndrome: Electrophysiological mechanisms and future therapeutic approaches. *International Journal of Molecular Medicine*. 2017; 39(3):519-26. (Review)

36. Wong P, Laxton V, Srivastava S, Chan Y, Tse G. The role of gap junctions in inflammatory and neoplastic disorders. *International Journal of Molecular Medicine*. 2017; 39(3):498-506. (Review)

37. Lee Y, Lin H, Chan Y, Li K, To O, Yan B, Liu T, Li G, Wong W, Keung W, Tse G. Mouse models of atherosclerosis: a historical perspective and recent advances. *Lipids in Health and Diseases*. 2017; 16(1):12. (Review)






Comparison of left atrial ultrastructure among the 3 groups. (A) Control group; (B) diabetes mellitus group; (C) alogliptin-treated DM group.

Source: Zhang X, Zhang Z, Zhao Y, Jiang N, Qiu J, Yang Y, Li J, Liang X, Wang X, Tse G, Li G, Liu T. Alogliptin, a Dipeptidyl Peptidase-4 Inhibitor, Alleviates Atrial Remodeling and Improves Mitochondrial Function and Biogenesis in Diabetic Rabbits. *Journal of the American Heart Association*. 2017; 6(5):e005945. Doi: 10.1161/JAHA.117.005945

B. Conference Papers

1. Tse, G., Gong, M., Wong, S.H., Wu, W.K.K., Bazoukis, G., Lampropoulos, K., Wong, W.T., Xia, Y., Wong, M.C.S., Liu, T., Woo, J. (2017) Frailty and clinical outcomes in advanced heart failure patients undergoing left ventricular assist device implantation: a systematic review and meta-analysis. *American College of Cardiology Asia Pacific Congress 2017*.

2. Yang, Y., Zhao, J., Qiu, J., Li, J., Liang, X., Zhang, Z., Zhang, X., Fu, H., Korantzopoulos, P., Letsas, K., Tse, G., Li, G., Liu, T. (2017) Xanthine oxidase inhibitor allopurinol prevents oxidative stress-mediated atrial remodeling in alloxan-induced diabetes rabbits. *American College of Cardiology Asia Pacific Congress 2017*. Best Poster Award.

3. Meng, L., Qi, W., He, J., Tse, G., Korantzopoulos, P., Letsas, K.P., Li, G., Fragakis, N., Liu, T. (2017) Excessive supraventricular ectopic activity and adverse cardiovascular outcomes: a systematic review and meta-analysis.

4. Li, K.H.C, Kui, C., Lee, E.K.M., Chan, J., Wong, S.H., Wu, W.K.K., Wong, W.T., Li, G., Liu, T., Yan, B.P., Tse, G., Keenan, I. (2017) The role of 3D printing in medical education and training: A narrative review. Abstract accepted by *Anatomical Society 2017*.

5. Tse, G., Wong, R., Wong, P., Chow, T.Y., To, O.T.L., Chan, Y.S., Lee, P.W., Li, G., Wu, W.K.K., Wong, W.T., Liu, T., Lip, G.Y., Yan, B.P. (2017) Electrocardiographic evidence of atrial cardiomyopathy in mitral stenosis: a retrospective analysis in a Chinese cohort. Abstract accepted by *Asia Pacific Heart Rhythm Society 2017*.

6. Tse, G., Wong, W.T., Gong, M., Letsas, K., Chan, Y.S., Yan, B.P., Li, G., Whittaker, P., Xia, Y., Liu, T. (2017) Tpeak – Tend as an electrocardiographic risk marker of arrhythmic and mortality outcomes: a systematic review and meta-analysis. Abstract accepted by *Asia Pacific Heart Rhythm Society 2017*. Invited oral presentation.

7. Yan, B.P.Y., Chan, L.L.Y., Sun, W., Tse, G., To, O.T.L., Lee, V.W.Y., Freedman, B. (2017) Increased yield for repeated handheld ECG screening at 6-12 month intervals to detect atrial fibrillation during outpatient clinic reviews. Abstract accepted by *European Society of Cardiology Congress 2017*. *Best Poster Award*. *European Heart Journal*. 38(suppl_1) 1 August 2017, hx493.P6057. DOI: 10.1093/eurheartj/ehx493.P6057.

8. Yan, B.P.Y., Chan, C.K.Y., Tse, G., Wong, M.C.S, To, O.T.L., Lee, V.W.Y. (2017) How to bridge residual distance to target LDL-C in acute coronary syndrome after initial statin therapy? Abstract accepted by *European Society of Cardiology Congress 2017*. *European Heart Journal*. 38(suppl_1) 1 August 2017, ehx504.P3681. DOI: 10.1093/eurheartj/ehx504.P3681.

9. Yan, B.P.Y., Chan, C.K.Y., Tse, G., Wong, M.C.S, To, O.T.L., Lee, V.W.Y. (2017) A paradox of under-treatment of acute coronary syndrome patients with low baseline LDL-C <1.8mmol/L. Abstract accepted by *European Society of Cardiology Congress 2017*. *European Heart Journal*. 38(suppl_1) 1 August 2017, ehx504.P3679. DOI: 10.1093/eurheartj/ehx504.P3679.



10. Liu, T., Gong, M., Yang, Y., Li, H., Liang, X., Zhang, Z., Yuan, M., Zhang, Y., Jiao, Z., Tse, G., Li, G. (2017) Rapamycin attenuates atrial fibrosis in 5/6 nephrectomized rats by inhibiting mTOR and pro-fibrotic signaling. Abstract accepted by *European Society of Cardiology Congress 2017*. *European Heart Journal*. 38(suppl_1) 1 August 2017, ehx502.P2689. DOI: 10.1093/eurheartj/ehx502.P2689.

11. Liu, T., Meng, L., Qi, W., He, J., Tse, G., Korantzopoulos, P., Letsas, K.P., Li, G., Fragakis, N. (2017) Excessive supraventricular ectopic activity and adverse cardiovascular outcomes: a systematic review and meta-analysis. Abstract accepted by *European Society of Cardiology Congress 2017*. *European Heart Journal*. 38(suppl_1) 1 August 2017, ehx501.P781. DOI: 10.1093/eurheartj/ehx501.P781.

12. Liu, T., Yuan, M., Zhang, Z., Tse, G., Feng, X., Korantzopoulos, P., Li, G., Xia, Y. (2017) Cancer and Risk of Atrial Fibrillation: a Systematic Review and Meta-analysis. Abstract accepted by *European Society of Cardiology Congress 2017*. *European Heart Journal*. 38(suppl_1) 1 August 2017, ehx504.P4618. DOI: 10.1093/eurheartj/ehx504.P4618.

13. Liu, T., Zhang, X., Zhang, Z., Zhao, Y., Jiang, N., Qiu, J., Yang, Y., Li, J., Liang, X., Wang, X., Tse, G., Li, G. (2017) Alogliptin, a DPP-4 Inhibitor, Alleviates Atrial Remodeling and Improves Mitochondrial Function and Biogenesis in Diabetic Rabbits. Abstract accepted by *European Society of Cardiology Congress 2017*. *European Heart Journal*. 38(suppl_1) 1 August 2017, ehx504.P3564. DOI: 10.1093/eurheartj/ehx504.P3564.

14. Li, K.H., Gong, M., Wong, W.T., To, O.T.L., Chan, Y.S., Yan, B.P., Li, G., Wong, S.H., Wu, W.K.K., Liu, T., Tse, G.* (2017) Tpeak – Tend for risk stratification in heart failure: a meta-analysis. Abstract accepted by the *European Society of Cardiology Congress 2017*. *European Heart Journal*. 38(suppl_1) 1 August 2017, ehx502.P1480. DOI: 10.1093/eurheartj/ehx502.P1480.

15. Tse, G., Gong, M., Wong, W.T., Letsas, K., Vassiliou, V.S., To, O.T.L., Chan, Y.S., Yan, B.P., Li, G., Whittaker, P., Wu, W.K.K., Xia, Y., Yan, G.X., Lui, K.O., Liu, T. (2017) Tpeak – Tend/QT ratio for arrhythmic risk stratification: a meta-analysis. Abstract accepted by *European Society of Cardiology Congress 2017*. *European Heart Journal*. 38(suppl_1) 1 August 2017, ehx493.P5338. DOI: 10.1093/eurheartj/ehx493.P5338.

16. Li, K.H., Gong, M., Li, G., Wong, W.T., Whittaker, P., Li, G., Liu, T., Tse, G. (2017) Tpeak-Tend for arrhythmic or mortality risk stratification in myocardial infarction: a meta-analysis. Abstract presented at the *Newcastle University Conference 2017*.

17. Tse, G., Gong, M., Chan, C., Chan, Y.S., Yan., B.P., Li, G., Whittaker, P., Wong, S.H., Lui, K.O., Wu, W.K.K., Wong, W.T., Liu, T. (2017) Total cosine R-to-T for predicting ventricular arrhythmic and mortality outcomes: a systematic review and meta-analysis. Abstract accepted by *EHRA EUROPACE - CARDIOSTIM 2017*. Europace (2017) 19 (suppl_3): iii193. DOI: https://doi.org/10.1093/ehjci/eux151.127.

18. Tse, G., Wong, W.T., Gong, M., Letsas, K., Chan, Y.S., Yan, B.P., Li, G., Whittaker, P., Xia, Y., Liu, T. (2017) Tpeak – Tend interval and arrhythmic outcomes in Brugada syndrome: a meta-analysis. Poster accepted by *Heart Rhythm Congress 2017*. Poster pubulished in *Heart Rhythm*; 14 (5) Supplement S1-S668. DOI: http://dx.doi.org/10.1016/j.hrthm.2017.04.011.

19. Tse, G., Tian, X.Y., Huang, Y., Wong, W.T. (2017) The direct renin inhibitor aliskiren prevents endothelial dysfunction in spontaneously hypertensive rat aortas. Abstract accepted by the *American Heart Association Arteriosclerosis Thrombosis and Vascular Biology Meeting May 2017* and published in *Arteriosclerosis Thrombosis and Vascular Biology* 37:A253.

20. Tse, G., Gong, M., Wong, W.T., Letsas, K., Chan, Y.S., Yan, B.P., Li, G., Whittaker, P., Xia, Y., Liu, T. (2017) The value of the Tpeak – Tend interval in predicting arrhythmic or mortality outcomes in the general population: a meta-analysis. Oral presentation at the *European Cardiac Arrhythmia Society Congress 2017*. Abstract published in J Interv Card Electrophysiol (2017) 48 (Suppl 1):S1–S134. PMID: 28286908. DOI 10.1007/s10840-017-0231-0.

21. Tse, G., Tian, X.Y., Huang, Y., Wong, W.T. (2017) The direct renin inhibitor aliskiren protects against impaired endothelium-dependent relaxation in aortas of spontaneously hypertensive rats. Abstract/Poster accepted by *Gordon Oxidative Stress 2017*.

22. Tse, G.*, Wong, W.T., Letsas, K.P., Chan, Y.S., To, T.L., Li, G., Yan, B.P., Liu, T. (2017) Comparisons of extrasystolic and dynamic pacing methods for the assessment of action potential restitution in an mouse model of acquired long QT syndrome. Abstract/Poster accepted by *Gordon Cardiac Arrhythmia Mechanisms Conference 2017*



C. Invited Interviews or Lectures

1. **Stem cells and 3D printing for treating cardiac diseases (30th December 2017)**
*Invited Interview by Cable TV, Hong Kong. 有線新聞部採訪邀請: 至fit男女.*

2. **Prognostic value of frailty indices in advanced heart failure patients undergoing left ventricular assist device (LVAD) implantation (3rd to 5th November 2017)**
*Invited International Faculty Speaker by the Organizing Committee for the 8th Chinese Heart Failure Symposium 2017*
*(第八届中国心力衰竭论坛). Dalian, PRC.*

3. **Electrocardiographic indices for arrhythmogenesis: what do we know? (17th July 2017)**
*Invited Guest Speaker by the Tianjin Institute of Cardiology, Tianjin Medical University, China.*

4. **Mechanisms of cardiac arrhythmias: insights from pre-clinical models (14th to 16th July 2017)**
*Invited Faculty Speaker for the 13th Annual Haihe Conference on Cardiovascular Diseases (第十三屆海河之濱心臟病學會議) organised by the Tianjin Institute of Cardiology, Tianjin Medical University, China.*

5. **Modelling Arrhythmias (February 2017)**
*Invited Faculty Speaker by the Organizing Committee of the Inaugural Symposium on "Reparative Medicine and Beyond" at the Ming Wai Lau Centre for Reparative Medicine, Karolinska Institutet.*

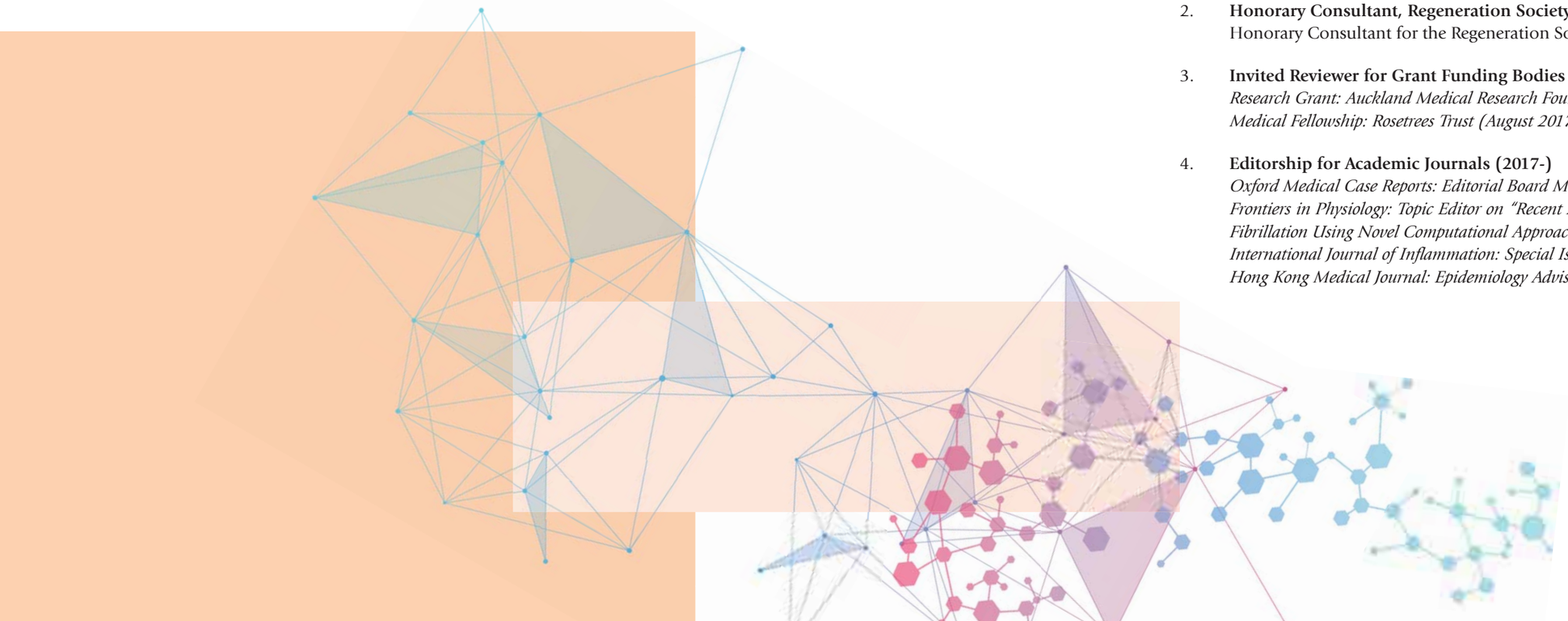
D. Academic and Professional Activities

1. **Co-Organizer, NSFC/RGC Conference: Cardiovascular Calcium Signalling Pathway: Role in Health and Disease (December 2017)**
Conference co-organizer for a two-day conference on Calcium Signalling.

2. **Honorary Consultant, Regeneration Society of Hong Kong (2017-)**
Honorary Consultant for the Regeneration Society of Hong Kong (香港再生會)

3. **Invited Reviewer for Grant Funding Bodies (2017-)**
*Research Grant: Auckland Medical Research Foundation, New Zealand (Sept 2017-)*
*Medical Fellowship: Rosetrees Trust (August 2017-)*

4. **Editorship for Academic Journals (2017-)**
*Oxford Medical Case Reports: Editorial Board Member*
*Frontiers in Physiology: Topic Editor on "Recent Advances in Understanding the Basic Mechanisms of Atrial Fibrillation Using Novel Computational Approaches"*
*International Journal of Inflammation: Special Issue Editor on "Cardiac Arrhythmias"*
*Hong Kong Medical Journal: Epidemiology Advisor*



# 06
# DIABETES AND OBESITY

## Principal Investigator

Professor Juliana Chan (Chair Professor, Department of Medicine and Therapeutics; Director, Hong Kong Institute of Diabetes and Obesity, CUHK)

## Team

Ronald CW Ma, Alice PS Kong, Andrea Luk, Wing Yee So, Risa Ozaki, Kitty Cheung, Elaine Chow, Katie Chan, Cadmon Lim, Heung Man Lee, Claudia Tam, Guozhi Jiang, Grace Cheung, Hou Yong, Ming C Leung, Kwun Kiu Wong, Fangying Xie, Noel Ng, Wei Wei Zeng, Lorena TF Cheung, Lee Ling Lim, Baoqi Fan, Ming Xing, Annie Fung, Phil Xie, Eric Lau, Bryan Ng, Kevin Wong

## Research Progress Summary

The team's ongoing Theme-based Research Scheme (TRS) where they use a multi-omic approach to discover a molecular signature of cardiovascular-renal complications in diabetes, they have completed genotyping of 7,003 DNA samples with detailed clinical information from the Hong Kong Diabetes Register (HKDR). The team has collaborated with Illumina and developed a customised version of a whole-genome genotyping array consisting of their top signals for rapid replication in another 7,000 samples from the Hong Kong Diabetes Biobank (HKBB) established through a network of Diabetes Centres and Renal Units in Hong Kong. By hosting this comprehensive genotype-phenotype dataset on diabetes complications consisting of more than 20,000 samples established since 1995, they are now leading the discovery and replication of their genome-wide association studies (GWAS) signals for diabetic kidney disease (DKD) through collaborations with top international groups. Supported by two major grants from the Australian National Health and Medical Research Council (NHMRC), the team is working closely with scientists from Monash University to study the epigenetic regulation of coronary heart disease as well as scientists from University of Sydney



to validate novel biomarkers in diabetic heart disease suing the samples from the landmark FIELD Study. They have now completed methylation analysis in 1,400 individuals using the Illumina methylation array. Working with collaborators from the Wellcome Trust Centre for Human Genetics in Oxford and Monash University, they have developed a new method for adjusting confounding due to cell sub-populations in the methylation data to overcome potential inter-ethnic differences in such distribution. They have completed analysis of miRNA microarray data from 96 samples and discovered novel miRNA associated with diabetic complications for further validation in their prospective HKDR cohorts using RT-PCR. Working with the team's nephrologists, they have used RNA-sequencing to survey gene expression changes in both diabetic and non-diabetic renal biopsies. Collectively, these multiomic data will form the basis for pathway-based analyses for discovery of common signals shared by these molecular signatures.





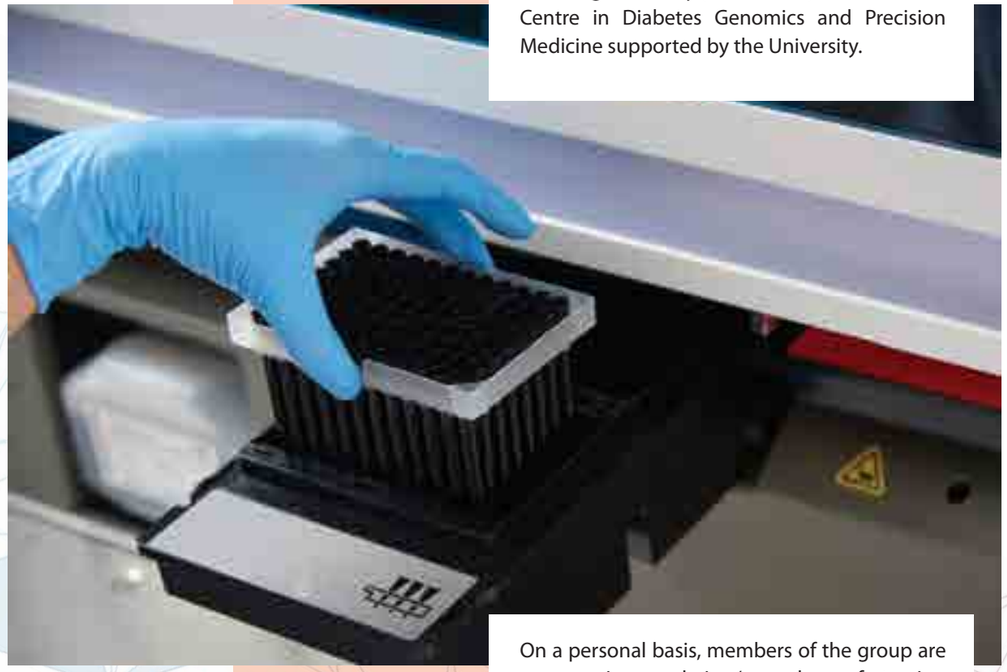
Their genomic discoveries continue to provide insights to their basic scientists in their efforts to unravel the mechanisms of diabetic complications with focus on the PPARδ and TGF-beta/Smad3-dependent pathways using cell lines and transgenic animals. These collaborative works have contributed to the awards of several research grants to their basic scientists for discovering novel therapies for these drug targets. In collaboration with their gynaecologists and obstetricians, they are now the leading group in Asia to use multiomic analysis to study the genetics of gestational diabetes and its impact on the health of offspring, supported by a major NIH grant. In a unique mother-offspring cohort followed up for over 20 years, they have discovered novel epigenetic signatures associated with gestational diabetes and adolescent obesity, which are now being validated in independent cohorts by their overseas collaborators.

In their ongoing epidemiological analysis, they have confirmed the high progression rate to diabetes in women with polycystic ovary syndrome (PCOS) and siblings of young-onset diabetes in whom they have also commenced genetic analysis. Together with their discovery of the high prevalence of auto-antibodies and low C peptide levels in the patients with young-onset diabetes, these data point to the urgency of conducting research to close the knowledge and care gaps in these young individuals who face long disease duration. From a mechanistic perspective, abnormal beta-cell biology is the main defect implicated in diabetes with glucotoxicity and oxidative stress as the mediating pathways. Having demonstrated the deleterious effects of silencing Sirtuin 3 (Sirt3) on beta-cell function in transgenic animals, they are now breeding the pancreatic-specific Sirt3 floxed mice in their laboratory to extend these observations. In a similar vein, the team has established a virus-induced cancer animal model and confirmed the differential effects of different blood glucose lowering drugs on cancer growth. Multiomic analysis of tumours treated with different drugs revealed novel druggable pathways implicated in cancer which are being validated in transgenic cell lines. Supported by both the Innovation Technology Committee and Health and Medical Research Fund, they are now using their biobanks and GWAS data to discover novel markers including miRNA and their association with different types of cancer.



Through these large numbers of projects, the team has trained no fewer than 20 MPhil/PhD students under the supervision of multiple investigators. Based on these research findings and working closely with the Phase 1 Clinical Trial Centre and other industrial partners, they are developing new proposals and translational projects to evaluate novel drugs / devices as well as use validated risk engines and biogenetic markers to personalise care.

These academic outputs have been commended and recognised by the RGC External Reviewers of their TRS project, selection of their submission entitled: 'Transforming delivery of diabetes care – from research to practice to policy' by the Faculty as one of the impact stories during the recent mock UGC Research Assessment Exercise with grading of 'outstanding / considerable reach and significance' by both internal and external reviewers and the establishment of the Chinese University of Hong Kong – Shanghai Jiao Tong University (CUHK-SJTU) Joint Research Centre in Diabetes Genomics and Precision Medicine supported by the University.



On a personal basis, members of the group are now serving as chairs / members of steering committees or working groups of local and international projects on the prevention and control of non-communicable disease including those convened by the Hong Kong Government and World Health Organization as well as landmark cardiovascular outcome trials in the field of diabetes and cardiovascular diseases.

## Recognitions

Awards and Fellowships

| Member's Full Name | Details |
|---|---|
| Juliana Chan<br>Ronald Ma | Received Support from the University for establishing The Chinese University of Hong Kong – Shanghai Jiao Tong University (CUHK-SJTU) Joint Research Centre in Diabetes Genomics and Precision Medicine |
| Juliana Chan | Submission of 'Transforming Delivery Of Diabetes Care – From Research To Practice To Policy' was selected as an impact story by the Faculty with grading of 'Outstanding or very considerable impacts in terms of their reach and significance' by both external and internal reviewers |
| Juliana Chan | Member, Food and Health Bureau – Hong Kong Government Steering Committee on the Prevention and Control of Noncommunicable Disease |
| Juliana Chan | Member, Food and Health Bureau – Working Group Underpinning the Hong Kong Government Steering Committee on the Prevention and Control of Noncommunicable Disease |
| Ronald Ma | Chair, Food and Health Bureau – Working Group on Lowering Content of Salt and Sugar in Food (WG) of the Committee on Reduction of Salt and Sugar in Food (CRSS) |
| Ronald Ma | Member, Committee on Reduction of Salt and Sugar in Food, Food and Health Bureau, Government Secretariat, The Government of the Hong Kong Special Administrative Region, The People's Republic of China |
| Ronald Ma | Member, World Health Organization (WHO) Ad Hoc Working Group on Science and Evidence for Ending Childhood Obesity |
| Ronald Ma | Co-chair, International Federation of Gynaecology and Obstetrics (FIGO) Expert Group on Adolescent, Pre-conception and Maternal Nutrition |
| Ronald Ma | Hong Kong Hospital Authority Central Committee (CC) on Genetic Services |
| Ronald Ma | Honorary Professor, NHMRC Clinical Trials Centre, University of Sydney, Australia |
| Alice Kong | Member, Food and Health Bureau – Working Group on Lowering Content of Salt and Sugar in Food (WG) of the Committee on Reduction of Salt and Sugar in Food (CRSS) |
| Alice Kong | Travel grant for oral presentation in Joint Scientific Meeting of the Asia – Oceania Association for the Study of Obesity (AOASO), Australian and New Zealand Obesity Society (ANZOS) and Obesity Surgery Society of Australia and New Zealand (OSSANZ) held on 4-6 October 2017 at Adelaide, Australia |
| Lorena Cheung | Travel grant from Hong Kong Society of Endocrinology, Metabolism and Reproduction (HKSEMR) for poster presentation in the Asia Association for the Study of Diabetes (AASD) held on 18-20 May 2017 at Nagoya, Japan |
| Lorena Cheung | Travel grant from Hong Kong Dietitian Association for poster presentation in the Food and Nutrition Conference and Expo held on 21-24 Oct 2017 at Chicago, USA |



| Member's Full Name | Details |
|---|---|
| Lorena Cheung | Travel grant for poster presentation in Joint Scientific Meeting of the Asia – Oceania Association for the Study of Obesity (AOASO), Australian and New Zealand Obesity Society (ANZOS) and Obesity Surgery Society of Australia and New Zealand (OSSANZ) held on 4-6 October 2017 at Adelaide, Australia |
| Chenzhao Ding | Scholarship "慈元堂" for oral presentation in 1st Interdisciplinary Behavioural Health Conference: Opportunities and Challenges held on 16-19 November 2017 at Changsha, Hunan, China |
| Chenzhao Ding | Travel grant for oral presentation in 15th Symposium of the International Diabetes Epidemiology Group (IDEG) 2017 held on 8-11 December 2017 at Abu Dhabi, UAE |
| Lee Ling Lim | Travel grant for oral presentation in Joint Scientific Meeting of the Asia – Oceania Association for the Study of Obesity (AOASO), Australian and New Zealand Obesity Society (ANZOS) and Obesity Surgery Society of Australia and New Zealand (OSSANZ) held on 4-6 October 2017 at Adelaide, Australia |
| Lee Ling Lim | Travel grant from Hong Kong Society of Endocrinology, Metabolism and Reproduction (HKSEMR) for poster presentation in International Diabetes Federation World Diabetes Congress held on 4-8 December 2017 at Abu Dhabi, UAE |
| Lee Ling Lim | Travel grant for oral presentation in 15th Symposium of the International Diabetes Epidemiology Group (IDEG) 2017 held on 8-11 December 2017 at Abu Dhabi, UAE |
| Noel Yat Hey Ng | Best Oral Presentation "Progression of glucose intolerance and cardiometabolic risk factors in Chinese women with polycystic ovary syndrome compared to healthy controls" at the Hong Society for Endocrinology Metabolism and Reproduction 34th Annual Scientific Meeting on 12 November 2017 |



Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Elaine Chow Juliana Chan (co-PI) | Effectiveness and Safety Study of the Percutaneous Optical Fibre Glucose Sensor (FiberSense) for Home Use in Diabetic and Prediabetic Individuals | Powders Pharmaceutical Inc. | 01/10/2017 | 30/09/2018 | 2,422,000 |
| Alice Kong | Early Detection of Liver Cancer in Type 2 Diabetes Using Serum MicroRNA | Innovation and Technology Commission – Innovation and Technology Fund | 01/01/2017 | 30/06/2018 | 1,396,790 |
| Katie Chan | Genome Wide Association of Copy Number Variations in Epithelial Cancer in People with Diabetes | Food and Health Bureau – Health Medical and Research Fund | 01/04/2017 | 30/03/2018 | 622,586 |
| Lorena TF Cheung (PhD student) | Lifestyle Factors and Their Relationships with the Weight and Glycemic Control in Non-obese and Obese Hong Kong Chinese Type 2 Diabetic Patients | Hong Kong Association for the Study of Obesity Research Grant | 01/01/2017 | 31/12/2018 | 50,000 |
| Lee Ling Lim (PhD student) | Association Between mTOR Genetic Polymorphism, Branched Chain Amino Acids and Body Mass Index in Chinese Patients with Type 2 Diabetes | Hong Kong Association for the Study of Obesity Research Grant 2016 | 01/07/2017 | 30/06/2018 | 25,000 |



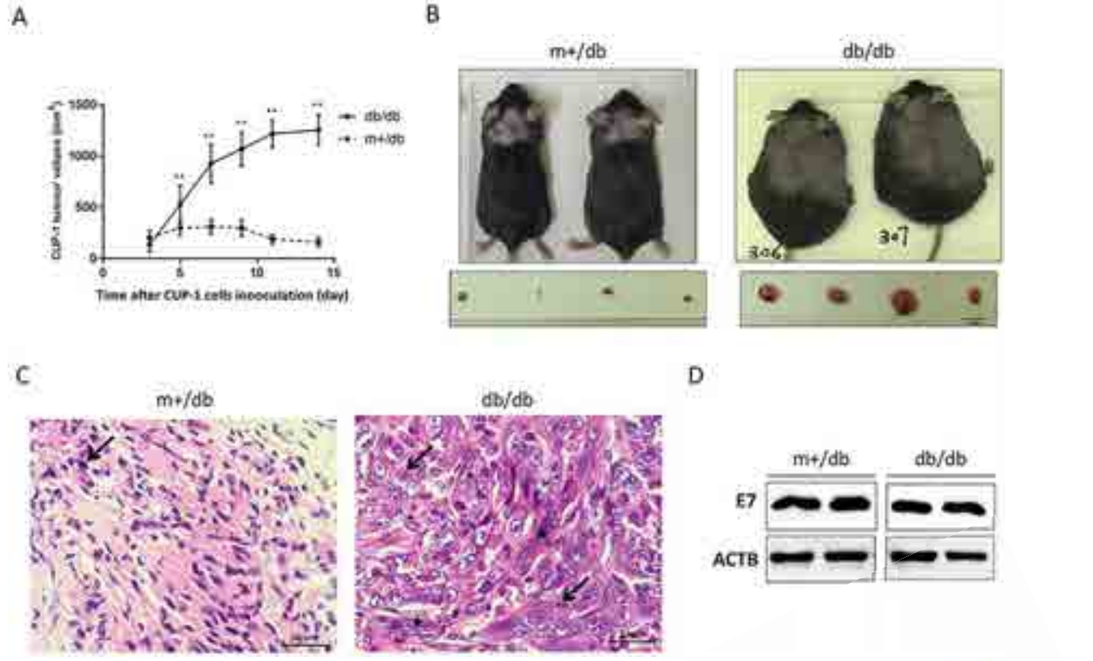
A series of diagrams showing the rapid growth of a tumour infected with a virus associated with cervical cancer in diabetic (db/db) and non-diabetic (m+/db) mice, confirming the promoting-effects of hyperglycemia on cancer growth.

Figure A shows the size of the tumour in diabetic (upper line) and non-diabetic mice (lower line).

Figure B shows the growth of the tumour on the back of the neck in non-diabetic (left panel) and diabetic (right panel) mice.

Figure C shows the large number of cancer cells in tumours from the diabetic (right panel) compared to non-diabetic mice (left panel).

Source: He L, Law PT, Boon SS, Zhang C, Ho WC, Banks L, Wong CK, Chan JC and Chan PK. Increased Growth of a Newly Established Mouse Epithelial Cell Line Transformed with HPV-16 E7 in Diabetic Mice. PLOS One. 2016;11:e0164490. Doi: 10.1371/journal.pone.0164490



## Publications

A. Journal Papers

1. Kong AP, Choi KC, Zhang J, Luk A, Lam SP, Chan MH, Ma RC, Chan JC, Wing YK. Curvilinear associations of sleep patterns during weekdays and weekends with glycemic control in type 2 diabetes: the Hong Kong Diabetes Registry. *Acta Diabetologica*. 2017; 54(2):151-62.

2. Cheung KK, Lau ES, So WY, Ma RC, Ozaki R, Kong AP, Chow FC, Chan JC, Luk AO. Low testosterone and clinical outcomes in Chinese men with type 2 diabetes mellitus – Hong Kong Diabetes Registry. *Diabetes Research and Clinical Practice*. 2017; 123:97-105.

3. Yeung MW, Wong GL, Choi KC, Luk AO, Kwok R, Shu SS, Chan AW, Lau ESH, Ma RC, Chan HL, Chan JC, Wong VW, Kong AP. Advanced liver fibrosis but not steatosis is independently associated with albuminuria in Chinese patients with type 2 diabetes. *Journal of Hepatology*. 2017; doi: 10.1016/j.jhep.2017.09.020. [Epub ahead of print]

4. Yang C, Kong AP, Cai Z, Chung AC. Persistent Organic Pollutants as Risk Factors for Obesity and Diabetes. *Current Diabetes Reports*. 2017; 17(12):132. (Review)

5. Luk AO, Lau ES, Cheung KK, Kong AP, Ma RC, Ozaki R, Chow FC, So WY, Chan JC. Gycaemic control and the risk of hospitalisation for infection in patients with type 2 diabetes: Hong Kong Diabetes Registry. *Diabetes – Metabolism Research and Reviews*. 2017; 33(8): doi: 10.1002/dmrr.2923. [Epub ahead of print]

6. Zhou Y, Chung AC, Fan R, Lee HM, Xu G, Tomlinson B, Chan JC, Kong AP. Sirt3 deficiency increased the vulnerability of the pancreatic beta cells to oxidative stress induced dysfunction. *Antioxidants and Redox Signaling*. 2017;27(13):962-76.

7. Zhang Y, Luk AO, Chow E, Ko GT, Chan MH, Ng M, Kong AP, Ma RC, Ozaki R, So WY, Chow CC, Chan JC. High risk of conversion to diabetes in first-degree relatives of individuals with young-onset type 2 diabetes: a 12-year follow-up analysis. *Diabetic Medicine*. 2017; 34(12):1701-9.

8. Ma RC, Cooper ME. Genetics of Diabetic Kidney Disease – From the worst of nightmares to the Light of Dawn? *Journal of the American Society of Nephrology*. 2017; 28: 389-99. (Editorial)

9. Fan B, Luk AO, Chan JC, Ma RC. MicroRNA and Diabetic Complications – a clinical perspective. *Antioxidants & Redox Signaling*. 2017; doi: 10.1089/ars.2017.7318 [Epub ahead of print] (Review)



10. Jason F, Fuchsberger C, Mahajan A, et al. Sequence data and association statistics from 12,940 type 2 diabetes cases and controls. *Scientific Data*. 2017; 4:170179.

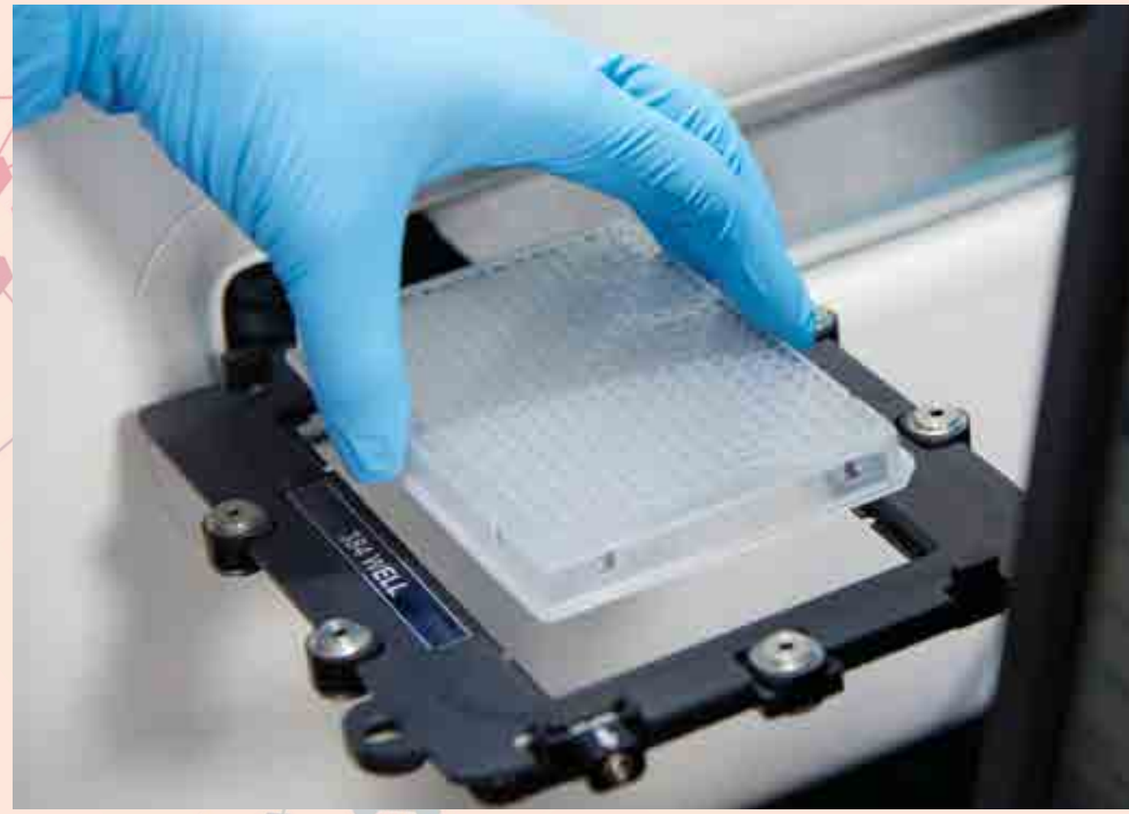
11. Ma RC, Popkin BM. Intergenerational diabetes and obesity – A cycle to break? *PLOS Medicine*. 2017; 14(10):e1002415. (Editorial)

12. Ma RC, Tsoi KY, Tam WH, Wong CK. Developmental origins of type 2 diabetes: a perspective from China. *European Journal of Clinical Nutrition*. 2017; 71(7):870-80. (Review)

13. Manning A, Highland HM, Gasser J, et al. A Low-Frequency Inactivating AKT2 Variant Enriched in the Finnish Population Is Associated With Fasting Insulin Levels and Type 2 Diabetes Risk. *Diabetes*. 2017; 66(7):2019-32.

14. Tam WH, Ma RC, Ozaki R, Li AM, Chan MH, Yuen LY, Lao TT, Yang X, Ho CS, Tutino GE, Chan JC. In Utero Exposure to Maternal Hyperglycemia Increases Childhood Cardiometabolic Risk in Offspring. *Diabetes Care*. 2017; 40(5):679-86.

15. He L, Law PT, Wong CK, Chan JC, Chan PK. Exendin-4 Exhibits Enhanced Anti-tumor Effects in Diabetic Mice. *Scientific Report*. 2017; 7(1):1791.



# 07
# EMERGING INFECTIOUS DISEASES

## Principal Investigator

Professor Shui Shan Lee

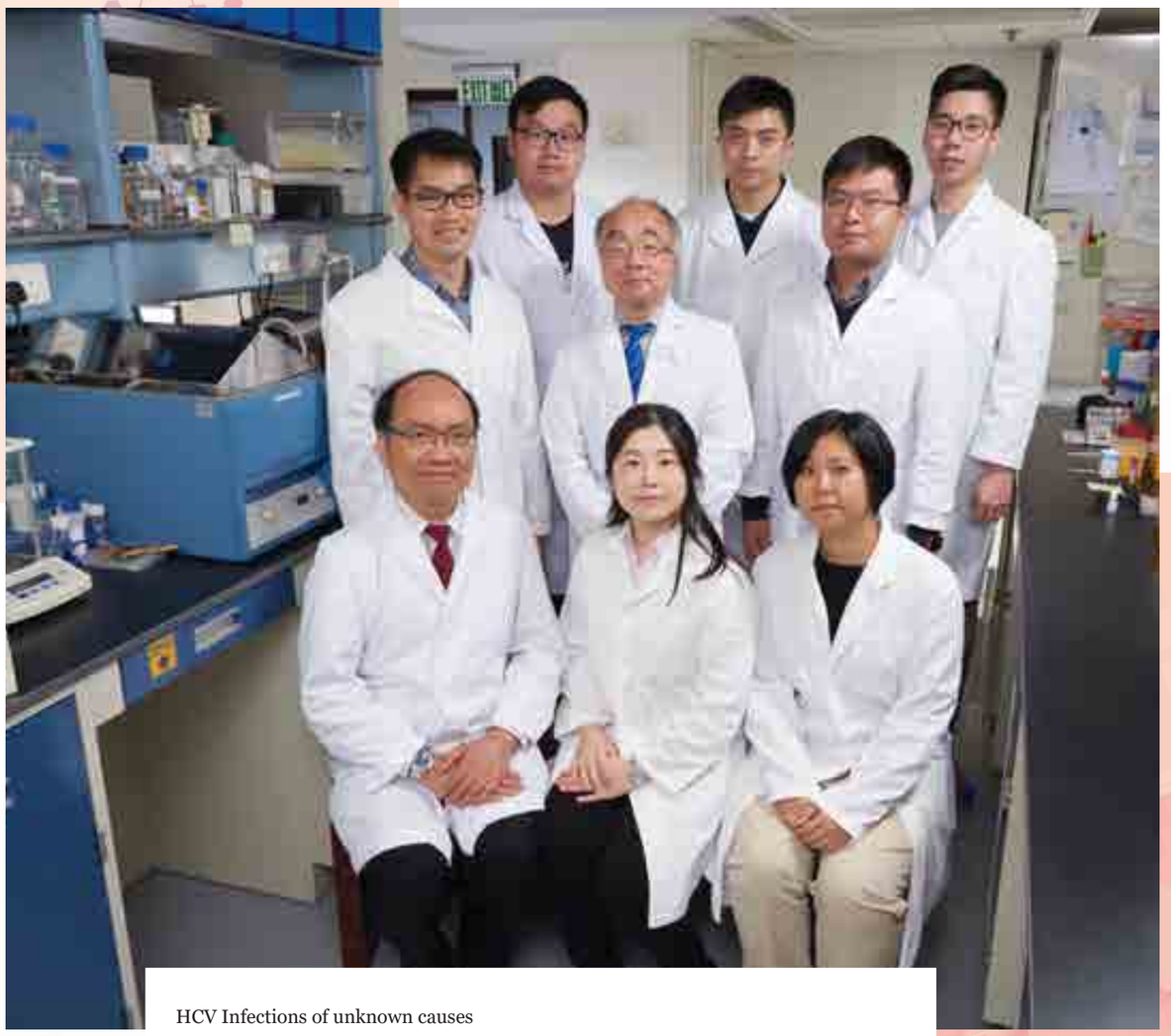
## Research Progress Summary

The main foci of the year were (a) emerging vector borne infections; (b) hepatitis C virus (HCV) infections of known cause; and (c) human immunodeficiency virus (HIV) treatment outcome.

### Emerging vector borne infections

The potential for Zika virus (ZIKV) to cause outbreaks remains an international concern. To characterise the intercontinental transmission of ZIKV, the team compiled and analysed more than 250 gene sequences together with their sequence-related geographic and temporal information, sampled across 27 countries spanning from 1947 to 2016. Although phylogeographic reconstruction supported the transmission route of the virus in Africa, South-eastern Asia, Oceania and Latin America, the team discovered that the Eastern Africa origin of ZIKV was disputable. On a molecular level, purifying selection was found to be responsible for the evolution of non-structural protein 5 and envelope protein E. Based on the estimation of the time of the most recent common ancestors for the non-structural protein 5 gene, the team hypothesised that potential historic events in the 1940s might have facilitated the spread of Zika virus from Africa to South-eastern Asia. Locally, dengue and chikunkunya continued to be periodically diagnosed though almost all were imported cases. In an attempt to estimate population risks, the team tested 3,827 healthy adults for IgG against dengue virus (DENV), of whom 86 of them (2.25%) gave a positive result. Neither ovitrap index nor residence location was associated with DENV serology. Sub-district level clustering was observed but no correlation could be confirmed with the residence location. The team could comfortably conclude that the cumulative exposure of Hong Kong residents to dengue has so far been low. For chikunkunya, RNA from 2 imported cases was extracted followed by phylogenetic analyses in conjunction with 471 complete CHIKV genomes from Genbank. The team could conclude that both imported cases belonged to the India Ocean Lineage (IOL), and indicated possible source from India.





### HCV Infections of unknown causes

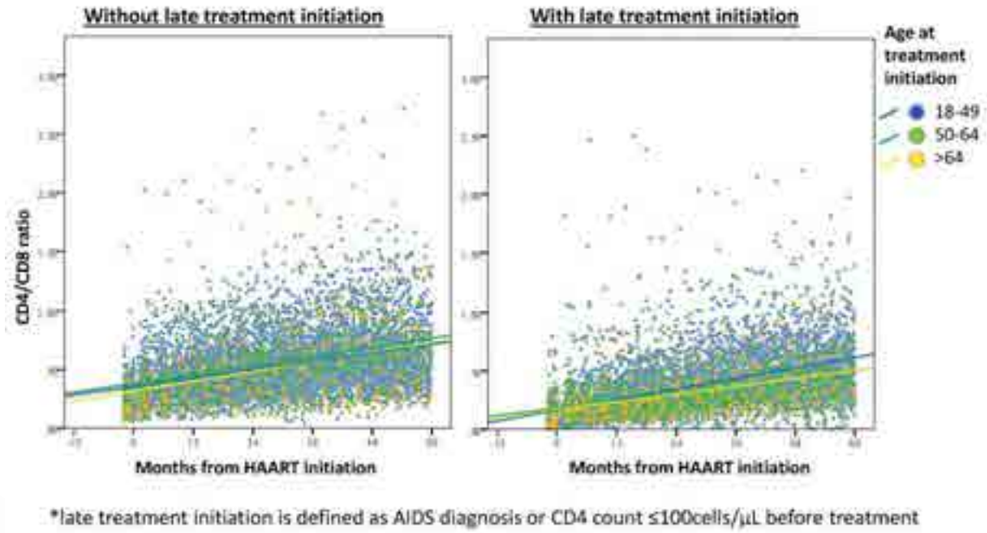
HCV has long been considered to be restricted to injection drug users and transfusion recipients. Its occurrence in otherwise healthy adults without identifiable route of transmission is a cause for concern. In collaboration with the Hong Kong Red Cross Blood Transfusion Service, a mixed method study was conducted on 91 HCV infected donors (≤0.02% positive rate) diagnosed in 2014-2016, of whom 46 of them were recruited in a mixed method study to examine their transmission routes. Final result of this study was published in 2017. A majority (75%) of the recruited donors were ribonucleic acid positive, with the predominant subtypes being 1b and 6a. While the specific route of transmission cannot be established for each person, associations with multiple parenteral exposures outside Hong Kong were observed. World Health Organisation has advocated for the global elimination of HCV by 2030. With a high proportion of HCV infected persons who are unaware of their infections, HCV elimination could be hard to achieve.



## HIV treatment outcome

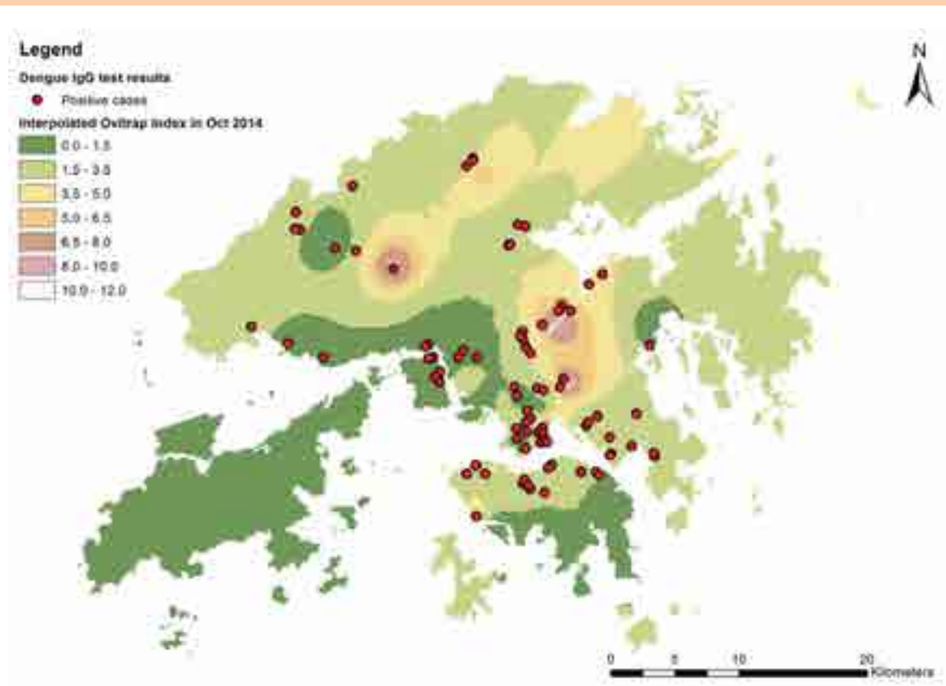
Antiretroviral therapy is currently the most important strategy for achieving control of the HIV epidemic on a global scale. To reduce morbidity and mortality, effective treatment outcomes are often set as targets to guide the programme development. In collaboration with all HIV treatment services in Hong Kong, a cohort has been established to assess treatment outcomes. In one study, the team proposed to define "optimal immune outcome" as a combination of a CD4 count ≥500/μL and a CD4/CD8 ratio ≥0.8. Of a total of 718 patients included for analysis (6353 person-years), less than half (318 out of 715) achieved CD4≥500/μL at the end of 4 years, of which only 33% (105 out of 318) concurrently achieved CD4/CD8 ratio ≥0.8. Cumulative viral load, the other experimental marker, played no significant role in affecting immune recovery. To examine the age effect, a separate study on 2754 patients was conducted, who were categorised by age at treatment initiation, viz., young adults (age 18-49), middle-aged (age 50-64) and elderly (≥65 years old). Late treatment initiation, defined as AIDS diagnosis or CD4 count ≤100cells/μL before treatment, was common in middle-aged and elderly, the former however had faster CD4 recovery (3.95 vs 3.36 cells/μL/month), but slower CD8 decline (-1.76 vs -4.34 cells/μL/month) and CD4/CD8 normalisation (0.009 vs 0.0101/month). As a transitional age group, the immune recovery of middle-aged patients was worrisome as it lagged behind young adults largely because of late treatment initiation.






Temporal analyses for illustrating changes of CD4/CD8 ratio following antiretroviral therapy and their variation with age and timing of treatment initiation in an HIV cohort study on immune recovery.

Source: Stanley Ho Centre for Emerging Infectious Diseases




Spatial analysis for examining the relationship between location of dengue virus IgG-positive cases (red dots) and interpolated ovitrap index by Inverse Distance Weighting (IDW)

Source: Stanley Ho Centre for Emerging Infectious Diseases

## Recognitions

Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| 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 | Exploration of the Harm Reduction Effects of Methadone Treatment in Hong Kong | Council for the AIDS Trust Fund | 01/07/2017 | 31/12/2018 | 462,326 |
| Denise Chan | An Exploratory Study of Pharmacologic Measure of Tenofovir Diphosphate and Emtricitabine Triphosphate in Dried Blood Spots as Adherence Testing for Monitoring Pre-exposure Prophylaxis | Council for the AIDS Trust Fund | 01/11/2017 | 30/10/2018 | 392,516 |
| 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 | 31/08/2018 | 343,368 |
| 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 | 31/05/2018 | 178,307 |





## Publications

A. Journal Papers

1. Yew WW, Leung CC, Zhang Y. Oxidative stress and TB outcomes in patients with diabetes mellitus? *Journal of Antimicrobial Chemotherary*. 2017; 72(6):1552-5.

2. Wong NS, Lee CK, Ng SC, Wong HK, Chan DPC, Lee SS. Prevalence of hepatitis C infection and its associated factors in healthy adults without identifiable route of transmission. *Journal of Viral Hepatitis*. 2018; 25:161-70. [Epub ahead of print]

3. Cheung EKH, Lee S, Lee SS. Pattern of exposure to information and its impacts on seasonal influenza vaccination uptake in nurses. *Journal of Hospital Infection*. 2017; 97(4): 376-83.

4. Ho DTW, Chan DPC, Lam CY, Liang DC, Lee SS, Kam JKM. At the advancing front of Chikungunya fever in Asia: Two imported cases in Hong Kong with novel amino acid changes. *Journal of Microbiology, Immunology and Infection*. 2017; doi: 10.1016/j.jmii.2017.08.006. [Epub ahead of print]

5. Kwan TH, Lee SS. Predictors of HIV Testing and Their Influence on PrEP Acceptance in Men Who Have Sex with Men: A Cross-Sectional Study. *AIDS and Behavior*. 2018; 22(4):1150-7. [Epub ahead of print]

6. Wong NS, Mao J, Cheng W, Tang W, Cohen MS, Tucker JD, Xu H. HIV linkage to care and retention in care rate among MSM in Guangzhou, China. *AIDS and Behavior*. 2018; 22(3):701-10. [Epub ahead of print]

7. Liang D, Leung RKK, Lee SS, Kam KM. Insights into intercontinental spread of Zika virus. *PLOS One*. 2017; 12(4):e0176710.

8. Wong NS, Tang W, Han L, Best J, Zhang Y, Huang S, Zheng H, Yang B, Wei C, Pan SW, Tucker JD. MSM HIV testing following an online testing intervention in China. *BMC Infectious Diseases*. 2017; 17(1):437. (Review)

9. Fung KH, Raghupathy R, Chan PD, Lui G, Lam CY, Cheung M, Chan AW, Lee N, Lee SS. HHV8 genotype study in an HIV+ patient with concurrent Kaposi sarcoma and extracavitary primary effusion lymphoma. *Journal of Clinical Pathology*. 2017; 70(9):814-6. (Correspondence)

10. Kwan TH, Lee SS, Chan DPC, Cheung M, Kam KM. Assessing the risk of dengue virus transmission in a non-endemic city surrounded by endemic and hyperendemic areas International. *International Journal of Infectious Diseases*. 2017; 55:99-101.

11. Lee SS, Wong N, Wong BCK, Wong KH, Chan KCW. Combining CD4 recovery and CD4: CD8 ratio restoration as an indicator for evaluating the outcome of continued antiretroviral therapy: an observational cohort study. *BMJ Open*. 2017; 7(9):e016886.

12. Lee SS, Cheung EK, Leung JN, Lee CK. Non-compliance to infectious disease deferral criteria among Hong Kong's blood donors. *Vox Sanguinis*. 2017; 112(5):425-33.

13. Lee SS, Newman RG. Methadone maintenance - lessons from two systems in China. *Harm Reduction Journal*. 2017; 14:66. [Epub ahead of print]

14. Wong NS, Chan KCW, Cheung EKH, Wong KH, Lee SS. Immune recovery of middle-aged HIV patients following antiretroviral therapy: An observational cohort study. *Medicine (Baltimore)*. 2017; 96(28):e7493.



B. Conference Papers

1. Kwan TH, Lee SS. HIV testing as the bridge between awareness and acceptance of PrEP among MSM. In: *2nd Asia Pacific AIDS and Co-infections Conference;* Hong Kong; 2017 Jun 1-3.

2. Cheung EKH, Lee SS, Leung JNS, Lee CK. Gender difference in compliance with self-deferral for blood donation on HIV-related risk. In: *2nd Asia Pacific AIDS and Co-infections Conference;* Hong Kong; 2017 Jun 1-3.

3. Kwan TH, Lee SS. Consideration regarding the service model on pre-exposure prophylaxis for men who have sex with men in the community. In: *2nd Asia Pacific AIDS and Co-infections Conference*; Hong Kong; 2017 Jun 1-3.

4. Poon CM, Wong NS, Kwan TH, Lee SS. Sex-networking patterns associated with regular HIV testing behaviour before diagnosis among HIV-positive men who have sex with men in Hong Kong. In: *2nd Asia Pacific AIDS and Co-infections Conference*; Hong Kong; 2017 Jun 1-3.



5. Kwan TH, Chan KCW, Tsang OTY, Lee MP, Lui GCY, Chan DPC, Lee SS. Predictors of short undiagnosed intervals after HIV infection in a cohort of newly diagnosed HIV patients. In: *2nd Asia Pacific AIDS and Co-infections Conference*; Hong Kong; 2017 Jun 1-3.

6. Wong NS, Chan KCW, Cheung EKH, Wong KH, Lee SS. Association between pre-treatment status and post-treatment immune recovery among Chinese HIV patients. In: *2nd Asia Pacific AIDS and Co-infections Conference*; Hong Kong; 2017 Jun 1-3.

7. Kwan CK, Chan DCP, Ho KM, Lee SS. Uncommon presentation of hepatitis C infection at Sexually Transmitted Infection clinic: a cross-sectional prevalence study. In: *2nd Asia Pacific AIDS and Co-infections Conference*; Hong Kong; 2017 Jun 1-3.

8. Chan DCP, Ho S, Lam JCY, Luo TY. Sexually Transmitted HCV infection in MSM in Hong Kong. In: *2nd Asia Pacific AIDS and Co-infections Conference*; Hong Kong; 2017 Jun 1-3.

9. Ng P, Chan DCP, Yew W, Lee SS. Study of Bedaquiline-Induced Cardiotoxicity in *in Vitro* and *Viro* Experimental Models, In: *The American Society for Microbiology (ASM) Microbe 2017*; USA; 2017 Jun 1-5.

10. Tam G, Chan DCP, Lee SS, Wong S, Yip B, Lee C, Ho F. Opt-out HIV testing in primary care setting. In: *9th IAS Conference on HIV Science*; France; 2017 Jul 23-26.

11. Kwan TH, Wong NS, Chan KCW, Tsang OTY, Lee MP, Chan DCP, Yam WC, Lee SS. Identification of rapid and emerging transmission clusters from genetic network. In: *9th IAS Conference on HIV Science*; France; 2017 Jul 23-26.

12. Kwan TH, Wong NS, Chan KCW, Tsang OTY, Lee MP, Chan DCP, Yam WC, Lee SS. Identification of rapid and emerging transmission clusters from genetic network. In: *12th International Workshop on HIV Transmission*; France; 2017 July 21-22.

13. Lee SS, Liang D, Chan CM, Lam CY, Wong CK, Chan DCP, Kam KM. Comparison between 12, 15 and 24 loci MIRU-VNTR Genotyping of Mycobacterium tuberculosis strains. In: *ISAAR & ICIC*; South Korea; 2017 Sep 14-16.

14. Wong NS, Chan KCW, Cheung EKH, Wong B, Lee SS.The varied rates of immune recovery of HIV patients on HAART by age category and their implications. In: *ISAAR & ICIC*; South Korea; 2017 Sep 14-16.

15. Kwan TH, Lee SS. Seasonality of sexual activities among men who have sex with men in Hong Kong. In: *INFECTION 2017*; Hong Kong; 2017 Sep 20.

16. Kwan TH, Wong NS, Chan KCW, Tsang OTY, Lee MP, Lui GCY, Chan DPC, Yam WC, Lee SS. Transmission network structure and newly diagnosed HIV infections: a molecular epidemiology study. In: *The Lancet-CAMS Health Summit*; Beijing, China; 2017 Dec 11-12.

17. Wong NS, Leung CC, Li Y, Poon CM, Yao S, Wong ELY, Lin C, Lau AKH, Lee SS. PM2.5 concentration and elderly tuberculosis: analysis of spatial and temporal associations. In: *The Lancet-CAMS Health Summit*; Beijing, China; 2017 Dec 11-12.

# 08

# MOLECULAR MICROBIOLOGY

*(Clinical Microbial Genomics)*

## Principal Investigator

Professor Guoping Zhao

## Team

Yu Ye, Wei Tan, Yuchen Wei

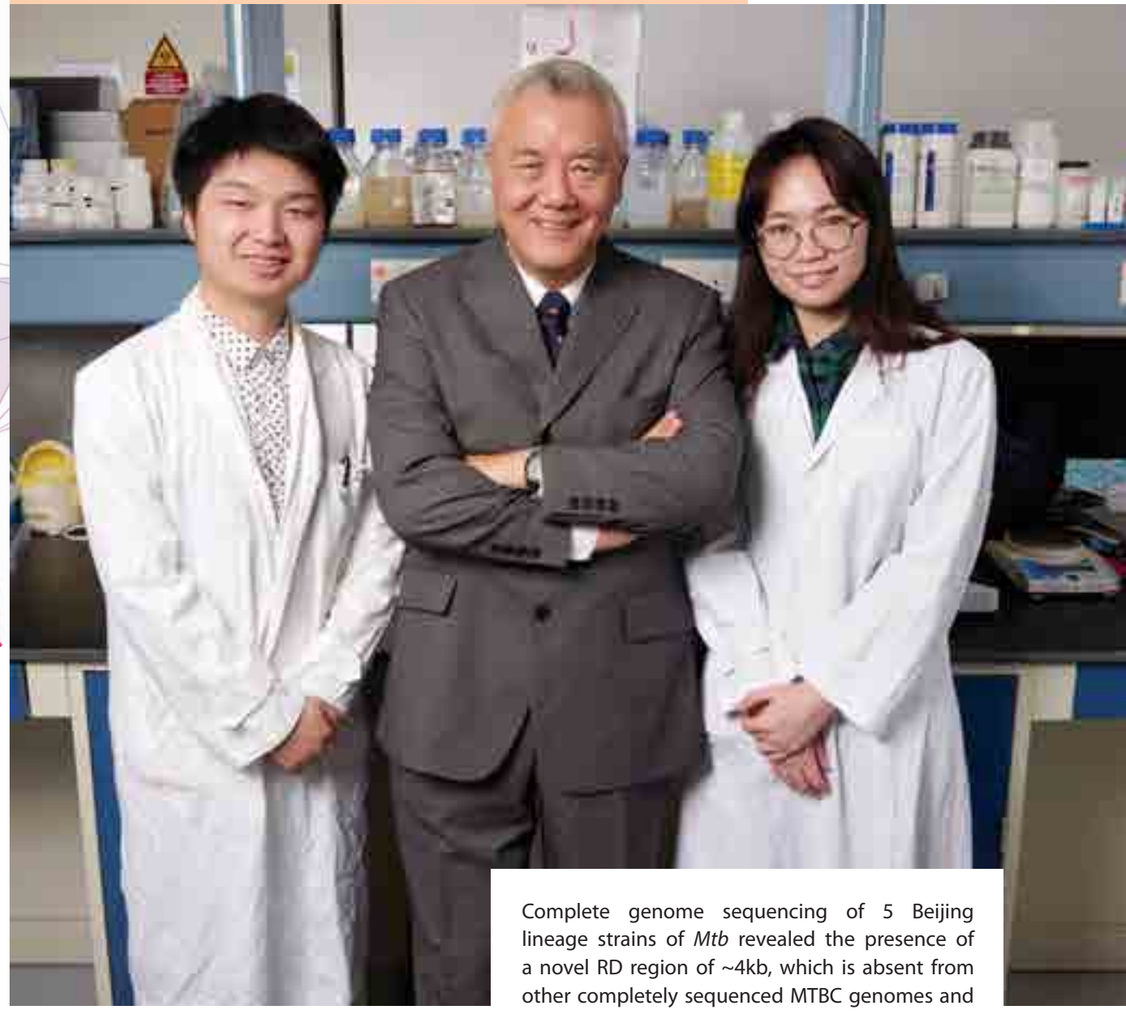
## Research Progress Summary

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

The research team led by Professor Guoping Zhao demonstrated that mycobacterial MazG is a 5-OH-dCTP-specific housecleaning enzyme involved in a pathway preventing the CG to TA mutation and ensuring the persistent infection of *Mtb* in mouse (*PLOS Pathog* 9: e1003814. 2013). The team's recent study showed that mycobacterial MazG potentiates 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) (revised to *PNAS*).

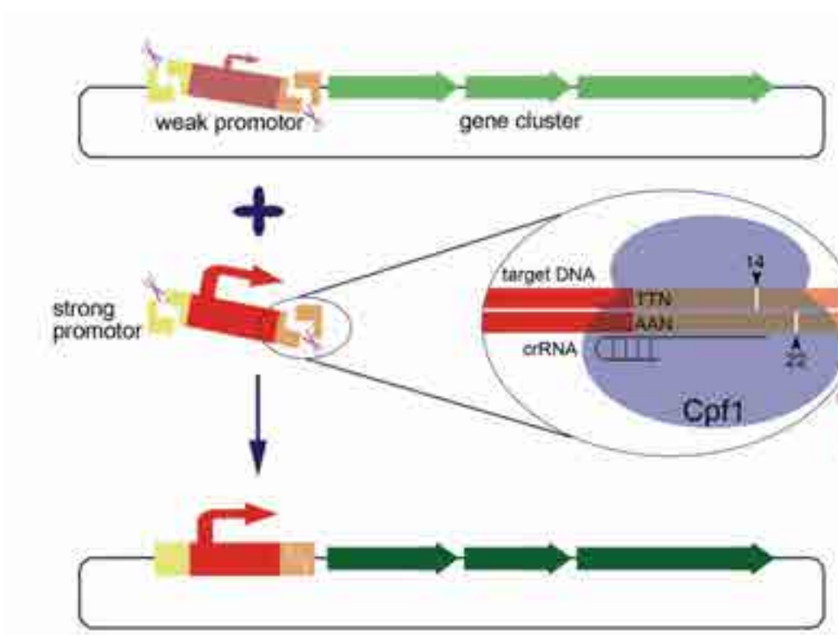
In order to understand the mechanism of persistence infection of *Mtb*, molybdenum cofactor (MoCo) biosynthesis genes, particularly, the characteristics of the multiple-copy genes, specially found in *Mtb* but different from that of *E. coli* or even *Mycobacterium smegmatis (Msm)*, have been under investigation. Interesting and novel discoveries have been observed via site-directed mutation experiments and corresponding biochemical and physiological mechanisms are being analysed.

In addition, aiming at understanding the critical survival mechanism of *Mtb* under hypoxia dormancy state, nitrate metabolism of both *Msm* and *Mtb* are studied via systematic comparison the related *Mtb* physiology against that of either physiologically phenocopied or genetically manipulated *Msm* models. Recent progresses were achieved in identification and characterisation of novel nitrate metabolism mechanisms in *Msm* besides the well studied NarGHJI-dependent nitrate assimilation system.



Complete genome sequencing of 5 Beijing lineage strains of *Mtb* revealed the presence of a novel RD region of ~4kb, which is absent from other completely sequenced MTBC genomes and designated M-NBjD1. Its potential impact in both physiology / pathology and evolutionary is under investigation. In order to facilitate the molecular manipulation of mycobacterial genomes, which has been the rate-limiting step for the research of the field, development of synthetic biology enabling technology, particularly the CRISPR/Cas9 related techniques, has been a new direction of the laboratory.




Schematic chart for substitution of the actII-orf4 promoter, employing Cpf1-assisted cleavage. A strong promoter was PCR amplified, containing the same flanking sequences as the actII-orf4 promoter. A pair of 17-nt spacer sequences were chosen nearby the promoter region, and both promoters were then cleaved by Cpf1 in vitro, followed by DNA ligation to form an engineered cluster.

Source: Lei C, Li SY, Liu JK, Zheng X, Zhao GP, Wang J. The CCTL (Cpf1-assisted Cutting and Taq DNA ligase-assisted Ligation) method for efficient editing of large DNA constructs in vitro. Nucleic Acids Research. 2017; 45(9):e74. Doi: 10.1093/nar/gkx018



## Recognitions

### Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Guoping Zhao | The molecular mechanism of GlnR-mediated global regulation of cellular metabolisms in actinomycetes | The National Natural Science Foundation of China | 01/01/2015 | 31/12/2019 | RMB 3,270,000 |
| Guoping Zhao | Characterisation of a novel nitrate reductase in *Mycobacterium smegmatis*, a model organism of *Mycobacterium tuberculosis* | The National Natural Science Foundation of China | 01/01/2017 | 31/12/2020 | RMB 800,000 |
| Guoping Zhao | Technical method of construction and stable heredity of artificial chromosome | Strategic Priority Research Program of the Chinese Academy of Sciences [No. XDB19040200] | 2016 | 2020 | |

## Publications

A. Journal Papers

1. Li C, Zhou L, Wang Y, Zhao GP, Ding XM. Conjugation of phi BT1-derived integrative plasmid pDZL802 in *Amycolatopsis mediterranei* U32. *Bioengineered*. 2017; 8(5):549-54.

2. Han XB, Shen LQ, Wang QJ, Cen XF, Wang J, Wu M, Li P, Zhao W, Zhang Y, Zhao GP. Cyclic AMP Inhibits the Activity and Promotes the Acetylation of Acetyl-CoA Synthetase through Competitive Binding to the ATP/AMP Pocket. *Journal of Biological Chemistry*. 2017; 292(4):1374-84.

3. Lei C, Li SY, Liu JK, Zheng X, Zhao GP, Wang J. The CCTL (Cpf1-assisted Cutting and Taq DNA ligase-assisted Ligation) method for efficient editing of large DNA constructs *in vitro*. *Nucleic Acids Research*. 2017; 45(9):e74.

4. Li C, Liu XQ, Lei C, Yan H, Shao ZH, Wang Y, Zhao GP, Wang J, Ding XM. Rif*Z*(AMED_0655) Is a Pathway-Specific Regulator for Rifamycin Biosynthesis in *Amycolatopsis mediterranei*. *Applied and Environmental Microbiology*. 2017; 83(8):e03201-16.

# 08

# MOLECULAR MICROBIOLOGY

*(Clinical Meta-genomics)*

## Principal Investigator

Professor Sunny Wong

## Team

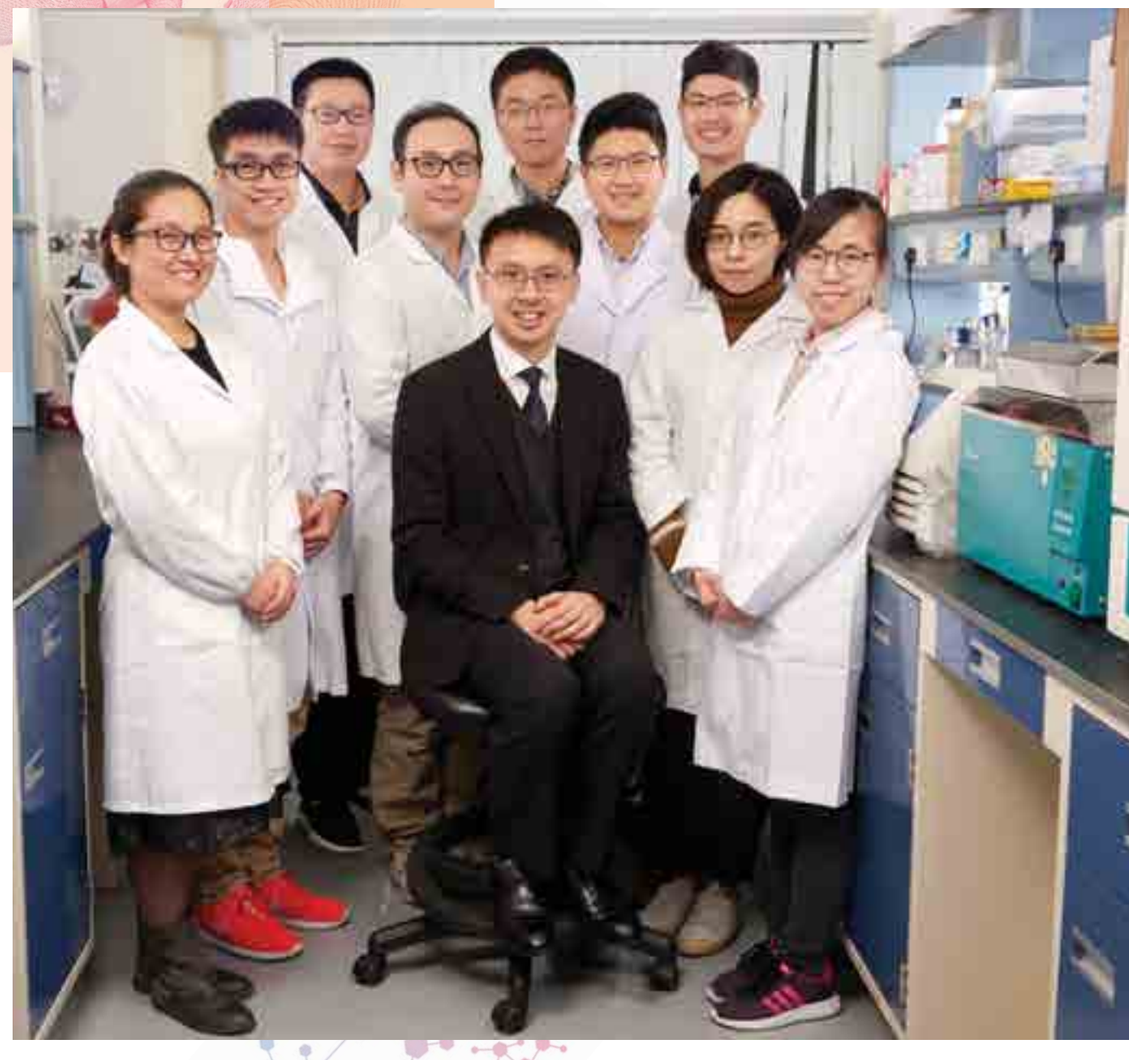
Thomas Kwong, Avis Shiu, Emily Kong, Kelvin Li

## Research Progress Summary

The human microbiota refers to the ecological community of microorganisms that inhabits the epithelial barrier including gastrointestinal tract. Harbouring trillions of bacteria, the gastrointestinal tract is lined by an epithelium maintained by a constant crosstalk between the gut microbiota, immunological cells and the mucosal barrier. Collectively, the entire microbial genome is about ~150 times larger than our own, providing a sizable functional repertoire for numerous physiological processes including digestion of food substances, energy harvest and metabolism, maturation of the immune system, and provision of colonisation resistance. Studies have found association between the gut microbiota and several diseases.

The major research focus of the research team is to understand the gut host-microbe relationships in context of diseases. Building upon their previous work, the research team led by Professor Sunny Wong has continued to study on the epidemiology and antibiotic resistance of *Clostridium difficile* in Hong Kong. Their work has revealed prevalent local *C difficile* ribotype strains and demonstrated their high resistance rates to several fluoroquinolones. These data inform the susceptibility patterns of these regionally prevalent ribotypes, and emphasise the need for continual surveillance on the disease. Apart from *C difficile*, they have also studied the gut microbiota in colorectal cancer. Building upon two previous sequencing studies to describe the metagenomic landscape in colorectal cancer, they have continued their work to demonstrate a causative role of gut microbiota on the cancer (Wong et al., *Gastroenterology* 2017). This work was highlighted in the editorial of *Gastroenterology* (Jobin C, *Gastroenterology* 2017), the top premier journal in the field. To further translate the work on colorectal cancer microbiota into clinical application, they have also evaluated the use of microbial marker as a diagnostic tool for colorectal neoplasia (Wong et al., *Gut* 2017). These works have brought them one step closer towards a non-invasive and more accurate diagnosis of advanced colorectal neoplasia. These works are only possible with the enormous support from the Li Ka Shing Institute of Health Sciences.



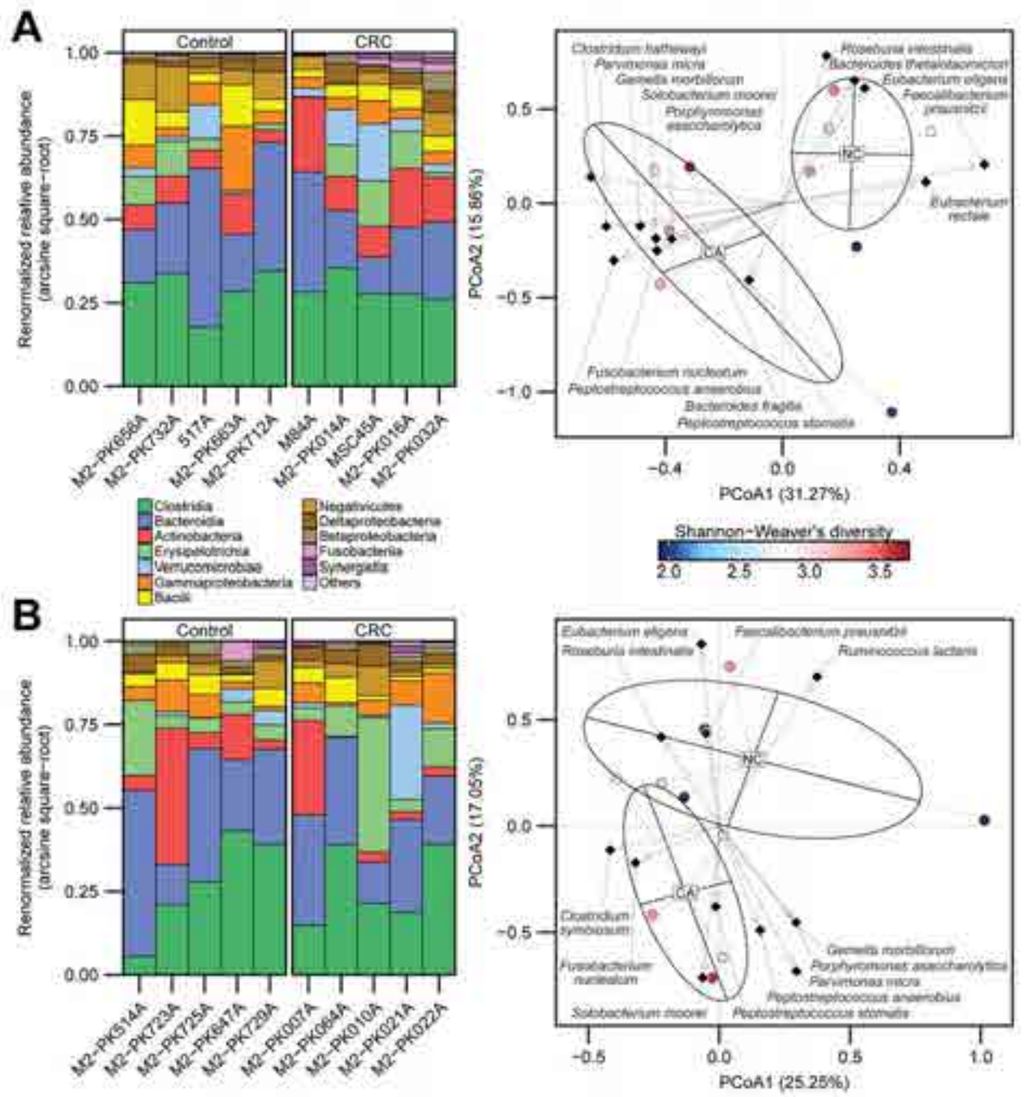


## Recognitions

Awards and Fellowships

| Member's Full Name | Details |
|---|---|
| Sunny Wong | Fellowship of the Royal College of Pathologists (FRCPath) |
| Sunny Wong | Fellowship of the Royal College of Physicians of Edinburgh (FRCPE) |
| Sunny Wong | Fellowship of the Hong Kong Academy of Medicine (FHKAM) |
| Sunny Wong | Fellowship of the Hong Kong College of Physicians (FHKCP) |
| Sunny Wong | Distinguished Research Paper Award for Young Investigators<br>Hong Kong College of Physicians |
| Sunny Wong | Youth Dream Maker Award, Youth Dream Makers Association |






Gut microbiota analysis of donor stools for murine stool gavage models (Panels A and B for two different models). Left sided figures represent the microbial composition (by genus) in the stool from five healthy controls and five colorectal cancer patients. Right sided figures represent the principal component analyses of stool microbiota composition, showing separate clustering of cancer and normal stool.

Source: Wong SH, Zhao L, Zhang X, Nakatsu G, Han J, Xu W, Xiao X, Kwong TN, Tsoi H, Wu WK, Benhua Z, Chan FK, Sung JJ, Wei H, Yu J. Gavage of Fecal Samples From Patients with Colorectal Cancer Promotes Intestinal Carcinogenesis in Germ-free and Conventional Mice. *Gastroenterology*. 2017; 153:1621-33. Doi: https://doi.org/10.1053/j.gastro.2017.08.022

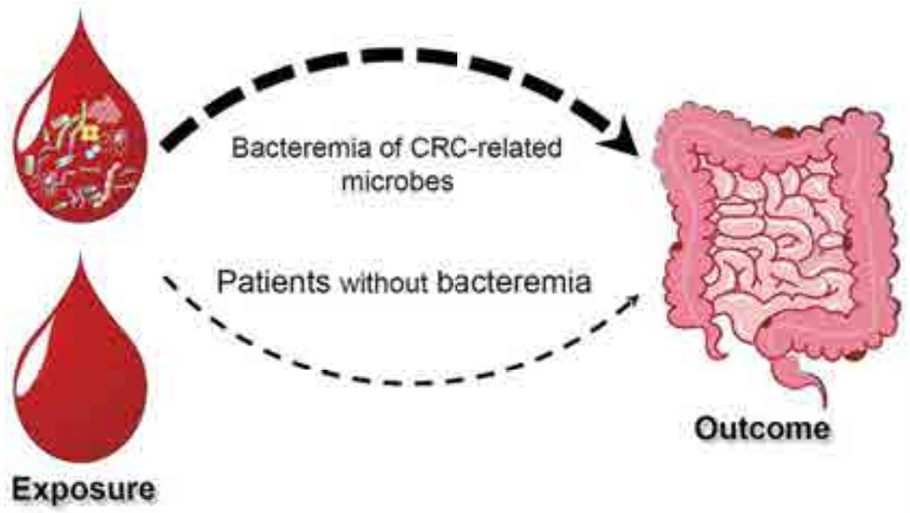
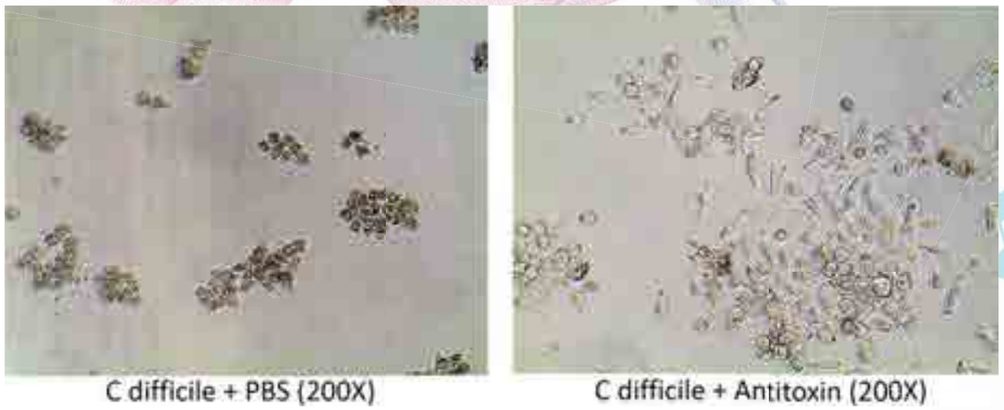



Diagram showing the relationship between bacteremia and colorectal cancer. The dysbiotic microenvironment in colorectal neoplasia can predispose patients to bacterial invasion to the vasculature, presenting with bacteremia in patients with advanced colorectal neoplasia.

Source: Prof. Sunny Wong




The cytotoxicity of Clostridium difficile toxin on colonic cells. A positive cytotoxicity assay showing typical cell rounding in >25% of the cells (left figure). Neutralization of this toxin in the cytotoxicity assay by C difficile antitoxin provides evidence that cell changes are due to the toxin (right figure).

Source: Prof. Sunny Wong



Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Sunny Wong | Combining Stool Microbial DNA and Micro-RNA Markers for Detection of Colorectal Neoplasia | Hong Kong College of Physicians Young Investigator Research Grant | 01/10/2016 | 30/09/2018 | 50,000 |
| Sunny Wong | Clarifying the Mechanisms of Ribotype 002 Virulence in *Clostridium Difficile* Infection | Research Grants Council – General Research Fund /Early Career Scheme | 01/01/2017 | 31/12/2010 | 1,050,589 |
| Sunny Wong | CRISPR-Cas9 Mediated Gene Splicing as a Novel Therapy for *Clostridium difficile* Infection | Shenzhen Science and Technology Innovation Commission | 06/11/2015 | 05/11/2017 | RMB 200,000 |
| Sunny Wong | A Metagenomic Study on Patients with Pre-malignant Neoplastic polyps | Croucher Foundation | 30/12/2013 | 29/12/2017 | 500,000 |

## Publications

A. Journal Papers

1. Wong SH, Zhao L, Zhang X, Nakatsu G, Han J, Xu W, Xiao X, Kwong TN, Tsoi H, Wu WK, Benhua Z, Chan FK, Sung JJ, Wei H, Yu J. Gavage of Fecal Samples From Patients with Colorectal Cancer Promotes Intestinal Carcinogenesis in Germ-free and Conventional Mice. *Gastroenterology*. 2017; 153:1621-33.

2. Wong SH, Kwong TN, Chow TC, Luk AK, Dai RZ, Nakatsu G, Lam TYT, Zhang L, Wu JC, Chan FK, Ng SS, Wong MC, Ng SC, Wu WK, Yu J, Sung JJ. Quantitation of faecal *Fusobacterium* improves faecal immunochemical test in detecting advanced colorectal neoplasia. *Gut*. 2017; 66:1441-8.

3. Wu WK, Li X, Wang X, Dai RZ, Cheng AS, Wang MH, Kwong T, Chow TC, Yu J, Chan MT, Wong SH. Oncogenes without a Neighboring Tumor-Suppressor Gene Are More Prone to Amplification. *Molecular Biology and Evolution*. 2017; 34:903-7.

4. Ho J, Dai RZ, Kwong TN, Wang X, Zhang L, Ip M, Chan R, Hawkey PM, Lam KL, Wong MC, Tse G, Chan MT, Chan FK, Yu J, Ng SC, Lee N, Wu JC, Sung JJ, Wu WK, Wong SH. Disease Burden of *Clostridium difficile* Infections in Adults, Hong Kong, China, 2006-2014. *Emerging Infectious Diseases*. 2017; 23:1671-9.

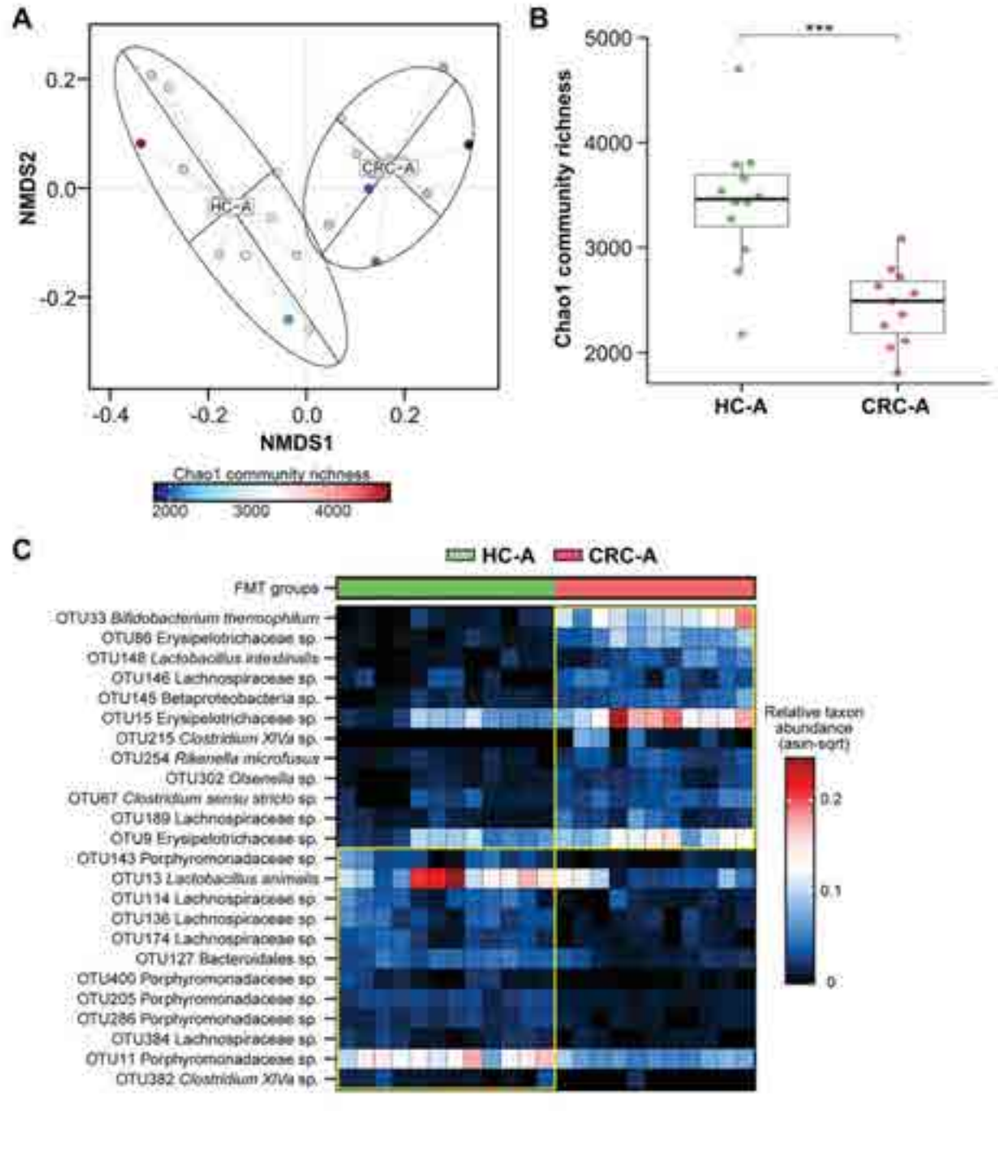
5. Chow VC, Kwong TN, So EW, Ho YII, Wong SH, Lai RW, Chan RC. Surveillance of antibiotic resistance among common *Clostridium difficile* ribotypes in Hong Kong. *Scientific Reports*. 2017; 7:17218.

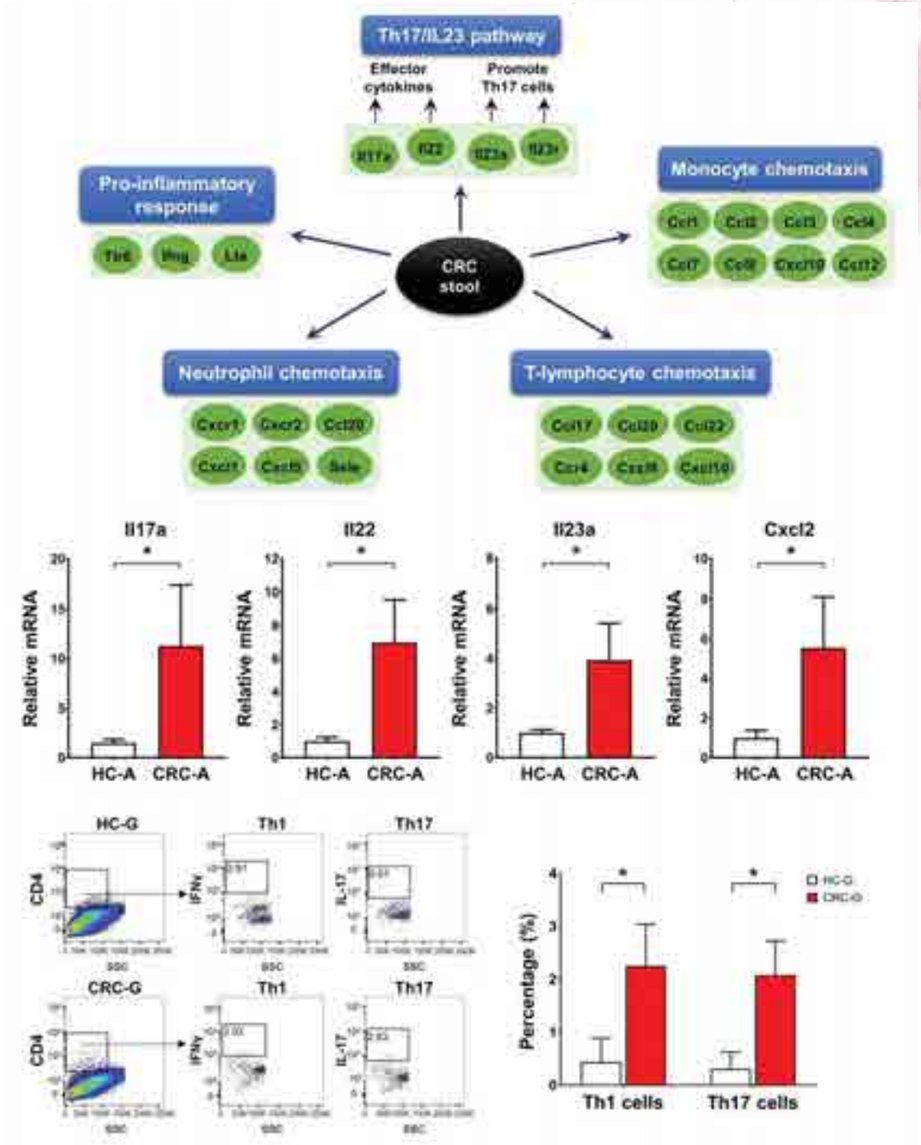




Gut microbiota in AOM mice after stool gavage. (*A*) Nonmetric multidimensional scaling (NMDS) ordination analysis of bacterial OTU community distance based on Bray-Curtis dissimilarity metrics of relative abundance profiles (HC-A, n = 12; CRC-A, n = 11). Data points are grouped by 95% confidence ellipses and color-coded by the magnitude of alpha index. (*B*) Comparison of Chao1 community richness between HC-A and CRC-A groups. The richness indexes were compared using the Wilcoxon rank-sum test. (*C*) Relative abundance heat-map of differentially enriched bacterial OTUs in AOM mice receiving CRC and healthy control stool. OTUs with false discovery rate ≤ .05, and average robust fold enrichment of ≥ 4 coupled with fold depletion of ≤ 1 are reported. ***P < .001.

Source: Wong SH, Zhao L, Zhang X, Nakatsu G, Han J, Xu W, Xiao X, Kwong TN, Tsoi H, Wu WK, Benhua Z, Chan FK, Sung JJ, Wei H, Yu J. Gavage of Fecal Samples From Patients with Colorectal Cancer Promotes Intestinal Carcinogenesis in Germ-free and Conventional Mice. *Gastroenterology*. 2017; 153:1621-33. Doi: https://doi.org/10.1053/j.gastro.2017.08.022






Effects of CRC stool on inflammatory factors. (*A*) Significant up-regulation in the expression of 33 transcripts by the Mouse Inflammatory Response and Autoimmunity PCR Array, after gavage of CRC stool to both AOM and germ-free mouse models. (*B*) A systematic diagram showing major inflammatory pathways implicated by up-regulated genes identified by the PCR array. (*C*) Quantitative RT-PCR validation was performed to confirm changes in expression of genes including *Il17a*, *Il22*, *Il23a*, and chemokine (C-X-R motif) ligand (*Cxcl2*). Expression levels were compared using the Mann-Whitney *U*test. (*D*) Flow cytometry analysis showing increased Th1 and Th17 cell infiltration in the colon of a germ-free mouse receiving CRC stool gavage . Bar charts showing proportion of Th1 and Th17 cells in the colons of the germ-free mice receiving CRC stool gavage. Percentages of Th1 and Th17 cells were compared using the Mann-Whitney *U* test. *P < .05, **P < .01.

Source: Wong SH, Zhao L, Zhang X, Nakatsu G, Han J, Xu W, Xiao X, Kwong TN, Tsoi H, Wu WK, Benhua Z, Chan FK, Sung JJ, Wei H, Yu J. Gavage of Fecal Samples From Patients with Colorectal Cancer Promotes Intestinal Carcinogenesis in Germ-free and Conventional Mice. *Gastroenterology*. 2017; 153:1621-33. Doi: https://doi.org/10.1053/j.gastro.2017.08.022



6. Xiao X, Nakatsu G, Jin Y, Wong S, Yu J, Lau JY. Gut Microbiota Mediates Protection Against Enteropathy Induced by Indomethacin. *Scientific Reports*. 2017; 7:40317.

7. Zhang R, Zheng Y, Mak TW, Yu R, Wong SH, Lau JY, Poon CC. Automatic Detection and Classification of Colorectal Polyps by Transferring Low-Level CNN Features From Nonmedical Domain. *IEEE Journal of Biomedical Health Informatics*. 2017; 21:41-7.

8. Ho J, Zhang L, Liu X, Wong SH, Wang MH, Lau BW, Ngai SP, Chan H, Choi G, Leung CC, Wong WT, Tsang S, Gin T, Yu J, Chan MT, Wu WK. Pathological Role and Diagnostic Value of Endogenous Host Defense Peptides in Adult and Neonatal Sepsis: A Systematic Review. *Shock*. 2017; 47:673-9. (Review)

9. Chen H, Cai W, Chu ES, Tang J, Wong CC, Wong SH, Sun W, Liang Q, Fang J, Sun Z, Yu J. Hepatic cyclooxygenase-2 overexpression induced spontaneous hepatocellular carcinoma formation in mice. *Oncogene*. 2017; 36:4415-26.

10. Zuo T, Wong SH, Lam K, Lui R, Cheung K, Tang W, Ching JY, Chan PK, Chan MC, Wu JC, Chan FK, Yu J, Sung JJ, Ng SC. Bacteriophage transfer during faecal microbiota transplantation in *Clostridium difficile* infection is associated with treatment outcome. *Gut*. 2018; 67(4):634-43. [Epub ahead of print]

11. Tse G, Gong M, Wong WT, Georgopoulos S, Letsas KP, Vassiliou VS, Chan YS, Yan BP, Wong SH, Wu WK, Ciobanu A, Li G, Shenthar J, Saguner AM, Ali-Hasan-Al-Saegh S, Bhardwaj A, Sawant AC, Whittaker P, Xia Y, Yan GX, Liu T. The Tpeak - Tend interval as an electrocardiographic risk marker of arrhythmic and mortality outcomes: A systematic review and meta-analysis. *Heart Rhythm* 2017; 14:1131-7.

12. Coker OO, Dai Z, Nie Y, Zhao G, Cao L, Nakatsu G, Wu WK, Wong SH, Chen Z, Sung JJ, Yu J. Mucosal microbiome dysbiosis in gastric carcinogenesis. *Gut*. 2018; 67(6):1024-32. [Epub ahead of print]

13. Tse G, Gong M, Wong CW, Chan C, Georgopoulos S, Chan YS, Yan BP, Li G, Whittaker P, Ciobanu A, Ali-Hasan-Al-Saegh S, Wong SH, Wu WKK, Bazoukis G, Lampropoulos K, Wong WT, Tse LA, Baranchuk AM, Letsas KP, Liu T, International Health Informatics Study N. Total cosine R-to-T for predicting ventricular arrhythmic and mortality outcomes: A systematic review and meta-analysis. *Annals of Noninvasive Electrocardiology*. 2018; 23(2):e12495. [Epub ahead of print]

14. Tse G, Wong CW, Gong M, Wong WT, Bazoukis G, Wong SH, Li G, Wu WK, Tse LA, Lampropoulos K, Xia Y, Liu T, Baranchuk A, International Health Informatics Study N. Predictive value of inter-atrial block for new onset or recurrent atrial fibrillation: A systematic review and meta-analysis. *International Journal of Cardiology*. 2018; 250:152-6. [Epub ahead of print]

15. Ho J, He W, Chan MT, Tse G, Liu T, Wong SH, Leung CCH, Wong WT, Tsang S, Zhang L, Chan RY, Gin T, Leung J, Lau BW, Wu WK, Ngai SP. Eosinophilia and clinical outcome of chronic obstructive pulmonary disease: a meta-analysis. *Scientific Reports*. 2017; 7:13451.

16. Tse G, Gong M, Nunez J, Sanchis J, Li G, Ali-Hasan-Al-Saegh S, Wong WT, Wong SH, Wu WK, Bazoukis G, Yan GX, Lampropoulos K, Baranchuk AM, Tse LA, Xia Y, Liu T, Woo J, International Health Informatics Study N. Frailty and Mortality Outcomes After Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis. *Journal of the American Medical Directors Association*. 2017; 18:1097; e1-10.



17. Tse G, Liu T, Li G, Keung W, Yeo JM, Fiona Chan YW, Yan BP, Chan YS, Wong SH, Li RA, Zhao J, Wu WK, Wong WT. Effects of pharmacological gap junction and sodium channel blockade on S1S2 restitution properties in Langendorff-perfused mouse hearts. *Oncotarget*. 2017; 8:85341-52.

18. Lee YT, Gong M, Chau A, Wong WT, Bazoukis G, Wong SH, Lampropoulos K, Xia Y, Li G, Wong MC, Liu T, Wu WK, Tse G, International Heath Informatics Study N. Pentraxin-3 as a marker of sepsis severity and predictor of mortality outcomes: A systematic review and meta-analysis. *Journal of Infection*. 2018; 76(1):1-10. [Epub ahead of print]

19. Bayoumy A, Gong MQ, Christien Li KH, Wong SH, Wu WK, Li GP, Bazoukis G, Letsas KP, Wong WT, Xia YL, Liu T, Tse G, International Health Informatics Study N. Spontaneous type 1 pattern, ventricular arrhythmias and sudden cardiac death in Brugada Syndrome: an updated systematic review and meta-analysis. *Journal of Geriatric Cardiology*. 2017; 14:639-43. (Letter)

20. Chan H, Ho J, Liu X, Zhang L, Wong SH, Chan MT, Wu WK. Potential and use of bacterial small RNAs to combat drug resistance: a systematic review. *Infection Drug Resistance*. 2017; 10:521-32. (Review)



B. Conference Papers

1. Wong SH, Ho J, Dai R, Lam LY, Ng SC, Wu JC, Sung JJ, Wu WK. Increasing incidence of *Clostridium difficile* infection and the use of proton-pump inhibitors: results from a territory-wide population study in Hong Kong. In: *United European Gastroenterology Week*; Barcelona, Spain; 2017 Oct.

2. Wong SH, Kwong TN, Chow TC, Luk AKC, Dai DZ, Nakatsu G, Zhang L, Lam TY, Wu JC, Chan FK, Ng SS, Wong MC, Ng SC, Wu WK, Yu J, Sung JJ. Quantitation of faecal *Fusobacterium* improves faecal immunochemical test in detecting advanced colorectal neoplasia. In: *Hong Kong College of Physicians Annual Scientific Meeting*; Hong Kong; 2017 Oct.

3. Outcomes of Clostridium difficile infection complicating ulcerative colitis in Hong Kong. In: *Asian Organization for Crohn's and Colitis (AOCC)*; Seoul, South Korea; 2017 Jun.

4. Wong S, Zhao L, Zhang X, Xu W, Xia X, Kwong T, Wu WK, Zeng B, Sung JJ, Wei H, Yu J. Stools from colorectal cancer patients promote intestinal carcinogenesis in animal models through inducing Th17-mediated inflammation. In: *Digestive Disease Week*; Chicago, USA; 2017 May.

5. Wong S, Tang W, Li A, Sung J, Ng S. Risk of Tuberculosis in Inflammatory Bowel Disease and Other Autoimmune Patients on Biologic Therapy: A Population-Based Study of 2,579 Patients. In: *Digestive Disease Week*; Chicago, USA; 2017 May.

6. Microbiome and the Pathogenesis of Intestinal Diseases. In: *The 1st Basic Science Research Workshop*; Seoul, South Korea; 2017 Jan.

7. Digestive Diseases: From Genomics to Metagenomics. In: *The 1st Basic Science Research Workshop*; Seoul, South Korea; 2017 Jan.

# 09
# INFLAMMATORY DISEASES

## Principal Investigator

Professor Hui-yao LAN

## Team

Inflammatory Diseases

## Research Progress Summary

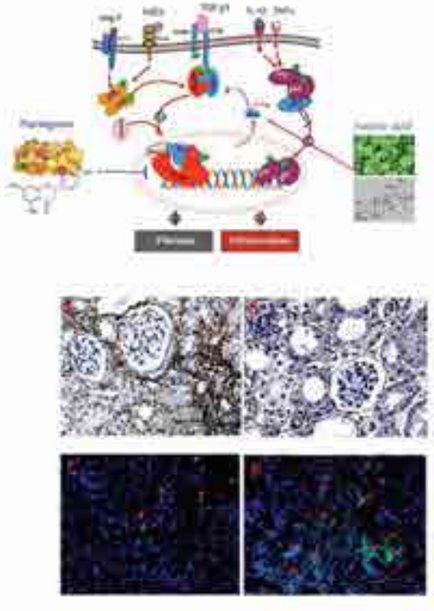
The research team of Inflammatory Diseases continued to work on new mechanisms of tissue scarring and tumour microenvironments by focusing on TGF-beta/Smad3 signalling. The identification of Smad3-dependent long non-coding RNA (lncRNAs) has resulted in a better understanding of the pathogenesis of lncRNAs in kidney diseases, as well as a new grant being awarded by the Research Grants Council. The team also identified a new role of Smad3 in type-2 diabetes and diabetic complications as mice lacking Smad3 were protected against diabetes and diabetic cardiopathy and nephropathy. Moreover, the team has made a breakthrough in the tumour microenvironment research by uncovering the essential role of Smad3 in the tumour microenvironment for driving cancer progression. This finding has been published on international recognised scientific journal *Nature Communications*. These research findings have been further translated clinically into the development of several novel immunotherapies for invasive cancers, including a genetically modified NK cell line, Smad3-targeted nanodrugs, and a novel traditional Chinese medicine formula. An Innovation and Technology Fund was awarded as the result of the development of this nanodrug. The on-going research in targeting Smad3-dependent tumour microenvironment shall remain as the team's research direction in the coming years.



## Recognitions

Awards and Fellowships

| Member's Full Name | Details |
|---|---|
| Jingyi Sheng | Young Investigator Award, East Meets West Symposium, 2017 |
| Yingying Zhang | Best Poster Award, East Meets West Symposium, 2017 |
| Philip Tang | Poster Presentation Award, Annual General Meeting and Scientific Meeting of Hong Kong Society of Immunology, 2017 |
| Patrick Tang | Young Investigators Travel Grants, International Society of Nephrology Frontiers, 2017/18 |



Rebalancing SMAD signalling with combined treatment of Smad3 inhibitor and Smad7 agonist produces better inhibitory effect on mouse obstructive renal fibrosis and cancer progression. Compared with the untreated group (A), renal collagen I (brown) in the treatment group (B) is significantly reduced. Cytotoxic NK cells (green cells) in allograft lung cancer are markedly increased in treatment group (D) compared to untreated group (C).

Source: Prof. Hui-yao Lan





Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Hui-yao Lan | Pathogenic Role of Macrophage-Derived Migration Inhibitory Factor (MIF) in Acute Kidney Injury | Research Grants Council – General Research Fund | 01/01/2017 | 31/12/2019 | 1,170,950 |
| Hui-yao Lan | Treatment of Diabetic Nephropathy by Targeting TGF-β/Smad Signaling with the Combination of Asiatic acid and Naringenin | Food and Health Bureau – Health and Medical Research Fund | 01/04/2017 | 31/03/2019 | 1,200,000 |
| Hui-yao Lan (Co-PI) | Mechanisms of Renal Inflammation: Role of Toll-like Receptor 4 | Research Grants Council – Collaborative Research Fund | 01/06/2017 | 31/05/2020 | 7,518,927 |
| Hui-yao Lan | Smad3 Promotes Cancer Progression by Inhibiting E4BP4-mediated NK Cell Development | CUHK Research Committee – Direct Grants | 01/06/2017 | 31/05/2018 | 52,500 |

## Publications

A. Journal Papers

1. Sun SF, Tang PM, Feng M, Xiao J, Huang XR, Li P, Ma RC, Lan HY. Novel lncRNA Erbb4-IR promotes diabetic kidney injury in db/db Mice by targeting miR-29b. *Diabetes*. 2018; 67(4):731-44. [Epub ahead of print]

2. Huang H, Xu C, Wang Y, Meng C, Liu W, Zhao Y, Huang XR, You W, Feng B, Zheng ZH, Huang Y, Lan HY, Qin J, Xia Y. Lethal (3) malignant brain tumor-like 2 (L3MBTL2) protein protects against kidney injury by inhibiting the DNA damage–p53–apoptosis pathway in renal tubular cells. *Kidney International*. 2018; 93(4):855-70. [Epub ahead of print]

3. Liu Z, Huang XR, Chen HY, Fung E, Liu J, Lan HY. Deletion of angiotensin-converting enzyme-2 promotes hypertensive nephropathy by targeting smad7 for ubiquitin degradation novelty and significance. *Hypertension*. 2017; 70(4):822-30.

4. Zhang JT, Wang Y, Chen JJ, Zhang XH, Dong JD, Tsang LL, Huang XR, Cai Z, Lan HY, Jiang XH, Chan HC. Defective CFTR leads to aberrant β-catenin activation and kidney fibrosis. *Scientific Reports*. 2017; 7(1): 5233.

5. Zhong X, Tu YJ, Li Y, Zhang P, Wang W, Chen SS, Li L, Chung AC, Lan HY, Chen HY, Li GS, Wang L. Serum levels of WNT1-inducible signaling pathway protein-1 (WISP-1): a noninvasive biomarker of renal fibrosis in subjects with chronic kidney disease. *American Journal of Translational Research*. 2017; 9(6):2920-32.

6. Tang Y, Chen J, Huang K, Luo D, Liang P, Feng M, Chai W, Fung E, Lan HY, Xu A. The incidence, risk factors and in-hospital mortality of acute kidney injury in patients after abdominal aortic aneurysm repair surgery. *BMC Nephrology*. 2017; 18(1):184.

7. Fu S, Tang Y, Huang XR, Feng M, Xu AP, Lan HY. Smad7 protects against acute kidney injury by rescuing tubular epithelial cells from the G1 cell cycle arrest. *Clinical Science*. 2017; 131(15):1955-69.

8. Yang C, Huang XR, Fung E, Liu HF, Lan HY. The Regulatory T-cell Transcription Factor Foxp3 Protects against Crescentic Glomerulonephritis. *Scientific Reports*. 2017; 7(1):1481.

9. Tang Y, Fung E, Xu A, Lan HY. C-reactive protein and ageing. *Clinical and Experimental Pharmacology and Physiology*. 2017; 44(S1):9-14.

10. Tang PMK, Zhou S, Meng XM, Wang QM, Li CJ, Lian GY, Huang XR, Tang YJ, Guan XY, Yan BPY, To KF, Lan HY. Smad3 promotes cancer progression by inhibiting E4BP4-mediated NK cell development. *Nature Communications*. 2017; 8:14677.

11. Wang YY, Jiang H, Pan J, Huang XR, Wang YC, Huang HF, To KF, Nikolic-Paterson DJ, Lan HY, Chen JH. Macrophage-to-Myofibroblast Transition Contributes to Interstitial Fibrosis in Chronic Renal Allograft Injury. *Journal of the American Society of Nephrology*. 2017; 28(7):2053-67.

12. Chan GC, Wu HJ, Chan KW, Yiu WH, Zou A, Huang XR, Lan HY, Lai KN, Tang SC. N-acetyl-seryl-aspartyl-lysyl-proline mediates the anti-fibrotic properties of captopril in unilateral ureteric obstructed BALB/C mice. *Nephrology*. 2018; 23(4):297-307.



B. Conference Papers

1. JH Li, XR Huang, Y Tang, Patrick Tang, AP Xu, HY Lan. Deletion of Smad3 exacerbates lupus nephritis by inhibiting Treg while promoting Th17 immunity. In: *2017 ISN-WCN*; Mexico City, Mexico; 2017 Apr 21-25.

2. JH Li, Y Tang, Patrick Tang, XR Huang, Jörg Klug, Andreas Meinhardt, Güter Fingerle-Rowson, AP Xu, HY Lan. Macrophage migration inhibitory factor is a novel biomarker, mediator, and therapeutic target for acute kidney injury. In: *2017 ISN-WCN*, Mexico City, Mexico; 2017 Apr 21-25.

3. Huang XR, Xu BH, You YK, Sun SF, Ma RCW, Lan HY. Smad3 is essential for the development of type 2 diabetic kidney disease. In: *European Medical and Clinical Congress*; Stockholm, Sweden; 2017 Aug 22-24.

4. Lan HY, Zhang Z, Wei LH, Huang XR. Diverse role of Smads in cardiac remodeling: mechanisms and therapeutic implications. In: *European Medical and Clinical Congress*; Stockholm, Sweden; 2017 Aug 22-24.

5. Lan HY. TGF-beta functions beyond fibrosis, In: *The Annual Congress of the Chinese Society of Nephrology*; Wuhan, China; 2017 Sep 13-15.

6. Lan HY. LncRNAs in Renal Fibrosis and Inflammation. In: *American Society of Nephrology Annual Conference*; New Orleans, USA; 2017 Nov 1-4.

7. Zhang YY, Tang PMK, Huang XR, Yu C, Lan HY. Novel lncRNA_9884 mediates diabetic kidney injury in db/db mice via MCP-1-dependent mechanism. In: *East Meets West Symposium*; Hong Kong; 2017 Sep 30 - Oct 1.

8. Sheng JY, Wang L, Xu BH, You YK, Tam RZ, Huang XR, Ma RCW, Lan HY. Smad3 deficiency protects against type-2 diabetes in db/db mice. In: *East Meets West Symposium*, Hong Kong; 2017 Sep 31 - Oct 1.

9. Lan HY. TGF-beta/Smad signaling in renal fibrosis. In: *Frontiers in Translation Medicine*, Kaohsiung, Taiwan; 2017 Nov 18.

10. Lan HY. Role of CRP in acute kidney injury, In: *The 2nd International Congress of Chinese Nephrologists (ICCN)*; Taipei, Taiwan; 2017 Dec 8-10.

C. Patent Applications

1. Treatment of cancer with a Smad3 inhibitor (US61/719,114; PCT/CN2013/086053; WO 2014/063659)

2. 纖維化的柚皮素和積雪草酸組合治療 (CN 104736151 A)

3. Modified NK cells and uses thereof (US 62/446, 106)

4. Naringenin and asiatic acid combination treatment of cancers (US 62/419,565)

# 09
# INFLAMMATORY DISEASES

## Principal Investigator

Professor Erik Fung

## Team

Laboratory for Heart Failure and Circulation Research – Leong-ting Lui, Xiaobo Yang, Qi Li, King-fai Cheng

## Research Progress Summary

The Undiagnosed heart Failure in frail Older individuals (UFO) study has successfully recruited over 100 subjects (out of 300 planned). Data from interim analysis suggest that diastolic dysfunction is prevalent in community-living elderly, and that frailty and heart failure (HF) subtypes recognised by professional societies can be further categorised into subphenotypes. The biomarkers or biosignatures used to characterise these subphenotypes may offer new approaches to early disease detection, monitoring, and classification. Deep, high-content analyses are currently underway to further analyse the physiological and biochemical difference among subphenotypes.





## Recognitions

Awards and Fellowships

| Member's Full Name | Details |
|---|---|
| Erik Fung | CUHK Junior Medical Clerkship 2016/2017 Exemplary Teachers' Award |

Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Erik Fung | Biomarker Profiling of Heart Failure and Frailty in the Elderly | CUHK Research Committee – Direct Grants | 01/07/2017 | 30/06/2018 | $150,000 |







## Publications

A. Journal Papers

1. Liu Z, Huang X, Chen H, Fung E, Liu J, Lan H. Deletion of Angiotensin-Converting Enzyme-2 Promotes Hypertensive Nephropathy by Targeting Smad7 for Ubiquitin Degradation. *Hypertension*. 2017; 70(4):822-30.

2. Tang Y, Fung E, Xu A, Lan H. C-reactive protein and ageing. *Clinical and Experimental Pharmacology and Physiology*. 2017;44:9-14.

3. Yang C, Huang X, Fung E, Liu H, Lan H. The Regulatory T-cell Transcription Factor Foxp3 Protects against Crescentic Glomerulonephritis. *Scientific Reports*. 2017;7(1): 1481.

# 10
# NEUROSCIENCE

## Principal Investigator

Dr. Owen Ko

## Team

Caroline Chen, Richard Li, Samuel Sy, Kuan-jung Wu, Leo Yan, Eva Zhao

## Research Progress Summary

Employing *in vivo* multiphoton and light sheet microscopy, microfluidics and single-cell RNA sequencing, Dr. Owen Ko's team focuses on two research themes:

1. Neural circuitry underlying sensory processing and learning

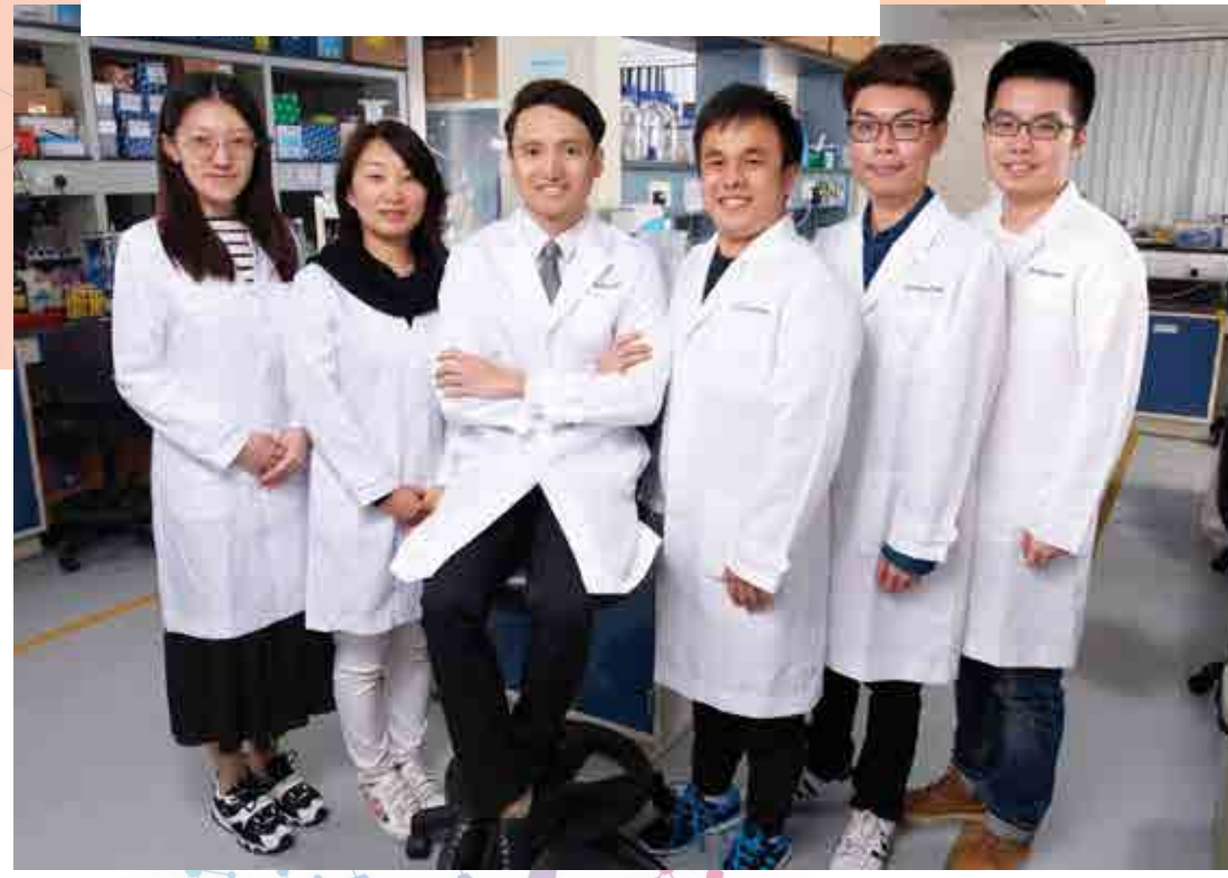
   a) The primary visual cortex has specific connection patterns with higher visual areas for higher order visual feature processing and recognition. The team is currently studying how the molecular identities of individual neurons related to their patterns of long range connections between defined areas of the brain specialised for visual processing, and what gene expression patterns underlie the emergence of the precise connection patterns during brain development, knowledge of which would help the team understand better the neurodevelopmental disorders.

   b) Recently, the zebrafish larva is emerging as an important model organism in the field of neuroscience, offering unique chance of whole-brain cellular resolution imaging of neuronal activities while the sensory environment is precisely manipulated and behavioral output monitored. The team has custom-built a high-speed light sheet microscopy for volumetric imaging of the entire brain of zebrafish larva, and employing the system for addressing fundamental questions of neural circuits underlying associative learning.



2. Pathogenesis underlying cerebral small vessel disease

   Another major focus of the lab is the pathogenesis of cerebral small vessel disease (SVD), a dominant cause of cognitive impairments in the elderly population. Sporadic SVD, the most common form of SVD, is more likely to develop in populations with cardiovascular risk factors (e.g. ageing, hypertension, diabetes) and variants of specific genes (e.g. Notch3 mutation, foxf2 segmental deletion). In animal models based on risk factors identified in human patients, the team is currently employing *in vivo* functional imaging, *in vitro* structural imaging and molecular interrogation techniques to uncover how local neurovascular coupling, cerebral vascular network morphology, and gene expression of neurovascular unit constituting cells are altered in cerebral SVD.





## Recognitions

Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Owen Ko | Untangling the pathogenesis of cerebral small vessel disease (SVD) | Faculty Innovation Award (Clinical Lecturer Scheme), Faculty of Medicine, CUHK | 01/10/2017 | 30/09/2020 | 750,000 |

## Publications

A. Journal Papers

1. Li Q, Ko H (co-1st author), Qian ZM, Yan LYC, Chan DCW, Arbuthnott GW, Ke Y, Yung WH. Refinement of learned skilled movement representation in motor cortex deep output layer. *Nature Communications*. 2017;8:15834.

2. Mok VCT, Lam BYK, Wong A, Ko H, Markus HS, Wong LKS. Early-and delayed-onset poststroke dementia – a revisit of the mechanisms. *Nature Reviews Neurology*. 2017;13(3):148-59.





Intrinsic signal optical imaging

*In vivo* two-photon imaging

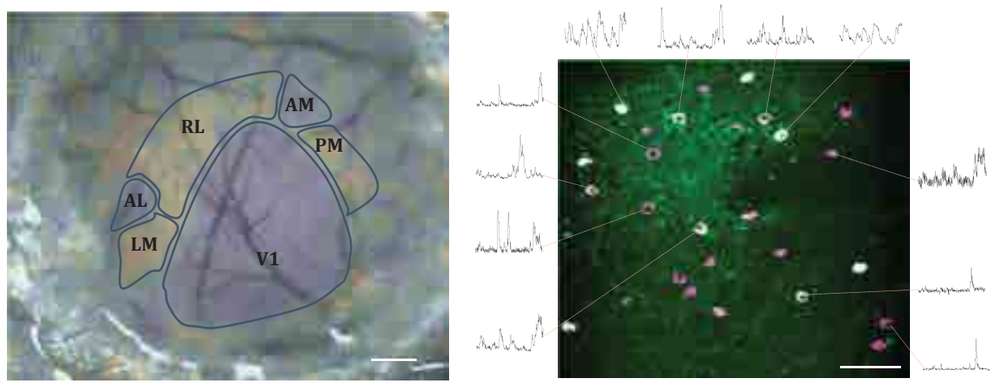



Figure legends: Left panel: the primary visual cortex (V1) and surrounding higher visual areas mapped by intrinsic signal optical imaging. Right panel: *in vivo* two-photon calcium imaging for recording neuronal activities, showing calcium transients of the V1 neurons during visual stimulation. Scale bars: left panel: 500 um; right panel: 100 um.
Copyright: Ko Lab @ LiHS 2018

Left panel: the primary visual cortex (V1) and surrounding higher visual areas mapped by intrinsic signal optical imaging. Right panel: in vivo two-photon calcium imaging for recording neuronal activities, showing calcium transients of the V1 neurons during visual stimulation. Scale bars: left panel: 500 um; right panel: 100 um.

Source: Dr. Owen Ko

# 11
# REPRODUCTION & DEVELOPMENT

## Principal Investigator

Professor Ronald Wang

## Team

Hui Xu, Nina Ching Yan Chu, Gene Chi Wai Man, Alex Bo Liang, Linda Ling Wu, Alan Wing Kwong Chan, Emma Yujing Xiong, Fangrong Wu, Ricky Qi Wu, Zinnat Hasina, Ying He, Melody Di Mao, Yi Song, Kennes Sze Wan Hung

## 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 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, including recurrent reproductive failure (e.g. recurrent miscarriage and recurrent implantation failure), endometriosis (e.g. angiogenesis, immunosuppression), endometrial cancer (e.g. lncRNA and HIF dysregulation), etc. For Development, the research team focused on the abnormal neurodevelopmental mechanism (e.g. cerebellar ataxia, Down's syndrome), embryopathy in maternal disease (e.g. pregestational and gestational diabetes), placental function (e.g. 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 2017, the team has published 13 papers and 1 book chapter (all LiHS acknowledged, 3 as 1st / corresponding author) and obtained 8 research grants (1 as PI including 1 ITF; and 7 as Co-I including 1 GRF, 2 HMRF, 2 OG Trust Fund and 2 Direct Grant).

Currently the team has 11 PhD students, 4 of them will submit their thesis in 2018.





## Recognitions

Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| TC Li | The Relationship between Toll-like Receptors and Chronic Endometritis Around the Time of Embryo Implantation in Women with Recurrent Miscarriage | SOGHK | 01/07/2017 | 31/06/2018 | 150,000 |
| Ronald Wang | Umbilical Cord Blood Mononuclear Cell Bank in Hong Kong and Treatment of Neonatal Cerebral Ischemia and Anaemia (ITS/208/16FX) | Innovation and Technology Fund | 01/10/2017 | 30/09/2019 | 2,865,000 |
| Ronald Wang (Co-I) | Association of Retinoid Deficiency with Inborn Nephron Deficit in Offspring Exposed to Maternal Diabetes (14174017) | Research Grants Council – General Research Fund | 01/10/2017 | 30/09/2020 | 1,212,780 |
| YL Chan | A Pilot Study on the Effect of a Modified Traditional Chinese Medicine Formula WuZi YanZong Pill on Improving Semen Quality in Men with Sub-optimal Parameters. | CUHK Research Committee – Direct Grant | 25/06/2017 | 24/06/2018 | 149,300 |
| Hui Xu | Effects of High Progesterone Level on the Day of Human Chorionic Gonadotrophin Administration in in-vitro Fertilization Cycles on Epigenetic Modification of Endometrium in Peri-implantation Period. (2016.058) | CUHK Research Committee – Direct Grant | 01/06/2017 | 31/05/2018 | 140,000 |
| Ronald Wang (Co-I) | A Study to Compare the Endometrial Features of Women Who Did and Did Not Benefit From Endometrial Scratch in the Cycle Preceding Frozen Embryo Transfer. (04152786) | Food and Health Bureau – Health and Medical Research Fund | 01/05/2017 | 30/04/2019 | 861,912 |
| Ronald Wang (Co-I) | Transcriptome NGS Analysis of Ovary Granulosa Cells of PCOS: A New Insight into the Causes and Potential Therapeutic Targets (04152646) | Food and Health Bureau – Health and Medical Research Fund | 01/04/2017 | 31/03/2019 | 696,248 |
| TC Li | The Prognostic Values of Micro Vessel Density (MVD) in the Peri-impkanttaion Endometrium of Women with Recurrent Miscarriage | SOGHK HKOG Trust Fund | 01/01/2017 | 31/12/2017 | 50,000 |



## Publications

A. Journal Papers

1. Huang J, Jin N, Qin H, Shi X, Liu YY, Cheung WC, Wang CC, Chan TF, Li TC. Transcriptomic Profiles in Peripheral Blood Between Women with Unexplained Recurrent Implantation Failure and Recurrent Miscarriage and the Correlation with Endometrium: A Pilot Study. *PLOS One*. 2017; 12(12):e0189159.

2. Cui L, Liang B, Yang YH, Zhu MH, Kwong J, Zheng HL, Wang CC. Inhibition of coiled coil domain containing protein 69 abrogates cell cycle arrest and enhances platinum-induced apoptosis in ovarian cancer cells. *Oncotarget*. 2017; 8(60):101634-48.

3. Chen XY, Mariee N, Jiang LM, Liu YY, Wang CC, Li TC, Laird S. Measurement of uterine natural killer (uNK) cell percentage in the peri-implantation endometrium from fertile women and women with recurrent reproductive failure: establishment of a reference range. *American Journal of Obstetrics and Gynecology*. 2017; 217(6):680.e1-6.

4. Xiong YJ, Wang JZ, Liu L, Chen XY, Xu H, Li TC, Wang CC, Zhang SY. Effects of high progesterone level on the day of human chorionic gonadotrophin administration in *in-vitro* fertilization cycles on epigenetic modification of endometrium in peri-implantation period. *Fertility and Sterility*. 2017; 108(2): 269-76.

5. Wu XK, Stener-Victorin E, Kuang HKY, Ma HL, Gao JS, Xie LZ, Hou LH, Hu ZX, Shai XG, Ge J, Zhang JF, Xue HY, Xu ZF, Liang RN, Ma HX, Yang HW, Li WL, Huang DM, Sun Y, Hao CF, Du SM, Yang ZW, Wang X, Yan Y, Chen XH, Fu P, Ding CF, Gao YQ, Zhou ZM, Wang CC, Wu TX, Liu JP, Ng EHY, L RS, Zhang HP. Effect of Acupuncture and Clomiphene in Chinese Women With Polycystic Ovary Syndrome A Randomized Clinical Trial. *Jama-Journal of the American Medical Association*. 2017; 317(24):2502-14.

6. Chen XY, Saravelos S, Liu YY, Huang J, Wang CC, Li TC. Correlation between three-dimensional power Doppler and morphometric measurement of endometrial vascularity at the time of embryo implantation in women with unexplained recurrent miscarriage. *Journal of Molecular Histology*. 2017; 48(3):235–42.

7. Lui NC, Tam WY, Gao CJ, Huang JD, Wang CC, Jiang LW, Yung WH, Kwan KM. Lhx1/5 control dendritogenesis and spine morphogenesis of Purkinje cells via regulation of Espin. *Nature Communications*. 2017; 8:15079.

8. Huang J, Qin H, Yang Y, Chen X, Zhang J, Laird S, Wang CC, Chan TF, Li TC. A comparison of transcriptomic profiles in endometrium during window of implantation between women with unexplained recurrent implantation failure and recurrent miscarriage. *Reproduction*. 2017; 153(6):749-58.

9. Lee LMY, Leung MBW, Kwok RCY, Leung YC, Wang CC, McCaffery PL, Copp AJ, Shum ASW. Perturbation of retinoid homeostasis increases malformation risk in embryos exposed to pregestational diabetes. *Diabetes*. 2017; 66(4):1041-51.

10. Man GCW, Zhang T, Chen XY, Wang JZ, Wu FR, Cheong Y, Wang CC, Li TC. The regulations and role of circadian clock and melatonin in uterine receptivity and pregnancy: an immunological perspective. *American Journal of Reproductive Immunology*. 2017; 78(2):e12715.





11. Chen XY, Man GCW, Liu YY, Wu FR, Huang J, Li TC, Wang CC. Physiological and pathological angiogenesis in endometrium at the time of embryo implantation. *American Journal of Reproductive Immunology*. 2017; 78(2):e12693.

12. Zhu Y, Tan YQ, Wang CC, Leung LK. The flame retardant 2,2′,4,4′-tetrabromo diphenyl ether enhances the expression of corticotropin-releasing hormone in the placental cell model JEG-3. *Chemosphere*. 2017; 174:499-505.

13. Rogers PAW, Adamson GD, Al-Jefout M, Becker CM, D'Hooghe TM, Dunselman GAJ, Fazleabas A, Giudice LC, Horne AW, Hull ML, Hummelshoj L, Missmer SA, Montgomery GW, Stratton P, Taylor RN, Rombauts L, Saunders PT, Vincent K, Zondervan KT, Albertsen H, Allaire C, Arosh J, Aznaurova Y, Brauer M, Bedaiwy MA, Calhaz-Jorge C, Choi S, Chwalisz K, Critchley H, Fonseca MF, Flores I, Forman A, Garcini F, Gargett C, Germano G, Hey-Cunningham A, Johnson NP, Koga K, McKinnon B, Miller K, Nap AW, Perheentupa A, Peterse D, Privato M, Rahmioglu N, Rolla E, Romano A, Saunders PT, Mills DS, Stratton P, Verhagen-Kamerbeck W, Wang CC, Williams C, Zhumataev M, Zondervan KT. Research priorities for endometriosis: recommendations from a global consortium of investigators in endometriosis. *Reproductive Sciences*. 2017; 24(2):202-26.

B. Books / Book Chapters

1. Li L, Han LS, Jiang XL, Leung PC, Wang CC. Overview of contraindicated Chinese medicines for pregnancy. In: Li XY, Ed. *Chinese Medical Therapies for Diabetes, Infertility, Silicosis and the Theoretical Basis*. Rijeka, Croatia: InTech; 2017: Ch. 3, pp. 27-64.

C. Conference Papers

1. Wang CC. Superior efficacy, safety and mechanism of green tea EGCG octaacetate in gynaecological diseases. In: *PSKL Symposium on Chemical Biology & Drug Discovery. Partner State Key Laboratory of Chirosciences*; The Hong Kong Polytechnic University, Hong Kong; 2017 Nov 16-17 (invited speaker)

2. Lin KN, Wang CC, Shum ASW. Maternal diabetes impairs fetal borwn adipose tissue development. In: *10th Developmental Origins of Health and Disease DOHad 2017*; Rotterdam, the Netherlands; 2017 Oct 15-18 (Selected Oral).

3. Wang CC, Man CW, Zhang T, Chu KO, Hui X, Chan TH. Superior therapeutic and anti-angiogenesis effects of oral pro-drug of green tea EGCG than other catechins, GnRH analogue and VEGFR inhibitor for treatment of endometriosis. In: *13th World Congress on Endometriosis*; Vancouver, Canada; 2017 May 17-20. (Poster)

4. Wang CC, Zhang T, Man CW, Liang B, Nagarkatti P, Nagarkatti M. Immunosuppression mediated by myeloid-derived suppressor cells (MDSC) in endometriosis. In: *13th World Congress on Endometriosis*; Vancouver, Canada; 2017 May 17-20. (Poster)

5. Liang B, Zhang T, Man CW, Wu L, Wang CC. Efficacy, safety and mechanism of commonly used Chinese herbal medicine formulae for treatment of endometriosis In: *13th World Congress on Endometriosis*; Vancouver, Canada; 2017 May 17-20. (Poster)

6. Liang B, Wu L, Cheung CW, Fung WY, Wong SW, Wang CC. Efficacy, safety and mechanism of new progestin and selective progesterone receptor modulator (SPRM) for treatment of endometriosis. In: *13th World Congress on Endometriosis*; Vancouver, Canada; 2017 May 17-20 . (Selected Oral)

7. Cui L, Kwong J, Wang CC. Inhibition of coiled coil domain containing protein 69 (CCDC69) enhance platinum-mediated apoptosis in ovarian cancer cells. In: *Annual Meeting of American Association for Cancer Research 2017*; Washington DC, USA; 2017Apr 1-5. (Poster)

8. Wang JZ, Man CW, Yang XY, Kwong J, Dou QP, Chan TH, Wang CC. A prodrug of green tea polyphenol (-)-epigallocatechin-3-gallate served as a potentially novel angiogenesis inhibitor in endometrioid endometrial cancer. In: *Annual Meeting of American Association for Cancer Research 2017*; Washington DC, USA; 2017 Apr 1-5. (Poster)

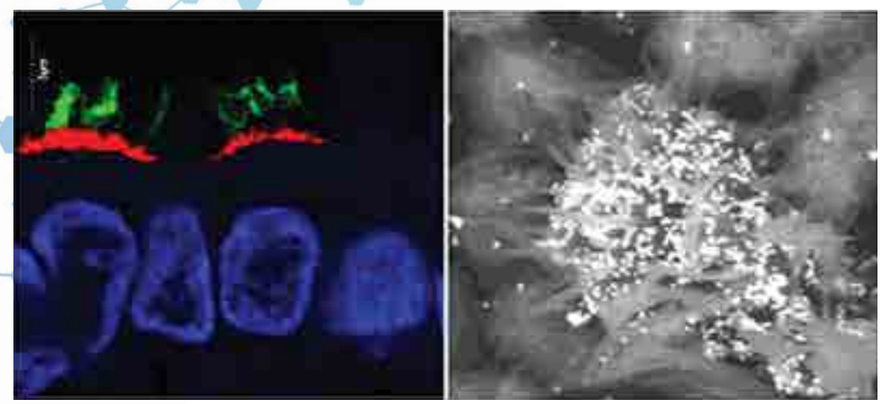
9. Yang XY, Zhao Y, Sun K, Li YY, Zhou JJ, Wang JZ, Sun H, Wang CC, Kwong J, Wang HT, Chung TKH. LncRNA HAND2-AS1 inactivates neuromedin U (NMU) and inhibits tumor invasion and metastasis in endometrioid endometrial carcinoma. In: *Annual Meeting of American Association for Cancer Research 2017*; Washington DC, USA; 2017 Apr 1-5. (Poster)



10. Wu L, Wang CC. Association of genetic variants in the promoter and start codon of PPARγ2 with gestational diabetes mellitus in Chinese population. In: *9th International DIP Symposium on Diabetes, Hypertension, Metabolic Syndrome & Pregnancy*; Barcelona, Spain; 2017 Mar 8-12. (Poster)

11. Wang CC, Tong Y, Mao DD, Tam WH. Efficacy, safety and mechanism of chinese herbal medicines for gestational diabetes mellitus: evidence from meta-analysis, animal and cellular studies. In: *9th International DIP Symposium on Diabetes, Hypertension, Metabolic Syndrome & Pregnancy*; Barcelona, Spain; 2017 Mar 8-12. (Poster)

12. Wang CC. Pattern recognition lectins in pathogenesis and prediction of clinical preeclampsia in first trimester of pregnancy. In: *9th International DIP Symposium on Diabetes, Hypertension, Metabolic Syndrome & Pregnancy*; Barcelona, Spain; 2017 Mar 8-12. (Poster)



MUC1 expression in the luminal epithelium. Left panel: double fluorescent immunostaining; red MUC1 and green tubulin. Right panel: scanning electron microscopy immunogold staining.

Source: Prof. Ronald Wang

# 12

# STEM CELLS AND TISSUE REGENERATION

*(Adult Stem Cell Biology and Applications)*

## Principal Investigator

Professor Gang Li

## Team

Wayne Lee, Jinfang Zhang, Sien Lin, Meiling Zhu, Lu Feng, Yang Liu, Bin Wang, Yan Wang, Shi Liu, Weiping Lin, Yujia Wang, Yucong Li, Pan Qi, Haixing Wang, Xingbo Cai

## Research Progress Summary

In 2017, the research team has 15 members (2 research assistant professors, 2 postdoctoral fellows, 4 research assistants, 1 visiting fellow and 6 PhD students) with the following research projects carried out: (1) Exploring the clinical application potentials of secretomes derived from fetal and adult human mesenchymal stem cells; (2) Biological roles of microRNAs and non-coding RNAs in bone, cartilage and tendon regeneration; (3) Development of industry contract research works on the pre-clinical studies of biological compounds and biophysical stimulations; and (4) Engaging in two clinical trials of autologous adult MSCs therapy for chondral lesion in wrist and knee in Hong Kong. These projects are in well progress as planned, with more than 26 peer-reviewed publications and over HK$ 8 million research grants secured by the team in 2017.





This year, Professor Gang Li has also successfully organised the 7th CUHK International Symposium and co-organised the 2017 Medical Frontier Forum: New Biomaterials and Tissue Repair and Regeneration (cum Chinese Academy of Engineering Forum, Shenzhen). Prof. Li has been invited to give keynote speeches and lectures at various national and international conferences and meetings for more than 20 times in 2017, and served as visiting professors in 3 universities, council members of 4 research societies, and editorial board members for 3 international journals. He also actively engages in knowledge transfer and provided advice/consultation service for Hong Kong Science Park, local and international healthcare related industries.

## Recognitions

Awards and Fellowships

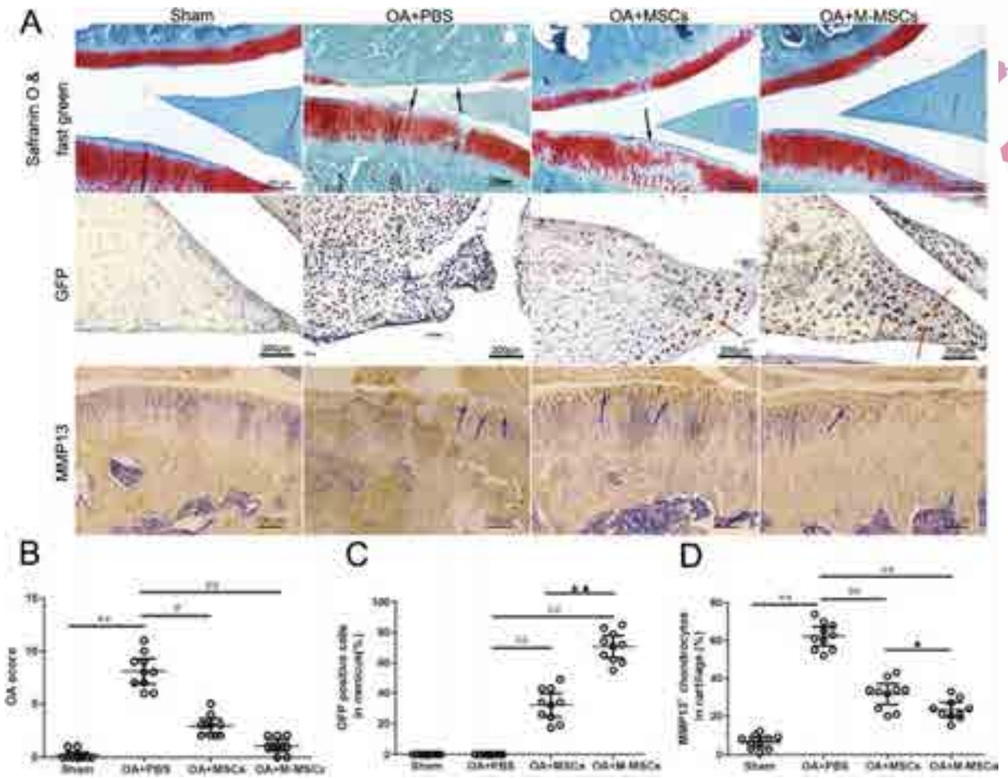
| Member's Full Name | Details |
|---|---|
| Gang Li | 中國醫學科技獎二等獎：「血管神經組織工程骨的構建與轉化研究」<br>2nd Prize, 2016 Medical Science and Technology Award of PR China, January 2017 |
| Gang Li | Best Poster Award (the only one at the meeting) 3rd World Congress of Limb Lengthening and Reconstruction Meeting, Lisbon, Portugal, September 2017. |
| Gang Li | Visiting Professor, Guang Dong Medical College, Dongguan, China. |
| Gang Li | Visiting Professor, Xijing Orthopadeic Hospital, The Fourth Military Medical University, Xian, China. |
| Gang Li | Visiting Professor, South Eastern University Medical School, Nanjing, China. |
| Gang Li | Associate Editor, Journal of Orthopaedic Translation |
| Gang Li | Member of Editorial Board, Calcified Tissue International |
| Gang Li | Member of Editorial Board, Bone and Joint Research |
| Gang Li | Council member, Chinese Orthopaedic Research Society, Chinese Orthopaedic Association（中國骨科醫學會基礎醫學組委員） |
| Gang Li | Council Member, Tissue Engineering and Regenerative Medicine Division, Chinese Association of Biomedical Engineering（中國生物醫學工程學會組織工程與再生醫學分會 理事會委員） |
| Gang Li | General Secretary, Division of Limb Deformity Correction and Reconstruction, Chinese Association of Orthopaedic Surgeons |
| Gang Li | Chairman of China Branch, International Limb Lengthening and Reconstruction Societies (ILLRS) and Association from Study and Application of the Methods of Ilizarov (ASAMI)（國際肢體延長和重建學會，Ilizarov方法研究和應用協會中國部主席） |
| Sien Lin | Student and Young Investigator Award<br>Tissue Engineering and Regenerative Medicine International Society – Asia Pacific (TERMIS-AP), September 2017, Nantong China. |
| Sien Lin | Best Poster of Guest Nation Award, Orthopaedic Research Society, San Diego, USA, March 2017.<br>Lin S, Lee YW, Zhang J, Cui L, Li G. "Prevention of Cartilage Degeneration by Targeting Smad2/3-MMP13 Signaling Pathway" |





The therapeutic effects of MSCs or M-MSCs on cartilage destruction in the surgically induced-OA rat model. (A) Representative images of Safranin O and Fast Green staining sections of the medial compartment of the knee joint, GFP signals (orange arrows) in medial meniscus, MMP13 signals (blue arrows) in articular cartilage of tibiae. Black arrows point to the damaged area of cartilage. Quantitative results of OA score (B), GFP positive cells in meniscus (C), and MMP13 signals in articular cartilage (D). The data are expressed as mean and 95% confidence intervals (CIs) (n = 10). **P < 0.01 vs. Sham; #P < 0.05, ##P < 0.01 vs. (OA + PBS); ▲P < 0.05, ▲▲P < 0.01 vs. (OA + MSCs).

Source: Lin SE, Lee WYW, Xu LL, Wang YJ, Chen YF, Ho KW, Qin L, Jiang XH, Cui L, Li G. Stepwise preconditioning enhances mesenchymal stem cell-based cartilage regeneration through epigenetic modification. *Osteoarthritis and Cartilage*. 2017;25(9):1541-50. Doi: 10.1016/j.joca.2017.05.008.






Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Gang Li | Mir-21調控間充質幹細胞成骨/軟骨分化的機制及應用研究 | 深圳市科技創新委員會 | 01/06/2017 | 30/11/2017 | RMB 260,000 |
| 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 |
| Gang Li | Is Smad7 a Potential Therapeutic Target for Preventing Osteoporotic Bone Loss? | Research Grants Council – General Research Fund | 01/01/2016 | 31/12/2018 | 821,097 |
| Gang Li | SOX11調控骨髓間充質幹細胞分化與遷移的研究及其在骨/軟骨再生中的應用 | The National Natural Science Foundation of China | 01/01/2014 | 31/12/2017 | RMB 700,000 |
| Gang Li (Co-PI) | 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 (Co-PI) | A Micro Array Chip based Single Cell Manipulation System for Characterization of Electrical Stimulation Induced Stem Cell Differentiation | The National Natural Science Foundation of China – Research Grant Council Joint Research Scheme | 01/01/2016 | 31/12/2019 | 400,000 |
| Gang Li | Development of Bio-scaffold Encapsulating Human Fetal Mesenchymal Stem Cells Secretion for Promoting Difficult Skin Wound Healing | Hong Kong Innovation Technology Commission | 01/03/2017 | 28/02/2019 | 1,969,301 |
| Gang Li | Development of Bio-scaffold Encapsulating Human Fetal Mesenchymal Stem Cells Secretion for Promoting Difficult Skin Wound Healing | Hong Kong Innovation Technology Commission Internship | 01/03/2017 | 28/02/2019 | 904,624 |
| Gang Li (Co-PI) | Functional Bone Regeneration in Challenging Bone Disorders and Defects | Research Grants Council – Theme-based Research Scheme | 01/11/2017 | 31/10/2022 | 333,333,333 |

## Publications

A. Journal Papers

1. Xu J, Sun YX, Wu TY, Wang B, Liu Y, Zhang JF, Lee WY, Kang QL, Chai YM, Li G. Porcine brain extract promotes osteogenic differentiation of bone marrow derived mesenchymal stem cells and bone consolidation in a rat distraction osteogenesis model. *PLOS One*. 2017; 12(11):e0187362.

2. Xu J, Sun YX, Wu TY, Liu Y, Shi L, Zhang JF, Kang QL, Chai YM, Li G. Enhancement of bone regeneration with the accordion technique via HIF-1α/VEGF activation in a rat distraction osteogenesis model. *Journal of Tissue Engineering and Regenerative Medicine*. 2018; 12(2):e1268-76. [Epub ahead of print]

3. Sun YX, Zhang JF, Li DJ, Xu LL, Pan XH, Li G. Comparing the osteoconductive potential between tubular and cylindrical beta-tricalcium phosphate scaffolds: an experimental study in rats. *Journal of Biomedical Materials Research: Part B - Applied Biomaterials*. 2017; doi: 10.1002/jbm.b.34011. [Epub ahead of print]

4. Liu Y, Li G, Zhang JF. The role of long non-coding RNA H19 in musculoskeletal system: A new player in an old game. *Experimental Cell Research*. 2017; 360(2):61-65. (Review)

5. Sun YX, Zhang JF, Xu Jia, Xu LL, Wu TY, Wang B, Pan XH, Li G. MicroRNA-144-3p inhibits bone formation in distraction osteogenesis through targeting Connexin 43. *Oncotarget*. 2017; 8:89913-22.

6. Hou YH, Ni M, Lin SE, Sun YX, Lin WP, Liu YM, Wang HB, He W, Li G, Xu LL. Tenomodulin highly expressing MSCs as a better cell source for tendon injury healing. *Oncotarget*. 2017; 8(44):77424-35.

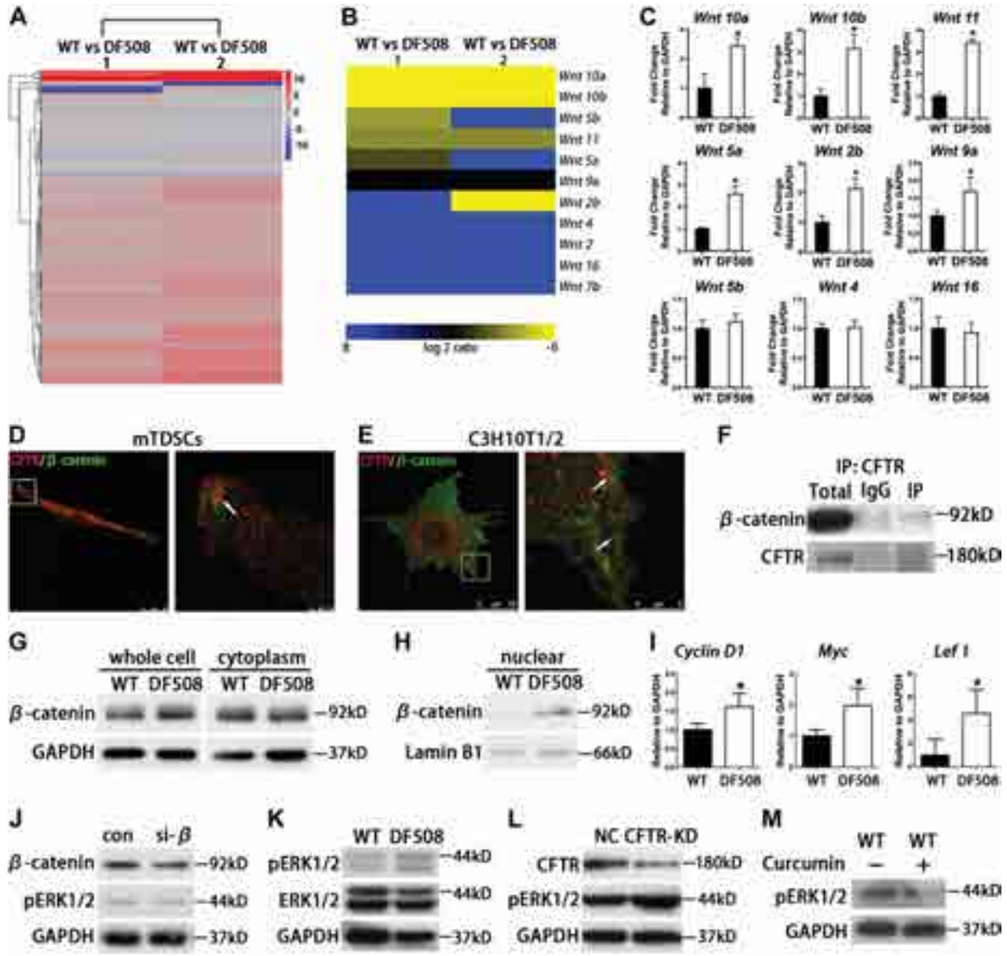
7. Yang Y, Lin S, Wang B, Gu W, Li G. Stem cell therapy for enhancement of bone consolidation in distraction osteogenesis: A contemporary review of experimental studies. *Bone Joint Research*. 2017; 6(6):385-90.

8. Xu J, Wu TY, Sun YX, Wang B, Zhang JF, Lee WYW, Chai YM, Li G. Staphylococcal enterotoxin C2 expedites bone consolidation in distraction osteogenesis. *Journal of Orthopedic Research*. 2017; 35(6):1215-25.

9. Chen YF, Lin SE, Sun YX, Guo J, Lu YF, Suen CW, Zhang JF, Zha Z, Ho KW, Pan XH, Li G. Attenuation of subchondral bone abnormal changes in osteoarthritis by inhibition of SDF-1 signaling. *Osteoarthritis and Cartilage*. 2017; 25(6):986-94.

10. Xu J, Chen YF, Liu Y, Zhang JF, Kang QL, Ho KW, Chai YM, Li G. Effect of SDF-1/Cxcr4 signaling antagonist AMD3100 on bone mineralization in distraction osteogenesis. *Calcified Tissue International*. 2017; 100(6):641-52.






Wnt/β-catenin and pERK1/2 signaling pathways were activated by dysfunctional CFTR. (a) Heat map of differently expressed genes between WT and DF508 by RNA-seq analysis (WT=1, DF508=2). (b) Heat map of FPKM values of the selected Wnts genes. (c) Expression of Wnt genes in TDSCs from WT and DF508 mice by Real-time PCR (n=3). (d) Co-localization of CFTR and β-catenin at cell membrane (indicated by white arrow) of TDSCs and (e) C3H10T1/2 cells by laser scanning confocal imaging. (f) β-catenin was enriched in CFTR pull down components in C3H10T1/2 cells by co-immunoprecipitation.

Source: Liu Y, Xu LL, Wu TY, Sun YX, Xu J, Lee YW, Wang B, Chang HC, Jiang XH, Zhang JF, Li G. CFTR mediates tenogenic differentiation of tendon derived stem cells and tendon repair: accelerating tendon injury healing by intervening its downstream signaling. *The FASEB Journal*. 2017; 31(9):3800-15. Doi: 10.1096/fj.201601181R

11. Sun YX, Xu J, Xu LL, Zhang JF, Chan KM, Pan XH, Li G. MiR-503 promotes bone formation in distraction osteogenesis through suppressing Smurf1 expression. *Scientific Reports*. 2017; 7(1):409.

12. Lin WP, Xu LL, Zwingenberger S, Gibon E, Goodman SB, Li G. Mesenchymal stem cells homing to improve bone healing. *Journal of Orthopaedic Translation*. 2017; 9: 19-27. (Review)

13. Liu Y, Suen CW, Zhang JF, Li G. Current concepts on tenogenic differentiation and clinical applications. *Journal of Orthopaedic Translation*. 2017; 9: 28-42. (Review)

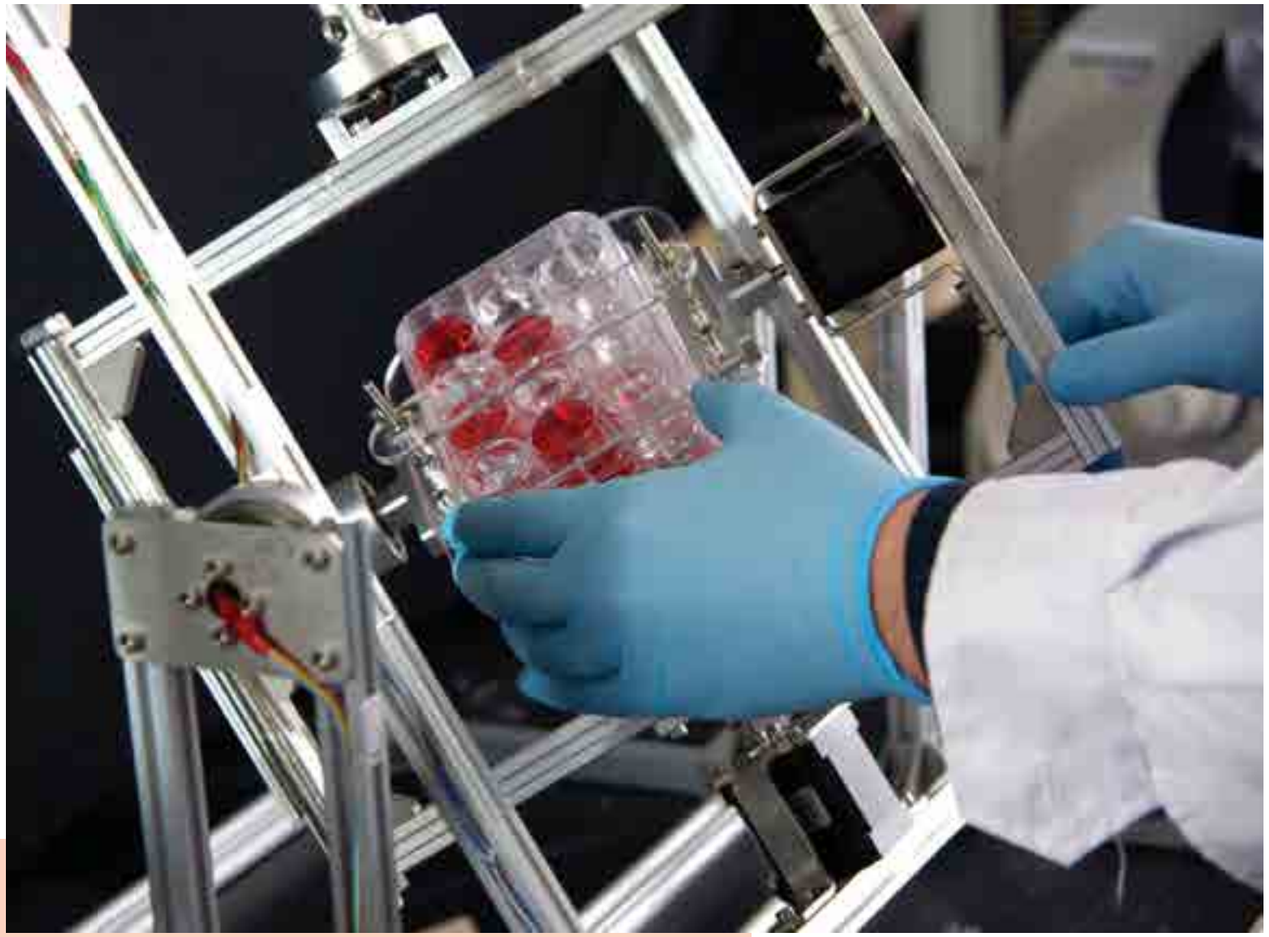
14. Lin YC, Li YJ, Rui YF, Dai GC, Shi L, Xu HL, Ni M, Zhao S, Chen H, Wang C, Li G, Teng GJ. The effects of high glucose on tendon-derived stem cells: implications of the pathogenesis of diabetic tendon disorders. *Oncotarget*. 2017; 8(11):17518-28.

15. Liu Y, Xu LL, Wu TY, Sun YX, Xu J, Lee YW, Wang B, Chang HC, Jiang XH, Zhang JF, Li G. CFTR mediates tenogenic differentiation of tendon derived stem cells and tendon repair: accelerating tendon injury healing by intervening its downstream signaling. *The FASEB Journal*. 2017; 31(9):3800-15.

16. Lin SE, Lee WYW, Xu LL, Wang YJ, Chen YF, Ho KW, Qin L, Jiang XH, Cui L, Li G. Stepwise preconditioning enhances mesenchymal stem cell-based cartilage regeneration through epigenetic modification. *Osteoarthritis and Cartilage*. 2017; 25(9):1541-50.

17. Lu YF, Liu Y, Fu WM, Xu J, Wang B, Sun YX, Wu TY, Xu LL, Chan KM, Zhang JF, Li G. Long noncoding RNA H19 accelerates tenogenic differentiation and promotes tendon healing through targeting miR-29b-3p and activating TGF-b1 signaling. *The FASEB Journal*. 2017; 31(3):954-64.





# 12

# STEM CELLS AND TISSUE REGENERATION

*(Stem Cell and Vascular Regeneration)*

## Principal Investigator

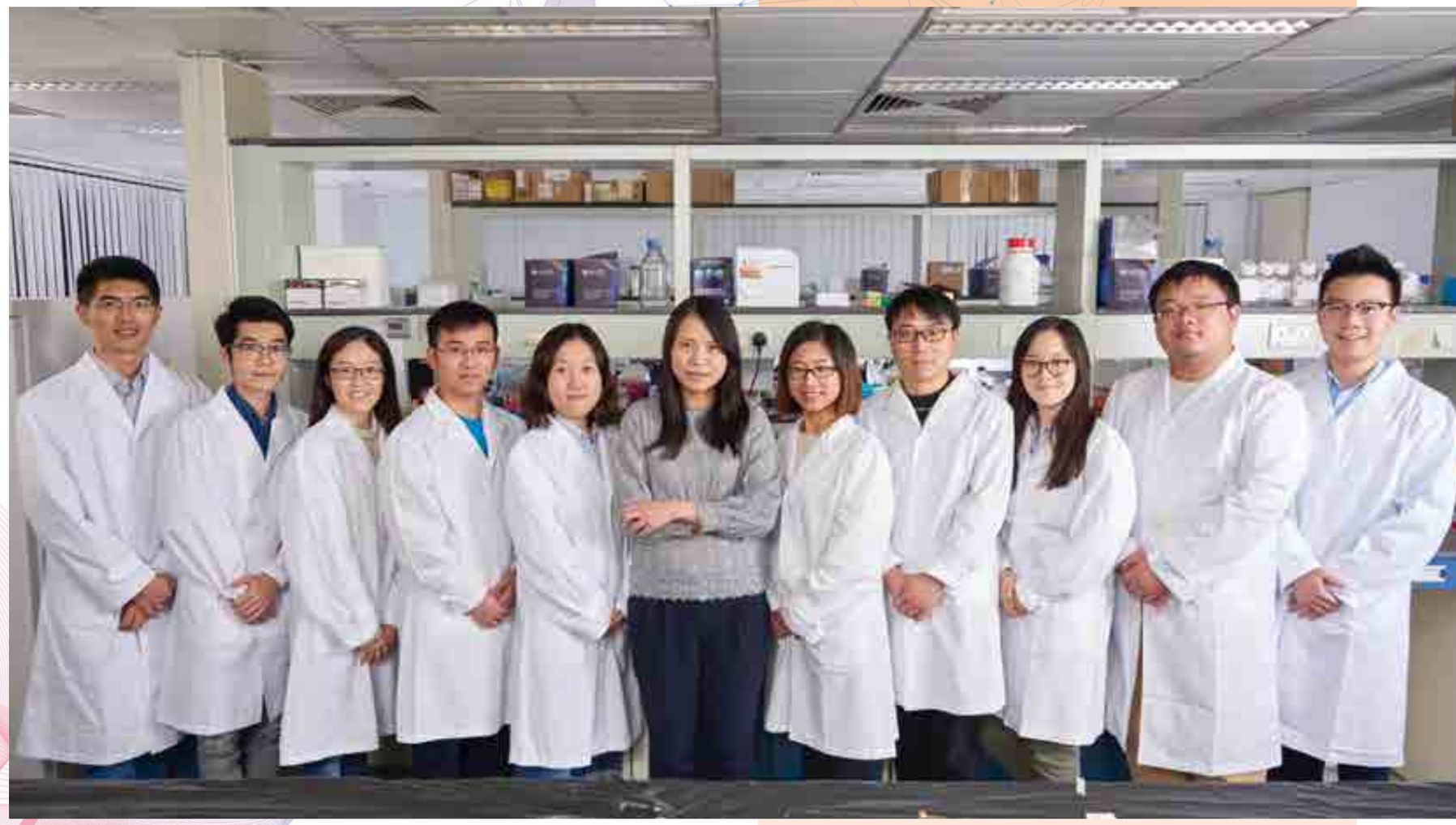
Professor Kathy Lui

## Team

Rachel Tam, Kelvin Yang, Vicken Chan, Jiatao Li, Xisheng Li, Jeffrey Leung, Di Liu, Cai Liang, Bao Sheng, Tiffany Fung

## Research Progress Summary

In the past year, Professor Kathy Lui and her team have been investigating mechanisms driving pathogenesis of cardiovascular diseases and developing strategies to drive cardiovascular regeneration. 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.



## Recognitions

Awards and Fellowships

| Member's Full Name | Details |
|---|---|
| Kathy Lui | Editorial Board Member, *Stem Book* (Harvard Stem Cell Institute) |
| Rachel Tam | Faculty Postdoctoral Fellowship 2017-2018 |



Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Kathy Lui | Driving pancreatic beta cell regeneration by VEGF modified mRNA | Research Grants Council – Early Career Scheme | 01/01/2016 | 31/12/2018 | 816,435 |
| Kathy Lui | Driving pancreatic beta cell regeneration by VEGF modified mRNA | Education fund from Research Grants Council – Early Career Scheme | 01/01/2016 | 31/12/2018 | 50,000 |



| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Kathy Lui | Studying the effect of hyperglycemia on development of the multipotent Islet1+ heart progenitors with implications on congenital heart diseases using human embryonic stem cells | Seed Fund from Lui Chi Woo Institute of Innovative Medicine (CARE programme) | 01/01/2016 | 31/12/2018 | 400,000 |
| Kathy Lui | Transplantation of vascularised pancreatic beta cells derived from human stem cells for Type-1 diabetic recipients | Food and Health Bureau – Health and Medical Research Fund | 01/06/2016 | 31/05/2018 | 1,199,992 |
| Kathy Lui | Unraveling the impact of hyperglycemia on survival and cell fate commitment of the human multipotent ISL1+ heart progenitors | Research Grants Council – General Research Fund | 01/01/2017 | 31/12/2018 | 902,460 |
| Kathy Lui | Driving vascular regeneration against diabetic endothelial dysfunction with immune intervention | Food and Health Bureau – Health and Medical Research Fund | 01/06/2017 | 31/05/2018 | 1,198,752 |
| Kathy Lui | Modelling human congenital heart disease in diabetes using the ISL1-Cre lineage tracing human pluripotent stem cells | Faculty of Medicine, CUHK – Faculty Innovation Award | 01/01/2017 | 31/12/2021 | 2,500,000 |
| Kathy Lui | Unraveling the Impact of Hyperglycemia on Human Second Heart Field Development | The Croucher Foundations' Croucher Innovation Award 2017 | 01/01/2017 | 31/12/2021 | 5,000,000 |
| Kathy Lui (Co-PI) | A multi-disciplinary study on the beneficial effects of PPARD in physical exercise against diabetic vascular complications: cellular crosstalk and energy metabolism | Research Grants Council – Collaborative Research Fund | 30/06/2017 | 29/06/2020 | 500,000 |

## Publications

A. Journal Papers

1. He LJ, Huang XZ, Kanisicak O, Li Y, Wang Y, Li Y, Pu WJ, Liu QZ, Zhang H, Tian XY, Zhao H, Liu XX, Zhang SH, Nie Y, Hu SS, Miao X, Wang QD, Wang FC, Chen T, Xu QB, Lui KO, Molkentin JD, Zhou B. Preexisting endothelial cells mediate cardiac neovascularization after injury. *Journal of Clinical Investigation*. 2017; 127(8):2968-81.

2. Zhang H, Huang XZ, Liu K, Tang J, He LJ, Pu WJ, Liu QZ, Li Y, Tian XY, Wang Y, Zhang LB, Yu Y, Wang HY, Hu RG, Wang FC, Chen T, Wang QD, Qiao ZY, Zhang L, Lui KO, Zhou B. Fibroblasts in an endocardial fibroelastosis disease model mainly originate from mesenchymal derivatives of epicardium. *Cell Research*. 2017;27(9):1157-77.

3. Tsang JC, Vong JS, Ji L, Poon LC, Jiang PY, Lui KO, Ni YB, To KF, Cheng YK, Chiu RW, Lo YM. Integrative single-cell and cell-free plasma RNA transcriptomics elucidates placental cellular dynamics. *Proceedings of the National Academy of Sciences of the United States of America*. 2017; 114(37):E7786-95.

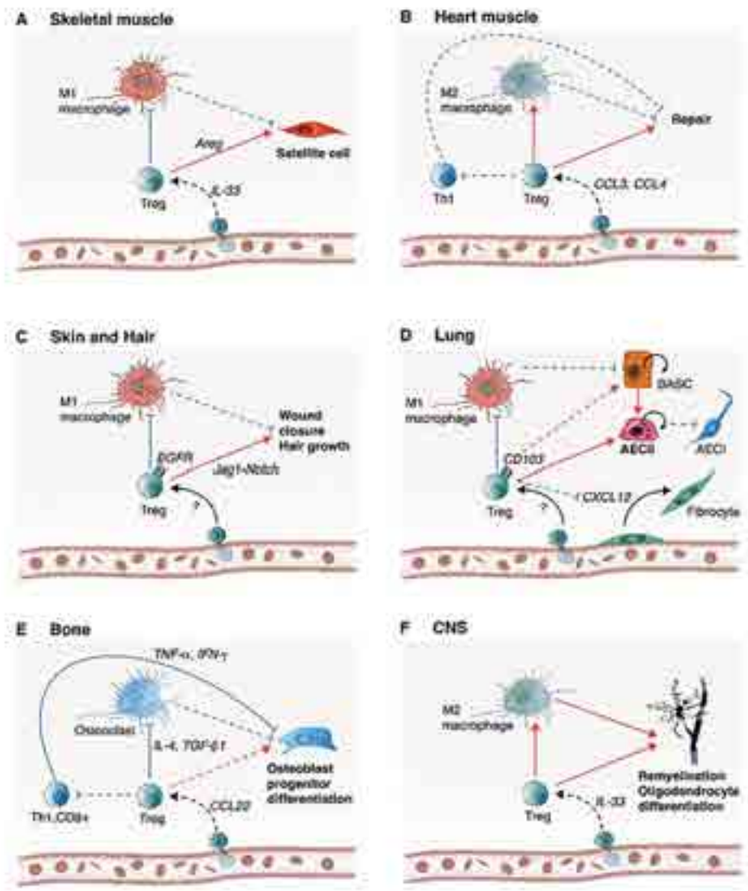
4. Lu S, Li JT, Lui KO. Individual Variation in Conditional beta Cell Ablation Mice Contributes Significant Biases in Evaluating beta Cell Functional Recovery. *Frontiers in Endocrinology*. 2017; 8:242.





Treg likely promote tissue repair and regeneration in a tissue-specific manner. Treg play an important role in the repair and regeneration of skeletal muscle, heart muscle, skin and hair, lung, bone, and central nervous system (CNS). (A) In skeletal muscle, IL-33 participates to Treg recruitment into the site of injury. Treg inhibit M1 macrophage-mediated inflammation, which promote transition to the resolution phase. Treg also directly activate satellite cell proliferation and differentiation through Areg. (B) In the heart, Treg are recruited via CCR5 signaling (e.g., CCL3 and CCL4) allowing inhibition of Th1 cell activity and inhibition of M1 macrophages. (C) In skin and hair, mechanism of Treg recruitment is still unknown, but upon recruitment, Treg inhibit M1 macrophage inflammatory activity and promote wound closure and hair growth *via* the Jag1-Notch signaling pathway. (D) In the lung, Treg inhibit M1 macrophage inflammatory activity and encourage proliferation and differentiation of damaged alveolar type 2 epithelial cells (AECII) into AECIs. This step can be mediated by Areg or CD103 to E-cadherin ligand-receptor binding. Alternatively, Treg could potentially activate progenitor bronchioalveolar stem cells (BASCs) to differentiate into AECII cells. Concurrently, Treg prevent fibrosis by inhibiting fibrocyte recruitment and proliferation *via* CXCL12. (E) In the bone, Treg are most likely recruited *via* CCL22, which act on inhibiting Th1, $CD8^+$, and M1 macrophages to support osteoblast progenitor differentiation. (F) In CNS, Treg are recruited by IL-33 and play a reparative role by encouraging M2 macrophage polarization to facilitate re-myelination and differentiation of oligodendrocytes. Treg may also directly act on oligodendrocytes *via* CCN3. Dashed lines indicate a hypothetical mechanism. Red arrows indicate induction, while blue arrows indicate inhibition.

Source: Li JT, Tan J, Martino MM, Lui KO. Regulatory T-Cells: Potential Regulator of Tissue Repair and Regeneration. *Frontiers in Immunology*. 2018;9:585. Doi: 10.3389/fimmu.2018.00585



# 12

# STEM CELLS AND TISSUE REGENERATION

*(Innovative Orthopaedic Biomaterial and Drug Translational Research)*

## Principal Investigator

Professor Ling Qin

## Team

Wing Ho Chau, Dick Chow, Bing Chen, Can Cui, Bingyang Dai, Xuan He, Le Huang, Ling Kong, Huafang Li, Ye Li, Wai Ching Liu, Jie Mi, Qianqian Pang, Li Tian, Wenxue Tong, Peng Wan, Jiali Wang, Jiankun Xu, Hao Yao, Jiang Yue, Ri Zhang, Nianye Zheng, Lizhen Zheng, Liangbin Zhou, Li Zou





## Research Progress Summary

The elderly population will reach 26.4% by 2036 in Hong Kong and will keep increasing. Ageing is closely associated with an increase of incidences of osteoporotic fracture, osteoarthritis, osteonecrosis and bone cancer. These severe musculoskeletal conditions and their associated morbidities and mortalities impose huge socioeconomic and healthcare burden to patients, families and the society. This leads to a high demand of new surgical interventions for orthopaedic surgeries, including fracture fixation and joint replacement that require various types of bone grafts and implants. The current global market for orthopaedic implants is estimated to worth USD46.5 billion. Therefore, there is an urgent need for further development or improvement of orthopaedic implants and supplements to accelerate musculoskeletal regeneration. The World Health Organization (WHO) designated 2000-2010 as the Bone Joint Decade and has subsequently extended it to 2020, which implies musculoskeletal diseases are a big challenge for the modern yet ageing society.

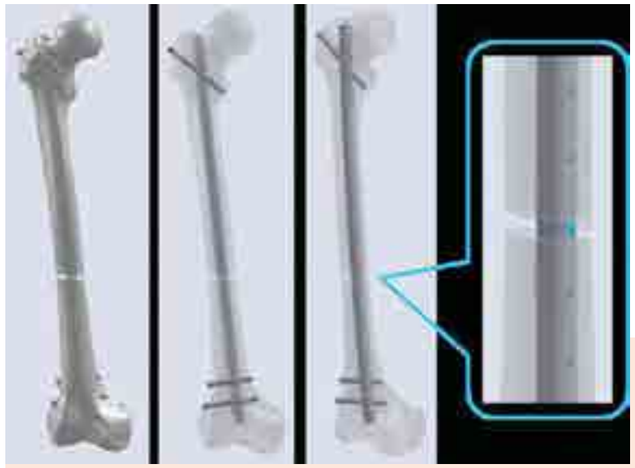



The research team led by Professor Ling Qin focuses on the research and development of innovative orthopaedic implants and drugs or supplements for prevention and treatment of skeletal disorders and injuries with limited healing potential, including patients with impaired healing capacity, large bone defects, and healing at different tissue types such as the bone-tendon/bone-cartilage interface. The team 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), endogenous and exogenous growth factors, and external biophysical stimuli to enhance musculoskeletal tissue regeneration. The goal of the team's 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 collaborate with local and international engineers and material scientists for developing innovative biomaterials and drugs, such as redesigning the current commercially available implant to incorporate with Mg-based components. Recently, the team tested different Mg-based alloys and has applied different coating to prevent the rapid degradation. One innovative approach is that they have modified current commercial available implants to incorporate Mg-based components to enhance bone healing. This hybrid implant, with both conventional titanium metal and Mg components, can deliver Mg to fracture sites also have great potential in facilitating and enhancing fracture healing, which could accelerate an early initiation of mobility and rehabilitation of patients with fractures.

Recently, with collective efforts and endeavours, the team has secured significant research, development and scientific competitive grants, including the Theme-based Research Scheme (T13-402/17-N) and Collaborative Research Fund (C4026-17W), which are two of the most competitive grants given by the Research Grants Council of the Hong Kong Special Administrative Region. The approval of these two milestone research funds acknowledges the scientific and translational value of the team's research and its high potential of application in the clinical setting.





Intramedullary nail and Mg-based metallic button placed in the fractured bone. The nail has multiple holes which allow placement of the button closest to the fracture. When the Mg button degrades and releases Mg ions, these would stimulate and enhance fracture healing.

Source: Wing Ho Chau

## Recognitions

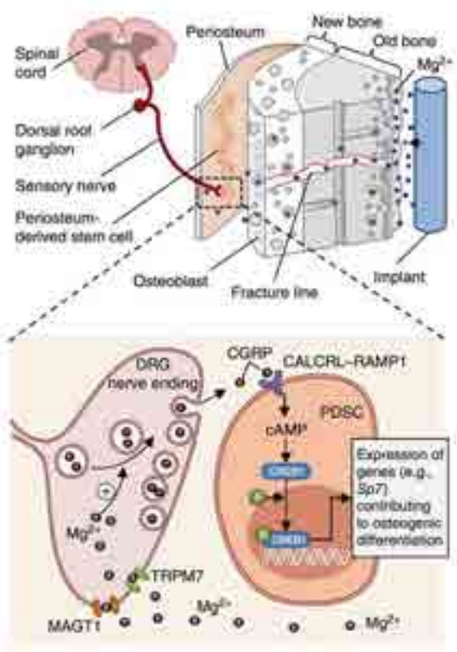
Awards and Fellowships

| Member's Full Name | Details |
|---|---|
| Jiankun Xu | Guest Nation China Best Poster by Orthopaedics Research Society (ORS) |
| Jiankun Xu | Tigris Education Fund Graduate Student Travel Scholarship by Tech Dragon Limited |
| Jiankun Xu | 2017 COA Travelling Scholarship by Hong Kong Orthopaedic Association |
| Hao Yao | Third Young Investigator Prize by The 3rd International Chinese Musculoskeletal Research Conference & the 5th International Biomedical Forum of West China |
| Li Zou | Best Presentation Award for Young Investigator by The 8th WACBE World Congress on Bioengineering |
| Bing Chen | Best Student Oral Presentation Award by The 8th WACBE World Congress on Bioengineering |
| Jiang Yue | APLAR-Celltrion Best Abstract Award by The 19th Congress of Asia Pacific League of Associations for Rheumatology – APLAR 2017 |



Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Ling Qin | Functional Bone Regeneration in Challenging Bone Disorders and Defects | Research Grants Council – Theme-based Research Scheme | 01/11/2017 | 31/10/2022 | 33,333,000 |




Schematic diagram showing diffusion of implant-derived $Mg^{2+}$ across the bone toward the periosteum that is innervated by DRG sensory neurons and enriched with PDSCs undergoing osteogenic differentiation into new bone (top). Inset (shown enlarged at bottom), the released $Mg^{2+}$ enters DRG neurons via $Mg^{2+}$ transporters or channels (i.e., MAGT1 and TRPM7) and promotes CGRP-vesicles accumulation and exocytosis. The DRG-released CGRP, in turn, activates the CGRP receptor (consisting of CALCRL and RAMP1) in PDSCs, which triggers phosphorylation of CREB1 via cAMP and promotes the expression of genes contributing to osteogenic differentiation.

Source: Zhang YF, Xu JK, Ruan YC, Yu MK, O'Laughlin M, Wise H, Chen D, Tian L, Shi DF, Wang JL, Chen SH, Feng JQ, Chow DHK, Xie XH, Zheng LZ, Huang L, Huang S, Leung K, Lu N, Zhao L, Li HF, Zhao DW, Guo X, Chan KM, Witte F, Chan HC, Zheng YF, Qin L. Implant-derived magnesium induces local neuronal production of CGRP to improve bone-fracture healing in rats. *Nature Medicine*. 2016;22(10):1160-9. Doi: 10.1038/nm.4162

## Publications

A. Journal Papers

1. Kong L, Zheng LZ, Qin L, Ho KK. Role of mesenchymal stem cells in osteoarthritis treatment. *Journal of Orthopaedic Translation*. 2017; 9:89-103. (Review)

2. Goodman SB, Qin L. Inflammation and the musculoskeletal system. *Journal of Orthopaedic Translation*. 2017; 10:A1-A2. (Editorial)

3. Wang JL, Xu JK, Song B, Chow DH, Yung PS, Qin L. Magnesium (Mg) based interference screws developed for promoting tendon graft incorporation in bone tunnel in rabbits. *Acta Biomater*. 2017; 63:393-410.

4. Chen SH, Zheng LZ, Zhang JY , Wu H, Wang N, Tong WX, Xu JK, Huang L, Zhang YF, Yang ZJ, Lin G, Wang XL, Qin L. A novel bone targeting delivery system carrying phytomolecule icaritin for prevention of steroid-associated osteonecrosis in rats. *Bone*. 2018; 106:52-60. [Epub ahead of print]

5. Lai YX, Cao HJ, Wang XL , Chen SK, Zhang M, Wang N, Yao ZH, Dai Y, Xie XH, Zhang P, Yao XS, Qin L. Porous composite scaffold incorporating osteogenic phytomolecule icariin for promoting skeletal regeneration in challenging osteonecrotic bone in rabbits. *Biomaterials*. 2018; 153:1-13. [Epub ahead of print]

6. Wang JL, Wu YH, Li HF, Liu Y, Bai XL, Chau WH, Zheng YF, Qin L. Magnesium alloy based interference screw developed for ACL reconstruction attenuates peri-tunnel bone loss in rabbits. *Biomaterials*. 2018; 157:86-97. [Epub ahead of print]

7. Ma H, Chen B, Qin L, Liao WH. Design and testing of a regenerative magnetorheological actuator for assistive knee braces. *Smart Materials and Structures*. 2017; 26(3):035013.

8. Chen B, Zhong CH, Zhao X, Ma H, Guan X, Li X, Liang FY, Cheng JCY, Qin L, Law SW, Liao WH. A wearable exoskeleton suit for motion assistance to paralysed patients. *Journal of Orthopaedic Translation*. 2017; 11:7-18.

9. Chen B, Zhao X, Ma H, Qin L, Liao WH. Design and characterization of a magneto-rheological series elastic actuator for a lower extremity exoskeleton. *Smart Materials and Structures*. 2017; 26(10):105008.

10. Lin S, Lee WY, Xu L, WANG Y, Chen Y, Ho KK, Qin L, Jiang X, Cui L, Li G. Stepwise preconditioning enhances mesenchymal stem cell-based cartilage regeneration through epigenetic modification. *Osteoarthritis and Cartilage*. 2017; 25(9):1541–50.



B. Conference Papers

1. Xu JK, Wang JL, Yue J, Yao H, Zheng NY, Ho KW, Yung SH, Chan KM, Qin L. TGF-β3 and IGF-1 Synthesized in Mg2+-treated Tendon-derived Stem Cell Sheet Secure Functional Repair of Torn Rotator Cuff in Rats. In: *37th Annual Congress of the Hong Kong Orthopaedic Association*; Hong Kong; 2017 Nov 4-5.

2. Zou L, Chu KS, Qin LY, Ma H, Liao WH, Qin L. Design Concept of a Wearable Therapeutic Device for Knee Joint: Treatment and Care of Knee Osteoarthritis (OA). In: *8th WACBE World Congress on Bioengineering*; Hong Kong; 2017 Jul 30 – Aug 2.

3. Chau WH, Cheng YS, Mak FT, Cheung KS, Qin L, Ng BK. A Novel Multi-planar External Fixator developed for Hip Distraction. In: *8th WACBE World Congress on Bioengineering*; Hong Kong; 2017 Jul 30 – Aug 2.

4. Li Y, Long J, Cao HJ, Li L, Wang XL, Lai YX, Qin L. In Vivo Evaluation of the PLGA/TCP/Mg Porous Scaffold Fabricated by 3D-printing for Bone Regeneration. In: *8th WACBE World Congress on Bioengineering*; Hong Kong; 2017 Jul 30 – Aug 2.

5. Chen B, Li X, Zhong CH, Zhao X, Law SW, Liao WH, Qin L. Design of a Wearable Exoskeleton Suit for Motion Assistance in Paraplegic Patients. In: *8th WACBE World Congress on Bioengineering*; Hong Kong; 2017 Jul 30 – Aug 2.

6. Chow DH, Wang JL, Wan P, Yang K, Qin L. Application of Microarc-Oxidation Treated Magnesium Pins for Fixation of Transverse Patellar Fracture in Rabbits. In: *8th WACBE World Congress on Bioengineering*; Hong Kong; 2017 Jul 30 – Aug 2.

7. Xu JK, Wang JL, Yue J, Yao H, Zheng NY, Yung SH, Qin L. TGF-β3 and IGF-1 Synthesized in Mg2+-treated Tendon-derived Stem Cell Sheet Secure Functional Repair of Torn Rotator Cuff in Rats. In: The *12th International Congress of Chinese Orthopaedic Association*; Zhuhai, China; 2017 Nov 15-18.

8. Zheng NY, Liu XD, Zhang,Ri, Ho I, Xu JK, Yao H, Wang JL, Yue J, Wang XL, Qin L. A novel animal model of cervical radiculopathy: mechanical allodynia, glia activation, cytokine elevation and MRI characterization. In: *The 12th International Congress of Chinese Orthopaedic Association*; Zhuhai, China; 2017 Nov 15-18.

9. Xu JK, Zhang YF, Wang JL, Ho KW, Yung SH, Chan KM, Qin L. Unravelling the Connection of Sensory Nerve System and Stem Cells in Magnesium-enhanced Bone Formation. In: *Orthopaedic Research Society 2017 Annual Meeting*; San Diego, California, USA; 2017 Mar 19-22.

10. Chow DH, Wang JL, Wan P, Yang K, Qin L. Fixation of Transverse Patellar Fracture in Rabbits Using Biodegradable Magnesium Pins Treated with Microarc Oxidation. In: *Orthopaedic Research Society 2017 Annual Meeting*; San Diego, California, USA. 2017 Mar 19-22.

11. Huang L, Wang XL, Wang N, Wu H, Zhang JY, Yang ZJ, Qin L. A novel bone targeting delivery system with osteogenic phytomolecule of traditional Chinese herb Epimedium for prevention of the estrogen-depletion induced osteoporosis in mice. In: *Orthopaedic Research Society 2017 Annual Meeting*; San Diego, California, USA; 2017 Mar 19-22.

# 13
# GENOMICS AND BIOINFORMATICS

## Principal Investigator

Professor Hao Sun

## Team

Jiajian Zhou, Kun Sun, Lu Ji, Karl SH So, Jie Yuan, Yingzhe Ding, Yile Huang

## Research Progress Summary

In the reporting period, Professor Hao Sun and his team were funded by several General Research Funds and one Collaborative Research Fund from the Research Grants Council for study of transcriptional regulation mechanisms in muscle stem cell quiescence, activation, and differentiation.









## Recognitions

Awards and Fellowships

| Member's Full Name | Details |
|---|---|
| Karl So | Faculty Postdoctoral Fellowship awarded by Faculty of Medicine, CUHK |



Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Hao Sun | LncRNA Dum Interacts with Dnmts to Regulate Dppa2 Expression during Myogenic Differentiation and Muscle Regeneration | CUHK Research Committee – Direct Grant | 30/06/2016 | 29/06/2017 | 25,000 |
| Hao Sun | Identification and Functional Characterization of Super Enhancer Associated RNAs (seRNAs) in Skeletal Myogenesis Using Integrated Genomic Approach | Research Grants Council – General Research Fund | 01/01/2016 | 31/12/2018 | 1,228,445 |
| Hao Sun | Integrating Large Intergenic Noncoding RNAs into Pax7 Mediated Regulatory Circuitry in Muscle Satellite Cells | Research Grants Council – General Research Fund | 01/01/2015 | 31/12/2017 | 623,277 |
| Hao Sun (Co-PI) | Elucidation of the Role of Pax7 in Muscle Stem Cells | Research Grants Council – Collaborative Research Fund | 30/06/2015 | 29/06/2018 | 5,221,440 |
| Hao Sun (Co-PI) | Transplantation of Vascularised Pancreatic Beta Cells Derived from Human Stem Cells for Type-1 Diabetic Recipients | Food and Health Bureau – Health and Medical Research Fund | 01/06/2016 | 31/05/2018 | 1,199,992 |
| Hao Sun (Co-PI) | Is Smad7 a Potential Therapeutic Target for preventing Osteoporotic Bone Loss? | Research Grants Council – General Research Fund | 01/01/2016 | 31/12/2018 | 821,097 |
| Hao Sun (Co-PI) | Functional Characterization of YY1 in Skeletal Muscle Stem Cells and Muscle Regeneration | Research Grants Council – General Research Fund | 01/01/2016 | 31/12/2018 | 1,182,869 |
| Hao Sun (Co-PI) | 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 (Co-PI) | Functional Characterization of Malat1 in skeletal Muscle Stem Cells and muscle Regeneration | Research Grants Council – General Research Fund | 01/01/2015 | 31/12/2017 | 1,086,500 |

## Publications

A. Journal Papers

1. Sun K, Lun FFM, Jiang P, Sun H. BSviewer: a genotype-preserving, nucleotide-level visualizer for bisulfite sequencing data. *Bioinformatics*. 2017; 33(21):3495-6.

2. An Y, Wang G, Diao Y, Long Y, Fu X, Weng M, Zhou L, Sun K, Cheung TH, Ip NY, Sun H, Wang H, Wu Z. A molecular switch regulating cell fate choice between muscle progenitor cells and brown adipocytes. *Developmental Cell*. 2017; 41(4):382-91.e5.

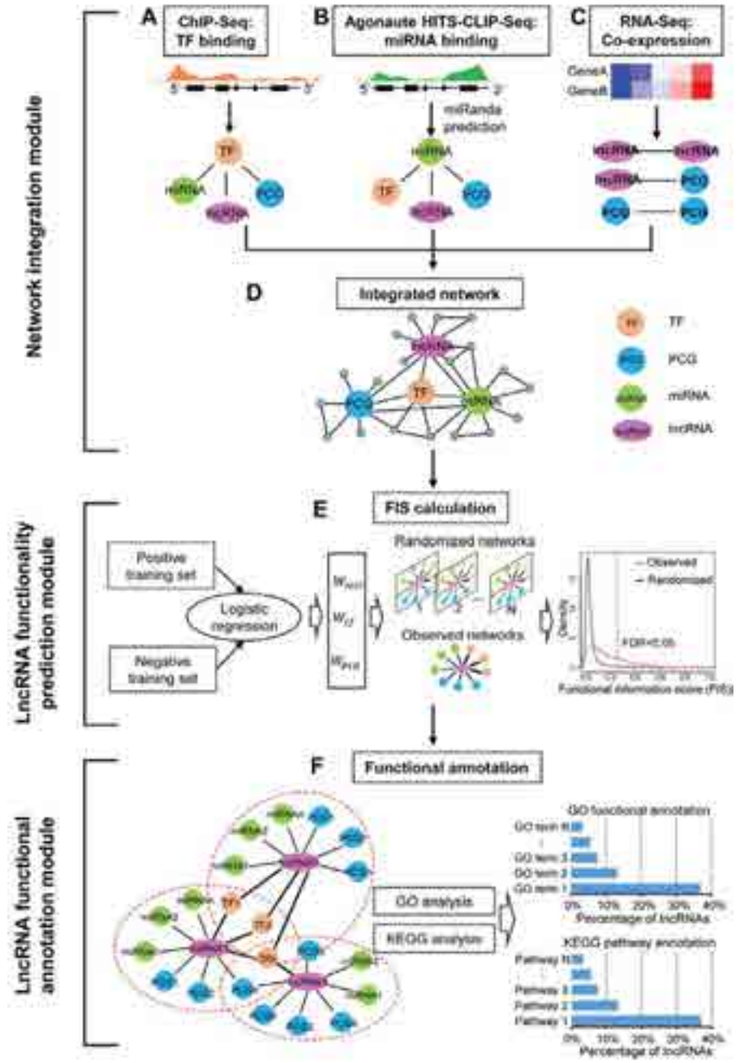
3. Peng X, So KK, He L, Zhao Y, Zhou J, Li Y, Yao M, Xu B, Zhang S, Yao H, Hu P, Sun H, Wang H. MyoD- and FoxO3-mediated hotspot interaction orchestrates super-enhancer activity during myogenic differentiation. *Nucleic Acids Research*. 2017; 45(15):8785-805.

4. Zhou J, Zhang S, Wang H, Sun H. LncFunNet: an integrated computational framework for identification of functional long noncoding RNAs in mouse skeletal muscle cells. *Nucleic Acids Research*. 2017; 45(12):e108.

5. Chen X, He L, Zhao Y, Li Y, Zhang S, Sun K, So K, Chen F, Zhou L, Lu L, Wang L, Zhu X, Bao X, Esteban MA, Nakagawa S, Prasanth KV, Wu Z, Sun H, Wang H. Malat1 regulates myogenic differentiation and muscle regeneration through modulating MyoD transcriptional activity. *Cell Discovery*. 2017; 3:17002.

6. Sun K, Wang H, Sun H. mTFkb: a knowledgebase for fundamental annotation of mouse transcription factors. *Scientific Reports*. 2017; 7(1):3022.






LncFunNet: a computational framework for functional lncRNA identification.
The figure was published by *Nucleic Acids Research*. 2017; 45(12):e108. doi: 10.1093/nar/gkx232

Source: Zhou JJ, Zhang SY, Wang HT, Sun H. LncFunNet: an integrated computational framework for identification of functional long noncoding RNAs in mouse skeletal muscle cells. *Nucleic Acids Research*. 2017;45(12):e108. Doi: https://doi.org/10.1093/nar/gkx232

# 13
# GENOMICS AND BIOINFORMATICS

## Principal Investigator

Professor Peiyong Jiang

## Research Progress Summary

In this year, Professor Peiyong Jiang and his team have made a number of achievements, including:

1. Developed a bioinformatics approach for urinary cell-free DNA analysis, revealing its origin and fragmentation patterns;

2. Developed a novel method for non-invasive fetal chromosomal examination using maternal plasma DNA, which eliminates the requirement of control group, thus improving the accuracy and reducing the cost;

3. Developed a sophisticated bioinformatics tool to enable integrative and synergistic analysis regarding single-cell and cell-free plasma RNA transcriptomics.



## Recognitions

Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Peiyong Jiang (Co-PI) | 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 (Co-I) | Research into Circulating Fetal Nucleic Acids | Research Grants Council – Theme-based Research Scheme | 01/01/2016 | 31/12/2020 | 37,286,000 |





## Publications

A. Journal Papers

1. Sun K, Chan KCA, Hudecova I, Chiu RWK, Lo YMD, Jiang P. COFFEE: control-free noninvasive fetal chromosomal examination using maternal plasma DNA. *Prenatal Diagnosis*. 2017;37(4):336-40.

2. Sun K, Lun F, Jiang P, Sun H. BSviewer: a genotype-preserving, nucleotide-level visualizer for bisulfite sequencing data. *Bioinformatics*. 2017; 33(21):3495-6.

3. Tsang J, Vong J, Ji L, Poon L, Jiang P, Lui K, Ni Y, To K, Cheng Y, Chiu R, Lo Y. Integrative single-cell and cell-free plasma RNA transcriptomics elucidates placental cellular dynamics. *Proceedings of the National Academy of Sciences*. 2017; 114(37):E7786-95.

4. Cheng T, Jiang P, Tam J, Sun X, Lee W, Yu S, Teoh J, Chiu P, Ng C, Chow K, Szeto C, Chan K, Chiu R, Lo Y. Genomewide bisulfite sequencing reveals the origin and time-dependent fragmentation of urinary cfDNA. *Clinical Biochemistry*. 2017; 50(9):496-501.

5. Vong J, Tsang J, Jiang P, Lee W, Leung T, Chan K, Chiu R, Lo Y. Single-Stranded DNA Library Preparation Preferentially Enriches Short Maternal DNA in Maternal Plasma. *Clinical Chemistry*. 2017; 63(5):1031-7.

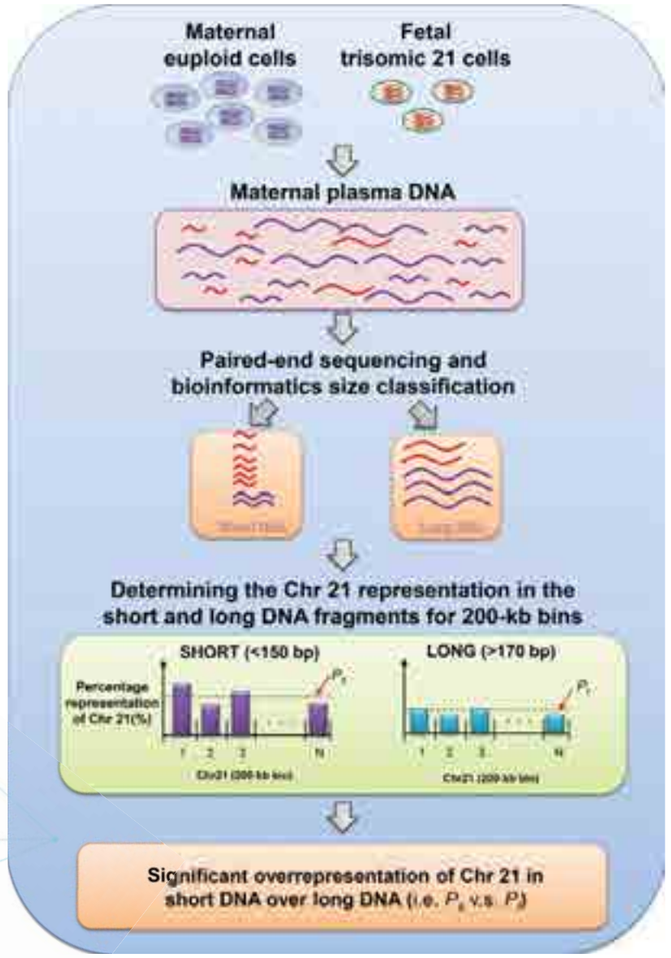
6. Lam W, Gai W, Sun K, Wong R, Chan R, Jiang P, Chan N, Hui W, Chan A, Szeto C, Ng S, Law M, Chan K, Chiu R, Lo Y. DNA of Erythroid Origin Is Present in Human Plasma and Informs the Types of Anemia. *Clinical Chemistry*. 2017; 63(10):1614-23.

7. Hudecova I, Jiang P, Davies J, Lo Y, Kadir R, Chiu R. Noninvasive detection of F8 int22h -related inversions and sequence variants in maternal plasma of hemophilia carriers. *Blood*. 2017; 130(3):340-7.

8. Peng XL, Jiang PY. Bioinformatics Approaches for Fetal DNA Fraction Estimation in Noninvasive Prenatal Testing. *International Journal of Molecular Sciences*. 2017; 18(12):453. (Review)

B. Conference Papers

1. Arram J, Kaplan T, Luk W, Jiang P. Leveraging FPGAS for accelerating short read alignment. *IEEE/ACM Transactions on Computational Biology and Bioinformatics*. 2017; 14(3):668-77.




Schematic workflow of control-free noninvasive fetal chromosomal examination. Maternal plasma contains a mixture of fetal DNA molecules (wavy red lines) and maternal DNA molecules (wavy black lines) originating from fetal and maternal cells, respectively. For a woman pregnant with a trisomic fetus, the short DNA originating from the affected chromosome would be overrepresented in her plasma compared with the long DNA molecules because the fetal DNA molecules are shorter than the maternal ones. After aligning the paired-end reads to the human reference genome, the cell-free DNA sizes are deduced by using the coordinates of the outermost nucleotide at each end. Plasma DNA molecules were sorted into two categories according to their sizes *in silico*. The plasma DNA molecules shorter than 150 bp and longer than 170 bp were assigned to the short and long categories, respectively. The chromosome being tested was divided into 200-kb bins, and the proportion of reads falling within each bin was calculated for the short and long categories, respectively. A paired Mann–Whitney rank-sum test was then performed using the proportions of reads between two categories. A p-value cutoff of 0.001 was used to determine the fetal chromosomal aneuploidy status.

Source: Sun K, Chan KCA, Hudecova I, Chiu RWK, Lo YMD, Jiang PY. COFFEE: control-free noninvasive fetal chromosomal examination using maternal plasma DNA. Prenatal Diagnosis. 2017;37(4):336-40. Doi: 10.1002/pd.5016

# 14
# NON-CODING RNAs

## Principal Investigator

Professor Huating Wang

## Team

Xiaona Chen, Yu Zhao, Karl So, Fengyuan Chen

## Research Progress Summary

During the past year, the team led by Professor Huating Wang continued the work on enhancer regulation and investigated functional roles of enhancers associated RNAs (eRNAs) in normal cellular processes and human diseases. Specifically, they have been focusing on the following projects: (1) to study the functional roles of eRNAs in skeletal muscle stem cells and muscle regeneration; (2) to elucidate the functional roles of a lncRNA, Sam in skeletal myoblast differentiation; and (3) to identify and characterise the enhancer deregulation in sarcopenia, a muscle weakening condition associated with ageing.

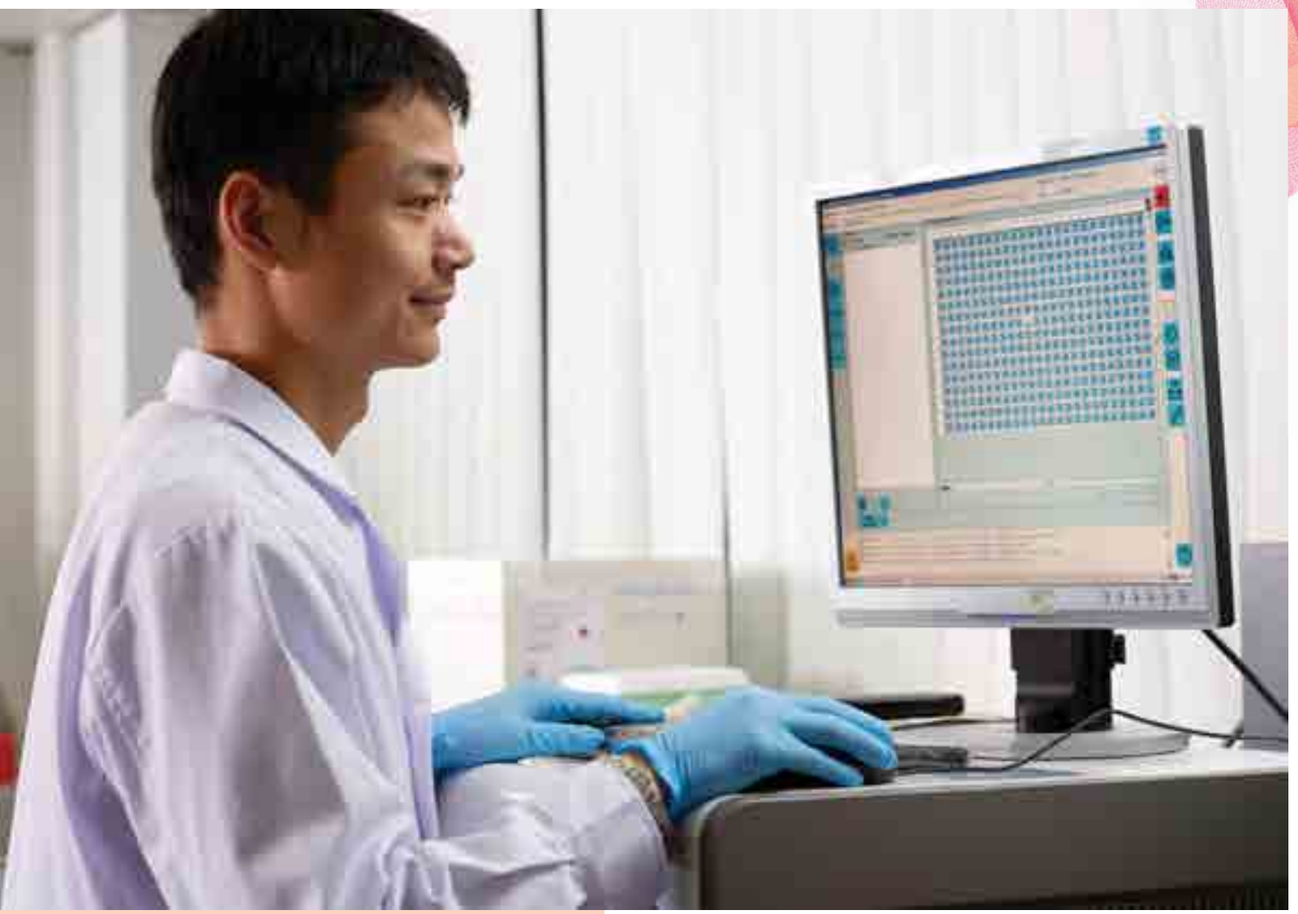




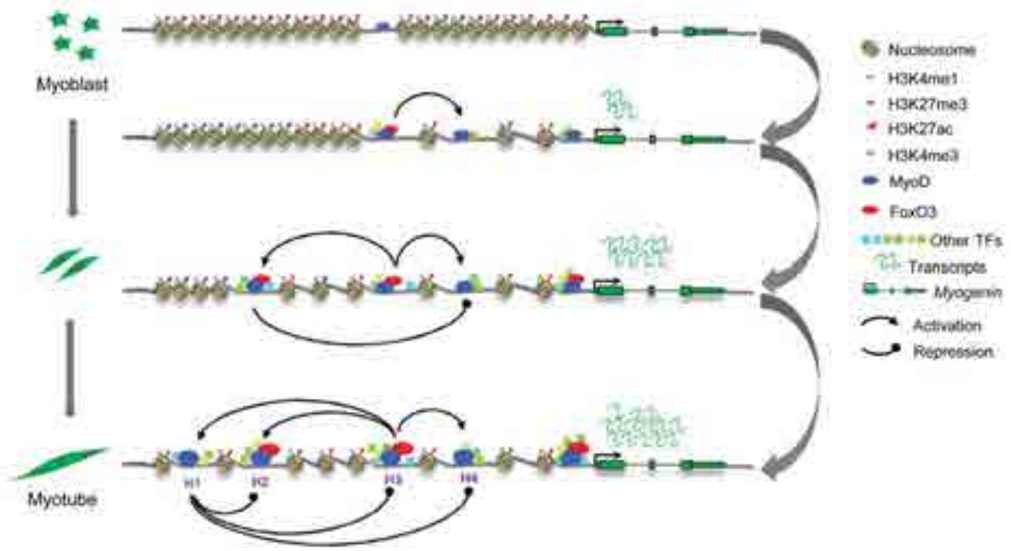
## Recognitions

Awards and Fellowships

| Member's Full Name | Details |
|---|---|
| Yu Zhao | Faculty Postdoctoral Fellowship awarded by Faculty of Medicine, CUHK |
| Karl So | Faculty Postdoctoral Fellowship awarded by Faculty of Medicine, CUHK |








Schematic illustration of MyoD/FoxO3 mediated hotspot interaction that orchestrates Myogenin SE activation during MB differentiation. The dominant H3 hotspot is primed in the MB by MyoD binding; upon early differentiation, binding of FoxO3 further amplifies its activity and subsequent interaction with H4; H3 next interacts with H2 and H1 to activate their formation; H1 appears to repress the other three hotspots thus acting as a brake. Altogether the hierarchical activation of the four hotspots orchestrates the Myogenin gene expression.

Source: Peng XL, So KK, He LQ, Zhao Y, Zhou JJ, Li YY, Yao MZ, Xu B, Zhang SY, Yao HJ, Hu P, Sun H, Wang HT. MyoD- and FoxO3-mediated hotspot interaction orchestrates super-enhancer activity during myogenic differentiation. *Nucleic Acids Research*. 2017;45(15):8785-805. Doi: 10.1093/nar/gkx488

Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| Huating Wang | LncRNA Dum Interacts with Dnmts to Regulate Dppa2 Expression during Myogenic Differentiation and Muscle Regeneration | CUHK Research Committee – Direct Grant | 30/06/2016 | 29/06/2017 | 25,000 |
| Huating Wang | Mechanistic Exploration of Super-enhancer Associated seRNA Function in Skeletal Muscle Cells | Research Grants Council – General Research Fund | 01/01/2016 | 31/12/2019 | 922,171 |
| Huating Wang (Co-I) | Identification and Functional Characterization of Super Enhancer Associated RNAs (seRNAs) in Skeletal Myogenesis using Integrated Genomic Approach | Research Grants Council – General Research Fund | 01/01/2016 | 31/12/2018 | 1,228,445 |
| Huating Wang (Co-I) | Role of a Newly Identified Long Noncoding RNA in Sarcopenia | Research Grants Council – General Research Fund | 01/01/2016 | 31/12/2018 | 1,009,452 |
| Huating Wang | 利用CRISPR-Cas9技術探索胚胎幹細胞中超級增強子的功能 | 中國科學院再生生物學重點實驗室開放課題 | 10/2015 | 10/2017 | RMB 50,000 |
| Huating Wang | Functional Characterization of YY1 in Skeletal Muscle Stem Cells and Muscle Regeneration | Research Grants Council – General Research Fund | 01/01/2015 | 31/12/2018 | 1,182,869 |
| Huating Wang (Co-I) | Integrating Large Intergenic Noncoding RNAs into Pax7 Mediated Regulatory Circuitry in Muscle Satellite Cells | Research Grants Council – General Research Fund | 01/01/2015 | 31/12/2018 | 623,277 |
| Huating Wang (Co-I) | Elucidation of the Role of Pax7 in Muscle Stem Cells | Research Grants Council – Collaborative Research Fund | 01/08/2015 | 31/07/2018 | 750,000 |
| Huating Wang | Functional Characterization of Malat1 in Skeletal Muscle Stem Cells and Muscle Regeneration | Research Grants Council – General Research Fund | 01/01/2014 | 31/12/2017 | 1,086,500 |
| Huating Wang (Co-I) | 多能幹細胞向中胚層細胞分化的研究機制 | 973 Program, China | 01/01/2014 | 31/12/2017 | RMB 1,080,000 |
| Huating Wang | Is there a Link between Systemic Muscle Mass, Muscle Strength, Serum and Muscle Expression of Myokines and LBX1 with Bone Mineral Density and Bone Quality in Adolescent Idiopathic Scoliosis? | Research Grants Council – General Research Fund | 01/01/2016 | 31/12/2018 | 593,675 |
| Huating Wang | Functional Study of Super-enhancers and Associated seRNAs in Skeletal Muscle Cells | CUHK Focused Innovations Scheme – Scheme B | 01/01/2017 | 31/05/2019 | 2,000,000 |
| Huating Wang | Linc-YY1 Promotes Myogenic Differentiation and Muscle Regeneration through an Interaction with the Transcription Factor YY1 | CUHK Research Committee – Direct Grant | 30/01/2017 | 29/01/2018 | 26,250 |

## Publications

A. Journal Papers

1. Li Y, Chen X, Sun H, Wang H. Long non-coding RNAs in the regulation of skeletal myogenesis and muscle diseases. *Cancer Letters*. 2018; 417:58-64. [Epub ahead of print]

2. Zhang J, Jiang Y, Zhao Y, Wang W, Xie Y, Wang H, Yang Y. Downregulation of tyrosine threonine kinase inhibits tumor growth via G2/M arrest in human endometrioid endometrial adenocarcinoma. *Tumor Biology*. 2017; 39(7):101042831771244.

3. Sun K, Wang H, Sun H. mTFkb: a knowledgebase for fundamental annotation of mouse transcription factors. *Scientific Reports*. 2017; 7(1):3022.

4. An Y, Wang G, Diao Y, Long Y, Fu X, Weng M, Zhou L, Sun K, Cheung TH, Ip NY, Sun H, Wang H, Wu Z. A molecular switch regulating cell fate choice between muscle progenitor cells and brown adipocytes. *Developmental Cell*. 2017; 41(4):382-91.e5.

5. Peng X, So KK, He L, Zhao Y, Zhou J, Li Y, Yao M, Xu B, Zhang S, Yao H, Hu P, Sun H, Wang H. MyoD- and FoxO3-mediated hotspot interaction orchestrates super-enhancer activity during myogenic differentiation. *Nucleic Acids Research*. 2017; 45(15):8785-805.

6. Zhou J, Zhang S, Wang H, Sun H. LncFunNet: an integrated computational framework for identification of functional long noncoding RNAs in mouse skeletal muscle cells. *Nucleic Acids Research*. 2017;45(12):e108.

7. Chen X, He L, Zhao Y, Li Y, Zhang S, Sun K, So K, Chen F, Zhou L, Lu L, Wang L, Zhu X, Bao X, Esteban MA, Nakagawa S, Prasanth KV, Wu Z, Sun H, Wang H. Malat1 regulates myogenic differentiation and muscle regeneration through modulating MyoD transcriptional activity. *Cell Discovery*. 2017; 3:17002.

B. Books / Book Chapters

1. So, K., Peng, X., Sun, H. and Wang, H. Whole Genome Chromatin IP-Sequencing (ChIP-Seq) in Skeletal Muscle Cells. In: E. Perdiguero and D. Cornelison, ed. *Methods in Molecular Biology Skeletal Muscle Development*. New York: Humana Press; 2017:15-25.

2. Peng, X., Sun, K., Zhou, J., Sun, H. and Wang, H. Bioinformatics for Novel Long Intergenic Noncoding RNA (lincRNA) Identification in Skeletal Muscle Cells. In: E. Perdiguero and D. Cornelison, ed. *Methods in Molecular Biology Skeletal Muscle Development*. New York: Humana Press; 2017:355-62.







C. Conference Papers

1. Peng X, So KK, He L, Zhao Y, Zhou J, Li Y, Yao M, Xu B, Zhang S, Yao H, Hu P, Sun H, Wang H. MyoD and FoxO3 mediated hotspot interaction orchestrates super-enhancer activity during myogenic differentiation. In: *2017 National Academic Conference for Cell Biology*, Xiamen, China; 2017 Sep 26-29.

2. Chen F, Zhou J, Li Y, Zhao Y, Sun H, Wang H. Deletion of YY1 in satellite cells reveals its function in regulating satellite cell metabolism. In: *The 8th Annual Meeting of Chinese Society for Development Biology*, China; 2017 May.

3. Peng X, So KK, He L, Zhao Y, Zhou J, Li Y, Yao M, Xu B, Yao H, Hu P, Sun H, Wang H. MyoD and FoxO3 mediated hotspot interaction orchestrates super-enhancer activity during myogenic differentiation. In: *The 2017 Myogenesis Gordon Research Conference*, Barga, Italy; 2017 Jun 11-16.

4. Peng X, So KK, He L, Zhao Y, Zhao J, Li Y, Yao M, Xu B, Yao H, Hu P, Sun H, Wang H. MyoD and FoxO3 mediated hotspot interaction orchestrates super-enhancer activity during myogenic differentiation. In: *The 2017 Conference on Genome Architecture in Cell Fate and Disease*, Hong Kong; 2017 Jul 2-7.

# 15
# CELLULAR SIGNALLING

## Principal Investigator

Professor William Wu

## Team

Tony Gin, Matthew TV Chan, Lin Zhang, Jeffery Ho, Coral S Zhao, Xiaodong Liu, Yuanyuan Tian, Shanglong Kou, Idy HT Ho, Taian Liu, Qing Li, Hung Chan, Xiansong Wang, Xiaoting Chen, Zhongqing Sun, TP Tam

## Research Progress Summary

**Cancer Genomics and Biology** – Cancer genomics were investigated from an evolutionary perspective so as to understand tumourigenesis at its root. Oncogenes and tumour-suppressor genes (TSGs) were found to cluster together in the human genome. Importantly, the existence of a neighbouring TSG suppresses amplification of an oncogene, shedding new light on a previously unappreciated protective mechanism of TSGs. In another study, they found that the expression of miR-379 was downregulated in osteosarcoma, in which miR-379 suppressed osteosarcoma cell proliferation and invasion *in vitro* and retarded the growth of osteosarcoma xenografts *in vivo*. Mechanistically, PDK1 was identified as the direct target of miR-379. These data suggest that miR-379 could function as a tumour-suppressing miRNA via targeting PDK1 in osteosarcoma.

**Infection** – A territory-wide population-based observational study was conducted to investigate the burden and clinical outcomes in Hong Kong. It was found that the incidence has an annual increase of 26% from 2006 to 2014. This increase was associated with elderly patients. These data suggest the need for further surveillance, especially in Asia.





**Systematic Reviews and Meta-analyses** – A meta-analysis was conducted to examine the association between eosinophilia and clinical outcome in patients with chronic obstructive pulmonary disease (COPD). While COPD patients with or without eosinophilia had a similar risk for exacerbation in 12 months and in-hospital mortality, eosinophilia was associated with reduced length of hospital stay and better performance in pulmonary function tests subsequent to steroidal and bronchodilator therapies. Improvement of quality of life was observed in eosinophilic subjects, independent of hospitalisation status. In conclusion, blood eosinophilia may be predictive of favourable response to therapeutic interventions in patients with stable COPD. Systemic reviews were also conducted to examine the roles of bacterial small RNAs in antibiotic resistance and endogenous host defence peptides in adult and neonatal sepsis.

## Recognitions

Grants and Consultancy

| Full Name of PI | Project Title | Funding Source | Start Date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Amount (HK$) |
|---|---|---|---|---|---|
| William Wu | Elucidating the Role of Autophagy in the Pathogenicity of *Clostridium difficile* Infection | Food and Health Bureau – Health and Medical Research Fund | 10/09/2016 | 09/09/2018 | 1,199,040 |
| William Wu | Targeting Defective Autophagy and its Molecular Sequelae in Non-alcoholic Fatty Liver Disease-related Hepatocellular Carcinoma | Research Grants Council – General Research Fund / Early Career Scheme | 01/01/2016 | 31/12/2018 | 813,275 |
| William Wu | The Role of Autophagy in CD24-Driven Colorectal Tumourigenesis | The Natural Science Foundation of Guangdong Province, Department of Science and Technology of Guangdong Province | 01/08/2015 | 01/08/2018 | 113,000 (RMB 100,000) |
| William Wu | Therapeutic Potential of Autophagosomal-lysosomal Impairment in Non-alcoholic Fatty Liver Disease | Shenzhen Science and Technology Programme, Shenzhen Science and Technology Innovation Commission | 06/11/2015 | 16/11/2017 | 226,000 (RMB 200,000) |
| William Wu | Detection and Characterization of Novel / Unrecognized Microbial Pathogens Associated with Unexplained Severe Sepsis | Food and Health Bureau – Commissioned Research on Control of Infectious Diseases | 01/04/2015 | 31/03/2017 | 300,000 |
| 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 |
| Matthew Chan | Targeting Anesthetic Depth to Prevent Postoperative Delirium: A Randomized Controlled Trial | Food and Health Bureau – Health and Medical Research Fund | 01/07/2016 | 30/06/2018 | 1,194,448 |
| Matthew Chan | The Role of Annexin II in Opioid-induced Hyperalgesia | Australian and New Zealand College of Anaesthetists | 01/01/2017 | 31/12/2017 | 344,612 (AUD 56,000) |
| Matthew Chan | Vascular Events In Surgery Patients Cohort Evaluation (VISION) – Cardiac Surgery Study | Research Grants Council – General Research Fund | 01/01/2015 | 31/12/2017 | 1,051,942 |
| Matthew Chan | Pharmacokinetics of Oseltamivir in Critically Ill Patients with Severe Influenza | Food and Health Bureau – Commissioned Research on Control of Infectious Diseases | 01/04/2015 | 31/03/2017 | 290,000 |
| Lin Zhang | Activating Mucolipin for Restoring Lysosomal Function in the Control of *Helicobacter Pylori* Colonization | Food and Health Bureau – Health and Medical Research Fund | 01/09/2017 | 31/08/2019 | 1,198,360 |
| Lin Zhang | The Mechanisms of Cathelicidin in *Fusobacterium nucleatum* induced Colon Cancer | The National Natural Science Foundation of China | 01/01/2015 | 31/12/2017 | 259,900 (RMB 230,000) |



## Publications

A. Journal Papers

1. Wu WK, Li X, Wang X, Dai RZ, Cheng AS, Wang MH, Kwong T, Chow TC, Yu J, Chan MT, Wong SH. Oncogenes without a neighboring tumor-suppressor gene are more prone to amplification. *Molecular Biology and Evolution*. 2017; 34(4):903-7.

2. Tse G, Liu T, Li G, Keung W, Yeo JM, Chan YW, Yan BP, Chan YS, Wong SH, Li RA, Zhao J, Wu WK, Wong WT. Effects of pharmacological gap junction and sodium channel blockade on S1S2 restitution properties in Langendorff-perfused mouse hearts. *Oncotarget*. 2017; 8(49): 85341-52.

3. Ho J, He W, Chan MT, Tse G, Liu T, Wong SH, Leung CC, Wong WT, Tsang S, Zhang L, Chan RYP, Gin T, Leung J, Lau BW, Wu WK, Ngai SP. Eosinophilia and clinical outcome of chronic obstructive pulmonary disease: a meta-analysis. *Scientific Reports*. 2017; 7(1):13451.

4. Li Z, Shen J, Chan MT, Wu WK. MicroRNA-379 suppresses osteosarcoma by targeting PDK1. *Journal of Cellular and Molecular Medicine*. 2017; 21(2):315-23.

5. Chan H, Ho J, Liu X, Zhang L, Wong SH, Chan MT, Wu WK. Potential and use of bacterial small RNAs to combat drug resistance: a systematic review. *Infection and Drug Resistance*. 2017; 10:521-32. (Review)

6. Ho J, Zhang L, Liu X, Wong SH, Lau BW, Ngai SP, Chan H, Choi G, Leung CC, Wong WT, Tsang S, Gin T, Yu J, Chan MT, Wu WK. Pathological role and diagnostic value of endogenous host defense peptides in adult and neonatal sepsis: a systematic review. *Shock*. 2017; 47(6):673-9. (Review)

7. Yu X, Zheng H, Chan MT, Wu WK. HULC: An oncogenic long non-coding RNA in human cancer. *Journal of Cellular and Molecular Medicine*. 2017; 21(2):410-7. (Review)

8. Li Z, Shen J, Chan MT, Wu WK. The role of microRNAs in intrahepatic cholangiocarcinoma. *Journal of Cellular and Molecular Medicine*. 2017; 21(1):177-84. (Review)

9. Yu X, Li Z, Zheng H, Ho J, Chan MT, Wu WK. Protective roles of melatonin in central nervous system diseases by regulation of neural stem cells. *Cell Proliferation*. 2017; 50(2):e12323. (Review)

10. Yu X, Li Z, Zheng H, Chan MT, Wu WK. NEAT1: A novel cancer-related long non-coding RNA. *Cell Proliferation*. 2017; 50(2):e12329. (Review)

11. Yu X, Li Z, Zheng H, Chan MT, Wu WK. CCAT2: a novel oncogenic long non-coding RNA in human cancers. *Cell Proliferation*. 2017; 50(3):e12342. (Review)

12. Yu X, Li Z, Zheng H, Ho J, Chan MT, Wu WK. Neuro-oncological ventral antigen 1 (NOVA1): Implications in neurological diseases and cancers. *Cell Proliferation*. 2017;5 0(4):e12348. (Review)

13. Yu X, Zheng H, Chan MT, Wu WK. BANCR: a cancer-related long non-coding RNA. *American Journal of Cancer Research*. 2017;7(9):1779-87. (Review)



14. Yu X, Zheng H, Chan MT, Wu WK. MicroRNAs: New players in cataract. *American Journal of Translational Research*. 2017;9(9):3896-903. (Review)

15. Chan MT, Chu MH, Lam CK, Jia B, Tsang S, Wu WK. Deep anesthesia: Too much of a good thing? *Canadian Journal of Anaesthesia*. 2017; 64(6):574-80. (Editorials)

16. Tse G, Wu WK, Gong M, Bazoukis G, Wong WT, Wong SH, Lampropoulos K, Baranchuk A, Tse LA, Xia Y, Li G, Wong MCS, Chan YS, Mu N, Dong M, Liu T; International Health Informatics Study (IHIS) Network. Patent foramen ovale closure versus medical therapy for stroke prevention: A systematic review and meta-analysis of randomized controlled trials. *F1000Research*. 2017; 6:2178. (Review)

17. Wong SH, Kwong TN, Chow TC, Luk AKC, Dai DZ, Nakatsu G, Zhang L, Lam TY, Wu JC, Chan FK, Ng SS, Wong MC, Ng SC, Wu WK, Yu J, Sung JJ. Quantitation of faecal *Fusobacterium* improves faecal immunochemical test in detecting advanced colorectal neoplasia. *Gut*. 2017; 66(8):1441-8.

18. Yu J, Feng Q, Wong SH, Liang Q, Qin Y, Tang L, Zhao H, Liang Y, Stenvang J, Wang X, Xu X, Chen N, Wu WK, Al-Aama J, Nielsen HJ, Kiilerich P, Jensen B, Yau PT, Lan Z, Jia H, Li J, Xiao L, Lam TY, Ng SC, Cheng AS, Wong VW, Chan FK, Xu X, Yang H, Madsen L, Datz C, Tilg H, Wang J, Brünner N, Kristiansen K, Arumugam M, Sung JJ, Wang J. Metagenomic analysis of faecal microbiome as a tool towards targeted non-invasive biomarkers for colorectal cancer. *Gut*. 2017; 66(1):70-8.

19. Li Z, Li X, Chen C, Chan MT, Wu WK, Shen J. Melatonin inhibits nucleus pulposus cell proliferation and extracellular matrix remodeling via the melatonin membrane receptors mediated PI3K-Akt pathway. *Journal of Pineal Research*. 2017; 63(3):e12435.

20. Zhou Y, Huang T, Kang W, Wong CC, Zhang B, Dong Y, Tong JH, Wu WK, Cheng AS, Yu J, To KF. TEAD1/4 exerts oncogenic role and is negatively regulated by miR-4269 in gastric tumourigenesis. *Oncogene*. 2017; 36(47):6518-30.

21. Tse G, Gong M, Nunez J, Sanchis J, Li G, Ali-Hasan-Al-Saegh S, Wong WT, Wong SH, Wu WK, Bazoukis G, Yan GX, Lampropoulos K, Baranchuk AD, Tse LA, Liu T, Woo J; International Health Informatics Study (IHIS) Network. Frailty and mortality outcomes after percutaneous coronary intervention: a systematic review and meta-analysis. *Journal of the American Medical Directors Association*. 2017; 18(12):1097.e1-1097.e10.

22. Li Z, Li X, Chan MT, Wu WK, Tan D, Shen J. Melatonin antagonizes interleukin-18-mediated inhibition on neural stem cell proliferation and differentiation. *Journal of Cellular and Molecular Medicine*. 2017; 21(9):2163-71.

23. Tse G, Gong M, Wong CW, Wong WT, Georgopoulos S, Letsas KP, Vassiliou VS, To OT, Chan YS, Yan BP, Wong SH, Li G, Whittaker P, Ali-Hasan-Al-Saegh S, Bhardwaj A, Sawant AC, Wu WKK, Chu A, Xia Y, Baranchuk A, Yan GX, Lui KO, Liu T. Prediction of arrhythmic and mortality outcomes using Tpeak – Tend interval and Tpeak – Tend/QT ratio in long QT syndrome populations: a systematic review and meta-analysis. *Heart Rhythm*. 2017; 14(8):1131-7.

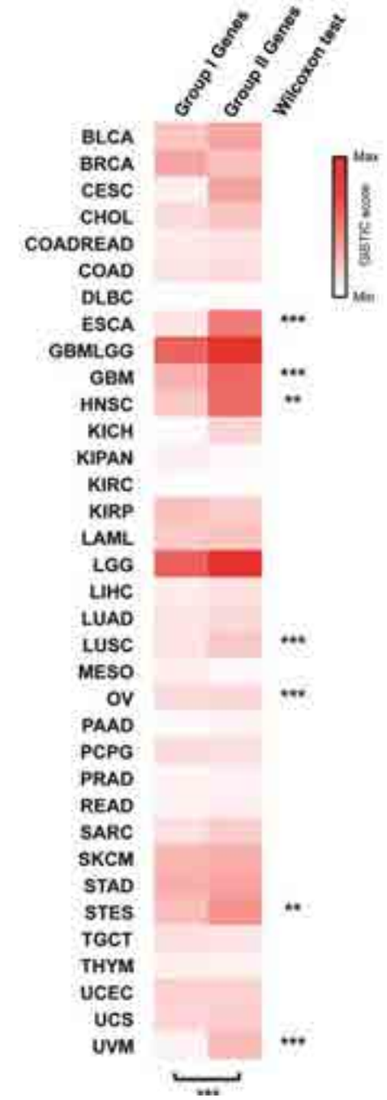
24. Wong CC, Zhang L, Wu WK, Shen J, Chan RL, Lu L, Hu W, Li MX, Li FL, Ren SX, Li YF, Li J, Cho CH. Cathelicidin-encoding *Lactococcus lactis* promotes mucosal repair in murine experimental colitis. *Journal of Gastroenterology and Hepatology*. 2017; 32(3):609-19.

25. Bayoumy A, Gong MQ, Christien Li KH, Wong SH, Wu WK, Li GP, Bazoukis G, Letsas KP, Wong WT, Xia YL, Liu T, Tse G; International Health Informatics Study (IHIS) Network. Spontaneous type 1 pattern, ventricular arrhythmias and sudden cardiac death in Brugada Syndrome: an updated systematic review and meta-analysis. *Journal of Geriatric Cardiology*. 2017; 14(10):639-43. (Letter to the Editor)

26. Liu Q, Wang Q, Liu H, Wu WK, Chan MT. Warning criteria for intraoperative neurophysiologic monitoring. *Current Opinion in Anaesthesiology*. 2017; 30(5):557-62. (Review)

27. Lam EK, Tai EK, Wu WK, Yu L, Wong HP, Shin VY, Cho CH. Differential effects of lipoteichoic acid and lipopolysaccharides on gastric cancer cell proliferation via distinctive involvement of TLR2 signaling mediators. *Archives of Digestive Disorder*. 2017; 1(1):22-7.






Effects of neighbouring TSG(s) on the propensity of oncogenes to copy number alterations and nonsynonymous point mutations. Oncogenes with a neighbouring TSG (i.e., within a 1.46-Mbp radius; Group I oncogenes) were amplified to a lesser extent in TCGA-sequenced cancer types than those without (Group II oncogenes). Wilcoxon test was used to compare the GISTIC scores of two groups of oncogenes. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ significantly different between groups.

Source: Wu WKK, Li XC, Wang XS, Dai RZW, Cheng ASL, Wang MHT, Kwong T, Chow TC, Yu J, Chan MTV, Wong SH. Oncogenes without a Neighboring Tumor-Suppressor Gene Are More Prone to Amplification. Molecular Biology and Evolution. 2017;34(4):903-7. Doi: https://doi.org/10.1093/molbev/msw295

# INTERVIEWS OF PRINCIPAL INVESTIGATORS
# 與首席研究員對話



Professor Gary Tse
謝家偉教授



Professor William Wu
胡嘉麒教授



Professor Siew Ng
黃秀娟教授



Dr. Owen Ko
高浩醫生



Professor Erik Fung
馮以文教授



# Interview with Professor Siew Ng
## 黃秀娟教授

*Professor Siew Ng has joined the Faculty of Medicine, CUHK since 2010, after staying in the UK for more than 15 years. Prof. Ng's major research interests are Inflammatory Bowel Disease (IBD) and Colorectal Cancer. She is the pioneer in carrying out the first large scale epidemiologic study of IBD across various countries in Asia-Pacific and an Asian Microbiota Consortium, and has recently published the valuable findings in the high impact journal, the Lancet.*



**1 We noted that you obtained your PhD in Immunology in Imperial College London in 2009 and joined the Department of Medicine and Therapeutics of CUHK in 2010. How does your experience doing a PhD or training overseas influence your career and life?**

If you ask me if I would do the same, I would definitely do my PhD in the UK again. I have learnt a lot of invaluable lessons, which include perseverance, patience and critical thinking, and above all how to embrace failures. There were times that experiments may not work (in fact most of the times!). What we must not forget is that negative findings are sometimes just as important and what matters is how we can turn these findings into something meaningful for the patients.

I was quite fortunate to have spent over 15 years in the UK and had the chance to be exposed to the British culture of research, which is somewhat innovative and creative. I was and am surrounded by peers who are very inspiring and industrious. Both the environment and people I met has shaped my way of thinking and made me want to be in the centre of cutting-edge of research. So, every time I meet a patient, I could hopefully deliver the best and the most updated care to them.



*The Colours of Life and Research: Prof. Ng (far right) and her research team from St Mark's Hospital, Imperial College in London attending the Royal Ascot in 2007 as part of their research team retreat.*

**2 You are leading a strong translational research team consisting of clinicians and basic scientists. What challenges have you encountered while building up the research team?**

Since joining The Chinese University of Hong Kong, Faculty of Medicine, it has always been my dream to develop a translational research team. I remembered when I first moved to Hong Kong about 7.5 years ago, I was interested in Inflammatory Bowel Diseases (IBD) which was a rare condition here at that time. I started as a one-man band, just basically one person, and I used to share my research staffs with other Principal Investigators.

I was very fortunate, because our ex-vice-chancellor, and my mentor, Prof. Joseph Sung, not only employed me but he gave me flexibilities and ample opportunities to explore my passion. I was working at the Prince of Wales Hospital then, and noted that our inpatient wards and endoscopy unit was in the same block as our research facilities and laboratories. This is a unique platform to do translational research because we can bring the scientists and clinicians together. Not many institutes around the world would have this luxury.

I think the biggest challenge is that scientists and clinicians are two types of people. Since they work at different pace, and have different ways of thinking, bringing them together to share a common goal takes time. It took me about 5 years to develop the team. You may not always need to find the best people, but what is more important is the right people for the team. Now we have a big team consisting of basic scientists, PhD students, research assistants, bioinformaticians and dietitians etc., who all have different expertise. When you look at things from different perspectives, you would get a lot of new ideas. The future is exciting yet challenging as we are developing more microbiome-related research for inflammatory diseases within the team and we hope to keep the momentum going.



*The Heroes / Heroin behind the Scene: Celebrating spring festival with her clinical and laboratory research team at her college (Lee Woo Sing) at CUHK. "Their passion, dedication and friendship are priceless."*

## 3

**Can you share with us how your research in IBD first started?**

I did my PhD in immunology. I worked with one cell type which was called the dendritic cell and it is an immune cell, also known as the conductor of the immune orchestra. It is probably one of the most important cells which dictate your immune responses subsequently and can cause many diseases if it does not work. This has stimulated my interest to continue working with IBD whereby we know the immune system is partly not functioning well. The disease would start quite young in teenage years and patients would have to live with it for a long time throughout their lives, and we do not have a cure yet.

When I first moved to Hong Kong, IBD was rare and people used to call it a "western" disease. However, after a few years, the outpatient wards were overwhelmed by young men and women who had IBD. We started thinking for research directions. One of the things we started working with was genetics, because we know that the genetics are quite different in the western and eastern populations. With all the new technologies, which we called GWAS (Genome-wide Association Study) and Immunochip platforms, we can genotype hundreds to thousands of patients to define the differences in genes and treatment pathways.

Later, we discovered that it could not be the genes that caused the disease, because our genetic profiles would not change in just 10 or 20 years. It is probably something in the environment that caused the disease. We first asked the question of why suddenly so many patients have this disease; and how common is it? To define how common a disease is, we look at the incidence of the disease. Then we look into the environment and identify some important factors or risks, such as hygiene factors, dietary factors including westernisation of diet, early childhood factors like breastfeeding or antibiotic use. All of these could help us to think about how to prevent the disease in the future.



## 4

**You have initiated the Asia-Pacific Crohn's and Colitis Epidemiology Study (ACCESS), a multi-country cohort to determine the incidence of IBD in Asia and to identify potential risk factors. Could you please share with us how does ACCESS benefit the identification and prevention of IBD? What are the future directions of this study?**

ACCESS is one of the best research initiatives I have done since working in Hong Kong. If it was not for our Dean, Prof. Francis Chan, I would not have embarked on something this ambitious because it was challenging to gather and lead many centers in over 10 countries around Asia-Pacific. He encouraged me and gave me the courage to do so. We asked a simple question: how common is the disease in Asia? We wanted to know not just about Hong Kong, but also the rest of the Asia-Pacific and to look at geographically differences. If you look at the literature, almost 20 years ago, there was nothing published for IBD within Asia region. I saw this as an opportunity.

Now, ACCESS has expanded to 25 centres, 20 cities and 13 countries. For the past 5 years, we have tracked over a thousand new cases of IBD. We genotyped them, we phenotyped them and we collected samples. Hopefully we would be able to look a bit deeper into some of the changes in the bacteria and microbiota. This is made possible because of the advancement in technologies.

Along the way, we noticed a few important things, including the importance of urbanisation and industrialisation in IBD development. When people move from countryside village area to city areas, they have a higher risk of getting the disease. As a massive urbanisation is going on in China, by 2030, I think more than 60% of people will be living in city areas. This will increase the incidence of IBD. Now is a golden opportunity to look at some of the environmental factors as we can compare people in both areas and to identify protective factors of the disease. We may have a chance to probably stop or to reduce the incidence by modulating our microbiome. Recently, we worked with colleagues from the University of Calgary and published a paper in the *Lancet* called *"The 21st Century Global Epidemiology of IBD"* which highlight the epidemic of IBD.



*Prof. Ng with her two mentors in Bordeaux, France during a Helicobacter pylori and Microbiome Meeting in 2017. "We chatted about work, life, and wine".*

## 5 What is your future research direction regarding IBD? Why do you think this direction would be significant and what impacts it would bring to the society?

I have been inspired Prof. Dennis Lo's work in the Non-Invasive Prenatal Testing. When I had my second child, I took the test myself and felt instantly reassured when the test result was negative. I brought up this example because research ideally should have impact on patients, for example, I would ask myself if I have certain diseases, what I would really want. We want to do research that we can translate for the benefits of the patients.

One of the possible research directions we are exploring is early life events and its impact on human diseases. We think that something happened quite early in your life. For example, when the mother gives birth to her baby, there might have been already transmission of the diseased bacteria which may lead to expression of the disease later on in life, especially if coupled by a trigger in the environment. We are working with Mount Sinai group in New York on a study called MECONIUM, which is the first stool of the baby. We realise that the meconium is supposedly sterile, but there are now some discoveries of certain microbiome changes inherited from the mother. If we can target at-risk people, which means people who have the disease who want to give birth to babies, and we want to prevent the baby from having the disease, we may need to change the bacteria profile early on in life. This is one of the directions we are working on.

The second key direction is on diet and how diet changes our microbiota including not just the bacteria family but other components like the virus and fungus in our guts. It is not only about what we eat now, but it is also related to what is being added to our food. We are now working with food additives, what we call emulsifier. These additives have been shown to change the bacteria flora in the mice and lead to obesity and inflammation. Now, one of our research directions is to look at how diet influences our microbiota, and whether we can use the transfer of bacteria (fecal microbiota transplantation) from healthy people to the unhealthy people to rebalance the microbiome.

Last but not least, we hope to find the cause of Crohn's Disease. Many years ago, the community regard stress and acid as the cause of peptic ulcer disease and stomach cancer until the discovery of a specific commensal in our gut called *Helicobacter pylori* because once this bacterium was identified and eradicated, peptic ulcer disease can now be cured. Therefore, there might be a "*Helicobacter pylori*-equivalent" for Crohn's disease which has yet been discovered. At least for now, we need to think of ways to prevent and slow down the disease from becoming more significant to the society.




*Loves Teaching and Researching in Asia and in Europe and in the States. Guest Keynote spaeaker in Barcelona in 2012, same year Prof. Ng was nominated to be the youngest member of the International IOIBD organisations.*



## 6 You have many on-going collaborations with various hospitals, institutions and universities all over the world. Can you share with us how would you initiate a collaboration? Since there should be a lot of potential opportunities and partners for collaborations?

I personally think that the world is getting smaller and smaller and that we can no longer work in isolation. My analogy for collaboration is like a successful marriage. Broadly speaking, you need to find the right partner. Before you find the right partner, you always have to find that if you two share the same interest and same vision during the first few dates. After that, you have to create opportunities for each other, and keep it all together. I guess you need to maintain the momentum so an ideal collaboration should be based on work both parties are interested and motivated and will benefit from. Sometimes the timing may not be right, you might find a collaborator who cannot participate because of lack of synergism or resources. It is alright to revisit this collaboration when the opportunity is ripe. Akin you dated someone and you did not meet him / her for a few years, but you could still reunite when the timing is right and you might even end up marrying this person.

I also think nothing could be compared to face-to-face meetings. It is not easy to collaborate just by telephone or teleconference. Ultimately, I think the best type of collaboration sometimes stems from trust and generosity.

Now, the Faculty of Medicine and the University are also supporting international collaboration via several platforms including student exchange, joint postgraduate programs and the development of the Office of Global Engagement which helps to bring people from different universities together.

*Co-director for Academy of Young Leaders with Prof. Henry Chan to train and aspire the next generation in academia and leadership 2016.*




## 7

**You are devoted in teaching and have received Exemplary Teaching Awards for three consecutive years. Would you please enlighten us about your teaching philosophies? Do you consider yourself more of a teacher or a mentor? Why?**

I feel humble with that because sometimes I feel that I am a student as well. I probably play the role of a mentor and teacher under different circumstances. I enjoy teaching. When I teach, I do not just like transfer the knowledge, but I prefer to provide some perspectives, principles, concepts and ideas which relate to the topics I teach. Because I would put myself into the shoes of the students, I would ask myself what I want to take away and what I want to learn. I believe most of the students only take away less than 50% of the content but they will remember some of the principles behind the material. I also like to use real life examples. One of the things I also enjoy very much is Medical Ethics, as it really inspires myself and hopefully the students to be good doctors.

## 8

**You are heavily involved in the Global Physician Stream (GPS) students, which is a newly developed programme. Can you explain to us more about the GPS programme? Apart from being beneficial to the development of students, how would the new GPS programme affect the research field?**

The GPS programme was created by the Faculty of Medicine in the CUHK a few years ago. It is a unique programme which allows student with high academic potentials to go through an accelerated MBChB program. The idea of GPS is to expose these students internationally, so they can become future leaders or clinician-scientists in whatever field they like to be in, ranging from sociology, to science. I personally believe that these students are future leaders in medicine and science, they are tomorrow's physicians. The programme provides a lot of workshops, oversea attachment and ample opportunities to meet International academics. I have 7 GPS mentees, they are really impressive and talented. If we are willing to put in the effort to guide the next generation, most of them who have passion and interest will undoubtedly excel. For example, more than half of my GPS students have published papers in high-impact journals, and they were exposed to media conference to deliver their work. Many had the opportunities to work in leading research units in other countries, such as London, or the US and they will bring different expertise to our society in the future.



## 9

**What are your expectations on the future collaborations with other PIs at the Institute?**

I am amazed by how much talents there are within this Institute, which I am a bit ashamed because I was not aware of it before. I think good work and good talents need to be promoted, so visibility is important. This Institute is doing very well and it could be a future direction to promote some of the great work. Now that I have read about them. I know who they are, what they do, and where to find them. It is also important to learn what facilities are available. I hope to create more opportunities for my postdoc scientists, students and research staffs to get together with others within the Institute. Many novel ideas are not always generated from formal meetings, but usually from a conversation over a cup of coffee or a beer during happy hour. These occasions are where great ideas are born and meaningful collaboration are developed!




*Prof. Ng performing a local dance on stage at Presidential Dinner with key leaders in the field and close collaborators at a major meeting in Seoul in 2015. "Collaboration can sometimes with fun!"*



*Prof. Siew Ng with her students on a press conference announcing their findings that 4.4 billion people worldwide are infected with Helicobacter pylori.*



## Interview with Professor William Wu
## 胡嘉麒教授

*Professor William Wu finished his Master and Doctor of Philosophy at The Chinese University of Hong Kong, and later joined the Faculty of Medicine as a Post-Doctoral Fellow since 2009. He then became a Research Assistant Professor at the Institute of Digestive Diseases, and is currently an Assistant Professor at the Department of Anaesthesia and Intensive Care. Prof. Wu's main research interests include cancer genomics & biology, autophagy, antimicrobial peptides, infection & sepsis, pain mechanism, and meta-analysis & retrospective observational study.*



**1 You have obtained a degree in Occupational Therapy at the Polytechnic University of Hong Kong in 2002, then you moved on to pursue a Master degree in Medical Sciences with Specialism in Pharmacology at the University of Hong Kong from 2003 to 2005. Why would there such a change from occupational therapy to pharmacology? Can you share with us the reasons behind this change?**

That would come to my personality. I am more an introvert who love having quiet time alone to think about different issues. For occupational therapist, it would require a lot of interactions with patients which does not fit me well. I prefer doing experiments with cells and mice more than that. During my undergraduate study, my results in basic sciences courses, such as physiology or neuroscience, were much better than the clinical or practical courses.

After my undergraduate study, I was sure that I did not want to become an occupational therapist. At that time, the University of Hong Kong happened to have a Master of Medical Sciences programme, so I gave it a try and finished the Master degree with specialisation in Pharmacology in 2003. I chose Pharmacology as my specialist strand because it is a fascinating subject which requires knowledge not only in the discipline itself, but also other subjects, including physiology, anatomy, biochemistry and molecular biology.

**2 You have studied and worked in three universities in Hong Kong. What are your observations, regarding the differences in academic and research cultures among the different universities you have been affiliated with?**

All the three universities are excellent and successful institutions. I would say PolyU would be focused more on applicability, whereas both HKU and CU are more comprehensive.

**3 Apart from the physical environment, what do you think is important for doing research?**

Regardless of institutions, I think collaboration is the most important for doing research. Since a lot of research topics nowadays would require efforts from various disciplines. In particular, collaborations between clinicians and scientists are pivotal for identifying unsolved clinical issues that are addressable by basic science and for translating findings from basic science into clinical utilities. Such collaborations have brought me a lot of satisfaction as a researcher, which I think it is somehow more important than having publications.

## 4

**In May 2013, you have been to Tel Aviv, Israel as a visiting scientist at the Tel Aviv Sourasky Medical Center. Any special experiences you can share with us since Israel is not on the popular "exchange" country list?**

For the research facilities and environment, Israel is of similar level with Hong Kong, in which a lot of outstanding academics and scientists are now working in Tel Aviv. Actually, many notable Nobel Laureates are Jews. Because of historical factors, there have been a lot of Israelis coming back to the country. Even though Hebrew and Arabic are the official languages of Israel, you could hear a lot of people communicating in English rather than these two languages in the laboratory.



*Prof. Wu and his two bosses.*

## 5

**The Pneumoconiosis Compensation Fund Board has granted a research fund to your research project focusing on malignant pleural mesothelioma. Mesothelioma is a type of cancer that develops from the thin layer of tissue covering many internal organs. We know that cancer genomics and biology is one of your research interests. Why would you choose mesothelioma among various types of cancers? Or you work on studying different types of cancers simultaneously?**

As I specialise in pharmacology, which is to study the drug effects on biological systems, I could readily appreciate that one type of drug may be effective in treating multiple diseases. In my research, I noticed that the interaction between the ubiquitin–proteasome system (UPS) and autophagy is a common mechanism underlying resistance to a type of drug known as proteasome inhibitors, which are now mainly used for the treatment of hematological malignancies. Clinical trials on the use of proteasome inhibitors for solid tumours, including mesothelioma, are in progress. I thus wondered whether targeting such interaction could enhance the effect of proteasome inhibitors for treating mesothelioma. There is no "limit" on the disease types we study as we focus on the drug actions but not the disease itself.



## 6

**Throughout your studies and work, Prof. Joseph Sung and Prof. Chi-Hin Cho had been your supervisors for quite a long period of time. What are the inspirations you get from them that can share with us? Do they have any influences on your career or research directions? If yes, in what ways that may have influenced you?**

Prof. Cho was the supervisor for both of my MPhil and PhD studies. He is one of the world-leading pharmacologists focusing on drug development for inflammation and cancers in the gastrointestinal tract. He did not only supervise me on academic aspects, but also paid attention to my other aspects of life and gave me lots of valuable advice. This affects my way in supervising my own students.

It was by chance that I met Prof. Joseph Sung, the former Vice-chancellor of CUHK, since I followed Prof. Cho from HKU to CUHK, then Prof. Sung became my co-supervisor. He gave me lots of advice, especially on the directions of research, such as to encourage me in doing research on the applicability of new therapies or to explore and discover insights for some unanswered questions.

## 7

**As a PI yourself now, do you still have close contacts with your supervisors?**

I still have frequent gatherings with Prof. Cho after he retired as an Emeritus Professor of Pharmacology. My fellow students and I would meet with Prof. Cho to celebrate his birthdays and the Chinese New Year. Prof. Joseph Sung is very busy and thus we do not meet very often. Nevertheless, I have been following his Facebook page to see updates from him.

## 8

**Being a member of the research team led by Prof. Joseph Sung, you received the State Natural Science Award (SNSA) second-class award in 2016. Could you please share with us about the awarded project "Integrative Research on Molecular Pathogenesis, Diagnostic Biomarkers and Prevention for Colorectal Cancer" and how does the award influence your future research?**

This research project consists of different aspects, including the epidemiology, screening, molecular pathogenesis and biomarkers of colorectal cancer. It involves different disciplines, from clinical gastroenterology to molecular biology. I am so happy and honoured to be a member of the team. From this award, I learnt that multidisciplinary collaboration is very important to the success of a big research project.



*Prof. Wu has been participating in a Christian fellowship at CUHK. The photo was taken during a gathering in Prof. Maggie Wang's home in 2018. A message on "Good News" was shared by Prof. K.F To.*

**9** **You have been affiliated with various departments and research units, such as pharmacology, digestive diseases and anesthesia & intensive care. How would these fields inter-connected with each other? Or how your experiences in these fields are beneficial to your work?**

In 2013, CUHK partnered with the Fourth Military Medical University (FMMU) to establish the State-Key Laboratory (SKL) of Digestive Diseases which is housed in the CUHK Li Ka Shing Medical Sciences Building. The laboratory carries out basic, translational and clinical research on gastrointestinal cancers, peptic ulcer bleeding, chronic liver disease and inflammatory bowel disease. I have been a key member of the SKL of Digestive Diseases for a long time already, and I would continue to work with the team on Digestive Diseases. At the same time, I am also working on pain mechanism and sepsis, which are key research areas of my current Department. I believe, in various specialties, the underlying disease mechanism may involve similar molecular biology, genetic and protein pathway abnormalities. Therefore, research in different fields could eventually interconnect with one another, in which new findings from one field very often inspire new ideas in another field.

**10** **You have been working as a researcher in Hong Kong for a long period of time, what are your point of views towards the research support, development and environment in Hong Kong?**

I am very grateful that the Hong Kong Government has provided strong support to scientific research. In particular, they strategically focus and allocate more resources to world-leading or outstanding research through funding opportunities like Areas of Excellence and Theme-based Research Scheme. At CUHK, we have sufficient and comprehensive equipment for all sorts of experiments. However, I think Hong Kong has been marginalised given the rapid development and tremendous investments in Research and Development (R&D) in Mainland China. Some major cities of China have actually got in front of Hong Kong now. Hong Kong needs to seize the opportunities to co-develop with Mainland China. More collaborations should also be done with Mainland China and other countries.



**11** **Besides being an outstanding researcher with over 200 publications and as PI of various grants, you have also contributed a lot to undergraduate teaching, postgraduate supervision and other university or external services. How would you maintain a balance between them?**

I think teamwork is very important. If everyone is willing to sacrifice and work with the team to go towards the same direction, the whole thing would be much easier. We cannot just work for ourselves.

**12** **Having received education in Hong Kong and being a native Hong Kong scientist in medical field, what advice would you give to fellow students who are interested in developing their career in scientific research?**

For students majoring in science subjects, the career path to become a scientist is relatively straight forward (I do not mean it is easy) – What you'd need are publications and more publications. To achieve this, one would need perseverance and genuine passion in science. However, for medical graduates, the situation is more complicated. After finishing the undergraduate training, he/she would need to take 1-year training as a houseman, then takes 6 more years to become a specialist. If someone would like to become a clinician-scientist, he/she would then need 3 to 4 more years to finish the PhD. The workload of providing clinical services in Hong Kong is very heavy. So, one can easily anticipate that not much time would be left for research. In my opinion, more resources should be put to groom clinician-scientists so that they would have more time to do research. Despite such challenges, we should encourage more young bright talents within the Faculty to pursue the career of clinician-scientist.

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

My team is still at the initial stage and would need much more time to build up and develop. It is important to learn from my mentors, including Prof. Joseph Sung, Prof. Chi Hin Cho and Prof. Jun Yu. Their experience is so valuable.



## Interview with Dr. Owen Ko
## 高浩醫生

*Dr. Owen Ko received his undergraduate medical sciences training at The Chinese University of Hong Kong. After completing the second year of studies, Dr. Ko pursued a one-year Intercalated Bachelor of Medical Sciences under the mentorship of Prof. Wing-ho Yung. He was then recommended to further pursue a three-year PhD programme in Neuroscience at University College London (UCL) in the UK under the supervision of Prof. Thomas Mrsic-Flogel. Dr. Ko has published papers in prestigious journals, such as Nature, Science, Nature Neuroscience, etc. throughout the years. He is currently a Clinical Lecturer at the Department of Medicine and Therapeutics.*



**1 You went for a one-year intercalated degree in medical sciences after the second year of pre-clinical training of MBChB at CUHK. Why would you go for that instead of continuing with clinical training? Have you been interested in doing research for a long time?**

I have had great interest in science and the history of science ever since I was small. In primary school, I started reading a lot about scientists, such as Dr. David Ho, whose research helped us understand more about HIV infection and led to "cocktail" therapy for AIDS in mid-1990s. I admire very much great ones before us like Dr. David Ho and I have always wanted to contribute to humanity, so in the end I decided to go to medical school for my undergraduate study.

In medical school, I realised that medical school education in the first few years mainly focused on memorisation of a large database of established conclusions from scientists, which is the absolute prerequisite for further training to become a clinician. This heavy demand imposed lots of constraints on learning more about research. Moreover, I felt that my quantitative skills were getting worse as learning in medical school was more about qualitative statements and reasoning. Both factors drove me to take the one-year intercalated degree in medical sciences after two years of pre-clinical studies, to further develop my interests and prepare myself for a research career.

**2 Would you suggest the younger generations to take an intercalated programme during their undergraduate study? Why?**

Yes, I would definitely recommend students to take the intercalated programme, especially those who are interested in doing research. In standard medical school courses, students would learn general methodologies of research, but that would not make much difference simply because there is not enough time, yet becoming a competent scientist takes years of dedication and devotion. The one-year intercalated programme is a great opportunity to equip them with more solid theoretical foundations and practical skills to explore research.

## 3

**Neuroscience is the scientific study of the nerve system, since when you have developed your interest in neuroscience? Any special reasons for that?**

In early to mid-twentieth century, neuroscientists mainly focused on studying the biophysics of neurons, which laid the foundation for the entire field. In 1963, Alan Hodgkin and Andrew Huxley became Nobel laureate in medicine for developing the Hodgkin-Huxley model of action potential, still probably the most successful mathematical model of a biological phenomenon up to date. I learnt this model in the first year of medical school, and was deeply impressed. Moreover, it has been for a long time that our understanding of the brains is comparatively much less than other organs in our bodies, whereby a lot of operating principles of the brain remain mysterious. These all attracted me to neuroscience research.

## 4

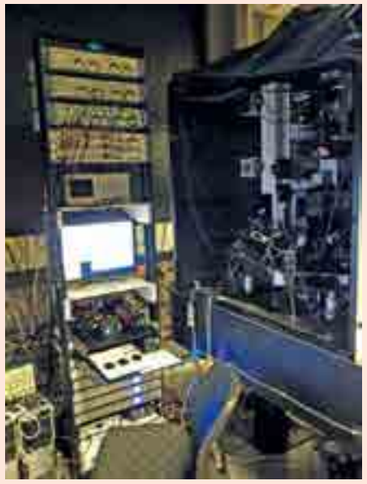
**You have two publications in the renowned journal *Nature*. The first one is on the development of a highly novel experiment approach to understand how neurons communicate with each other, and the second one is on neuronal circuit development. Can you tell us more about these two papers?**

Both publications of mine stem from the highly collaborative and very supporting environment provided by my PhD supervisor, Professor Thomas Mrsic-Flogel at the University College London (UCL). I was his first PhD student after he joined UCL, and he was a rising star in the field back then.

To put it in short: The brain is made up of neurons, whose intrinsic properties determining input-output transformation and the patterns of connections between neuron give rise to the complex array of computations the brain can perform. We developed a novel experimental approach to relate the connection patterns between neurons to their functionality. With the methodology advancement, we revealed that in the visual cortex, neurons are not randomly connected, but by a "like-to-like" rule, whereby neurons with more similar visual feature selectivity are more likely connected. In the second and a few other later publications, we reported how this pattern of structured connectivity arise in the visual cortex under influence by an interplay of factors including visual experience, spontaneous neuronal activity and rules of synaptic plasticity, which are also likely general principles governing neurodevelopment in other cortical sensory areas.









*Dr. Ko and the experimental setup he built at University College London (UCL).*

## 5

**What are you currently working on? Such as follow-up related to the two papers?**

Currently, on fundamental neuroscience, my team has been working on neural circuitry underlying sensory processing and behavior. Apart continuing studies in mouse visual cortex, I recently developed lots of interest in utilising zebrafish as another model organism. When studying the brain, we have always wanted to be able to observe more neurons in action in the brain. A 5-day old zebrafish larva is already capable of processing visual, auditory, odour and tactile information to drive a complex array of innate behavior (e.g. optomotor reflex, rheotaxis), while the activity of a major proportion of neurons (>80%) can be simultaneously monitored. As a start, we have custom-built a high-speed light sheet microscope for zebrafish brain imaging and we wish to use this platform to study how zebrafish larvae process odour and perform tasks such as chemotaxis, associative learning. On translational neuroscience, I am currently adopting techniques from basic neuroscience to study pathophysiology of cerebral small vessel disease and Parkinson's disease. I am also a newbie to the field trying to establish a foundation for translational research in the lab.

## 6

**Gerald Choa Neuroscience Centre is a multi-disciplinary research centre, in which you are one of the Principal Investigators and Executive Committee members. The centre includes members coming from Faculty of Science and Faculty of Engineering as well. Why is that important to involve the other disciplines in the study of neuroscience?**

Multi-disciplinary approach is becoming increasing important in research nowadays. This is especially applicable to studying the brain, which involves a lot of physical and engineering techniques. Thus, researchers from engineering fields play an integral and vital role in the brain research community nowadays too.

## 7 Being a scientist as well as a clinician, how do you perceive these 2 roles? Do you enjoy either one more?

Being researcher or clinician require very different skills and mindsets, yet having a clinical background helps a researcher identify the most clinically important questions to address. This is also one major reason that I chose to return to Hong Kong to complete medical school instead of pursuing a pure research career abroad. Currently, I have chosen to focus on research, yet I firmly believe the clinical exposure I have had is highly beneficial to my future academic career.



*Dr. Ko in front of the Main Building at UCL*

## 8 You have been doing great and attained excellent results through the academic years. Any tips you can share with fellow students on studying medical sciences?

I highly recommend students to read more on the history of science and medicine. It will not lead to better grades in exams, but it is essential for developing a good overview of the field. How the great ones before us advanced science and made discoveries provide very good hints on tackling scientific problems, and this is something very hard to learn in traditional classes or textbooks.



## 9 As a successful clinician and scientist, what advices would you like to give to the younger generation who would like to pursue a career in medical sciences?

To pursue a medical research career, I believe nowadays it is increasingly important to develop multidisciplinary skills, especially quantitative skills. I once read that Linus Pauling suggested that students who are interested in biomedical research should pursue an undergraduate degree in a quantitative subject such as mathematics, physics or chemistry first. While it does not necessarily apply to everyone, it is a very good perspective worth considering.



*Dr. Ko and his PhD supervisor, Prof. Thomas Mrsic-Flogel, watching football match.*

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

Recently I have committed to full time research and put all my efforts into building the lab and training of postdocs and graduate students. In five years' time: Firstly, I aim to build up a strong systems neuroscience lab and provide an intellectually enriching environment for researchers in the locality who share the interest in studying the brain to join. Secondly, I am bringing in techniques from the field of systems neuroscience and aim to be able to address a few key questions regarding pathophysiological processes in neurological diseases.

# Interview with Professor Erik Fung
# 馮以文教授

*Professor Erik Fung is a medical graduate at The Chinese University of Hong Kong. He then received his PhD and postdoctoral training at Harvard Medical School, University of Cambridge and Imperial College of London, and he was the recipient of Prince Philip Graduate Exhibition Scholarship at University of Cambridge. Prof. Fung has had a lot of research, clinical and teaching experiences in renowned institutions, such as Tufts University School of Medicine and University of Southern California. He has joined CUHK since 2016 as an Assistant Professor at the Department of Medicine and Therapeutics, with a research focus in advanced Heart Failure and advanced disorders.*





**1 Since your undergraduate studies, you seem to be a regular commuter traveling a lot to USA, the UK and Hong Kong. Why would you decide to travel around and stay sometime in each of these 3 places? Anything special of each place may have attracted you to go back there again?**

Each of these places offers something unique. Depending on my stage of personal, educational, scientific and professional development, I have found these interactions and exposures to be of vital importance in enriching my knowledge and skills. Like many physician-scientists who have returned to Hong Kong after years abroad, I do hope to contribute my expertise and international experiences to the local scientific community and to society in general.

*After Year 2 of medical studies at CUHK (MED2), Prof. Fung had spent his summer vacation in 2000 at the Vascular Medicine and Atherosclerosis Unit of Brigham and Women's Hospital, Harvard Medical School, to learn the art of vascular biology from Prof. Peter Libby and Dr. Masanori Aikawa.*







*After MED4, Prof. Fung undertook an overseas elective in the A&E Department of Whipps Cross University Hospital, an affiliated hospital of Barts and The London School of Medicine and Dentistry.*

**2 You have spent the longest period of time in USA. Is USA your most favorite place? Why?**

After my PhD study in Cambridge, England which I very much enjoyed and found extraordinarily special in every way, I wanted to further my training in a clinical environment that offered highly regimented, structured training. During the early to mid 2000s, the UK clinical training pathways were undergoing reforms and there was much uncertainty at that time. The US was a suitable choice for me to continue my professional development, given the established clinical training programmes. I had been a predoctoral visiting fellow at Harvard from 2002 to 2003 when I deferred from medical studies at CUHK for a whole year, so I was lucky to have had some idea about what clinical and scientific training was about in the US.

## 3

**Your 1st bachelor degree is a double degree with a Bachelor of Science in Microbiology and a Bachelor of Arts in Music. This is a quite interesting combination of majors. Can you share with us why you would come up with these choices? And what was your major for your degree in Music?**

Before medical school, I had completed undergraduate study and majored in piano performance. As I had grown up playing the piano and having had training and a profound interest in performance of classical music, I pursued the opportunity for a double degree. I was very grateful for a part-scholarship in music which allowed me to explore both science and arts simultaneously. Looking back, it was such a luxury to have the time to figure out priorities and better understand the world. I have found that my various 'survival' skills and knowledge learnt during those years could still be applied to my current academic life. For instance, writing a grant application is not too dissimilar from completing an assignment in counterpoint or composition in terms of structuring its contents and creatively working within the confines of a set of rules.

## 4

**Do you still play piano nowadays? People always think the complex relationship between Art and Science is like "creativity versus logic". What do you think about this statement as a scientist as well as a musician?**

Yes, I still play the piano but rarely these days. Arts and science are not mutually exclusive, and I see them as complementary to represent elements in the universe. But on the broad scheme, there is always a set of rules governing the composition of a piece of music on the time scale and within specific physical limits. The creative arts operate within the confines of physical limits, yet innovative science requires creativity which is artistic and sometimes not necessarily or initially logical. Perhaps, this is another example of 'yin' and 'yang'.

## 5

**When did you start your interest in doing research?**

My interest began probably during my first year of medical studies, MED1. After lecture in cardiovascular physiology given by Professor Ronald Fiscus one day, I approached him for a research project and he kindly agreed to let me work with him. That continued for several years. Those times were challenging as I had to juggle both medical studies and basic scientific research into cyclic nucleotide signalling in vascular tissues and cells. That exposure gave me plenty of time to see and experience the operation of a basic science lab. Through many late nights and early hours, I was fortunate to eventually publish a few papers and abstracts during medical school. To confirm whether the clinician-scientist pathway was indeed suitable, I undertook a year of predoctoral fellowship research with Professor Peter Libby and Dr. Masanori Aikawa at Harvard Medical School in Boston (2002-03) which further pushed me into the direction of taking up a PhD study at Cambridge University after clinical internship. So, I strongly encourage medical students interested in the clinical sciences to explore for themselves the higher calling.



*From summer 2002 to 2003, Prof. Fung had fortunately been granted deferment from medical studies at CUHK to take up his appointment as Visiting Research Fellow in Cardiovascular Medicine at Brigham and Women's Hospital, Harvard Medical School. Towards the end of his research year, he became one of the first to successfully perform gene knockdown by RNA interference (RNAi) in human primary macrophages, immune cells that were thought to be extremely difficult to silence at that time. He subsequently perform additional experiments and published a paper in Circulation 2007;115:2948–2956.*




## 6

**Microbiology is the study of microscopic organisms, including both fundamental research as well as clinical aspects of microorganism. What leads you to pursue a second degree in medicine and surgery which is more on the side of clinical skills instead of the basic sciences in microbiology?**

In North America, it is natural to major in a biomedical science subject as part of the pre-medical curriculum. I had switched from Biology to Microbiology because of my interest in pathology, genetics, immunology, pathogenesis of microbial diseases etc. Also, those areas were highly relevant to clinical medicine and provided me with the opportunity to have some biomedical exposure before committing to medical studies.




*Before returning to Hong Kong in autumn of 2003 as a MED5 student, Prof. Fung undertook a visiting exchange clerkship in General Surgery at Massachusetts General Hospital, Boston, to prepare himself for a return to full-time clinical studies.*

## 7

**You have taken up research, academic or clinical posts in various specialties, such as medical genetics, diabetes or immunology, cardiology etc., and now you are an academic cardiologist. Can you share with us your experiences through clinical and research training? Why have you chosen cardiovascular medicine as a field of your specialisation?**

I have always been drawn to the field of cardiovascular science and inflammation since my early exposures to research in cardiovascular physiology and vascular biology. I owe a lot to the clinical and research mentors with whom I have worked. I have been very fortunate to have access to a variety of great teachers and role models in institutions during my development. I have chosen cardiovascular medicine because of my passion for complex mechanisms and the circulatory system.




*Following a 1-year rotating medical and surgical internship at PWH, Prof. Fung went on to study for a PhD in Medical Genetics (immunology and immunogenetics) at the University of Cambridge, UK, under Prof. John Todd and Prof. Linda Wicker. Thereafter, he completed an internal medicine residency, and fellowships in cardiovascular medicine and heart failure / transplant cardiology in the USA. Prof. Fung expresses gratitude to various mentors and institutions that have shaped his clinical and scientific development.*

## 8 According to the Department of Health, heart diseases have been the third leading cause of deaths in Hong Kong since 1960s. "Heart diseases" refers to a broad spectrum of diseases which would damage the heart and may eventually lead to heart failure. What are your point of views towards the current trend in Hong Kong in heart diseases? Do you think the Government has done enough in Public Health Education? What have been done in trying to tackle the third largest killer in Hong Kong?

Recent official figures from the Secretary for Food and Health indicate that cardiovascular disease is now the second leading cause of death in Hong Kong behind cancer. With ageing of the population, the incidence of both cancer and cardiovascular disease will likely increase. While more resources could be allocated for advanced cardiac diseases and end-of-life programmes, primary prevention and public health education remain critically important.

## 9 Since you are quite new to the Institute as well as for the Faculty, can you briefly explain to us your research interest and future research directions?

Our group, the Laboratory for Heart Failure and Circulation Research, is focused on circulatory disorders and, particularly, heart failure. We use a combination of epidemiological, clinical and basic scientific information and tools to formulate questions, develop projects and analyse results. Ultimately, we are striving to create knowledge that can potentially impact on clinical and public health outcomes. Towards these goals, I am establishing clinical and basic research programmes that overlap with one another in scope, thereby allowing students and trainees to benefit from both. I believe it is of vital importance to train and develop young scientists, clinicians and leaders of the future. For example, a PhD student, who is herself a physician, and I are currently studying novel serine proteases at the cellular and molecular levels that have not been looked at in the cardiovascular system, and we are also investigating their roles as biomarkers in heart failure and cardiorenal syndrome. Such research platform allows trainees and students to diversify their skill sets and knowledge base.



## 10 You are a physician, a researcher, an instructor and a supervisor. How would you balance your time in dealing with all these roles? While pursuing your PhD in the UK, you were also a researcher and clinician in USA, and there were other "overlapping moments" in your career path. How do you feel about that? Would you feel too occupied or do you enjoy taking up several roles at the same time?

Each role has different priorities and challenges, and many physician-scientists on the PWH Campus do them extraordinarily well. For myself, I think the patients' interest always comes first and I treasure the patient-doctor relationship. For clinical teaching, there are often many opportunities to combine teaching and clinical service on the hospital wards. As for research supervision, I very much enjoy original scientific research and I find mentoring research students very gratifying and rewarding. The combination of all these roles makes an academic physician's job very interesting and the challenges are different every day.

## 11 As a graduate of The Chinese University of Hong Kong and a successful physician and researcher, what advices would you like to give to the younger generation who would like to pursue a career in medical sciences?

Every individual will have his or her unique career pathway. It is definitely worthwhile exploring early in one's career, be open-minded to different possibilities and avenues, and the higher calling will come. It is a great privilege to be a medical doctor and physician-scientist. Although young students and trainees are concerned about the big changes and challenges in the coming years, there remains vast opportunities for each individual and these are indeed rapidly evolving yet exciting times.



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

I would like to have established my laboratory as a place where original research is generated, and to have international appeal to young clinicians and scientists locally and from abroad. It is important to have international talents and scholars grace the laboratory, exchange ideas and develop collaborations. These interactions are invaluable and highly stimulating. I think they help to move ideas and thoughts forward. Firstly, I will try my very best to continue building my laboratory. At the moment, we have a total of five members. We expect to grow to an eight-member group in the coming months. Scientifically, we are working on several interesting clinical and basic translational studies (e.g. ***U***ndiagnosed heart ***F***ailure in frail ***O***lder individuals (UFO), HF decompensation, HARE), and are continuing to develop bioinformatics and database infrastructure such as the ***S***hatin ***A***dvanced ***H***eart ***F***allure ***RE***gistry (SAHFIRE) and ***S***hatin ***P***ulmonary ***H***yp***E***rtension ***RE***gistry (SPHERE). We look forward to leveraging these resources for new discoveries in the coming years.



## Interview with Professor Gary Tse
## 謝家偉教授

*Professor Gary Tse started his medical and scientific training at the University of Cambridge in 2005. Later, he conducted research in cardiovascular MRI at the Royal Brompton Hospital while undertaking clinical training at Imperial College London. Prof. Tse has also studied Public Health at the University of Manchester and received his PhD in Systems Biology from Cambridge. Prof. Tse was awarded a Clinical Assistant Professorship in Medicine and Therapeutics by the Croucher Foundation and has joined The Chinese University of Hong Kong since 2016.*



**1 You have spent great deal of time in the UK, why would then decide to move to Hong Kong?**

Many people have asked me this question. I am actually from Hong Kong and have lived in the UK since the age of 12, after primary school. It was by chance that I was recruited back to The University of Hong Kong in 2015 close to the end of my clinician-scientist training. They were looking for someone to lecture in pre-clinical medicine. As the position involved teaching basic science to medical students, I fitted their candidate profile to make biochemistry and biomedical science more clinically relevant and interesting for medical students.

**2 Why would you start a Doctoral Degree after your 3-year pre-clinical medicine studies instead of continuing with clinical medicine directly?**

Again, it was serendipity that brought me onto pursuing further scientific training. The reason is that the medical course at Cambridge, where I was an undergraduate at Trinity Hall, is intensely scientific. In fact, the course is called "Medical and Veterinary Sciences Tripos", which emphasises the scientific basis of medicine. I always had a passion for understanding the mechanisms behind human physiology and how our homeostatic systems can go wrong; therefore, pursuing a PhD seemed like a natural path. In places such as the UK or US, research training is more common than Hong Kong. As to why I did not continue onto clinical medicine directly, it was more the fact that the pre-clinical course is more or less pure science, so it was more natural to pursue doctoral studies. Around half a year before I completed my Bachelors degree in Natural Sciences, there was a doctoral training award advertised in my own Faculty and, so I applied for the program.

**3 Would you share with us more about the "Medical and Veterinary Tripos" at Cambridge? It seems to be quite different to the medical study in Hong Kong.**

At Cambridge, students studying Veterinary and Medicine would take this "Medical and Veterinary Tripos" in the first two years together. The courses cover basic sciences, such as scientific basis of medicine, biology of disease, etc. This is quite different from the medical study in Hong Kong since the courses in Hong Kong are more case-based rather than basic-science based. The pre-clinical training with more focus on basic science would encourage more undergraduate students to engage in research. The Global Physician-Leadership Stream (GPS) offered by the Faculty of Medicine, CUHK, has included more science and research elements, which would be more comprehensive and may foster interest in the undergraduate students.

## 4

**You have declined a MPhil offer to study at the Cambridge-MIT Institute in Computational Biology and to take up a Bioscience for the Future Collaborative Areas in Science Doctoral Training Award with industrial partnership. What are the rationales behind? Can you share with us more about the doctoral training award with industrial partnership? Is that something like internship? How would that contribute to your PhD studies?**

This is one of my regrets looking back, turning down the chance to learn more about computational biology. From my pre-clinical studies, I have always been fascinated by electrophysiology of the heart. Over the past decades, researchers have focused on understanding the minutiae of the molecular details of how the heart beats. Now we have moved in the opposite direction of trying to put all pieces of the puzzle together to understand the emergence of complexity at the systems level. Through computational modelling methods, we can appreciate the intricate spatio-temporal coordination of each heart cell to generate functional behavior. It is not only intellectually challenging to understand the philosophy of top-down causality in systems biology, but also clinically relevant. Our research focuses on elucidating why ventricular arrhythmias, which can lead to sudden cardiac death, occur in diseases such as long QT syndrome. We know a long QT interval increases the risk of these events, but this is not exclusive: not all QT prolongation is the same. This illustrate why an understanding of the system as a whole is important, many factors contribute, and ventricular arrhythmias only happen when the conditions are just right, for example when restitution dynamics are abnormal.

But back to answering your question, collaboration between university and industry is very important, as we can be the bridge between pre-clinical discovery and translational application of the research outputs to clinical practice.



*Prof. Tse joined a Formal Ball Dinner during his study in the UK.*



## 5

**You excel in many different aspects, such as medicine, public health, health care management, cardiology, etc. How do they contribute to your career? How do they interconnect with each other?**

I am not sure "excel" is the right word, but I am definitely fascinated by all aspects of medical science. I am from the school of thought that believes everything is connected and interconnected. We have experts in every field (such as molecular cardiology, public health) but what is needed is bringing these disciplines together. What I try to convey to medical students and clinical colleagues (whether successfully or not), is that basic science can lead to translational application and changes to clinical practice.

Let's take cardiac arrhythmias, my main research interest, as an example, an understanding of basic electrophysiology has led to the proposal of refining electrocardiographic (ECG) markers for risk stratification in sudden cardiac death and stroke. Proposal for these markers is only possible when we have an understanding of how they are generated. It is only through epidemiological and meta-analytical studies that we can determine their effects at the population level. However, without engaging the clinician-managers who are responsible for decision and policy making, the research insights cannot be used to benefit patients.

## 6

**Among all these fields, it seems that your current interest is more on cardiology. Why would you choose cardiology among all the other interests? Or if you were concurrently working on other fields as well?**

Cardiology is a good choice because it suits all types of personalities. For example, those who are keen interventionalists can do plenty of procedures in the catheterisation laboratory, whereas those interested in bioelectricity can focus on cardiac electrophysiology. Cardiac electrophysiology is sufficiently complex which offers studies different approaches, from molecular biology and genetics to epidemiological studies at the population level. Also, many of my previous supervisors or mentors have cardiology as their main research interest. This provided me ample opportunity to work on the problems of cardiovascular disease.

## 7

**Then how about the two master degrees in Health Management and Public Health Medicine? Why would you choose to study these two areas?**

Public Health has a wider scope and include more clinicians who also focus on the current trend and development in the society as a whole, rather than just focusing on clinical duties. While some scientific results have been translated into practical uses for clinical services, such as screening tests, we need to carry out cost-effective analysis to encourage the society to invest more resources and to promote the new screening tests to the public. This would involve not only medical knowledge, but also the understandings of the Public Health of the society.



*Prof. Tse attended the Shrove Feast at the Oxford and Cambridge Club.*

## 8 Throughout the years, you have been awarded with many competitive awards, scholarships or fellowships. Apart from having excellent academic results, what do you think are the qualities or characteristics that get the attention of the judges? Can you share with our fellow students any tips on applying for competitive awards or scholarships?

On success and failure, the saying "Oh, the difference between nearly right and exactly right" sums it up. Also, saying that you would do something and actually doing it are very different things.

## 9 You conducted research in cardiovascular MRI at the Royal Brompton Hospital whilst undertaking clinical training at the Imperial College London. Currently, you are a clinician-scientist. You have always been taking up different posts at the same time. How do you manage your time to handle all the tasks?

This boils down to personality I believe. I get bored very easily and hence I need different jobs to occupy my life at any one time. If I get stuck in doing one thing only, be it research, teaching, admin or clinical service, it won't suit me.

## 10 You have more than 60 publications within 2-year time, how did you do that?

Effective team work and collaborations are essential. Everybody is good at different aspects for different studies. The key is good project management and understanding how each team player can maximize their potential.



## 11 As a successful clinician-scientist, what advices would you like to give to the younger generations who are interested in research or to pursue a career in medical sciences?

I would suggest contacting different people and speaking to them about their research experiences and how you can become involved. If there is little outcome, then find someone who would be happy to "show you the ropes". For us, we always welcome students who have absolutely no research experience to join our team. I am pleased to report that many first-year medical students (and soon several high school students) have published with our team, with many publications as first authors.

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

As a new principal investigator with minimal start-up funding, it is very difficult to have sustained research output without support. However, with the help of supportive colleagues and hard-working team members, we are pleased to have contributed significantly over the past year or so to the literature. In 5 years, I hope to expand our basic and translational research team and run a multidisciplinary research programme involving basic scientists, engineers, computational biologists and clinicians to better understand the processes underlying cardiac arrhythmias.





*Prof. Tse at the Trinity May Ball.*

# FROM SCIENCE TO IMPACTS
# 從科學到影響



Professor Jun Yu
于君教授



Professor Ling Qin
秦嶺教授

# Interview with Professor Jun Yu
## 于君教授

*Gastrointestinal cancers are the top killers in Chinese population because early cancers are silent and difficult to diagnose. Professor Jun Yu and her team has utilised various genomic and epigenetic approaches to unveil novel biomarkers for cancer screening and diagnosis with much higher sensitivity and specificity while comparing with conventional biomarkers. Prof. Yu and the team hope to provide more population-based and simple methods for early diagnosis and management of Gastrointestinal cancers which would ultimately improve patients care in the future.*





**1 Why would you decide to start the research in biomarkers for Gastrointestinal cancers? What are the differences between conventional and your novel biomarkers?**

Our biomarkers discovery is based on long term molecular pathogenesis investigations, genome, epigenetics sequencing and RNA screening of Gastrointestinal (GI) cancers. We have focused on biomarkers investigations at least since 2005. The traditional biomarkers for GI cancers is of very low sensitivity. The current biomarkers can be traced back to 30 or 40 years ago in terms of ELISA base detection in blood. Protein biomarkers, for example, include the Alpha-fetoprotein for liver cancer, the CEA and CA19-9 for Gastrointestinal cancer, the sensitivity is low as 30%.

The three GI cancer types (colorectal cancer, gastric cancer and liver cancer) in total account for 40% of overall malignancies in Chinese. The incidence of colorectal cancer increases so rapidly that it overtook lung cancer in 2012 and became the top one cancer type in Hong Kong. That's why we put a lot of efforts to evaluate the molecular alterations, based on genome sequencing and aim to identify new biomarkers for early diagnosis and screening, as well as for prognostics predictions.

**Impact case**

| Marker | ↑/↓ | prog | Publication | Patents | | | |
|---|---|---|---|---|---|---|---|
| | | | | USA | China | HK | Taiwan |
| miR-92a | ↑ | | Gut 2012 | | | | |
| miR-135b | ↑ | | Clin Cancer Res 2014 | | | | |
| miR-221 | ↑ | | Br J Cancer 2014 | | | | |
| TBX3 | | ↑ | Oncogene 2010 | | | | |
| SLC12A5 | | ↑ | Gut 2013 | | | | |
| CA4 | | ↑ | Gut 2013 | | | | |
| DACT2 | | ↑ | Oncogene 2013 | | | | |
| Bacterial markers* | ↑ | | Gut 2015<br>Clin Cancer Res 2016 | | | | |

*PCT/CN2017/098682 Filing date: 23 Aug 2017
17 filed (US 3, China 6, HK 4, Taiwan 3, PCT 1), with 2 already granted (US 1, Taiwan 1)

*Biomarkers and Patents - Colorectal Cancer*

## 2 Can you introduce to us the biomarkers and the progress of your research development? Any actual impacts have been resulted yet?

Our biomarkers discovery has been resulted in 35 patent applications nationally and internationally, of which 15 have been granted from the US, Hong Kong, mainland China and Taiwan. In collaboration with biotechnology companies, non-invasive diagnosis kits for gastric cancer and colorectal cancer have been developed, and the stool-based detection of colorectal cancer has got the approval from the Chinese Food and Drug Administration (CFDA) in March this year.

The team pioneered the application of plasma miRNA in the diagnosis of colorectal cancer and identified miR-92 as a plasma biomarker for colorectal cancer (CRC). Moreover, we further identified that stool based miR-92 biomarker is more sensitive than fecal immunochemical testing (FIT), the conventional method for CRC. The identified biomarkers provide a chance to develop markers for population-based practice in clinical and screening uses.

For gastric cancer, our group has identified numerous novel tumour suppressor genes mediated by epigenetic dysregulation which are related to the disease initiation, progression and prognosis. Some of these abnormalities could serve as promising biomarkers for prognostication of gastric cancer. We then developed non-invasive diagnostic strategies of cell-free methylated DNA in blood as tumour-specific detection. The blood methylated RNF180 DNA detection kit has been established.



## 3 You have mentioned about collaborations with biotechnology companies. How would you describe the role played by the industry in enhancing your research developments or bringing impacts to the society?

For the two detection kits mentioned just now, we have signed license transfer agreements with two companies. The major role for the companies is to validate the biomarkers in multiple hospitals and medical centres. The CFDA has a list of appointed hospitals and centres for clinical sample validation. In order to submit application to CFDA, at least 2,000 samples are required. Then, with their own factories, the biotech companies can help to develop kits for actual uses. Also, the companies would have employed lawyers, who know the regulations well to facilitate the applications of approval from CFDA or FDA.

## 4 Any difficulties you have encountered in collaborating with industrial partners?

We do have some issues with the pricing of the kits. Our original purpose for developing these biomarkers and detection kits is to improve the population-based healthcare by providing cheap and widely-available detection kits in order to provide more opportunities to diagnose the diseases in earlier stages and to get curative therapy, therefore increase the life span and improve the quality of life for patients with GI cancers. I have talked to the companies that we do not want to put a high price for such detection kits as we hope to provide simple, convenient and low-cost ways for applying to population-based screenings and detections. Therefore, I am thinking in the future if possible to set-up our own company to provide real services to the population.

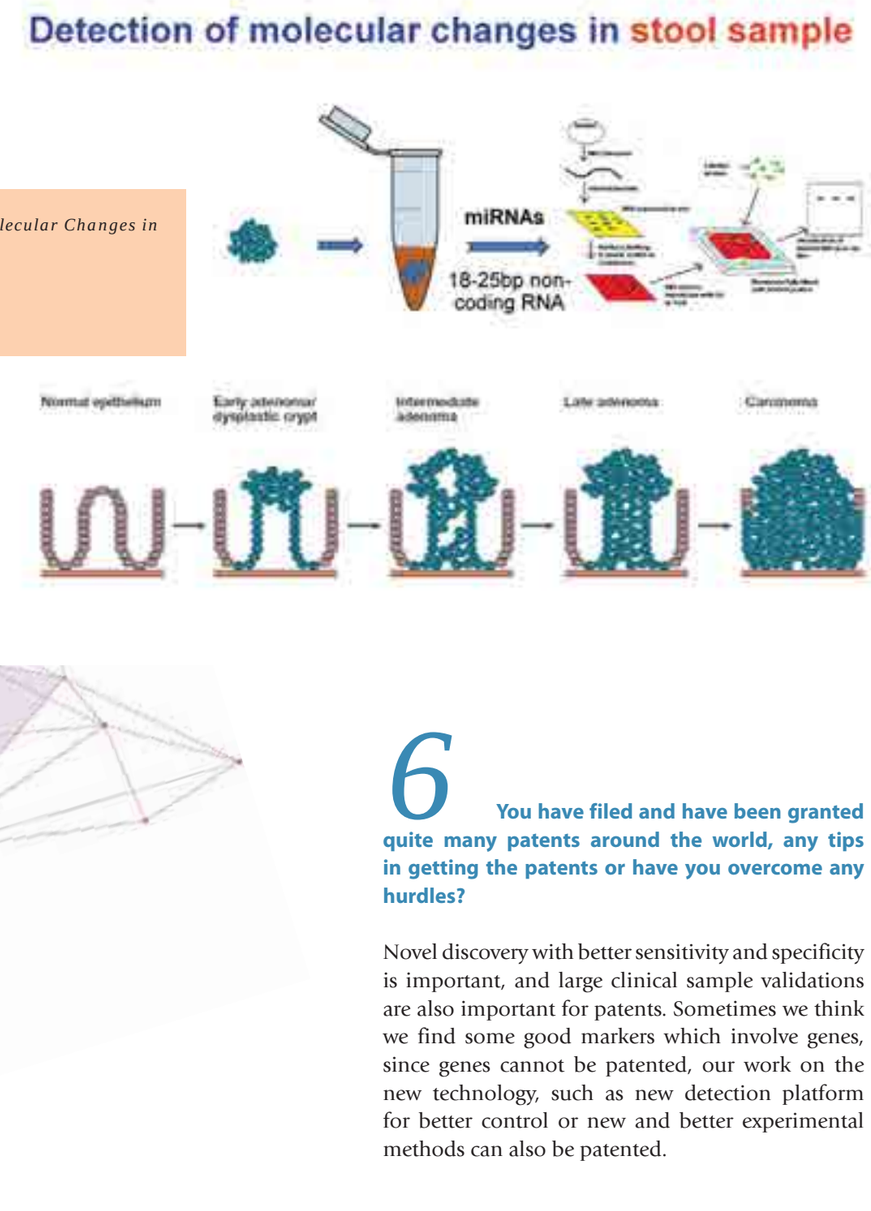
## 5 What do you think are some essential elements in turning your valuable research findings into some 'real' impacts to the society?

I think it is important to identify trustable and reliable biotech company. Then, we need to patent all important discoveries as soon as possible better before submitting for publications. Marker validation is another critical step, our markers and samples were not only validated in Hong Kong and China, but also sometimes in America and Europe. Last but not the least, even if you got the pharmaceutical companies to develop the detection kits and finish all the validations at different hospitals or medical centres, still the final important step is to get approval from FDA or CFDA for populational-based use.



*Prof. Jun Yu working in her laboratory*






*Decetion of Molecular Changes in Stool Sample*

## 6 You have filed and have been granted quite many patents around the world, any tips in getting the patents or have you overcome any hurdles?

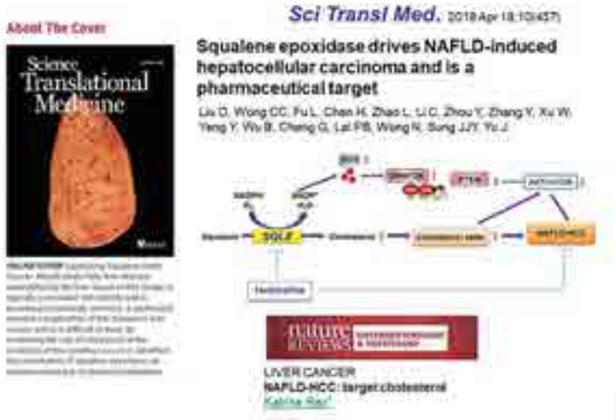
Novel discovery with better sensitivity and specificity is important, and large clinical sample validations are also important for patents. Sometimes we think we find some good markers which involve genes, since genes cannot be patented, our work on the new technology, such as new detection platform for better control or new and better experimental methods can also be patented.

## 7 Apart from publications, how do you and your team share these findings and impacts with other people?

Giving lectures or conference presentations nationally and internationally can be a way to share the findings, exchange ideas, know some new people and biotech companies.

For example, in China, the biotech companies would pay attention to the programme of different conferences or symposiums and they would assess if any of the titles or presentations are related to translational medicine or have potentials to be translated into actual applications. Again, one important step before sharing your findings and data in lectures or conference is to patent your findings first.

In our case, the biotech companies which were attracted by our topics may compare our presented biomarkers with the traditional markers in terms of sensitivity or other parameters. They will know that our discovery is a novel one and will approach us. After the lecture, the companies may leave their contacts and continue to communicate with us through different channels. If they were really interested in our discovery, we would then refer them to our knowledge transfer office of CUHK for further discussions.




*Science Translational Medicine*



## 8 What are the research directions with these biomarkers in the coming few years? What are the expected impacts from the research?

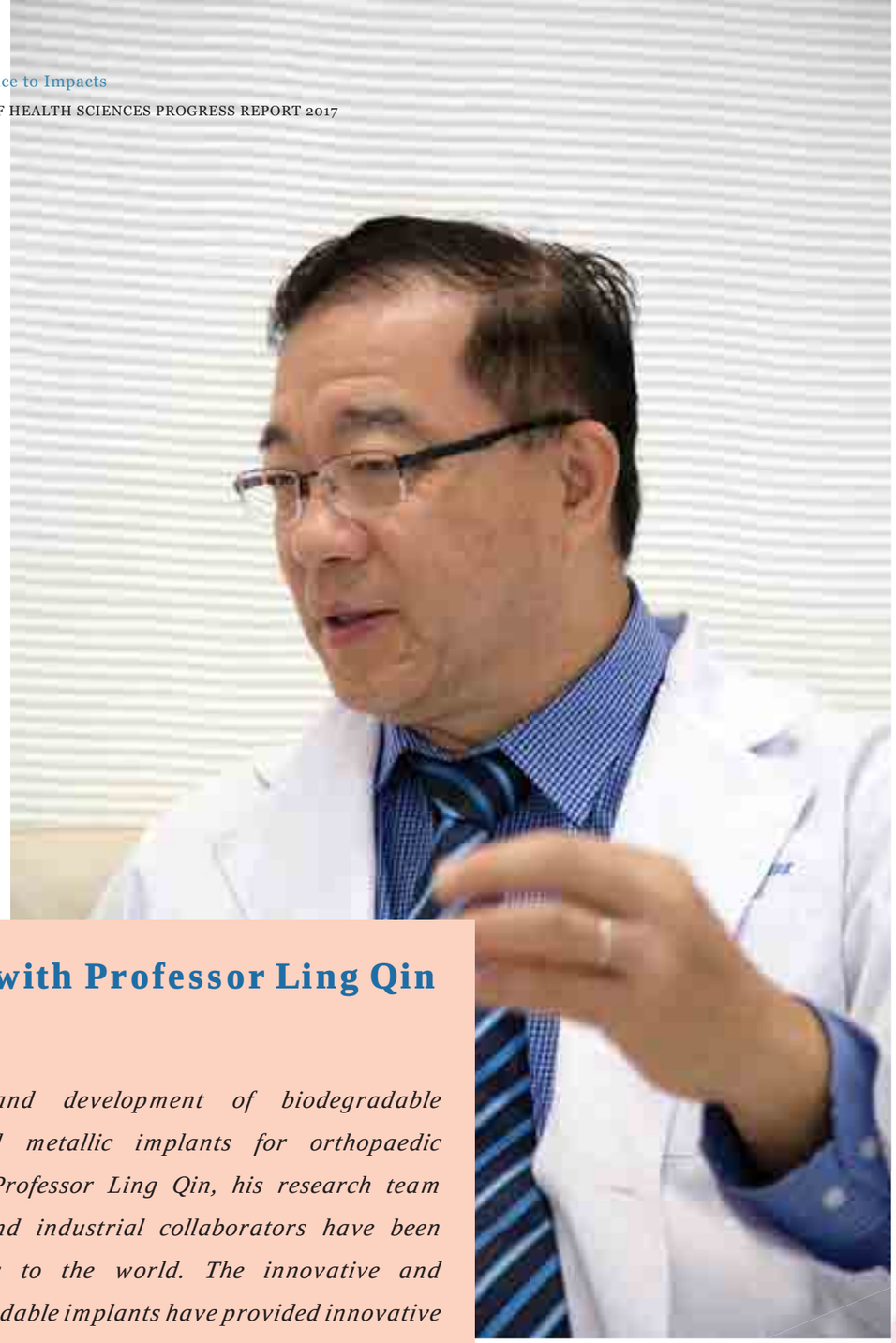
In the near future, we are trying to combine various biomarkers of host gene upregulation and stool microbiome of CRC patients and aim to identifiy the best panel of the detection markers with enhanced sensitivity and specificity over 90%, hoping to develop a next generation molecular detection kit for colorectal cancer screening and early diagnosis. In addition to screening or diagnostic biomarkers, we hope to identify new therapeutics targets to prevent and treat major GI cancer types.

Liver cancer is another cancer we will focus on. There are about 30% of Hong Kong population suffering from fatty liver, which may lead to liver diseases in the coming decades such as fatty liver associated hepatitis, fibrosis and even liver cancer. Apart from diagnostic biomarkers, we are also developing cancer cell therapeutic target drug. There is an antifungal drug which has potential role in preventing or treating the fatty liver-associated liver cancer. We have already applied for patent for this discovery before having publications.






*Stool miR92a detection kit*



## Interview with Professor Ling Qin
## 秦嶺教授

*The research and development of biodegradable magnesium-based metallic implants for orthopaedic applications by Professor Ling Qin, his research team and academic and industrial collaborators have been bringing impacts to the world. The innovative and patented biodegradable implants have provided innovative treatments for osteoporotic fracture, osteonecrosis, and tendon-bone insertion repair. Apart from clinical impacts, the research and publications from the team have also been served as key references for regulatory bodies, such as Food and Drug Administration in the US or Chinese Food and Drug Administration, for establishing ISO standards and guidelines for developing biodegradable metallic implants.*



### 1 What are the current situations or trends on bone problems in Hong Kong or around the world?

Around the world, there are more than 8.9 million osteoporotic fracture annually, resulting in an osteoporotic fracture occurring every three seconds. Apart from daily accidents, such as traffic accidents, aging population is another critical issue not only in Hong Kong but in the whole world. Bone problems, such as hip fractures, would affect the life span of people or even increase in death rates, due to the complications caused after the bone fractures. It does not only affect the patients, but also the family, and health care system, which may cause socioeconomic problems. In Hong Kong, 15,000 new osteoporotic fractures, including 5,500 hip fractures, are estimated to occur every year. These patients occupy 17% of the orthopaedic in-patient beds, and this continues to increase exponentially, with annual treatment costs for osteoporotic fracture over HK$300 million [International Osteoporosis Foundation. Asia-Pacific Regional Audit - Epidemiology, costs & burden of osteoporosis in 2013. https://www.iofbonehealth.org/data-publications/regional-audits/asia-pacific-regional-audit].

### 2 What are the characteristics of the conventional orthopaedic implants? And what are the differences between the conventional one and your innovative implants?

Conventional orthopaedic implants developed for fixation of bone fracture and tendon/ligament-bone insertion (TBI) are made of permanent metals, such as stainless steel or titanium. These kinds of implants work well for healthy bones, but are too hard for osteoporotic bones which have been softened. Since the fixation interface is very weak, the fixation quality is challenged and the prognosis of the fixation may not be so promising, and loosening of screws and plates may take place. So, the implants, initially starting with dynamic compression plates and then with better connections of screws, that is locking nails have been developed, and the whole structure will help to hold and fix the softer bones together.

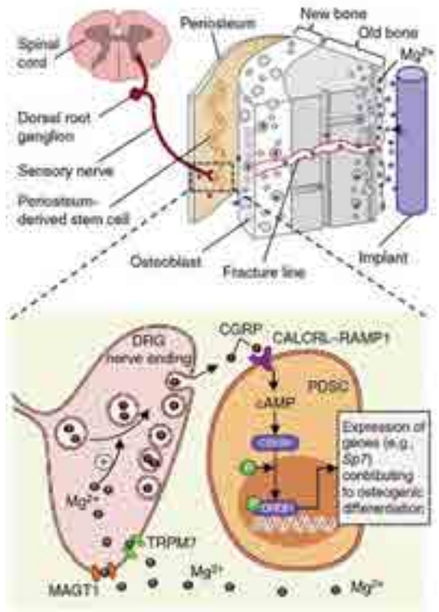
One of the challenges is that the recovery and repairing ability of osteoporotic bones are poor. By simple conversion, the recovery potential of osteoporotic fractures is only around 1/3 of the normal bones as the normal bones would have sufficient bone marrow stem cells for repairing. To deal with this problem, the first thing we can work on is the material design but not totally satisfactory. Another one is that we can incorporate bone growth stimulating agents, such as Bone Morphogenetic Protein (BMP), which is very expensive, into the design of implants.



*Professor Ling Qin and his team are looking for and designing suitable biometals and their hybrid fracture fixation systems or orthopaedic applications.*

## 3 Why would you choose pure magnesium (Mg) or its alloys instead of other materials for the implants? What are the advantages and difficulties that you and your team have encountered while studying on using Mg to make degradable implants?

We start directly with Magnesium (Mg) but not the other metals because there had been studies and evidences on using Mg for implants. It was not that successful until recent years because of the issue in purity of Mg and alloying techniques. Also, there are only a few metals on the periodic tables of elements that are found in human bodies and are relatively safe to be made into implants, since other metals can be toxic. Mg is one of the essential elements in our bodies, and 60% of Mg in our bodies are found in bones. Mg can be made into implants, such as screws and plates. Although Mg is not as hard as stainless steel or titanium, it is good enough to provide initial stability in low-weight bearing sites, and would then start to degrade in our bodies after certain period of time. During degradation, Mg implants would release Mg ions into the bone which would enhance bone formation, and one of novel mechanisms may through regulation of neuropathways which are important for bone formation.




*Schematic diagram showing the repair mechanism of Mg ions in the bone fracture. The released Mg ions from the Mg based implants enhance the new bone formation at the fracture gap via promoting more production of the neuropeptide. (Zhang Y, Xu J, Ruan Y, Qin L*, et al. Nat Med 2016 Oct;22(10):1160–9. PMCID: PMC52935352016)*

Most successful clinical cases for using Mg implants are with small bone fractures. For larger bones, pure Mg implants may not be hard enough to sustain and hold the structure. Therefore, our research team has been working to combine or incorporate other materials with Mg to develop a hybrid system. For places in need of healing process, Mg would be used to make the parts, whereas for some cases that a long-term fixation is required, other metals, such as titanium would be used. It is a whole system design instead of an individual piece for safe clinical applications. The relevant concept has been just published by a leading translation medical journal *Journal of Orthopaedic Translation* (Tian L et al. Hybrid fracture fixation systems developed for orthopaedic applications: A general review. *Journal of Orthopaedic Translation*. 2018. (In Press) https://www.sciencedirect.com/science/article/pii/S2214031X18300548).



## 4 Apart from the bone fractures you have mentioned just now, can the biodegradable Mg implants be used in other situations? Such as tendon-bone insertion (TBI) repair?

Yes, we have a number of studies published or unpublished on developing Mg screws and wires for suture and TBI fixation. Dr. Jiali Wang is currently the postdoctoral fellow in our team whose thesis and a few relevant papers, including a most recent on published in *Biomaterials* (Wang J et al. Magnesium alloy-based interference screw developed for ACL reconstruction attenuates peri-tunnel bone loss in rabbits. *Biomaterials*. 2018 Mar;157:86–97. https://www.sciencedirect.com/science/article/pii/S2214031X18300548). The results are encouraging that the Mg screws and wires released Mg ions which stimulate tendon and bone junctional healing with less peri-tunnel bone loss and more fibrocartilage regenerated at the interface area.

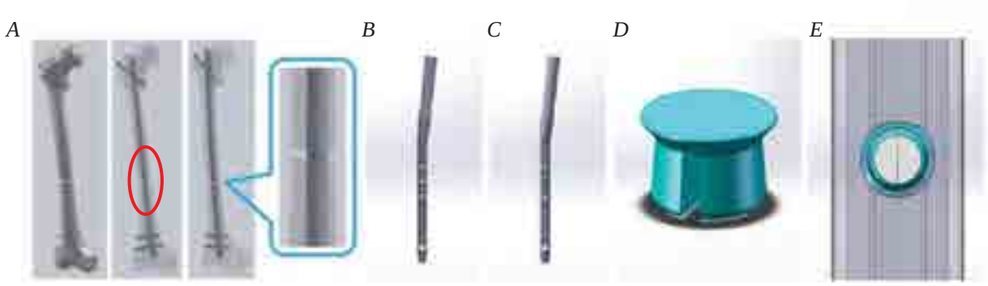
## 5 How long would it take for the Mg implants to degrade in human bodies?

As mentioned before, the degradable rate varies, depending on the materials (purity and alloying), processing technologies or the volume size. We have done some follow-up studies for up to 3 years that are led by our collaborator, Dr. DW Zhao, from Dalian. We found out that the Mg implants would stay in the human bodies for over 2 years, which would help to regenerate and heal the bone healing with implantation over time. Findings have been published in *Biomaterials* (Zhao D et al. Vascularized bone grafting fixed by biodegradable magnesium screw for treating osteonecrosis of the femoral head. *Biomaterials*. 2015 Dec 15;81:84–92. https://www.sciencedirect.com/science/article/pii/S0142961215009485) and we were subsequently also invited to write relevant reviews on that (Zhao D et al. Current status on clinical applications of magnesium-based orthopaedic implants: A review from clinical translational perspective. *Biomaterials*. 2016 Oct 11;112:287–302. https://www.sciencedirect.com/science/article/pii/S0142961216305580).

## 6 Can you share with us the Research & Development (R&D) process of the Mg-based orthopaedic implants? How is the current process?

We have been doing testing on both animal models and then human patients. We have accumulated around 200 successful clinical cases by our collaborators in Mainland China using pure Mg screws. We also have patented a number of special designs, including Mg-containing hybrid system as a potential product that is a specially designed bone nails with the combination of titanium and Mg. The nail is a titanium or Mg alloy or pure Mg rod with lots of holes, Mg-based paste would be injected in the hollow center, which would then be released slowly in the body to stimulate bone formation.

Another successful case involves atypical bone fracture with patient suffering from osteoporosis after drug treatment which hinder the healing process of the bone fracture, in which biodegradable Mg-based metallic hybrid implants do play a significant bone healing promotion role in this special case. This R&D is based on our preclinical study that has been published in *Nature Medicine* in 2016 (Zhang Y et al. *Nat Med*. 2016 Oct;22(10):1160–9. PMID: PMC5293535. https://www.nature.com/articles/nm.4162).




*Design of the modified Ti intramedullary nail (IMN) and the Mg buttons. A, B&C: the modified IMN with several holes in the middle. Mg plug can be inserted into the holes (red ovals) near the fracture site; D: the design of Mg button; E: the assembled Ti IMN with Mg buttons. After assembling, Mg buttons will be located near the fracture site to deliver the Mg ions to the fracture site for healing enhancement.*



*Design of innovative Mg-based hollow stent to be inserted into proximal femur to facilitate the delivery of stem cells and bioactive materials.*



## 7 What are the potential clinical impacts of Biodegradable Magnesium Implants in the near future?

Currently, conventional orthopaedic implants are available worldwide with modifications, such as implants being made to match patients' different body sizes. However, these implants are not biodegradable, which may not fit the needs of osteoporotic fractures or osteonecrosis, and cases with potential complications such as infections.

Elderly is usually prone to infection after surgery. From our recent findings, Mg ions released during implants degradation not only stimulate bone formation by one-third, but also would interact with body fluid and create an alkaline environment which would inhibit the growth of bacteria and work as an "anti-biotic". This is another clinical impact of biodegradable Mg implants.

## 8 Apart from clinical impacts, your research work has also changed the international standards on testing biodegradable implants. Can you explain to us more on that?

In order to comply with ISO standards, all implants must be tested for biosafety and cell toxicity, such as through short-term tests or any other screenings. Before, people did not expect the implants are degradable. Later on, there are inventors developing biodegradable materials, such as polymer, which raises the attention from the public and the regulatory bodies. There comes one of the big challenges for biodegradable materials or products.

Under current ISO standards, there are specific culture systems and certain volume ratios for *in vitro* cell toxicity test. The materials would be cultured for 72 hours. Then the culture medium would be used to culture cells to check the cell viability, with over 75% being acceptable and anything lower than that is considered as indication of toxic.

For permanent metal or degradable polymers, even if the materials are toxic, there would not be any challenges for passing the tests because the release of the elements or short-chain products is very slow and probably nothing would happen in 72 hours. But for non-permanent or what we called biodegradable metal-based materials, during *in vitro* tests, there may be the problems of too high concentration of ions or pH value becomes too high because of the release of ions to the culture medium. However, this may not be true for *in vivo* situations. Because during *in vivo* situations, after the degradation process, the ions would go into the circulation system. We have carried out tests on both animals and human but the serum Mg level has never been above the physiological level. Just like in the renal failure model, kidney is the organ responsible for filtering ions and we observe no significant differences between degradable metals and non-degradable metals.

In general, the Mg or its alloy-based biodegradable materials may show cell toxicity *in vitro* but may be safe *in vivo*. That's why we published our work to propose modifications of current ISO standards. Even editors of the journal *Acta Biomaterialia* provided some inputs in the paper since they also agree with our propositions. If certain Mg-based biodegradable materials could not pass the current ISO cell toxicity tests, we proposed to dilute the current treatment solution 6 to 10 times according to the *in vitro* and *in vivo* data of Mg ion levels (Wang J et al. Recommendation for modifying current cytotoxicity testing standards for biodegradable magnesium-based materials. *Acta Biomater*. 2015 Jul;21:237–49. https://www.sciencedirect.com/science/article/pii/S1742706115001828). Degradation rate depends on the environment and bones in different locations would result in various degradation rates. Our publication provides data and evidences which becomes the major references during the discussion in establishing the new ISO standards for testing the biosafety of biodegradable metals.

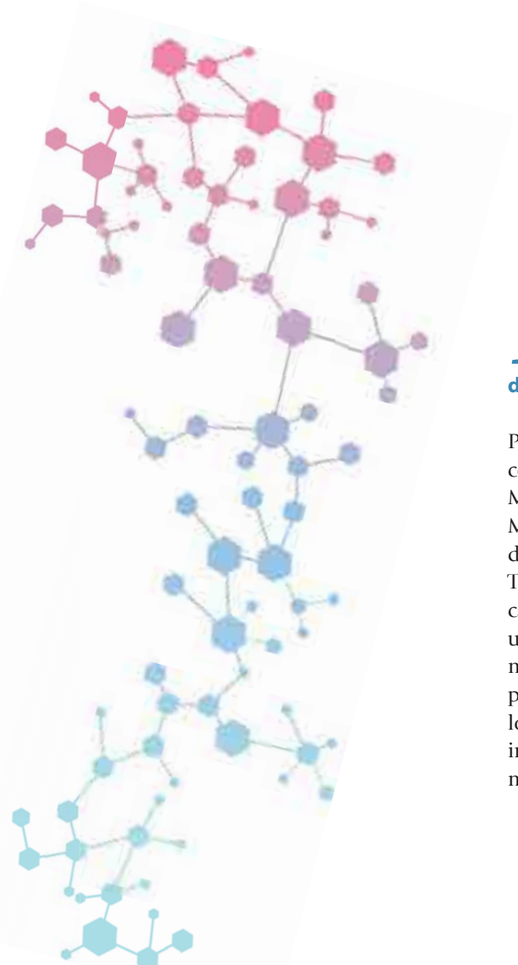
## 9 Since all these researches would also require expertise in other fields like material sciences and chemistry, how do you manage to recruit all necessary personnel?

We have a lot of collaborators from various fields and from different biomaterials institutes. One of my collaborators for the Theme-based Research Scheme is an expert in biomaterials from City University of Hong Kong. They have published a paper in *Nature* last year about the biodegradable materials, and key finding has even become the Nature cover page (Wu G et al. Dual-phase nanostructuring as a route to high-strength magnesium alloys. *Nature*. 2017 May 4;545(7652):80–3. https://www.nature.com/articles/nature21691). Also, industrial collaborators provide platforms in developing these implants.



## 10 How many patents have you obtained through the development of the innovative Mg implants?

We have obtained 5 patents. A local company has submitted agreement to acquire all my patents to our University. This company has a large manufacturing site in Nansha located within Guangdong-Hong Kong-Macao Greater Bay Area. We foresee that this company would play an important role in biomedical industry development of that area.



## 11 With that large manufacturing site, when will your products be ready to release to the Public?

Normally, it takes several years to get all the approvals required for the product to be available to the public. Our industrial collaborator is a Hong Kong-based company that has submitted all documents to China Food and Drug Administration (CFDA) for getting approval of the Mg screws. CFDA raised a lot of questions and we have addressed them all. We should be in the final stage for getting the approval before starting regulatory clinical trials. For the above mentioned patients who have been treated with Mg screws, they would only be regarded as clinical studies, yet these clinical cases are essential references.

## 12 Can you share with us some ideas about your future research direction with these implants?

Previously, we have tried 3D-printing technique to fabricate biodegradable Mg-containing composite scaffolds, but it was not so successful to print pure Mg or Mg-based alloys. Therefore, we have adopted to use other techniques, such as Mg injection molding by using Mg powder and plastic for molding. We have developed a Mg-based hollow hip screw for treatment of osteonecrosis of hip. There are a lot of holes on the surface of this unique Mg-based screw, where we can inject Mg- containing cement which would then sit inside the body for filling up bony space and healing enhancement. The initial cost for fabricating the mold is expensive. However, once the mold is made, mass production would be possible and the cost for producing large quantity of Mg-based implants will be low. Furthermore, 3D-printing may facilitate the development of personalised implants to fit each individual's needs, especially after overcoming material and manufacture limitations in the near future.

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| | |
|---|---|
| Address: | Li Ka Shing Medical Sciences Building,<br>The Chinese University of Hong Kong, Prince of Wales Hospital,<br>Shatin, the New Territories, HKSAR, The People's Republic of China |
| 地址： | 中華人民共和國香港特別行政區<br>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. Sing Chow, The Loft Studio |
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