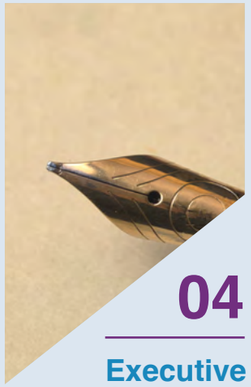
CONTENT 目錄



04

Executive Summary

報告摘要



12

Governance and Administration

管治與行政



22

The Li Ka Shing Medical Sciences Building

李嘉誠醫學大樓



54

Appendix- Reports on Research Activities

附錄 - 科研活動報告



56

Non-technical Summary

非技術性報告



87

Technical Reports on Research Programmes

研究項目：
技術性報告

24

Research Facilities

研究設施



40

Research Activities and Outputs

科研動態



324

Interview of Principal Investigators

與首席
研究員
對話



346

From Science to Impact

從科學到
影響



EXECUTIVE SUMMARY

報告摘要





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

Executive Summary
報告摘要

The year 2021 continued to be challenging due to the coronavirus pandemic. Given the travel restrictions, a lot of international meetings, seminars and workshops were run in a hybrid mode but researchers at the Institute managed to adjust their mode of work flexibly. Despite all the challenges, our researchers continued to push forward the biomedical science and many of them had made splendid achievements in the year.

My research team has been focusing on the biology of cell-free DNA (cfDNA) and its potential implication in diagnostic utility. Recently, the realisation of nonrandom fragmentation of cfDNA in the blood circulation has attracted great interest in the 'fragmentomics' study. We have demonstrated that the nonrandom fragmentation was attributed to the various nucleases in the blood circulation. In addition, we have developed a number of fragmentomic markers of plasma DNA, including fragment sizes, preferred ends, jagged ends and end motifs. Of note, such fragmentomic analysis could inform the tissue of origin of plasma DNA and the potential diagnostic applications have been illustrated in both the pregnancy and cancer models. In our review published in *Science* (Apr 2021), we have shared our thoughts on the molecular analyses of plasma DNA, including epigenetic, fragmentomic and topologic features. We envision that a multimodal analysis of the different molecular features of plasma DNA would be translated into a wide range of applications in diagnostics.

Siew Ng and her research team specialise in faecal microbiota transplantation (FMT). Gut microbiota are well implicated to play a significant role in the pathogenesis of obesity. With the promising results of FMT in animal models, a double-blind, randomised, placebo-controlled trial was hence followed which demonstrated that repeated FMTs are potentially safe and could lead to increased and sustained engraftment of donors' microbiota in patients with obesity and type 2 diabetes mellitus (T2DM). The study is also the first time demonstrating that lifestyle intervention pairing with FMT could further improve recipients' microbiota profile, reducing low-density lipoprotein cholesterol and improving liver stiffness, thereby providing a strong scientific basis to further develop FMT as a treatment modality for obesity and diabetes. The study was published in *Gut* (March 2021).

Ling Qin and his research team, specialising in biomaterial and drug translational research, found that the synthesis of calcitonin gene-related peptide (CGRP) in lumbar dorsal root ganglion (DRG) declined in osteoporotic bone fracture model. Their series of studies published in *Nature Medicine* and elsewhere have highlighted CGRP as a crucial osteoanabolic factor. Recently, their team has successfully developed flexible microelectrodes to be implanted at DRGs with minimal invasive surgery to promote fracture healing via CGRP regulation. The results showed that 20-min electrical stimulation daily could promote the biosynthesis and release of CGRP by activating Ca^{2+}/CaMKII/CREB signalling pathway and action potential, respectively. CGRP expression could further enhance type-H blood vessels formation and bone regeneration, thereby accelerating the healing of osteoporotic fracture. The findings were published in *Advanced Science* (October 2021).

Over the past year, a number of our Principal

Investigators were honoured for their achievements in scientific research. In particular, it was humbling for myself to be selected as a recipient of the “2021 Breakthrough Prize in Life Sciences” for the discovery that fetal DNA is present in maternal blood and can be used for the prenatal testing of trisomy 21 and other genetic disorders.

I am also pleased to be named with Rossa Chiu, Allen Chan three of the “Top 20 Translational Researchers of 2021” by an authoritative scientific journal *Nature Biotechnology*. With an increase in investments in innovation and technology in Asia, we look forward to more representation of scientists in the region featuring on this and other rankings of research productivity.

Jun Yu and her research team received the second-class prize of the National Natural Science Awards from the PRC Ministry of Science and Technology, the top science accolade in China, for the research breakthrough in non-alcoholic fatty liver disease and related cancer. It is worth mentioning that Vincent Wong, a member of Jun Yu’s team who specialises in fatty liver research, was recognised as one of the “Highly Cited Researchers 2021”. This is the third consecutive year for him to be named with this accolade released by *Clarivate Analytics*, to identify the world’s top researchers whose papers are ranked in the top 1% by citations in their respective fields of study and year of publication.

Siew Ng received the First-class Natural Science Award among the Higher Education Outstanding Scientific Research Output Awards (Science and Technology) 2020 from the PRC Ministry of Education in honour of the integrative research on epidemiology, pathogenesis and therapeutics in inflammatory bowel disease carried out collaboratively with the Dean and Joseph Sung. This accolade recognises significant contributions to scientific discovery, technological innovation, science and technology advancement, and implementation of patented technologies. Besides, Siew Ng was named by *Clarivate Analytics* as one of the “Highly Cited Researchers 2021”. It is the second consecutive year for her to receive this honour.

Gang Li received the first-class award in Science Advances from the PRC Ministry of Science and Technology for his achievements in new musculoskeletal tissue regeneration technologies. This award is one of the most prestigious national awards in China.

Robotics and AI is a new research area being specialised by the LiHS-affiliated Principal Investigator. Zheng Li and his research team members were awarded a bronze prize in the International Exhibition Inventions of Geneva 2021, recognising their remarkable performance in the development of the intelligent magnetic anchored and guided endoscope for minimally invasive surgery. The International Exhibition Inventions of Geneva is one of the most noteworthy yearly events devoted exclusively to inventions.

I would also like to congratulate Ronald Ma for being awarded the Croucher Senior Medical Research Fellowship by the Croucher Foundation in recognition of his excellent achievements in scientific research in medicine and the support that gives to the next generation of clinician scientists. Ronald aims to make use of the large multi-omic and clinical dataset generated, as well as the availability of a large prospective cohort for independent validation, to develop clinical tools including polygenic risk scores, for the prediction of diabetes complications and outcome. He will also be developing algorithms for patient stratification and treatment selection in diabetes.

In addition, Peiyong Jiang is the first scholar among institutions in Hong Kong being elected



as Senior Member of the National Academy of Inventors (NAI), in recognition of his inventive work in producing technologies that have the potential to make a real impact on the welfare of society. NAI is a member organisation with individual inventor members and Fellows from institutions worldwide, founded to recognise and encourage inventors with patents issued from the U.S. Patent and Trademark Office, enhance the visibility of academic technology and innovation, encourage the disclosure of intellectual property, educate and mentor innovative students, and translate the inventions of its members to benefit society.

We are particularly grateful to Dr. Li Ka Shing and the Li Ka Shing Foundation for their unstinting support throughout the years. With their donation of HK$30 million in April 2021, a series of renovation projects have been kicked off by stages to reorganise the research space with equipment acquisition, as well as to expand and upgrade the animal holding facilities in LiHS. It is expected the projects will be completed by the end of 2022. We believe these timely developments will provide passionate researchers with better support in their life science research and lay a foundation for our enhanced productivity and competitiveness in the coming years.

新型冠狀病毒大流行繼續為 2021 年帶來不少的挑戰。許多國際會議、研討會和講座因各地的旅遊限制改以網上或混合模式進行，但研究所的研究人員因應疫情靈活調整了他們的工作模式。儘管挑戰接踵而來，我們的研究人員仍孜孜不倦繼續推動生物醫學科學的發展，當中更有許多人在這一年取得卓越的成就。

我的研究團隊一直專注於游離 DNA（cfDNA）的生物學及其在診斷效用方面的潛在影響。最近，cfDNA 在血液循環中非隨機片段化的實現引起了團隊對「片段組學」研究的極大興趣，並證明非隨機片段歸因於血液循環中的各種核酸酶。此外，我們開發了許多血漿 DNA 的片段標記，包括片段大小、首選末端、鋸齒狀末端和末端基序。值得注意的是，這種片段組分析可以揭示血漿 DNA 的組織來源，並且在妊娠和癌症模型中證明了其在診斷方面的潛在應用。2021 年 4 月，我們在《科學》雜誌發表評論並分享了我們對血漿 DNA 分子分析的見解，包括表觀遺傳、片段組和拓撲特徵。我們預視針對血漿 DNA 不同分子特徵的多模式分析將轉化為廣泛的診斷應用。

黃秀娟和她的研究團隊專注研究糞便微生物群移植（FMT）。腸道微生物群在肥胖的發病機制中扮演重要的角色。由於 FMT 在動物模型中有望成為針對肥胖和代謝性疾病的療法，研究團隊對肥胖和第 2 型糖尿病（T2DM）患者進行了一項隨機雙盲對照試驗，證明重複的 FMT 具潛在的安全性，甚至可令捐贈者的微生物群持續在受者的腸道生長。這項研究還首次證明 FMT 配合生活方式干預可以進一步改善受者的微生物群、降低低密度脂蛋白膽固醇並改善肝臟纖維化，從而為進一步發展 FMT 作為治療肥胖和糖尿病的方式提供強而有力的科學依據。有關研究成果於 2021 年 3 月在英國腸胃病學會的官方期刊《Gut》發表。

秦嶺和他的研究團隊專門從事生物材料和藥物轉化研究，他們發現骨質疏鬆性骨折模型的腰椎背根神經節（DRG）中降鈣素基因相關肽（CGRP）的合成能力下降。研究團隊曾在《自然醫學》雜誌和其他期刊發表的一系列研究證實 CGRP 是關鍵的骨合成代謝因子。最近，他們還成功研發可通過微創手術植入柔性微電極於 DRGs，以調控 CGRP 合成與釋放促進骨折癒合。研究結果顯示，每天 20 分鐘的脈衝式電刺激可通過激活 DRG 神經元內的 Ca^{2+}/CaMKII/CREB 信號通路，顯著地增加 CGRP 陽性神經元數目；並通過激發動作電位促進 CGRP 在骨折部位的釋放。CGRP 表達可進一步增強 H 型血管及新骨骼生長，從而加速骨質疏鬆性骨折的癒合。是項研究結果於 2021 年 10 月在科學期刊《Advanced Science》發表。



在過去一年，研究所多位首席研究員憑藉他們在科學研究方面的成就及貢獻屢獲殊榮。我因發現胎兒 DNA 存在於母體血液中並可用於針對染色體異常唐氏症和其他遺傳疾病的產前檢測而被推舉獲得 2021 年「生命科學突破獎」，實感榮幸。

與此同時，我很高興與趙慧君、陳君賜一同被權威科學期刊《Nature Biotechnology》評為 2021 年「全球 20 位頂尖轉化研究科學家」。隨著外界對亞洲創新科技的大力支持，我們樂見有更多香港科學家憑藉其研究成果，躋身研究產出排名之前列。

于君和她的研究團隊因在非酒精性脂肪肝疾病及相關癌症方面的研究突破獲中國科學技術部頒發「國家自然科學獎二等獎」，這是中國最高的科學榮譽。值得一提的是，于君團隊中專門從事脂肪肝研究的黃煒燊被評為 2021 年「高被引學者（Highly Cited Researchers）」之一。這是他連續第三年獲得《Clarivate Analytics》頒發的這一榮譽，以表彰其論文在相關研究領域和出版年份內的引用率排名前百分之一，是世界頂級的研究人員。

黃秀娟榮獲中國教育部頒發 2020 年「高等教育優秀科研成果獎（科學技術）自然科學一等獎」，以表彰其與陳家亮院長及沈祖堯在炎症性腸病的流行病學、發病機制和治療學方面的綜合研究。這獎項旨在表揚對科學發現、技術創新、科技進步和專利技術實施的重大貢獻。此外，黃秀娟同被《Clarivate Analytics》評為 2021 年「高被引學者（Highly Cited Researchers）」之一，這是她連續第二年獲此殊榮。

李剛因其在肌肉骨骼組織再生新技術方面的成就獲得了中國科學技術部「科技進步一等獎」，這是中國享負盛名的國家級獎項之一。

機械人和人工智能是研究所首席研究員專注研究的一個新領域。李崢和他的研究團隊在 2021 年日內瓦國際發明展中獲得銅獎，表揚他們發明用於微創手術的智能磁錨引導內窺鏡方面的卓越表現。日內瓦國際發明展是創新發明方面最值得關注的年度活動之一。

我亦祝賀馬青雲獲裘槎基金會頒授「裘槎優秀醫學科研者獎」，以表揚他在醫學科學研究方面卓越的成就以及對栽培新一代年青醫學科學家的貢獻。馬青雲旨在利用大型多組學和臨床數據集，以及適用於獨立驗證的大型前瞻性隊列，開發包括多基因風險評分在內的臨床工具，以預測糖尿病併發症和結果。另外，他亦將發明一套算法用於糖尿病患者分層和選擇合適的治療。

此外，江培勇是香港院校中首位獲選為美國國家發明家學院（NAI）高級會員的學者，表揚他在生產技術方面的創新研究，為社會大眾帶來裨益。美國國家發明家學院是一個由來自世界各地院校的個人發明家和其研究夥伴組成的成員組織。這組織旨在表彰和鼓勵擁有美國專利商標局頒發的專利的發明家，提高學術技術和創新的知名度，鼓勵知識產權的披露，教育和指導富有創意的學生，並將其成員的發明轉化以造福社會。

在此，我們特別鳴謝李嘉誠博士和李嘉誠基金會多年來對研究所的慷慨支持。承蒙李博士及其基金會於 2021 年 4 月捐贈三千萬港元，研究所已分階段開展一系列翻新工程及重整研究空間，並購置先進科研設備以擴展和升級研究所內的動物設施。相關項目預計於 2022 年底竣工。我們相信，這些適時的發展將在生命科學的研究上為研究人員提供更好的支持，並為研究所未來提升生產力和競爭力奠定重要基礎。

GOVERNANCE AND ADMINISTRATION

管治與行政





GOVERNANCE AND ADMINISTRATION

管治與行政

Steering Committee
督導委員會

The Steering Committee of the Li Ka Shing Institute of Health Sciences (LiHS) was formed in 2007. The 15th meeting of the Steering Committee was held on 10 December 2021 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 2021 年 12 月 10 日舉行，會上各成員就研究所的未來發展發表了寶貴的意見。





MEMBER 成員

DENNIS LO
盧煜明

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



MEMBER 成員

WAI-YEE CHAN
陳偉儀

- **Pro-Vice-Chancellor/Vice-President, CUHK**
- **Director, Institute for Tissue Engineering and Regenerative Medicine (iTERM) , CUHK**
- **Li Ka Shing Professor of Biomedical Sciences**
- **Professor, School of Biomedical Sciences, CUHK**
- 香港中文大學副校長（策略發展）
- 香港中文大學組織工程與再生醫學研究所所長
- 李嘉誠生物醫學講座教授
- 香港中文大學生物醫學學院教授



MEMBER 成員

TONY MOK

莫樹錦

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



MEMBER 成員

LING QIN

秦嶺

- **Assistant Dean (Mainland Affairs), Faculty of Medicine, CUHK**
- **Director, Musculoskeletal Degeneration and Regeneration/Musculoskeletal Research Laboratory, CUHK**
- **Director, CUHK Hong Kong-Shenzhen Innovation and Technology Research Institute (Futian)**
- **Director, Innovative Orthopaedic Biomaterials and Drug Translational Research Laboratory of LiHS, CUHK**
- **Choh-Ming Li Professor of Department of Orthopaedics and Traumatology, Faculty of Medicine, CUHK**
- 香港中文大學醫學院助理院長（內地事務）
- 香港中文大學骨關節肌肉研究實驗室主任
- 香港中文大學深港創新研究院（福田）院長
- 香港中文大學李嘉誠健康科學研究所骨科創新生物材料和藥物實驗室主任
- 香港中文大學卓敏矯形外科及創傷學教授

Secretary:
Cecilia Leung
Assistant Secretary of LiHS, CUHK

秘書長：
梁欣欣
香港中文大學李嘉誠健康科學研究所助理秘書

In this photo, from left to right in the front row:
Cecilia Leung, Dennis Lo, Sammy Tang, and other team members.
相片中前排左至右為：梁欣欣、盧煜明、鄧麗華及其他行政團隊成員。

LIHS OFFICE
研究所辦公室

As of December 2021, a total of 20 staff members in the LiHS Office were in post, including administrative, scientific, research and technical staff. During the reporting period, the LiHS office oversaw the general administration of the Institute, the Li Ka Shing Medical Sciences Building, and various core facilities, including the Biomedical Computing Centre, the Molecular Biology Core Facilities, and the Cell Biology Core Facilities.

截至 2021 年 12 月底，研究所辦公室共已聘任 20 名僱員，包括行政、科學、研究及技術人員，負責研究所的日常運作，並支援重點科研設施的運作，包括生物醫學計算機中心、分子生物學重點科研設施、和細胞生物學重點科研設施。



李嘉誠醫學大樓

THE LI KA SHING MEDICAL SCIENCES BUILDING

The Li Ka Shing Institute of Health Sciences was housed inside the 11-storey Li Ka Shing Medical Sciences Building. As of December 2021, there were approximately 530 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.

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 2021 年 12 月，約有 530 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



Research Facilities
研究設施

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

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



Li Ka Shing Translational Omics Platform
李嘉誠轉化組學平台



Thermo Scientific Orbitrap Eclipse Tribrid Liquid Chromatography - Mass Spectrometer
高解析三重軌道離子阱液相色譜 - 質譜聯用儀



Thermo Scientific TSQ Altis Triple Quadrupole Liquid Chromatography - Mass Spectrometer
三重四極桿液相色譜 - 質譜聯用儀

The **Li Ka Shing Translational Omics Platform** (LKS TOP) aims to build a state-of-the-art, multi-omics platform specialising in cutting-edge genomics, proteomics and metabolomics. The platform consists of a series of best-in-class research facilities that will offer screening and discovery techniques for precision medicine, microbiota and nutrition science, biomarker discovery, dissection of health effects resulting from air pollutants and drug development in emerging infectious diseases (e.g. COVID-19), cardiometabolic diseases, cancers, childhood diseases, and traditional Chinese medicine (TCM).

The platform consists of two liquid chromatography-mass spectrometry systems, the Thermo Scientific Orbitrap Eclipse Tribrid and Thermo Scientific TSQ Alits Triple Quadrupole liquid chromatography-mass spectrometry systems. They provide the world's fastest and ultra-sensitive identification, screening and quantification of molecules from a large number of clinical samples and traditional Chinese herbs for genotyping, novel biomarkers discovery and drug development.

李嘉誠轉化組學平台（LKS TOP）旨在建立一個專門研究尖端科技的基因組學、蛋白質組學和代謝組學的先進多組學平台。這平台包括一系列世界一流的科研設施，將推動精準醫學、微生物群、營養科學和生物標誌物的發現；解構空氣污染物對健康之影響；及為傳染病學（例如 2019 新型冠狀病毒病）、心血管代謝疾病、癌症、兒童疾病和中醫藥的藥物開發提供篩選的技術支援。

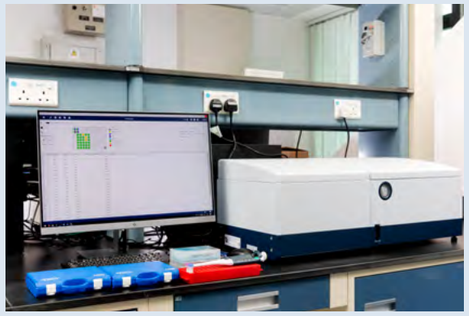
平台包括Thermo Scientific Orbitrap Eclipse 高解析三重軌道離子阱和 Thermo Scientific TSQ Altis 三重四極桿定量液相色譜 - 質譜聯用儀兩台，提供全球最快及最靈敏的鑑定、篩查及定量方法，供研究員從大量臨床樣本和傳統中醫藥中篩選出有價值的生化分子，用於基因分型、新型生物標誌物發現和藥物開發。

The platform also includes rapid, robust, high-throughput, cost-effective and efficient systems, Bruker MALDI and IR Biotypers, for the identification and taxonomical classification of micro-organisms.

平台還包括兩個快速、強大、高通量和高效系統，Bruker 基質輔助激光解吸電離質譜儀和 Bruker 傅立葉變換紅外光譜儀，用於微生物的鑑定和分類。



Bruker MALDI Biotyper
基質輔助激光解吸電離質譜儀



Bruker IR Biotyper
傅立葉變換紅外光譜儀

Moreover, the platform is equipped with Beckman Coulter CytoFlex LX microbial community flow cytometry for examining cytometric fingerprints for microbiota associated diseases.

此外，平台配備了 Beckman Coulter CytoFlex LX 微生物群落流式細胞儀，用於檢查與微生物群相關疾病的細胞指紋圖譜。



Beckman Coulter CytoFlex LX
微生物群落流式細胞儀



Emulate Intestine Chips
and Human Emulation System
仿真腸芯片和人體仿真系統

Finally, this platform is equipped with Emulate intestine chips and Human Emulation System, a powerful *in vitro* system which enables the studying of the effects of bacteria on gut tissue and bacteria-specific metabolites.

最後，這平台配備了仿真腸芯片和人體仿真系統，這是一個功能強大的體外系統，用於研究細菌對腸道組織和細菌特異性代謝產物的影響。

Chun-kit Choi has been appointed to promote LKS TOP as a key platform for multi-disciplinary research and foster collaborations with researchers through this platform. Making use of the advanced equipment at the platform, Chun-kit is studying the characterisation of complex phenotypes in various diseases for diagnostics development, drug designs and precision microbial therapy. He has also collaborated with Man-nin Chan from CUHK Faculty of Science to decipher and quantify the pollutant in the collected air samples and evaluate the corresponding health effect by utilising high-resolution mass spectrometry.

蔡俊傑獲委任推廣李嘉誠轉化組學平台作為多學科研究的重要平台，並通過這平台促進與研究人員的合作。透過平台的先進設備，他正研究各種疾病中複雜表型的表徵，用於診斷開發、藥物設計和精準微生物治療。他亦與香港中文大學理學院的陳文年合作，利用高解析度質譜技術解構和量化採集空氣樣本中的污染物，以評估其對健康的影響。



The platform has officially been opened to the research community in the Faculty with effect from 13 December 2021. A wide-ranging technical seminar series that introduces the major equipment was held. Although all seminars were run virtually due to the COVID-19 pandemic, research staff and students participated actively in them. Interested researchers can make online reservations for these equipment items via the Li Ka Shing Institute of Health Sciences Registration and Booking System. In-house training on the basic operation of the equipment will be provided by staff members of this platform.

平台於 2021 年 12 月 13 日起正式開放，並舉行了一系列多元化技術研討會，介紹其主要設備。儘管在疫情下所有研討會都以網上進行，但研究人員和學生積極參與其中。有興趣的研究人員可透過網上系統預約使用各種設備，平台亦會為研究人員提供培訓，介紹儀器的基本操作。

Biomedical Computing Centre
生物醫學計算中心

The **Biomedical Computing Centre** (BCC) is one of the important facilities in the Institute. It is essential for supporting biomedical research in the fields of next-generation sequencing analysis, bioinformatics, data analysis, artificial intelligent (AI) based data analysis, and translational genomics.

The Centre enhanced its data centre infrastructure (core network and structured cabling) and the overall computing servers, storage systems capacity, high-speed file systems and data management since the third quarter of 2021. All systems upgrades are based on the existing data centre infrastructural architecture together with the expansion of the usage of 13 IT equipment racks in the Research Data Centre (RDC) at Hong Kong Children's Hospital (HKCH).

The Institute was carrying out the major computing servers, storage systems and IT infrastructure upgrades in the past year. These system upgrades included replacement of Computing Servers, expansion of the 3-tiered High-speed Storage Systems, enhancement of the BCC Computing Architecture, and fully upgrade of the networking architecture to 100Gbps and 200Gpbs capacity.

The targets of the systems upgrades will also increase BCC's computing and storage facilities, as well as Graphics Processing Unit (GPU) systems by more than 5000 CPU cores and the addition of 30PB storage capability.

生物醫學計算中心是研究所內的重要設施之一，亦是支援次世代排序（NGS）、數據分析、人工智能數據分析、生物信息學、及研究轉譯基因組學的重要設施。

中心自 2021 年第三季度開始，啟動及進行增強數據中心基礎設施（核心網絡和結構化佈線）以及對整體計算服務器、存儲系統容量、高速文件系統和數據管理等進行強化。所有系統升級或整合均基於現有數據中心基礎設施架構以及擴展使用香港兒童醫院內研究數據中心的 13 個 IT 設備機架。

過去一年，研究所開展了主要計算、存儲系統和 IT 基礎設施升級。這些系統升級包括更換計算服務器，擴展三層高速存儲系統，增強中心計算架構，並將網絡架構全面升級至 100Gbps 和 200Gpbs 核心綫容量。

系統升級的最終目標是將中心的計算能力和存儲設施儲存量大幅提升及增強新的計算服務器。新增服務器達 5000 多個 CPU 內核和大幅增加 30PB 的系統存儲能力。

The upgrade exercise covers the following areas:

- Fully utilise the extra establishment of the 13 new computer and IT equipment racks at the HKCH RDC to host 20 units of new general purpose computing servers (Dell PowerEdge R740, Intel Xeon Gold 6230R 26 core CPU, 1TB RAM). Type 1 servers are targeted for primary analysis with higher server computing power and larger storage system capacity.
- Acquisition and deployment of extra 20 units of High Performance Computing Servers; Type 2a and 2b servers: Dell PowerEdge R840 server with Intel Xeon Gold 8260 24 core CPU, 2TB memory in BCC for supporting intensive data analysis.
- Integration of 4 units of Ultra High Performance Computing Servers; Type 3 servers with extra high memory for intensive and deep data analysis that requires large system memory: Dell PowerEdge R840 server with Intel Xeon Platinum 8270 2.7GHz 26 core CPU, 3TB memory.
- The three types of servers are now providing a total of 3,376 CPU cores and a total of 253.29 TFLOPS processing power.
- The deployment of new general-purpose Graphics Processing Unit (GPU) systems for a new Artificial Intelligent (AI) data analysis architecture with 4 units of Dell PowerEdge C4140 GPU Servers, each with 2 x Intel 6420R, 2.4GHz, 24 Core, 4 x NVidia GPU Tesla V100.
- The new general-purpose GPU systems are providing a total of 16 x NVidia GPU Tesla V100 GPU cards and an overall 81,920 CUDA Cores, 500 TFLOPS Tensor Performance.

是次中心設施及系統升級規劃的主要領域包括：

- 充分利用在香港兒童醫院內研究數據中心內額外建立的 13 個新計算機和 IT 設備機架來放置 20 台新的通用計算服務器（類型 1 服務器：Dell PowerEdge R740、Intel Xeon Gold 6230R 26 核 CPU、1TB RAM）。類型 1 服務器是支援主要初步數據分析為目標，具備比原有系統更高的服務器計算能力和更大的存儲系統容量。
- 添置和部署額外的 20 台高性能計算服務器；2a 類和 2b 類服務器：Dell PowerEdge R840 服務器，配備 Intel Xeon Gold 8260 24 核 CPU、2TB 內存，用於支持第二級密集的數據分析。
- 整合 4 台超高性能計算服務器：此等服務器為中心新增及具有超高內存的類別 3 服務器，用於支援需要大系統內存的密集和深度數據分析及研究：Dell PowerEdge R840 服務器，配備 Intel Xeon Platinum 8270 2.7GHz 26 核 CPU，3TB 內存。
- 中心計算架構內的新增加三種計算服務器現能提供整體 3,376 個 CPU 核心服務和整體 253.29 TFLOPS 的計算能力。
- 購入及部署 AI 數據分析架構內新的通用 GPU 系統，這些新 GPU 系統配備 4 台 Dell PowerEdge C4140 GPU 服務器，每台配備 2 枚 Intel 6420R、2.4GHz、24 核 CPU、4 枚 NVidia GPU Tesla V100。
- 這個新的通用 GPU 系統架構及設施總共能提供 16 枚 NVidia GPU Tesla V100 GPU 卡和整體 81,920 個 CUDA 內核，500 TFLOPS Tensor 運算效能。





- Integration of two large-scale GPU systems: Nvidia DGX A100 with 8 x NVIDIA A100 Tensor Core GPUs and 2 units of IBM Power 9 AC922 GPU Servers with 8 x NVIDIA A100 Tensor Core GPUs in cluster.
- These new GPU systems will be integrated into a new GPU AI cluster computing architecture that can provide over 6 PetaFLOPS AI operations and 10 PetaOPS INT8.
- Deployment of new tiered storage architecture with a 3-tiered storage system for supporting remote backup, data recovery scheme, high speed and additional data security storage systems architecture.
- Tier 1 storage systems are high speed storage systems with BeeGFS Parallel File System and 2.746PB Usable Capacity and 16 ~ 30GBs I/O Throughput utilising Dell Scalable CPU Servers.
- Tier 2 Storage systems is a High Throughput Distributed Storage Systems, 6.342PB Usable Capacity 8 - 10GBs I/O Throughput utilising Dell EMC Isilon PowerScale A2000 Storage Systems (32 nodes).
- Tier 3 Storage Systems consists of two internal storage classes:

  1. Near Online Storage: supports active online data and reference data; 6.384PB usable capacity 16GBps I/O throughput;

  2. Storage systems and facilities for Backup and Archive of critical datasets: 4.5PB usable capacity 8GBps I/O throughput. The systems are support by Oracle ZS7-2 high-end Storage Appliance and Oracle SL150 LTO 8 Tape Library Systems.

  The integration of storage architecture and system has increased the overall capacity at the center, allowing us to accommodate more high-speed computing servers and storage systems. This new storage system architecture can provide a data capacity of 30PB (raw capacity) in total.

- 整合兩個大型 GPU 系統：配備 8 枚 NVIDIA A100 Tensor Core GPU 的 NVida DGX A100 服務器及 2 台配備 8 枚 NVIDIA A100 Tensor Core GPU IBM Power 9 AC922 GPU 服務器。
- 這些新的 GPU 系統將被集成到一個新的 GPU AI 集群計算架構中，可以提供超過 6 PetaFLOPS AI 運作和 10 PetaOPS INT8 運算能力。
- 部署及整合新的分層存儲系統及架構，擴大及增強中心現有的三層儲存系統，以支持遠程備份、快速數據恢復方案、高速和附加數據安全存儲系統架構。
- 第一層 (Tier 1) 存儲系統： 為一具高速儲存系統（使用 BeeGFS 並行文件系統）的儲存系統、2.746PB 可用容量和 16 ~ 30GBs I/O 吞吐量和 Intel 可擴展 CPU 服務器。
- 第二層（Tier 2）存儲系統是高吞吐量分佈式存儲系統，高達 6.342PB 總可用容量， 8 - 10GBs I/O 吞吐量。系統整合新 增 的 Dell EMC Isilon PowerScale A2000（32 節點） 存儲系統。
- 第三層（Tier 3）存儲系統由兩個內部存儲類別系統組成：

  1. 在線存儲系統 : 支持常用在線數據和參考數據應用；總 6.384PB 可用容量及支援 16GBs I/O 吞吐量；

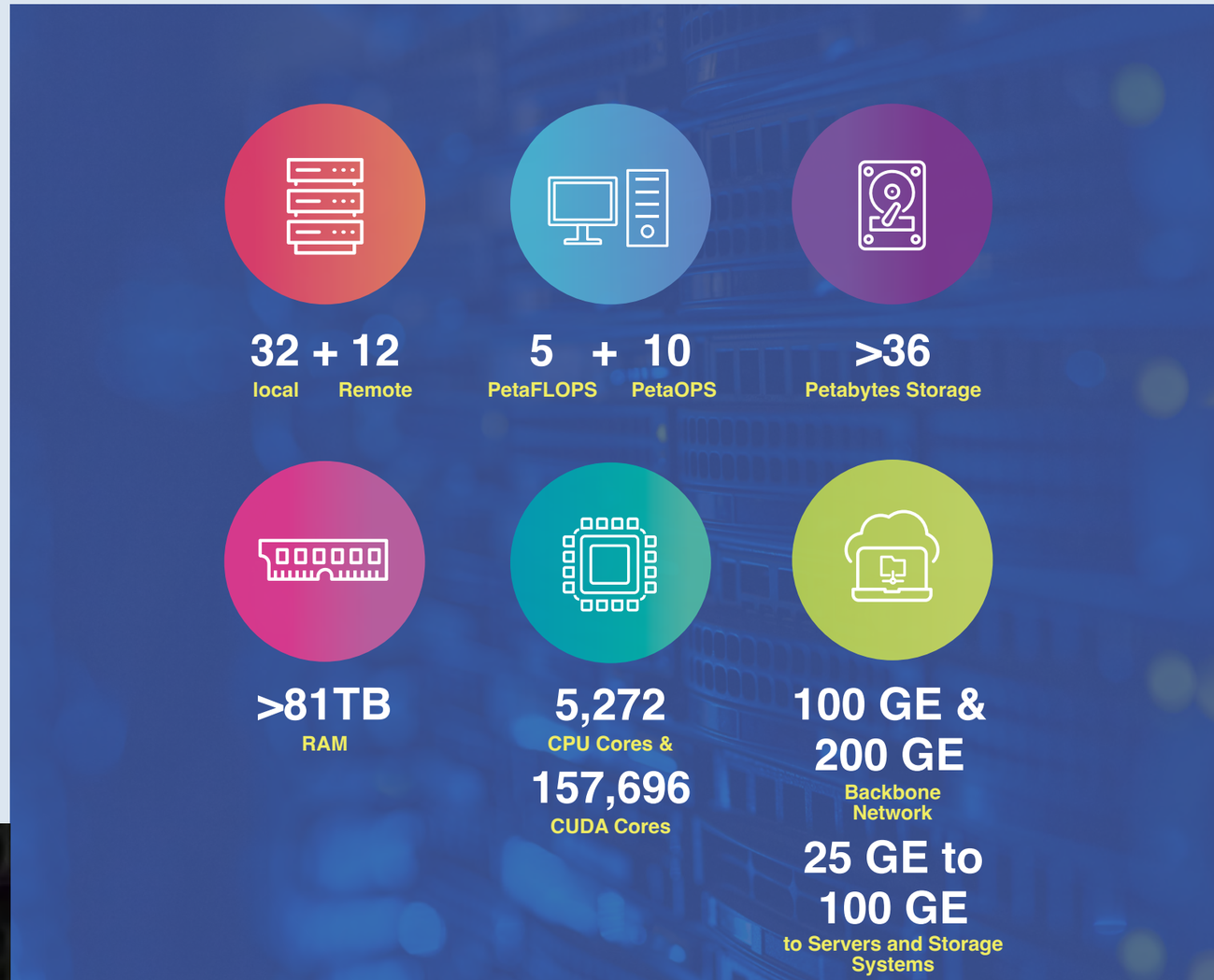
  2. 用於關鍵數據集備份和存檔的儲存系統和設施 : 4.5PB 總可用容量及支援 8GBs I/O 吞吐量。 系統整合 Oracle ZS7-2 高端儲存設備和 Oracle SL150 LTO 8 磁帶庫系統支持系統。

  是次儲存系統架構整合能提升中心整體容量以容納更多更高速計算服務器及高速儲存器系統。此新儲存系統架構能提供 30PB (原始容量) 總數據容量。



- Enhancement of the core computing network in BCC and RDC: The core network environment consists of two high speed network architecture: Infiniband (IB) HDR network with 200 Gbps and 100 Gbps non-blocking, low latency and high-throughput core IB network and a 100 Gbps, 40 Gps and 25 Gbps High-throughput Core Ethernet Backbone network.
- The two new core network architecture can help to support 54.0 Tb/s throughput (IB core) and 41.6 Tb/s bandwidth (ethernet core) and can support high-density ethernet and IB host connections with 25 GbE, 40 GbE, 100 GbE or 200 GbE ports for direct servers and storage systems connection.

- 增強中心和香港兒童醫院研究數據中心內的核心計算網絡。核心網絡環境由兩個高速網絡架構組成：具有 200 Gbps 和 100 Gbps 低延遲和高吞吐量核心 Infiniband (IB) 網絡的 100 Gbps Enhanced Data Rate (EDR) 、200 Gbps High Data Rate (HDR) 非阻塞 I/O 網絡及 100 Gbps、40 Gps 和 25 Gbps 高吞吐量核心以太網骨幹核心網絡。
- 中心新的兩個核心網絡架構有助於支持 54.0 Tb/s 帶寬吞吐量（IB 核心網絡）和 41.6 Tb/s 帶寬吞吐量（以太網核心網絡），並可以支持 25 GbE、40 GbE、100 GbE 或 200 GbE 的高密度以太網絡和 IB 網絡。支援用於各直接連接服務器和存儲系統的網絡端口。



Core Facilities

重點科研設施

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

研究所內的**重點科研設施**包括：

Molecular Biology Core Facilities
分子生物學
重點科研設施

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

Molecular Biology Core Facilities
分子生物學重點科研設施

The **Molecular Biology Core Facilities** provide comprehensive molecular research platforms to perform a variety of functions, including **Sample Quality Control**, **Transfection**, **Molecular Analysis**, and **Data Analysis**.

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

Sample Quality Control • 樣本品質管制

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



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

評估 DNA 和 RNA 片段的長度、濃度和質量，以備後續實驗使用。

- Agilent 2100 Bioanalyzer
  生物分析儀



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



- Invitrogen Qubit 2.0 Fluorometer
  螢光定量儀

Transfection • 基因轉染

Electroporation
電脈衝穿孔

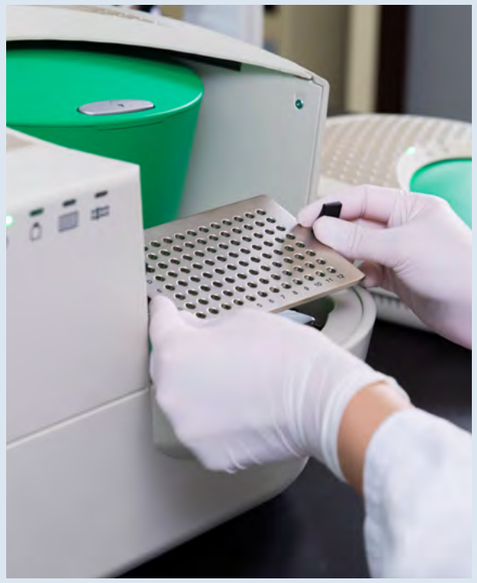


To transfect any DNA vectors (expression plasmids, shRNA vectors) into difficult-to-transfect cell lines and primary cell.
將 DNA 載體 (表達質粒或 shRNA 載體) 轉染成細胞株及初代細胞。

- Amaxa Nucleofector II
  電穿孔轉殖儀

Molecular Analysis • 分子分析

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



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

- Bio-Rad QX200 Droplet Digital PCR System
  微滴式數位聚合酶鏈式反應系統

  Reaction mixture is partitioned into 20,000 nanolitre-sized droplets, enabling absolute quantitation of targeted DNA and RNA molecule within a single sample.
  反應混合物被分成二萬個納升大小的液滴，於單一樣本中對目標 DNA 和 RNA 核酸分子進行絕對定量。



- Illumina iScan Microarray System
  芯片掃描系統



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

Multi-purpose Imaging System
多功能成像系統



To detect and analyse reproducible fluorescence and chemiluminescence gel and blot images. Stain-free imaging function is also available for researchers to perform total protein normalisation in gel and blot.
檢測和分析可重現的螢光和化學發光凝膠和印跡圖像。研究員亦可使用無漬成像功能在凝膠和印跡中進行總蛋白標準化。

- Bio-Rad ChemiDoc MP Imaging System
  多色螢光及化學發光成像系統

Bead-based Suspension Analysis
磁珠懸浮偵測



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

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

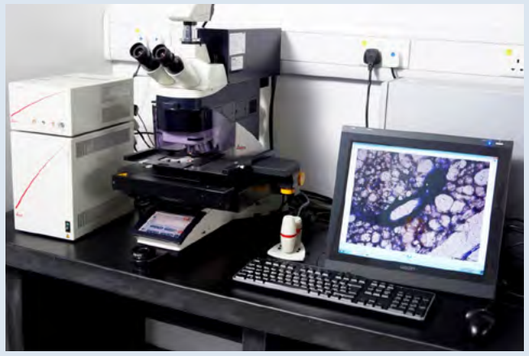
Cell Biology Core Facilities
細胞生物學重點科研設施

The **Cell Biology Core Facilities** provide comprehensive cellular research platforms to perform **Cell Selection**, and **Cell Culturing**.

細胞生物學重點科研設施為研究員提供全面的研究設備以進行**細胞篩擇**及**細胞培育**。

Cell Selection • 細胞篩擇

Microdissection
顯微切割



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

利用非接觸及無污染技術，分離一個或一群目標細胞。

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

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



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

以雷射激光照射流動中的細胞，分類並收集目標細胞。

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



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

Cell Culturing • 細胞培養

Cell Expansion & Testing
細胞擴增和測試

Cell Culture Facilities equipped with NSF49 certified Class II Type A2 Biosafety Cabinets, which facilitate the culturing of animal cells, animal cell lines and human cell lines. In view of increasing demand of cell culture facilities in recent years, Cell Culture Facilities have been expanded and enhanced in the past year. The doubled capacity of cell culture facilities would benefit Principal Investigators from a wide spectrum of cell related specialties and speed up research work.

細胞培養設施內設有符合 NSF49 標準的第二等級 Type A2 生物安全櫃，可供研究員培育動物細胞、動物細胞株及人類細胞株。為配合日益增長的需求，研究所於去年擴充細胞培育設施，設施容量倍增後，有助提升研究效率並有利於研究與細胞相關的項目。

RESEARCH ACTIVITIES AND OUTPUTS

科研動態







Research Activities And Outputs
科研動態



Research Areas and Teams
研究領域隊伍

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

研究所內的研究隊伍可大致分為兩大研究範疇，是為「**疾病及病理生物**」和「**創新技術**」。

Diseases and Pathobiology • 疾病及病理生物

Research Area 研究領域	Principal Investigator 首席研究員
Digestive Diseases 消化疾病研究	Jun Yu 于君
Emerging Infectious Diseases and Microbiota 防疫研究及腸道微生物學	Siew Ng 黃秀娟
	Renee Chan 陳韻怡
	Peter Cheung 張栢恒
Asian Cancers 亞洲癌症研究	Qian Tao 陶謙
Cardiovascular Medicine 心血管疾病研究	Xiaoqiang Yao 姚曉強
	Alex Lee 李沛威
Diabetes and Obesity 糖尿病與肥胖症研究	Juliana Chan 陳重娥
	Ronald Ma 馬青雲
Inflammatory Diseases 炎症性疾病研究	Hui-yao Lan 藍輝耀
	Erik Fung 馮以文
	Chris Mok 莫家斌
Neuroscience and Neurotechnology 神經科學及神經技術	Owen Ko 高浩
	Hei Ming Lai 黎曦明
Reproduction and Development 生殖與發育研究	Ronald Wang 黃志超
Nephrology 腎臟疾病研究	Cheuk Chun Szeto 司徒卓俊

New Technologies • 創新技術

Research Area 研究領域	Principal Investigator 首席研究員
Molecular Diagnostics 分子診斷學	Dennis Lo 盧煜明 Rossa Chiu 趙慧君
	Nelson Tang 鄧亮生
	Allen Chan 陳君賜
	Jacky Lam 林偉棋
Stem Cells and Tissue Regeneration 幹細胞及組織再生研究	Gang Li 李剛
	Kathy Lui 呂愛蘭
	Wayne Lee 李郁偉
Biomaterial and Drug Translational Research 生物材料與藥物轉譯研究	Ling Qin 秦嶺
Genomics and Bioinformatics 基因組學與生物訊息學	Hao Sun 孫昊
	Peiyong Jiang 江培勇
Non-coding RNAs and Cellular Signalling 非編碼核糖核苷酸研究及細胞訊號轉導	Huating Wang 王華婷
	William Wu 胡嘉麒
Robotics & AI 人工智能	Zheng Li 李崢

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 283 publications from these teams were published.

Among the publications, 133, 49 and 46 were published in journals with impact factors greater than 4, 10 and 15, 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 283 篇學術論文，當中有 133、49 及 46 篇分別刊登於影響分子高於 4、10 及 15 的學術刊物。

RESEARCH

REVIEW SUMMARY

MEDICINE

Epigenetics, fragmentomics, and topology of cell-free DNA in liquid biopsies

Y. M. Dennis Lo*, Diana S. C. Han, Peiyong Jiang, Rossa W. K. Chiu

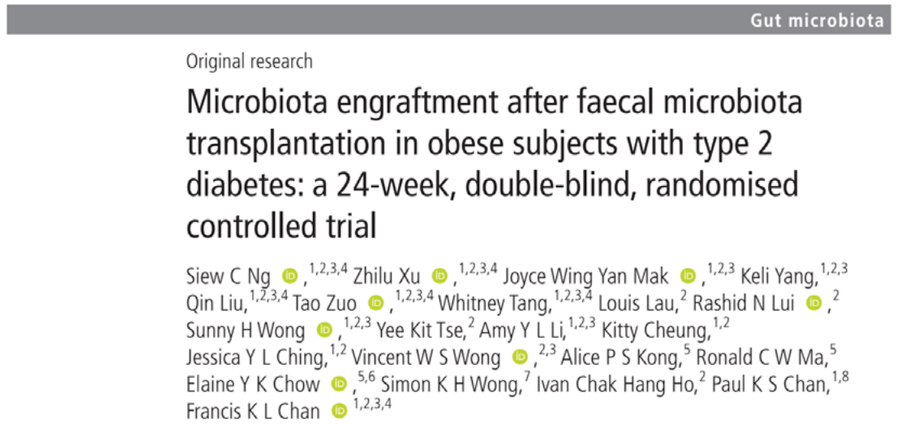
chondrial DNA without regard to its form. The study of such characteristics has also enhanced our understanding of the biology and generation of cell-free DNA. The roles of nucleases in plasma DNA biology, such as deoxyribonuclease 1–like-3, have been explored by using gene-deletion mouse models and confirmed in humans bearing nuclease gene mutations, with potential implications for the pathogenesis of autoimmune diseases.

Author (s): Dennis Lo et al.

Journal: *Science,* April 2021

Cell-free DNA (cfDNA) in blood plasma comprises a mixture of fragmented DNA molecules from various bodily tissues, being applied to noninvasive prenatal testing, oncology, and monitoring of organ transplant recipients. Methylomic, fragmentomic, and topologic features of cell-free DNA fragments bear information directed toward their origin tissues. For instance, the use of patterns of DNA methylation of cfDNA molecules enables tracing their tissue sources. The nucleosomal organisation and nuclease content of the tissue of origin play important roles in the fragmentation profile of plasma DNA molecules, leading to characteristic signatures in the form of fragment sizes, nucleotide motifs at the fragment ends, single-stranded jagged ends, and the tissue-preferred genomic locations of the fragmentation endpoints. In addition to double-stranded linear fragments, there exist other topological forms of cfDNA molecules, namely circular and single-stranded molecules. On the basis of these features, liquid biopsies hold promise for the noninvasive detection of tissue-specific pathologies with a range of clinical applications. One advantage of using these nongenetic features is the potentially large number of markers that can be developed, for example, facilitating the differentiation of cancer and noncancer cells with the ability to locate the tissue of origin of detected cancer, even possibly including cancers of unknown primary.

血漿中的遊離 DNA (cfDNA) 是包含來自身體各種組織的片段 DNA 分子的混合物，用於無創產前檢測、腫瘤學和器官移植受者的監測。游離 DNA 的甲基化組學、片段化組學和拓撲學相關的特徵攜帶有其指向組織來源的信息。例如，使用 cfDNA 分子的 DNA 甲基化模式可以追踪它們的組織來源。組織特異的核小體組織和核酸酶含量在血漿 DNA 分子片段化過程中起重要作用，從而產生特殊的分子特徵， 包括片段大小、片段末端的核苷酸基序、單鏈鋸齒狀末端和組織偏好斷裂位點。除了雙鏈線性 DNA，cfDNA 分子還存在其他拓撲形式，即環狀分子和單鏈分子。基於這些特徵，液體活檢有望用於無創檢測組織特異性病理，並具有一系列臨床應用。使用這些特徵的一個優點是可以開發潛在的大量分子標記，例如，有利於區分癌症和非癌細胞，並能夠定位檢測到的癌症的組織來源，甚至可能診斷未知原發性位點的癌症。


Gut microbiota

Original research

Microbiota engraftment after faecal microbiota transplantation in obese subjects with type 2 diabetes: a 24-week, double-blind, randomised controlled trial

Siew C Ng [1,2,3,4] Zhilu Xu [1,2,3,4] Joyce Wing Yan Mak [1,2,3] Keli Yang,[1,2,3] Qin Liu,[1,2,3,4] Tao Zuo [1,2,3,4] Whitney Tang,[1,2,3,4] Louis Lau,[2] Rashid N Lui [2] Sunny H Wong [1,2,3] Yee Kit Tse,[2] Amy Y L Li,[1,2,3] Kitty Cheung,[1,2] Jessica Y L Ching,[1,2] Vincent W S Wong [2,3] Alice P S Kong,[5] Ronald C W Ma,[5] Elaine Y K Chow [5,6] Simon K H Wong,[7] Ivan Chak Hang Ho,[2] Paul K S Chan,[1,8] Francis K L Chan [1,2,3,4]

Author (s): Siew Ng et al.

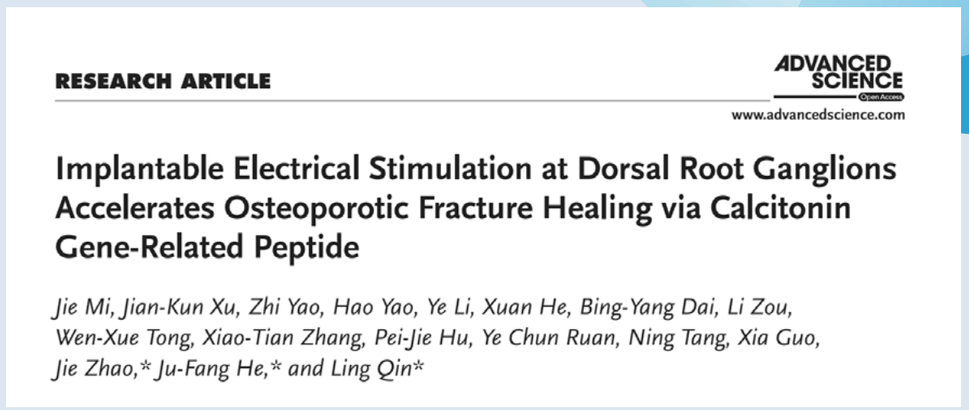
Journal: *Gut,* April 2022 (Epub March 2021)

Gut microbiota is implicated in the pathogenesis of obesity. Faecal microbiota transplantation (FMT) has reported promising results in animal models. Siew Ng and her team performed a double-blind, randomised, placebo-controlled trial aiming to investigate whether combining FMT with lifestyle modification could enhance the engraftment of favourable microbiota in obese patients with type 2 diabetes mellitus (T2DM) and lead to favourable clinical outcomes.

61 obese subjects with T2DM were randomly assigned to three parallel groups: FMT plus lifestyle intervention (LSI), FMT alone, or sham transplantation plus LSI every 4 weeks for up to week 12. FMT solution was prepared from six healthy lean donors. Their results showed that repeated FMTs were safe and led to increased and sustained engraftment of donors' microbiota in patients with obesity and T2DM. They have, for the first time, demonstrated that adding lifestyle intervention to FMT further improved recipients' microbiota profile, reduced low-density lipoprotein cholesterol, and improved liver stiffness on fibroscan.

Their work has provided a strong scientific basis for researchers to further develop FMT as a potentially promising treatment modality for obesity and diabetes. Refining donor selection criteria and metagenomic profile of lean microbiota render FMT as a potential therapy for metabolic syndrome in the future.

腸道微生物群與肥胖密切相關。糞便微生物群移植（FMT）有望成為針對肥胖和代謝性疾病的療法。黃秀娟和她的團隊對肥胖和 T2DM 患者進行了一項隨機雙盲對照試驗。受試者被隨機分為三組：FMT，FMT 加生活方式幹預及安慰劑加生活方式幹預。FMT 溶液來自六名健康捐獻者。結果表明 FMT 是安全的。供體微生物群可長期定植在肥胖和 T2DM 患者的腸道。他們首次證明，將 FMT 與生活方式幹預相結合可進一步改善受者的微生物群，並降低低密度脂蛋白膽固醇，改善肝臟纖維化。 他們的研究為進一步開發 FMT 作為治療肥胖和糖尿病的前景提供了強有力的科學依據。


RESEARCH ARTICLE

ADVANCED SCIENCE Open Access

www.advancedscience.com

Implantable Electrical Stimulation at Dorsal Root Ganglions Accelerates Osteoporotic Fracture Healing via Calcitonin Gene-Related Peptide

Jie Mi, Jian-Kun Xu, Zhi Yao, Hao Yao, Ye Li, Xuan He, Bing-Yang Dai, Li Zou, Wen-Xue Tong, Xiao-Tian Zhang, Pei-Jie Hu, Ye Chun Ruan, Ning Tang, Xia Guo, Jie Zhao, Ju-Fang He,* and Ling Qin**

Author (s): Ling Qin et al.

Journal: ***Advanced Science,*** **January 2022 (Epub October 2021)**

Ling Qin and his team found that the synthesis of calcitonin gene-related peptide (CGRP) in lumbar dorsal root ganglion (DRG) declined in the osteoporotic bone fracture model. Given their series of studies published in Nature Medicine and elsewhere highlighted that CGRP is a crucial osteoanabolic factor, in the present project they have successfully developed flexible microelectrodes that can be implanted at DRGs by minimally invasive surgery to promote fracture healing via regulating the synthesis and release of CGRP. The results showed that 20-min daily electrical stimulation increased the number of CGRP-expressing neurons in rat lumbar DRGs by activating Ca^{2+}/CaMKII/CREB signalling pathway and promoted the release of CGRP at fracture callus through action potential firing, and the released CGRP significantly promoted type-H blood vessels formation and bone regeneration, which finally accelerated the healing of the osteoporotic fracture.

秦嶺和他的團隊發現骨質疏鬆骨折模型的腰椎背根神經節（DRG）合成降鈣素基因相關肽（CGRP）合成能力下降，鑒於其團隊前期 Nature Medicine 等文章已證實 CGRP 是關鍵的促進成骨因子，現成功研發可通過微創手術植入的柔性電極，以此調控 DRG 中 CGRP 合成與釋放。該項研究顯示，每日 20 分鐘的脈衝式電刺激可啟動大鼠 DRG 神經元內的 Ca^{2+}/CaMKII/CREB 信號通路，顯著地增加 CGRP 陽性神經元數目並通過激發動作電位而促進 CGRP 在骨折部位釋放，繼而增強 H 型血管及新骨生長，實現加速骨質疏鬆性骨折癒合。

Grants
補助金及其他資助

Our Principal Investigators and their teams affiliated to the Institute have received grants of over **HK$1.44 billion** during this reporting period. In particular, grants under the General Research Fund (GRF) scheme of the Research Grants Council (RGC) of **HK$35 million** are listed below:

此外，在本報告年度期間，研究所各項目負責人及其小組成員所取得的補助金及其他資助合計逾**港幣十四億四千萬**，其中研究資助局的優配研究金共逾**港幣三千五百萬**，獲資助研究項目的詳情如下：

Project Title 研究題目	Principal Investigators/ Research Team 研究所首席研究員 / 小組	Amount (HK$)
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2018 – 30/06/2021) Elucidating a Novel Tumor Promoting Gene Ring Finger Protein 6 in Colorectal Cancer	Jun Yu	1,229,089
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2020 – 31/12/2022) Defining the Role of RNA N6-Methyladenosine Writer Methyltransferase Like 3 (METTL3) in Colorectal Cancer	Jun Yu	1,532,422
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2019 – 31/12/2021) Combinatorial Blockade of *De Novo* Cholesterol Biosynthesis and PCSK9 as a Synergistic Therapy for KRAS-Mutant Colorectal Cancer	Jun Yu	971,368
Research Grants Council (RGC) – General Research Fund (GRF) (01/02/2020 – 31/12/2022) Functional Grouping of Rhinovirus by its Association with Clinical Outcomes for Better Disease Management and Therapeutic Development	Renee Chan	874,450
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2021 – 31/12/2023) Role of the Heme Oxygenase-1/Carbon Monoxide Axis in the Regulation of Ion Transport and Pro-inflammatory Cytokine Secretion in Airway Epithelia: *In Vitro* and *In Vivo* Studies	Renee Chan	996,285
Research Grants Council (RGC) – General Research Fund (GRF) (15/07/2018 – 14/07/2021) Establishment of a Parallel Platform for the Mechanistic Studies of Function and Inhibition of Influenza Polymerase	Peter Cheung	505,298
Research Grants Council (RGC) – General Research Fund (GRF) (01/07/2019 – 30/06/2022) Establishment of Highly Accurate Nuclear Run-On RNA Sequencing Platforms to Study the Genome-wide Mechanisms of Transcription and Mutation by Influenza Polymerase	Peter Cheung	558,272
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2019 – 30/06/2021) Regulation of Tumor Cell Invasion/ Metastasis and EMT/ Stemness by a New Ras Antagonist which is Silenced by CpG Methylation in Esophageal Cancer	Qian Tao	929,280
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2020 – 31/12/2022) Role of TRPC5 in Endothelium-dependent Contraction in Hypertensive Model of Mice	Xiaoqiang Yao	1,042,225
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2019 – 31/12/2021) Unraveling the Link between Maternal Hyperglycaemia and Childhood Obesity: Genome-wide Methylation Analysis in a Prospective Cohort of Untreated Gestational Diabetes	Juliana Chan Ronald Ma	970,517
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2021 – 31/12/2023) Delineating the Metabolic Architecture and Response to Anti-hyperglycaemic Drug Treatment in Lean Type 2 Diabetes in Chinese	Juliana Chan Ronald Ma	1,178,778
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2020 – 31/12/2022) The Effect of *In Utero* Hyperglycaemia, Maternal Overnutrition and Interaction with Postnatal Lifestyle on Cardiometabolic Risk at Young Adulthood – Extension of HAPO Follow Up Study	Ronald Wang Ronald Ma	1,158,019
Research Grants Council (RGC) – General Research Fund (GRF) (01/07/2021 – 31/12/2023) Regulatory Role of Smad3 in SARS-CoV-2 N Protein-induced Acute Kidney Injury in db/db Mice	Hui-yao Lan	1,125,732
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2020 – 31/12/2022) Role of TGF-beta/Smad3 Signaling in Lupus Nephritis	Hui-yao Lan Cheuk-chun Szeto	1,064,682
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2019 – 31/12/2021) Regulatory Role and Mechanism of Smad3 in Immunosuppression of Neutrophil Anticancer Activities	Hui-yao Lan	1,151,040
Research Grants Council (RGC) – General Research Fund (GRF) (01/09/2021 – 31/08/2023) Epithelium Caveolin and its Calcium Signaling Pathway in Endometrium of Recurrent Miscarriage	Ronald Wang	775,732
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2020 – 30/06/2022) Dysregulation of Retinoic Acid Homeostasis and Signaling in Fetal Islet Development under Maternal Diabetic or High Glucose Conditions	Ronald Wang	770,053

Project Title 研究題目	Principal Investigators/ Research Team 研究所首席研究員 / 小組	Amount (HK$)
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2021 – 31/12/2023) The Role of Lgr5 in Cartilage Development and Mesenchymal Stem Cells Mediated Cartilage Repair	Gang Li	996,285
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2021 – 31/12/2023) Engineering the Biomimetic Structural Mechanical Heterogeneity of Cell-adaptable Nanocomposite Hydrogels for Biomedical Applications	Gang Li	1,185,400
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2019 – 31/12/2021) Modulating Osteoarthritis Development via Balancing Endogenous Expression of Smad3 and Smad7	Gang Li	953,029
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2021 – 31/12/2023) Studying the Functional Mechanism of Endothelial YY1 in Postischemic Angiogenesis	Kathy Lui Huating Wang	1,195,542
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2019 – 31/12/2021) Novel Biological Action of Long Noncoding RNA LBX1-AS1 on Osteocytogenesis and Osteocyte Function in Adolescent Idiopathic Scoliosis	Wayne Lee	861,601
Research Grants Council (RGC) – General Research Fund (GRF) (01/08/2020 – 31/07/2022) Exploration of Effects and Molecular Mechanism of Ginkgolide B in Treating Ageing-related Osteoporosis	Wayne Lee	920,567
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2021 – 31/12/2023) Identification of a Central to Sympathetic Neural Circuit in Magnesium-promoted Bone Regeneration using Retrograde Tracing and Single-cell RNA-seq	Ling Qin	1,126,379
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2020 – 31/12/2022) Calcitonin Gene-Related Peptide Induced by Electrical Stimulation at Single Dorsal Root Ganglion Accelerates Osteoporotic Fracture Healing	Ling Qin	1,115,145
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2019 – 31/12/2021) Genome-wide Computational Identification and *in Vivo* CRISPR Screen of Key Transcription Factors (TFs) and TF Hotspots Governing Muscle Satellite Cell Lineage Progression	Hao Sun	1,136,632
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2019 – 31/12/2021) Mechanistic Investigation of Linc-p27 Function in Skeletal Muscle Satellite Cell and Muscle Regeneration	Hao Sun	970,697
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2021 – 31/12/2023) Functional Characterization of ATF3 in Skeletal Muscle Stem Cells and Muscle Regeneration	Huating Wang	1,394,799
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2021 – 31/12/2023) 3D Genome Rewiring during Muscle Stem Cell Linage Development and Aging	Huating Wang	1,194,637
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2021 – 31/12/2023) Investigating the Functional Significance of Three-dimensional Structures of Topologically Associating Domains	Huating Wang	1,195,542
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2020 – 31/12/2022) Elucidation of Post-Transcriptional Regulatory Functions of DHX36 in Skeletal Muscle Stem Cells and Muscle Regeneration	Huating Wang	1,111,376
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2020 – 31/12/2022) Large Scale Interaction Analysis of RNA Binding Proteins/LncRNAs to Identify LncRNA Nuclear Localization Mechanisms	Huating Wang	1,115,175
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2021 – 31/12/2023) m6A Modification Controls the Autophagic Response to Helicobacter Pylori Infection	William Wu	1,195,290
Research Grants Council (RGC) – General Research Fund (GRF) (01/01/2019 – 31/12/2021) A Mechanistic Study of the Therapeutic Effect of Butyrate in Non-alcoholic Steatohepatitis: Involvement of Autophagy	William Wu	971,635
Total:		**35,472,973**

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：

2 March 2021

Visit to the Institute and the State Key Laboratory of Translational Oncology by Mr. Jiang Jian-Xiang, Director of the Department of Educational, Scientific and Technological Affairs of The Liaison Office of the Central People's Government in the Hong Kong Special Administrative Region.

中央人民政府駐香港特別行政區聯絡辦公室教科部部長蔣建湘先生參觀研究所及轉化腫瘤學國家重點實驗室（2021 年 3 月 2 日）。





19 April 2021

Visit to the Institute and the State Key Laboratory of Translational Oncology by Mr. Liu Zhimin, General Manager of Beijing-Hong Kong Exchange of Personnel Centre.

京港人才交流中心總經理劉志明先生參觀研究所及轉化腫瘤學國家重點實驗室（2021 年 4 月 19 日）。



2 June 2021

Visit to the Institute and the State Key Laboratory of Translational Oncology by Mr. Alfred Sit, Secretary for Innovation and Technology and Ms. Rebecca Pun, Commissioner for Innovation and Technology of the HKSAR Government.

香港特別行政區政府創新及科技局局長薛永恒先生及創新科技署署長潘婷婷女士參觀研究所及轉化腫瘤學國家重點實驗室（2021 年 6 月 2 日）。



8 June 2021

Visit to the Institute and the State Key Laboratory of Translational Oncology by Mr. Hsu Hoi Shan, Director and President of the Beijing - Hong Kong Academic Exchange Centre.

京港學術交流中心董事兼總裁徐海山先生參觀研究所及轉化腫瘤學國家重點實驗室（2021 年 6 月 8 日）。

REPORTS ON 科研活動報告
RESEARCH ACTIVITIES

APPENDIX
附錄

01
Digestive Diseases
消化疾病研究
- Jun Yu

02
Molecular Diagnostics
分子診斷學
- Dennis Lo
- Rossa Chiu
- Nelson Tang
- Allen Chan
- Jacky Lam

03
Emerging Infectious Diseases and Microbiota
防疫研究及腸道微生物學
- Siew Ng
- Renee Chan
- Peter Cheung

04
Asian Cancers
亞洲癌症研究
- Qian Tao

05
Cardiovascular Medicine
心血管疾病研究
- Xiaoqiang Yao
- Alex Lee

06
Diabetes and Obesity
糖尿病與肥胖症研究
- Juliana Chan
- Ronald Ma

07
Inflammatory Diseases
炎症性疾病研究
- Hui-yao Lan
- Erik Fung
- Chris Mok

08
Neuroscience and Neurotechnology
神經科學及神經技術
- Owen Ko
- Hei Ming Lai

09
Reproduction and Development
生殖與發育研究
- Ronald Wang

10
Stem Cells and Tissue Regeneration
幹細胞及組織再生研究
- Gang Li
- Kathy Lui
- Wayne Lee

11
Biomaterial and Drug Translational Research
生物材料與藥物轉譯研究
- Ling Qin

12
Genomics and Bioinformatics
基因組學與生物訊息學
- Hao Sun
- Peiyong Jiang

13
Non-coding RNAs and Cellular Signalling
非編碼核糖核苷酸研究及細胞訊號轉導
- Huating Wang
- William Wu

14
Nephrology
腎臟疾病研究
- Cheuk Chun Szeto

15
Robotics & AI
機械人與人工智能
- Zheng Li

非技術性報告

NON-TECHNICAL SUMMARY

01

DIGESTIVE DISEASES
消化疾病研究

Gastrointestinal (GI) diseases, including GI tract cancers and non-alcoholic fatty liver disease (NAFLD) are major diseases in Hong Kong and they cause significant morbidity and mortality. The multidisciplinary team of scientists and clinicians led by Jun Yu specialises in GI basic research, focusing on 1) understanding the role of gut microbial dysbiosis; 2) genetic, epigenetic and epitranscriptomic mechanisms in the pathogenesis of GI cancers and NAFLD; as well as translational research including 3) identification of probiotic bacteria that suppress disease development; and 4) the discovery of molecular diagnostic markers and therapeutic targets of GI cancers and NAFLD.

消化道疾病如消化道腫瘤和脂肪性肝病是香港常見病。于君帶領的研究團隊由跨學科科研人員和醫生組成，團隊的主要工作包括 1）研究腸道微生態和消化道疾病的關係；2）闡明消化道疾病的分子機制； 3）益生菌防治消化道腫瘤；4）開發新的診斷標誌和治療靶標。

于君

JUN YU



盧煜明

DENNIS LO



02

MOLECULAR DIAGNOSTICS
分子診斷學

Dennis Lo and Rossa Chiu are pioneers in the field of molecular diagnostics. Their research addresses the use of cell-free DNA and RNA found in human circulation to enable non-invasive means to assess fetal diseases, cancer, autoimmune diseases and post-transplantation monitoring. In the reporting year, Dennis and Rossa, together with Allen Chan have been named the "Top 20 Translational Researchers of 2020" by the journal, *Nature Biotechnology*. Dennis has been bestowed the eminent awards of the Breakthrough Prize in Life Sciences and the Royal Medal in Biological Sciences by the Royal Society.

趙慧君

ROSSA CHIU



02

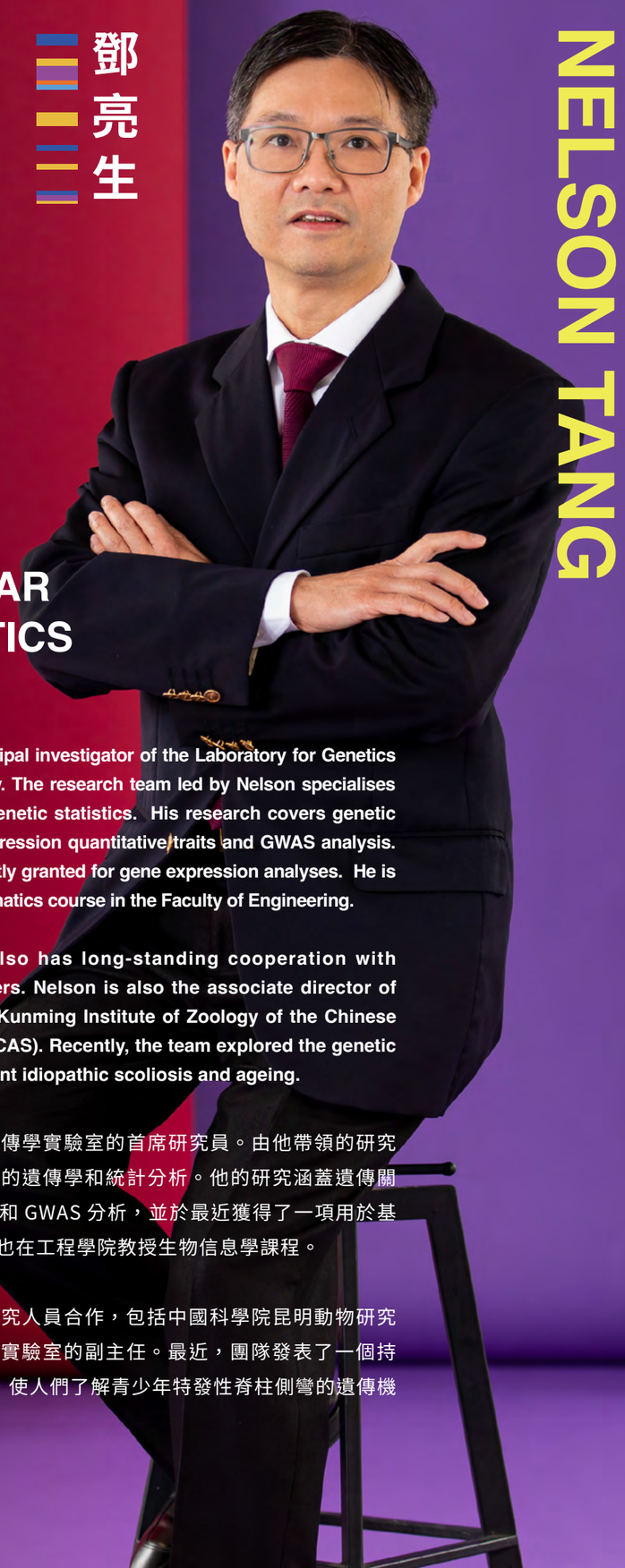
MOLECULAR DIAGNOSTICS
分子診斷學

盧煜明及趙慧君是研究分子診斷學的先驅。他們利用血中游離核酸發展非侵入性手段來評估胎兒疾病、癌症、自身免疫性疾病和移植後監測。今年，他們和陳君賜同獲科學期刊《自然生物科技（Nature Biotechnology）》評為「2020 年全球 20 位頂尖轉化研究科學家」。盧煜明更被授予生命科學突破獎和英國皇家學會的皇家生物科學獎章等傑出獎項。

02

MOLECULAR DIAGNOSTICS
分子診斷學

鄧亮生
NELSON TANG



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

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

鄧亮生是疾病易感性遺傳學實驗室的首席研究員。由他帶領的研究小組專門從事複雜性狀的遺傳學和統計分析。他的研究涵蓋遺傳關聯研究、表達數量性狀和 GWAS 分析，並於最近獲得了一項用於基因表達分析的專利。他也在工程學院教授生物信息學課程。

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

02

MOLECULAR DIAGNOSTICS
分子診斷學

陳君賜
ALLEN CHAN



The research team led by Allen Chan has established the clinical utility of plasma Epstein-Barr virus (EBV) DNA for screening of nasopharyngeal carcinoma (NPC). In their previous large-scale prospective clinical trial, plasma EBV DNA analysis was shown to be effective for early NPC detection and bring about survival improvement. Currently, the team is carrying out a re-screening exercise for all the 20,000 recruited subjects at 4 years after the initial screening. This was aimed to explore the implications of EBV DNA positivity among non-NPC subjects. The finding would be crucial for the recommendation on the optimal screening interval using plasma EBV DNA.

由陳君賜帶領的研究團隊確立了血漿 EB 病毒 DNA 用於鼻咽癌篩查的臨床用途，證明其有效檢測早期鼻咽癌及改善存活。現時，團隊正為全部 20,000 個參加者進行複查。此次研究的目的在於探索 EB 病毒 DNA 陽性在非鼻咽癌患者的含義及制定篩查的合適間距。

林偉棋

JACKY LAM

02

MOLECULAR DIAGNOSTICS
分子診斷學



The research team led by Jacky Lam focuses on the potential clinical application of cell-free DNA in cancer diagnostics. Using nasopharyngeal cancer (NPC) as a model, the team has investigated the differentiating molecular characteristics of plasma Epstein-Barr virus (EBV) DNA between NPC and non-NPC subjects. Such discoveries have been translated into the development of novel diagnostic assays with much improved performance compared to the conventional testing for NPC screening. Plasma EBV DNA serves as an archetypal type of circulating tumour DNA. The team continues to explore ways to enhance accuracy and efficiency of NPC screening modalities.

由林偉棋帶領的團隊的研究集中於游離 DNA 在癌症檢測的臨床應用。以鼻咽癌作模型，研究小組分析血漿 EB 病毒 DNA 在癌症及非癌症患者的分子特徵，藉此開發嶄新的檢測技術，提升鼻咽癌篩查方法的表現。他們亦繼續探索方法去提升準確度和效率。

黃秀娟

SIEW NG

03

EMERGING INFECTIOUS DISEASES AND MICROBIOTA
防疫研究及腸道微生物學



As pioneers in microbiome diagnostics and therapeutics, Siew Ng is leading her research team to translate metagenomics-derived faecal microbial signatures into non-invasive biomarkers and oral live biotherapeutics for treatment of COVID-19, colorectal cancer, autism and obesity. This year, they identified novel bacteria markers for early detection of autism. The team was also amongst the first in the world to show that COVID-19 vaccines worked more effectively in people with a particular gut bacterium (*Bifidobacterium adolescentis*) and those who lack it had lower antibody response to vaccines. This implies that modulating the gut has potential to power up the impact of COVID vaccines.

作為微生物菌群診斷和治療的先驅，黃秀娟正帶領她的研究團隊將源自於宏基因組的糞便微生物特徵轉化為非侵入性生物標誌物和口服活體生物藥，適用治療新冠肺炎、大腸癌、自閉症和肥胖症。今年，團隊鑑別出全新的細菌標誌物，可及早診斷自閉症，也是全球首個團隊證實腸道內有青春雙歧桿菌的人，在接種新冠肺炎疫苗後能產生更好的免疫保護，這揭示調控腸道微生物有望提高新冠肺炎疫苗的效能。



陳韻怡

RENEE CHAN

03

EMERGING INFECTIOUS DISEASES AND MICROBIOTA
防疫研究及腸道微生物學

Renee Chan's research focuses on respiratory virus infections. Her team studies the epidemiology of rhinovirus and identifies clinically important genotypes and their role in viral interference against influenza virus and SARS-CoV-2. They construct cutting-edge respiratory disease model 'mini-airways' to elucidate disease patterns, associate them in vitro readouts with clinical phenotypes and translate them into the practice of precision medicine.

Renee and her team also pioneer the use of the tailor-made nasal strip as a non-invasive and self-administered tool to collect the nasal epithelial lining fluid for SARS-CoV-2 viral antigen, mucosal antibody detection and host mediators monitoring. It drives the collaborative mucosal study of respiratory diseases related to acute and chronic local inflammations.

陳韻怡專注研究呼吸道病毒，她及其團隊致力尋找和臨床關聯的病毒基因型及其在干擾流感和新型冠狀病毒的機制，構建尖端的類呼吸系統疾病模型，並將模型數據轉化為實踐精準醫學的基礎。他們率先使用鼻紙條，推動在呼吸道黏膜炎症疾病的研究。



張栢恒

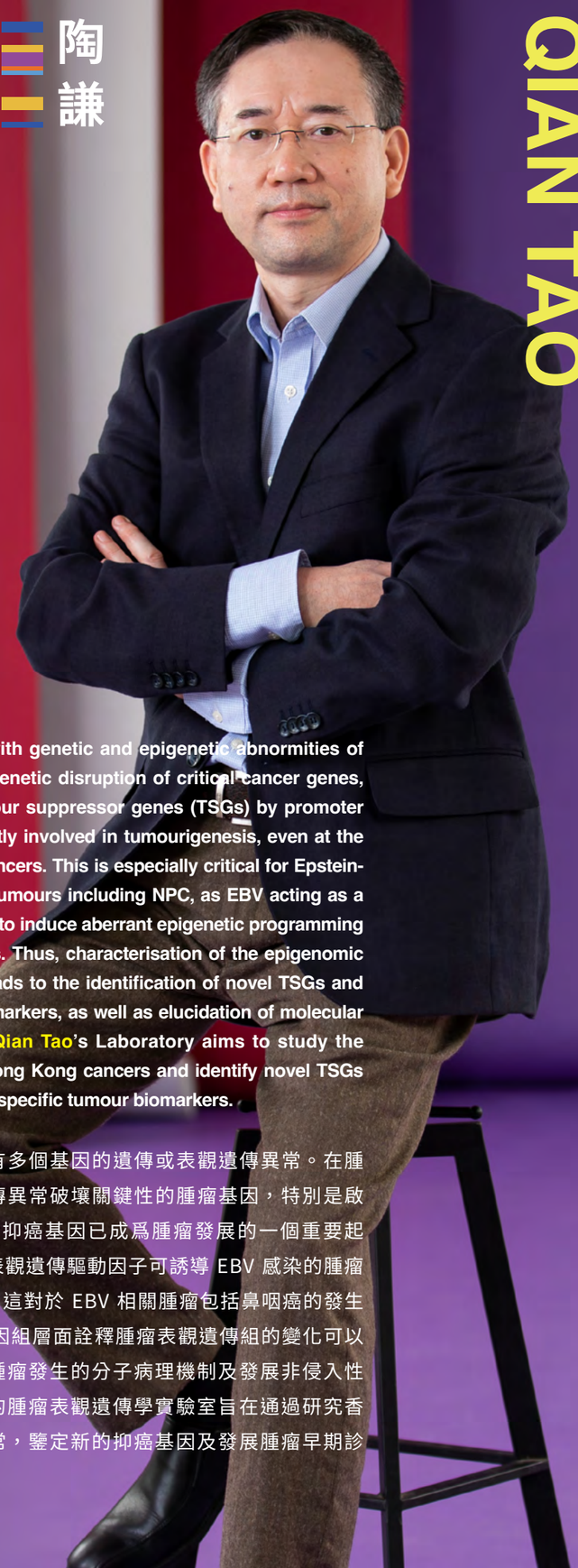
PETER CHEUNG

03

EMERGING INFECTIOUS DISEASES AND MICROBIOTA
防疫研究及腸道微生物學

The interests of Peter Cheung and his research team lie in the gene transcription of RNA viruses (influenza and coronaviruses). RNA viruses encode their RNA polymerases to replicate the viral genome. The error-prone transcription process of viral RNA polymerases is the main driving force for viral genetic diversity essential for adaption to the host. They are interested in understanding the structural basis of polymerase transcription and its regulation by developing a novel genomics platform and using Cryo-EM. These fundamental insights are essential in the basic understanding of gene transcription and virus evolution and the biomedical research for the development of antiviral drugs and vaccines for infectious diseases.

張栢恒及其團隊的研究方向在於 RNA 病毒 (流感和冠狀病毒) 的基因轉錄。 RNA 病毒編碼其 RNA 聚合酶以復制病毒基因組。病毒 RNA 聚合酶容易出錯的轉錄過程是病毒遺傳多樣性的主要驅動力，這對於適應宿主至關重要。團隊通過開發新的基因組學平台和使 Cryo-EM 來了解聚合酶轉錄的結構基礎及其調控。這些基本見解對於基因轉錄和病毒進化的基本理解以及開發抗病毒藥物和傳染病疫苗的生物醫學研究至關重要。



陶謙

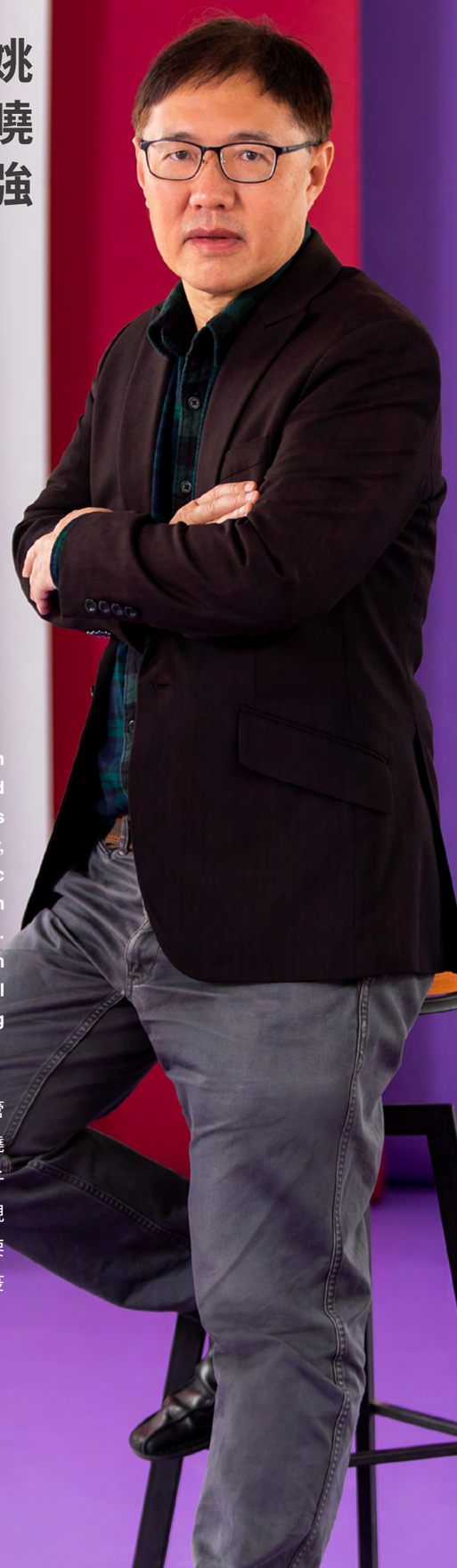
QIAN TAO

04

ASIAN CANCERS
亞洲癌症研究

Cancer is a gene disease with genetic and epigenetic abnormities of multiple cancer genes. Epigenetic disruption of critical cancer genes, especially silencing of tumour suppressor genes (TSGs) by promoter CpG methylation, is frequently involved in tumourigenesis, even at the early pathogenic stage of cancers. This is especially critical for Epstein-Bar virus (EBV)-associated tumours including NPC, as EBV acting as a strong epigenetic modulator to induce aberrant epigenetic programming of EBV-infected tumour cells. Thus, characterisation of the epigenomic abnormalities of tumours leads to the identification of novel TSGs and non-invasive epigenetic biomarkers, as well as elucidation of molecular pathogenic mechanisms. Qian Tao's Laboratory aims to study the epigenomic alterations of Hong Kong cancers and identify novel TSGs epigenetically inactivated as specific tumour biomarkers.

腫瘤是一種基因疾病，具有多個基因的遺傳或表觀遺傳異常。在腫瘤的發展過程中，表觀遺傳異常破壞關鍵性的腫瘤基因，特別是啟動子 CpG 甲基化沉默失活抑癌基因已成爲腫瘤發展的一個重要起因。EBV 作為一個強大的表觀遺傳驅動因子可誘導 EBV 感染的腫瘤細胞的異常表觀遺傳編程，這對於 EBV 相關腫瘤包括鼻咽癌的發生和發展尤其重要。 在全基因組層面詮釋腫瘤表觀遺傳組的變化可以發現新的抑癌基因，闡明腫瘤發生的分子病理機制及發展非侵入性的表觀遺傳標誌物。陶謙的腫瘤表觀遺傳學實驗室旨在通過研究香港腫瘤的表觀遺傳組學異常，鑒定新的抑癌基因及發展腫瘤早期診斷的分子標記物。



姚曉強

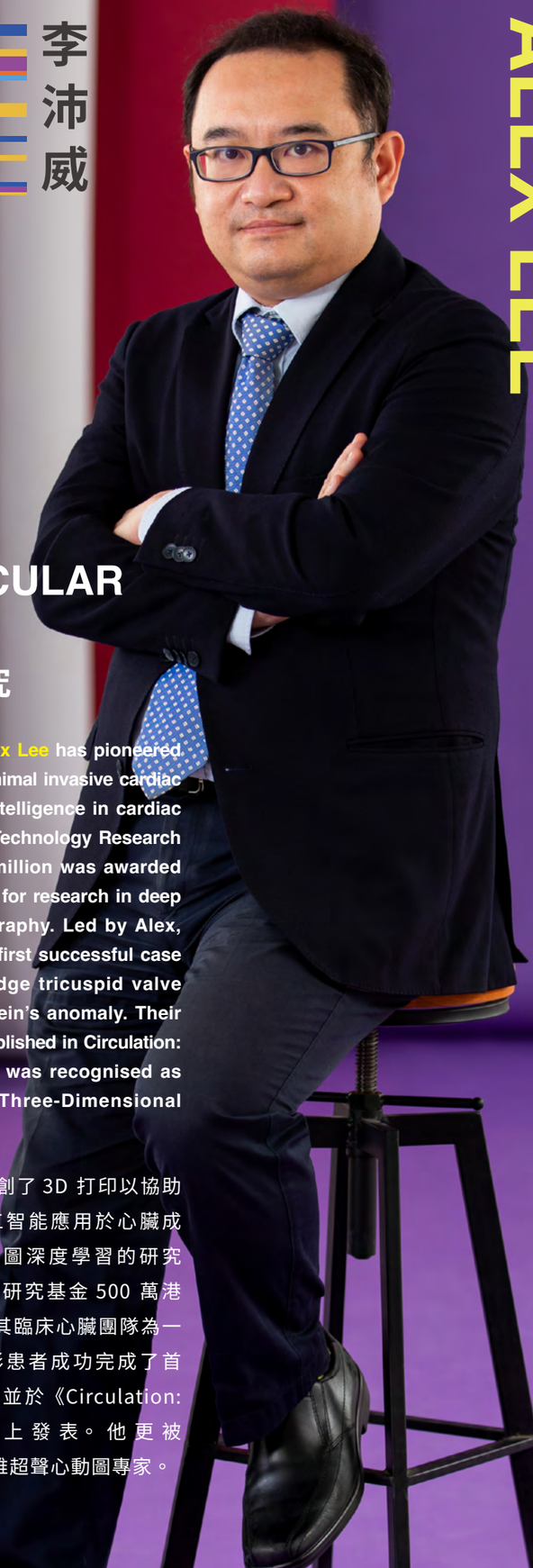
XIAOQIANG YAO

05

CARDIOVASCULAR MEDICINE
心血管疾病研究

Research team led by Xiaoqiang Yao has been working on Ca^{2+}-permeable ion channels and endoplasmic reticulum stress-related proteins in cardiovascular system and cancer. Recently, the novel function of Orai1 channels in cardiac hypertrophy and role of TRPM2 channels in atherosclerotic progress have been uncovered. The strategy of active immunisation with TRPM2 peptide in vaccine platform for potential treatment of atherosclerosis was being developed currently.

姚曉強帶領的研究團隊一直致力於心血管系統及癌症中的鈣離子通道的研究。姚曉強及其團隊的近期研究發現了 Orai1 離子通道在心臟肥大中的重要作用。另外還發現 TRPM2 離子通道在動脈粥樣硬化中有重要作用。他們現正在開發 TRPM2 短肽用作疫苗，用以治療動脈粥樣硬化。



李沛威

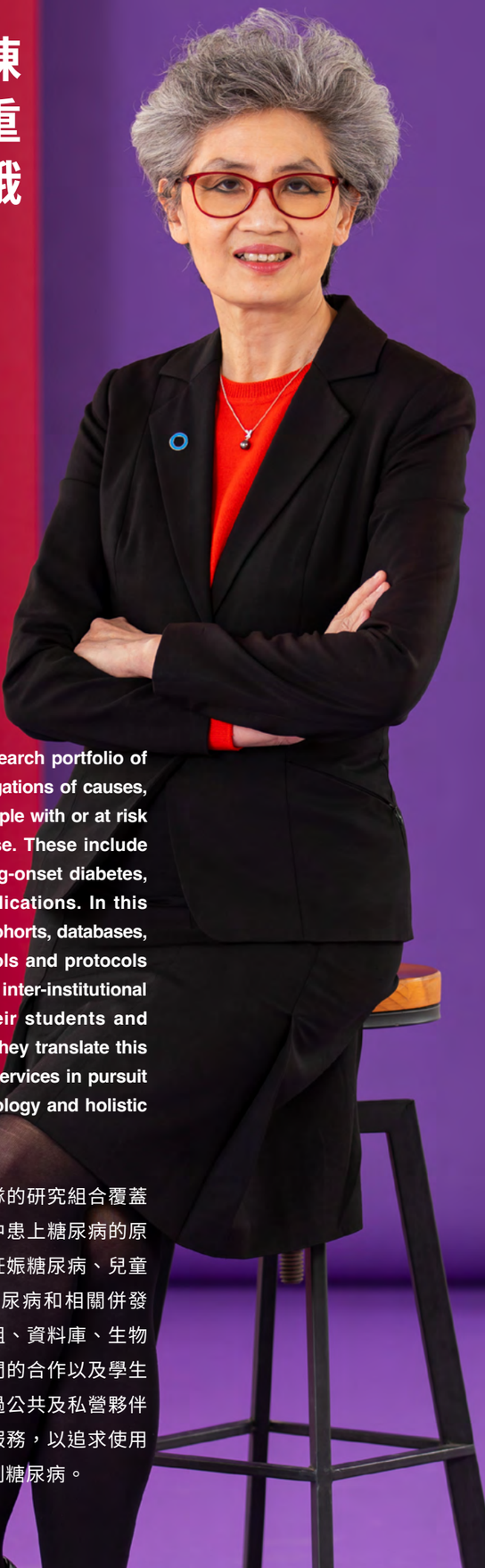
ALEX LEE

05

CARDIOVASCULAR MEDICINE
心血管疾病研究

The research team led by Alex Lee has pioneered in 3D printing for complex minimal invasive cardiac interventions and artificial intelligence in cardiac imaging. An Innovation and Technology Research Fund amounting to HKD 5 million was awarded to Alex and his collaborators for research in deep learning in 3D echocardiography. Led by Alex, the Heart Team reported the first successful case of percutaneous edge-to-edge tricuspid valve repair in a patient with Ebstein's anomaly. Their pioneering experience was published in Circulation: Cardiovascular Imaging. He was recognised as an Expertscape Expert in Three-Dimensional Echocardiography.

由李沛威領導的研究團隊開創了 3D 打印以協助複雜微創心臟手術和以人工智能應用於心臟成像的先河。於 3D 超聲心動圖深度學習的研究上，其團隊獲頒創新及科技研究基金 500 萬港元的資助。在他的帶領下，其臨床心臟團隊為一位埃勃斯坦三尖瓣下移畸形患者成功完成了首例經皮三尖瓣緣對緣修復，並於《Circulation: Cardiovascular Imaging》上發表。他更被 Expertscape 網站公認為三維超聲心動圖專家。



陳重娥

JULIANA CHAN

06

DIABETES AND OBESITY
糖尿病與肥胖症研究

Led by a team of physician scientists, the research portfolio of Juliana Chan and her team transcends investigations of causes, trajectories, interventions and outcomes in people with or at risk of developing diabetes during their life course. These include gestational diabetes, childhood obesity, young-onset diabetes, usual-onset diabetes and associated complications. In this overarching spectrum, they have established cohorts, databases, biobanks, experimental models, analytical tools and protocols to advance their scientific knowledge through inter-institutional collaborations and the development of their students and fellows. Through public-private-partnerships, they translate this knowledge into technologies, prototypes and services in pursuit of using precision medicine, innovative technology and holistic care for prevention and control of diabetes.

在醫生科學家團隊的領導下，陳重娥及其團隊的研究組合覆蓋了對糖尿病患者或高風險人士在其生命過程中患上糖尿病的原因、軌跡、干預措施和結果的調查。這包括妊娠糖尿病、兒童肥胖症、年輕發病的糖尿病、通常發病的糖尿病和相關併發症。在這個總體範圍內，他們已經建立了群組、資料庫、生物庫、實驗模型、分析工具和協定，通過機構間的合作以及學生和研究員的發展來推進他們的科學知識。通過公共及私營夥伴合作，他們將這些知識轉化為技術、原型和服務，以追求使用精准醫學、創新技術和整體護理來預防和控制糖尿病。



馬青雲

RONALD MA

06

DIABETES AND OBESITY
糖尿病與肥胖症研究

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

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

藍輝耀

HUI-YAO LAN

07

INFLAMMATORY DISEASES
炎症性疾病研究

In the past year, the research team led by Hui-yao Lan discovered TGF-β as a master regulator in acute and chronic kidney and cardiovascular diseases under diabetes and hypertensive conditions. TGF-β signals through its downstream molecule Smad3 to mediate acute kidney injury and fibrosis, and to promote cancer by triggering tumour-associated macrophages to become cancer-associated fibroblasts. The most novel and important discovery is that SARS-CoV-2 N protein can bind and activate Smad3 to cause cell death and acute kidney injury. Targeting Smad3 with a pharmacological inhibitor SIS3 can protect kidneys from COVID-19 acute kidney injury.

在過去的一年裡，藍輝耀帶領的研究團隊發現 TGF-β 是糖尿病和高血壓腎臟和心血管疾病的主要因子。TGF-β 通過活化 Smad3 引起急性腎損傷和纖維化，並觸發腫瘤巨噬細胞變為纖維細胞來促進癌症進展。更重要的發現是，新冠病毒殼核蛋白 (SARS-CoV-2 N) 可以結合並激活 Smad3，導致細胞死亡和急性腎損傷。靶向抑製 Smad3 可以保護腎臟免受 COVID-19 引起急性腎損傷。

馮以文

ERIK FUNG



07

INFLAMMATORY DISEASES
炎症性疾病研究

The main focus of Laboratory for Heart Failure + Circulation Research (LHFCR) is on heart failure, frailty, and inflammageing. Three longitudinal cohorts totalling over 1,700 participants have been recruited to date. During 2021, 7 research articles have been published. The most impactful one was an original research article published in *The Lancet Healthy Longevity* based on an Health and Medical Research Fund (HMRF) from the Food and Health Bureau awarded to Erik Fung, who was the first author. Seven competitive research grants including a new General Research Fund (GRF) were awarded. Erik was the recipient of an internationally competitive prize "Healthy Longevity Catalyst Award 2021" from the U.S. National Academy of Medicine. The total sum of grants and funding support raised in 2021 was HKD 4,488,773.

心衰竭及循環系統研究室專注於心衰竭、虛弱和老年炎症。至今，超過 1700 名長者已參加三組縱向研究。馮以文在 2021 年發表了七篇論文，包括具影響力的 *The Lancet Healthy Longevity*（由食物及衞生局的醫療衞生研究基金（HMRF）資助），並獲取七項研究資助，包括優配研究金（GRF）。他也獲得美國國家醫學院頒發 Healthy Longevity Catalyst Award。全年籌集資金達 4,488,773 港元。

莫家斌

CHRIS MOK



07

INFLAMMATORY DISEASES
炎症性疾病研究

The major objective of Chris Mok and his research team is to understand the interplay between the host adaptive immunity and the viral determinants of respiratory viruses such as influenza viruses and coronaviruses using a combination of clinical, virological, immunological, and structural approaches. The team is particularly interested in understanding how adaptive immunity is regulated and sharpened by the evolution of respiratory viruses which will help to further improve the current vaccines.

The research foci of the team include 1) pathogenicity of zoonotic viruses in humans; 2) viral immunology on respiratory diseases; and 3) prophylactic and treatment options for respiratory infection.

莫家斌及其研究團隊的主要目標是結合臨床、病毒學、免疫學以及結構化方法，研究宿主適應性免疫與呼吸道病毒（例如：流感病毒和冠狀病毒）之間的相互作用。團隊着重於研究呼吸道病毒的進化是如何調節與增强宿主的適應性免疫，這將有助進一步優化當前的疫苗。

團隊的研究方向包括 1) 人畜共患病病毒對人類的致病性；2) 呼吸道疾病的病毒免疫學；3) 呼吸道感染的預防和治療。

高浩

OWEN KO

08

NEUROSCIENCE AND NEUROTECHNOLOGY
神經科學及神經技術

Owen Ko and his team consist of members with diverse backgrounds in medicine, chemistry, biology and engineering. The team utilises a combination of imaging, biochemical and molecular tools to 1) study gliovascular dysfunction in the pathogenesis of neurodegenerative diseases; 2) develop new biomedical imaging tools; and 3) investigate fundamental principles governing the operation of neural circuits. The team seeks to enhance their basic understanding of how the brain works from a systems neuroscience perspective. Armed with novel tools and knowledge, they further aim to uncover pathogenesis underlying neurodegenerative diseases and to guide the development of novel therapeutics.

高浩及其團隊成員來自多種背景，包括醫學、化學、生物以及工程專業，融合運用影像學、生物化學、分子生物等多學科技術，圍繞三個主要問題展開研究：1) 神經退化性疾病病理過程中腦血管、膠質細胞功能異常；2) 新型成像方法的開發；3) 大腦神經迴路的運行機制。他們著力從系統神經科學層面，進一步加強對大腦工作模式的理解，並基於全新的工具和發現，揭示神經退化性疾病的病理過程，並建立新的診療方法。

黎曦明

HEI MING LAI

08

NEUROSCIENCE AND NEUROTECHNOLOGY
神經科學及神經技術

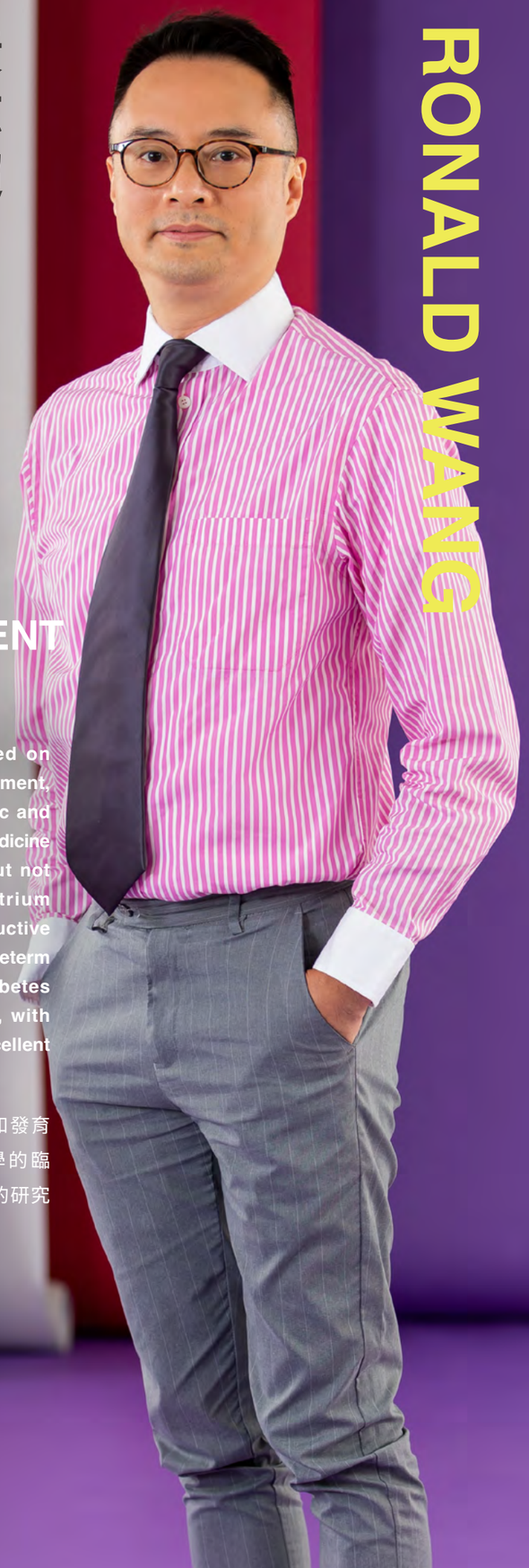
The research team led by Hei Ming Lai focused on the development of technologies for understanding and tackling neuropsychiatric disorders. They use a multidisciplinary approach to generate creative ideas to solve difficult problems, including but not limited to protein engineering, nanotechnology, optical systems, computational methods, and chemical engineering. Ultimately, the team aims to build a scientifically sound theory of how psychiatric phenomena arises from human brain structures and compositions.

由黎曦明帶領的研究團隊專注開發用於理解和治療精神疾病的技術，以多學科及具創意的方法來解決各種遇到的難題，牽涉蛋白質改造、納米技術、光學系統、計算機工程和化學工程等範疇。他們團隊最大的目標是建立一套科學理論去說明精神現像如何從大腦結構和組成中產生。

09

黃志超

RONALD WANG



REPRODUCTION AND DEVELOPMENT
生殖與發育研究

Ronald Wang and his team focused on research in reproductive and development, and actively involved in clinical, basic and translational studies of reproductive medicine and maternal medicine, including but not limited to endometriosis, endometrium imaging, endometrial cancer, reproductive failure, polycystic ovary syndrome, preterm birth, preeclampsia, gestational diabetes mellitus, and cord blood stem cells, with significant research collaboration, excellent progress and fruitful research output.

黃志超及其團隊主要研究工作以生殖和發育為主，積極參與生殖醫學和母胎醫學的臨床、 基礎及轉化研究。團隊建立重大的研究合作，工作進展傑出，研究成果卓越。

10

李剛

GANG LI



STEM CELLS AND TISSUE REGENERATION
幹細胞及組織再生研究

The main research interests of the research team led by Gang Li are on musculoskeletal tissue regeneration using tissue engineering approaches, including the novel developments and applications of distraction histogenesis techniques, the use of mesenchymal stem cells (MSCs) with biomaterials and biological factors for musculoskeletal tissue engineering. The team closely collaborated with local and international clinicians and scientists. In the past year, they continued to focus on the research on bone and cartilage regeneration; distraction histogenesis novel clinical applications for the treatment of diabetic foot ulcers and stroke. In 2021, despite the continuous negative impacts of the global pandemic of COVID-19, the team still obtained substantial competitive external funding supports and generated more than 20 SCI indexed publications.

由李剛帶領的研究團隊的主要研究興趣是使用新型組織工程方法進行肌肉骨骼組織再生，包括牽引組織發生技術的新發展，間充質乾細胞與生物材料及其他因數的聯合應用，促進肌肉骨骼組織再生。其研究團隊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，他們繼續專注於骨和軟骨再生的研究，尤其是在牽張組織技術應用在糖尿病足潰瘍和腦中風的新臨床應用取得創新性發現。 2021 年，儘管全球在新型冠狀病毒大流行下的負面影響不斷，研究團隊仍然獲得了大量的政府研究資金支援，並且發表了 20 篇 以上的 SCI 論文。

呂愛蘭

KATHY LUI

10

STEM CELLS AND TISSUE REGENERATION
幹細胞及組織再生研究

Cardiovascular disease is the leading cause of death worldwide in the past three decades. The research team led by Kathy Lui has been interested in regenerating the aged or damaged cardiovascular system. They have studied the pathogenesis of cardiovascular diseases, and the crosstalk between cardiovascular diseases and inflammation. Recently, the team also studied the pathophysiological origin of diabetes which is one of the major risk factors leading to cardiovascular disorders. They have utilised human pluripotent stem cells as a platform for disease modelling and drug screening.

在過去三十年，心血管疾病是全世界人類死亡的主要原因。呂愛蘭帶領的團隊一直對老化或受損的心血管系統的再生研究感興趣。他們研究了心血管疾病的發病機制，以及心血管疾病與炎症之間的相互作用。最近，其研究團隊還研究了作為導致心血管疾病主要危險因素的糖尿病的病理生理學起源。他們還利用人類多能幹細胞構建了用於疾病建模和藥物篩選的平台。

李郁偉

WAYNE LEE

10

STEM CELLS AND TISSUE REGENERATION
幹細胞及組織再生研究

Wayne Lee and his team's main research interests are on the role of osteocytes in various musculoskeletal problems (such as adolescent idiopathic scoliosis, osteoporosis, sarcopenia, and osteoarthritis), and the clinical application of cell therapy for osteoarthritis with specific focus on GMP manufacturing and quality control. The team is also working closely with industrial partners to develop novel biomaterials and medical imaging systems for orthopedics application. With the support from local and international collaborators, in the past year, the team continued research on degenerative change of osteocyte lacuno-canalicular network and its biological link to exercise and mechanical loading.

李郁偉及其研究團隊聚焦於骨細胞在多種骨骼肌肉疾病（例如：青少年特發性脊柱側彎、骨質疏鬆、少肌症、骨關節炎等）中的基礎研究及細胞治療（例如：良好生產規範及質量控制等）在骨關節炎中的臨床應用。此外，團隊與產業方夥伴共同研發可應用於骨科臨床的新型生物材料及醫學影像系統。通過與本地和海外夥伴的密切合作，該研究團隊在過去的一年繼續開展了有關骨細胞縫隙網絡的退行性變及其與運動和機械負荷生物學聯繫的系列研究項目。



秦嶺

LING QIN

11

BIOMATERIAL AND DRUG TRANSLATIONAL RESEARCH

生物材料與藥物轉譯研究

The multidisciplinary research team led by Ling Qin has contributed to the development of innovative biomedical, tissue engineering products or supplements, as well as clinical indication-orientated treatment regimens and protocols that utilise bioactive and biodegradable materials/implants, endogenous and exogenous growth factors, and biophysical stimuli to enhance tissue regeneration for challenging musculoskeletal disorders. Their R&D strategies facilitate both anatomical and functional restoration to achieve better treatment outcomes and early rehabilitation, as well as to reduce its associated morbidity and mortality.

由秦嶺帶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、組織工程材料，以及機體補充劑，並且利用具有生物活性和可降解特質的材料 / 內置物、內源性和外源性的生長因子，以及生物物理刺激療法去改善疑難肌肉骨骼疾病的組織再生。他們所研發的策略同時改善機構性和功能性的修復，以達到良好的治療效果及加快康復的速度與質量，並且降低相關的術後併發症和死亡率。



孫昊

HAO SUN

12

GENOMICS AND BIOINFORMATICS

基因組學與生物訊息學

The research team led by 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.

生物資訊學和基因組學是一門正在迅速興起的邊緣學科，它位於分子生物學、計算機、數學等多個領域的交叉點上。隨著第二代基因測序技術的普及，生物資訊和基因組學已經成為生物醫學研究的重要領域。由孫昊所領導的生物資訊學和基因組學研究小組致力於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，二代測序數據的算法和數據挖掘，及開發二代測序技術在轉化醫學中的應用。

江培勇

PEIYONG JIANG

12

GENOMICS AND BIOINFORMATICS
基因組學與生物訊息學

In this academic year, Peiyong Jiang and his team have made a number of important achievements. The team developed artificial intelligence (AI) algorithm, named HK model, in detecting DNA methylation on basis of the 3rd generation sequencing technologies, improving the accuracy to 90% from < 5%. They revealed a large proportion of long cell-free DNA molecules in maternal plasma. The HK model can be used for deducing the maternal inheritance of the foetus, by making use of long plasma DNA molecules in maternal blood circulation. The technological development and scientific findings would provide new possibilities for developing high-performance diagnostic tools for cancer detection and non-invasive prenatal testing.

本學年，江培勇及其團隊取得了多項重要成果。該團隊基於第三代測序技術開發了名為 HK 模型的人工智能 (AI) 算法，用於檢測 DNA 甲基化，將準確率從 <5% 提高到 90%。他們在母體血漿中發現了很大一部分長的遊離 DNA 分子。 HK 模型可通過利用母體血液循環中的長血漿 DNA 分子來推斷胎兒的母系遺傳。新技術的發展和科學發現將為開發用於癌症檢測和無創產前檢測的高性能診斷工具提供新的可能性。

王華婷

HUATING WANG

13

NON-CODING RNAS AND CELLULAR SIGNALLING
非編碼核糖核苷酸研究及細胞訊號轉導

The regenerate ability of skeletal muscle after injury is remarkable, owing to adult muscle stem cells. These cells are normally in a quiescent stage but can be rapidly activated upon injury, followed by proliferative expansion and differentiation into multinucleated myofiber to repair the damaged muscle tissues. Understanding how each phase of stem cell activities is regulated is the first step towards harnessing the regenerative potential of stem cell for therapeutic treatments of many skeletal muscle related diseases, such as aging inflicted Sarcopenia. The research group led by Huating Wang thus dedicates to decipher both transcriptional and post-transcriptional gene regulatory mechanisms aiming to gain a better understanding of stem cell behavior in the process of regeneration.

骨骼肌具有強大的再生能力，這是由於成年肌肉幹細胞的存在。這些細胞通常處於靜息狀態期，但是在受傷時可以被快速激活，然後進行增殖性擴張並分化為多核肌纖維，以修復受損的肌肉組織。研究以上每個階段中肌肉幹細胞活性的調控才有可能將它們用於衰老引起的肌少症等肌肉相關疾病的治療。因此，由王華婷帶領的小組致力於解密肌肉幹細胞中轉錄和轉錄後基因調控機制，旨在更好地了解肌肉再生過程中幹細胞的行為。



13

WILLIAM WU
胡嘉麒

NON-CODING RNAS AND CELLULAR SIGNALLING
非編碼核糖核苷酸研究及細胞訊號轉導

William Wu and his research team are devoted to the pursuit of excellence in research on the molecular mechanisms of diseases of public health significance, including infection, inflammation, cancer and chronic pain. They are particularly interested in the roles of autophagy and gut microbes, and the combined use of evolutionary biology principles with genomic and clinical big data as an investigative approach.

胡嘉麒及其研究團隊致力於開展與公眾健康密切相關的前沿科學研究，包括感染、炎症、癌症與慢性疼痛等的分子機制。研究團隊尤對細胞自噬和腸道微生物感興趣，並擅長結合進化生物學及基因組和臨床大數據作為研究手段。



14

CHEUK CHUN SZETO
司徒卓俊

NEPHROLOGY
腎臟疾病研究

Cheuk Chun Szeto and his team focus on the metabolic disturbances in chronic kidney disease, and urinary biomarker for glomerular diseases. They studied the role of adipokines and other metabolomic disturbances in chronic kidney disease, with particular focus on patients receiving peritoneal dialysis. The complicated relations between obesity, circulating bacterial fragments, and cardiovascular disease in kidney disease was explored. In addition, they determined the application of urinary biomarkers, notably urinary levels of podocyte associated molecules, for the monitoring and risk stratification of diabetic kidney disease and hypertensive nephrosclerosis.

司徒卓俊及其研究團隊的研究重點是慢性腎病的代謝紊亂和腎小球疾病的尿液生物標誌物。他們研究了脂肪因子和其他代謝組學紊亂在慢性腎病，特別是腹膜透析的患者中的作用。他們也探討了腎臟疾病中肥胖、血液中細菌碎片和心血管疾病之間的複雜關係。此外，他們也對尿生物標誌物的應用，特別是足細胞相關分子的尿水平，用於監測糖尿病腎病和高血壓腎硬化的風險分層，做了一系列的臨床研究。

15

ROBOTICS & AI
機械人與人工智能



ZHENG LI
李崢

Zheng Li and his team focus on intelligent medical robotic technologies, including novel mechanism design, sensing, motion control and artificial intelligence, to tackle clinical problems and improve the experience of clinicians and patients. Smart robots, such as flexible endoscope robot, magnetic anchored and guided endoscope (MAGS) robot, electromagnetically actuated soft-tethered (EAST) colonoscope robot, soft hand rehabilitation robot, etc. The team has been developed by integrating artificial intelligence to the robots. These robots are expected to collaborate with clinicians in the future to provide safe and effective services to patients.

李崢和他的團隊聚焦於研究智能醫療機器人技術，包括新型機構設計、傳感、運動控制和人工智能，用以解決臨床問題並提升醫生及患者的體驗。通過結合機器人與人工智能， 該團隊開發了柔性內窺鏡機器人、磁錨定內窺鏡機器人 (MAGS)、電磁驅動軟體腸鏡機器人 (EAST) 和軟體康復機器人等智能機器人。這些機器人有望在未來與臨床醫生合作，為患者提供安全有效的服務。

研究項目：技術性報告

TECHNICAL REPORTS ON RESEARCH PROGRAMMES

于君

JUN YU



01 DIGESTIVE DISEASES

Gut microbiota in Colorectal Cancer:

Dietary fat intake is associated with increased risk of colorectal cancer (CRC). In this study, the team led by Jun Yu examined the role of high-fat diet (HFD) in driving CRC through modulating gut microbiota and metabolites. They found that HFD promotes colorectal carcinogenesis in CRC mice models, an effect that was attenuated by antibiotics treatment, suggesting that the microbiota underlies HFD-induced CRC. Next, metagenome sequencing revealed that HFD triggered a significant shift in the microbiome composition in HFD-fed mice. Pathogenic bacteria *Alistipes sp. Marseille-P5997* and *Alistipes sp. 5CPEGH6* were increased while the levels of probiotic *Parabacteroides distasonis* was depleted. Moreover, microbial dysbiosis was associated with compromised gut barrier function in HFD fed mice. Faecal microbiota transplantation of HFD-fed mice stool to germ-free mice was found to accelerated chemically-induced CRC, confirming the functional role of dysbiosis in HFD-induced CRC development. Finally, metabolomic analysis demonstrated that the gut metabolite lysophosphatidic acid was elevated with HFD fed mice. Lysophosphatidic acid was found to promote CRC growth and impair gut barrier function. In summary, their work showed that gut dysbiosis as a crucial link to diet-induced CRC. *(Gastroenterology, 2021)*

Gut microbial dysbiosis has pivotal involvement in CRC. The team is the first to report a comprehensive mapping of the intratumoural gut microbiome heterogeneity in CRC patients. To this end, they collected multiple biopsies (N=436) from patients with CRC (N=36) or adenomas (N=32), with 2-6 samples from each tumour plus 2-5 biopsies from adjacent normal tissues for each patient. They then performed microbial genome sequencing on these samples, and discovered that there are substantial differences in intratumoural microbial communities even within the same tumour. In particular, abundances of some CRC-associated pathobionts (eg, *Fusobacterium*, *Bacteroides*, *Parvimonas*, and *Prevotella*) were found to be highly varied within a single neoplasia. Moreover, they found that the intra-neoplasia variation in abundance of individual microbes changed along the adenoma-carcinoma sequence. They also observed that tumour intrinsic factors KRAS mutation and microsatellite instability were correlated with of intratumoural microbial heterogeneity. Their work thus shed light on the impact of microbial heterogeneity on CRC development. *(Gastroenterology, 2021)*

Recently, there is a great interest in utilising beneficial microbes for the prevention of cancer. Using faecal shotgun metagenomic sequencing, they identified *Lactobacillus gallinarum* as a commensal bacterium that is the most depleted in the stool of CRC patients as compared to healthy subjects. They thus hypothesise that it might be preventive against CRC. Indeed, the oral gavage of *L. gallinarum* was found to suppress CRC in $Apc^{Min/+}$ and AOM-induced CRC mice models. *In vitro* studies revealed that the *L. gallinarum* culture-supernatant (5%, 10% and 20%) concentration-dependently suppressed cell proliferation and colony formation of CRC cell lines, but had no effect on colon normal cells. Consistently, *L. gallinarum* culture-supernatant significantly promoted apoptosis in CRC cells and patient-derived CRC organoids, but not in normal colon epithelial cells. Using LC-MS/MS, they further identified that indole-3-lactic acid (ILA) as an active component of *L. gallinarum* culture-supernatant that was also enriched in the gut of *L. gallinarum*-treated mice. ILA displayed anti-CRC growth *in vitro* and inhibited intestinal tumourigenesis *in vivo*. Their study therefore identified a novel chemopreventive probiotic *L. gallinarum* that produces the antitumour metabolite ILA to prevent CRC. Sugimura N, Li Q, Chu ESH, et al. *Lactobacillus gallinarum* modulates the gut microbiota and produces anti-cancer metabolites to protect against colorectal tumourigenesis. *(Gut, 2021)*

Research Progress Summary



Principal Investigator
Jun Yu

Team Members
Vincent Wong, Dennis Wong, Jennifer Zhang, Huarong Chen

Molecular Mechanisms of Colorectal Cancer:

RNA N^6-methyladenosine (m^6A) is the most abundant RNA modification in the human and emerging studies have suggested that it plays a critical role in tumourigenesis. They therefore investigated that role of YTHDF1, a m^6A reader, in colorectal tumourigenesis. In multiple patient cohorts, YTHDF1 DNA copy number gain is a frequent event in CRC and contributes to its overexpression, and the overexpression of YTHDF1 is significantly associated with metastatic gene signature in patient tumours. YTHDF1 knockout in mice dampened CRC development, whereas YTHDF1 overexpression promotes cell growth in CRC cells and primary organoids, and lung and liver metastasis *in vivo*, thereby confirming the oncogenic role of YTHDF1 in CRC. Integrative multiomics analysis identified RhoA activator ARHGEF2 as a downstream target of YTHDF1. YTHDF1 binds to m^6A modified ARHGEF2 mRNA resulting in enhanced mRNA translation. ARHGEF2 activated RhoA signalling, cell growth and metastatic ability. Finally, ARHGEF2 siRNA delivered by LNP significantly suppressed tumour growth and metastasis *in vivo*. They thus identified a novel epitranscriptome YTHDF1-m6A-ARHGEF2 axis that drives CRC, and validated the therapeutic potential of targeting this axis in CRC. *(Gastroenterology, 2021)*

Cancer stem cells (CSCs) comprise a tiny portion of the growing tumour, but they are highly tumourigenic cells essential for tumour maintenance and a root cause of therapy resistance and tumour relapse. Targeting of CSCs might therefore an attractive approach to eradicate tumours and prevent tumour metastasis. Here, the team performed CRISPR/Cas9-based dropout screening (Epi-Drug sgRNA library) to identify genes that are specifically essential in CSCs. Using two CSCs models, they revealed 44 essential genes for CSC growth, including genes involved in cholesterol biosynthesis (HMGCR, FDPS, and GGPS1). Accordingly, genetic or pharmacological inhibition of cholesterol biosynthesis genes HMGCR or FDPS impaired self-renewal capacity and tumourigenic potential of spheroid models *in vitro* and *in vivo*. Effect of HMGCR or FDPS inhibition was rescued by cholesterol and geranylgeranyl diphosphate (GGPP), suggesting that cholesterol related metabolites contribute to CSCs survival and growth. Finally, they showed that the combination of cholesterol biosynthesis blockade and chemotherapy were synergistic in suppressing CSCs *in vitro* and *in vivo*. their data suggest that cholesterol biosynthesis as a potential target for CSCs-based therapy. *(Oncogene, 2021)*

Using whole genome sequencing, the team have previously identified the amplification of Ring finger protein 6 (RNF6), a RING-domain E3 ubiquitin ligase, CRC. In this study, they further generated a colon-specific RNF6 transgenic mice, and demonstrated that the colon-specific overexpression of RNF6 promotes the development of chemically-induced CRC in mice. To elucidate the molecular mechanism of RNF6 as a transcription factor, they next performed integrated chromatin immunoprecipitation (ChIP)-sequencing and RNA-sequencing to identify SF3B2 as the target

of RNF6. Knockout of SF3B2 abrogated the effect of RNF6 overexpression on CRC cell growth and migration/invasion, verifying SF3B2 as a functional target of RNF6. Targeting of the RNF6-SF3B2 axis with pladienolide B (SF3B2 inhibitor) suppressed the growth of RNF6-overexpressing CRC cells and potentiated the effect of 5-fluorouracil, leading to tumour regression in xenograft models. Their findings suggest RNF6-SF3B2 axis as an actionable target in CRC. *(Oncogene, 2021)*

Molecular Mechanisms of Liver Diseases:

Metabolites play an important role in the etiology of liver diseases, including hepatocellular carcinoma (HCC). To investigate this, the team has analysed two independent patients with 102 HCC patients and 100 healthy controls. Portal/central vein serum, liver tissues, and stools samples from these subjects were subjected to global metabolomic profiling analysis. Detailed metabolomic evaluation showed distinct clusters of metabolites that differentiate HCC and control individuals ($p<0.001$). HCC patients had higher levels of portal vein serum and HCC metabolites of DL-3-phenyllactic acid, L-tryptophan, glycocholic acid and 1-methylnicotinamide than healthy controls, which were associated with impaired liver function and poor survival. On the other hand, HCC patients had lower levels of linoleic acid and phenol in portal vein and stool samples than healthy controls. Linoleic acid and phenol significantly inhibited HCC cell proliferation, inferring their anti-HCC function. They thus identified key metabolites could be involved in hepatocarcinogenesis in humans. *(Gut, 2021)*

Nonalcoholic fatty liver disease (NAFLD) is now the major cause of liver disease and a healthcare burden worldwide. In this study, the team identified a novel gene, Squalene Epoxidase (SQLE) as the driver of NAFLD that is highly up-regulated in human NASH and mouse models of NASH. Using a novel SQLE transgenic mice model, they demonstrated that SQLE overexpression in mice triggered spontaneous insulin resistance, hepatic steatosis, liver injury, and accelerated diet-induced NASH. Mechanistically, SQLE caused hepatic cholesterol accumulation, and triggered inflammatory NF-κB signalling and steatohepatitis. Moreover, SQLE directly binds to CA3, which in turn promotes de novo hepatic lipogenesis by inducing sterol regulatory element-binding protein 1C activation. Combined targeting SQLE (terbinafine) and CA3 (acetazolamide) synergistically ameliorated NASH in mice with better efficacy to either drug alone. Lastly, serum SQLE with CA3 could distinguish patients with NASH from steatosis and healthy controls, thus confirming their clinical relevance. *(Gastroenterology, 2021)*

Non-alcoholic steatohepatitis (NASH) is a severe form of NAFLD associated with inflammation and hepatocyte damage, which could progress to cirrhosis and HCC. The development of NASH is closely related to the hepatic immune microenvironment. Natural Killer (NK) cells are a major immune cell type found in the liver; however, its role in NASH is unknown. In this study, they investigated the contribution of NK cells to NASH using NK-deficient mice ($Nfil3^{-/-}$). Absence of NK cells ameliorated diet-induced NASH models with significantly reduced liver inflammation and damage. Mechanistically, they found that NK cells isolated from NASH liver secreted high levels of pro-inflammatory cytokines to induce hepatic JAK/STAT1/3 signalling, leading to increased oxidative damage and apoptosis. The neutralization of NK cells with PK136 antibody suppressed NASH development in mice model, suggesting that modulation of NK cells provides a potential therapeutic strategy for NASH. *(Cellular and Molecular Gastroenterology and Hepatology, 2021)*



Research and Scholarship

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Jun Yu Vincent Wong Henry Chan Jennifer Zhang Joseph Sung	National Natural Sciences Awards	Ministry of Sciences and Technology, China
Jun Yu	Five Continents Women Science and Technology Award	China Medical Women's Association
Joseph Sung Vincent Wong	Clarivate Analytics Highly Cited Researchers 2021	Clarivate

Fellowships

Member's Name	Details	
	Fellowship	Organisation
Jun Yu	Council Member	American Gastroenterology Association Microbiome and Microbial Therapy Section, USA
		International Cancer Microbiome Consortium, UK
	AGA Fellow	American Gastroenterology Association, USA
	Vice Chairman	China Anti-Cancer Association Committee on Gut Microbiome
		China Medical Women's Association Division of Digestive Disease
		Hong Kong Scientist Association
	Member	International Cancer Genome Consortium, USA
		American Association for Cancer Research, USA
Vincent Wong	Member	American Association for the Study of Liver Diseases
		European Association for the Study of the Liver
	Council Member	Asia-Pacific High Energy Physics Panel
		Hong Kong Association for the Study of Liver Diseases
Chi Chun Wong	Member	American Gastroenterology Association, USA

Member's Name	Details	
	Fellowship	Organisation
Jennifer Zhang	Member	American Gastroenterology Association, USA
		Tumour Microecology of China anti-Cancer Association
		Chronic Disease Management of China Medicinal Biotech Association
		Hong Kong Immunology Association
Huarong Chen	Member	Society For Leukocyte Biology
		China Anti-Cancer Association

Academic Editorship

Member's Name	Details	
	Role	Journal
Jun Yu	Deputy Chief Editor	Journal of Gastroenterology and Hepatology
	Associate Editor	Oncogene
		Oncogenesis
		Scientific Reports
		The World Journal of Gastroenterology
		Journal of Digestive Disease
	International Advisor	Advances in Digestive Medicine
	Advisory Board	EBioMedicine
	Editorial Board Member	Gut
		Journal of Gastroenterology & Hepatology Research
		Scientific Reports
		World Journal of Gastrointestinal Pharmacology and Therapeutics
		Journal of Pathology & Laboratory Medicine
		Journal of Next Generation Sequencing & Applications
		Oncogenesis
		The Open Hepatology Journal
		Pragmatic and Observational Research
		ISRN Gastroenterology
		International Journal of Clinical Medicine
		Insight Knowledge
		The Open Gastroenterology Journal
Vincent Wong	Associate Editor	Clinical Gastroenterology and Hepatology
	Editorial Board Member	JHEP Reports
		Hepatology Communications
		Alimentary Pharmacology & Therapeutics

Member's Name	Details	
	Role	Journal
Dennis Wong	Editorial Board Member	Frontiers in Medicine
	Guest Editorial Member	Cells
Jennifer Zhang	Editorial Board Member	Frontiers in Oncology
		Frontiers in Cell and Developmental Biology
Huarong Chen	Guest Editor	Diagnostics

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Jun Yu	Chair	AGA DDW Abstract Review Committee-Microbiome
		AGA DDW Abstract Review Committee-Oncology
	Reviewer	Gastroenterology
		Gut
		Nature Communication
		American Journal of Gastroenterology
		American Journal of Pathology
		Annals Oncology
		BMC Cancer
		BMC Gastroenterology
		British Journal of Cancer
		Alimentary Pharmacology & Therapeutics
		Cancer
		Cancer Research
		Cancer Letters
		Carcinogenesis
		Cell Death & Disease
		Clinical Cancer Research
		Clinical Gastroenterology and Hepatology
		eBioMedicine
		Hepatology
		Human Molecular Genetics
		Life Sciences
		International Journal of Cancer
		International Journal of Oncology
		Journal of Gastroenterology & Hepatology
		The Journal of Hematology & Oncology
		Journal of Hepatology

Member's Name	Details	
	Role	Journal
Jun Yu	Reviewer	Journal of Molecular Medicine
		Journal of Pathology
		Liver International
		Lancet
		Molecular Cancer Research
		Molecular Cancer Therapeutics
		Carcinogenesis
		Molecular Oncology
		Nature Reviews Gastroenterology and Hepatology
		New England Journal of Medicine
		Oncogene
		Science Translational Medicine
Vincent Wong	Reviewer	Gastroenterology
		Gut
		Hepatology
		Journal of Hepatology
Dennis Wong	Reviewer	Oncogene
		Pathology
		Pharmacological Research
		Pharmaceutics
		Theranostics
		Expert Opinion on Investigational Drugs
		Journal of Gastroenterology & Hepatology
		Molecules
		Metabolites
Jennifer Zhang	Reviewer	Frontiers in Oncology
		Journal of Gastroenterology & Hepatology
Xiang Zhang	Reviewer	Journal of Leukocyte Biology
		Cancer Letters
Huarong Chen	Reviewer	Molecular Cancer
		Theranostics
		Oncogene
		Frontiers in Immunology
		Cells

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Jun Yu	Funding to Support State Key Laboratory of Digestive Diseases	Innovation and Technology Commission – Innovation and Technology Fund	2018	Current	10,000,000
	Exploiting Epitranscriptome Dysregulation in Colorectal Carcinogenesis and Metastasis: Mechanisms and Novel Therapeutic Approaches	Research Grants Council – Collaborative Research Fund	01/07/2020	30/06/2023	6,158,384
	Evaluation of SQLE as a Novel Therapeutic Target in Non-alcoholic Fatty Liver Disease	Food and Health Bureau – Health and Medical Research Fund	01/07/2020	30/06/2023	1,498,772
	Elucidating a Novel Tumor Promoting Gene Ring Finger Protein 6 in Colorectal Cancer	Research Grants Council – General Research Fund	01/01/2018	30/06/2021	1,229,089
	The Role and Mechanism of Methylation Modification and Its Regulatory Genes in the Development of Colorectal Cancer	National Natural Science Foundation of China	01/01/2020	31/12/2023	RMB 2,000,000
	Molecular Pathogenesis of Hepatitis B Associated HCC	Guangdong Natural Scientific Funding	01/05/2018	30/04/2023	RMB 3,000,000
	Prospective of Colorectal Cancer Screening Biomarkers and Population Gradient Screening Programs	National Key R&D Program of China	01/09/2018	31/12/2021	RMB 9,000,000
	Translational Cancer Genomic	Gordon Research Conference	01/05/2019	30/04/2021	USD 20,000
	Function of the Immune Receptor Regulator DOK1 in Therapy Response of Gastric Cancer	Germany/ Hong Kong Joint Research Scheme 2018/19	01/01/2019	31/12/2021	90,000
	Defining the Role of RNA N6- Methyladenosine Writer Methyltransferase Like 3 (METTL3) in Colorectal Cancer	Research Grants Council – General Research Fund	01/01/2020	31/12/2022	1,532,422

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Jun Yu	Identification and Characterization of Genes and Microenvironment Factors Driving the Metastasis of Upper Gastrointestinal Tract Cancers	Research Grants Council – Collaborative Research Fund	01/07/2019	30/06/2022	4,416,717
	Exploiting Stemness as a Cancer Cell Vulnerability Using Hepatocellular Carcinoma (HCC) as a Model System	Research Grants Council – Collaborative Research Fund	01/04/2019	31/03/2022	6,990,790
	Fighting Disease Recurrence and Promoting Tissue Repair after Liver Transplantation: Translating Basic Discoveries to Clinical Excellence	Research Grants Council – Theme-based Research Scheme	01/12/2019	30/11/2024	45,000,000
	The Interaction of Key Intestinal Pathogens and Host Factors in Promoting the Development of Colorectal Cancer	National Key R&D Program of China	01/11/2020	30/10/2025	RMB 22,000,000
	Assess Antibiotic Resistome Flows from Pollution Hotspots to Environments and Explore the Control Strategies	Research Grants Council – Theme-based Research Scheme	01/12/2020	31/11/2025	29,000,000
	Regulation and Mechanism of Tumor-intrinsic Oncogene Pathways in Mediating an Immune Suppressed Microenvironment in Hepatocellular Carcinoma	Research Grants Council – Collaborative Research Fund	01/06/2018	30/06/2021	7,544,147
Dennis Wong	A Novel Epigenetic Therapy for KRAS-mutant Colorectal Cancer	Health and Medical Research Fund – Research Fellowship Scheme	30/09/2019	29/09/2022	1,499,371
	Branched Chain Amino Acids (BCAA) Restriction to Alleviate Colorectal Cancer Metastasis	Health and Medical Research Fund – Research Fellowship Scheme	01/12/2021	30/11/2024	1,499,880
Dennis Wong	SLC25A22 Drives Oncometabolite Succinate to Promote Cancer Stemness in KRAS-mutant Colorectal Cancer	Research Grants Council – Early Career Scheme	01/01/2021	31/12/2023	936,520
	Combinatorial Blockade of De Novo Cholesterol Biosynthesis and PCSK9 as a Synergistic Therapy for KRAS-Mutant Colorectal Cancer	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	971,368
	Mitochondrial Glutamate Transporter (SLC25A22) Promotes the Tumorigenicity of KRAS-mutant Colorectal Cancer through Regulating DNA and Histone Methylation	National Natural Science Foundation of China	01/01/2018	31/12/2021	RMB 530,000
Huarong Chen	RNA N6-Methyladenosine Methyltransferase- like 3 (METTL3) is a Potential Therapeutic Target for Immunotherapy in Colorectal Cancer	Health and Medical Research Fund – Research Fellowship Scheme	01/09/2021	31/08/2023	1,475,400

Publications

A. Journal Papers

1. Li Q, Hu W, Liu WX, Zhao LY, Huang D, Liu XD, Chan H, Zhang Y, Zeng JD, Coker OO, Kang W, Ng SSM, Zhang L, Wong SH, Gin T, Chan MTV, Wu JL, Yu J, Wu WKK. *Streptococcus thermophilus* inhibits colorectal tumorigenesis through secreting β-galactosidase. *Gastroenterology*. 2021;160(4):1179-1193.e14. doi:10.1053/j.gastro.2020.09.003.

2. Zhang J, Hoedt EC, Liu Q, Berendsen E, Teh JJ, Hamilton A, O' Brien AW, Ching JYL, Wei H, Yang K, Xu Z, Wong SH, Mak JWY, Sung JJY, Morrison M, Yu J, Kamm MA, Ng SC. Elucidation of *Proteus mirabilis* as a key bacterium in Crohn's disease inflammation. *Gastroenterology*. 2021;160(1):317-330.e11. doi:10.1053/j.gastro.2020.09.036.

3. Chen H, Gao S, Liu W, Wong CC, Wu J, Wu J, Liu D, Gou H, Kang W, Zhai J, Li C, Su H, Wang S, Soares F, Han J, He HH, Yu J. RNA n6-methyladenosine methyltransferase METTL3 facilitates colorectal cancer by activating the m6A-GLUT1-mTORC1 axis and is a therapeutic target. *Gastroenterology*. 2021;160(4):1284-1300.e16. doi:10.1053/j.gastro.2020.11.013.

4. Zhang X, Coker OO, Chu ESH, Fu K, Lau HCH, Wang YX, Chan AWH, Wei H, Yang X, Sung JJY, Yu J. Dietary cholesterol drives fatty liver-associated liver cancer by modulating gut microbiota and metabolites. *Gut*. 2021;70(4):761-774. doi:10.1136/gutjnl-2019-319664.

5. Liang JQ, Wong SH, Szeto CH, Chu ESH, Lau HC, Chen Y, Fang J, Yu J, Sung JJY. Fecal microbial DNA markers serve for screening colorectal neoplasm in asymptomatic subjects. *Journal of Gastroenterology and Hepatology*. 2021;36(4):1035-1043. doi:10.1111/jgh.15171.

6. Chen Y, Cheng WY, Shi H, Huang S, Chen H, Liu D, Xu W, Yu J, Wang J. Classifying gastric cancer using FLORA reveals clinically relevant molecular subtypes and highlights LINC01614 as a biomarker for patient prognosis. *Oncogene*. 2021;40(16):2898-2909. doi:10.1038/s41388-021-01743-3.

7. Kang X, Li W, Liu W, Liang H, Deng J, Wong CC, Zhao S, Kang W, To KF, Chiu PWY, Wang G, Yu J, Ng EKW. LIMK1 promotes peritoneal metastasis of gastric cancer and is a therapeutic target. *Oncogene*. 2021;40(19):3422-3433. doi:10.1038/s41388-021-01656-1.

8. Liu W, Zhang X, Xu H, Li S, Lau HCH, Chen Q, Zhang B, Zhao L, Chen H, Sung JJY, Yu J. Microbial community heterogeneity within colorectal neoplasia and its correlation with colorectal carcinogenesis. *Gastroenterology*. 2021;160(7):2395-2408. doi:10.1053/j.gastro.2021.02.020.

9. Rahaman S, Li X, Yu J, Wong K-C. CancerEMC: Frontline non-invasive cancer screening from circulating protein biomarkers and mutations in cell-free DNA. *Bioinformatics*. 2021;37(19):3319-3327. doi:10.1093/bioinformatics/btab044.

10. Liu D, Wong CC, Zhou Y, Li C, Chen H, Ji F, Go MYY, Wang F, Su H, Wei H, Cai Z, Wong N, Wong VWS, Yu J. Squalene epoxidase induces nonalcoholic steatohepatitis via binding to carbonic anhydrase III and is a therapeutic target. *Gastroenterology*. 2021;160(7):2467-2482.e3. doi:10.1053/j.gastro.2021.02.051.

11. Teh JJ, Berendsen EM, Hoedt EC, Kang S, Zhang J, Zhang F, Liu Q, Hamilton AL, Wilson-O'Brien A, Ching J, Sung JJY, Yu J, Ng SC, Kamm MA, Morrison M. Novel strain-level resolution of Crohn's disease mucosa-associated microbiota via an *ex vivo* combination of microbe culture and metagenomic sequencing. *ISME Journal*. 2021;15(11):3326-3338. doi:10.1038/s41396-021-00991-1.

12. Chen H, Liu W, Wang Y, Liu D, Zhao L, Yu J. SARS-CoV-2 activates lung epithelial cell proinflammatory signaling and leads to immune dysregulation in COVID-19 patients. *EBioMedicine*. 2021;70:103500. doi:10.1016/j.ebiom.2021.103500.

13. Liu J, Geng W, Sun H, Liu C, Huang F, Cao J, Xia L, Zhao H, Zhai J, Li Q, Zhang X, Kuang M, Shen S, Xia Q, Wong VWS, Yu J. Integrative metabolomic characterisation identifies altered portal vein serum metabolome contributing to human hepatocellular carcinoma. *Gut*. Published online 2021. doi:10.1136/GUTJNL-2021-325189.

14. Liu Y, Ling L, Wong SH, Wang MH, Fitzgerald JR, Zou X, Fang S, Liu X, Wang X, Hu W, Chan H, Wang Y, Huang D, Li Q, Wong WT, Choi G, Zou H, Hui DS, Yu J, Tse G, Gin T, Wu WK, Chan MT, Zhang L. Outcomes of respiratory viral-bacterial co-infection in adult hospitalized patients. *EClinicalMedicine*. 2021;37. doi:10.1016/j.eclinm.2021.100955.

15. Yang J, Wei H, Zhou Y, Szeto CH, Li C, Lin Y, Coker OO, Lau HCH, Chan AWH, Sung JJY, Yu J. High-fat diet promotes colorectal tumorigenesis through modulating gut microbiota and metabolites. *Gastroenterology*. 2022;162(1):135-149.e2. doi:10.1053/j.gastro.2021.08.041. (Epub ahead of print)

16. Wang F, Zhang X, Liu W, Zhou Y, Wei W, Liu D, Wong CC, Sung JJY, Yu J. Activated natural killer cell promotes nonalcoholic steatohepatitis through mediating jak/stat pathway. *Cellular and Molecular Gastroenterology and Hepatology*. 2022;13(1):257-274. doi:10.1016/j.jcmgh.2021.08.019. (Epub ahead of print)

17. Xu H, Wong CC, Li W, Zhou Y, Li Y, Wang L, Liu L, Yu J. RING-finger protein 6 promotes colorectal tumorigenesis by transcriptionally activating SF3B2. *Oncogene*. 2021;40(47):6513-6526. doi:10.1038/s41388-021-01872-9.

18. Wang S, Wong CC, Zhang Y, Huang J, Li C, Zhai J, Wang G, Wei H, Zhang X, He HH, Yu J. ZNF545 loss promotes ribosome biogenesis and protein translation to initiate colorectal tumorigenesis in mice. *Oncogene*. 2021;40(48):6590-6600. doi:10.1038/s41388-021-01938-8.

19. Gao S, Soares F, Wang S, Wong CC, Chen H, Yang Z, Liu W, Go MYY, Ahmed M, Zeng Y, O'Brien CA, Sung JJY, He HH, Yu J. CRISPR screens identify cholesterol biosynthesis as a therapeutic target on stemness and drug resistance of colon cancer. *Oncogene*. 2021;40(48):6601-6613. doi:10.1038/S41388-0c21-01882-7.

20. Zhang J, Zhai J, Wong CC, Chen H, Wang X, Ji J, Yu J. A novel amplification gene PCI domain containing 2 (PCID2) promotes colorectal cancer through directly degrading a tumor suppressor promyelocytic leukemia (PML). *Oncogene*. 2021;40(49):6641-6652. doi:10.1038/s41388-021-01941-z.

21. Liu W, Gou H, Wang X, Li X, Hu X, Su H, Li S, Yu J. TTPAL promotes gastric tumorigenesis by directly targeting NNMT to activate PI3K/AKT signaling. *Oncogene*. 2021;40(49):6666-6679. doi:10.1038/s41388-021-01838-x.

22. Li R, Ong Q, Wong CC, Chu ESH, Sung JJY, Yang X, Yu J. O-GlcNAcylation inhibits hepatic stellate cell activation. *Journal of Gastroenterology and Hepatology*. 2021;36(12):3477-3486. doi:10.1111/jgh.15690.

23. Jiang B, Mu Q, Qiu F, Li X, Xu W, Yu J, Fu W, Cao Y, Wang J. Machine learning of genomic features in organotropic metastases stratifies progression risk of primary tumors. *Nature Communications*. 2021;12(1):1-15. doi:10.1038/s41467-021-27017-w.

24. Wang S, Gao S, Zeng Y, Zhu L, Mo Y, Wong CC, Bao Y, Su P, Zhai J, Wang L, Soares F, Xu X, Chen H, Hezaveh K, Ci X, He A, McGaha T, O'Brien C, Rottapel R, Kang W, Wu J, Zheng G, Cai Z, Yu J, He HH. N6-methyladenosine reader YTHDF1 promotes ARHGEF2 translation and RhoA signaling in colorectal cancer. *Gastroenterology*. Published online December 28, 2021. doi:10.1053/j.gastro.2021.12.269. (In press)

25. Sugimura N, Li Q, Siu E, Chu H, Cheuk H, Lau H, Fong W, Liu W, Liang C, Nakatsu G, Chin A, Su Y, Coker OO, Ka W, Wu K, Ka F, Chan L, Yu J, Leung FK. Lactobacillus gallinarum modulates the gut microbiota and produces anti-cancer metabolites to protect against colorectal tumourigenesis. *Gut*. 2021;0:gutjnl-2020-323951. doi:10.1136/gutjnl-2020-323951.

26. Peng Y, Wong CC, Yu J. The paradox of immunotherapy in NASH-HCC. *Signal Transduction and Targeted Therapy*. 2021;6(1):1-2. doi:10.1038/s41392-021-00654-9. (Editorial)

27. She J, Wong CC, Yu J. Targeted prebiotics alter the obese gut microbiome in humans. *Signal Transduction and Targeted Therapy*. 2021;6(1):1-2. doi:10.1038/s41392-021-00758-2. (Editorial)

28. Kang X, Zhang R, Kwong TN, Lui RN, Wu WK, Sung JJ, Yu J, Wong SH. Serrated neoplasia in the colorectum: Gut microbiota and molecular pathways. *Gut Microbes*. 2021;13(1):1-12. doi:10.1080/19490976.2020.1863135. (Review)

29. Lau HCH, Sung JJY, Yu J. Gut microbiota: Impacts on gastrointestinal cancer immunotherapy. *Gut Microbes*. 2021;13(1):1-21. doi:10.1080/19490976.2020.1869504. (Review)

30. Wang F, Lau JKC, Yu J. The role of natural killer cell in gastrointestinal cancer: Killer or helper. *Oncogene*.2021;40(4):717-730. doi:10.1038/s41388-020-01561-z. (Review)

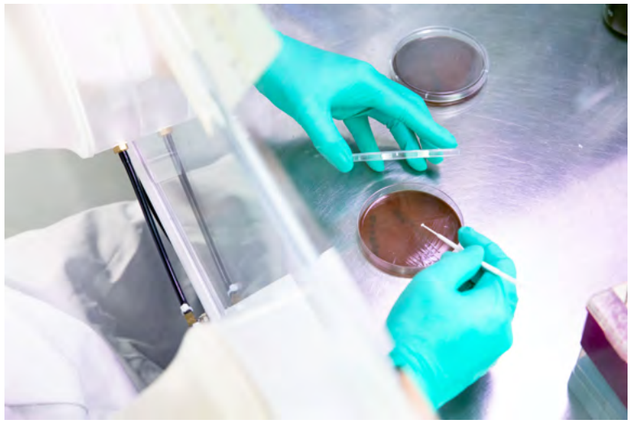
31. Xu H, Liu L, Li W, Zou D, Yu J, Wang L, Wong CC. Transcription factors in colorectal cancer: Molecular mechanism and therapeutic implications. *Oncogene.* 2021;40(9):1555-1569. doi:10.1038/s41388-020-01587-3. (Review)

32. Wen J, Lau HCH, Peppelenbosch M, Yu J. Gastric microbiota beyond H. pylori: An emerging critical character in gastric carcinogenesis. *Biomedicines*. 2021;9(11):1680. doi:10.3390/biomedicines9111680. (Review)

33. Peng Y, Nie Y, Yu J, Wong CC. Microbial metabolites in colorectal cancer: *Basic and clinical implications*. *Metabolites*. 2021;11(3):159. doi:10.3390/metabo11030159. (Review)

34. Lin Y, Wang G, Yu J, Sung JJY. Artificial intelligence and metagenomics in intestinal diseases. *Journal of Gastroenterology and Hepatology*. 2021;36(4):841-847. doi:10.1111/jgh.15501. (Review)

35. Cheung H, Yu J. Machine learning on microbiome research in gastrointestinal cancer. *Journal of Gastroenterology and Hepatology*. 2021;36(4):817-822. doi:10.1111/jgh.15502. (Editorial)



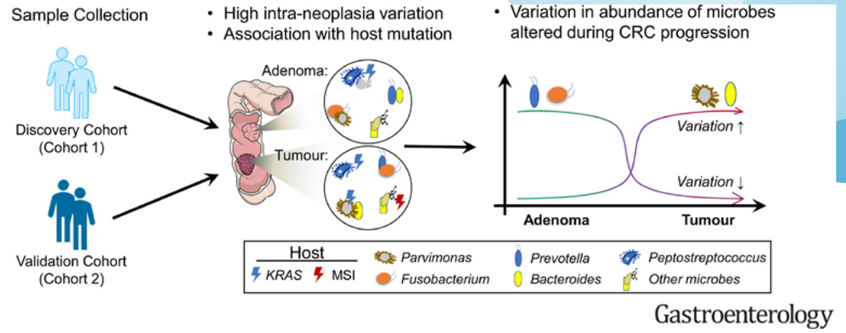
Patents

1. US Patent:
   - Inventors: Ka Kei Wu, Jun Yu
   - Title: Use of Streptococcus Thermophilus for Treatment and Prevention of Colorectal Cancer
   - Patent Application No. 62/799,162

2. China Patent:
   - Inventors: Ka Kei Wu, Jun Yu
   - Title: 結腸直腸癌的治療性和預防性處理
   - Application No. 202010077512.3

3. US Patent:
   - Inventors: Jun Yu, Ka Kei Wu, Qing Li
   - Title: Probiotic composition for treating and preventing colorectal cancer
   - Application No. 63/229,933

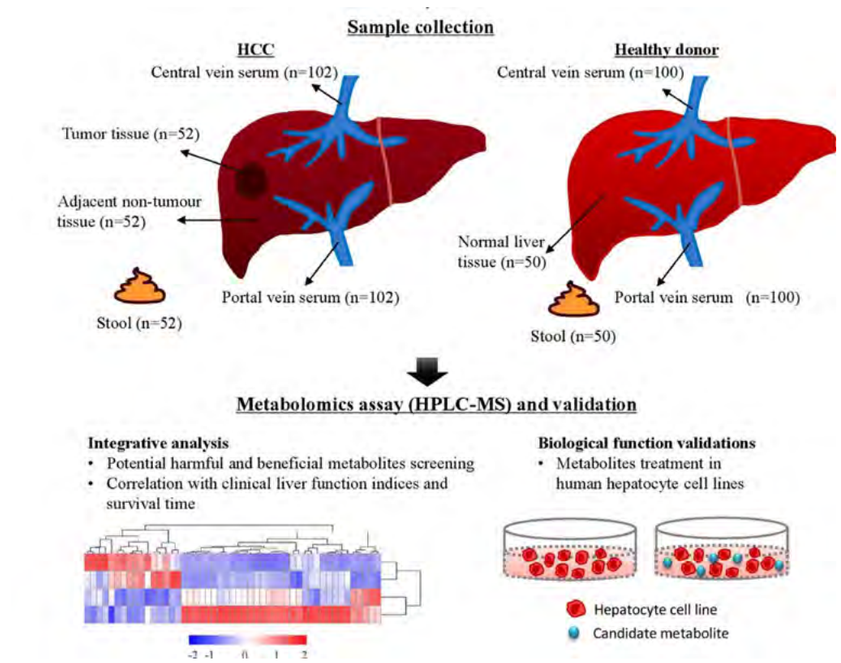
4. China Patent:
   - Inventors: Jun Yu, Ka Kei Wu, Qing Li
   - Title: 用於預防和治療結直腸直腸癌的益生菌組合物
   - Application No. 202111411744.9



Gastroenterology

The microbial community within a colorectal tumour or precancerous adenoma is heterogeneous, and such heterogeneity is significantly correlated with adenoma-carcinoma sequence and CRC-associated genetic alterations (KRAS mutation and microsatellite instability). The findings have provided new insight for the contribution of gut microbiota heterogeneity in CRC progression.

Source: Liu W, Zhang X, Xu H, Li S, Lau HCH, Chen Q, Zhang B, Zhao L, Chen H, Sung JJY, Yu J. Microbial community heterogeneity within colorectal neoplasia and its correlation with colorectal carcinogenesis. Gastroenterology. 2021;160(7):2395-2408. doi:10.1053/j.gastro.2021.02.020.



Hepatocellular carcinoma (HCC) patients had distinct clusters of metabolites in portal and central vein serum, liver tissue and stool samples. In portal vein, Jun Yu and her team identified elevated and depleted metabolites signifying that they might play a role in HCC development.

Source: Liu J, Geng W, Sun H, Liu C, Huang F, Cao J, Xia L, Zhao H, Zhai J, Li Q, Zhang X, Kuang M, Shen S, Xia Q, Wong VWS, Yu J. Integrative metabolomic characterisation identifies altered portal vein serum metabolome contributing to human hepatocellular carcinoma. Gut. Published online 2021. doi:10.1136/gutjnl-2021-325189.

盧煜明

DENNIS LO



02 MOLECULAR DIAGNOSTICS

Circulating Fetal Nucleic Acids

趙慧君

ROSSA CHIU



Principal Investigators

Dennis Lo, Rossa Chiu

Team Members

Allen Chan, Alice Cheng, Rebecca Chan, Jacky Lam, Peiyong Jiang, Diana Han, Masashi Yukawa, Stephanie Yu, Lois Choy, Kam Wing Chan, Wanxia Gai, Daisy Hu, Yoyo Jin, Chris Kum, Angel Lai, Patty Tse, Saravanan Ramakrishnan, Huimin Shang, Sarah Sin, Ting Ting Xie, Henson Yu, Qing Zhou, Lizhen Ma, Chen Ding, Sherwood Fung, Lilian Zhong, Denis Odinokov, Jeremy Chiu, Wenlei Peng, On Yee Tse, Ze Zhou, Yuwei Gao, Guangya Wang, Guannan Kang, Xi Hu, Claire Yang

Research Progress Summary



Led by Dennis Lo and Rossa Chiu, the project team has been pursuing a novel facet of cell-free DNA biology, which the team termed as fragmentomics. This refers to the analysis of the ending patterns and fragmentation characteristics of cell-free DNA molecules. This research area has attracted little attention in the past. Cell-free DNA molecules exist in circulation in a naturally fragmented form. By studying the end sequences of cell-free DNA molecules systematically and across the whole genome, the team initially made the surprising observation that cell-free DNA fragmentation is a non-random process. There are genomic locations which featured more regularly at cell-free DNA ends than others which have been termed as the preferred ends. Those findings then prompted the team to investigate the ends of cell-free DNA from various angles. The team found certain motif sequences to be overrepresented among cell-free DNA molecules and then showed that the ends may be blunt or jagged in nature in both plasma and urine. Those intriguing observations spurred the team to study the biological basis by exploring the roles of various DNA digesting enzymes, including Deoxyribonuclease 1 Like 3 (DNase1L3), Deoxyribonuclease I (DNase1) and DNA Fragmentation Factor Subunit Beta (Dffb). During this journey, the team uncovered pathologies with altered activity levels of those enzymes that would be associated with perturbations in the cell-free DNA profiles. In other words, by improving their understanding of biological mechanisms, one may ultimately find novel ways to develop diagnostic tests. One of the team's research publications on fragmentomics (Han et al. *Genome Res* 2021; 31: 2008-2021) has been featured on the cover of the journal, *Genome Research*. Interestingly, since the research team began the exploration of fragmentomics, interests from other groups on the topic have also gathered momentum. In other words, the team's academic pursuit has led to the emergence of a new research field and the journal, *Science*, even has invited the team to contribute a review on the topic (Lo et al. *Science* 2021; 372: eaaw3616).

On the other hand, the team has been actively harnessing the power of applying single molecule sequencing to the analysis of cell-free DNA. First, the team made the surprising observation that there was an under-appreciated population of long cell-free DNA molecules in maternal plasma. This class of cell-free DNA molecules enabled new and additional information to be gathered about pregnancy health and fetal genetic profile as shown by the work in Yu et al. (*Proceedings of the National Academy of Sciences U S A* 2021; 118: e2114937118). Second, cytosine methylation of CpG dinucleotides is one important strategy to distinguish tissue origin of cell-free DNA molecules or one that allows the detection of pathological processes associated with aberrant methylation profile via cell-free DNA analysis. Bisulfite sequencing has remained as the key technology to study DNA methylation. However, bisulfite converts all unmethylated cytosines into thymine residues, even when the cytosines are out of the context of CpG sites. Consequently, bisulfite sequencing results in reduced sequence resolution and adds ambiguity. To resolve this, the team has attained a major achievement by successfully developing an approach based on studying the kinetic features of single molecule sequencing data to distinguish methylated cytosine without the need for bisulfite treatment. The team believes this method would greatly enhance and facilitate any genetic and genomic studies focused on DNA methylation. Those data have been published in Tse et al. *Proceedings of the National Academy of Sciences* USA 2021; 118: e2019768118. Since the release of the publication, they have been approached by a dozen of research groups to provide the bioinformatics code to enable their adoption of the published methodology.

Research and Scholarship

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Dennis Lo	The ESHG Mendel Award 2021	European Society of Human Genetics (ESHG)
	Breakthrough Prize in Life Sciences	Breakthrough Prize
	Royal Medal - Biological Sciences	Royal Society
Dennis Lo Rossa Chiu Allen Chan	Top 20 Translational Researchers of 2020	Nature Biotechnology

Academic Editorship

Member's Name	Details	
	Role	Journal
Dennis Lo	Associate Editor	Clinical Chemistry
		Genomic Medicine
	Senior Editor	eLife
	Editorial Board member	Cancer Communications
		Journal of Pathology
		Philosophical Transactions of the Royal Society B
		Disease Markers
		Prenatal Diagnosis
		Journal of Genomes and Exomes
		Marrow
		American Journal of Hematology
Rossa Chiu	Associate Editor	Clinical Chemistry
		Human Genetics and Genomics Advances
	Editorial Board member	Clinical Biochemistry
		Critical Reviews in Clinical Laboratory Sciences
		The Clinical Biochemist Reviews

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Dennis Lo	Centre for Novostics	Innovation and Technology Commission – InnoHK Scheme	01/05/2020	30/04/2025	Not to be disclosed
	Genomic Approaches for Predicting Severity of Organ Dysfunction and Outcomes in Sepsis: A Prospective Cohort Study in Adult Critically Ill Patients with Sepsis	The Chinese University of Hong Kong Faculty of Medicine – Faculty Innovation Award	01/01/2020	31/12/2022	750,000
Dennis Lo	Plasma DNA as a Platform Technology for Cancer Detection	Research Grants Council – Theme-based Research Scheme	01/12/2016	30/11/2021	28,570,000
Rossa Chiu	Plasma DNA as a Platform Technology for Cancer Detection	The Chinese University of Hong Kong – Focused Innovations Scheme C	01/12/2016	30/11/2021	2,093,500

Publications

A. Journal Papers

1. Lo YMD, Han DSC, Jiang P, Chiu RWK. Epigenetics, fragmentomics, and topology of cell-free DNA in liquid biopsies. *Science*. 2021;372(6538). doi:10.1126/science.aaw3616. (Review)

2. Chiu RWK, Lo YMD. Cell-free fetal DNA coming in all sizes and shapes. *Prenatal Diagnosis*. 2021;41(10):1193-1201. doi:10.1002/pd.5952. (Review)

3. Tse OYO, Jiang P, Cheng SH, Peng W, Shang H, Wong J, Chan SL, Poon LCY, Leung TY, Chan KCA, Chiu RWK, Lo YMD. Genome-wide detection of cytosine methylation by single molecule real-time sequencing. *Proceedings of the National Academy of Sciences*. 2021;118(5):e2019768118. doi:10.1073/pnas.2019768118.

4. Zhou Z, Cheng SH, Ding SC, Heung MMS, Xie T, Cheng THT, Lam WKJ, Peng W, Teoh JYC, Chiu PKF, Ng C-F, Jiang P, Chan KCA, Chiu RWK, Lo YMD. Jagged ends of urinary cell-free DNA: Characterization and feasibility assessment in bladder cancer detection. *Clinical Chemistry*. 2021;67(4):621-630. doi:10.1093/clinchem/hvaa325.

5. Sin STK, Ji L, Deng J, Jiang P, Cheng SH, Heung MMS, Lau CSL, Leung TY, Chan KCA, Chiu RWK, Lo YMD. Characteristics of fetal extrachromosomal circular DNA in maternal plasma: Methylation status and clearance. *Clinical Chemistry*. 2021;67(5):788-796. doi:10.1093/clinchem/hvaa326.

6. Han DSC, Lo YMD. The nexus of cfDNA and nuclease biology. *Trends in Genetics*. 2021;37(8):758-770. doi:10.1016/j.tig.2021.04.005. (Review)

7. Danesi R, Lo YMD, Oellerich M, Beck J, Galbiati S, Re MD, Lianidou E, Neumaier M, van Schaik RHN. What do we need to obtain high quality circulating tumor DNA (ctDNA) for routine diagnostic test in oncology? – Considerations on pre-analytical aspects by the IFCC workgroup cfDNA. *Clinica Chimica Acta*. 2021;520:168-171. doi:10.1016/j.cca.2021.05.033.

8. Lo YMD. Noninvasive prenatal testing: Advancing through a virtuous circle of science, technology and clinical applications. *Prenatal Diagnosis*. 2021;41(10):1190-1192. doi:10.1002/pd.5978. (Commentary)

9. Ma ML, Yakovenko S, Zhang H, Cheng SH, Apryshko V, Zhavoronkov A, Jiang P, Chan KCA, Chiu RWK, Lo YMD. Fetal mitochondrial DNA in maternal plasma in surrogate pregnancies: Detection and topology. *Prenatal Diagnosis*. 2021;41(3):368-375. doi:10.1002/pd.5860.

10. Han DSC, Ni M, Chan RWY, Wong DKL, Hiraki LT, Volpi S, Jiang P, Lui KO, Chan KCA, Chiu RWK, Lo YMD. Nuclease deficiencies alter plasma cell-free DNA methylation profiles. *Genome Research*. 2021;31(11):2008-2021. doi:10.1101/gr.275426.121.

11. Yu SCY, Jiang P, Peng W, Cheng SH, Cheung YTT, Tse OYO, Shang H, Poon LC, Leung TY, Chan KCA, Chiu RWK, Lo YMD. Single-molecule sequencing reveals a large population of long cell-free DNA molecules in maternal plasma. *Proceedings of the National Academy of Sciences*. 2021;118(50):e2114937118. doi:10.1073/pnas.2114937118.

12. Gai W, Zhou Z, Agbor-Enoh S, Fan X, Lian S, Jiang P, Cheng SH, Wong J, Chan SL, Jang MK, Yang Y, Liang RH, Chan WK, Ma ES, Leung TY, Chiu RW, Valantine H, Chan KA, Lo YD. Applications of genetic-epigenetic tissue mapping for plasma DNA in prenatal testing, transplantation and oncology. *eLife*. 2021;10. doi:10.7554/elife.64356.

13. Vong JSL, Ji L, Heung MMS, Cheng SH, Wong J, Lai PBS, Wong VWS, Chan SL, Chan HLY, Jiang P, Chan KCA, Chiu RWK, Lo YMD. Single cell and plasma RNA sequencing for RNA liquid biopsy for hepatocellular carcinoma. *Clinical Chemistry*. 2021;67(11):1492-1502. doi:10.1093/clinchem/hvab116.



Cell-free DNA in plasma consists of fragments of DNA and has been used for noninvasive prenatal testing, cancer liquid biopsies, and transplantation monitoring. Han et al. demonstrate the interrelationships between nucleases, cell-free DNA fragmentation, and DNA methylation, which are depicted in this artistic illustration. The railroad (representing DNA) enters a red tunnel (representing a blood vessel) in the distant mountain. The railroad has red and green sign posts, denoting methylated cytosines and unmethylated cytosines on the DNA, respectively. Barriers of different colors are different nucleases, preferring to cleave (down position) or not cleave (up position) the DNA. DNASE1 (red barriers) prefers to cleave at unmethylated cytosines, while DNASE1L3 (green barriers) prefers to cleave at methylated cytosines. Thus, nuclease-mediated cell-free DNA fragmentation is informed by underlying DNA methylation. (Cover art using watercolor and colored pencils on paper by Carmen Ng [https://www.carmen-ng.com/], based on a concept from Dennis Lo.

Source: Cover illustration of journal issue publishing Han et al. Nuclease deficiencies alter plasma cell-free DNA methylation profiles. Genome Research 2021; 31: 2008-2021.

鄧亮生

NELSON TANG



02 MOLECULAR DIAGNOSTICS

Genetics of Disease Susceptibility



Principal Investigator

Nelson Tang

Team members

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

Research Progress Summary

Research directions:

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

Research into Genetics of Disease Susceptibility (GDS):

The mission of the GDS laboratory is to identify disease predisposition genes for common diseases, also known as complex traits. The research group involved in the development of various analysis methods and wet laboratory validation of the results generated from such analysis. The team also participates in international consortiums in studies of healthy aging (including bone and other phenotypes), breast cancer, and genetic susceptibility to adolescent idiopathic scoliosis and tuberculosis. With the advance in sequencing and other technology, the team acquires biological data in an unprecedented volume nowadays. The analysis and statistic method become limiting factors in handling such huge volume of data.

Research and Scholarship

Academic Editorship

Member's Name	Details	
	Role	Journal
Nelson Tang	Editorial Board Member	Frontiers in Pediatrics
		Journal of Pediatric Biochemistry (Official journal of World Society of Child Science)
		Genes — Open Access Journal of Genetics & Genomics
		Frontiers in Genetics

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Nelson Tang	Reviewer	Hong Kong Medical Journal
		The 52nd Union World Conference on Lung Health
		Journal of International Medical Research
		Gene
		Journal of Medical Genetics
		Medical Review

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Nelson Tang	Paediatric Biomonitoring Reference Values for Metals and Trace Elements in Urine: A Survey of Hong Kong Children	Food and Health Bureau	04/10/2021	03/10/2024	1,009,167
	Investigating the Key Factors Regulating Healthy Ageing in Chinese Longevity Family Cohort	Ministry of Science and Technology of China	01/01/2020	31/12/2022	RMB 876,000
Nelson Tang	Establishment Hong Kong Branch of CAS Center for Excellence in Animal Evolution and Genetics	The Chinese University of Hong Kong – Vice-Chancellor's One-off Discretionary Fund	01/06/2020	31/05/2023	12,000,000
	Pilot Study on the Changes of Transcriptome for Neuronavigated Repetitive Transcranial Magnetic Stimulation (rTMS) in the Management of Depression in Major Neurocognitive Disorders	The Chinese University of Hong Kong – Research Committee - Direct Grants	29/06/2020	28/06/2021	40,400
	Prediction of Clinical Outcomes by Determining the Kinetics of Serum Proadrenomedullin, Procalcitonin, and C-Reactive Protein in Adult Patients with Bloodstream Infections	The Chinese University of Hong Kong – Research Committee - Direct Grants	30/06/2019	29/06/2021	149,775

Publications

A. Journal Papers

1. Tam CHT, Lim CKP, Luk AOY, Ng ACW, Lee HM, Jiang G, Lau ESH, Fan B, Wan R, Kong APS, Tam WH, Ozaki R, Chow EYK, Lee KF, Siu SC, Hui G, Tsang CC, Lau KP, Leung JYY, Tsang MW, Kam G, Lau IT, Li JKY, Yeung VTF, Lau E, Lo S, Fung S, Cheng YL, Chow CC, Hu M, Yu W, Tsui SKW, Huang Y, Lan H, Szeto CC, Tang NLS, Ng MCY, So WY, Tomlinson B, Chan JCN, Ma RCW. Development of genome-wide polygenic risk scores for lipid traits and clinical applications for dyslipidemia, subclinical atherosclerosis, and diabetes cardiovascular complications among East Asians. *Genome Medicine*. 2021;13(1). doi:10.1186/s13073-021-00831-z.

2. Ji LD, Xu ZF, Tang NLS, Xu J. Natural selection of ATP2B1 underlies susceptibility to essential hypertension. *Frontiers in Genetics*. 2021;12. doi:10.3389/fgene.2021.628516. (Editorial)

3. Lee AWT, Ng JKW, Liao J, Luk AC, Suen AHC, Chan TTH, Cheung MY, Chu HT, Tang NLS, Zhao MP, Lian Q, Chan WY, Chan DYL, Leung TY, Chow KL, Wang W, Wang LH, Chen NCH, Yang WJ, Huang JY, Li TC, Lee TL. Single-cell RNA sequencing identifies molecular targets associated with poor in vitro maturation performance of oocytes collected from ovarian stimulation. *Human Reproduction (Oxford, England)*. 2021;36(7):1907-1921. doi:10.1093/humrep/deab100.

4. Huang D, Liu AYN, Leung KS, Tang NLS. Direct measurement of B lymphocyte gene expression biomarkers in peripheral blood transcriptomics enables early prediction of vaccine seroconversion. *Genes*. 2021;12(7). doi:10.3390/genes12070971.

5. Tang NLS, Dobbs MB, Gurnett CA, Qiu Y, Lam TP, Cheng JCY, Hadley-Miller N. A decade in review after idiopathic scoliosis was first called a complex trait-A tribute to the late Dr. Yves cotrel for his support in studies of etiology of scoliosis. *Genes*. 2021;12(7). doi:10.3390/genes12071033. (Review)

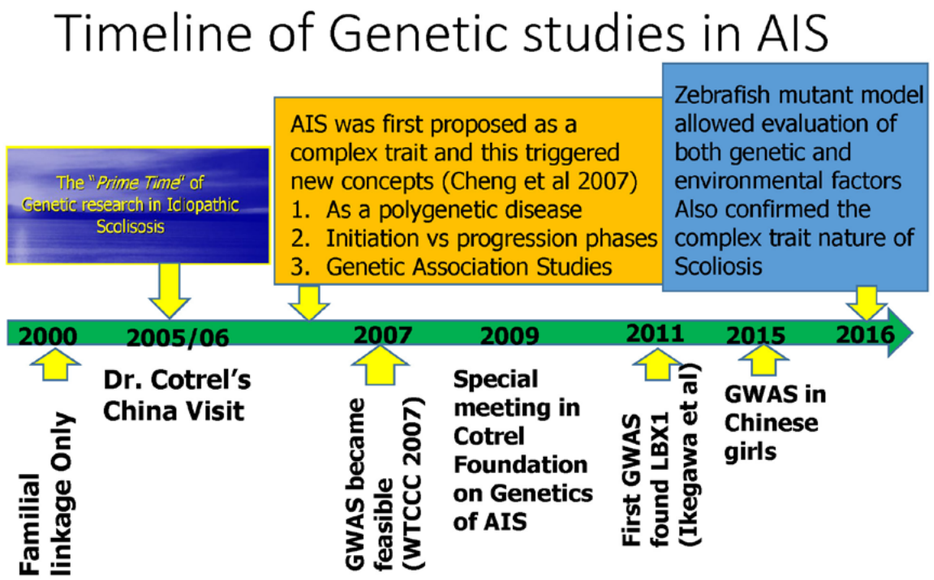
6. Xu L, Feng Z, Dai Z, Lee WYW, Wu Z, Liu Z, Sun X, Tang N, Cheng JC-Y, Qiu Y, Zhu Z. A functional SNP in the promoter of LBX1 is associated with the development of adolescent idiopathic scoliosis through involvement in the myogenesis of paraspinal muscles. *Frontiers in Cell and Developmental Biology*. 2021;9. doi:10.3389/fcell.2021.777890.

7. van de Stadt SIW, Mooyer PAW, Dijkstra IME, Dekker CJM, Vats D, Vera M, Ruzhnikov MRZ, van Haren K, Tang N, Koop K, Willemsen MA, Hui J, Vaz FM, Ebberink MS, Engelen M, Kemp S, Ferdinandusse S. Biochemical studies in fibroblasts to interpret variants of unknown significance in the ABCD1 gene. *Genes*. 2021;12(12):1930. doi:10.3390/genes12121930.



A group photo of an annual reunion of the research group into etiology of scoliosis of the Cotrel Foundation in the Institut de France. The Late Dr. Yves Cotrel was in the first row on the right. (Courtesy of the Cotrel Foundation).

Source: Tang, N.L.S.; Dobbs, M.B.; Gurnett, C.A.; Qiu, Y.; Lam, T.P.; Cheng, J.C.Y.; Hadley-Miller, N. A Decade in Review after Idiopathic Scoliosis Was First Called a Complex Trait—A Tribute to the Late Dr. Yves Cotrel for His Support in Studies of Etiology of Scoliosis. Genes 2021, 12, 1033.



Timeline of research breakthrough in the genetics of AIS and the subsequent studies confirming the complex trait model of AIS which the team first proposed and published 15 years ago.

Source: Tang, N.L.S.; Dobbs, M.B.; Gurnett, C.A.; Qiu, Y.; Lam, T.P.; Cheng, J.C.Y.; Hadley-Miller, N. A Decade in Review after Idiopathic Scoliosis Was First Called a Complex Trait—A Tribute to the Late Dr. Yves Cotrel for His Support in Studies of Etiology of Scoliosis. Genes 2021, 12, 1033.



陳君賜

ALLEN CHAN

02 MOLECULAR DIAGNOSTICS

Plasma Nucleic Acids Research



Principal Investigator

Allen Chan

Team members

Jacky Lam , Wanxia Gai, Charles Chan, Sherwood Fung, Vicky Lee, Irene Tse, Amy Tsang, Maggie Li, Patrick Lee, Vivien Lin, Jack Cheung, Kaede Chau, Olive Wong, Sze Wan Wong

Research Progress Summary

Allen Chan and his research team have completed the re-screening activities of all the study participants and are currently performing the data analysis and preparing for the manuscript.

In addition, they have organised the virtual Nasopharyngeal Cancer (NPC) Screening Conference on 4-6 November 2021 and invited over 40 experts from various disciplines to discuss on NPC screening. Their ultimate goal is to develop recommendations on the use of EBV-based markers for screening of NPC.



Research and Scholarship

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Allen Chan	Top 20 Translational Researchers of 2020	Nature Biotechnology
Jacky Lam	Postgraduate Research Output Award 2020	The Chinese University of Hong Kong

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Allen Chan	Convenor	Nasopharyngeal Cancer Screening Conference
Jacky Lam	Organising Committee Member	Nasopharyngeal Cancer Screening Conference

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Allen Chan	Centre for Novostics	Innovation and Technology Commission – InnoHK Scheme	01/05/2020	30/04/2025	Not to be disclosed
	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. Vong JSL, Ji L, Heung MMS, Cheng SH, Wong J, Lai PBS, Wong VWS, Chan SL, Chan HLY, Jiang P, Chan KCA, Chiu RWK, Lo YMD. Single cell and plasma RNA sequencing for RNA liquid biopsy for hepatocellular carcinoma. *Clinical Chemistry*. 2021;67(11):1492-1502. doi:10.1093/clinchem/hvab116.

2. Yu SCY, Jiang P, Peng W, Cheng SH, Cheung YTT, Tse OYO, Shang H, Poon LC, Leung TY, Chan KCA, Chiu RWK, Lo YMD. Single-molecule sequencing reveals a large population of long cell-free DNA molecules in maternal plasma. *Proceedings of the National Academy of Sciences of the United States of America*. 2021;118(50):e2114937118. doi:10.1073/pnas.2114937118.

3. Zhou Z, Cheng SH, Ding SC, Heung MMS, Xie T, Cheng THT, Lam WKJ, Peng W, Teoh JYC, Chiu PKF, Ng CF, Jiang P, Chan KCA, Chiu RWK, Lo YMD. Jagged ends of urinary cell-free DNA: Characterization and feasibility assessment in bladder cancer detection. *Clinical Chemistry*. 2021;67(4):621-630. doi:10.1093/clinchem/hvaa325.

4. Fung SYH, Chan KCA, Wong EWY, Ng CWK, Cho R, Yeung ZWC, Lam JWK, Chan JYK. Droplet digital PCR of tumor suppressor gene methylation in serial oral rinses of patients with head and neck squamous cell carcinoma. *Head & Neck*. 2021;43(6):1812-1822. doi:10.1002/hed.26647.

5. Han DSC, Ni M, Chan RWY, Wong DKL, Hiraki LT, Volpi S, Jiang P, Lui KO, Chan KCA, Chiu RWK, Lo YMD. Nuclease deficiencies alter plasma cell-free DNA methylation profiles. *Genome Research*. 2021;31(11):2008-2021. doi:10.1101/gr.275426.121.

6. Gai W, Zhou Z, Agbor-Enoh S, Fan X, Lian S, Jiang P, Cheng SH, Wong J, Chan SL, Jang MK, Yang Y, Liang RHS, Chan WK, Ma ESK, Leung TY, Chiu RWK, Valantine H, Chan KCA, Lo YMD. Applications of genetic-epigenetic tissue mapping for plasma DNA in prenatal testing, transplantation and oncology. *eLife*. 2021;10:e64356. doi:10.7554/eLife.64356.

7. Tse OYO, Jiang P, Cheng SH, Peng W, Shang H, Wong J, Chan SL, Poon LCY, Leung TY, Chan KCA, Chiu RWK, Lo YMD. Genome-wide detection of cytosine methylation by single molecule real-time sequencing. *Proceedings of the National Academy of Sciences of the United States of America*. 2021;118(5):e2019768118. doi:10.1073/pnas.2019768118.

8. Ma MJL, Yakovenko S, Zhang H, Cheng SH, Apryshko V, Zhavoronkov A, Jiang P, Chan KCA, Chiu RWK, Lo YMD. Fetal mitochondrial DNA in maternal plasma in surrogate pregnancies: Detection and topology. *Prenatal Diagnosis*. 2021;41(3):368-375. doi:10.1002/pd.5860.

9. Sin STK, Ji L, Deng J, Jiang P, Cheng SH, Heung MMS, Lau CSL, Leung TY, Chan KCA, Chiu RWK, Lo YMD. Characteristics of fetal extrachromosomal circular DNA in maternal plasma: Methylation status and clearance. *Clinical Chemistry*. 2021;67(5):788-796. doi:10.1093/clinchem/hvaa326.



02 MOLECULAR DIAGNOSTICS

Plasma Nucleic Acids Research



Principal Investigator

Jacky Lam

Team members

Patrick Lee, Vivien Lin, Jack Cheung, Man Na Law

Research Progress Summary

Jacky Lam, together with Allen Chan and his team, have continued their prospective screening study of nasopharyngeal carcinoma (NPC) which was first launched in 2013. The study has established the screening utility of plasma Epstein-Barr virus (EBV) DNA for NPC. The study is now in the second phase, which all the participants would be offered re-screening. Jacky and the team have discovered the differentiating molecular characteristics of plasma EBV DNA between NPC and non-NPC subjects, including quantitative, size and methylation characteristics. The discoveries have led to the development of novel sequencing-based assays that have more superior performance than the conventional PCR-based assay for early detection of NPC. In addition, the team has derived a risk score based on the EBV single nucleotide variant profile for NPC prediction. The team continues to optimise the sequencing-based assay for clinical application, in terms of both accuracy and cost-effectiveness.

In November 2021, Jacky and Allen have organised the virtual Nasopharyngeal Cancer Screening Conference 2021 aiming to propose recommendations for NPC screening. In the 3-day conference, over 200 participants from all over the world have joined the conference and shared their opinions.

Research and Scholarship

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Jacky Lam	Postgraduate Research Output Award 2020	The Chinese University of Hong Kong

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Jacky Lam	Organising Committee Member	Nasopharyngeal Cancer Screening Conference
		Breast Cancer Conference 2021
	Reviewer	Clinical Chemistry

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Jacky Lam	Investigating the Molecular Characteristics of Epstein-Barr Virus DNA in Plasma to Enhance Surveillance of Recurrence of Nasopharyngeal Carcinoma	Research Grants Council – Early Career Scheme	01/09/2021	31/08/2023	598,491

Publications

A. Journal Papers

1. Zhou Z, Cheng SH, Ding SC, Heung MMS, Xie T, Cheng THT, Lam WKJ, Peng W, Teoh JYC, Chiu PKF, Ng CF, Jiang P, Chan KCA, Chiu RWK, Lo YMD. Jagged ends of urinary cell-free DNA: Characterization and feasibility assessment in bladder cancer detection. *Clinical Chemistry*. 2021;67(4):621-630. doi:10.1093/clinchem/hvaa325.

2. Fung SYH, Chan KCA, Wong EWY, Ng CWK, Cho R, Yeung ZWC, Lam JWK, Chan JYK. Droplet digital PCR of tumor suppressor gene methylation in serial oral rinses of patients with head and neck squamous cell carcinoma. *Head and Neck*. 2021;43(6):1812-1822. doi:10.1002/hed.26647.



Jacky Lam and volunteers of the NPC Screening Programme.

Source: Jacky Lam



03 EMERGING INFECTIOUS DISEASES AND MICROBIOTA

Fecal Microbiota Transplantation

Research Progress Summary

As pioneers in microbiome diagnostics and therapeutics, Siew Ng and her research team focus on translating metagenomic-derived microbiota signatures into novel biomarkers and oral biotherapeutics. This year, the research team has made several cutting-edge discoveries on the role of the gut microbiota with COVID-19 and its vaccine safety and efficacy. They were amongst the first in the world to discover that germs in gut (gut microbiota) modulate human immunity and disease severity in COVID-19. The team discovered that 80% of COVID-19 patients suffered from lingering symptoms known as “long COVID” including memory loss, poor sleep and hair loss after COVID-19 recovery, which was linked to abnormal gut microbiota (dysbiosis). In a recent collaborative research project between Faculty of Medicine in The Chinese University of Hong Kong (CUHK) and The University of Hong Kong (HKU), the team showed that the efficacy of COVID-19 vaccines, especially SinoVac, correlated with a unique probiotic bacterium, *Bifidobacterium adolescentis*, and that people who lacked *Bifidobacterium adolescentis* in their gut had a lower antibody response to COVID-19 vaccines. This novel finding implies that *Bifidobacterium adolescentis* can serve as a potential therapeutic option to enhance efficacy of COVID-19 vaccines, and is consistent with their earlier clinical findings that a microbiota-based regimen developed by The Chinese University of Hong Kong led to enhanced antibody response among COVID-19 patients. This discovery offers a novel approach to optimise vaccine efficacy and safety through modulation of the gut microbiota. Their data were announced in press conferences which gained widespread media coverage in over 10 countries globally.

Evolving from their work in Fecal Microbiota Transplantation (FMT), the team has identified specific bacteria markers that can predict response to FMT in individuals with obesity, and they are developing personalised microbiota therapeutics for the treatment of obesity and metabolic diseases. Their center will also serve as the sole provider of FMT service to the entire Hospital Authority in Hong Kong covering 13 public hospitals for recurrent *Clostridioides difficile* infections.



Research Progress Summary



Principal Investigator

Siew Ng

Team members

Francis Chan, Paul Chan, Joyce Mak, Lin Zhang, Qin Liu, Zhilu Xu, Jingwan Zhang, CP Cheung, Whitney Tang, Jessica Ching, Fen Zhang, Amy Li, Clinical FMT Team

In the field of microbiome diagnostics, the team has pioneered non-invasive tools for detection and prediction of Autism Spectrum Disorders (ASD). They found that bacteria associated with neurotransmitter activities were substantially reduced in children with ASD and that five unique species of bacteria identified in children with ASD were not typically found in the guts of children without the condition. Using a machine learning analysis, their proprietary algorithm of these bacteria markers achieved a sensitivity of over 80% in distinguishing children with ASD from typically developing children. Their work published in *Gut* (Impact Factor 23.06) was selected for press release by the *British Medical Journal Group* leading to significant recognition locally and internationally whereby over 100 media outlets, including web, newspapers, trade periodicals and bloggers worldwide picked up the news with an estimated target audience of 12 million. Siew received interviews from *Reuters Health* and *Wall Street Journal*. These promising discoveries have since attracted a research donation of HK$48 million from The D. H. Chen Foundation for the establishment of the Hub of Advanced Technology for Child Health (HATCH) to further develop novel non-invasive markers to predict ASD in early life.

With their leading-edge discoveries in microbiome medicine and the establishment of the Microbiota I-Centre (MagIC) at the Hong Kong Science and Technology Park, Siew and her team were selected for a visit by the Chief Executive of Hong Kong SAR, Mrs. Carrie Lam, to gain insight on the team's innovations of developing novel classes of microbiome diagnostic and live biotherapeutics for common diseases.

In the reporting period, the team has published 31 peer reviewed articles and reviews in international journals, 20 international conference abstracts and filed for 22 patents related to their discovery. Siew was awarded the highly cited Researcher by Clarivate which is the second consecutive year she is receiving this honour.



Research and Scholarship

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Siew Ng	Higher Education Outstanding Scientific Research Output Awards (Science and Technology) 2020 – First-class award in Natural Sciences – Integrative Research on Epidemiology, Pathogenesis and Therapeutics in IBD	Ministry of Education
	Highly Cited Researchers 2021	Clarivate
	Meritorious Research Award	Lo Ying Shek Chi Wai Foundation
	Women of Power 2021	Prestige Hong Kong
	Outstanding Project Team on COVID-19 Research Award	Food and Health Bureau, HKSAR
	Scientific Award	8th World Congress on Targeting Microbiota, International Society of Microbiota
	Most Read Articles 2021	Gut Journal
	GUT Best Papers 2021	Gut Journal
Winnie Lin	Distinguished Investigator Awards	9th Annual Meeting of Asian Organization for Crohn's and Colitis 2021

Fellowships

Member's Name	Details	
	Fellowship	Organisation
Raphael Lau	Hong Kong PhD Fellowship	Research Grants Council of Hong Kong
Zhi Lu Xu	Faculty Postdoctoral Fellowship	The Chinese University of Hong Kong

Academic Editorship

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

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Siew Ng	Chair Reviewer	Digestive Disease Week 2022, American Gastroenterological Association (AGA) Institute Council
	Reviewer	Journal of Hepatology
		New England Journal of Medicine
		Nature Medicine
		Nature Reviews Gastroenterology & Hepatology
		Gastroenterology
		Gut
		American Journal of Gastroenterology
		Clinical Gastroenterology and Hepatology
		Journal of Crohn's and Colitis
		Alimentary Pharmacology and Therapeutics
		Gastrointestinal Endoscopy
		Journal of Gastroenterology
		Inflammatory Bowel Disease
		Journal of Gastroenterology and Hepatology
		World Journal of Gastroenterology
		Digestive Diseases and Sciences
		BMC Gastroenterology
		European Journal of Gastroenterology & Hepatology
	Judge	Asian Pacific Association of Gastroenterology / JGH Foundation Clinician-Scientist Training Fellowship 2021

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Siew Ng	Establishment of the Hub of Advanced Technology for Child Health (HATCH)	D.H. Chen Foundation	10/2021	09/2024	48,240,000
	Novel Strategies to Facilitate Early Detection, Prevention and Intervention for Long-term Health Problems Related to COVID-19 (NovITor-COVID study)	Food and Health Bureau – Health and Medical Research Fund	04/2021	05/2026	45,991,725
	Modulation of Gut Microbiota to Enhance Health and Immunity in Vulnerable Individuals during COVID-19 Pandemic	Food and Health Bureau – Health and Medical Research Fund	04/2021	05/2024	9,980,840
	Midstream Research Programme: A Microbiome-based Noninvasive Diagnostic Test for Early Colorectal Cancers	Innovation and Technology Commission	01/2021	12/2024	4,600,000
	HKSTP-KingMed Co-Incubation Scheme	Hong Kong Science and Technology Parks Corporation	01/2021	12/2024	4,000,000
	ICARUS –IBD: International Study of COVID-19 Antibody Response Under Sustained Immune Suppression in Inflammatory Bowel Disease	The Chancellor Masters and Scholars of the University of Oxford	11/2020	04/2022	102,960
	IBD GIVES-21: Global IBD Visualization of Epidemiology Studies (GIVES) in the 21st Century	The Leona M. & Harry B. Helmsley Charitable Trust	09/2020	08/2023	15,564,946
	Recurrence Rates in High-risk Subjects with Baseline Advanced Colorectal Adenomas Followed up at Different Surveillance Intervals: A Multi-center Randomised Controlled Trial in Four Chinese Cities	Food and Health Bureau – Health and Medical Research Fund	09/2020	09/2023	1,460,388
Siew Ng	Launching of a bacteria-based Non-invasive Diagnostic Test for Early Colorectal Cancer Detection	The Chinese University of Hong Kong Technology and Business Development Fund	09/2020	08/2021	175,211
	Early Detection and Surveillance of COVID-19 Infection by Non-invasive Ophthalmic Evaluations	Food and Health Bureau – Commissioned Research on the Novel Coronavirus Disease (COVID-19)	08/2020	07/2022	4,822,810
	Elucidating Driver Bacteria in Crohn's Disease for Therapeutic Manipulation	Croucher Foundation – Croucher Senior Medical Research Fellowship	08/2020	08/2022	2,877,860
	Role of Gastrointestinal Tract and Gut Microbiota in Pathogenesis of Coronavirus Disease 2019 (COVID-19): A Missing Site for Viral Replication & Transmission	Food and Health Bureau – Commissioned Research on the Novel Coronavirus Disease (COVID-19)	06/2020	05/2021	4,076,580
	Technology Start-up Support Scheme for Universities	Innovation and Technology Commission – Innovation and Technology Fund	04/2020	03/2021	500,000
	Mother-to-Infant Transfer of Bacteriome, Virome, Fungome and Metabolome in Health and Crohn's Disease (Mommy-CD)	The Leona M. & Harry B. Helmsley Charitable Trust	10/2019	09/2022	19,727,952
	A Randomised, Placebo-controlled Study on Fecal Microbiota Transplantation for Patients with Irritable Bowel Syndrome with Fecal and Mucosal Microbiota Assessment	Food and Health Bureau – Health and Medical Research Fund	06/2019	05/2021	1,301,112
	Health@InnoHK: Microbiota I-Center (MagIC)	Innovation and Technology Commission	05/2019	06/2024	350,200,000

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Siew Ng	PACIfIC: Prevalence, Characteristics, and Genetics of Adherent-invasive *Escherichia coli* in Crohn's disease patients: Comparative Study between France and Hong-Kong	The French National Research Agency / Research Grants Council Joint Research Scheme	02/2018	01/2022	2,611,942
	The ENIGMA Studies – Eastern Inflammatory Bowel Disease Gut Microbiota	The Leona M. & Harry B. Helmsley Charitable Trust	03/2017	02/2021	14,259,211

Publications

A. Journal Papers

1. Olivera PA, Zuily S, Kotze PG, Regnault V, Al Awadhi S, Bossuyt P, Gearry RB, Ghosh S, Kobayashi T, Lacolley P, Louis E, Magro F, Ng SC, Papa A, Raine T, Teixeira FV., Rubin DT, Danese S, Peyrin-Biroulet L. International consensus on the prevention of venous and arterial thrombotic events in patients with inflammatory bowel disease. *Nature Reviews Gastroenterology and Hepatology*. 2021;18(12):857-873. doi:10.1038/s41575-021-00492-8.

2. Shi HY, Zhu X, Li WL, Mak JWY, Wong SH, Zhu ST, Guo SL, Chan FKL, Zhang ST, Ng SC. Modulation of gut microbiota protects against viral respiratory tract infections: A systematic review of animal and clinical studies. *European Journal of Nutrition*. 2021;60(8):4151-4174. doi:10.1007/s00394-021-02519-x. (Review)

3. Teh JJ, Berendsen EM, Hoedt EC, Kang S, Zhang J, Zhang F, Liu Q, Hamilton AL, Wilson-O'Brien A, Ching J, Sung JJY, Yu J, Ng SC, Kamm MA, Morrison M. Novel strain-level resolution of Crohn's disease mucosa-associated microbiota via an ex vivo combination of microbe culture and metagenomic sequencing. *ISME Journal*. 2021;15(11):3326-3338. doi:10.1038/s41396-021-00991-1.

4. Yau YK, Mak WYJ, Lui NSR, Ng WYR, Cheung CYK, Li YLA, Ching YLJ, Chin ML, Lau HSL, Chan KLF, Chan KSP, Ng SC. High prevalence of extended-spectrum beta-lactamase organisms and the COVID-19 pandemic impact on donor recruitment for fecal microbiota transplantation in Hong Kong. *United European Gastroenterology Journal*. 2021;9(9):1027-1038. doi:10.1002/ueg2.12160.

5. Zhilu X, Xiangqian D, Keli Y, Caroline C, Jingwan Z, Yu L, Tao Z, Cheung CL, Yang S, Fengrui Z, KI CF, Jy SJ, Jun Y, Anthony B, Nicolas B, Jean-Frédéric C, Sunny Hei W, Yinglei M, Siew C N. Association of adherent-invasive Escherichia coli with severe gut mucosal dysbiosis in Hong Kong Chinese population with Crohn's disease. *Gut Microbes*. 2021;13(1):e1994833. doi:10.1080/19490976.2021.1994833.

6. Rubin DT, Modesto I, Vermeire S, Danese S, Ng SC, Kwok KK, Koram N, Jones TV. Worldwide post-marketing safety surveillance experience with tofacitinib in ulcerative colitis. *Alimentary Pharmacology & Therapeutics*. 2022;55(3):302-310. doi:10.1111/apt.16619. (Epub ahead of print)

7. Yang K, Niu J, Zuo T, Sun Y, Xu Z, Tang W, Liu Q, Zhang J, Ng EKW, Wong SKH, Yeoh YK, Chan PKS, Chan FKL, Miao Y, Ng SC. Alterations in the gut virome in obesity and type 2 diabetes mellitus. *Gastroenterology*. 2021;161(4):1257-1269. doi:10.1053/j.gastro.2021.06.056.

8. Zhang F, Wan Y, Zuo T, Yeoh YK, Liu Q, Zhang L, Zhan H, Lu W, Xu W, Lui GCY, Li AYL, Cheung CP, Wong CK, Chan PKS, Chan FKL, Ng SC. Prolonged impairment of short-chain fatty acid and L-isoleucine biosynthesis in gut microbiome in patients with COVID-19. *Gastroenterology*. 2022;162(2):548-561. doi:10.1053/j.gastro.2021.10.013. (Epub ahead of print)

9. Lau HCH, NG SC, Yu J. Targeting the gut microbiota in coronavirus disease 2019: Hype or hope? *Gastroenterology*. 2022;162(1):9-16. doi:10.1053/j.gastro.2021.09.009. (Commentary, Epub ahead of print)

10. Sasson AN, Ingram RJM, Zhang Z, Taylor LM, Ananthakrishnan AN, Kaplan GG, Ng SC, Ghosh S, Raman M. The role of precision nutrition in the modulation of microbial composition and function in people with inflammatory bowel disease. *Lancet Gastroenterology & Hepatology*. 2021;6(9):754-769. doi:10.1016/s2468-1253(21)00097-2.

11. Zhang L, Zhan H, Xu W, Yan S, Ng SC. The role of gut mycobiome in health and diseases. *Therapeutic Advances in Gastroenterology*. 2021;14:1-18. doi:10.1177/17562848211047130. (Review)

12. D'Amico F, Solitano V, Aletaha D, Hart A, Magro F, Selmi C, Ng SC, Al Awadhi S, Choy E, Schulze-Koops H, Bossuyt P, Olivera PA, Kotze PG, Ghosh S, Peyrin-Biroulet L, Danese S. Biobetters in patients with immune-mediated inflammatory disorders: An international delphi consensus. *Autoimmunity Reviews*. 2021;20(7):102849. doi:10.1016/j.autrev.2021.102849. (Review)

13. Wan Y, Zuo T, Xu Z, Zhang F, Zhan H, Chan D, Leung TF, Yeoh YK, Chan FKL, Chan R, Ng SC. Underdevelopment of the gut microbiota and bacteria species as non-invasive markers of prediction in children with autism spectrum disorder. *Gut*. 2021;0:1-9. doi:10.1136/gutjnl-2020-324015.

14. Burke KE, D'Amato M, Ng SC, Pardi DS, Ludvigsson JF, Khalili H. Microscopic colitis. *Nature Reviews Disease Primers*. 2021;7(1):1-17. doi:10.1038/s41572-021-00273-2.

15. Xu Z, Chan FKL, Ng SC. Dysbiosis in SARS-CoV-2-infected patients. *Gastroenterology*. 2021;160(6):2195-2196. doi:10.1053/j.gastro.2021.01.198. (Letter)

16. Zuo T, Yeoh YK, Ng SC. The new foe and old friends: Are we ready for microbiota-based therapeutics in treating COVID-19 patients?. *Gastroenterology*. 2021;160(6):2193-2195. doi:10.1053/j.gastro.2021.01.196. (Letter)

17. Ianiro G, Mullish BH, Hvas CL, Segal JP, Kuijper EJ, Costello SP, Kelly CR, Allegretti JR, Fischer M, Iqbal TH, Satokari R, Kao D, van Prehn J, Ng SC, Bibbò S, Baunwall SMD, Quraishi MN, Sokol H, Zhang F, Keller J, Masucci L, Quaranta G, Kassam Z, Sanguinetti M, Tilg H, Gasbarrini A, Cammarota G. SARS-CoV-2 vaccines and donor recruitment for FMT. *Lancet Gastroenterology & Hepatology*. 2021;6(4):264-266. doi:10.1016/s2468-1253(21)00032-7. (Letter)

18. Mao R, Rieder F, Ben-Horin S, Kaplan GG, Ng SC, Wong GL, Ghosh S, Chen MH. Implications of COVID-19 for patients with pre-existing digestive diseases: An update. *Lancet Gastroenterology & Hepatology*. 2021;6(4):258-260. doi:10.1016/s2468-1253(21)00025-x. (Commentary)

19. Ungaro RC, Brenner EJ, Gearry RB, Kaplan GG, Kissous-Hunt M, Lewis JD, Ng SC, Rahier JF, Reinisch W, Steinwurz F, Underwood FE, Zhang X, Colombel JF, Kappelman MD. Effect of IBD medications on COVID-19 outcomes: Results from an international registry. *Gut*. 2021;70(4):725-732. doi:10.1136/gutjnl-2020-322539.

20. Wang L, Aschenbrenner D, Zeng Z, Cao X, Mayr D, Mehta M, Capitani M, Warner N, Pan J, Wang L, Li Q, Zuo T, Cohen-Kedar S, Lu J, Ardy RC, Mulder DJ, Dissanayake D, Peng K, Huang Z, Li X, Wang Y, Wang X, Li S, Bullers S, Gammage AN, Warnatz K, Schiefer AI, Krivan G, Goda V,

Kahr WHA, Lemaire M, Genomics England Research Consortium, Lu CY, Siddiqui I, Surette MG, Kotlarz D, Engelhardt KR, Griffin HR, Rottapel R, Decaluwe H, Laxer RM, Proietti M, Hambleton S, Elcombe S, Guo CH, Grimbacher B, Dotan I, Ng SC, Freeman SA, Snapper SB, Klein C, Boztug K, Huang Y, Li D, Uhlig HH, Muise AM. Gain-of-function variants in SYK cause immune dysregulation and systemic inflammation in humans and mice. *Nature Genetics*. 2021;53(4):500-510. doi:10.1038/s41588-021-00803-4.

21. Yeoh YK, Zuo T, Lui GCY, Zhang F, Liu Q, Li AYL, Chung ACK, Cheung CP, Tso EYK, Fung KSC, Chan V, Ling L, Joynt G, Hui DSC, Chow KM, Ng SSS, Li TCM, Ng RWY, Yip TCF, Wong GLH, Chan FKL, Wong CK, Chan PKS, Ng SC. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. *Gut*. 2021;70(4):698-706. doi:10.1136/gutjnl-2020-323020.

22. Zuo T, Liu Q, Zhang F, Yeoh YK, Wan Y, Zhan H, Lui GCY, Chen Z, Li AYL, Cheung CP, Chen N, Lv W, Ng RWY, Tso EYK, Fung KSC, Chan V, Ling L, Joynt G, Hui DSC, Chan FKL, Chan PKS, Ng SC. Temporal landscape of human gut RNA and DNA virome in SARS-CoV-2 infection and severity. *Microbiome*. 2021;9(1):1-16. doi:10.1186/s40168-021-01008-x.

23. Ng SC, Xu Z, Mak JWY, Yang K, Liu Q, Zuo T, Tang W, Lau L, Lui RN, Wong SH, Tse YK, LiAYL, Cheung K, Ching JYL, Wong VWS, Kong APS, Ma RCW, Chow EYK, Wong SKH, Ho ICH, Chan PKS, Chan FKL. Microbiota engraftment after faecal microbiota transplantation in obese subjects with type 2 diabetes: A 24-week, double-blind, randomised controlled trial. *Gut*. 2021;0:1-8. doi:10.1136/gutjnl-2020-323617.

24. Ran Z, Wu K, Matsuoka K, Jeen YT, Wei SC, Ahuja V, Chen M, Hu PJ, Andoh A, Kim HJ, Yang SK, Watanabe M, Ng SC, Hibi T, Hilmi IN, Suzuki Y, Han DS, Leung WK, Sollano J, Ooi CJ, Qian J. Asian Organization for Crohn's and Colitis and Asia Pacific Association of Gastroenterology practice recommendations for medical management and monitoring of inflammatory bowel disease in Asia. *Journal of Gastroenterology and Hepatology*. 2021;36(3):637-645. doi:10.1111/jgh.15185. (Review)

25. Hu J, Zhang L, Lin W, Tang W, Chan FKL, Ng SC. Review article: Probiotics, prebiotics and dietary approaches during COVID-19 pandemic. *Trends in Food Science & Technology*. 2021;108:187-196. doi:10.1016/j.tifs.2020.12.009. (Review)

26. Lau LHS, Guo CLT, Yip TCF, Mak JWY, Wong SH, Lam KLY, Wong GLH, Ng SC, Chan FKL. Risks of post-colonoscopic polypectomy bleeding and thromboembolism with warfarin and direct oral anticoagulants: A population-based analysis. *Gut*. 2022;71(1):100-110. doi:10.1136/gutjnl-2020-323600. (Epub ahead of print)

27. Zuo T, Liu Q, Zhang F, Lui GCY, Tso EYK, Yeoh YK, Chen Z, Boon SS, Chan FKL, Chan PKS, Ng SC. Depicting SARS-CoV-2 faecal viral activity in association with gut microbiota composition in patients with COVID-19. *Gut*. 2021;70(2):276-284. doi:10.1136/gutjnl-2020-322294.

28. Zhang F, Zuo T, Yeoh YK, Cheng FWT, Liu Q, Tang W, Cheung KCY, Yang K, Cheung CP, Mo CC, Hui M, Chan FKL, Li CK, Chan PKS, Ng SC. Longitudinal dynamics of gut bacteriome, mycobiome and virome after fecal microbiota transplantation in graft-versus-host disease. *Nature Communications*. 2021;12(1):1-11. doi:10.1038/s41467-020-20240-x.

29. Zhang J, Hoedt EC, Liu Q, Berendsen E, Teh JJ, Hamilton A, O' Brien AW, Ching JYL, Wei H,Yang K, Xu Z, Wong SH, Mak JWY, Sung JJY, Morrison M, Yu J, Kamm MA, Ng SC. Elucidation of Proteus mirabilis as a key bacterium in Crohn's disease inflammation. *Gastroenterology*. 2021;160(1):317-330. doi:10.1053/j.gastro.2020.09.036.

B. Conference Abstract



1. Xu Z, Mak JWY, Lin Y, Yang K, Liu Q, Zhang F, Lau I, Li A, Cheung K, Tang W, Ching JYL, Chan PK, Chan FKL, Ng SC. Recipient's gut bacteria composition predicts efficacy of fecal microbiota transplantation in inducing weight loss in obese subjects. In: *United European Gastroenterology Week 2021*. Virtual. 2021 October 3-5.

2. Hong HS, Leung WK, Ng KMC, Sze ASF, Li M, Leung CM, Lo FH, Lam BCY, Chan KH, Shan EHS, Tsang SWC, Hui AJ, Chow WH, Ng SC, Park SH, Yang SK, Mak JWY, Ye BD. Differences in direct healthcare cost utilization in the first year of IBD diagnosis: A binational study. In: *United European Gastroenterology Week 2021*. Virtual. 2021 October 3-5.

3. Sandborn W, D'Haens G, Sands BE, Panaccione R, Ng SC, Lawendy N, Kulisek N, Guo X, Mundayat R, Su C, Panes J. Tofacitinib for the treatment of ulcerative colitis: Up to 7.8 years of safety data from global clinical trials. In: *American College of Gastroenterology Annual Meeting 2021*. Las Vegas, United States. 2021 October 25-27.

4. Sandborn W, D'Haens G, Sands BE, Panaccione R, Ng SC, Lawendy N, Kulisek N, Guo X, Mundayat R, Su C, Panes J. Tofacitinib for the treatment of ulcerative colitis: Up to 7.8 years of safety data from global clinical trials. In: *United European Gastroenterology Week 2021*. Virtual. 2021 October 3-5.

5. Mak JWY, Sun Y, Wilson-O'Brien AL, Lin X, Morrison M, Ching JYL, Niu J, Hamilton AL, Feng R, Tang W, Or L, Trakman GL, Lin W, Chen MH, Mao Y, Kamm MA, Ng SC. Childhood antibiotics are a risk factor for developing Crohn's disease. The ENIGMA international cohort study. In: *Asia Pacific Digestive Week 2021*. Kuala Lumpur, Malaysia. 2021 August 19-22.

6. Agrawal M, Brenner EJ, Mak JW, Zhang X, Kaplan G, Ng SC, Ungaro RC, Colombel JF, Kappelman M. COVID-19 outcomes among racial and ethnic minority individuals with inflammatory bowel diseases in the United States. In: *Digestive Disease Week 2021*. Virtual. 2021 May 21-23.

7. Buie M, Quan J, Windsor JW, Coward S, Gearry R, Hansen T, King JA, Kotze PG, Ng SC, Panaccione R, Seow CH, Underwood FE, Kaplan G. Global hospitalization trends for Crohn's disease and ulcerative colitis: Systematic review with temporal analyses. In: *Digestive Disease Week 2021*. Virtual. 2021 May 21-23.

8. Dubinsky MC, D'Haens GR, Sandborn WJ, Ng SC, Panés J, Su C, Lawendy N, Lazariciu I, Gardiner S, Mundayat R, Kulisek N, Modesto I, Torres J. Association between the prior duration of remission and efficacy outcomes in patients with ulcerative colitis treated with tofacitinib 10 mg

twice daily who were in stable remission and either dose-reduced to tofacitinib 5 mg twice daily or remained on 10 mg twice daily: 6-month data from the double-blind, randomised riveting study. In: *16th Congress of European Crohn's and Colitis Organisation 2021*. Virtual. 2021 July 2-3 & 8-10.

9. Kang S, Klerk A, Noon E, Teh JJ, Zhang J, Zhang F, Liu Q, Hamilton AL, Wilson-O'Brien A, Trakman GL, Lin WY, Ching JY, Sung JJ, Yu J, Ng SC, Kamm MA, Morrison M. Food additives enhance pro-inflammatory bacterial growth in Crohn's disease mucosa-associated microbiota. The ENIGMA study. In: *Digestive Disease Week 2021*. Virtual. 2021 May 21-23.

10. Kaplan G, Underwood FE, Tanyingoh D, Agrawal M, Ungaro RC, Brenner EJ, Gearry R, Kissous-Hunt M, Lewis JD, Ng SC, Rahier JF, Reinisch W, Steinwurz F, Zhang X, Kappelman M, Colombel JF. The first and second wave of COVID-19 in patients with inflammatory bowel disease: A temporal trend analysis. In: *Digestive Disease Week 2021*. Virtual. 2021 May 21-23.

11. Lau LHS, Guo CLT, Yip TCF, Mak JW, Wong SH, Lam LYK, Wong GL, Ng SC, Chan FK. Risks of post-colonoscopic polypectomy bleeding and thromboembolism with warfarin and direct oral anticoagulants: A population-based analysis. In: *Digestive Disease Week 2021*. Virtual. 2021 May 21-23.

12. Mak JW, Yuen NTK, Yip TCF, Lam RHM, Lam BKH, Chan FK, Ng SC. Stopping 5-aminosalicylic acid in patients with ulcerative colitis who are in clinical remission does not increase risks of flare. In: *Digestive Disease Week 2021*. Virtual. 2021 May 21-23.

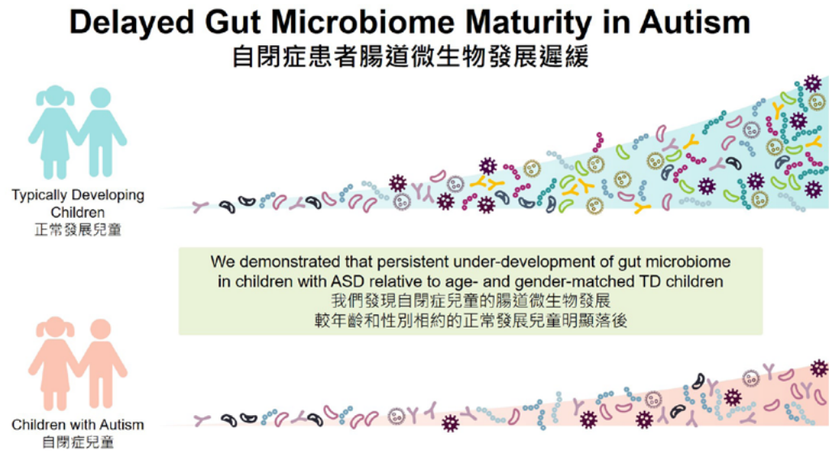
13. Rubin DT, Modesto I, Vermeire S, Danese S, Ng SC, Kwok K, Koram N, Jones TV. Worldwide post-marketing safety surveillance experience with tofacitinib in ulcerative colitis. In: *Digestive Disease Week 2021*. Virtual. 2021 May 21-23.

14. Teh JJ, Kang S, Schooth LF, Loayza JJJ, Zhang J, Zhang F, Liu Q, Hamilton AL, Wilson-O'Brien A, Ching JY, Sung JJ, Yu J, Ng SC, Kamm MA, Morrison M. Novel characterization of the secretomes of Crohn's disease mucosa-associated microbiota, and their modulation of inflammation through NF-kB signalling. The ENIGMA study. In: *Digestive Disease Week 2021*. Virtual. 2021 May 21-23.

15. Trakman GL, Lin WY, Hamilton AL, Wilson-O'Brien A, Stanley A, Or L, Ching JY, Yu J, Morrison M, Ng SC, Kamm MA. Food as a risk factor for the development and perpetuation of Crohn's disease. An international case-control study of food and food additive intake from birth till now. The ENIGMA study. In: *Digestive Disease Week 2021*. Virtual. 2021 May 21-23.

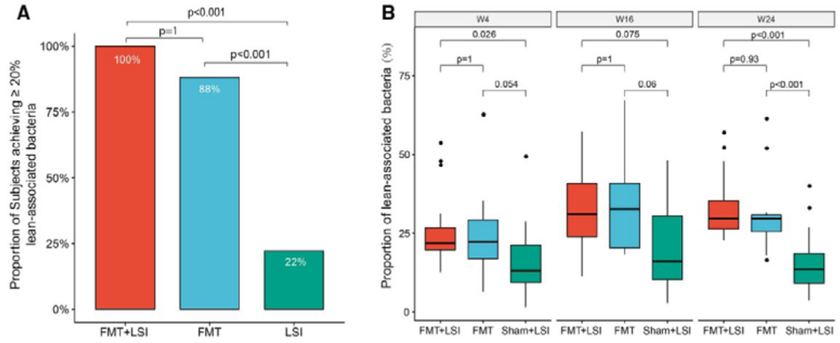
16. Ungaro R, Brenner E, Agrawal M, Gearry RB, Kaplan GG, Kissous-Hunt M, Ng SC, Rahier JF, Reinisch W, Steinwurz F, Zhang X, Lewis JD, Kappelman MD, Colombel JF. 5-aminosalicylates are not associated with adverse outcomes in inflammatory bowel disease patients with COVID-19: Analysis from an international registry. In: *16th Congress of European Crohn's and Colitis Organisation 2021*. Virtual. 2021 July 2-3 & 8-10.

17. Zuo T, Zhang F, Wan Y, Li A, Mak JW, Lau L, Cheung CP, Cheung K, Tang W, Ching JY, Chan PK, Chan FK, Ng SC. Multi-omics analysis identified specific fecal and mucosal bacteria and metabolites associated with response to fecal microbiota transplantation for obesity. In: *Digestive Disease Week 2021*. Virtual. 2021 May 21-23.



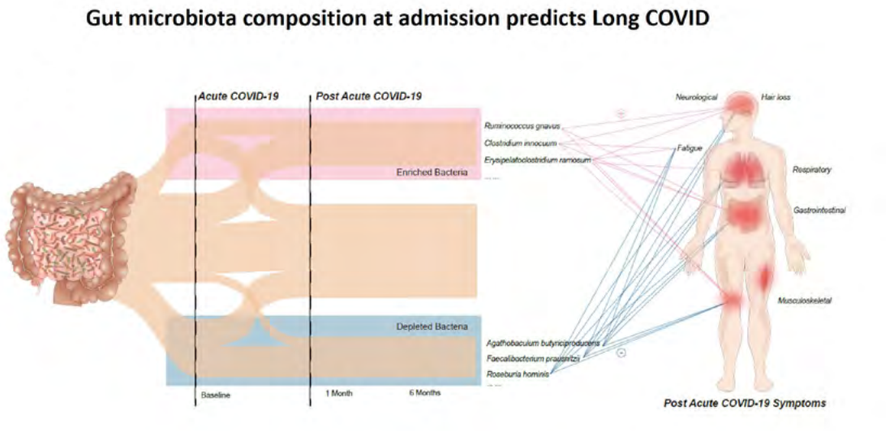
The study of Siew Ng's team showed for the first time that the gut microbiota of children with autism is abnormally developed and lags that of age-matched peers.

Source: Siew Ng



Faecal microbiota analysis showing FMT led to durable engraftment of lean-associated microbiota in obese subjects with type 2 diabetes.
(A) Proportion of subjects with ≥20% lean-associated microbiota at W24. (B) Boxplot depicting of the percentage of lean-associated microbiota at W4, W16 and W24. Significance between treatment arms were calculated by Mann-Whitney U test with Bonferroni correction. FMT, faecal microbiota transplantation; LSI, lifestyle intervention.

Source: Ng SC, Xu ZL, Mak JWY, et al. Ng SC, Xu Z, Mak JWY, Yang K, Liu Q, Zuo T, Tang W, Lau L, Lui RN, Wong SH, Tse YK, Li AYL, Cheung K, Ching JYL, Wong VWS, Kong APS, Ma RCW, Chow EYK, Wong SKH, Ho ICH, Chan PKS, Chan FKL. Microbiota engraftment after faecal microbiota transplantation in obese subjects with type 2 diabetes: A 24-week, double-blind, randomised controlled trial. Gut. 2021;0:1-8. doi:10.1136/gutjnl-2020-323617.



Schematic summary of associations between gut microbiome and development of post-acute COVID-19 syndrome. The team found overlap of bacteria species such as R. gnavus, C. innocuum, Erysipelatous ramosum remained altered from baseline to follow-up and exhibited association with several PACS symptoms.

Source: Liu Q, Mak JWY, Su Q, Yeoh YK, Lui GCY, Ng SSS, Zhang F, Li AYL, Lu W, Hui DSC, Chan PKS, Chan, FKL, Ng SC. Gut Microbiota Dynamics in a Prospective Cohort of Patients with Post-acute COVID-19 Syndrome. Gut. Accepted Manuscript.



Press Conference on 2 December 2021: Joint CUHK-HKU study discovers efficacy of COVID-19 vaccines correlates with a probiotic bacterium, *Bifidobacterium adolescentis*

Source: https://www.med.cuhk.edu.hk/press-releases/joint-cuhk-hku-study-discovers-efficacy-of-covid-19-vaccines-correlates-with-a-probiotic-bacterium-bifidobacterium-adolescentis



Press Conference on 31 March 2021: CU Medicine Study Shows Modulation of Gut Microbiota Helps Enhance Safety and Efficacy of COVID-19 Vaccine

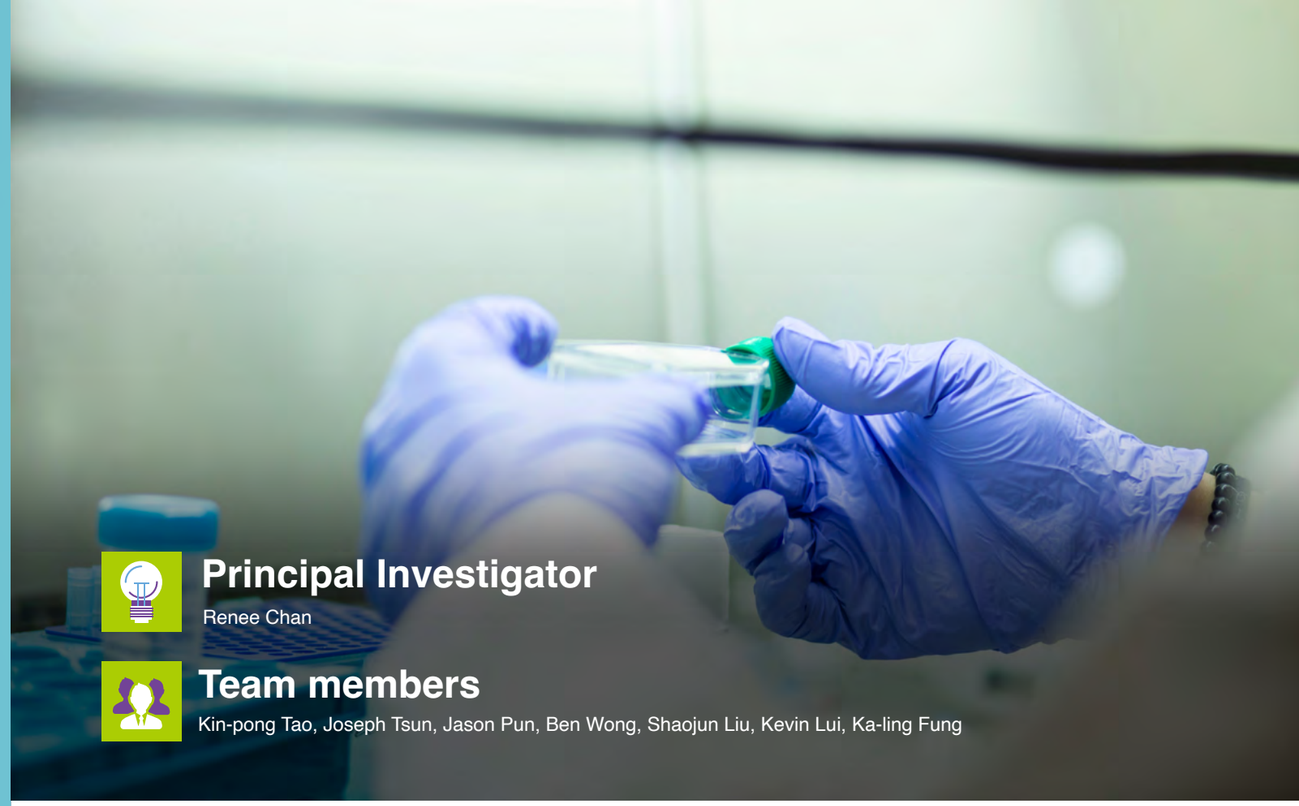
Source: https://www.cpr.cuhk.edu.hk/en/press/cu-medicine-study-shows-modulation-of-gut-microbiota-helps-enhance-safety-and-efficacy-of-covid-19-vaccine/



陳韻怡

RENEE CHAN

03 EMERGING INFECTIOUS DISEASES AND MICROBIOTA



Principal Investigator

Renee Chan

Team members

Kin-pong Tao, Joseph Tsun, Jason Pun, Ben Wong, Shaojun Liu, Kevin Lui, Ka-ling Fung

Research Progress Summary

Renee Chan and her team have been awarded the Innovation and Technology Fund – Partnership Research Programme by the Innovation and Technology Commission of the Hong Kong Special Administrative Region of China to expand her work on the respiratory mucosal immunity projects:

Pioneer in using nasal strip for SARS-CoV-2 detection

Hospitalised paediatric patients with coronavirus disease 2019 (COVID-19) experienced frequent nasopharyngeal swabs during their inpatient period. The unpleasant feelings of these children inspired Renee's team to look for an alternative method for these kids. They pioneered to tailor-made nasal strip using special absorbent material for the collection of nasal epithelial lining fluid (NELF) from children. The length of nasal strips is much shorter (2-3cm long) than that of the nasopharyngeal swab and can be customised in different sizes to fit subjects at different ages to detect viruses. It can be self-administered by the users even at their school-age (Demostration available at https://youtu.be/R5L0eLeprwA). Another key benefit is that specimens collected by the nasal strip are stable at room temperature for at least 72 hours. This stability of nasal strip samples at room temperature potentially allows the specimens to be posted to the laboratory which usually takes at least a day. These findings have been published in the *Journal of Infection*. With this niche, mucosal samples can be collected in a longitudinal manner unprecedentedly. It also ensures the low dropout rate throughout our prospective studies, as the biological sample can be collected by themselves and mailed to the laboratory directly.

Mucosal antibody induced by SARS-CoV-2 infection

The nasal strip sample is exciting because it also allows the measurements of the mucosal antibody, microbiota and host mediators in a standardised fashion. The team expanded the use of the NELF samples to monitor and elucidate the important role of SARS-CoV-2 specific nasal immunoglobulin A (IgA) between asymptomatic and symptomatic paediatric patients (n=34) and adult patients (n=47) of different severities at different timepoints of the disease course for six months. They reported that children had higher nasal antibodies and lower viral loads early after diagnosis compared to adults with a mild infection. The early occurrence of the IgA on the mucosal surface would relate to the decline in viral load. Their mucosal immunity study is scant in the field and unique in Hong Kong. The mucosal immunity is remarkably important as it is directly guarding the site of infection, however, available research was overwhelmed with the serological readouts. These findings have been uploaded to the preprint server *medRxiv.*

Mucosal antibody induced by SARS-CoV-2 vaccine

Renee's team also evaluated the mucosal and serological antibody induction by the two SARS-CoV-2 vaccines in 88 adults in Hong Kong for three months. The team found that Comirnaty (mRNA vaccine) induces S1-specific IgA and IgG responses with neutralising activity in the nasal mucosa while a similar response is not seen with CoronaVac (inactivated vaccine) which may provide additional protection. However, whether such widespread immunological response by Comirnaty may produce inadvertent adverse effects in other tissues warrants further investigation. These findings have been published in the *Frontiers in Immunology*.

This study opens up a new arm of research in studying respiratory diseases related to acute and chronic local inflammations, such as neonatal sepsis, obstructive sleep apnoea and rhinitis within the Department.

Research and Scholarship

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Shaojun Liu	Nature Review Immunology Poster Prize at 15th World Immune Regulation Meeting	Swiss Institute of Allergy and Asthma Research

Academic Editorship

Member's Name	Details	
	Role	Journal
Renee Chan	Associate Editor	Frontiers in Medicine: Infectious Diseases - Surveillance, Prevention and Treatment
	Review Editor	Frontiers for Young Minds – Human Health
	Academic Editor	PLoS One
	Editorial Board Member	Journal of Virological Methods

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Renee Chan	Reviewer	The Lancet Child & Adolescent Health
		JAMA Paediatrics
		Emerging Microbes & Infections
		Stem Cell Research & Therapy
		Frontiers in Medicine
		Frontiers for Young Minds
		Journal of Pediatric Infectious Diseases
		Respiratory Research
		PLoS One
	Abstract Rating Reviewer	Joint annual Scientific Meeting 2021 - The Hong Kong Paediatric Society, Hong Kong College of Paediatricians, Hong Kong Paediatric Nurses Association and Hong Kong College of Paediatric Nursing
		ATS 2021 - Assembly on Allergy, Immunology, and Inflammation

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Renee Chan	Nasal Epithelial Lining Fluid - A Single Specimen for the Detection of SARS-CoV-2 Antigen and SARS-CoV-2 Specific Antibody	The Chinese University of Hong Kong Research Committee – Direct Grant	08/06/2021	07/06/2022	32,000

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Renee Chan	SARS-CoV-2 Receptor Distribution, Replication and Immune Response Induced in the Respiratory Epithelial Cells of Paediatric and Adult and the Existence of Alternative Receptor	Food and Health Bureau – Commissioned Research on the Novel Coronavirus Disease (COVID-19)	01/05/2020	30/04/2022	1,810,820
	A Mechanistic Investigation of the Inhibition of Apoptotic Pathways by Rhinovirus C in Asthmatic Nasopharyngeal Epithelial Cells	The Chinese University of Hong Kong Research Committee – Direct Grant	30/06/2020	29/06/2021	62,000
	Development of a Rapid Test for SARS-CoV-2 Mucosal Antigen and Antibody	Innovation and Technology Commission – Partnership Research Programme	01/11/2021	30/04/2023	1,760,000
	The Establishment of Non-invasive Nasal Epithelial Lining Fluid Collection Method for the Detection of Localized IgA and Mucosal Immune Response	Hong Kong Institute of Allergy Research Grant	01/09/2020	31/08/2021	90,000
	Functional Grouping of Rhinovirus by its Association with Clinical Outcomes for Better Disease Management and Therapeutic Development	Research Grants Council – General Research Fund	01/02/2020	31/12/2022	874,450
	Role of the Heme Oxygenase-1/Carbon Monoxide Axis in the Regulation of Ion Transport and Pro-inflammatory Cytokine Secretion in Airway Epithelia: *in Vitro* and *in Vivo* Studies	Research Grants Council – General Research Fund	01/01/2021	31/12/2023	996,285
	A Study to Assess the Efficacy of Plasma and Urine Biomarkers for Early Detection of Necrotizing Enterocolitis	The Chinese University of Hong Kong Research Committee – Direct Grant	15/06/2021	14/06/2022	149,700
	The Safety of High Flow Nasal Cannula and Noninvasive Ventilation for Treatment of Patients with COVID-19 Complicated by Respiratory Failure	Food and Health Bureau – Commissioned Research on the Novel Coronavirus Disease (COVID-19)	01/05/2020	31/10/2021	767,623
Renee Chan	Optimization of Clinical Treatment of Severe Influenza to Reduce Morbidity and Mortality	Food and Health Bureau – Commissioned Programme for Influenza Research	01/09/2019	31/08/2022	4,996,960

Publications

A. Journal Papers

1. Cao L, Zhao S, Lou J, Zheng H, Chan RWY, Chong MKC, Chen Z, Chan PKS, Zee BCY, Wang MH. Differential influence of age on the relationship between genetic mismatch and A(H1N1) pdm09 vaccine effectiveness. *Viruses-Basel*. 2021;13(4):619. doi:10.3390/V13040619.

2. Chan RWY, Chan KCC, Lui GCY, Tsun JGS, Chan KYY, Yip JSK, Liu S, Yu MWL, Ng RWY, Chong KKL, Wang MH, Chan PKS, Li AM, Lam HS. Mucosal antibody response to SARS-CoV-2 in paediatric and adult patients: A longitudinal study. *medRxiv*. Published online September 29, 2021. doi:10.1101/2021.09.27.21264219.

3. Chan RWY, Liu S, Cheung JY, Tsun JGS, Chan KC, Chan KYY, Fung GPG, Li AM, Lam HS. The mucosal and serological immune responses to the novel coronavirus (SARS-CoV-2) vaccines. *Frontiers in Immunology*. 2021;12. doi:10.3389/fimmu.2021.744887.

4. Leung KKY, Hon KL, Ip P, Chan RWY. Critically ill children in paediatric intensive care unit are no less susceptible to infectious diseases amid the COVID-19 pandemic. *Hong Kong Medical Journal*. 2021;27(6):461-463. doi:10.12809/hkmj209029. (Commentary)

5. Qu F, Zhao S, Cheng G, Rahman H, Xiao Q, Chan RWY, Ho YP. Double emulsion-pretreated microwell culture for the in vitro production of multicellular spheroids and their in situ analysis. *Microsystems & Nanoengineering*. 2021;7(1):1-12. doi:10.1038/s41378-021-00267-w.

6. Tao KP, Chong M, Pun JC, Tsun JG, Chow SM, Ng CS, Wang MH, Chan Z, Chan PK, Li AM, Chan RW. Suppression of influenza virus infection by rhinovirus interference at the population, individual and cellular levels. *medRxiv*. Published online August 10, 2021. doi:10.1101/2021.08.09.21256656.

7. Zhao S, Lou J, Cao L, Zheng H, Chen Z, Chan RWY, Zee BCY, Chan PKS, Chong MKC, Wang MH. An early assessment of a case fatality risk associated with P.1 SARS-CoV-2 lineage in Brazil: An ecological study. *Journal of Travel Medicine*. 2021;28(7). doi:10.1093/jtm/taab078. (Editorial)

8. Zhao S, Lou J, Cao L, Zheng H, Chong MKC, Chen Z, Chan RWY, Zee BCY, Chan PKS, Wang MH. Real-time quantification of the transmission advantage associated with a single mutation in pathogen genomes: A case study on the D614G substitution of SARS-CoV-2. *BMC Infectious Diseases*. 2021;21(1):1-8. doi:10.1186/S12879-021-06729-w.

9. Zhao S, Lou J, Chong MKC, Cao L, Zheng H, Chen Z, Chan RWY, Zee BCY, Chan PKS, Wang MH. Inferring the association between the risk of COVID-19 case fatality and N501Y substitution in SARS-CoV-2. *Viruses-Basel*. 2021;13(4):638. doi:10.3390/v13040638.

B. Conference Papers

1. Chan RWY, Tao KP, Tsun JGS, Hui KPY, Wong GWK, Chan MCW, Hui DSC, Chan PKS, Chan KCC, Lam HS, Li AM. SARS-CoV-2 replication and immune response induced in the respiratory epithelial cells of paediatic and adult subjects. In: *Health Research Symposium 2021*. Hong Kong. 2021 November 23.

2. Chan RWY, Liu SJ, Cheung JY, Tsun JGS, Chan KC, Chan KYY, Fund GPG, Li AM, Lam HS. Study on the mucosal and serological immune response to the noel coronavirus (SARS-CoV-2) Vaccines. In: *Joint Annual Scientific Meeting 2021 (Hybrid meeting) The Hong Kong Paediatric Society, Hong Kong College of Paediatricians, Hong Kong Paediatric nurses Association & Hong Kong College of Paediatric Nursing*. Hong Kong. 2021 October 30.

3. Wong BKS, Tsun JGS, Chan LLY, Tao KP, Long X, Chow SMW, Ng CSH, Lau RWH, Leung TF, Li AM, Chan RWY. Innate immune response of human influenza A virus and Rhinovirus A16 in patients' nasopharnygeal aspirates and human airway models. In: *Joint Annual Scientific Meeting 2021 (Hybrid meeitng) The Hong Kong Paediatric Society, Hong Kong College of Paediatricians, Hong Kong Paediatric nurses Association & Hong Kong College of Paediatric Nursing*. Hong Kong. 2021 October 30.

4. Islam MA, Tsun JGS, Tao KP, Yu JW, Wong BKS, Wai CY, Chan RWY. Rhinovirus-C replication kinetics in neonatal mice lung explant. In: *European Academy of Allergy and Clinical Immunology Hybrid Congress 2021*. Kraków, Poland. 2021 July 10-12.

5. Chan RWY, Chan KCC, Lui GCY, Tsun JGS, Chan KYY, Yip JSK, Liu SJ, Ng RWY, Chong KKL, Chan PKS, Li AM, Lam HS. Mucosal antibody response to SARS-CoV-2 in paediatric and adult patients: A longitudinal study from active infection to convalescent phase. In: *World immune Regulation Meeting XV: Immune Activation, Effector Functions and Immune Tolerance*. Virtual. 2021 June 30 - July 3.

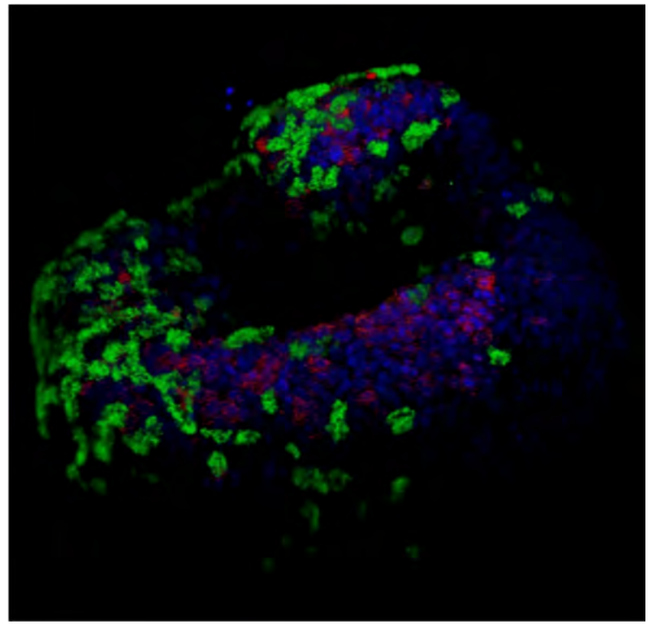
6. Tsun JGS, Liu S, Lui GCY, Chan KCC, Chan KYY, Ng RWY, Chan PKS, Li AM, Lam S, Chan RWY. The dual-use of nasal strip in the surveillance of active and convalescent SARS-CoV-2 cases. In: *European Respiratory Society International Congress 2021*; 2021 September 5-8. doi:10.1183/13993003.congress-2021.pa3484



Renee Chan and her team have introduced a nasal strip test as a sensitive and accurate method to detect SARS-CoV-2 and the mucosal antibody against the virus. It could be a superior tool for community based surveillance test since it is a simple, less irritative and low risk method which is easy to administer in subjects of a wide age range.

From left: Renee Chan, Assistant Professor; Simon Lam, Professor; Albert Li, Chairman; and Kate Chan, Assistant Professor, of the Department of Paediatrics at CU Medicine.

Source: Renee Chan



Human bronchial organoid at its apical out orientation. It recapitulates the cell population of human bronchial epithelium and is utilized for drug screening. This image shows one organoid with its ciliated cells stained in green, basal cells strained in red and the nucleus in blue.

Source: Renee Chan



張栢恒

PETER CHEUNG

03 EMERGING INFECTIOUS DISEASES AND MICROBIOTA



Principal Investigator

Peter Cheung

Team members

Wing Ying Au, Xinzhou Xu

Research Progress Summary

RNA Virus as Public Health Concern

RNA viruses are a major player in zoonotic disease transmission with severe public health consequences (Binder et al. *Science.* 1999; 284; 1311-1313). Zoonotic transmission resulting from the increasing human interaction with wild environments has led to a number of pandemics originated from wildlife reservoirs, as was seen with the emergence of the H1N1 and the highly pathogenic H5N1 Influenza A Virus (IAV), the Severe Acute Respiratory Syndrome Coronavirus (SARS) in 2003 and 2019, Bunyaviruses, Enterovirus 71 (EV71), Dengue, Japanese Encephalitis Virus, Hepatitis C Virus. Modern medicine has struggled to overcome and predict their biological variety and high adaptation rates that allow them to adapt to new host species and antiviral therapeutics. The replication of the viral genetic material by almost all RNA viruses is error prone. This trait is advantageous to the virus, ensuring sustained adaptivity to the host (Boivin et al. *Journal of Biological Chemistry*. 2010; 285: 28411-28417; Domingo et al. *Microbiology and Molecular Biology Reviews*. 2012; 76: 159-216) and the environments, and Peter Cheung has shown it to be critical for host transmission (Luk et al. *Journal of Virology*. 2015; 89: 9939-9951) and pathogenesis (Cheung et al. *Nature Communications*. 2014; 5: 4794). Thus, it is of paramount importance to understand the vital processes that govern viral replication and adaptation to human population.

Viral Polymerase as Engine for Replication

The RNA-dependent RNA polymerase (RdRP) is the central machinery for viruses' transcription and genome replication processes. RdRP lacks proofreading (except coronavirus), thus relying on viral RdRP for maintaining genome integrity. RdRP synthesizes long nucleotide acid chains via template-directed biosynthesis using nucleotide triphosphates (NTPs) as substrates (Fig. 1A).

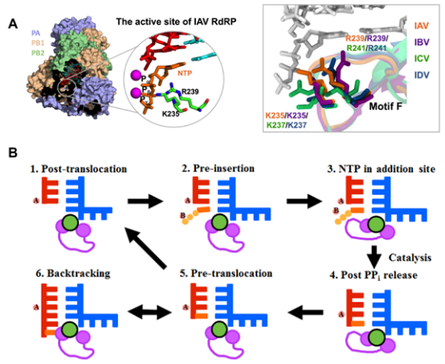
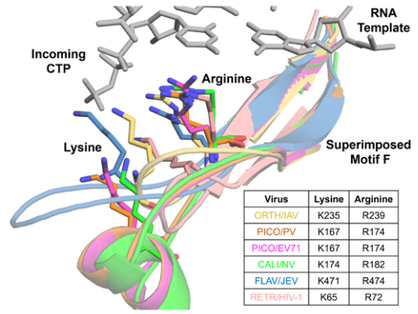


Fig. 1. Viral RdRP cycles through different functional states for nucleotide addition. (A) Left: The cryo-EM structure of IAV elongation complex comprised of PA, PB1 and PB2 domains. Right: The active site with NTP bound and conserved motifs. (B) The five functional states and the conformational transitions in the nucleotide addition cycle (NAC).

The catalytic process of RdRP is mainly composed of two stages: initiation and elongation. The initiation stage is unstable, and requires the precise control at the synthesis initiation site, at which point the incorporation of several nucleotides allow conversion to a stable elongation stage. The elongation stage consists of thousands of cycles of nucleotide additions (NAC). For each NAC, RdRP undergoes multiple functional states with conformational changes (Fig. 1B). NAC consists of four steps: NTP binding, closing of active site, phosphoryl transfer, and translocation.

RdRP catalytic core contains the pre-A (also known as F) and A-E motifs. Structure-based alignment with RNA- and DNA-dependent RNA polymerases, including viruses from Picornaviridae, Flaviviridae, Caliciviridae, and Retroviridae families shows a well-conserved configuration in Motif F (Fig. 2), which has been speculated and showed by us (Xu et al. *Nucleic Acids Research.* 2021; 49: 8796-8810) and others to play essential roles in controlling the rate and fidelity of viral transcription (Yin and Steitz. *Cell*. 2004; 116: 393-404).



Virus	Lysine	Arginine
ORTH/IAV	K235	R239
PICO/PV	K167	R174
PICO/EV71	K167	R174
CALI/NV	K174	R182
FLAV/JEV	K471	R474
RETR/HIV-1	K65	R72

Fig. 2. Structural alignment of RdRp active sites of *Picornaviridae/Poliovirus* (PICO/PV PDB: 3OLA), Enterovirus 71 (EV71 PDB: 5F8I), *Caliciviridae*/ Norwalk Virus (CALI/ NV PDB: 3BSO), *Flaviviridae*/ JEV (FLAV/ JEV PDB: 4MTP), and *Retroviridae*/ HIV-1 (RETR/HIV-1 PDB: 4MTP)z aligned to IAV RdRP complex (PDB: 6SZV). Critical K and R residues on Motif F are coloured. Grey atoms are incoming CTP pairing with the template.

Viral Polymerase as Driver for Diversity

Proper NTP substrates readily cause active site closure for NTP incorporation, whereas incorrect substrates would lead to instability (Gong and Peersen. *Proceedings of the National Academy of Sciences USA.* 2010; 107: 22505-22510; Shi et al. *Nucleic Acids Research*. 2020; 48: 1392-1405; Wang et al. *Nature Communications*. 2020; 11: 2605). Thus, polymerase sites, regions, or interactions that coordinate NTP and subsequently affect impact active site closure may affect fidelity. The choice of the correct NTP matched with the template nucleoside is critical for preserving the fidelity of the synthesis. However, low-level mismatch occurrences in replication might enable RNA viruses to deal with selection pressure during adaptation or co-evolution with their hosts (Crotty et al. *Nature Medicine*. 2000; 6: 1375-1379).

Previous Work Done in Polymerase NAC and Fidelity

Due to its vital role for viral replication, RdRP is an essential target for antiviral therapy. Peter and his team have spent over a decade to study polymerase NAC and reveal the structural basis of how polymerases maintain replicational fidelity by developing and employing state-of-the-art enzymology assays to quantify RdRP replication and cleavage activities of eukaryotes and vial polymerases (Tse et al. *Nature Catalysis*. 2019; 2: 228-235; Wang et al. *Biophysical Chemistry*. 2021; 277: 106652; Xu et al. *Nucleic Acids Research.* 2021; 49: 8796-8810; Zhang et al. *Accounts of Chemical Research*. 2016; 49: 687-694).

At the virus level, their work has revealed how RNA viruses adapt to the host environment to cause disease (Cheung et al. *Nature Communications*. 2014; 5: 4794), provided novel targets for antiviral therapies, and revealed RdRP mutations conferring drug resistance to NTP analogues (Choy et al. *Antiviral Research*. 2020; 178: 104786; Wang et al. *Biophysical Chemistry*. 2021; 277: 106652). At the structural level, their work (Xu et al. *Nucleic Acids Research.* 2021; 49: 8796-8810) using Molecular Dynamics (MD) simulations and enzymology identified critical fidelity control mechanisms, which lies in the catalytic core or active site of RdRP incorporating to the newly synthesised RNA (Xu et al. *Nucleic Acids Research.* 2021; 49: 8796-8810). Peter employed a mechanism-insight driven approach by developing a novel enzymology assay tightly integrated with MD simulation of the RdRP structure to identify a mutation K235R in the catalytic core of the RdRP within Motif F that confer both increased polymerase activity and enhanced fidelity (Fig. 2), the first such RdRP ever discovered.

Previous Work Done in Elucidating the Inhibition Mechanism of NuA to Viral RdRps

Peter and his team have profound experiences in NuA's inhibition of IAV and SARS-CoV-2 RdRps. For example, they discovered how ribavirin inhibits IAV viral replication by mutagenesis (Cheung et al. *Nature Communications*. 2014; 5: 4794). They discovered the first Ribavirin-resistant IAV virus with enhanced transcriptional fidelity (Cheung et al. *Nature Communications*. 2014; 5: 4794). Using this tightly coupled platform, they elucidated the mechanisms by which NTP analogue (NuA) Favipiravir terminates RNA synthesis by RdRP and induces mutation once the NTP analogue is incorporated into the newly synthesised strand (Wang et al. *Biophysical Chemistry*. 2021; 277:106652). They are amongst the first to demonstrate that the NTP analogue Remdesivir suppresses live SARS-CoV-2 replication (Choy et al. *Antiviral Research*. 2020; 178: 104786). Then, they elucidated structurally how Remdesivir inhibits transcription by delayed chain termination by inhibiting RdRp NSP12 translocation and cleavage by exoribonuclease NSP14 (Zhang et al. *Physical Chemistry Chemical Physics*. 2021; 23: 5852-5863). These findings lay a solid foundation for us to investigate how NuA interferes with the kinetics of IAV RdRp.

Diagnostics for SARS-CoV-2

Improved diagnostics are needed to manage the ongoing COVID-19 pandemic. Recently, the research team enhanced the color changes and sensitivity of colorimetric SARS-CoV-2 RT-LAMP assays based on triarylmethane dyes. They determined a mechanism for the color changes and obtained sensitivities of 10 RNA copies per microliter (Suarez et al. *Analytical Method.* 2022; 14; 378-382). They performed meta-analysis to comprehensively analyse three standard nucleic acid assays, namely digital PCR (dPCR), quantitative PCR (qPCR), and LAMP. They demonstrated interestingly that all three tests consistently perform better with pharyngeal swabs utilising SARS-CoV-2 open reading frame 1ab primer with RNA extraction. dPCR was demonstrated to be the most sensitive, followed by qPCR and LAMP. However, their accuracy does not vary considerably. Instead, accuracy relies on experimental settings, meaning that additional efforts should be dedicated to optimising the experimental setups for the nucleic acid assays. Hence, the findings of Peter's team might be a reference for improving and creating a standard nucleic acid test technique that is applicable in laboratories worldwide (Au and Cheung, *Lancet Microbe*. 2021; 2: E704-E714).

Research and Scholarship

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Peter Cheung	Reviewer	Microbiology Spectrum
		Emerging Infectious Diseases
		Biochemical Engineering Journal

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Peter Cheung	Establishment of a Parallel Platform for the Mechanistic Studies of Function and Inhibition of Influenza Polymerase	Research Grants Council – General Research Fund	15/07/2018	14/07/2021	505,298
	Establishment of Highly Accurate Nuclear Run-on RNA Sequencing Platforms to Study the Genome-wide Mechanisms of Transcription and Mutation by Influenza Polymerase	Research Grants Council – General Research Fund	01/07/2019	30/06/2022	558,272

Publications

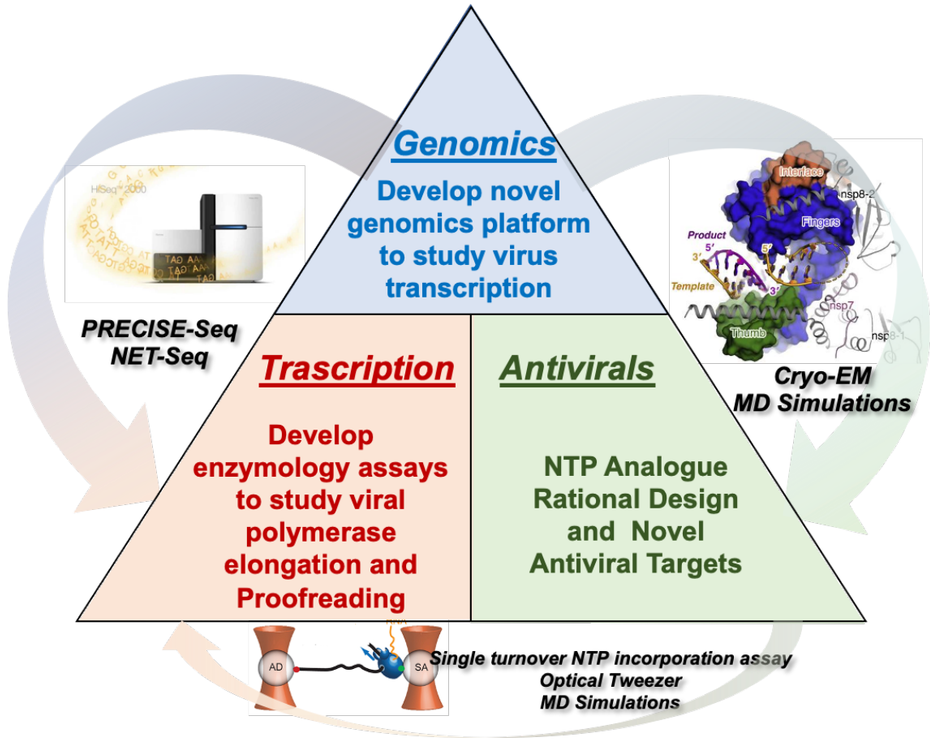
A. Journal Papers

1. Suarez GD, Suarez DA, Kiu Tang YY, Zhang J-X, Li J, Nagl S, Cheung PP-H. Uncovering mechanisms of RT-LAMP colorimetric SARS-CoV-2 detection to improve assay reliability. *Analytical Methods*. doi:10.1039/d1ay01395e. (Epub ahead of print)

2. Au WY, Cheung PPH. Diagnostic performances of common nucleic acid tests for SARS-CoV-2 in hospitals and clinics: A systematic review and meta-analysis. *The Lancet Microbe*. 2021;2(12):e704-e714. doi:10.1016/s2666-5247(21)00214-7. (Review) (Epub ahead of print)

3. Xu X, Zhang L, Tung Sem Chu J, Wang Y, Wing Hong Chin A, Hang Chong T, Dai Z, Lit Man Poon L, Pak-Hang Cheung P, Huang X. A novel mechanism of enhanced transcription activity and fidelity for influenza A viral RNA-dependent RNA polymerase. *Nucleic Acids Research*. 2021;49(15):8796-8810. doi:10.1093/nar/gkab660.

4. Wang Y, Yuan C, Xu X, Chong TH, Zhang L, Cheung PPH, Huang X. The mechanism of action of T-705 as a unique delayed chain terminator on influenza viral polymerase transcription. *Biophysical Chemistry*. 2021;277(April):106652. doi:10.1016/j.bpc.2021.106652. (Epub ahead of print)



To better understand the structural mechanisms underlying the highly complex processes of SARS-CoV-2 gene expression and replication, genomic data must be linked to polymerase structure. Peter Cheung and his team propose to bridge this genomics-structural divide by utilizing their highly interdisciplinary expertise in genomics, bioinformatics, cryo-EM, computational biology, chemical synthesis, enzymology, and virology.

Source: Peter Cheung



04 ASIAN CANCERS

Cancer Epigenetics



Principal Investigator

Qian Tao

Team members

Lili Li, Lijun Peng, Jianlian Xie, Chu Wu, Xiaoxue Chai, Jun Zhou, Andrew Chen, Johnson Liu

Research Progress Summary

Qian Tao and his research team work on the epigenomic alterations of cancers and identify novel TSGs epigenetically inactivated. The team studies the epigenetic disruption of cell signalling regulation *via* silencing signalling TSGs by promoter CpG methylation in tumourigenesis. One important aspect is Epstein-Bar virus (EBV)-induced aberrant epigenetic programming in EBV-associated tumours including NPC. Despite the findings from extensive whole-genome sequencing studies, CpG methylation-related gene silencing remains the most common genetic alteration detected in NPC, while epigenomic studies have led to the identification of a series of cancer genes frequently methylated in NPC. These genes include regulators of cell signalling and epigenetic modifiers, supporting that viral-induced epigenetic abnormalities have a key role in NPC pathogenesis.

The team previously identified a novel epigenetically disrupted gene *ZDHHC1* functioning as a tumour suppressor in multiple malignancies. They further found that *ZDHHC1* protein is an S-palmitoyltransferase and p53 as a substrate for *ZDHHC1*-mediated palmitoylation. This novel form of posttranslational modification of p53 is required for its nuclear translocation. Thus, the epigenetic feedback loop formed by *ZDHHC1* and p53 sheds light on the inactivation of p53 without genetic mutations. In another study, they identified *ZBTB28* as a tumour suppressor gene by inducing autophagy-related apoptosis in cervical cancer. *ZBTB28* promoter methylation could be a biomarker for cervical cancer screening. Meanwhile, the team also identified the epigenetic disruption of TSG promoter methylation as potential epigenetic biomarkers for cancer diagnosis, including TET1 methylation which got a US patent recently.

Research and Scholarship

Academic Editorship

Member's Name	Details	
	Role	Journal
Qian Tao	Vice-President	The Epigenetics Society
	Editorial Board Member	Clinical Epigenetics
		Epigenomes
		PLoS One
		Cancer Communications
		Epigenetic Diagnosis & Therapy
		Microorganisms
		Journal of Clinical Epigenetics
	Panel member and Reviewer	China State Natural Science Award (Ministry of Science and Technology)
		National Natural Science Foundation of China
	Reviewer	Worldwide Cancer Research, USA (American Institute for Cancer Research)
		Singapore Academic Research Council, Ministry of Education, Singapore
		Foundation for Polish Science, Poland
		Multi-Year Research Grant, University of Macau, Macau
		Health and Medical Research Fund, Food and Health Bureau, Hong Kong
		Children's Cancer and Leukaemia Group, UK
		Tencent XPLORER Prize
		Guangdong Science and Technology Department
		Faculty Promotion Committee of Cancer Hospital/ State Key Laboratory of Oncology in South China, Sun Yat-sen University, Guangdong, China
	Advisor Committee	Science and Technology Advisor Committee for Shenzhen
		Basic Research in Shenzhen
	Academic Advisor	State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Hospital, Guangdong, China
		Key Laboratory of Biotherapy of Zhejiang Province, Zhejiang University, China
		Key Laboratory of Ministry of Education, Cancer Research Institute, Central South University, Hunan, China
Qian Tao	Overseas Board Member	Oncology Section/China Association of Pathophysiology
	Visiting Chair Professor	National Research Center for Urologic Oncology of China/Beijing, Peking University 1st Hospital & Institute of Urology, Beijing, China
		State Key Laboratory of Oncology in South China, The Cancer Institute, Sun Yat-sen University and SYSU Affiliated Zhongshan Hospital, Guangdong, China
		Hunan Yale (XiangYa) School of Medicine, Central South University, Changsha, China

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Qian Tao	Reviewer	Nature Communications
		Blood
		Cancer Research
		Lancet
		Cell Death & Differentiation
		The Journal of Pathology
		Oncogene
		Nucleic Acids Research
		Epigenetics
		Clinical Epigenetics
		Advanced Science
	Organising Committee	6th Conference of Epigenetics and Biomedicine, Shenzhen, China

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Qian Tao	Regulation of Tumor Cell Invasion/ Metastasis and EMT/ Stemness by a New Ras Antagonist which is Silenced by CpG Methylation in Esophageal Cancer	Research Grants Council – General Research Fund	01/01/2019	30/06/2021	929,280
	Mechanism of Inflammasome Activation by SARS-CoV-2	Research Grants Council – Collaborative Research Fund	01/06/2021	31/05/2024	8,431,247

Publications

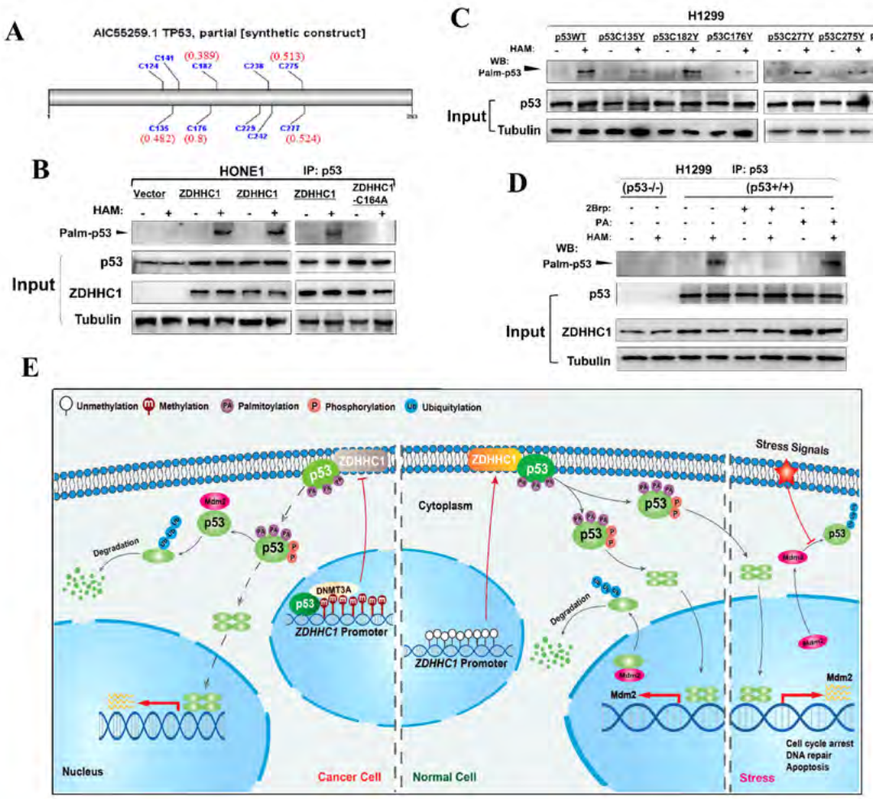
A. Journal Papers

1. Tang J, Peng W, Feng Y, Le X, Wang K, Xiang Q, Li L, Wang Y, Xu C, Mu J, Xu K, Ji P, Tao Q, Huang A, Deng CX, Lin Y, Xiang T. Cancer cells escape p53's tumor suppression through ablation of ZDHHC1-mediated p53 palmitoylation. *Oncogene*. 2021;40(35):5416-5426. doi:10.1038/s41388-021-01949-5.

2. Li L, Gong Y, Xu K, Chen W, Xia J, Cheng Z, Li L, Yu R, Mu J, Le X, Xiang Q, Peng W, Tang J, Xiang T. ZBTB28 induces autophagy by regulation of FIP200 and Bcl-XL facilitating cervical cancer cell apoptosis. *Journal of Experimental and Clinical Cancer Research*. 2021;40(1). doi:10.1186/s13046-021-01948-0.

B. Patents

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



The epigenetic regulatory loop formed by ZDHHC1, p53, and DNMT3A.

Source: Qian Tao





姚曉強

XIAOQIANG YAO

05

CARDIOVASCULAR MEDICINE

Vascular Medicine - Basic Research



Principal Investigator

Xiaoqiang Yao

Team members

Mingxu Xie, Yunting Zhang, Jingxuan Li, Xiao Li, Jun Zhang, Zhenchuan Lei, Wentao Peng

Research Progress Summary

Research group led by Xiaoqiang Yao has been working on Ca^{2+}-permeable ion channels and endoplasmic reticulum stress-related proteins in cardiovascular system and cancer. Recently, the novel function of Orai1 channels in cardiac hypertrophy and role of TRPM2 channels in atherosclerotic progress have been uncovered. The strategy of active immunisation with TRPM2 peptide in vaccine platform for potential treatment of atherosclerosis was being developed currently. In addition, the novel functional role of TRPML2 channels in prostate cancer progression was identified and the research is supported by Hong Kong RGC Area of Excellence Grant, General Research Fund and Health and Medical Research Fund.



Research and Scholarship

Academic Editorship

Member's Name	Details	
	Role	Organisation
Xiaoqiang Yao	Associate Editor	Frontiers in Pharmacology
		Scientific Reports
	Guest Editor	Cells

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Xiaoqiang Yao	Reviewer	Circulation Research
		Cell Reports
		Cardiovascular Research
		British Journal of Pharmacology
		Laboratory Investigation

Grants and Consultancy

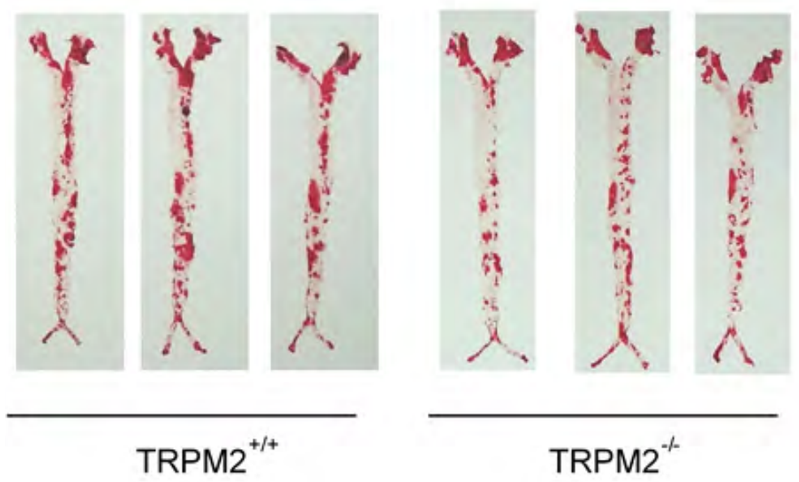
Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Xiaoqiang Yao	Role of TRPC5 in Endothelium-dependent Contraction in Hypertensive Model of Mice	Research Grants Council – General Research Fund	01/01/2020	31/12/2022	1,042,225
	Plant Bioreactor for Pharmaceutical Proteins	Research Grants Council – Research Impact Fund	01/06/2019	31/05/2024	5,000,000
	Targeting TRPM2 as A Potential Therapeutic Strategy for Spontaneous Atherosclerosis	Food and Health Bureau – Health and Medical Research Fund	01/09/2019	31/08/2022	1,181,050
	Centre for Organelle Biogenesis and Function	Research Grants Council – Areas of Excellence Scheme	01/01/2014	31/12/2021	47,250,000

Publications

A. Journal Papers

1. Yu H, Xie M, Meng Z, Lo CY, Chan FL, Jiang L, Meng X, Yao X. Endolysosomal ion channel MCOLN2 (Mucolipin-2) promotes prostate cancer progression via IL-1β/NF-κB pathway. *British Journal of Cancer*. 2021;125(10):1420-1431. doi:10.1038/s41416-021-01537-0.

2. Yu L, Xie M, Zhang F, Wan C, Yao X. TM9SF4 is a novel regulator in lineage commitment of bone marrow mesenchymal stem cells to either osteoblasts or adipocytes. *Stem Cell Research and Therapy*. 2021;12(1):1-16. doi:10.1186/s13287-021-02636-8.



A Schematic Figure showing that TRPM2 knockout significantly slows down the atherosclerotic progression as indicated by en face Oil Red O staining of atherosclerotic plaques in mouse aorta.

Source: Xiaoqiang Yao



05 CARDIOVASCULAR MEDICINE

Heart Diseases - Cardiac Imaging and Intervention



Principal Investigator

Alex Lee

Team members

Randolph Wong, Yiting Fan, Kevin Kam, Kent So, Xueting Wang, Kandy Li, Sophia Yip, Judy Yiu, Ada Yu, Josie Chow, Margaret Lee

Research Progress Summary

The team led by Alex Lee has published a study on adult onset cardiac variant Fabry disease, for the first time in Hong Kong. They identified a high prevalence of undiagnosed Fabry disease among Chinese patients with left ventricular hypertrophy. In the area of structural and valvular heart disease, they published a research article on novel mechanism of functional mitral regurgitation in JACC Asia; they developed a new automated software for 3D analysis of the left atrial appendage for device closure in collaboration with School of Technology, IPCA, Barcelos, Portugal and published their result in the Journal of *American Society of Echocardiography*. Using artificial intelligence, they developed in collaboration with the School of Biomedical Engineering, Sun Yat-sen University, Guangzhou, People's Republic of China, a deep learning-based automated left ventricular ejection fraction assessment using 2-D echocardiography, and published their results in American Journal of Physiology. Additionally, they published an original article on *The Annals of Thoracic Surgery* on the prevalence of thoracic aortic aneurysm in hypertensive patients detected using point-of-care ultrasound device.

The team has successfully organised the "Echo guidance for screening and interventions in Structural Heart Diseases" online training in March, May and October 2021, with excellent feedback from the 49 attendees from Asia-pacific region. "Echocardiography in Heart Failure: Beyond Diagnosis Live Webinar" was held in November 2021 and attracted over 360 international attendees from around the globe.

"CUHK POCUS for Heart Failure Introductory Preceptorship Program" was held in April to September 2021 for 29 doctors in Hong Kong to provide training on POCUS image acquisition and interpretation and the use of POCUS in clinical decisions for management of heart failure. The team also held "CUHK Transthoracic Echo Course for Anesthesiologists" to develop trainer competence in comprehensive echocardiographic examination for 24 Hong Kong doctors.

Research and Scholarship

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Alex Lee	Expertise in Three-Dimensional Echocardiography	Expertscape

Academic Editorship

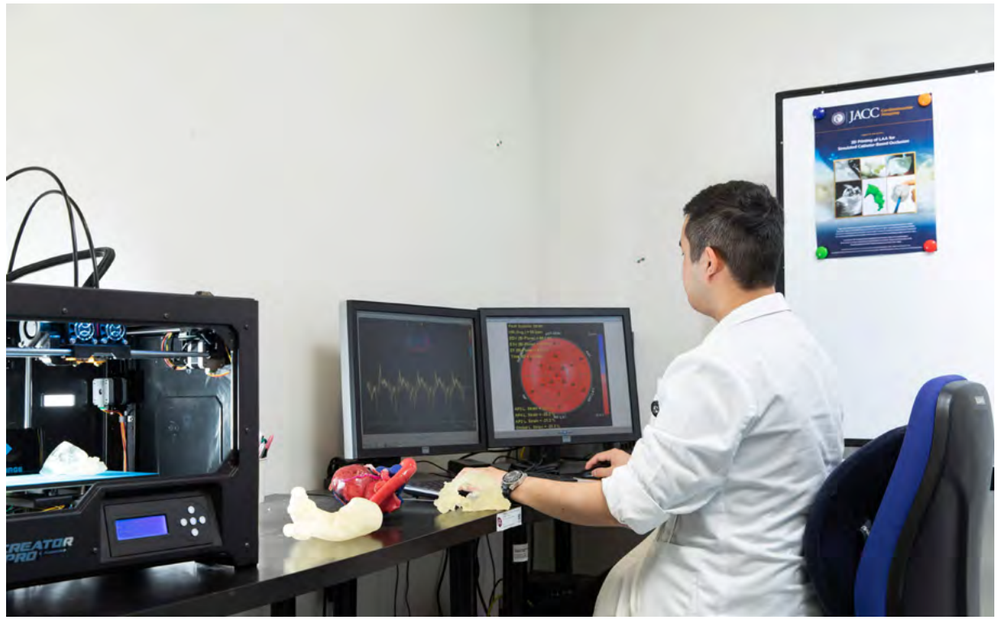
Member's Name	Details	
	Role	Journal
Alex Lee	JAPSC Editorial Board Member	Journal of Asian Pacific Society of Cardiology
	Section Editor	JACC: Asia
	Associate Editor	Frontiers in Cardiovascular Medicine

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Alex Lee	Reviewer	JASE
		Circulation Cardiovascular Imaging
		JACC: Asia
	Abstract grader	EuroEcho 2021 Congress

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Alex Lee	3D Echo Biobank for Atrioventricular Valve Regurgitation and Transcatheter Repair	Abbott Medical (Hong Kong) Ltd	01/09/2021	31/08/2023	900,000
	3D Printing Technology for Planning Left Atrial Appendage Occlusion: A Randomised Trial	Food and Health Bureau – Health and Medical Research Fund	01/05/2018	30/04/2021	1,191,977
	A Multinational, Multicenter Study to Assess the Effects of Oral Sildenafil on Mortality in Adults with Pulmonary Arterial Hypertension	Pfizer Corporation Hong Kong Limited	25/10/2018	31/08/2023	2,399,028
	Speeding up Examination of Heart Diseases through the Use of 3D Echocardiography and Machine Learning	Innovation & Technology Commission – Midstream Research Programme for Universities	01/04/2021	31/03/2023	1,251,200
	Automatic Retinal Image Analysis (ARIA) to Predict Coronary Artery Disease in HIV-infected Individuals	Centre for Health Protection AIDS Trust Fund	04/2019	03/2021	560,462
	Non-interventional Study on Edoxaban Treatment in Routine Clinical Practice for Patients with Non Valvular Atrial Fibrillation (ETNA-AF-Hong Kong)	Daiichi Sankyo Hong Kong Ltd	29/09/2017	30/09/2021	176,772.5



Publications

A. Journal Papers

1. Fan Y, Kam K, So K, Lam YY, Lee APW. Imaging for transcatheter edge-to-edge repair for tricuspid regurgitation in ebstein anomaly. *Circulation: Cardiovascular Imaging*. 2021;14(11):e013327. doi:10.1161/circimaging.121.013327. (Editorial, Epub ahead of print)

2. Chan JSK, Lau DHH, Fan Y, Lee APW. Age-related changes in left ventricular vortex formation and flow energetics. *Journal of Clinical Medicine*. 2021;10(16):3619. doi:10.3390/jcm10163619.

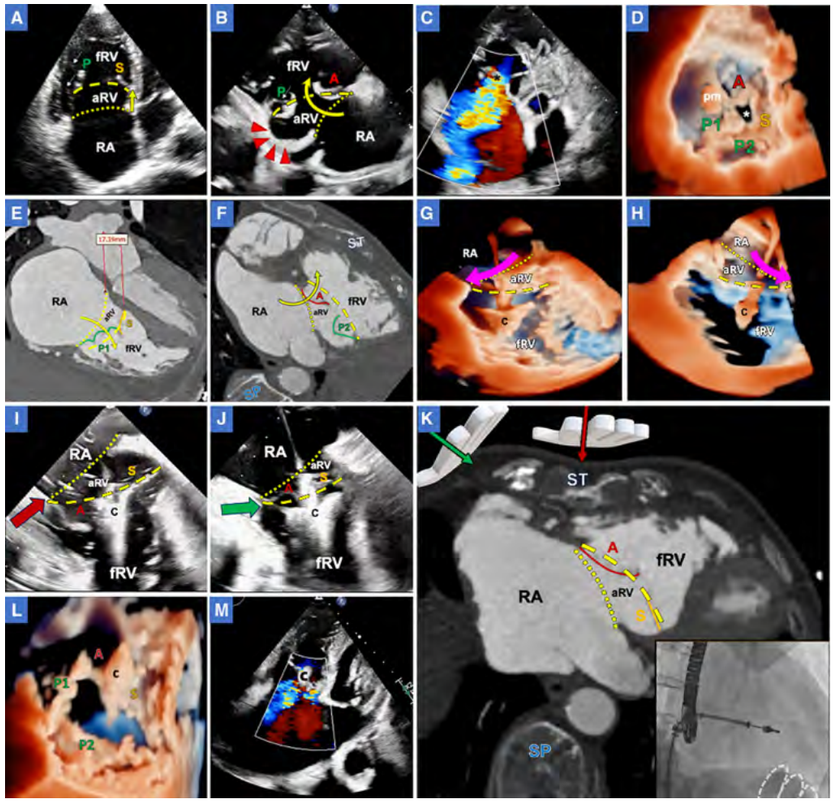
3. Lee APW, Fan Y, Baig FN, Lam YY. Mechanisms of mitral regurgitation: New insights from 3D echocardiography and implications for transcatheter repair. *JACC: Asia*. 2021;1(1):115-6. doi:10.1016/j.jacasi.2021.04.004. (Letter)

4. Mao Z, Zhao L, Huang S, Fan Y, Lee APW. Direct 3D ultrasound fusion for transesophageal echocardiography. *Computers in Biology and Medicine*. 2021;134:104502. doi:10.1016/j.compbiomed.2021.104502.

5. Fan Y, Lee APW. Valvular disease and heart failure with preserved ejection fraction. *Heart Failure Clinics*. 2021;17(3):387-395. doi:10.1016/j.hfc.2021.02.005.

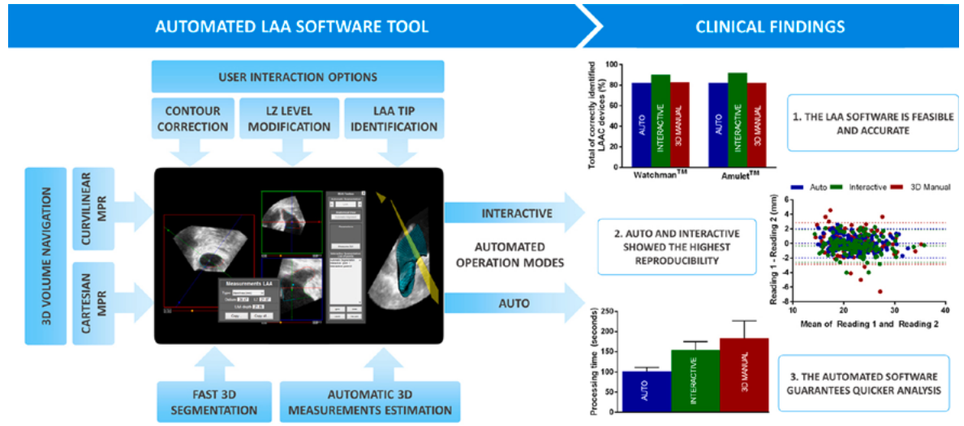
6. Fan Y, Chan TN, Chow JTY, Kam KKH, Chi WK, Chan JYS, Fung E, Tong MMP, Wong JKT, Choi PCL, Chan DKH, Sheng B, Lee APW. High prevalence of late-onset fabry cardiomyopathy in a cohort of 499 non-selective patients with left ventricular hypertrophy: The Asian fabry cardiomyopathy high-risk screening study (Asian-fame). *Journal of Clinical Medicine*. 2021;10(10):2160. doi:10.3390/jcm10102160.

7. Zhong X, Chen W, Shi Z, Huan Z, Ma L, Liu W, Yang X, Xu Y, Jiang Y, Lee APW, Guo R. Three-dimensional transesophageal echocardiography measurement of mitral valve area in patients with rheumatic mitral stenosis: Multiplanar reconstruction or 3D direct planimetry? *International Journal of Cardiovascular Imaging*. 2021;37(1):99-107. doi:10.1007/s10554-020-01950-1.



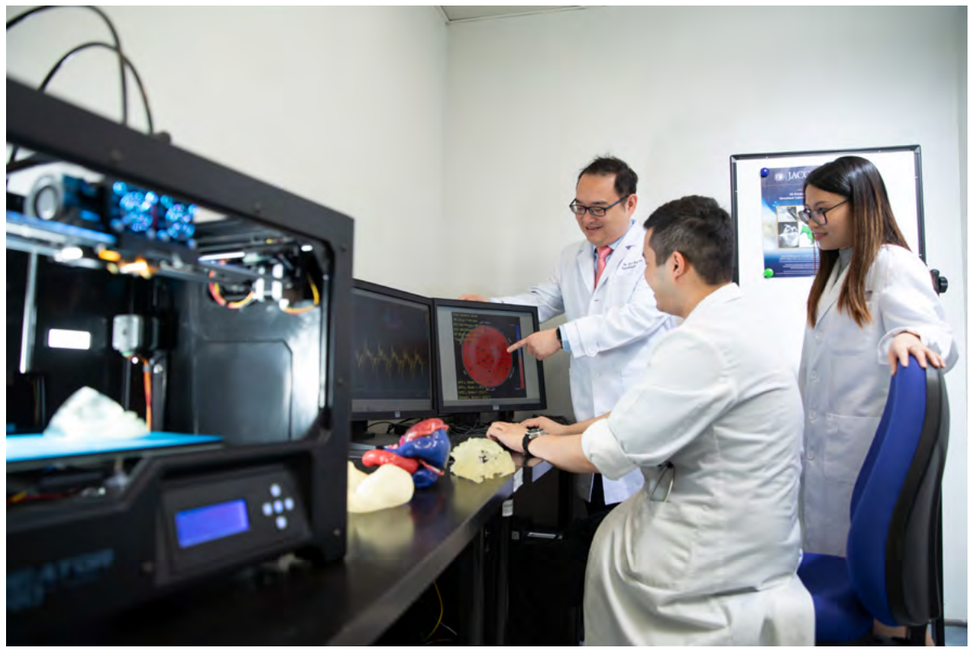
Transcatheter edge-to-edge repair (TEER) for tricuspid valve regurgitation in Ebstein anomaly
Preprocedural echocardiography (**A–D**) and computed tomography (CT; **E** and **F**). **A**, Four-chamber view showing apical displacement (yellow arrow) of the septal (S) and posterior leaflet (P) with leaflet tethering (white arrows) to underlying right ventricle (RV) myocardium. **B**, RV inflow view showing spiral displacement (curved arrow) of the functional tricuspid valve (TV) orifice and delamination/thinning of the RV inlet myocardium (red arrow heads). **C**, Wide leaflet gap with torrential tricuspid regurgitation (TR). **D**, Three-dimensional (3D) echocardiography showing 4-leaflet morphology (type IIIB) of the TV without leaflet fenestrations. **E** and **F**, CT showing anterior and superior rotation of the functional tricuspid orifice. **G** through **J**, Intraprocedural imaging. Live 3D transesophageal echocardiography (TEE) in the low esophageal TV-focused (**G**) and RV inflow-outflow views (**H**) showing, respectively, outward rotation of the guide and superior steering of the clip delivery system (CDS; pink arrows) to align with the rotated TV plane. **I**, Failed initial attempts to grasp both leaflets with anterior leaflet losing capture. Sternal compression (red arrow) did not reduce TV dimension. **J**, Right parasternal chest compression (green arrow) facilitated leaflet grasping. **K**, Relations between compressive directions and TV plane orientation on CT. Oblique right parasternal compression (palm with green arrow) would markedly reduce functional tricuspid orifice dimension (dashed line). Small insert: operator's hand position (dashed outline) on right anterior oblique fluoroscopic view during right parasternal compression. **L**, Postprocedural 3D echocardiography showing one clip implanted in the anteroseptal commissure with TV bicuspidization. **M**, TR reduction with mild-to-moderate residual regurgitation at 4 mo. A indicates anterior leaflet; aRV, atrialized RV; asterisk, leaflet coaptation gap; C, MitraClip; dashed line, functional tricuspid orifice; dotted line, anatomic atrioventricular groove; fRV, functional RV; pm, anterior papillary muscle; RA, right atrium; SP, spine; and ST, sternum.

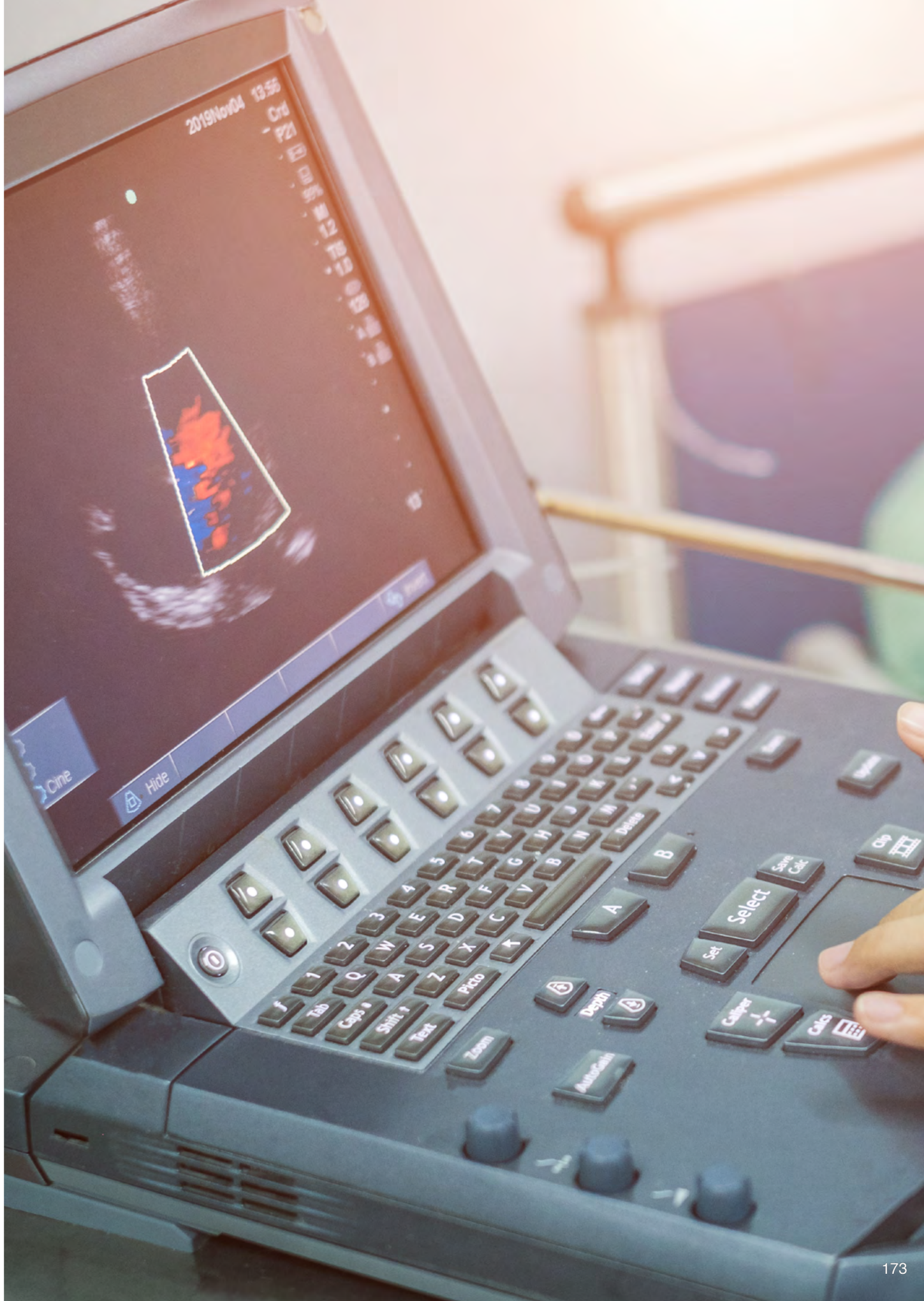
Source: Fan Y, Kam K, So K, Lam YY, Lee APW. Imaging for Transcatheter Edge-to-Edge Repair for Tricuspid Regurgitation in Ebstein Anomaly. Circulation: Cardiovascular Imaging. 2021;14(11):e013327. doi:10.1161/CIRCIMAGING.121.013327.



Graphical abstract. Main findings of the automated LAA software and its validation study.

Source: Morais P, Fan Y, Queirós S, D'hooge J, Lee APW, Vilaça JL. Feasibility and accuracy of automated three-dimensional echocardiographic analysis of left atrial appendage for transcatheter closure. Journal of the American Society of Echocardiography. 2022;35(1):124-133. doi:10.1016/j.echo.2021.08.023.





陳重娥

JULIANA CHAN



06 DIABETES AND OBESITY

Using Data Science to Monitor Trends, Identify Unmet Needs and Evaluate Effectiveness

Led by Andrea Luk, the team has curated data from the Hospital Authority (HA) territory-wide Electronic Medical Record (EMR) system to establish the Hong Kong Diabetes Surveillance Database (HKDSD) consisting of 4 million people who ever had blood glucose measurement (2000-2019). Using this dataset, they have reported the persistently high rate of pneumonia as a leading cause of death as well as the failure for the incidence of end stage kidney disease (ESKD) to decline in contrast to the declining trend of cardiovascular disease and all-cause death over the years. The amplifying effect of young age of diagnosis on ESKD and the high mortality rate even after renal replacement therapy especially in young people is particularly worrying. Despite these unmet clinical needs, in a pooled analysis of national data on mortality rate in people with diabetes (2000-2016), Hong Kong had the largest decline in death rate with 4% per year amongst 16 high income countries/areas. This impressive drop of nearly 70% in death rate during this 16-year period was in part driven by the territory-wide implementation of data-driven diabetes assessment, education and management program in both primary and secondary settings, complemented by public awareness programs, health care reform and public health policies in Hong Kong.

Led by Elaine Chow, they have developed comprehensive methodologies to evaluate the real-world evidence (RWE) of impacts of common drugs in type 2 diabetes, adjusted for multiple biases. Using the HKDSD and Hong Kong Diabetes Register (HKDR), they had reported reduced risks of pneumonia and related death amongst metformin and renin angiotensin system inhibitors (RASi) users compared with non-users in type 2 diabetes. They also found that use of both drugs was associated with reduced risk of all-cause death including cardiovascular-renal-cancer death, further supporting the need to develop systems to ensure that patients with diabetes are assessed and put on these lifesaving drugs.

On an international front, Juliana Chan was a lead investigator in the International Diabetes Mellitus Practice Survey where The Chinese University of Hong Kong contributed to the reporting of lack of improvement in glycaemic control in countries outside Western Europe and North America despite the introduction of many new glucose lowering drugs. Although there was increasing screening for albuminuria, there remained high rate of chronic kidney disease in these low- and middle-income countries. In this survey, they also found that 20-30% of patients with type 2 diabetes had depressive symptoms while 1 in 7 insulin-treated patients discontinued insulin at some stage averaging 1-2 months during their course of treatment in both patients with type 1 and type 2 diabetes.

In two large scale multicentre randomised studies, they evaluated the effectiveness of using the web-based Joint Asia Diabetes Evaluation (JADE®) Platform, designed and operated by the Asia Diabetes Foundation as a knowledge transfer project, to improve quality of care in 25,000 patients with type 2 diabetes from 10 countries in Asia versus usual care. In agreement with their previous studies conducted in China and Hong Kong, they confirmed once again the utility of the JADE-assisted care delivered by a doctor-nurse team in reducing multiple cardiometabolic risk factors, reducing default rate and improving clinical outcomes in patients with or without complications such as diabetic kidney disease.



Principal Investigator

Juliana Chan

Team members

Ronald Ma, Alice Kong, Andrea Luk, Elaine Chow, Wing Yee So, Hongjiang Wu, Risa Ozaki, Kitty Cheung, Cadmon Lim, Stephanie Cheung, Natural Chu, Baoqi Fan, Heung Man Lee, Dandan Mao, Mei Shi, Ming Wai Poon, Claudia Tam, Raymond Wan, Feifei Cheng, Eric Lau, Noel Ng, Aimin Yang, Chun Hei Tam, Hou Yong, Huanyi Cao, Jamie Cheung, Sandra Choi, Yingnan Fan, Chuiguo Huang, Qiao Jin, He Jia, Wang Ke, Andy Kuo, James Ling, Kit Ying Tsoi, Tsz Fung Tsoi, Sylvia Qiu, Kwun Kiu Wong, Rebecca Yue, Xinge Zhang

Using Precision Medicine to Predict, Classify and Personalise Care in Young Onset Diabetes

In their ongoing PRISM Project (**P**recision Medicine to **R**edefine **I**nsulin **S**ecretion and **M**onogenic Diabetes in Chinese Patients with Young Onset Diabetes, YOD) commissioned by the Health and Medical Research Fund (HMRF), they have completed the recruitment of 884 patients with YOD with 442 randomised to receive multidisciplinary care guided by clinical and biogenetic markers. In this project, they discovered that 5% of patients with YOD had autoimmune markers whilst 3% had monogenic diabetes or maturity onset diabetes of the young (MODY). Early identification of patients with latent autoimmune diabetes of the young (LADA) is important to avoid delayed insulin treatment while patients with MODY may be switched back from insulin to oral glucose lowering drugs. In addition, these young patients carried varying combinations of common genetic variants for YOD, late onset type 2 diabetes and cardiovascular-renal complications which interact to modify clinical course. Due to the silent nature of monogenic diabetes and high penetrance, screening of family members of these index patients is important to avoid delayed diagnosis and intervention of affected family members. Furthermore, they discovered that more than 10% of these young patients had variants of unknown origin which required ascertainment through functional studies or family co-segregation studies. With detailed clinical evaluation, they noted the phenotypic heterogeneity of these young patients in whom genetic, life course, autoimmune, non-genetic hereditary, hormonal and psychosocial-behavioural risk factors interact in a complex manner to contribute to the diversity of clinical presentation, trajectories and outcomes in these young patients.

Using their community-, family- and clinic-based cohorts including healthy subjects, high risk individuals and patients with diabetes, the team has measured fasting plasma C peptide and glucose to define the insulin resistance and deficiency status during the progression from normal glucose tolerance to diabetes in community-dwelling individuals as well as glycaemic deterioration and insulin requirement in patients with diabetes. In young people without diabetes, insulin resistance was a major predictor for incident diabetes in addition to sex, obesity and lipid abnormalities. In patients without auto-

antibodies and preserved beta cell function, both insulin deficiency and resistance predicted early insulin requirement after adjusting for confounders.

In patients with type 2 diabetes, 8% had LADA although only 50% of them were insulin deficient based on absolute plasma C peptide level. On the other hand, 35% of patients with type 2 diabetes had insulin deficiency although only 50% of them had autoimmune markers. Patients with autoantibodies and/or insulin insufficiency were highly responsive to insulin treatment albeit also at high risk of severe hypoglycaemia. While their pharmacoepidemiological analysis using HKDSD indicated declining use of sulphonylureas (SU) in their patients with type 2 diabetes, supported by the Theme-Based Research Scheme led by Ronald Ma and Elaine Chow, they had reported the greater glucose lowering effects of SU amongst patients with type 2 diabetes who carried genetic variants of *CYP2C9*. The latter is known to be associated with reduced metabolism of gliclazide, which is the most common SU used in their community. These studies emphasised the importance of using comprehensive clinical profiling and biogenetic markers to classify patients in order to personalise care.

Translational Research in Beta Cell Biology and Diabetes-Cancer Link

In collaboration with Xiaoyu Tian from the School of Biomedical Science and Guy Rutter from Imperial College London, Alice Kong continues to use experimental models to elucidate the role of SIRT3 pathway in the development of diabetes. Using transgenic mice, she had reported silencing of this pathway had led to the development of fatty liver and dedifferentiation of beta cells. In support of their previous experiments regarding the cancer-promoting effect of hyperglycaemia on cancer growth in a diabetes-cancer animal model, using colon cancer cell lines, they demonstrated the legacy effect of high glucose medium on promoting the continuing cancer cell growth despite return to a normoglycemic environment. This programming effect of hyperglycaemia was in part mediated through endoplasmic reticulum (ER) stress resulting in reduced apoptosis of the cancer cells and resistance to anti-cancer drugs which used ER pathway to induce cell death.

In support of the deleterious effect of hyperglycaemia on abnormal cell growth, led by Juliana, they have reported the risk association of glycaemic burden with liver cancer and that of glycaemic variability and all-site cancer as well as death due to cardiovascular and cancer events in patients with more than 10 years of diabetes and especially in those with obesity. To this end, supported by an Innovation Technology Commission (ITC) grant and using the HKDR biobank, Alice had reported the predictive role of several miRNAs on incident liver cancer 4-6 years before its occurrence making them potential markers for early detection and intervention.

From Genomic Medicine to Drug Discovery

Led by Ronald, their multiomic project, supported by the Impact Research Fund and TRS, continues to generate a wealth of academic output aimed at elucidating the genetic regulation of diabetic complications (see report in Lab 602). Through these projects, they have genotyped more than 30,000 patients in multiple cohorts with detailed phenotypes and multiple outcomes. Using this huge resource, Ronald has performed comprehensive analysis including the use of Mendelian Randomisation and reported the independent predictive role of DNA telomeres on glycemic deterioration, cardiovascular-renal complications and all-cause death. By using genomic data available from publicly available resources together with their proprietary databases, they have developed multiple genetic risk scores consisting of common variants which predicted insulin requirement, deterioration of kidney function as well as multiple lipid traits and cardiovascular disease. Using adipose tissues collected during metabolic surgery, they have also performed multiomic analysis and reported novel epigenetic pathways implicated in both general and visceral adiposity associated with type 2 diabetes.

In their collaborative project with Astra Zeneca, they continued to make progress in using long-read and short-read whole genome sequencing to discover novel pathways implicated in diabetic kidney disease (DKD) using bioinformatics and computational biology, supplemented by multiomic analysis in their other datasets. They have also developed human glomerular and tubular cell lines which will be used to test the functional significance of novel pathways in DKD discovered in these analyses, in collaboration with the biologists and bioinformatists of the sponsor for possible drug development.

Technologies and Therapeutics

Both Andrea and Elaine are leading the non-oncology early phase clinical trials at the CUHK Phase 1 Clinical Trial Centre where they have established the insulin/glucose clamp techniques to evaluate the insulin secretory function and its action in controlled settings. Supported by a RGC grant, Andrea is evaluating the insulin secretory function in both lean and obese patients with YOD. Supported by an investigator-initiated study sponsored by Hua Medicine which had taken the first ever glucose kinase activator (GKA) to phase 3 clinical trial, Elaine is evaluating the effects of this novel drug in patients with GK-MODY and early onset type 2 diabetes. These *state-of-the-art* physiological studies continue to provide new insights in their pursuit of precision medicine of reclassifying diabetes for targeted therapies with companion diagnostics.

In a similar vein, Juliana is currently a national lead for a phase 3 study evaluating the efficacy and safety of a novel aldose reductase inhibitor in patients with type 2 diabetes with heart failure and preserved ejection fraction (HFpEF). In this clinical trial, they are working closely with Erik Fung, their cardiologist, to set up the *state-of-the-art* facilities including echocardiogram and cardiopulmonary exercise testing (CPET) along with metabolomic analytical platform for in depth analysis. Given the genetic determinant for the aldose reductase pathway, this is another molecule with potential for precision medicine in diabetes for preventing complications.

Having spearheaded the collaboration with a local biotechnology company in developing a 28-day continuous glucose monitoring (CGM) system, Elaine had been funded by the Innovation and Technology Commission (ITC) to lead a multi-centre trial in Greater Bay Area for registering this innovative CGM system with National Medical Products Administration (NMPA). Supported by competitive and investigator-initiated industry grants, Elaine is now studying the use of different CGM systems in patients with DKD to improve glycaemic control as well as using CCM to enhance the effects of lifestyle modification in people with pre-diabetes.

Informed by the mechanistic studies conducted by their team which confirmed the effects of 2 Chinese Medicine (CM) formulation in improving beta cell function and insulin resistance, they had been supported by a CUHK Strategic Grant to evaluate the effects of a novel CM formulation with an aim to revert prediabetes in high risk subjects for diabetes. This study was conducted in collaboration with Zhixiu Lin of the CUHK Hong Kong Institute of Integrated Medicine and Phase 1 Clinical Trial Centre. Supported by Paul KS Chan, we are exploring the effects of this novel CM formula on microbiota and multiomic changes and their correlations with beta-cell function and insulin resistance. Guided by the promising results of this pilot study, they have applied for an ITC grant to develop this novel formulation as a proprietary CM with scientific evaluation in phase 1 and phase 2 study aimed at applying for registration with indication for prevention and progression of type 2 diabetes.

Knowledge Transfer, International Profile and People Development

As an International Diabetes Federation (IDF) Centre of Excellence in Diabetes Care, the team continues to build professional capacity through their Master, Diploma and Certificate Courses in Endocrinology, Diabetes and Metabolism and their annual Hong Kong Diabetes and Cardiovascular Risk Factor – East Meets West Symposium organised by the Hong Kong Institute of Diabetes and Obesity. Several of their PhD graduates and fellows have graduated and are now academic leads in other institutions. These include Lee Ling Lim who is now Associate Professor at the University of Malaya; Guozhi Jiang, Associate Professor at the Sun Yat Sun Medical University; Feifei Cheng, Assistant Professor at Shanghai Jaiotung University; Rosemary Yeung, Assistant

Professor at University of Alberti and Dr Calvin Ke, Assistant Professor at University of Toronto in Canada. XL Yang, who used to be a research assistant professor in CUHK, is now Professor at Tianjian University who continues to be a close collaborator in the field of epidemiology, prevention and management of gestational diabetes.

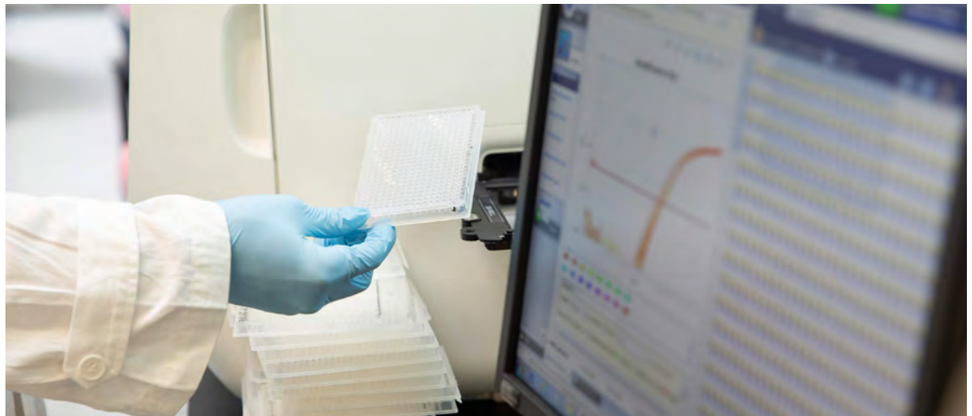
The Chinese University of Hong Kong, as one of the leading universities in diabetes research, most of the Principal Investigators (PIs) of the diabetes research team are serving on editorial boards of leading diabetes journals and committees of international organisations in the field of diabetes, obesity and related disease, including the IDF (Diabetes Atlas), American Diabetes Association (Precision Medicine) and KDIGO (Kidney Disease Improving Global Outcome) Practice Guidelines. Some are members of steering committees of global outcome clinical trials and consultants of global and regional advisory boards of multinational companies including Astra Zeneca, Bayer, Boehringer Ingelheim, Celltrion, Merck Sharpe Dohme, Sanofi, Pfizer and Viatris Pharmaceuticals. Apart from serving on Food and Health Bureau and Hospital Authority committees on diabetes, noncommunicable disease (NCD) and drug utilisation, most of the PIs are members of grant review committees of ITC, RGC and HMRF and contribute to the scholastic development in Hong Kong.

On the knowledge transfer front, the team continues to promote the JADE platform through the ADF, governed by the CUHK Foundation and implement the JADE-assisted data-driven diabetes prevention and care program at the CUHK Yao Chung Kit Diabetes Assessment Centre in partnership with the CU Medical Centre.

Awards and Recognitions

Several of their postgraduate students have received awards from the Faculty of Medicine or conferences for their excellent performance. Jamie Cheung, a PhD student and a qualified pharmacist from Canada received the Hong Kong PhD Fellowship Scheme (HKPFS) 2020-2021 award under the mentorship of Alice. Noel Ng, their PhD graduate, received a 3-year postdoctoral fellowship from the new RGC scheme on a topic related to polycystic ovarian syndrome under the mentorship of Ronald.

In 2021, Ronald Ma received the Senior Croucher Fellowship and Elaine received the Hong Kong College of Physician Young Researcher Award. At the International Congress of Diabetes and Metabolism and Asian Association for Study of Diabetes (AASD) Scientific Meeting, Ronald delivered the Pan Xiao Ren Epidemiology Award Lecture bestowed by the Asian Association for Study in Diabetes. At the Virtual IDF Congress, Juliana delivered the Hellmut Mehnert Award Lecture in recognition of her extensive knowledge in the field of diabetes. For the second consecutive year, the CUHK was ranked number 1 in Asia for Endocrinology and Metabolism by the United States News Best Global Universities Rankings. In recognition of the impacts of their 3 decades of research, their JADE-assisted, data-driven diabetes care model was published as one of the 5 CUHK impact stories in the 2020 Research Assessment Exercise.



Research and Scholarship

Research Awards and Recognitions

Member's Name	Details	
	Award / Recognition	Organisation
The Chinese University of Hong Kong Endocrine and Diabetes Team	Number 1 in Asia for Endocrinology and Metabolism	Best Global Universities Rankings U.S. News
The Chinese University of Hong Kong	Transforming Diabetes Care: From Research to Practice to Community	Impact Case of Research Assessment Exercise 2020 from the University Grants Committee
Juliana Chan	Hellmut Mehnert Award	University of Oxford
Ronald Ma	Xiaoren Pan Distinguished Research Award for Epidemiology of Diabetes in Asia	Asian Association for Study of Diabetes
Dandan Mao	Young Investigator Award	American Diabetes Association

Fellowships

Member's Name	Details	
	Fellowship	Organisation
Ronald Ma	Croucher Senior Medical Research Fellowship	Croucher Foundation
Eric Lau	Faculty Postdoctoral Fellowship	The Chinese University of Hong Kong Faculty of Medicine
Aimin Yang	Impact Research Fellowship	The Chinese University of Hong Kong Research Committee

Academic Editorship

Member's Name	Details	
	Role	Journal
Juliana Chan	International Advisor	The Lancet Diabetes and Endocrinology

Member's Name	Details	
	Role	Journal
Juliana Chan	Editorial Board Member	Diabetes Metabolism Research Review
		Journal of Diabetes
Ronald Ma	Expert Editor	Journal of Diabetes Investigation
	Editorial Board Member	PLOS Medicine
		Obesity Reviews
	Associate Editor	Journal of Diabetes Investigation
Alice Kong	Editor-in-chief	Primary Care Diabetes
	Editorial Board Member	Diabetes Technology & Therapeutics
Andrea Luk	Associate Editor	Diabetic Medicine
Elaine Chow	Associate Editor	Primary Care Diabetes

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Juliana Chan Ronald Ma	Using Whole Genome Sequencing, Computational Biology and Functional Analysis to Discover Biological Pathways Implicated in Diabetic Kidney Disease	AstraZeneca Investigator Initiated Study	2019	2022	8,970,000
Juliana Chan Andrea Luk	Precision Medicine to Redefine Insulin Secretion and Monogenic Diabetes (PRISM) in Chinese Patients with Young Onset Diabetes	Food and Health Bureau – Health and Medical Research Fund Commissioned Grant	2019	2024	8,457,718
Juliana Chan	Self-managing Healthy Eating & Active Lifestyle for Impeding 3-Highs (High Blood Glucose, High Blood Pressure and High Cholesterol) Mobile Application (SHEALF3 APP) (Renamed as Citybite APP)	Innovation and Technology Fund for Better Living via Asia Diabetes Foundation	2018	2022	4,247,006
	Conducting Diabetes Health Seminars and Weight Management Short Courses for Clinical Research	The Chinese University of Hong Kong Jockey Club Multi-Cancer Prevention Programme	2019	2021	600,000
Juliana Chan Elaine Chow	Real-World Evidence on the Effects of Metformin on Clinical Outcomes in Patients with Type 2 Diabetes at Different Stages of Chronic Kidney Disease	Merck (Germany) Investigator Initiated Study via Asia Diabetes Foundation	2020	2021	1,265,000
	Effects of Dorzagliatin on 1st Phase Insulin and Beta-Cell Glucose Sensitivity in Individuals with Recent-Onset Type 2 Diabetes and Monogenic Diabetes	Hua Medicine Investigator Initiated Study	2020	2021	1,290,863
Juliana Chan Andrea Luk	Development of an ABC-S Model to Predict Atherosclerotic Cardiovascular Disease in Chinese Patients with Type 2 Diabetes for Early Intervention	Lilly (USA) Investigator Initiated Study via Asia Diabetes Foundation	2020	2021	780,000
Juliana Chan	Transforming Diabetes Care: From Research to Practice to Community	The Chinese University of Hong Kong Research Committee's One-off Project Impact Enhancement Fund	2019	2021	500,000
	Using Modern and Traditional Technologies to Redefine and Prevent Young Onset Diabetes	The Chinese University of Hong Kong Funding for Research Sustainability of Major Research Grants Council Funding Schemes	2019	2022	500,000
	Aldose Reductase Inhibition for Stabilisation of Exercise Capacity in Heart Failure: A Multicenter, Randomised, Placebo-controlled Study to Evaluate the Safety and Efficacy of AT-001 in Patients with Diabetic Cardiomyopathy / Stage B Heart Failure at High Risk of Progression to Overt Heart Failure (Stage C Heart Failure)	Applied Therapeutics	2021	2024	1,500,000

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Ronald Ma	A Nanotechnology Platform for Profiling Diabetes-related MiRNA for Precision Medicine	Innovation and Technology Commission – Midstream Research Programme for Universities	2021	2023	5,998,400
	Croucher Senior Medical Research Fellowship	Croucher Foundation	2021	2022	2,272,948
	Precision Medicine in Diabetes	Croucher Foundation	2021	2022	2,000,000
	Unraveling the Link between Maternal Hyperglycaemia and Childhood Obesity: Genome-Wide Methylation Analysis in a Prospective Cohort of Untreated Gestational Diabetes	Research Grants Council – General Research Fund	2019	2021	970,517
Ronald Ma Juliana Chan	Translating Multi-Omic Discoveries to Transform Diabetes Care and Reduce Diabetic Complications	Research Grants Council – Research Impact Fund	2019	2024	8,400,000
Ronald Ma	Translating Multi-Omic Discoveries to Transform Diabetes Care and Reduce Diabetic Complications	Research Committee Funding for Research Sustainability of Major Research Grants Council Funding Schemes	2019	2024	500,000
Alice Kong	The Impact of Cognitive Behavioral Therapy for Insomnia on Glycemic Control in Older Type 2 Diabetes Comorbid with Insomnia	Food and Health Bureau – Health and Medical Research Fund	2021	2023	1,484,694
Andrea Luk	Delineating The Metabolic Architecture and Response to Anti-Hyperglycaemic Drug Treatment in Lean Type 2 Diabetes in Chinese	Research Grants Council – General Research Fund	2021	2023	1,178,778
Elaine Chow	Effectiveness and Safety Study of the Continuous Glucose Monitoring System (Fibersense) for Home Use (Including In-Clinic Sessions) in Patients with Diabetes	Innovation and Technology Commission – Guangdong Hong Kong Technology Cooperation Funding Scheme	2020	2022	5,674,000
Elaine Chow Juliana Chan	A Phase 1b/2a Ascending Dose Study of the Safety, Tolerability and Preliminary Efficacy of Sublingual Liraglutide in Patients with Type 2 Diabetes	Innovation and Technology Commission – Partnership Research Programme	2020	2021	3,680,203
Elaine Chow	Continuous Glucose Monitoring as An Adjunct to Lifestyle Modification in Individuals with Impaired Glucose Tolerance: A Randomised Controlled Trial	Food and Health Bureau – Health and Medical Research Fund	2020	2023	1,344,796



Publications

A. Journal Papers

1. Steenblock C, Schwarz PEH, Ludwig B, Linkermann A, Zimmet P, Kulebyakin K, Tkachuk VA, Markov AG, Lehnert H, de Angelis MH, Rietzsch H, Rodionov RN, Khunti K, Hopkins D, Birkenfeld AL, Boehm B, Holt RIG, Skyler JS, DeVries JH, Renard E, Eckel RH, Alberti KGMM, Geloneze B, Chan JC, Mbanya JC, Onyegbutulem HC, Ramachandran A, Basit A, Hassanein M, Bewick G, Spinas GA, Beuschlein F, Landgraf R, Rubino F, Mingrone G, Bornstein SR. COVID-19 and metabolic disease: Mechanisms and clinical management. *The Lancet Diabetes and Endocrinology*. 2021;9(11):786-798. doi:10.1016/s2213-8587(21)00244-8. (Review)

2. Bloomgarden Z, Chan JCN. Rationale for glycemic control to improve cardiovascular outcome: Lessons from East and West. *Journal of Diabetes.* 2021;13(9):698-700. doi:10.1111/1753-0407.13204. (Commentary)

3. Bornstein SR, Rubino F, Ludwig B, Rietzsch H, Schwarz PEH, Rodionov RN, Khunti K, Hopkins D, Birkenfeld AL, Boehm B, Amiel S, Holt RIG, Skyler JS, DeVries JH, Renard E, Eckel RH, Zimmet P, Alberti KG, Geloneze B, Chan JC, Mbanya JC, Onyegbutulem HC, Ramachandran A, Basit A, Hassanein M, Spinas GA, Beuschlein F, Mingrone G. Consequences of the covid-19 pandemic for patients with metabolic diseases. *Nature Metabolism.* 2021;3(3):289-292. doi:10.1038/s42255-021-00358-y. (Review)

4. Wu H, Lau ESH, Yang A, Zhang X, Ma RCW, Kong APS, Chow E, So W-Y, Chan JCN, Luk AOY. Data resource profile: The Hong Kong diabetes surveillance database (HKDSD). *International Journal of Epidemiology.* 2021;1-9. doi:10.1093/ije/dyab252. (Epub ahead of print)

5. Cheng F, Ng NYH, Tam CHT, Zhang Y, Lim CKP, Jiang G, Ng ACW, Yau TTL, Cheung LP, Xu A, Chan JCN, Ma RCW. Association between FGF19, FGF21and lipocalin-2, and diabetes progression in pcos. *Endocrine Connections.* 2021;10(10):1243-1252. doi:10.1530/ec-21-0082.

6. Yang L, Webb SE, Jin N, Lee HM, Chan TF, Xu G, Chan JCN, Miller AL, Ma RCW. Investigating the role of dachshund b in the development of the pancreatic islet in zebrafish. *Journal of Diabetes Investigation.* 2021;12(5):710-727. doi:10.1111/jdi.13503.

7. Chan JCN, Lim L-L, Shaw JE, Aguilar-Salinas CA, Gregg EW. Data on diabetes-specific distress are needed to improve the quality of diabetes care – authors' reply. *The Lancet.* 2021;397(10290):2150. doi:10.1016/s0140-6736(21)00664-4. (Letter)

8. Ming X, Chung ACK, Mao D, Cao H, Fan B, Wong WKK, Ho CC, Lee HM, Schoonjans K, Auwerx J, Rutter GA, Chan JCN, Tian XY, Kong APS. Pancreatic sirtuin 3 deficiency promotes hepatic steatosis by enhancing 5-hydroxytryptamine synthesis in mice with diet-induced obesity. *Diabetes.* 2021;70(1):119-131. doi:10.2337/db20-0339.

9. Rossing P, Filippatos G, Agarwal R, Anker SD, Pitt B, Ruilope LM, Chan JCN, Kooy A, McCafferty K, Schernthaner G, Wanner C, Joseph A, Scheerer MF, Scott C, Bakris GL. Finerenone in predominantly advanced CKD and type 2 diabetes with or without sodium-glucose cotransporter-2 inhibitor therapy. *Kidney International Reports.* 2022;7(1):36-45. doi:10.1016/j.ekir.2021.10.008. (Epub ahead of print)

10. Wang K, Yang A, Shi M, Tam CCH, Lau ESH, Fan B, Lim CKP, Lee HM, Kong APS, Luk AOY, Tomlinson B, Ma RCW, Chan JCN, Chow E. CYP2C19 loss-of-function polymorphisms are associated with reduced risk of sulfonylurea treatment failure in Chinese patients with type 2 diabetes. *Clinical Pharmacology and Therapeutics.* 2022;111(2):461-469. doi:10.1002/cpt.2446. (Epub ahead of print)

11. Jin N, Lee H, Hou Y, Yu ACS, Li J, Kong APS, Lam CCH, Wong SKH, Ng EKW, Ma RCW, Chan JCN, Chan T. Integratome analysis of adipose tissues reveals abnormal epigenetic regulation of adipogenesis, inflammation, and insulin signaling in obese individuals with type 2 diabetes. *Clinical and Translational Medicine.* 2021;11(12). doi:10.1002/ctm2.596. (Letter, Epub ahead of print)

12. Cheng F, Luk AO, Wu H, Tam CHT, Lim CKP, Fan B, Jiang G, Carroll L, Yang A, Lau ESH, Ng ACW, Lee HM, Chow E, Kong APS, Keech AC, Joglekar MV., So WY, Hardikar AA, Chan JCN, Jenkins AJ, Ma RCW. Relative leucocyte telomere length is associated with incident end-stage kidney disease and rapid decline of kidney function in type 2 diabetes: Analysis from the Hong Kong diabetes register. *Diabetologia.* 2022;65(2):375-386. doi:10.1007/s00125-021-05613-1. (Epub ahead of print)

13. Lee HM, Wong WKK, Fan B, Lau ES, Hou Y, O CK, Luk AOY, Chow EYK, Ma RCW, Chan JCN, Kong APS. Detection of increased serum miR-122-5p and miR-455-3p levels before the clinical diagnosis of liver cancer in people with type 2 diabetes. *Scientific Reports.* 2021;11(1):23756. doi:10.1038/s41598-021-03222-x.

14. Yang A, Shi M, Wu H, Lau ESH, Ma RCW, Kong APS, So WY, Luk AOY, Chan JCN, Chow E. Long-term metformin use and risk of pneumonia and related death in type 2 diabetes: A registry-based cohort study. *Diabetologia.* 2021;64(8):1760-1765. doi:10.1007/s00125-021-05452-0.

15. Jin Q, Lau ES, Luk AO, Ozaki R, Chow EY, So T, Yeung T, Loo K, Lim CK, Kong AP, So WY, Jenkins AJ, Chan JC, Ma RC. Skin autofluorescence is associated with progression of kidney disease in type 2 diabetes: A prospective cohort study from the Hong Kong diabetes biobank. *Nutrition, Metabolism and Cardiovascular Diseases.* 2022;32(2):436-446. doi:10.1016/j.numecd.2021.10.007. (Epub ahead of print)

16. Mao D, Lau ESH, Wu H, Yang A, Shi M, Fan B, Tam CHT, Chow E, Kong APS, Ma RCW, Luk A, Chan JCN. Risk associations of long-term HbA1c variability and obesity on cancer events and cancer-specific death in 15,286 patients with diabetes - a prospective cohort study. *The Lancet Regional Health - Western Pacific.* 2022;18:100315. doi:10.1016/j.lanwpc.2021.100315. (Epub ahead of print)

17. Aschner P, Gagliardino JJ, Ilkova H, Lavalle F, Ramachandran A, Mbanya JC, Shestakova M, Bourhis Y, Chantelot J-M, Chan JCN. High prevalence of depressive symptoms in patients with type 1 and type 2 diabetes in developing countries: Results from the international diabetes management practices study. *Diabetes Care.* 2021;44(5):1100-1107. doi:10.2337/dc20-2003.

18. Jin Q, Lau ESH, Luk AOY, Ozaki R, Chow EYK, Cheng F, So T, Yeung T, Loo K man, Lim CKP, Kong APS, Jenkins AJ, Chan JCN, Ma RCW. Skin autofluorescence is associated with higher risk of cardiovascular events in Chinese adults with type 2 diabetes: A prospective cohort study from the Hong Kong diabetes biobank. *Journal of Diabetes and its Complications.* 2021;35(10). doi:10.1016/j.jdiacomp.2021.108015.

19. Tam CHT, Lim CKP, Luk AOY, Ng ACW, Lee H, Jiang G, Lau ESH, Fan B, Wan R, Kong APS, Tam W, Ozaki R, Chow EYK, Lee K, Siu S, Hui G, Tsang C, Lau K, Leung JYY, Tsang M, Kam G, Lau I, Li JKY, Yeung VTF, Lau E, Lo S, Fung S, Cheng Y, Chow C, Hu M, Yu W, Tsui SKW, Huang Y, Lan H, Szeto C, Tang NLS, Ng MCY, So W, Tomlinson B, Chan JCN, Ma RCW. Development of genome-wide polygenic risk scores for lipid traits and clinical applications for dyslipidemia, subclinical atherosclerosis, and diabetes cardiovascular complications among East Asians. *Genome Medicine.* 2021;13(1):29. doi:10.1186/s13073-021-00831-z.

20. Mbanya JC, Aschner P, Gagliardino JJ, İlkova H, Lavalle F, Ramachandran A, Chantelot JM, Chan JCN. Screening, prevalence, treatment and control of kidney disease in patients with type 1 and type 2 diabetes in low-to-middle-income countries (2005–2017): The international diabetes management practices study (IDMPS). *Diabetologia.* 2021;64(6):1246-1255. doi:10.1007/s00125-021-05406-6.

21. Chan JCN, Gagliardino JJ, Ilkova H, Lavalle F, Ramachandran A, Mbanya JC, Shestakova M, Dessapt-Baradez C, Chantelot J-M, Aschner P. One in seven insulin-treated patients in developing countries reported poor persistence with insulin therapy: Real world evidence from the cross-sectional international diabetes management practices study (IDMPS). *Advances in Therapy.* 2021;38(6):3281-3298. doi:10.1007/s12325-021-01736-4.

22. Lee HM, Lee SC, He L, Kong APS, Mao D, Hou Y, Chung ACK, Xu G, Ma RCW, Chan JCN. Legacy effect of high glucose on promoting survival of HCT116 colorectal cancer cells by reducing endoplasmic reticulum stress response. *American Journal of Cancer Research*. 2021;11(12):6004-6023. (Epub ahead of print)

23. Thewjitcharoen Y, Wanothayaroj E, Krittiyawong S, Nakasatien S, Tsoi TF, Lim CKP, Chan JCN, Himathongkam T. Phenotypic and genetic heterogeneity in a Thai glucokinase mody family reveals the complexity of young-onset diabetes. *Frontiers in Endocrinology (Lausanne)*. 2021;12. doi:10.3389/fendo.2021.690343.

24. Li N, Li J, Zhang C, Liu G, Leng J, Liu J, Wang L, Li W, Yu Z, Hu G, Chan JCN, Yang X. Usefulness of cut-off points of international criteria for prediction of post-partum diabetes and prediabetes among Chinese women with gestational diabetes. *Diabetes/Metabolism Research and Reviews*. 2021;37(8). doi:10.1002/dmrr.3456.

25. Wu H, Lau ESH, Yang A, Szeto C-C, Ma RCW, Kong APS, Chow E, So W-Y, Chan JCN, Luk AOY. Trends in kidney failure and kidney replacement therapy in people with diabetes in Hong Kong, 2002-2015: A retrospective cohort study. *The Lancet Regional Health - Western Pacific*. 2021;11:100165. doi:10.1016/j.lanwpc.2021.100165.

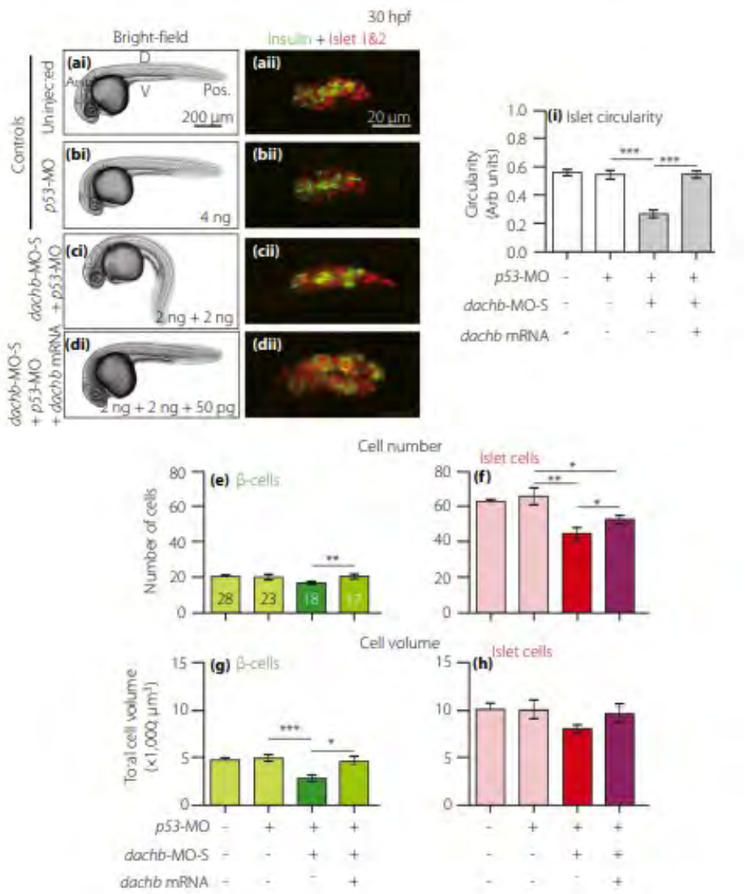
26. Mao D, Cao H, Shi M, Wang CC, Kwong J, Li JJX, Hou Y, Ming X, Lee HM, Tian XY, Wong CK, Chow E, Kong APS, Lui VWY, Chan PKS, Chan JCN. Increased co-expression of PSMA2 and GLP-1 receptor in cervical cancer models in type 2 diabetes attenuated by exendin-4: A translational case-control study. *EBioMedicine*. 2021;65:103242. doi:10.1016/j.ebiom.2021.103242.

27. Cheng F, Luk AO, Wu H, Lim CKP, Carroll L, Tam CHT, Fan B, Yang A, Lau ESH, Ng ACW, Lee HM, Chow E, Kong APS, Keech AC, Joglekar M V., So WY, Jenkins AJ, Chan JCN, Hardikar AA, Ma RCW. Shortened relative leukocyte telomere length is associated with all-cause mortality in type 2 diabetes - Analysis from the Hong Kong diabetes register. *Diabetes Research and Clinical Practice*. 2021;173:108649. doi:10.1016/j.diabres.2021.108649.

28. Wu H, Lau ESH, Yang A, Fan B, Ma RCW, Kong APS, Chow E, So W-Y, Chan JCN, Luk AOY. Young age at diabetes diagnosis amplifies the effect of diabetes duration on risk of chronic kidney disease: A prospective cohort study. *Diabetologia*. 2021;64(9):1990-2000. doi:10.1007/s00125-021-05494-4.

29. Ling J, Poon EWM, Yang A, Yeung T, Loo K, Ozaki R, Ma RCW, Luk AOY, Kong APS, Chan JCN, Chow E. Glycemic variability and time in range during self-titration of once daily insulin glargine 300 u/ml versus neutral protamine hagedorn insulin in insulin-naïve Chinese type 2 diabetes patients. *Diabetes Therapy*. 2021;12(5):1399-1413. doi:10.1007/s13300-021-01046-6.

30. Lim L-L, Lau ESH, Fu AWC, Ray S, Hung Y-J, Tan ATB, Chamnan P, Sheu WHH, Chawla MS, Chia Y-C, Chuang L-M, Nguyen D-C, Sosale A, Saboo BD, Phadke U, Kesavadev J, Goh S-Y, Gera N, Huyen Vu TT, Ma RCW, Lau V, Luk AOY, Kong APS, Chan JCN. Effects of a technology-assisted integrated diabetes care program on cardiometabolic risk factors among patients with type 2 diabetes in the asia-pacific region. *JAMA Network Open*. 2021;4(4):e217557. doi:10.1001/jamanetworkopen.2021.7557.



Genetic variation of DACH1 was first discovered by the research team in Chinese patients with young onset diabetes which had been validated in multiple Asian cohorts. In collaboration with Hong Kong University of Science and Technology, they used zebra fish models to elucidate the functional significance of this gene.

Injection of dachb messenger ribonucleic acid (mRNA) rescues the effect of splice-blocking dachb-morpholino (dachb-MO-S) on the development of the pancreatic islet in embryos at 30 h post-fertilization (hpf). Embryos were (a) uninjected (control) or they were injected at the one-cell stage with (b) p53-MO (control), (c) 2 ng dachb-MO-S + 2 ng p53-MO or (d) 2 ng dachb-MO-S + 2 ng p53-MO + 50 pg dachb mRNA. (ai–di) Bright-field images were acquired at 30 hpf, after which the embryos were whole-mount double-immunolabeled with antibodies to insulin (green) and islet 1 and 2 (red) to show the localization of the b-cells and islet cells in the endocrine pancreas, respectively. (aii–dii) These are all single optical sections taken through the middle of pancreatic islet. (e,f) The number of (e) b-cells and (f) islet cells, and (g,h) the volume of (g) b-cells and (h) islet cells. (i) The circularity of the pancreatic islet. The data are presented as the mean – standard error of n = 10 to 28 embryos, such that the number is shown in the respective bars in panel (e). The asterisks indicate significant differences at $P < 0.05$*, $P < 0.01$** or $P < 0.001$*** using the Mann–Whitney U-test. Ant., anterior; D, dorsal; NS, not significant; Pos. posterior; V, ventra

Source: Yang L, Webb SE, Jin N, Lee HM, Chan TF, Xu G, Chan JC, Miller AL, Ma RC. Investigating the role of dachshund b in the development of the pancreatic islet in zebrafish. Journal of Diabetes Investigation. 2021;12(5):710-727. doi: 10.1111/jdi.13503.



06 DIABETES AND OBESITY

Research Progress Summary

Epidemiology of Diabetes and Diabetes complications in Asians

The research team led by Ronald Ma has continued to generate novel insights on the epidemiology of diabetes and diabetic complications in Asians, to help inform the formulation of strategies and policies to address this important public health burden. With recent support from the Theme-based Research Scheme (TRS) on Diabetes Complications and ongoing support from a Research Impact Fund (PC: Ronald), they have charted the natural history of diabetic kidney disease and the progressive decline in renal function using various novel analytic approaches, including latent trajectory analysis. This work has highlighted the heterogeneity of decline in renal function, and identified subgroups at particular risk of renal dysfunction. They have recently used proteomics, metabolomics and other omics approach to identify predisposing factors and markers associated with rapid renal function decline and the development of diabetic kidney disease. They have also conducted studies to examine sub-phenotype in diabetic kidney disease, and the long-term impact of acute kidney injury on progression of diabetic kidney disease. The team is also using big-data analytics to examine the epidemiology of diabetes complications based on population-based administrative data. Both Ronald and Andrea Luk have been invited to contribute to the recent International Diabetes Federation (IDF) Diabetes Atlas, leading subgroups on type 1 Diabetes in adults and young-onset diabetes, respectively.

Earlier work has also highlighted the burden of young-onset diabetes, and conditions that predispose to young-onset diabetes. The team has completed of one of the longest follow-up studies to investigate the impact of Polycystic Ovary Syndrome (PCOS) on the development of glucose intolerance and diabetes among young women. This work has now extended to the long-term follow-up cardiovascular complications and metabolic outcomes in women with PCOS and their offspring, as well as analyses based on population-based data.

Genetics of Diabetes and Gestational Diabetes

Work from the research team has contributed significantly to advance the understanding of the genetic basis of type 2 diabetes. Together with colleagues across Asia, they have completed one of the largest genome-wide association studies (GWAS) for type 2 diabetes, and identified 61 novel loci for type 2 diabetes. This study has considerably expanded the number of genetic loci associated with type 2 diabetes in Asians, and would form the basis of future translation towards clinical prediction and care. They are currently investigating the role of these markers in the development of glucose intolerance and other metabolic abnormalities among adolescents and children.

In a project supported by Research Grants Council – General Research Fund, Andrea is leading an analysis to identify monogenic forms of diabetes among the research team's cohort of patients with young-onset diabetes. This work will provide complementary information on rare genetic variation that contributes to the heritability of diabetes in Asians, and help to advance precision medicine in diabetes.

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

Research Progress Summary



Principal Investigator

Ronald Ma

Team members

Andrea Luk, Risa Ozaki, Wing Yee So, Hongjiang Wu, Cadmon Lim, Heung Man Lee, Claudia Tam, Raymond Wan, Ming Wai Poon, Guozhi Jiang, Noel Ng, Fefei Cheng, Eric Lau, Aimin Yang, Baoqi Fan, Vince Chan, Chi Wai Ng, Yong Hou, Chun Hei Tam, Charmaine Lee, Kit Ying Tsoi, Qiao Jin, Chuiguo Huang, Yingnan Fan, Tsz Fung Tsoi, Xinge Zhang, Kqun Kiu Wong

Long-term Consequences of Gestational Diabetes and Related Biomarkers

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

Genetic and Novel Biomarkers of Diabetes Complications

In work supported by the Research Grants Council Theme-based Research Scheme (TRS), Ronald's team has completed one of the largest genome-wide association studies for diabetes complications globally, and identified a number of genomic regions associated with diabetic kidney disease in Asians. In addition, through the TRS, the team has established the multi-centre Hong Kong Diabetes Biobank (HKDB), which forms a unique dataset with detailed clinical phenotyping, multi-omics profiling and long-term follow-up which would serve to advance future epidemiology research as well as biomarker discovery. Ongoing works include investigating the biological mechanisms whereby the new genes impact the development of diabetes complications, with views to develop novel treatments to target diabetes complications. With ongoing support from the Research Grants Council Research Impact Fund, they are continuing their work on biomarkers for diabetes complications, and have expanded that effort to incorporate metabolomic profiling to integrate into their multi-omics analyses to obtain a better picture of key disease pathways. The research team has also shown the utility of leukocyte

telomere length (LTL) as a biomarker for diabetes-related complications, as well as other diabetes-related outcomes.

Precision Medicine in Diabetes

Through support from the Research Grants Council Research Impact Fund and the Croucher Foundation, the team aims to bring some of the discoveries generated from their work to translate to the bedside to impact on clinical care. This includes incorporating their biomarkers into clinical management of patients with diabetes, development of various polygenic risk scores, as well as pharmacogenomics studies to stratify patients based on treatment response for a better selection of glucose-lowering and other treatments. They are also developing genetic risk scores for stratifying risk of type 1 diabetes in Chinese. The research team has recently been invited to contribute to a major global initiative on Precision Medicine in Diabetes, including leading a systematic review of biomarkers relevant to predicting diabetes complications.

COVID-19 and Diabetes

Since the pandemic began, COVID-19 has impacted on every aspect of daily life. People with diabetes have increased susceptibilities to COVID-19 and adverse outcomes following COVID-19 infections. The research team has been conducting epidemiological analyses relating to diabetes and COVID-19, including the impact of diabetes treatments on outcome, as well as genetic studies relating to adverse outcome in COVID-19.

Much of their research is highly multidisciplinary and collaborative, with ongoing collaborations with more than 20 research groups across the world.

Research and Scholarship

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Ronald Ma	Croucher Senior Research Fellow (2020-2021)	Croucher Foundation
	Member	Lancet Clinical Commission on Diabetes
	Executive Board Member	Asian Association for the Study of Diabetes (AASD)
	Section Lead	International Diabetes Federation (IDF) Diabetes Atlas 2021
	Co-chair, Workgroup on Precision Prognostics, Precision Medicine in Diabetes Initiative	American Diabetes Association (ADA) Precision Medicine in Diabetes Initiative (PMDI)
	Panel Member	RGC Biology and Medicine Panel
Andrea Luk	Co-lead	Epidemiology section, and Member, Lancet Clinical Commission on Diabetes
	Section Lead	International Diabetes Federation (IDF) Diabetes Atlas 2021

Fellowships

Member's Name	Details	
	Fellowship	Organisation
Ronald Ma	Croucher Senior Medical Research Fellowship (2020-2021)	Croucher Foundation
Noel Ng	RGC Postdoctoral Fellowship	Research Grants Council
Feifei Cheng	Faculty Postdoctoral Fellowship	Faculty of Medicine, The Chinese University of Hong Kong

Academic Editorship

Member's Name	Details	
	Role	Journal
Ronald Ma	Expert Editor (from 11/2020)	Journal of Diabetes Investigation
	Member of Editorial Board	PLOS Medicine
		Obesity Reviews
	Associate Editor	Diabetologia
Andrea Luk	Associate Editor	Diabetic Medicine



Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Ronald Ma	Reviewer	PLOS Medicine
		Diabetes Care
		Diabetologia
		Diabetes
		Diabetic Medicine
		Journal of Diabetes Investigation
		Diabetes/Metabolism Research and Reviews
		Diabetes Research and Clinical Practice
		Journal of Clinical Endocrinology and Metabolism
		American Journal of Clinical Nutrition
		Annals of Human Biology
		Clinical Endocrinology
		Obesity Reviews
		Obesity
		International Journal of Obesity
		IETE Technical Review
		Nephrology Dialysis Transplantation
		PLOS One
Andrea Luk	Reviewer	Diabetes Care
		Diabetologia
		Diabetic Medicine
		Diabetes
		Obesity and Metabolism
		Journal of Diabetes
		Diabetes/Metabolism Research and Reviews
		Diabetes Research and Clinical Practice
		Cardiovascular Diabetology
		Journal of Clinical Endocrinology and Metabolism
		Lancet Regional Health Western Pacific
	Programme Committee Stream Lead	Diabetes complications, World Diabetes Congress 2022, Lisbon, Portugal

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Ronald Ma	A Nanotechnology Platform for Profiling Diabetes-related MiRNA for Precision Medicine	Innovation and Technology Commission – Midstream Research Programme for Universities	01/06/2021	30/11/2023	5,998,400
	Research Talent Hub - PiH/198/21	Innovation and Technology Commission	01/06/2021	30/11/2023	1,005,000
	Research Talent Hub - InP/198/21	Innovation and Technology Commission	12/07/2021	30/11/2023	541,393.54
	Research Talent Hub - PiH/242/21	Innovation and Technology Commission	12/07/2021	30/09/2022	490,677.41
	Research Talent Hub - InP/198/21	Innovation and Technology Commission	18/10/2021	30/11/2023	561,208.06
	Croucher Senior Medical Research Fellowship	Croucher Foundation	01/05/2021	30/04/2022	2,272,948
	Precision Medicine in Diabetes	Croucher Foundation	01/05/2021	30/04/2023	2,000,000
	Diabetes and Telomere Length	The Chinese University of Hong Kong – Direct Grant	30/06/2021	29/06/2022	32,000
	Translating Multi-omic Discoveries to Transform Diabetes Care and Reduce Diabetic Complications	Research Grants Council – Research Impact Fund	01/05/2019	30/04/2024	8,400,000
	Translating Multi-omic Discoveries to Transform Diabetes Care and Reduce Diabetic Complications	Research Committee – Research Impact Matching Fund	01/05/2019	30/04/2024	3,401,550
	Translating Multi-omic Discoveries to Transform Diabetes Care and Reduce Diabetic Complications	Research Committee – Funding for Research Sustainability of Major Research Grants Council Funding Schemes	27/05/2019	30/04/2024	500,000

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Ronald Ma	Unraveling the Link between Maternal Hyperglycaemia and Childhood Obesity: Genome-wide Methylation Analysis in a Prospective Cohort of Untreated Gestational Diabetes	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	970,517
	Unraveling the Link between Maternal Hyperglycaemia and Childhood Obesity: Genome-wide Methylation Analysis in a Prospective Cohort of Untreated Gestational Diabetes	Research Incentive Scheme top-up for Research Grants Council – General Research Fund	01/01/2019	31/12/2021	20,000
	Progression of Glucose Intolerance and Cardiometabolic Risk Factors over a Decade in Chinese Women with Polycystic Ovary Syndrome: A Case-control Study	The Chinese University of Hong Kong – Direct Grant	05/06/2020	04/06/2021	62,000
	Genomic Medicine in Diabetic Kidney Disease	University Grants Committee – Research Matching Grant Scheme	01/06/2020	30/11/2026	2,344,848.67
	Precision Medicine in Diabetes	University Grants Committee – Research Matching Grant Scheme	01/12/2021	30/11/2026	500,000
	A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter, Event-driven Phase III Study to Investigate the Efficacy and Safety of Finerenone on the Reduction of Cardiovascular Morbidity and Mortality in Subjects with Type 2 Diabetes Mellitus	Bayer HealthCare Limited	04/01/2016	07/07/2021	2,073,177.5

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Ronald Ma	Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Assess Cardiovascular Outcomes Following Treatment with Ertugliflozin (MK-8835/ PF-04971729) in Subjects with Type 2 Diabetes Mellitus and Established Vascular Disease, the Vertis CV Study	Merck Sharp & Dohme (Asia) Limited	28/02/2017	07/07/2021	958,505
	A Phase 3b, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of TRC101 in Delaying Chronic Kidney Disease Progression in Subjects with Metabolic Acidosis	Tricida, Inc.	01/04/2019	31/12/2024	1,605,460
	PIONEER 12 China Multi-regional Clinical Trial: Efficacy and Safety of Oral Semaglutide Versus Sitagliptin in Subjects with Type 2 Diabetes Mellitus Treated with Metformin	Novo Nordisk Hong Kong Limited	01/08/2019	06/04/2023	2,332,500
	Semaglutide Cardiovascular Outcomes Trial in Patients with Type 2 Diabetes (SOUL)	Novo Nordisk Hong Kong Limited	29/08/2019	29/07/2024	9,424,000
	A Multicenter, Multinational, Prospective, Interventional, Single-arm, Phase IV Study Evaluating the Clinical Efficacy and Safety of 26 Weeks of Treatment with Insulin Glargine 300U/ml (Gla-300) in Patients with Type 2 Diabetes Mellitus Uncontrolled on Basal Insulin	Sanofi-Aventis Hong Kong Limited	01/08/2019	31/12/2021	424,250
	FAME 1 EYE - The Fenofibrate and Microvascular Events in Type 1 Diabetes Eye. A Randomised Trial to Evaluate the Efficacy on Retinopathy and Safety of Fenofibrate in Adults with Type 1 Diabetes; A Multicenter Double-blind Placebo-controlled Study in Australia and Internationally	University of Sydney	01/08/2019	31/12/2024	348,160

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Ronald Ma	Effect and Safety of Semaglutide 2.4mg Once-weekly on Weight Management in Subjects with Overweight or Obesity	Novo Nordisk Hong Kong Limited	08/12/2020	31/12/2024	2,176,500
	A Non-blinded Retrospective Biomarker Add-on Study to FIGARO-DKD for Bioprofiling the Pharmacodynamic Response to Finerenone in FIGARO-DKD Subjects (FIGARO-BM)	Bayer HealthCare Limited	15/10/2021	31/12/2023	105,000
	Precision Medicine to Redefine Insulin Secretion and Monogenic Diabetes (PRISM) in Chinese Patients with Young Onset Diabetes	Food and Health Bureau - Health and Medical Research Fund Commissioned Grant	01/09/2019	31/08/2024	8,457,718
	Characterising the Hazards of Cardiac Arrhythmias and Adverse Clinical Outcomes Accompanying Hypoglycaemic Nadir in Frail Elderly Diabetics on Insulin: A Prospective, Longitudinal, Observational, Follow-up Study	Health and Medical Research Fund	01/04/2018	31/03/2021	1,197,580
	The Effect of In Utero Hyperglycaemia, Maternal Overnutrition and Interaction with Postnatal Lifestyle on Cardiometabolic Risk at Young Adulthood - Extension of HAPO Follow-up Study	Research Grants Council – General Research Fund	01/01/2020	31/12/2022	1,158,019
	To Develop A Community-based Exercise Programme to Prevent Diabetic Shoulder Problems in Hong Kong Chinese Elderly	Health and Medical Research Fund	01/10/2020	30/09/2022	775,188
Ronald Ma Andrea Luk	Precision Medicine to Redefine Insulin Secretion and Monogenic Diabetes (PRISM) in Chinese Patients with Young Onset Diabetes	Food and Health Bureau – Health and Medical Research Fund Commissioned Grant	01/09/2019	31/08/2024	8,457,718

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Andrea Luk	A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter, Event-Driven Phase III Study to Investigate the Efficacy and Safety of Finerenone, In Addition To Standard of Care, on the Progression of Kidney Disease in Subjects with Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease	Bayer Healthcare Limited	04/01/2016	31/12/2021	1,690,787.5
	A Trial Investigating the Pharmacokinetic Properties of Fast-Acting Insulin Aspart in Chinese Subjects with Type 1 Diabetes or Type 2 Diabetes	Novo Nordisk Hong Kong Limited	03/12/2020	31/12/2022	2,672,830
	Delineating the Metabolic Architecture and Response to Anti-hyperglycaemic Drug Treatment in Lean Type 2 Diabetes in Chinese	Research Grants Council – General Research Fund	01/01/2021	31/12/2023	1,178,778
	Randomised, Double-blind (within Dose Groups), Placebo-controlled and Parallel Group Trial to Investigate the Effects of Different Doses of Oral BI685509 Given over 20 Weeks	Boehringer Ingelheim Limited	15/06/2021	31/12/2023	610,000
	ReFINEDR: Observational Study of Routine Ophthalmological Examinations of Patients Included in the 2 Bayer Sponsored Phase 3 Clinical Trials FIDELIO and FIGARO to Investigate the Effect of Finerenone on Delaying the Progression of Diabetic Retinopathy	Bayer Healthcare Limited	16/02/2021	31/12/2023	80,500
	Innovative Diagnosis and Treatment for Shrimp Allergy	Research Committee – Research Impact Matching Fund	01/06/2020	31/05/2025	8,397,098

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Andrea Luk	Commissioned Programme on Early Phase Testing of Novel Pharmaceutical Products in the Phase 1 Clinical Trial Centre, the Chinese University of Hong Kong	Food and Health Bureau – Health and Medical Research Fund Commissioned Grant	02/05/2019	01/05/2024	50,000,000
Noel Ng	Evaluation of the Long-term Healthcare Impact of Polycystic Ovary Syndrome	Health and Medical Research Fund	01/10/2021	30/09/2023	1,304,136

Publications

A. Journal Papers

1. Mao D, Lau ESH, Wu H, Yang A, Shi M, Fan B, Tam CHT, Chow E, Kong APS, Ma RCW, Luk A, Chan JCN. Risk associations of long-term HbA1c variability and obesity on cancer events and cancer-specific death in 15,286 patients with diabetes - A prospective cohort study. *The Lancet Regional Health - Western Pacific.* 2022;18:100315. doi:10.1016/j.lanwpc.2021.100315. (Epub ahead of print)

2. Lee HM, Lee SC, He L, Kong APS, Mao D, Hou Y, Chung ACK, Xu G, Ma RC, Chan JCN. Legacy effect of high glucose on promoting survival of HCT116 colorectal cancer cells by reducing endoplasmic reticulum stress response. *American Journal of Cancer Genetics.* 2021;11(12):6004. doi: pmc/articles/pmc8727802/. (Epub ahead of print)

3. Hindy G, Dornbos P, Chaffin MD, Liu DJ, Wang M, Selvaraj MS, Zhang D, Park J, Aguilar-Salinas CA, Antonacci-Fulton L, Ardissino D, Arnett DK, Aslibekyan S, Atzmon G, Ballantyne CM, Barajas-Olmos F, Barzilai N, Becker LC, Bielak LF, Bis JC, Peloso GM, et al. Rare coding variants in 35 genes associate with circulating lipid levels—a multi-ancestry analysis of 170,000 exomes. *The American Journal of Human Genetics.* 2022;109(1):81-96. doi:10.1016/j.ajhg.2021.11.021. (Epub ahead of print)

4. Jin N, Lee H, Hou Y, Yu ACS, Li J, Kong APS, Lam CCH, Wong SKH, Ng EKW, Ma RC, Chan JCN, Chan T. Integratome analysis of adipose tissues reveals abnormal epigenetic regulation of adipogenesis, inflammation, and insulin signaling in obese individuals with type 2 diabetes. *Clinical and Translational Medicine.* 2021;11(12). doi:10.1002/ctm2.596. (Letter, Epub ahead of print)

5. Mao D, Yuen L-Y, Ho C-S, Wang CC, Tam CHT, Chan MHM, Lowe WLJ, Ma RC, Tam WH. Maternal and neonatal 3-epi-25-hydroxyvitamin D concentration and factors influencing their concentrations. *Journal of the Endocrine Society.* 2022;6(1):1-9. doi:10.1210/jendso/bvab170.

6. Wu H, Lau ES, Yang A, Zhang X, Ma RC, Kong AP, Chow E, So W-Y, Chan JC, Luk AO. Data Resource Profile: The Hong Kong diabetes surveillance database (HKDSD) data resource basics. *International Epidemiological Association.* doi:10.1093/ije/dyab252. (Data Resource Profile)

7. Jin Q, Lau ES, Luk AO, Ozaki R, Chow EY, So T, Yeung T, Loo K man, Lim CK, Kong AP, So WY, Jenkins AJ, Chan JC, Ma RC. Skin autofluorescence is associated with progression of kidney disease in type 2 diabetes: A prospective cohort study from the Hong Kong diabetes biobank. *Nutrition, Metabolism, and Cardiovascular Diseases: NMCD.* 2022;32(2). doi:10.1016/j.numecd.2021.10.007. (Epub ahead of print)

8. Lee HM, Wong WKK, Fan B, Lau ES, Hou Y, O CK, Luk AOY, Chow EYK, Ma RCW, Chan JCN, Kong APS. Detection of increased serum miR-122-5p and miR-455-3p levels before the clinical diagnosis of liver cancer in people with type 2 diabetes. *Scientific Reports.* 2021 111. 2021;11(1):1-11. doi:10.1038/s41598-021-03222-x.

9. Jin Q, Ma RCW. Metabolomics in diabetes and diabetic complications: Insights from epidemiological studies. *Cells.* 2021;10(11):2832. doi:10.3390/cells10112832.

10. Cheng F, Luk AO, Wu H, Tam CHT, Lim CKP, Fan B, Jiang G, Carroll L, Yang A, Lau ESH, Ng ACW, Lee HM, Chow E, Kong APS, Keech AC, Joglekar M V., So WY, Hardikar AA, Chan JCN, Jenkins AJ, Ma RCW. Relative leucocyte telomere length is associated with incident end-stage kidney disease and rapid decline of kidney function in type 2 diabetes: Analysis from the Hong Kong diabetes register. *Diabetologia.* 2022;65(2):375-386. doi:10.1007/s00125-021-05613-1. (Epub ahead of print)

11. Saini V, Joglekar M V., Wong WKM, Jiang G, Nassif NT, Simpson AM, Ma RCW, Dalgaard LT, Hardikar AA. Manipulating cellular micrornas and analyzing high-dimensional gene expression data using machine learning workflows. *STAR protocols.* 2021;2(4). doi:10.1016/j.xpro.2021.100910.

12. Wang K, Yang A, Shi M, Tam CCH, Lau ESH, Fan B, Lim CKP, Lee HM, Kong APS, Luk AOY, Tomlinson B, Ma RCW, Chan JCN, Chow E. CYP2C19 loss-of-function Polymorphisms are associated with reduced risk of sulfonylurea treatment failure in Chinese patients with type 2 diabetes. *Clinical Pharmacology and Therapeutics.* 2022;111(2):461-469. doi:10.1002/cpt.2446. (Epub ahead of print)

13. Liu J, Li J, Li W, Li N, Huo X, Wang H, Leng J, Yu Z, Ma RCW, Hu G, Fang Z, Yang X. Predictive values of serum metabolites in early pregnancy and their possible pathways for gestational diabetes: A nested case-control study in Tianjin, China. *Journal of diabetes and its complications.* 2021;35(12). doi:10.1016/j.jdiacomp.2021.108048.



14. Ng NYH, Liu KH, Tam CHT, Jiang G, Cheng F, Hou Y, Yau TT, Ozaki R, Chan MH, Lim CK, Sahota DS, Li TC, Cheung LP, Tam WH, Chu WCW, Ma RCW. The relationship between visceral adiposity and cardiometabolic risk in Chinese women with polycystic ovary syndrome. *Obesity research & clinical practice.* 2021;15(6):593-599. doi:10.1016/j.orcp.2021.09.004.

15. Chu LCH, Sugiyama T, Ma RCW. Recent updates and future perspectives on gestational diabetes mellitus: An important public health challenge. *Journal of diabetes investigation.* 2021;12(11):1944-1947. doi:10.1111/jdi.13670.

16. He Y, Tam CHT, Yuen LY, Catalano PM, Ma RCW, Tam WH. Optimal gestational weight gain for Chinese women - Analysis from a longitudinal cohort with childhood follow-up. *The Lancet Regional Health - Western Pacific*. 2021;13. doi:10.1016/j.lanwpc.2021.100190.

17. Zhou Q, Wang Y, Gu Y, Li J, Wang H, Leng J, Li W, Yu Z, Hu G, Ma RCW, Fang ZZ, Yang X, Jiang G. Genetic variants associated with beta-cell function and insulin sensitivity potentially influence bile acid metabolites and gestational diabetes mellitus in a Chinese population. *BMJ open diabetes research & care.* 2021;9(1). doi:10.1136/bmjdrc-2021-002287.

18. Ma RCW, Ng NYH, Cheung LP. Assisted reproduction technology and long-term cardiometabolic health in the offspring. *PLOS Medicine*. 2021;18(9). doi:10.1371/journal.pmed.1003724.

19. Cheng F, Ng NYH, Tam CHT, Zhang Y, Lim CKP, Jiang G, Ng ACW, Yau TTL, Cheung LP, Xu A, Chan JCN, Ma RCW. Association between FGF19, FGF21 and lipocalin-2, and diabetes progression in PCOS. *Endocrine Connections*. 2021;10(10):1243. doi:10.1530/ec-21-0082.

20. Jin Q, Lau ESH, Luk AOY, Ozaki R, Chow EYK, Cheng F, So T, Yeung T, Loo K man, Lim CKP, Kong APS, Jenkins AJ, Chan JCN, Ma RCW. Skin autofluorescence is associated with higher risk of cardiovascular events in Chinese adults with type 2 diabetes: A prospective cohort study from the Hong Kong diabetes biobank. *Journal of diabetes and its complications*. 2021;35(10). doi:10.1016/j.jdiacomp.2021.108015.

21. Wu H, Lau ESH, Yang A, Szeto CC, Ma RCW, Kong APS, Chow E, So WY, Chan JCN, Luk AOY. Trends in kidney failure and kidney replacement therapy in people with diabetes in Hong Kong, 2002-2015: A retrospective cohort study. *The Lancet Regional Health - Western Pacific*. 2021;11:100165. doi:10.1016/j.lanwpc.2021.100165.

22. Gibbons KS, Chang AMZ, Ma RCW, Tam WH, Catalano PM, Sacks DA, Lowe J, David McIntyre H. Prediction of large-for-gestational age infants in relation to hyperglycemia in pregnancy - A comparison of statistical models. *Diabetes Research And Clinical Practice*. 2021;178. doi:10.1016/j.diabres.2021.108975.

23. Ong KL, Wu L, Januszewski AS, O'Connell R, Xu A, Scott RS, Sullivan DR, Rye KA, Li H, Ma RCW, Li L, Gebski V, Jenkins AJ, Jia W, Keech AC. The relationship of neutrophil elastase and proteinase 3 with risk factors, and chronic complications in type 2 diabetes: A fenofibrate intervention and event lowering in diabetes (field) sub-study. *Diabetes & Vascular Disease Research*. 2021;18(4). doi:10.1177/14791641211032547.

24. Wang H, Yang W, Liu J, Leng J, Li W, Yu Z, Li J, Cw Ma R, Hu G, Fang Z, Wang Y, Yang X. Serum concentrations of SFAs and CDKAL1 single-nucleotide polymorphism rs7747752 are related to an increased risk of gestational diabetes mellitus. *The American Journal of Clinical Nutrition*. 2021;114:1698-1707. doi:10.1093/ajcn/nqab225.

25. Wu H, Lau ESH, Yang A, Fan B, Ma RCW, Kong APS, Chow E, So WY, Chan JCN, Luk AOY. Young age at diabetes diagnosis amplifies the effect of diabetes duration on risk of chronic kidney disease: A prospective cohort study. *Diabetologia*. 2021;64(9):1990-2000. doi:10.1007/S00125-021-05494-4. (Data Resource Profile)

26. Goodrich JK, Singer-Berk M, Son R, Sveden A, Wood J, England E, Cole JB, Weisburd B, Watts N, Caulkins L, Dornbos P, Koesterer R, Zappala Z, Zhang H, Maloney KA, Dahl A, Aguilar-Salinas CA, Atzmon G, Barajas-Olmos F, Barzilai N, Udler MS, et al. Determinants of penetrance and variable expressivity in monogenic metabolic conditions across 77,184 exomes. *Nature Communications*. 2021 121. 2021;12(1):1-15. doi:10.1038/s41467-021-23556-4.

27. Wong WKM, Joglekar M V., Saini V, Jiang G, Dong CX, Chaitarvornkit A, Maciag GJ, Gerace D, Farr RJ, Satoor SN, Sahu S, Sharangdhar T, Ahmed AS, Chew YV, Liuwantara D, Heng B, Lim CK, Hunter J, Januszewski AS, Sørensen AE, Akil ASA, Gamble JR, Loudovaris T, Kay TW, Thomas HE, O'Connell PJ, Guillemin GJ, Martin D, Simpson AM, Hawthorne WJ, Dalgaard LT, Ma RCW, Hardikar AA. Machine learning workflows identify a microrna signature of insulin transcription in human tissues. *iScience*. 2021;24(4):102379. doi:10.1016/j.isci.2021.102379.

28. Lim LL, Lau ESH, Fu AWC, Ray S, Hung YJ, Tan ATB, Chamnan P, Sheu WHH, Chawla MS, Chia YC, Chuang M, Nguyen DC, Sosale A, Saboo BD, Phadke U, Kesavadev J, Goh SY, Gera N, Thanh T, Vu H, Ma RCW, Lau V, Luk AOY, Kong APS, Chan JCN. Effects of a technology-assisted integrated diabetes care program on cardiometabolic risk factors among patients with type 2 diabetes in the Asia-Pacific region the jade program randomized clinical trial + supplemental content. Orig Investig I Diabetes Endocrinol *JAMA Network Open*. 2021;4(4):217557. doi:10.1001/jamanetworkopen.2021.7557.

29. Yang A, Shi M, Wu H, Lau ESH, Ma RCW, Kong APS, Wing &, So Y, Luk AOY, Chan JCN, Chow E. Long-term metformin use and risk of pneumonia and related death in type 2 diabetes: A registry-based cohort study. *Diabetologia.* doi:10.1007/s00125-021-05452-0.

30. Ling J, Poon EWM, Yang A, Yeung T, Loo K, Ozaki R, Ma RCW, Luk AOY, Kong APS, Chan JCN, Chow E. Glycemic variability and time in range during self-titration of once daily insulin glargine 300 u/ml versus neutral protamine hagedorn insulin in insulin-naïve Chinese type 2 diabetes patients. *Diabetes Therapy*. 2021;12(5):1399-1413. doi:10.1007/s13300-021-01046-6.

31. Dong L, Li JC, Hu ZJ, Huang XR, Wang L, Wang HL, Ma RCW, Lan HY, Yang SJ. Deletion of Smad3 protects against diabetic myocardiopathy in db/db mice. *Journal of Cellular and Molecular Medicine*. 2021;25(10):4860. doi:10.1111/jcmm.16464.

32. Tam CHT, Lim CKP, Luk AOY, Ng ACW, Lee H man, Jiang G, Lau ESH, Fan B, Wan R, Kong APS, Tam W hung, Ozaki R, Chow EYK, Lee K fai, Siu S chung, Hui G, Tsang C chi, Lau K piu, Leung JYY, Tsang M wo, Kam G, Lau I tim, Li JKY, Yeung VTF, Lau E, Lo S, Fung S, Cheng Y lun, Chow C chung, Hu M, Yu W, Tsui SKW, Huang Y, Lan H, Szeto C chun, Tang NLS, Ng MCY, So W yee, Tomlinson B, Chan JCN, Ma RCW. Development of genome-wide polygenic risk scores for lipid traits and clinical applications for dyslipidemia, subclinical atherosclerosis, and diabetes cardiovascular complications among east asians. *Genome Medicine*. 2021;13(1). doi:10.1186/s13073-021-00831-z.

33. Cheng CK, Luo JY, Lau CW, Cho WC shing, Ng CF, Ma RCW, Tian XY, Huang Y. A GLP-1 analog lowers ER stress and enhances protein folding to ameliorate homocysteine-induced endothelial dysfunction. *Acta Pharmacologica Sinica*. 2021 4210. 2021;42(10):1598-1609. doi:10.1038/s41401-020-00589-x.

34. Sheng J, Wang L, Tang PMK, Wang HL, Li JC, Xu BH, Xue VW, Tan RZ, Jin N, Chan TF, Huang XR, Ma RCW, Lan HY. Smad3 deficiency promotes beta cell proliferation and function in db/db mice via restoring Pax6 expression. *Theranostics*. 2021;11(6):2845-2859. doi:10.7150/thno.51857.

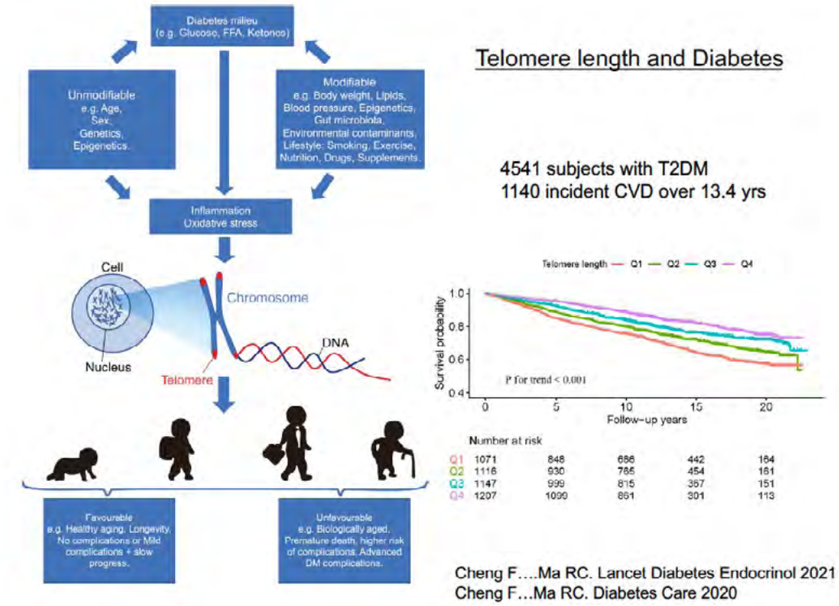
35. Yang L, Webb SE, Jin N, Lee HM, Chan TF, Xu G, Chan JCN, Miller AL, Ma RCW. Investigating the role of dachshund b in the development of the pancreatic islet in zebrafish. *Journal of Diabetes Investigation*. 2021;12(5):710-727. doi:10.1111/jdi.13503.

36. Cheng F, Luk AO, Wu H, Lim CKP, Carroll L, Tam CHT, Fan B, Yang A, Lau ESH, Ng ACW, Lee HM, Chow E, Kong APS, Keech AC, Joglekar M V., So WY, Jenkins AJ, Chan JCN, Hardikar AA, Ma RCW. Shortened relative leukocyte telomere length is associated with all-cause mortality in type 2 diabetes- analysis from the Hong Kong diabetes register. *Diabetes Research And Clinical Practice*. 2021;173. doi:10.1016/j.diabres.2021.108649.

37. Chan JCN, Lim LL, Wareham NJ, Shaw JE, Orchard TJ, Zhang P, Lau ESH, Eliasson B, Kong APS, Ezzati M, Aguilar-Salinas CA, McGill M, Levitt NS, Ning G, So WY, Adams J, Bracco P, Forouhi NG, Gregory GA, Guo J, Hua X, Klatman EL, Magliano DJ, Ng BP, Ogilvie D, Panter J, Pavkov M, Shao H, Unwin N, White M, Wou C, Ma RCW, Schmidt MI, Ramachandran A, Seino Y, Bennett PH, Oldenburg B, Gagliardino JJ, Luk AOY, Clarke PM, Ogle GD, Davies MJ, Holman RR, Gregg EW. The lancet commission on diabetes: Using data to transform diabetes care and patient lives. *Lancet*. 2021;396(10267):2019-2082. doi:10.1016/S0140-6736(20)32374-6.

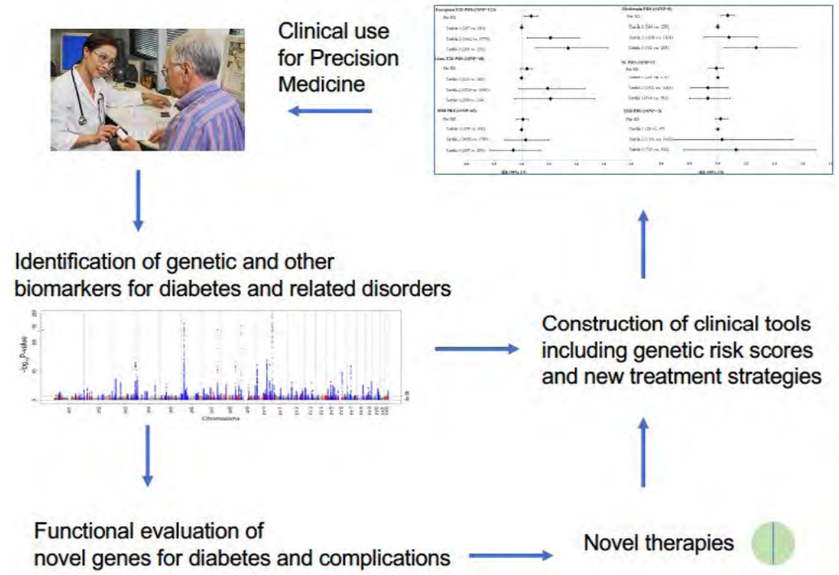
38. Luk AOY, Wu H, Lau ESH, Yang A, So WY, Chow E, Kong APS, Hui DSC, Ma RCW, Chan JCN. Temporal trends in rates of infection-related hospitalisations in Hong Kong people with and without diabetes, 2001-2016: A retrospective study. *Diabetologia*. 2021;64(1):109-118. doi:10.1007/s00125-020-05286-2.





Telomere Length in diabetes.

Source: Diabetes, metabolic disease and telomere length (Lancet Diabetes Endocrinology 2021)



Overall summary of research objectives of team.

Source: Ronald Ma



藍輝耀

HUI-YAO LAN

07 INFLAMMATORY DISEASES

Research Progress Summary

The research team of Hui-yao Lan has been very productive with several important findings in year 2021.

Firstly, the team is continuous their research into the role and mechanisms of TGF-β/Smad signalling in acute and chronic kidney diseases by identifying that TGF-β is a master regulator of diabetic complications including cardiopathy and nephropathy. They discovered that TGF-β signals through its downstream mediator of Smad3 to mediate diabetic myocardiopathy and nephropathy via a number of Smad3-dependent non-coding RNAs. They also found that latent form of TGF-β (inactive) and Smad7 are renal protective in diabetic nephropathy. Thus, targeting Smad3 or Smad3-dependent non-coding RNAs or overexpression of Smad7 may be a novel and specific therapeutic strategy for combating diabetic complications. All these findings have been published in internationally-well recognised journals as listed below. Specifically, they found that db/db lacking Smad3 are protected from diabetes and Smad3 deficiency promotes beta cell proliferation and function in db/db mice via restoring Pax6 expression (*Theranostics* 2021 Jan 1;11(6):2845-2859).

Secondly, they are continuously working on neuroimmune-related acute kidney and heart diseases by identifying that a neuron peptide Y (NPY) is produced by macrophages (CD68+NPY+) and protects against acute kidney and myocardial infarction by shifting proinflammatory M1 macrophages to reparative M2 macrophages. Results of “Neuropeptide Y (NPY) attenuates cardiac remodelling and deterioration of function following myocardial infarction” has been published in *Molecular Therapy* (2021 Oct 8;S1525-0016(21)00499-8). This is the first study to report that NPY is cardioprotective and is a novel therapeutic agent for acute myocardial infarction. This new finding may lead to develop as a novel therapy for acute myocardial infarction. Thus, this new discovery is highly significant both scientifically and clinically in cardiovascular medicine.

Thirdly, they have extended their previous discovery of macrophage-to-myofibroblast transition (MMT) in tissue fibrosis to cancer progression. They found that TGF-β1 can activate its downstream molecule Smad3 to promote cancer by triggering tumour-associated macrophages (TAM) to become cancer-associated fibroblasts (CAF) via the macrophage-



Research Progress Summary



Principal Investigator

Hui-yao Lan

Team members

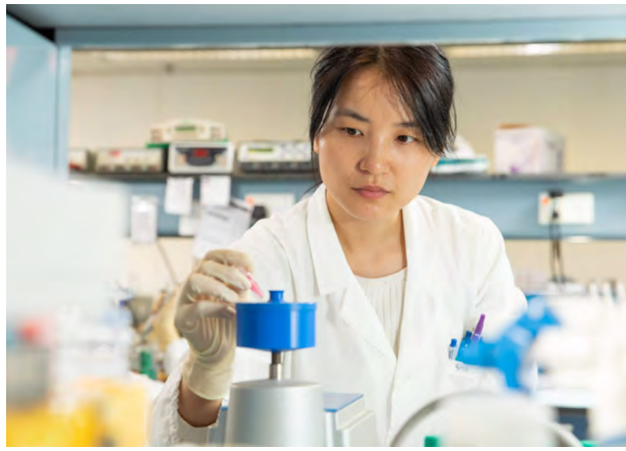
Xiaoru Lan, Guangyu Lian, Thomas Mak, Biao Wei, Choilai Chung, Yuyan Qin, Huijun He, Jiaoyi Chen, Junzhe Chen, Qixia Shen, Yuchen Wang, Jiangchun Li, Liying Liang, Wenbiao Wang, Wenqian Xu, Wenjiang Wu, Yu Zhong

myofibroblast transition mechanism (MMT). These findings have been published in *Advanced Science* (2021 Nov17;e2101235) with a *Press Release* on 23 December, 2021.

Lastly, they also found that macrophages mediate crescent glomerulonephritis via TLR4-dependant mechanism as deletion of TLR4 from macrophages resulted in the shift from inflammatory macrophages to the anti-inflammatory macrophages. Such important findings have been published in *Cellular and Molecular Life Sciences* (2021 Oct;78(19-20):6721-6734).

More excitingly, the research team has been also studying COVID-19 associated acute kidney injury (AKI) because up to 45% of critically ill COVID-19 patients develop AKI with higher mortality secondary to the lung injury. They identified that one of SARS-CoV-2 proteins, SARS-CoV-2 N protein is a key mediator for AKI and induces AKI via the Smad3-dependent G1 cell cycle arrest mechanism. Targeting Smad3 with a Smad3 inhibitor can prevent SARS-CoV-2 N protein-induced AKI. These findings are highly significant both scientifically and clinically and may lead to the development of novel therapy for COVID-19 AKI with a patent filled. These findings have been also published in an internationally high impact journal *Advanced Science* (2021 Nov 23;e2103248) with a Press Release on 29 November, 2021.

In summary, 2021 was a year worthy of the team's respect and memory. They are looking forward to achieving even greater goals in 2022.



Research and Scholarship

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Hui-yao Lan Patrick Tang	Gold Medal with Congratulations of the Jury - 2021	The 2021 Special Edition of the Geneva International Exhibition of Inventions
Hui-yao Lan	Science and Technology Progress Award (3rd Class) - 2021	Sichuan Provincial Government, China
	Distinguished Scientist Award	Chinese American Society of Nephrology

Academic Editorship

Member's Name	Details	
	Role	Journal
Hui-yao Lan	Editor-in Chief	Integrative Medicine in Nephrology and Andrology
	Editor	Clinical and Experimental Pharmacology and Physiology
	Executive Editor	International Journal of Biological Sciences
	Associate Editor	Journal of Clinical and Molecular Medicine
		Frontiers in Psychology
		Molecular Therapy

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Hui-yao Lan	Reviewer	Journal of American Society of Nephrology
		Kidney International
		Scientific Reports
		Kidney Disease
		Diabetic Nephropathy

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Hui-yao Lan	Regulatory Role of Smad3 in SARS-CoV-2 N Protein-induced Acute Kidney Injury in db/db Mice	Research Grants Council – General Research Fund	01/07/2021	31/12/2023	1,125,732
	Translating Multi-omic Discoveries to Transform Diabetes Care and Reduce Diabetic Complications	Research Grants Council – Research Impact Fund	01/03/2019	28/02/2024	12,000
	Role of TGF-Beta/Smad3 Signaling in Lupus Nephritis	Research Grants Council – General Research Fund	01/01/2020	31/12/2022	1,064,682
	Mechanism of Renal Inflammation: Role of Toll-like Receptor 4	Research Grants Council – Collaborative Research Fund	30/06/2017	29/06/2021	7,518,927
	Terminal Shortening Triggers the Molecular Regulation Mechanism of Neutrophil Capture in Acute Kidney Injury	Zhejiang University – Collaborative Research Fund	01/01/2019	31/12/2021	RMB 700,000
	Research Laboratory with Guangdong Province Hospital on Immunological and Genetic Kidney Diseases	Guangdong Provincial Department of Science and Technology, China	01/01/2020	31/01/2022	RMB 1,000,000
	Neuropeptide Y is a Novel Therapeutic Agent for Acute Myocardial Infarction	Food and Health Bureau – Health and Medical Research Fund	01/04/2020	31/03/2023	1,499,600
	Prevention and Treatment of Diabetes and Diabetic Complications by Targeting Smad3 with a Smad3 Inhibitor SIS3	Food and Health Bureau – Health and Medical Research Fund	01/04/2019	31/03/2022	1,500,000
	Regulatory Role and Mechanism of Smad3 in Immunosuppression of Neutrophil Anticancer Activities	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	1,151,040

Publications

A. Journal Papers

1. Wang W, Chen J, Hu D, Pan P, Liang L, Wu W, Tang Y, Huang XR, Yu X, Wu J, Lan HY. SARS-CoV-2 N protein induces acute kidney injury via Smad3-dependent G1 cell cycle arrest mechanism. *Advanced Science*. Published online 2021:2103248. doi:10.1002/advs.202103248. (Epub ahead of print)

2. Tang PCT, Chung JYF, Xue VWW, Xiao J, Meng XM, Huang XR, Zhou S, Chan ASW, Tsang ACM, Cheng ASL, Lee TL, Leung KT, Lam EWF, To KF, Tang PMK, Lan HY. Smad3 promotes cancer-associated fibroblasts generation via macrophage–myofibroblast transition. *Advanced Science*. Published online 2021:2101235. doi:10.1002/advs.202101235. (Epub ahead of print)

3. Qin YY, Huang XR, Zhang J, Wu W, Chen J, Wan S, Yu XY, Lan HY. Neuropeptide Y attenuates cardiac remodeling and deterioration of function following myocardial infarction. *Molecular Therapy.* Published online 2021. doi:10.1016/j.ymthe.2021.10.005. (Epub ahead of print)

4. You YK, Wu WF, Huang XR, Li H Di, Ren YP, Zeng JC, Chen H, Lan HY. Deletion of Smad3 protects against C-reactive protein-induced renal fibrosis and inflammation in obstructive nephropathy. *International Journal of Biological Sciences*. 2021;17(14):3911-3922. doi:10.7150/ijbs.62929.

5. Xue VW, Chung JYF, Tang PCT, Chan ASW, To THW, Chung JSY, Mussal F, Lam EWF, Li C, To KF, Leung KT, Lan HY, Tang PMK. USMB-shMincle: A virus-free gene therapy for blocking M1/M2 polarization of tumor-associated macrophages. *Molecular Therapy - Oncolytics*. 2021;23:26-37. doi:10.1016/J.OMTO.2021.08.010.

6. Yang F, Chen J, Huang XR, Yiu WH, Yu X, Tang SCW, Lan HY. Regulatory role and mechanisms of myeloid TLR4 in anti-GBM glomerulonephritis. *Cellular and Molecular Life Sciences*. 2021;78(19-20):6721-6734. doi:10.1007/s00018-021-03936-1.

7. Chung JYF, Chan MKK, Tang PCT, Chan ASW, Chung JSY, Meng XM, To KF, Lan HY, Leung KT, Tang PMK. AANG: A natural compound formula for overcoming multidrug resistance via synergistic rebalancing the TGF-β/Smad signalling in hepatocellular carcinoma. *Journal of Cellular and Molecular Medicine*. 2021;25(20):9805-9813. doi:10.1111/jcmm.16928.

8. Lv LL, Wang C, Li ZL, Cao JY, Zhong X, Feng Y, Chen J, Tang TT, Ni HF, Wu QL, Wang B, Lan HY, Liu BC. SAP130 released by damaged tubule drives necroinflammation via miRNA-219c/Mincle signaling in acute kidney injury. *Cell Death & Disease*. 2021;12(10). doi:10.1038/S41419-021-04131-7. (In press, Epub ahead of print)

9. Yang Q, Gao L, Hu X, Wang J, Zhang Y, Dong Y, Lan HY, Meng X. Smad3-targeted therapy protects against cisplatin-induced AKI by attenuating programmed cell death and inflammation via a NOX4-dependent mechanism. *Kidney Diseases*. 2021;7(5):372-390. doi:10.1159/000512986. (Epub ahead of print)

10. Wu W, Huang XR, You Y, Xue L, Wang XJ, Meng X, Lin X, Shen J, Yu X, Lan HY, Chen H. Latent TGF-β1 protects against diabetic kidney disease via Arkadia/Smad7 signaling. *International Journal of Biological Sciences*. 2021;17(13):3583-3594. doi:10.7150/ijbs.61647.

11. Li Y, Yuan Y, Huang Z xing, Chen H, Lan R, Wang Z, Lai K, Chen H, Chen Z, Zou Z, Ma H bin, Lan HY, Mak TW, Xu Y. GSDME-mediated pyroptosis promotes inflammation and fibrosis in obstructive nephropathy. *Cell Death & Differentiation*. 2021;28(8):2333-2350. doi:10.1038/s41418-021-00755-6.

12. Wang L, Wang HL, Liu TT, Lan HY. TGF-beta as a master regulator of diabetic nephropathy. *International Journal of Molecular Sciences*. 2021;22(15):7881. doi:10.3390/ijms22157881. (Review)

13. Chung JYF, Chan MKK, Li JSF, Chan ASW, Tang PCT, Leung KT, To KF, Lan HY, Tang PMK. TGF-β signaling: From tissue fibrosis to tumor microenvironment. *International Journal of Molecular Sciences*. 2021;22(14):7575. doi:10.3390/ijms22147575.

14. Chen XC, Li ZH, Yang C, Tang JX, Lan HY, Liu HF. Lysosome depletion-triggered autophagy impairment in progressive kidney injury. *Kidney Diseases*. 2021;7(4):254-267. doi:10.1159/000515035. (Review, Epub ahead of print)

15. Gu YY, Dou JY, Huang XR, Liu XS, Lan HY. Transforming growth factor-β and long non-coding RNA in renal inflammation and fibrosis. *Frontiers in Physiology*. 2021;12:572. doi:10.3389/fphys.2021.684236. (Review)

16. Dong L, Li JC, Hu ZJ, Huang XR, Wang L, Wang HL, Ma RCW, Lan HY, Yang SJ. Deletion of Smad3 protects against diabetic myocardiopathy in db/db mice. *Journal of Cellular and Molecular Medicine*. 2021;25(10):4860-4869. doi:10.1111/jcmm.16464. (Review)

17. Chen J, Wang W, Tang Y, Huang XR, Yu X, Lan HY. Inflammatory stress in SARS-COV-2 associated acute kidney injury. *International Journal of Biological Sciences.* 2021;17(6):1497-1506. doi:10.7150/IJBS.58791. (Review)

18. Lian GY, Wang QM, Mak TSK, Huang XR, Yu XQ, Lan HY. Inhibition of tumor invasion and metastasis by targeting TGF-β-Smad-MMP2 pathway with Asiatic acid and Naringenin. *Molecular Therapy - Oncolytics*. 2021;20:277-289. doi:10.1016/j.omto.2021.01.006.

19. Cao JY, Wang B, Tang TT, Wen Y, Li ZL, Feng ST, Wu M, Liu D, Yin D, Ma KL, Tang RN, Wu QL, Lan HY, Lv LL, Liu BC. Exosomal miR-125b-5p deriving from mesenchymal stem cells promotes tubular repair by suppression of p53 in ischemic acute kidney injury. *Theranostics*. 2021;11(11):5248-5266. doi:10.7150/thno.54550.

20. Zhang P, Yu C, Yu J, Li Z, Lan HY, Zhou Q. Arid2-IR promotes NF-κB-mediated renal inflammation by targeting NLRC5 transcription. *Cellular and Molecular Life Sciences*. 2021;78(5):2387-2404. doi:10.1007/s00018-020-03659-9.

21. Tang PCT, Chan ASW, Zhang CB, García Córdoba CA, Zhang YY, To KF, Leung KT, Lan HY, Tang PMK. TGF-β1 signaling: Immune dynamics of chronic kidney diseases. *Frontiers in Medicine*. 2021;8:106. doi:10.3389/fmed.2021.628519. (Review)

22. Yiu WH, Li Y, Lok SWY, Chan KW, Chan LYY, Leung JCK, Lai KN, Tsu JHL, Chao J, Huang XR, Lan HY, Tang SCW. Protective role of kallistatin in renal fibrosis via modulation of Wnt/β-catenin signaling. *Clinical Science*. 2021;135(3):429-446. doi:10.1042/CS20201161.

23. Zhou Q, Guo H, Yu C, Huang XR, Liang L, Zhang P, Yu J, Zhang J, Chan TF, Ma RCW, Lan HY. Identification of Smad3-related transcriptomes in type-2 diabetic nephropathy by whole transcriptome RNA sequencing. *Journal of Cellular and Molecular Medicine*. 2021;25(4):2052-2068. doi: 10.1111/jcmm.16133.

24. Gu YY, Lu FH, Huang XR, Zhang L, Mao W, Yu XQ, Liu XS, Lan HY. Non-coding RNAs as biomarkers and therapeutic targets for diabetic kidney disease. *Frontiers in Pharmacology*. 2021;11:2342. doi:10.3389/fphar.2020.583528. (Review)

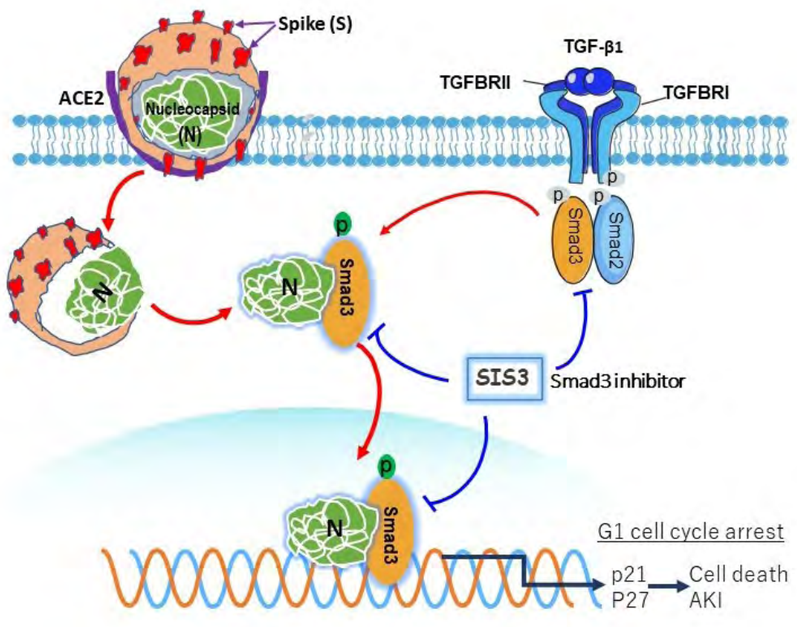
25. Gu YY, Zhang M, Cen H, Wu YF, Lu Z, Lu F, Liu XS, Lan HY. Quercetin as a potential treatment for COVID-19-induced acute kidney injury: Based on network pharmacology and molecular docking study. *PLOS ONE*. 2021;16(1):e0245209. doi:10.1371/journal.pone.0245209.

26. Tang PMK, Zhang YY, Hung JSC, Chung JYF, Huang XR, To KF, Lan HY. DPP4/CD32b/NF-κb circuit: A novel druggable target for inhibiting CRP-driven diabetic nephropathy. *Molecular Therapy*. 2021;29(1):365-375. doi:10.1016/j.ymthe.2020.08.017.

27. Sheng J, Wang L, Tang PMK, Wang HL, Li JC, Xu BH, Xue VW, Tan RZ, Jin N, Chan TF, Huang XR, Ma RCW, Lan HY. Smad3 deficiency promotes beta cell proliferation and function in db/db mice via restoring Pax6 expression. *Theranostics*. 2021;11(6):2845-2859. doi:10.7150/thno.51857.

B. Patents

1. Inventors: LAN Hui Yao, YU Xueqing
   Title: SMAD3 抑制劑治療 COVID-19 急性腎損傷
   Patent Application No. CN202110776692.9

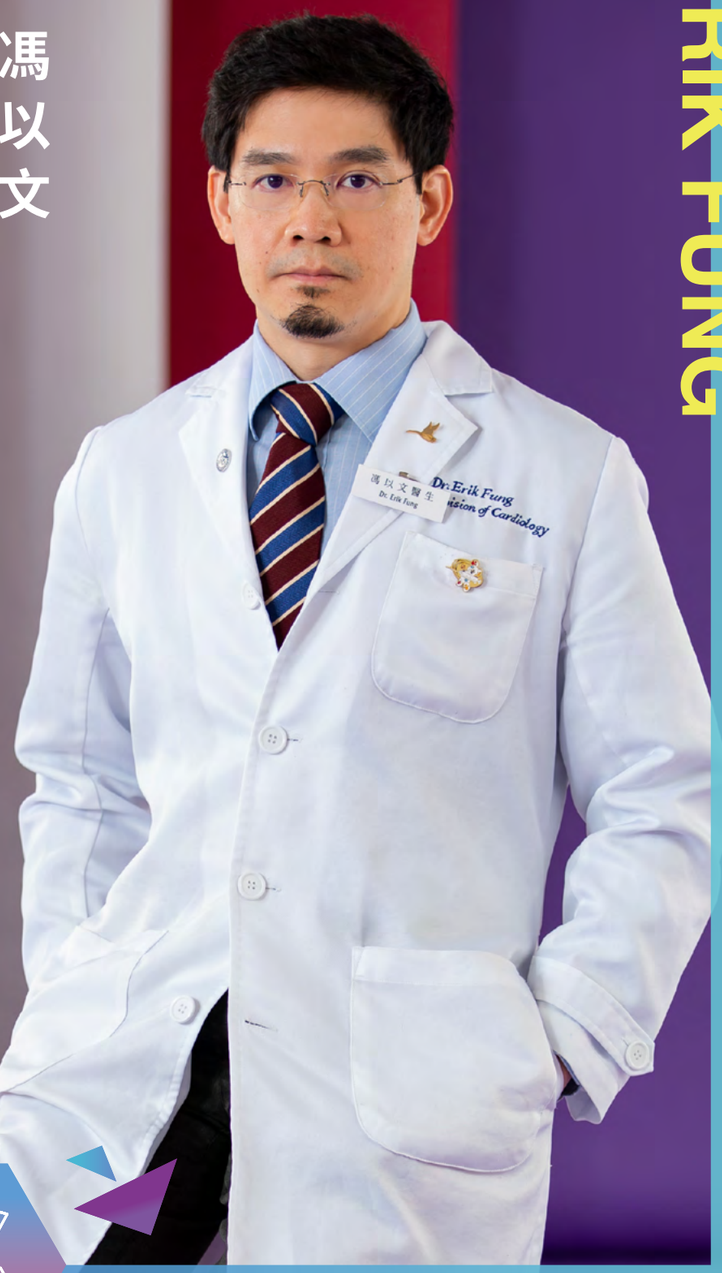


SARS-CoV-2 N protein binds and activates Smad3-dependent cell death pathway.

Source: Hui-yao Lan's team

馮以文

ERIK FUNG



07 INFLAMMATORY DISEASES



Principal Investigator

Erik Fung

Team members

Leong Ting Lui, Amy Chung, Hiu Wing Lau, Suyi Xie, Man Hei Lam, Ka Pok Leung, Hangqi Luo, Donghao Guo, Yidan Hao, Ka Man Yu

Research Progress Summary

Erik Fung is the founder of a start-up, PROTABOLIS LIMITED, which was in operation as of November 2021. Mission of the start-up is to maximise potential of health recovery and enhancement of exercise capacity.

During the past year, Erik chaired and delivered lectures in a number of local and international conferences, including:

1. "Section 3: Conceptualization and Measurement of Frailty in Advanced Heart Failure";
2. "Asian Pacific Society of Cardiology Consensus Statement on Sports Cardiology: Pre-participation Cardiovascular Screening in Young Competitive Athletes".

Other than collaborating with 7 Hong Kong researchers, Erik and his team also fostered research collaboration with researchers at University of New South Wales and EMBL Australia (Australia), University of Copenhagen (Denmark), Huawei Finland (Finland), Universitat Autònoma de Barcelona (Spain), University College London, University of Oxford and Imperial College London (United Kingdom), and University of Pittsburgh School of Medicine (United States of America).

Research and Scholarship

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Erik Fung	Healthy Longevity Catalyst Award 2021	U.S. National Academy of Medicine
	Doctor of Medicine by Research	Imperial College London, UK

Fellowships

Member's Name	Details	
	Fellowship	Organisation
Erik Fung	Fellow	American College of Cardiology
	Faculty Postdoctoral Fellowship	Faculty of Medicine, The Chinese University of Hong Kong

Academic Editorship

Member's Name	Details	
	Role	Journal
Erik Fung	Editorial Board Member	International Journal of Cardiology

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Erik Fung	Reviewer	JACC: Asia
		Aging
		Transplantation Direct
		Transplantation
		Genes
		Diabetic Medicine
		BMC Geriatrics
		Circulation: Heart Failure
		European Heart Journal
		Journal of American Heart Association
		Open Heart
		European Journal of Preventive Cardiology
		Heart
		ESC Heart Failure
		CHEST
	Conference Abstracts Reviewer	International Society of Heart & Lung Transplantation (ISHLT) 2020, 40th Annual Meeting and Scientific Sessions (22–25 April 2020). Proceedings in the *Journal of Heart and Lung Transplantation*.



Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Erik Fung	Fingerprinting Exhaled Volatile Compounds in Aging-Related Preclinical Heart Failure Using Breath Biopsy	United States National Academy of Medicine — Healthy Longevity Catalyst Award 2021-2022	09/2021	09/2022	USD 50,000
	Heart Failure Society of America–Asia Pacific Advanced Heart Failure Forum (HFSA–Conference) 2022 (Amended From HFSA–APAHFF 2021)	The Croucher Foundation — Croucher Foundation Sponsorship of Conferences, Workshops and Symposia 2021-2022	06/2021	08/2022	100,000
	Express Heart Check at Elderly Community Centres Across 18 Districts of Hong Kong (香港十八區長者地區中心心臟快速檢查)	The Social Innovation and Entrepreneurship (SIE) Fund, ORKTS — Knowledge Transfer Project Fund (KPF) 2021-2022	04/2021	09/2022	388,652
	Early Biomarkers in SARS-CoV-2 Infection: Correlation with Short/ Medium/Long-Term Clinical Outcomes, and Implications on Acute Patient Management and Long-term Medical and Health Care	Food and Health Bureau — COVID Studies	03/2021	02/2024	9,868,154
	Aldose Reductase Inhibition for Stabilization of Exercise Capacity in Heart Failure	Research Grants Council – Research Matching Grant Scheme	09/2021	30/09/2022	110,811
	LevOsimendan to Relieve End-Stage Heart Failure Symptoms in Cardiac Resynchronization Therapy Non-Responders (LORE-CRT) Study	Research Grants Council – Research Matching Grant	06/2021	30/09/2022	150,000
	A Profiling Study on Changes in Blood Metabolites in Response to Initiation of Edoxaban and/or Cardiovascular Medications	Research Grants Council – Research Matching Grant	06/2021	30/09/2022	11,519
Erik Fung	LevOsimendan to Relieve End-Stage Heart Failure Symptoms in Cardiac Resynchronization Therapy Non-Responders (LORE-CRT) Study	Synmosa BioPharma (Hong Kong) Company Ltd - Industry Research Donation	03/2021	05/2023	300,000
	DISCOVER CaReMe Global Registry	AstraZeneca (Hong Kong) - Industry Sponsored Research	12/2021	12/2022	703,125
	Aldose Reductase Inhibition for Stabilization of Exercise capacity in Heart Failure (ARISE-HF): A Multicenter, Randomized, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AT-001 in Patients with Diabetic Cardiomyopathy / Stage B Heart Failure at High Risk of Progression to Overt Heart Failure (Stage C Heart Failure)	Applied Therapeutics Inc. - Industry Sponsored Research	12/2020	03/2025	1,598,218
	ETNA-AF Global: Non-Interventional Study on Edoxaban Treatment in Routine Clinical Practice for Patients with Nonvalvular Atrial Fibrillation in Hong Kong (ETNA-AF-Hong Kong)	Daiichi Sankyo Hong Kong Ltd. - Industry Sponsored Research	09/2017	10/2022	168,282



Publications

A. Journal Papers

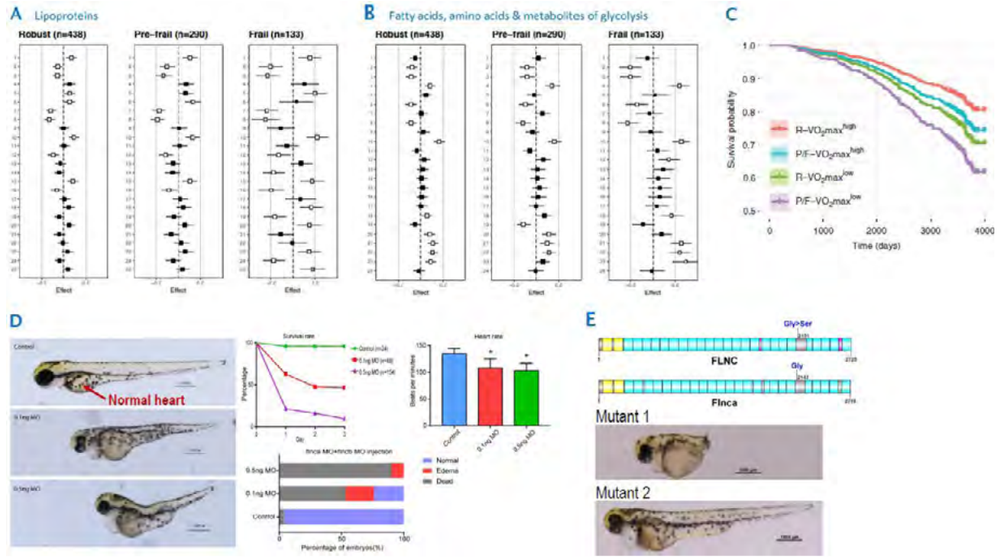
1. Fung E, Lui LT, Huang L, Cheng KF, Lau GHW, Chung YT, Ahmadabadi BN, Xie S, Lee JSW, Hui E, So WY, Sung JJY, King I, Goggins WB, Chan Q, Järvelin MR, Ma RCW, Chow E, Kwok T. Characterising frailty, metrics of continuous glucose monitoring, and mortality hazards in older adults with type 2 diabetes on insulin therapy (HARE): A prospective, observational cohort study. *The Lancet Healthy Longevity*. 2021;2(11):e724-e735. doi:10.1016/S2666-7568(21)00251-8.

2. Ojanen X, Cheng R, Törmäkangas T, Rappaport N, Wilmanski T, Wu N, Fung E, Nedelec R, Sebert S, Vlachopoulos D, Yan W, Price ND, Cheng S, Wiklund P. Towards early risk biomarkers: Serum metabolic signature in childhood predicts cardio-metabolic risk in adulthood. *eBioMedicine*. 2021;72:103611. doi:10.1016/j.ebiom.2021.103611.

3. Fung E, Cheng HY, Choi KC, Hui DSC, Yang C, Chair SY. Differential risks for heart failure hospitalization following severe respiratory infection by common pathogens. *European Journal of Preventive Cardiology*. 2021;(Ci):10-13. doi:10.1093/eurjpc/zwab123. (Letter, Epub ahead of print)

4. Teekakirikul P, Zhu W, Gabriel GC, Young CB, Williams K, Martin LJ, Hill JC, Richards T, Billaud M, Phillippi JA, Wang J, Wu Y, Tan T, Devine W, Lin J huey, Bais AS, Klonowski J, de Bellaing AM, Saini A, Wang MX, Emerel L, Salamacha N, Wyman SK, Lee C, Li HS, Miron A, Zhang J, Xing J, McNamara DM, Fung E, Kirshbom P, Mahle W, Kochilas LK, He Y, Garg V, White P, McBride KL, Benson DW, Gleason TG, Mital S, Lo CW. Common deletion variants causing protocadherin-α deficiency contribute to the complex genetics of BAV and left-sided congenital heart disease. *HGG advances*. 2021;2(3). doi:10.1016/j.xhgg.2021.100037. (Epub ahead of print)

5. Luk A, Zhang X, Fung E, Wu H, Lau ES, Yang A, Chow E, Kong AP, Ma RC, Chan JC. 223-OR: Heart failure with reduced, midrange and preserved ejection fraction in Chinese with type 2 diabetes: Risk factors and prognosis. *Diabetes*. 2021;70(Supplement_1):223-OR. doi:10.2337/db21-223-or. (Meeting abstract)



The Laboratory for Heart Failure + Circulation Research (LHFCR) leverages metabolomic profiling of human study cohorts (A & B), cardiorespiratory exercise physiology (C), and animal models of cardiomyopathy (D & E; morpholino oligonucleotides and CRISPR gene editing to disrupt the function of the filamin C gene in collaboration with Hui Zhao, SBS) to study mechanisms of heart failure. FLNC or flnc, filamin C; MO, morpholino oligonucleotide; P/F, pre-frail/frail; R, robust.

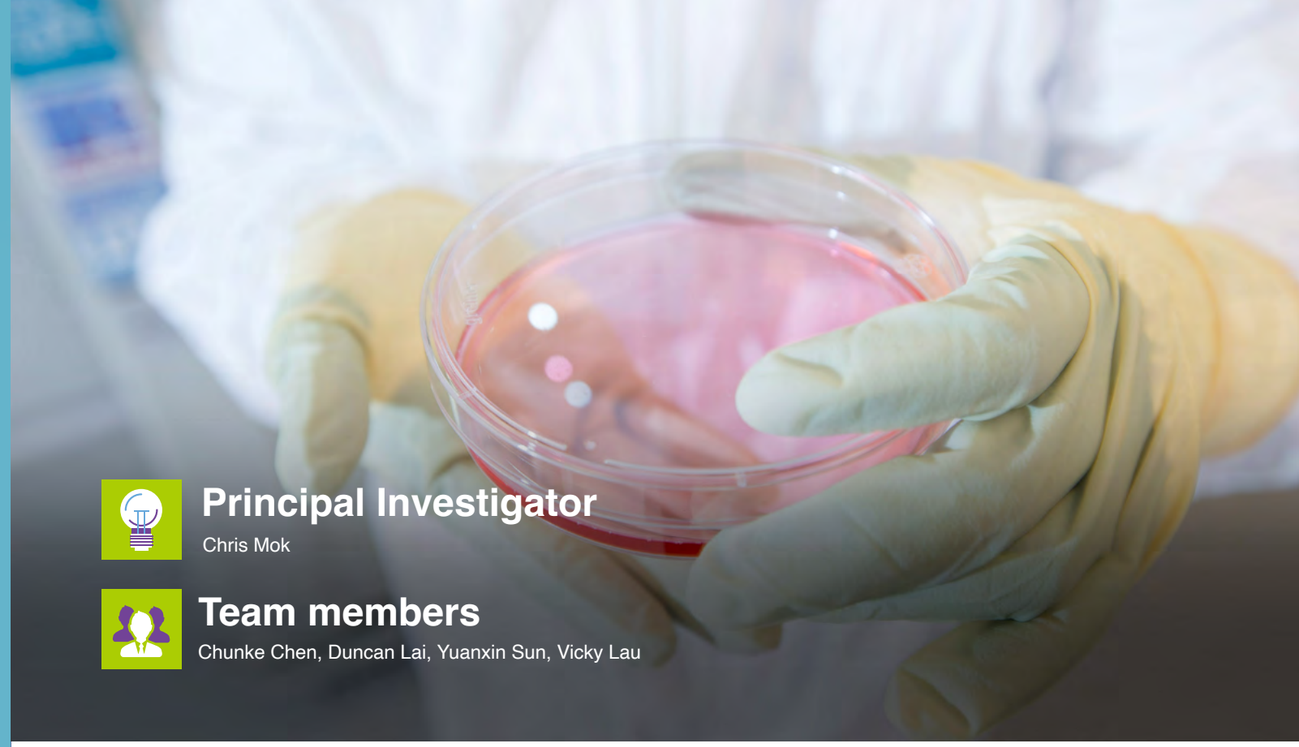
Source: Erik Fung and members of Laboratory for Heart Failure & Circulation Research, The Chinese University of Hong Kong.

莫家斌

CHRIS MOK



07 INFLAMMATORY DISEASES



Principal Investigator

Chris Mok

Team members

Chunke Chen, Duncan Lai, Yuanxin Sun, Vicky Lau

Research Progress Summary

The research group led by Chris Mok mainly focuses on understanding how the virus infection or vaccination determine the pathogenesis and immunity in host. With the experience of the related topic, they have established very solid platforms for molecular, clinical, virologic as well as immunological studies. In 2021, the team put their effort to investigate the immunological features in humans that are mediated by the stimulation of SARS-CoV-2, the cause of COVID-19 that emerged in late 2019 leading to a devastating pandemic. So far, over 500 million COVID-19 infections including more than 5 million deaths have been reported to the World Health Organization. Many COVID-19 vaccines were rapidly developed, evaluated and deployed with over 4 billion doses of COVID-19 vaccines administered worldwide. These include inactivated whole virus, lipid nanoparticle (LNP)-encapsulated mRNA, adenovirus-vectored and protein sub-unit vaccines. The safety, immunogenicity and efficacy of these vaccines have been evaluated in separate clinical trials but there are few “head-to-head” comparisons of different vaccines. Moreover, the novel SARS-CoV-2 variants have emerged and are rapidly becoming the dominant SARS-CoV-2 virus circulating globally. It is important to define reductions in antibody and T cell response in vaccinated individuals to understand potential loss of protection from vaccination. Addressing these questions together with comparing the similar features in vaccine cohorts will help to justify the performance of different COVID-19 vaccines and is also of use in helping the development of the next generation of COVID-19 vaccines. Chris’s team has set up a longitudinal study cohort to monitor their humoral and cellular immune responses from the participants who received the COVID-19 vaccine. The results provided important implications for understanding the performance of different COVID-19 vaccines and served as references for the policy making of the government.

Comparison of the Immunogenicity of BNT162b2 and CoronaVac COVID-19 Vaccines in Hong Kong (Mok et al 2021 *Respirology*)

The two types of COVID-19 vaccines which are included in this study use mRNA (Pfizer-BioNTec, BNT162b2), and whole virion inactivation (Sinovac, CoronaVac) as their approaches respectively. All these vaccines are so far only evaluated at their own designated population and countries and there is still lack of prospective study to "side-by-side" compare the immunogenicity and kinetic of different vaccines. In particular, the differences on the long-term responses of either humoral (B cell) or cellular (T cell) immune responses between these vaccines are not yet clear. In this study, the team showed that BNT162b2 elicited significantly higher $PRNT_{50}$, $PRNT_{90}$, sVNT, spike receptor binding, spike N terminal domain binding, spike S2 domain binding, spike FcR binding and antibody avidity levels than CoronaVac one month after the second dose of vaccine. Both vaccines induced SARS-CoV-2 specific $CD4^+$ and $CD8^+$ T cell responses at 1-month post-vaccination but CoronaVac elicited significantly higher structural protein-specific $CD4^+$ and $CD8^+$ T cell responses.

A Randomised Control Trial using CoronaVac or BNT162b2 vaccine as a third dose in adults vaccinated with two doses of CoronaVac (Mok et al 2021 *AJRCCM*)

CoronaVac is one of the WHO approved inactivated virus vaccines and over 750 million doses have been administered in more than 40 countries. However, breakthrough infections, some leading to severe disease and death have been reported in CoronaVac vaccinated adults have raised concern. Given the results suggesting a less than optimal protection afforded by the CoronaVac vaccine, it becomes relevant to consider the rationale for providing a booster dose with either an additional dose of CoronaVac or BionTech to those with low neutralising antibody titers after the two dose CoronaVac schedule. However, there is so far no scientific evidence to inform such a policy decision. They thus conducted a Randomised Clinical Trial (RCT) study to compare the immunogenicity of using BNT162b2 and CoronaVac as a third dose for adults with low antibody response to two doses of CoronaVac. It showed that both CoronaVac and BNT162b2 vaccines boosted antibody responses in CoronaVac immunised individuals but BNT162b2 was markedly superior in immunogenicity. BNT162b2 not only elicited a higher level of SARS-CoV-2 specific antibodies but also led to higher levels of cross-neutralising antibody levels to different variants of concern. The adverse reactions were mild and short-lived.

Altered ISGylation drives aberrant macrophage-dependent immune responses during SARS-CoV-2 infection (Munnur et al 2021 *Nature Immunology*)

Interferon stimulated gene 15 (ISG15) is a ubiquitin-like modifier frequently induced during virus infections and involved in versatile host defence mechanisms. Not surprisingly, many viruses including SARS-CoV-2 have evolved de-ISGylating activities to antagonise its effect. In this study, the team compared ISG15-driven macrophage responses upon infection by two (+) RNA viruses, Zika and SARS-CoV-2 as well as by influenza virus. All three viruses triggered induction of ISGylating enzymes; while influenza and Zika viruses induced cellular ISGylation, SARS-CoV-2 triggered hydrolysis of ISG15 modifications instead, to generate free ISG15, which appeared in the extracellular space via a non-classical autophagy-related secretory process. Increased extracellular ISG15 was also reflected in serum samples from COVID-19 patients. The high ratio of free versus conjugated ISG15 in SARS-CoV-2 infected cells correlated directly with macrophage polarisation towards a M1 phenotype, increased secretion of pro-inflammatory cytokines, and attenuated cell surface presentation of MHCI/II. This phenomenon was recapitulated by expressing the wild-type but not the catalytically inactive PLpro de-ISGylating enzyme of SARS-CoV-2. In vitro characterisation of purified wild-type and mutant PLpro revealed its higher de-ISGylating compared to its de-ubiquitylating activity. Quantitative proteomic analyses of PLpro substrates revealed several metabolic enzymes that have been implicated in the biogenesis of secretory granules that transport inflammatory cytokines. Further proteomic analyses of the secretome from SARS-CoV-2 infected macrophages revealed that besides ISG15, they were enriched in non-classical secretory proteins and cytokines. Collectively, the results indicate that increased proportions of free ISG15 dramatically alter macrophage responses and is likely a key feature of cytokine storms triggered by highly pathogenic respiratory viruses such as influenza and SARS-CoV-2.



Research and Scholarship

Academic Editorship

Member's Name	Details	
	Role	Journal
Chris Mok	Associate Editor	Virology Journal
		Frontier of Immunology
	Guest Editor	Viruses

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Chris Mok	Reviewer	Virology Journal
		Emerging Infectious Diseases
		EBiomedicine
		Science immunology
		Nature Communication
		Emerging Microbes & Infections
		Biosensors and Bioelectronics
		Plos Biology

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Chris Mok	Long-term Longitudinal Comparisons of Health Status and Immune Responses in Convalescent COVID-19 and Vaccinated Cohorts in Hong Kong	Food and Health Bureau – Health and Medical Research Fund	01/04/2021	31/05/2025	24,000,000
	Development of Anti-influenza Drugs Based on Anti-flu Herbs Ganlanye and Furongye (Leaves of Canarium Album (Lour.) Raeusch and Folium Hibisci Mutabilis)	Food and Health Bureau – Health and Medical Research Fund	01/05/2021	31/03/2024	1,500,000
	Preclusion of an Antigenically Disruptive Mutation in Egg-based H3N2 Seasonal Influenza Vaccines by Mutational Incompatibility	Food and Health Bureau – Health and Medical Research Fund	01/05/2020	30/04/2022	1,488,520

Publications

A. Journal Papers

1. Mok CKP, Cohen CA, Cheng SMS, Chen C, Kwok KO, Yiu K, Chan TO, Bull M, Ling KC, Dai Z, Ng SS, Lui GCY, Wu C, Amerasinghe GK, Leung DW, Wong SYS, Valkenburg SA, Peiris M, Hui DS. Comparison of the immunogenicity of BNT162b2 and CoronaVac COVID-19 vaccines in Hong Kong. *Respirology*. Published online 2021. doi:10.1111/resp.14191. (Epub ahead of print)

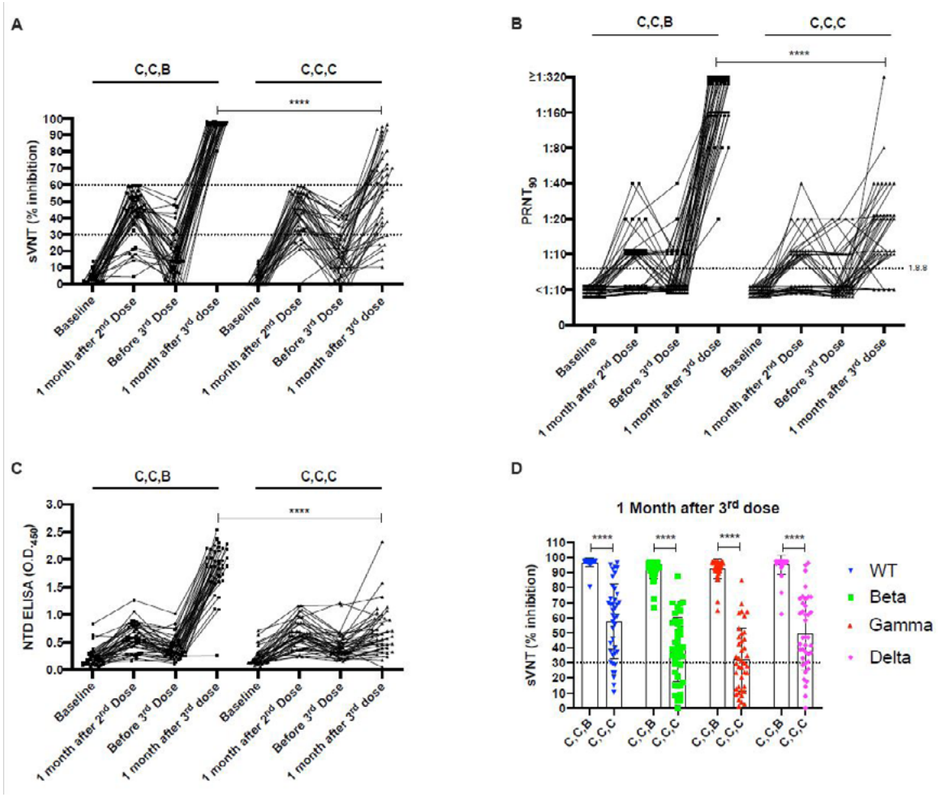
2. Vanhove B, Marot S, So RT, Gaborit B, Evanno G, Malet I, Lafrogne G, Mevel E, Ciron C, Royer P-J, Lheriteau E, Raffi F, Bruzzone R, Mok CKP, Duvaux O, Marcelin A-G, Calvez V. XAV-19, a swine glyco-humanized polyclonal antibody against SARS-CoV-2 spike receptor-binding domain, targets multiple epitopes and broadly neutralizes variants. *Frontiers in Immunology*. 2021;12(11):1-11. doi:10.3389/fimmu.2021.761250.

3. Munnur D, Teo Q, Eggermont D, Lee HHY, Thery F, Ho J, van Leur SW, Ng WWS, Siu LYL, Beling A, Ploegh H, Pinto-Fernandez A, Damianou A, Kessler B, Impens F, Mok CKP, Sanyal S. Altered ISGylation drives aberrant macrophage-dependent immune responses during SARS-CoV-2 infection. *Nature Immunology*. 2021;22(11):1416-1427. doi:10.1038/s41590-021-01035-8.

4. Au KK, Chen C, Chan YM, Wong WWS, Lv H, Mok CKP, Chow CK. Tracking the transcription kinetic of SARS-CoV-2 in human cells by reverse transcription-droplet digital PCR. *Pathogens*. 2021;10(10):1-11. doi:10.3390/pathogens10101274.

5. Montague Z, Lv H, Otwinowski J, DeWitt WS, Isacchini G, Yip GK, Ng WW, Tsang OTY, Yuan M, Liu H, Wilson IA, Peiris JSM, Wu NC, Nourmohammad A, Mok CKP. Dynamics of B cell repertoires and emergence of cross-reactive responses in patients with different severities of COVID-19. *Cell Reports*. 2021;35(8):109173. doi:10.1016/j.celrep.2021.109173.

6. Lv H, Tsang OTY, So RTY, Wang Y, Yuan M, Liu H, Yip GK, Teo QW, Lin Y, Liang W, Wang J, Ng WW, Wilson IA, Peiris JSM, Wu NC, Mok CKP. Homologous and heterologous serological response to the N-terminal domain of SARS-CoV-2 in humans and mice. *European Journal of Immunology*. 2021;51(9):2296-2305. doi:10.1002/eji.202149234.



Antibody responses of individuals before and after the third dose of either BNT162b2 or CoronaVac. The levels of antibodies after the third dose of either BNT162b2 or CoronaVac were detected from the plasma collected from vaccinated adult individuals who had received two doses of CoronaVac. (A) Surrogate virus neutralisation test (sVNT). (B) PRNT90 (C) NTD-specific IgG antibodies (D) The % inhibition against the wild type, beta, gamma and delta variants. C,C,B and C,C,C indicate the vaccines (C: CoronaVac; B: BNT162b2)

Source: Mok CKP, Cheng SMS, Chen C, Yiu K, Chan T-O, Lai KC, Ling KC, Sun Y, Peiris M, Hui DS. A RCT using CoronaVac or BNT162b2 vaccine as a third dose in adults vaccinated with two doses of CoronaVac. https://doi.org/101164/rccm202111-2655LE. Published online January 11, 2022. doi:10.1164/rccm.202111-2655le.

高浩

OWEN KO



08 NEUROSCIENCE AND NEUROTECHNOLOGY



Principal Investigator

Owen Ko

Team members

Danny Chan, Leo Yan, Samuel Sy, Jenny Zhang, Zhongqi Li, Junzhe Huang, Yanling Jin, Ziyu Wang, Jing Lyu, Roy Chan, Clement Chiu, Crystal Feng, Juno Yau

Research Progress Summary

Gliovascular Dysfunction in Aging and Neurodegeneration

Brain health critically depends on diverse gliovascular cells, each serving crucial homeostatic functions in the maintenance of neural circuit functionality. Over the past decades, accumulating evidence point to causal roles of gliovascular dysfunction in various neurodegenerative diseases. Owen Ko and his team adopt a multimodal approach combining genetic manipulation, molecular assays, *in vivo* functional and structural imaging to uncover how aging and neurodegenerative disease-related genetic mutations cause gliovascular dysfunction. They are also interested in the development of disease-modifying therapeutics, as exemplified by their recent works identifying glucagon-like peptide-1 receptor agonist (GLP-1RA) as a promising potential treatment for age-related vasculopathy (Zhao, Li and Vong et al., *Nature Communications,* 2020 Sep 4;11(1):4413), which can also reverse transcriptomic aging signature in many brain cell types in a genome-wide manner (Li, Chen, Vong and Zhao et al., *Communications Biology,* 2021 Jun 2;4(1)656), implicating broad applicability of GLP-1RAs to the primary prevention and secondary treatment of age-related neurodegeneration (US/PCT patent application filed in 2021). Currently, the team is extending their works in this direction to (i) further investigate the peripheral effects of GLP-1R agonism in aging via multi-omics, and (ii) develop companion diagnostic tools for assessing the anti-aging effects of GLP-1R agonists.

Development of Imaging Tools and Methods

Bottlenecks in neural circuit and brain disorder investigations are often due to methodological limitations. The research team is actively developing imaging tools for pre-clinical investigations and potential clinical applications.

(i) They work closely with the Lai lab of LiHS to develop new techniques for high-throughput three-dimensional molecular profiling in intact tissues. These techniques will not only empower their investigations of neural circuit functions in health and disease, but also benefit other fields of biomedical sciences. Their recent works include the development of a new hydrophilic tissue-clearing chemical cocktail solution, and a method for the thermostabilisation of antibodies that permit heat-accelerated deep immunostaining of intact tissues (Lai et al., manuscript under revision; 3 US/PCT patent applications filed in 2021).

(ii) Driven by the need for better neuroimaging-based diagnostic tools for age-related neurodegenerative disorders, such as Alzheimer's disease (AD), they have been working with industrial collaborators to develop new neuroimaging probes and techniques. They are exploring two technical approaches, whereby they (1) design molecular targeting MRI probes with both amyloid-binding and T_1 MRI signal-generating properties and undergo *ex vivo* and *in vivo* tests in animal models of AD, and (2) develop workflow for hyperpolarised ^{13}C magnetic resonance spectroscopic imaging (MRSI) of neurodegeneration-associated brain metabolic changes.

Neural Circuit Mechanisms of Sensory Processing and Behaviour in Health and Disease

They aim to attain a better understanding of the neural circuit basis of sensorimotor behaviour and learning. To achieve this goal, they must uncover how neurons across different brain regions encode behavioural task-relevant information, such as sensory features and predicted outcomes, to instruct decision making and the generation of motor commands. In their lab, they develop platforms on which (i) larval zebrafish are subject to spatiotemporally precise chemical stimulation (Sy et al., manuscript under review; preprint: *bioRxiv,* 2021 Feb 20; doi:10.1101/2021.02.20.431946), or (ii) mice learn to execute complex forelimb motor and general locomotor tasks in response to visual cues, while neuronal activities are recorded from different brain areas by light sheet or multiphoton microscopy. Combined with circuit tracing techniques, they are studying the neural coding of (i) ecologically significant odors and odor mixtures in larval zebrafish, and (ii) distinct task-related information along pathways connecting visual areas to association and motor areas in mouse. In the future, they plan to extend their investigations to animal models of neuropsychiatric diseases.



Research and Scholarship

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Owen Ko	Awardee of Excellent Young Scientists Fund (Hong Kong and Macau)	The National Natural Science Foundation of China

Academic Editorship

Member's Name	Details	
	Role	Journal
Owen Ko	Guest / Associate Editor	BMC Biology

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Owen Ko	*Ad hoc* reviewer	Nature Communications
		eLife
		Seminars in Cell and Developmental Biology
		Neural Regeneration Research
		Laboratory Investigation
		Frontiers in Neuroscience
		STAR Protocols

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Owen Ko	Development of Novel Therapeutic Drugs for Niemann-Pick Disease, Type C	Science, Technology and Innovation Commission of Shenzhen Municipality	30/07/2021	31/07/2023	RMB 1,000,000

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Owen Ko	Novel MRI-based Machine Learning Tool to Detect Mild Cognitive Impairment Associated with Alzheimer's Disease	Food and Health Bureau – Health and Medical Research Fund	01/09/2021	31/08/2023	911,140
	A Comprehensive Survey on Alpha-Synuclein Pathologies in Colonic Submucosal Biopsies of Prodromal Parkinson's Disease Patients – An Exploratory Study	Food and Health Bureau – Health and Medical Research Fund	01/09/2021	31/08/2023	965,803
	Construction of a MesoSPIM Light Sheet Microscope	The Chinese University of Hong Kong Research Committee – Academic Equipment Grant	23/02/2021	31/08/2021	1,063,000
	Clearing the Way for Better Tissue Diagnostics - a Midstream Development Project on Accessible Three-dimensional Histology Methods and Platform	Innovation and Technology Commission – Midstream Research Programme	01/04/2021	31/10/2023	4,700,000
	Investigating Neurovascular and Astrocyte Dysfunction in Neurodegenerative Diseases – Matching Fund	Research Grants Council – Research Matching Grant Scheme	01/06/2020	31/05/2022	1,000,000
	Investigating Neurovascular and Astrocyte dysfunction in neurodegenerative Diseases	The Croucher Foundation	01/06/2020	31/05/2025	5,000,000
	The Role of IL33 in Synaptic Dysfunctions and Pathogenesis of Alzheimer's Disease	Research Grants Council – Collaborative Research Fund	01/04/2020	31/03/2023	5,586,951
	A Pilot Test in Search for Novel Plasma Biomarkers in REM Sleep Behavior Disorder, a Prodromal Stage of Alpha-Synucleinopathy Neurodegeneration, in a Prospective Family Cohort	The Chinese University of Hong Kong Research Committee – Direct Grant	30/06/2020	29/06/2022	149,200

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Owen Ko	Novel Carbobicyclic Nucleosides and Repurposed Drugs for the Treatment of SARS-CoV-2 Infection	The Chinese University of Hong Kong – Faculty of Medicine	12/03/2020	11/03/2021	1,050,000
	Cellular Mechanisms of Synaptic Functions and Plasticity in Health and Neurodegenerative Diseases	Research Grants Council – Area of Excellence Scheme	01/07/2019	30/06/2025	77,516,000
	Design and Characterization of Novel MRI Contrast Agents for Alzheimer's Disease	Videns Incorporation Ltd.	01/02/2019	30/06/2021	2,560,000
	Elucidating the Cellular Functions of the Spinocerebellar Ataxia-Causing Gene CCDC88C and Its Pathogenic Roles in Neurological Conditions	The Chinese University of Hong Kong Research Committee – Funding for Research Sustainability of Major Research Grants Council Funding Schemes	27/05/2019	30/06/2021	500,000
	Nanorobots Swarm for Stroke Treatment: Pilot Study	The Chinese University of Hong Kong Research Committee – Funding for Research Sustainability of Major Research Grants Council Funding Schemes	01/06/2019	31/05/2021	625,000
	High-content Screening of Small Molecules for Inhibiting Microglia Phagocytotic Clearance of Inhibitory Synapses in the Management of Chronic Pain	The Chinese University of Hong Kong Research Committee – Funding for Research Sustainability of Major Research Grants Council Funding Schemes	15/05/2019	14/05/2021	625,000

Publications

A. Journal Papers

1. Sy SKH, Chan DCW, Lai H-M, Li Z, Wong KKY, Choi CHJ, Mok VCT, Hu Y, Ko H. A neural circuit basis for bilateral olfactory input-enhanced chemosensory avoidance navigation. *bioRxiv*. Published online January 1, 2021:2021.02.20.431946. doi:10.1101/2021.02.20.431946. (In press)

2. Wong A, Yin Ka Lam B, Kit Yi Mak M, Chiu Wa Lam L, Wing Chi Au L, Ka Fung Yiu B, Wong C, Yee Tong H, Ki Yeung S, Chiu Wing Chu W, Shi L, Wai Hong Leung T, Oi Yan Soo Y, Yuk Lun Lau A, Yiu Ming Ip B, Chi Yui Kwok T, Ko H, Chung Tong Mok V, Yin Ka LAM B. Aerobic exercise in older people with subclinical sporadic cerebral small vessel disease: A randomized clinical trial. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*. 2021;7(1):e12224. doi:10.1002/trc2.12224.

3. Ismail M, Mok VCT, Wong A, Au L, Yiu B, Wang Z, Chu WCW, Chan AYY, Fan FSY, Ma SH, Ip V, Ip B, Ma K, Leung H, Soo YOY, Leung TWH, Ko H, Lau AYL, Lam BYK. Risk factors for delayed-onset dementia after stroke or transient ischemic attack—a five-year longitudinal cohort study. *International Journal of Stroke*. Published online 2021. doi:10.1177/17474930211026519. (Epub ahead of print)

4. Lam BYK, Yiu B, Ampil E, Chen CLH, Dikot Y, Dominguez JC, Ganeshbhai PV, Hilal S, Kandiah N, Kim SY, Lee JY, Ong AP, Senanarong V, Leung KT, Wang H, Yang YH, Yong T, Arshad F, Alladi S, Wong S, Ko H, Lau AYL, Mok VCT. High burden of cerebral white matter lesion in 9 Asian cities. *Scientific Reports*. 2021;11(1). doi:10.1038/s41598-021-90746-x.

5. Li Z, Chen X, Vong JSL, Zhao L, Huang J, Yan LYC, Ip B, Wing YK, Lai HM, Mok VCT, Ko H. Systemic GLP-1R agonist treatment reverses mouse glial and neurovascular cell transcriptomic aging signatures in a genome-wide manner. *Communications Biology*. 2021;4(1). doi:10.1038/s42003-021-02208-9.

6. Liu W, Au LWC, Abrigo J, Luo Y, Wong A, Lam BYK, Fan X, Kwan PWL, Ma HW, Ng AYT, Chen S, Leung EYL, Ho CL, Wong SHM, Chu WC, Ko H, Lau AYL, Shi L, Mok VCT. MRI-based Alzheimer's disease-resemblance atrophy index in the detection of preclinical and prodromal Alzheimer's disease. *Aging*. 2021;13(10):13496-13514. doi:10.18632/aging.203082.

7. Li Z, Ip B, Mok VCT, Ko H. Neurovascular ageing: transcriptomic readout and implications on therapeutic targeting in Alzheimer's disease. *Neural Regeneration Research*. 2021;16(12):2411-2412. doi:10.4103/1673-5374.313042. (Editorial)

8. Lau AYL, Ming BY, Ko H, Lam BYK, Shi L, Ma KKY, Au LWC, Soo YOY, Leung TWH, Wong A, Mok VCT. Pandemic of the aging society-sporadic cerebral small vessel disease. *Chinese Medical Journal*. 2021;134(2):143-150. doi:10.1097/cm9.0000000000001320. (Review)

9. Wang Q, Tian Y, Du X, Ko H, Ip BYM, Leung TWH, Yu SCH, Zhang L. Magnetic navigation of collective cell microrobots in blood under ultrasound doppler imaging. *IEEE/ASME Transactions on Mechatronics*. Published online 2021. doi:10.1109/tmech.2021.3109346. (Epub ahead of print)

10. Wang Q, Jin D, Wang B, Xia N, Ko H, Ip BYM, Leung TWH, Yu SCH, Zhang L. Reconfigurable magnetic microswarm for accelerating tPA-mediated thrombolysis under ultrasound imaging. *IEEE/ASME Transactions on Mechatronics*. Published online August 11, 2021:1-1. doi:10.1109/tmech.2021.3103994. (Epub ahead of print)

11. Lo HS, Hui KPY, Lai HM, He X, Khan KS, Kaur S, Huang J, Li Z, Chan AKN, Cheung HHY, Ng KC, Ho JCW, Chen YW, Ma B, Cheung PMH, Shin D, Wang K, Lee MH, Selisko B, Eydoux C, Guillemot JC, Canard B, Wu KP, Liang PH, Dikic I, Zuo Z, Chan FKL, Hui DSC, Mok VCT, Wong KB, Mok CKP, Ko H, Aik WS, Chan MCW, Ng WL. Simeprevir potently suppresses SARS-CoV-2 replication and synergizes with remdesivir. *ACS Central Science*. 2021;7(5):792-802. doi:10.1021/acscentsci.0c01186.

12. Wang B, Chan KF, Yuan K, Wang Q, Xia X, Yang L, Ko H, Wang YXJ, Sung JJY, Chiu PWY, Zhang L. Endoscopy-assisted magnetic navigation of biohybrid soft microrobots with rapid endoluminal delivery and imaging. *Science Robotics*. 2021;6(52). doi:10.1126/scirobotics.abd2813.

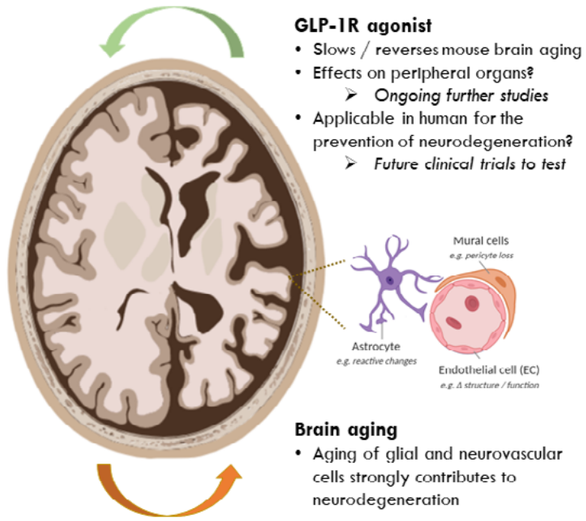
B. Patents

1. Ko H, Li Z, Chen X, Huang J, Zhao L, Vong SL, Yan LYC, Lai HM, Mok VCT. A method for reversing aging brain functional decline.
   - PCT Patent Application: 2021 Dec 16; PCT/CN2021/138827.
   - US Provisional Patent Application: 2020 Dec 16; US63/126,122.

2. Lai HM, Ko H. Efficient antibody DNA-barcoding reagents for multiplexed molecular imaging.
   - PCT Patent Application: 2021 Jun 18; PCT/CN2021/100919.
   - US Provisional Patent Application: 2020 Jun 18; US 63/040,557.

3. Lai HM, Tang Y, Ko H. Efficient and effective tissue clearing agents and their compositions.
   - PCT Patent Application: 2021 May 25; PCT/CN2021/095690.
   - US Provisional Patent Application: 2020 Jun 3; US 63/029,582.

4. Lai HM, Lau ZYH, Ko H. Thermodynamically stabilized antibodies for deep immunolabeling and tissue imaging.
   - PCT Patent Application: 2021 May 21; PCT/CN2021/095327.
   - US Provisional Patent Application: 2020 May 21; US 63/028,022.



Gliovascular dysfunction strongly contributes to age-related neurodegeneration. They demonstrated that GLP-1R agonism can potently slows brain aging. Ongoing further works in their lab are exploring the effects of GLP-1R agonism on peripheral organs in aging, and the role of altered central nervous system GLP-1 signaling in natural aging.

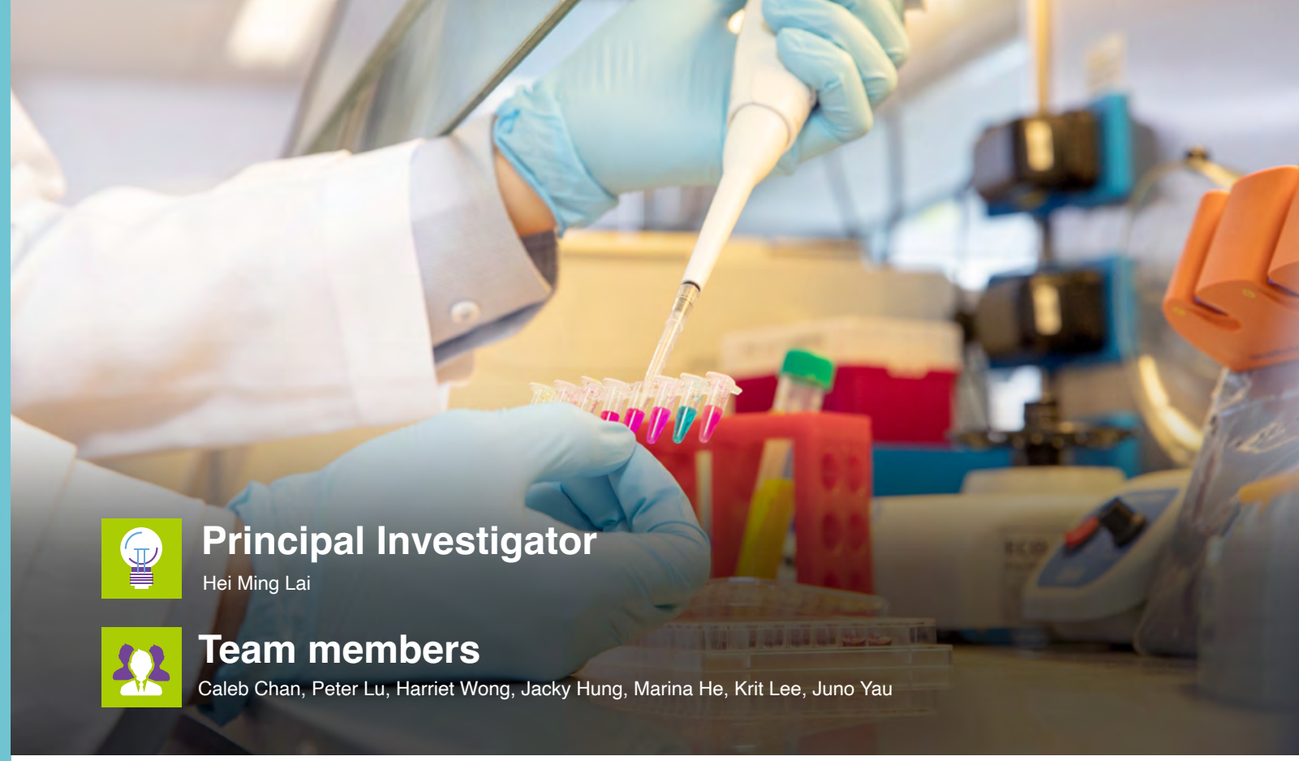
Sources: Owen Ko's laboratory



黎曦明

HEI MING LAI

08 NEUROSCIENCE AND NEUROTECHNOLOGY



Principal Investigator

Hei Ming Lai

Team members

Caleb Chan, Peter Lu, Harriet Wong, Jacky Hung, Marina He, Krit Lee, Juno Yau

Research Progress Summary

This is the first year of the establishment of the laboratory led by Hei Ming Lai at the Li Ka Shing Institute of Health Sciences. As the research team has been building the infrastructure for investigation of complex, abstract psychiatry disorders, they are pleased to report the significant progresses in pursuing that goal. In addition, various foundational technologies have been developed for mapping of the brain's neurocircuitry and molecular compositions.

Building Concrete Infrastructures for Understanding Abstract Mental Phenomena

One of the biggest problems in psychiatry is to link matter to mind. As the first psychiatry research laboratory in Hong Kong, they reflected deeply on what is the nature of mental phenomena, such as emotions, thoughts, social interactions, and their disorders. They went back to the basic scientific principle to plan their project: testable hypotheses based on the best-known evidence. They thus arrived at a creative yet practical experimental approach: rather than inferring mental states of animals based on human experiences, which can be biased and, on some occasions, non-testable, they seek to obtain unbiased observations and classification on the behavioural and mental processes that reflect a "mous-onality" – defined as a statistically biased way of action and reaction towards internal and external stimuli. They then took 3 approaches to monitor these processes, (1) the use of six high speed infrared cameras and thermal imaging cameras for 3D reconstruction of mouse behaviour round-the-clock in a sound-, smell- and light-proof enclosure, to minimise disturbances on their circadian rhythm and percepts, (2) the implantation of Neuropixels probe on the mouse subject being observed, which will stream thousands of neuronal spiking activities across multiple brain regions to

correlate with the behaviours, and finally (3) the use of an observer mouse co-behaving with the subject mouse and also with Neuropixels probe implanted – representing an evolutionarily tuned "sensor" that should ensure the extraction of most relevant cues on the subject mouse' mental and social state. This approach, inspired by the phenomena of transference and countertransference in psychiatry, has not been proposed by others and will provide a solid foundation on the investigation of abstract psychiatric symptoms that has been disruptive to patients' social lives but elusive to capturing by machines and algorithms.

The capturing system is currently around 80% completed and they very much look forward to kickstart the project next year.

Developing Necessary Technologies for Mapping Neurocircuits and Molecular Compositions

Another bottleneck in understanding neuropsychiatry is the complexity of brain structures and compositions. Since the technologies for mapping neurocircuitries in the desired resolution and throughput has yet to exist, the team aims to develop them in-house. One major challenge is the use of 3D fluorescent labelling strategies to label dozens of molecules in a whole intact brain, such that subsequent imaging using tissue clearing techniques would be useful. In contrast to the centuries-old wisdom that tissue immunostaining should be carried out at ambient temperatures, they developed thermo-immunohistochemistry where deliberate the use of high temperatures, along with a new chemical engineering method to stabilize commercial antibodies, which can help achieve fast, deeply penetrating immunostaining. They also generated proteins with unnatural amino acids for additional multiplexing capabilities and functionalities. Combined, these technologies can make high-throughput mapping of brain circuitries feasible, which is important to generate confident data for understanding molecular underpinnings of neuronal functions. In addition, the laboratory team is glad to announce that with the generous support from the Academic Equipment Grant, they are constructing a mesoscale selective plane illumination microscope (mesoSPIM) to image large, centimetre-scale cleared tissues – a platform of emerging significance to understand all kinds of tissues in their 3D context. Upon its completion, they will be honoured to make it open to serve other CUHK research groups.

Serendipitous Discoveries and Spin-off Technologies

Since they implemented a diversified approach to the development of novel technologies, with multiple trial and errors they inevitably stumbled across many interesting discoveries upon careful observations. These include an artificial chaperone that can potentially benefit industrial production of pharmaceuticals and biotechnology applications involving the use of enzymes, a room temperature synthesis method for producing cesium lead halide perovskite nanocrystals with record-high photoluminescent quantum yields – a very promising material for the next generation flexible LED displays and solar cells, as well as a low-cost synthesis method for producing molecular beacons for qPCR and other nucleic acid diagnostics. The development of 3D histology technologies is also benefitting renal hemodynamics and colorectal cancer research. Lai and his team very much look forward to more exciting science to come with their firm foundation laid in the Institute.



Research and Scholarship

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Hei Ming Lai	Faculty Innovation Award 2020	Faculty of Medicine, The Chinese University of Hong Kong

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Hei Ming Lai	Reviewer	Laboratory Investigations

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Hei Ming Lai	Developing Practical Next Generation Histology Chemical Technologies	Faculty Innovation Award, Faculty of Medicine, The Chinese University of Hong Kong	01/01/2021	31/12/2023	750,000
	Clearing the Way for Better Tissue Diagnostics – A Midstream Development Project on Accessible Three-dimensional Histology Methods and Platform	Innovation and Technology Commission – Innovation and Technology Fund for Midstream Research Programme for Universities	01/03/2021	31/08/2023	4,700,000
Hei Ming Lai, Caleb Chan	Clearing The Way for Better Tissue Diagnostics – A Midstream Development Project on Accessible Three-dimensional Histology Methods and Platform	Innovation and Technology Commission – Innovation and Technology Fund for Research Talent Hub	01/03/2021	31/08/2023	1,005,000

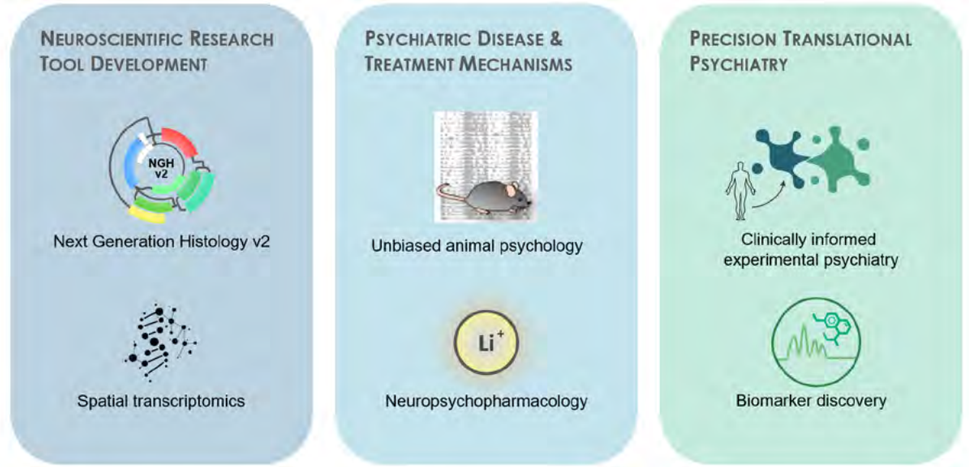
Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Hei Ming Lai, Peter Lu	Clearing The Way for Better Tissue Diagnostics – A Midstream Development Project on Accessible Three-dimensional Histology Methods and Platform	Innovation and Technology Commission – Innovation and Technology Fund for Research Talent Hub	01/04/2021	31/08/2023	971,500
Hei Ming Lai, Yuan He	Clearing The Way for Better Tissue Diagnostics – A Midstream Development Project on Accessible Three-dimensional Histology Methods and Platform	Innovation and Technology Commission – Innovation and Technology Fund for Research Talent Hub	01/03/2021	31/08/2023	264,600
Hei Ming Lai	Development of A MesoSPIM Light Sheet Microscope v5.1-Based Next Generation Histology Tissue Diagnostic Platform	The Chinese University of Hong Kong – Academic Equipment grant (2020/21 2nd round)	01/02/2021	31/08/2021	1,063,000
	A Comprehensive Survey on Alpha-Synuclein Pathologies in Colonic Submucosal Biopsies of Prodromal Parkinsons's Disease Patients – An Exploratory Study	Food and Health Bureau – Health and Medical Research Fund	01/09/2021	31/08/2023	965,803

Publications

A. Journal Papers

1. Li Z, Chen X, Vong JSL, Zhao L, Huang J, Yan LYC, Ip B, Wing YK, Lai HM, Mok VCT, Ko H. Systemic GLP-1R agonist treatment reverses mouse glial and neurovascular cell transcriptomic aging signatures in a genome-wide manner. *Communications Biology*. 2021;4(1):1-6. doi:10.1038/s42003-021-02208-9.

2. Lo HS, Hui KPY, Lai HM, He X, Khan KS, Kaur S, Huang J, Li Z, Chan AKN, Cheung HHY, Ng KC, Ho JCW, Chen YW, Ma B, Cheung PMH, Shin D, Wang K, Lee MH, Selisko B, Eydoux C, Guillemot JC, Canard B, Wu KP, Liang PH, Dikic I, Zuo Z, Chan FKL, Hui DSC, Mok VCT, Wong KB, Mok CKP, Ko H, Aik WS, Chan MCW, Ng WL. Simeprevir potently suppresses SARS-CoV-2 replication and synergizes with remdesivir. *ACS Central Science*. 2021;7(5):792-802. doi:10.1021/acscentsci.0c01186.



Three main research directions of Hei Ming Lai and his team's laboratory.

Source: Hei Ming Lai



黃志超

RONALD WANG



09 REPRODUCTION AND DEVELOPMENT

Research Progress Summary

Ronald Wang and his team from the Department of Obstetrics & Gynaecology focus on the field of Reproduction and Development. The team covered a wide spectrum of clinical, basic and genetic studies of female and male reproduction, and embryo and fetal development in human and mice. The team has many intradepartmental (TY Leung in fetal medicine and prenatal diagnosis; Liona Poon and WH Tam in maternal medicine; TC Li in assisted reproductive technology), interdepartmental (Simon Lam in neonatology; WS Poon in neurosciences; Ronald Ma in diabetes; Huating Wang, Kathy Chan and Tong Leung, Anna Tsang in stem cells, Alisa Shum in developmental biology), intrauniversity (KM Kwan in developmental biology), interuniversity (HKU, Ernest Ng and Raymond Li in O&G; Thomas Leung and Bill Chan in drug development), many other regional, national and international research collaboration in the field.

Ronald is the Licensee of Assisted Reproductive Technology Unit for IVF treatment and PGT; the Director of The Chinese University of Hong Kong-Sichuan University Joint Laboratory in Reproductive Medicine and the Deputy Director of Prenatal Genetic Diagnosis Centre. His team members are the cord members of World Endometriosis Society Research Working Group and also International Core Outcome Measure for Infertility Trials Initiative. The team has published 3 reviews, 22 papers and 3 book chapters and obtained 6 new research grants (4 as PI or Co-PI including Collaborative Research Fund, General Research Fund, Health and Medical Research Fund, and the Ministry of Science and Technology; and 2 as Co-I including Health and Medical Research Fund and the Ministry of Science and Technology). The team members also received 1 international conference, 1 exchange and 1 outstanding student awards and they have 2 new PhD students awarded with Hong Kong PhD Fellowship Scheme (HKPFS) with or without Hong Kong Special Administrative Region Scholarship.



Research Progress Summary



Principal Investigator

Ronald Wang

Team members

Judy Zhang, Maran Leung, Linda Wu, Nina Chu, Yi Song, Kennes Hung, Zinnat Hasina, Meng Li, Rui Zhe Zhang, Ruo Fan Qi, Wei Li, Alan Chan, Alice Lin, Scott Lin, Easo Wong, Ying Ying Zhang, Wen Jing Ding, Ken Tam, Sophia Tan, Kenean Getaneh Tlaye, Yiran Li, Olena Getsko, Xu Zheng, Gashaw Garedew Woldeamanuel, Yang Ding, Xiao Yi Bai

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Ronald Wang	江西省引進培養創新創業高層次人才，雙千計劃——第二批引進類創新領軍人才	中國江西省
Sophia Tan	Eurasia-Pacific Uninet Mach Grant	Uninet Ernst Mach
Rui Zhe Zhang	Outstanding Oral Presentation Award	Asia Pacific Initiative on Reproduction 2021
Kennes Hung	Outstanding Students Awards 2021	The Chinese University of Hong Kong

Fellowships

Member's Name	Details	
	Fellowship	Organisation
Ronald Wang	Directorship	The Chinese University of Hong Kong - Sichuan University Joint Laboratory for Reproductive Medicine
Woldeamanuel Gashaw Garedew	Hong Kong PhD Fellowship Scheme	Research Grants Council
Olena Getsko	Hong Kong PhD Fellowship Scheme	Research Grants Council
	Hong Kong Special Administrative Region Scholarship	Hong Kong Special Administrative Region Government

Research and Scholarship

Academic Editorship

Member's Name	Details	
	Role	Journal
Ronald Wang	Guest Editor	Evidence-Based Complementary and Alternative Medicine

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Ronald Wang	Reviewer	Poland Grants OPUS National Science Centre
		RCOG World Congress 2021
		Journal of Ethnopharmacology
		Human Reproduction (Open)
		PLoS ONE
		Molecular Biology Reports
		Human Reproduction
		Americal Journal of Reproductive Immunology
		Gynecologic Oncology
		Human Immunology
		Journal of Assisted Reproduction and Genetics
		Frontiers in Pharamcology
		Gene
		JAMA Internal Medicine
		Molecular Pharmacology
		Frontiers Cell and Developmental Biology
		Fertility and Sterility

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Ronald Wang	早發型子癇前期發病機制及整體化防控策略的研究;開發適宜藥物靶向投遞系統,探索老藥新用的防治前景	Ministry of Education, Ministry of Science and Technology	01/12/2021	30/11/2025	RMB 27,777,000
	利用多組學和系統生物學技術,篩選疾病生物標誌與潛在靶標	Ministry of Education, Ministry of Science and Technology	01/12/2021	30/11/2025	RMB 6,500,000
	Epithelium Caveolin and its Calcium Signaling Pathway in Endometrium of Recurrent Miscarriage	Research Grants Council – General Research Fund	01/09/2021	31/08/2023	775,732
	Receptor Tyrosine Kinase Inhibitor Sunitinib as Novel Immunotherapy to Inhibit Myeloid-derived Suppressor Cells for Treatment of Endometriosis	Food and Health Bureau – Health and Medical Research Fund	01/09/2021	29/2/2023	1,360,000
	A Super-Resolution Fluorescence Microscopy Platform for Live-cell and Animal-tissue Imaging	Research Grants Council – Collaborative Research Fund	30/06/2021	29/06/2024	7,154,250
	Transdermal Peptide Delivery of siRNA for the Treatment of Cervical Cancer and Melanin-related Diseases	Innovation and Technology Commission – Partnership Research Programme	01/08/2020	31/07/2022	975,826.5
	Transdermal Peptide Delivery of siRNA for the Treatment of Cervical Cancer and Melanin-related Diseases	Innovation and Technology Commission – Re-industrialisation Funding Scheme	01/08/2020	31/07/2022	1,000,000
	Transdermal Peptide Delivery of siRNA for the Treatment of Cervical Cancer and Melanin-related Diseases	Innovation and Technology Commission – Research Talent Hub	01/08/2020	31/07/2022	2,570,153.53
	Transdermal Peptide Delivery of siRNA for the Treatment of Cervical Cancer and Melanin-related Diseases	Donation	01/08/2020	31/07/2022	47,600
	Transdermal Peptide Delivery of siRNA for the Treatment of Cervical Cancer and Melanin-related Diseases	Research Grants Council - Research Matching Grant Scheme	01/08/2020	31/07/2022	23,800

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Ronald Wang	The Effect of In Utero Hyperglycaemia, Maternal Overnutrition and Interaction with Postnatal Lifestyle on Cardiometabolic Risk at Young Adulthood – Extension of HAPO Follow Up Study.	Research Grants Council – General Research Fund	01/01/2020	31/12/2022	1,158,019
	A Metabolomic Approach to Redefine Diagnostic Criteria and Classification of Polycystic Ovary Syndrome	Food and Health Bureau – Health and Medical Research Fund	01/04/2019	31/03/2021	1,499,999
	Umbilical Cord Blood Mononuclear Cell Bank in Hong Kong and Treatment of Neonatal Cerebral Ischemia and Anaemia	Innovation and Technology Commission – Innovation and Technology Fund	01/10/2017	31/03/2021	2,864,999
	Umbilical Cord Blood Mononuclear Cell Bank in Hong Kong and Treatment of Neonatal Cerebral Ischemia and Anaemia	Innovation and Technology Commission – Re-industrialisation Funding Scheme	01/10/2017	31/03/2021	3,000,001
	Umbilical Cord Blood Mononuclear Cell Bank in Hong Kong and Treatment of Neonatal Cerebral Ischemia and Anaemia	Internships and Postdoctoral Fellowships	01/10/2017	31/03/2021	3,051,431
	A Pilot Study on Developing A One-step Thawing Method on Human Blastocysts with Transcriptomic and Methylomic Comparison to Conventional Vitrified-thawing Method	Food and Health Bureau – Health and Medical Research Fund	01/10/2021	30/09/2023	929,940
	Netrin-1促進子宮內膜異位症發生發展及其介導疼痛敏化的作用機制研究	National Natural Science Foundation of China	01/01/2020	31/12/2023	RMB 530,000
	Dysregulation of Retinoic Acid Homeostasis and Signaling in Fetal Islet Development under Maternal Diabetic or High Glucose Conditions	Research Grants Council – General Research Fund	01/01/2020	30/06/2022	770,053
	宮腔液外泌體MicroRNA介導子宮內膜炎症反應的機制初探	National Natural Science Foundation of China	01/10/2019	30/09/2022	RMB 100,000
Ronald Wang	Evaluation of Aspirin Non-responsiveness in Preeclampsia Prevention: A Pharmacometabolomics Approach	Food and Health Bureau – Health and Medical Research Fund	01/08/2019	31/01/2021	989,600
	Do Endometrial Leucocytes and Angiogenesis in the Peri-implantation Period Predict Hypertensive Disorders in the Subsequent Pregnancy?	Food and Health Bureau – Health and Medical Research Fund	01/08/2019	31/01/2021	477,196
	A Double Blinded, Randomized Placebo Controlled Trial on Effect of Traditional Chinese Medicine Formula Wuzi Yanzong Pill on Improving Semen Qualities in Men with Sub-optimal Parameters	Food and Health Bureau – Health and Medical Research Fund	01/05/2019	30/04/2022	1,114,156
	Cervicovaginal Fluid Biomarker for the Identification of Spontaneous Preterm Birth	Innovation and Technology Commission – Innovation and Technology Fund	01/04/2018	30/06/2021	1,870,200
	Cervicovaginal Fluid Biomarker for the Identification of Spontaneous Preterm Birth	Innovation and Technology Commission – Re-industrialisation Funding Scheme	01/04/2018	30/06/2021	1,911,000

Publications

A. Journal Papers

1. Chen X, Man GCW, Hung SW, Zhang T, Fung LWY, Cheung CW, Chung JPW, Li TC, Wang CC. Therapeutic effects of green tea on endometriosis. *Critical Reviews in Food Science and Nutrition*. Published online 2021. doi:10.1080/10408398.2021.1986465. (Review, Epub ahead of print)

2. Hung SW, Zhang R, Tan Z, Chung JPW, Zhang T, Wang CC. Pharmaceuticals targeting signaling pathways of endometriosis as potential new medical treatment: A review. *Medicinal Research Reviews*. 2021;41(4):2489-2564. doi:10.1002/med.21802. (Review)

3. Tam C, Rao S, Waye MMY, Ng TB, Wang CC. Autophagy signals orchestrate chemoresistance of gynecological cancers. *Biochimica et Biophysica Acta - Reviews on Cancer*. 2021;1875(2). doi: 10.1016/j.bbcan.2021.188525. (Review)

4. Li J, Wu Q, Ng EHY, Mol BWJ, Wu XK*, Wang CC. Effects of medicines and supplements on spontaneous pregnancy and semen parameters in male infertility: A systematic review update and network meta-analysis. *Engineering*. 2021 (Accepted) doi: 10.1016/j.eng.2021.07.009. (Review, In press)

5. Hung SW, Liang B, Gao Y, Zhang R, Tan Z, Zhang T, Chung PWJ, Chan TH, Wang CC. An In-Silico, In-Vitro and In-Vivo combined approach to identify NMNATs as potential protein targets of ProEGCG for treatment of endometriosis. *Frontiers in Pharmacology*. 2021;12. doi:10.3389/fphar.2021.714790.

6. Li X, Milosavljevic A, Elsea SH, Wang CC, Scaglia F, Syngelaki A, Nicolaides KH, Poon LC. Effective aspirin treatment of women at risk for preeclampsia delays the metabolic clock of gestation. *Hypertension*. Published online 2021:1398-1410. doi:10.1161/hypertensionaha.121.17448. (Epub ahead of print)

7. Zhao Y, Man GCW, Wang J, Liu Y, Kwong J, Zhang T, Chung JPW, Wang CC, Chen X, Li TC. The identification of endometrial immune cell densities and clustering analysis in the mid-luteal phase as predictor for pregnancy outcomes after IVF-ET treatment. *Journal of Reproductive Immunology*. 2021;148. doi:10.1016/j.jri.2021.103431.

8. Zhao Y, Man GCW, Chan LKY, Guo X, Liu Y, Zhang T, Kwong J, Wang CC, Chen X, Li TC. Multiplexed fluorescent immunohistochemical staining of four endometrial immune cell types in recurrent miscarriage. *Jove-journal of Visualized Experiments*. 2021;(174). doi:10.3791/62931.

9. He Y, Hung SW, Liang B, Zhang R, Gao Y, Chu CY, Zhang T, Xu H, Chung JPW, Wang CC. Receptor tyrosine kinase inhibitor sunitinib as novel immunotherapy to inhibit myeloid-derived suppressor cells for treatment of endometriosis. *Frontiers in Immunology*. 2021;12. doi: 10.3389/fimmu.2021.641206.

10. Wu Q, Li J, Ng EHY, Liu JP, Mol BWJ, Wu XK, Wang CC, Kuang HY, Ma HL, Gao JS, Hou LH, Hu ZX, Shao XG, Ge J, Zhang JF, Xue HY, Xu XF, Liang RN, Ma HX, Yang HW, Huang DM, Sun Y, Hao CF, Du SM, Ding CF, Gao YQ, Wu TX, Stener-Victorin E, Zhang H, Legro RS. Do baseline AMH levels in women with polycystic ovary syndrome predict ovulation rate and time to ovulation: A secondary analysis of PCOSAct trial? *BJOG-An International Journal of Obstetrics and Gynaecology*. 2021;128(9):1477-1486. doi:10.1111/1471-0528.16742.

11. Mao D, Cao H, Shi M, Wang CC, Kwong J, Li JJX, Hou Y, Ming X, Lee HM, Tian XY, Wong CK, Chow E, Kong APS, Lui VWY, Chan PKS, Chan JCN. Increased co-expression of PSMA2 and GLP-1 receptor in cervical cancer models in type 2 diabetes attenuated by exendin-4: A translational case-control study. *EBioMedicine*. 2021;65. doi:10.1016/j.ebiom.2021.103242.

12. Wu L, Song Y, Zhang Y, Liang B, Deng Y, Tang T, Ye YC, Hou HY, Wang CC. Novel genetic variants of PPAR gamma 2 promoter in gestational diabetes mellitus and its molecular regulation in adipogenesis. *Frontiers in Endocrinology*. 2021;11. doi: 10.3389/fendo.2020.499788.

B. Book / Book Chapter

1. He Y, Hung KSW, Xu H, Wang CC. Chapter 18: Immunosuppression and immunotherapy in endometriosis: Review of pathophysiology, recent development and future perspectives. In: Mor G and Koga K, ed. Immunology of Endometriosis: Pathogenesis and Management Volume 2. *Elsevier*; 2021: 271-296.

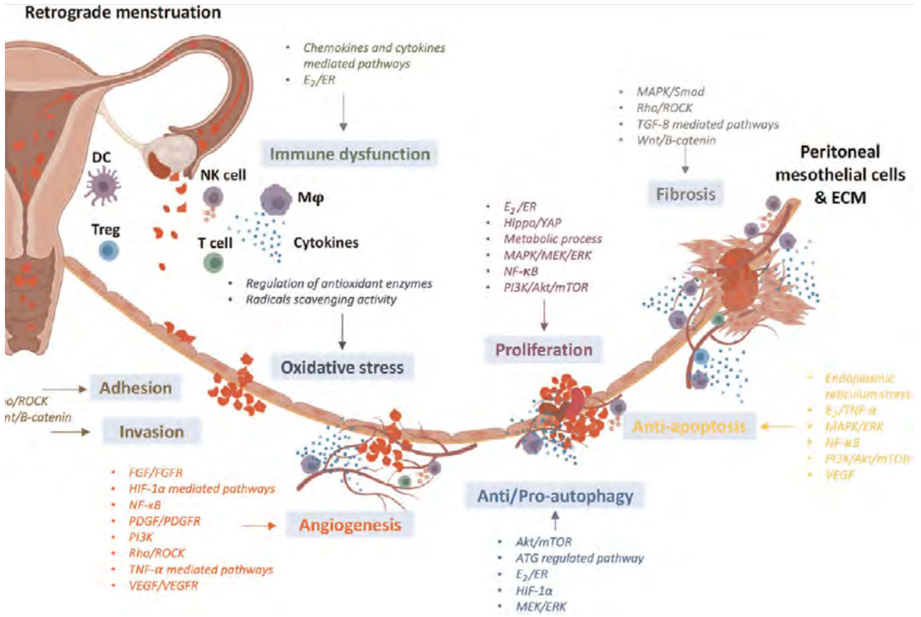
2. Zhang T, Li TC, Chung JPW, Wang CC. Chapter 6: Auto-immunity factors: Evidence, mechanism and therapeutic potential. In: Immunology of Endometriosis: Etiology and Management. Koga K and Mor G, ed. *Elsevier*; 2021: 85-104.

C. Patents

1. Inventors: 黃志超、 張睿喆、 耿科、 李業菁、 李百靈、 高峻
Title: 基於 OCT 的子宮內膜檢測分析方法、裝置、設備及存儲介質
SIPO 202110760679.4
Publication No.: CN113520317A
Publication Date: 22 October 2021

2. Umbilical cord blood mononuclear cells and red cell fraction improve neurogenesis and behavioral recovery after hypoxia-ischemic brain damage. US patent US 63/211,946.

3. Inventors: 黃志超、 張睿喆、 耿科、 李業菁、 李百靈、 高峻
Title: 無創 OCT 直接應用於子宮內膜的檢測方法、設備及系統
SIPO 202110567731.4
Publication No.: CN113273968A
Publication Date: 20 August 2021



Pathophysiology of endometriosis. The schematic diagram was created using BioRender.com. Akt, protein kinase B; ATG, autophagy-related genes; DC, dendritic cells; E2, estrogen; ECM, extracellular matrix; ER, estrogen eceptor; ERK extracellular signal-regulated kinase; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptors; HIF, hypoxia-inducible factors; MΦ, macrophages; MAPK, mitogen-activated protein kinase; MEK, ERK kinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κB; NK, natural killer; PDGF, plateletderived growth factor; PDGFR, platelet-derived growth factor receptor; PI3K, phosphoinositide 3-kinases; Rho, Ras homolog family; ROCK, Rho-associated coiled-coil kinase; VEGF, vascular endothelial growth factor; TGF, transforming growth factor; TNF, tumor necrosis factor; Treg, regulatory T cells; Wnt, wingless-type mouse mammary tumor virus integration site family; YAP, Yes-associated protein.

Source: Hung SW, Zhang R, Tan Z, Chung JPW, Zhang T, Wang CC. Pharmaceuticals targeting signaling pathways of endometriosis as potential new medical treatment: A review. Medicinal Research Reviews. 2021;41(4):2489-2564. doi:10.1002/med.21802.



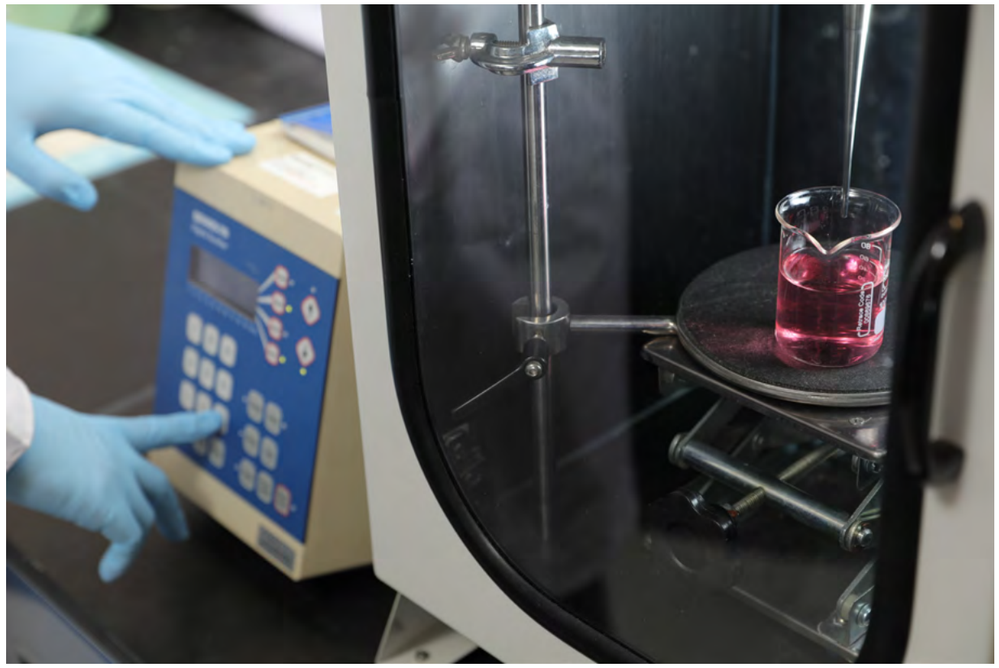
10 STEM CELLS AND TISSUE REGENERATION

Adult Stem Cell Biology and Applications

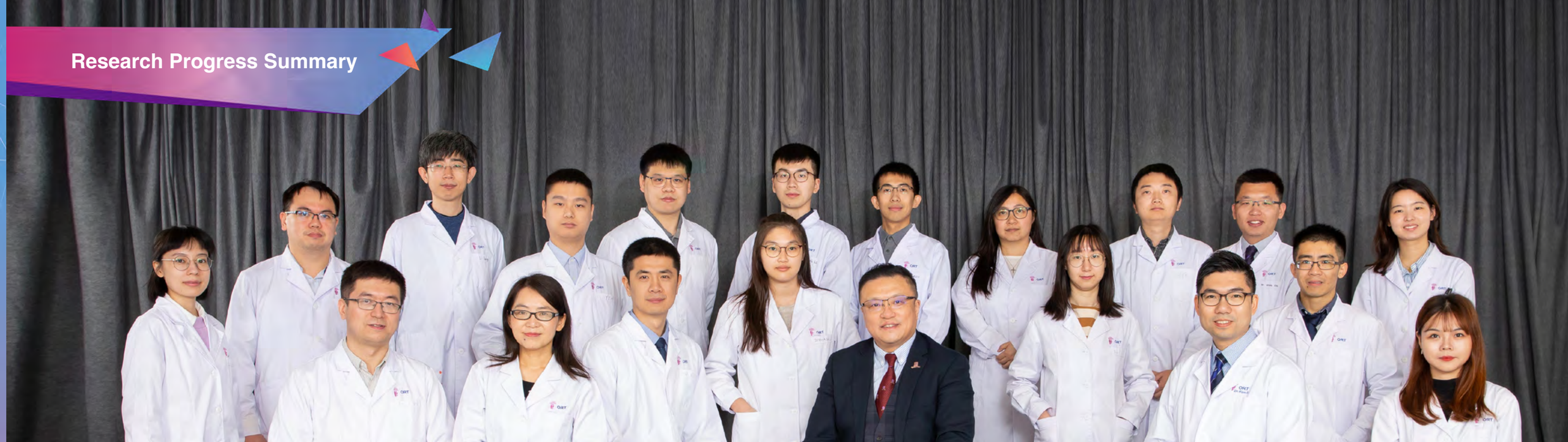
Research Progress Summary

In 2021, there are 16 members in the research team led by Gang Li (1 Research Assistant Professor, 4 Postdoctoral Fellows, 2 Research Associates, 9 PhD Students) with the following research programs carried out: (1) Development and mechanistic studies of tibial cortex transverse transport (TTT) surgery for the management of diabetic foot ulcers. (2) Development and mechanistic studies of cranial bone transport (CBT) surgery for the management of ischemic stroke and Alzheimer's disease. (3) Novel therapy strategies for osteoporotic bone fracture and chronic wounds. (4) Industry and Hong Kong Government contract research works on pre-clinical studies of biological compounds and biophysical stimulations. These research programs have been progressed well as planned, with more than 20 peer-reviewed publications and over HK$10 million research grants income.

Gang has been invited to give keynote speeches and lectures at various national and international conferences and meetings (virtual form) for more than 10 times in 2021, and continuously serves as visiting professors at many prestigious universities such as Monash University, Australia; University of Malaya, Malaysia; Guangdong Medical University China, etc. He also serves as the council member or member-at-large for 4 prestigious national research societies, and editorial board members for 6 international journals. Notably Gang and his collaborators from mainland China won the First-Class Award in Science Advances, Ministry of Science and Technology of the People's Republic of China in 2021 for his achievements in new musculoskeletal tissue regeneration technologies, which is one of the most prestigious national awards in China.



Research Progress Summary



Principal Investigator

Gang Li

Team members

Sien Lin, Yan Wang, Lu Feng, Weiping Lin, Linlong Li, Yucong Li, Haixing Wang, Xiaoting Zhang, Yuan Li, Zhengmeng Yang, Shanshan Bai, Min Wang, Xuan Lu, Yongkang Yang, Zhaowei Jiang, Yuejun Lin

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Gang Li	First-Class Award in Science Advances	Ministry of Science and Technology, China

Fellowships

Member's Name	Details	
	Fellowship	Organisation
Gang Li	Adjunct Professor	Australian Regenerative Medicine Institute, Monash University, Australia
	Visiting Professor and Assessor of Teaching Program	Department of Orthopaedic Surgery and Traumatology, University of Malaya, Malaysia
	Visiting Professor	Guang Dong Medical College, China

Research and Scholarship

Member's Name	Details	
	Fellowship	Organisation
Gang Li	Visiting Professor	Shenzhen Baoan People's Hospital, Shenzhen, China
		China Medical University, Shenyang, China
	General Secretary, Division of Limb Deformity Correction and Reconstruction	Chinese Association of Orthopaedic Surgeons
	Co-Chairman	China Branch, International Limb Lengthening and Reconstruction Societies
		Association from Study and Application of the Methods of Ilizarov
	骨橫搬糖足學組副主任委員	中國骨科醫師協會
	Council Member of Academic Division	Hong Kong Association of Scientists
	Vice Chairman, Branch of Regenerative Biomaterials	Chinese Association of Materials
	Member-at-Large (Global position)	Tissue Engineering and Regenerative Medicine International Society Asia Pacific
	Council and Funding Member	Hong Kong Society of Cell Biology
	Fellow	International Combined Orthopaedic Research Societies
	Fellow	American Orthopaedic Research Society

Academic Editorship

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

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Gang Li	Reviewer	Stem Cells Research and Therapy
		Biomaterials
		Stem Cells
		Frontiers in Cell Biology
		Science Advances
		Cytotherapy
		Journal of Physiology
		Journal of Chemical Engineering

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Gang Li	The Role of LGR5 in Cartilage Development and Mesenchymal Stem Cells Mediated Cartilage Repair	Research Grants Council – General Research Fund	01/01/2021	31/12/2023	996,285
	Engineering the Biomimetic Structural and Mechanical Heterogeneity of Cell-Adaptable Nanocomposite Hydrogels for Biomedical Applications	Research Grants Council – General Research Fund	01/01/2021	31/12/2023	1,185,400
	Modulating Osteoarthritis Development via Balancing Endogenous Expression of Smad3 and Smad7	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	953,029
	Exploiting the True Joint Progenitor Cell for Articular Cartilage Repair	Research Grants Council – Collaborative Research Fund	01/06/2019	31/05/2022	7,370,000
	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
	Aging, Skeletal Degeneration and Regeneration	Research Grants Council – Areas of Excellence Scheme	01/05/2021	30/04/2029	64,889,000

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Gang Li	Effect of Sesamin on Promoting Osteoporotic Fracture Healing	Food and Health Bureau – Health and Medical Research Fund	01/09/2020	28/02/2023	1,337,032
	Effects of Danshen and Jixuecao Extracts on Glucocorticoid Induced Bone Loss and Growth Suppression	Food and Health Bureau – Health and Medical Research Fund	01/07/2019	30/06/2022	1,495,584
	Development of Staphylococcal Enterotoxins C2 (SEC2) as a Drug to Promote Osteoporotic Fracture Healing	Innovation Technology Commission – Partnership Research Programme	01/04/2020	30/09/2022	2,268,318
	Development of Staphylococcal Enterotoxins C2 (SEC2) as a Drug to Promote Osteoporotic Fracture Healing	Innovation Technology Commission – Postdoctoral Fellowship Matching Programme	01/04/2020	30/09/2022	2,682,861
	Studies of Cranial Bone Transport for Stroke Management	The Government of the Hong Kong Special Administrative Region – PGM-01 Research Matching Scheme	01/01/2021	31/12/2025	800,000

Publications

A. Journal Papers

1. Yang Z, Feng L, Wang H, Li Y, Lo JHT, Zhang X, Lu X, Wang Y, Lin S, Tortorella MD, Li G. DANCR mediates the rescuing effects of sesamin on postmenopausal osteoporosis treatment via orchestrating osteogenesis and osteoclastogenesis. *Nutrients.* 2021;13(12):4455. doi:10.3390/nu13124455.

2. Deng Y, Zhang X, Li R, Li Z, Yang B, Shi P, Zhang H, Wang C, Wen C, Li G, Bian L. Biomaterial-mediated presentation of wnt5a mimetic ligands enhances chondrogenesis and metabolism of stem cells by activating non-canonical Wnt signaling. *Biomaterials*. 2022;281. doi:10.1016/j.biomaterials.2021.121316. (Epub ahead of print)

3. Li Y, Yang Y, Wang M, Zhang X, Bai S, Lu X, Li Y, Waldorff EI, Zhang N, Lee WYW, Li G. High slew rate pulsed electromagnetic field enhances bone consolidation and shortens daily treatment duration in distraction osteogenesis. *Bone & Joint Research*. 2021;10(12):767-779. doi:10.1302/2046-3758.1012.bjr-2021-0274.r1.

4. Shakoor A, Wang B, Fan L, Kong L, Gao W, Sun J, Man K, Li G, Sun D, Shakoor A, Fan L, Gao W, Sun J, Sun D, Wang B, Li G, Kong L, Man K, Kong H. Automated optical tweezers manipulation to transfer mitochondria from fetal to adult MSCs to improve antiaging gene expressions. *Small*. 2021;17(38):2103086. doi: 10.1002/smll.202103086.

5. Yang Z, Feng L, Huang J, Zhang X, Lin W, Wang B, Cui L, Lin S, Li G. Asiatic acid protects articular cartilage through promoting chondrogenesis and inhibiting inflammation and hypertrophy in osteoarthritis. *European Journal of Pharmacology*. 2021;907. doi: 10.1016/j.ejphar.2021.174265.

6. Wang P, Wang M, Zhuo T, Li Y, Lin W, Ding L, Zhang M, Zhou C, Zhang J, Li G, Wang H, Xu L. Hydroxysafflor yellow A promotes osteogenesis and bone development via epigenetically regulating β-catenin and prevents ovariectomy-induced bone loss. *The International Journal of Biochemistry & Cell Biology.* 2021;137. doi: 10.1016/j.biocel.2021.106033.

7. Li Y, Xu J, Mi J, He X, Pan Q, Zheng L, Zu H, Chen Z, Dai B, Li X, Pang Q, Zou L, Zhou L, Huang L, Tong W, Li G, Qin L. Biodegradable magnesium combined with distraction osteogenesis synergistically stimulates bone tissue regeneration via CGRP-FAK-VEGF signaling axis. *Biomaterials.* 2021;275:120984. doi: 10.1016/j.biomaterials.2021.120984.

8. Shi L, Liu Y, Yang Z, Wu T, Lo HT, Xu J, Zhang J, Lin W, Zhang J, Feng L, Li G. Vasoactive intestinal peptide promotes fracture healing in sympathectomized mice. *Calcified Tissue International.* 2021;109(1):55-65. doi:10.1007/s00223-021-00820-9.

9. Lin W, Chen S, Wang Y, Wang M, Lee WYW, Jiang X, Li G. Dynamic regulation of mitochondrial-endoplasmic reticulum crosstalk during stem cell homeostasis and aging. *Cell Death and Disease. 2021;12(9):794.* doi:10.1038/s41419-021-03912-4.

10. Kong L, Wang Y, Wang H, Pan Q, Zuo R, Bai S, Zhang X, Lee WY, Kang Q, Li G. Conditioned media from endothelial progenitor cells cultured in simulated microgravity promote angiogenesis and bone fracture healing. *Stem Cell Research & Therapy*. 2021;12(1):1-14. doi:10.1186/S13287-020-02074-Y/FIGURES/7.

11. Zong Z, Zhang X, Yang Z, Yuan W, Huang J, Lin W, Chen T, Yu J, Chen J, Cui L, Li G, Wei B, Lin S. Rejuvenated ageing mesenchymal stem cells by stepwise preconditioning ameliorates surgery-induced osteoarthritis in rabbits. *Bone & Joint Research*. 2021;10(1):10-21. doi:10.1302/2046-3758.101.BJR-2020-0249.R1.

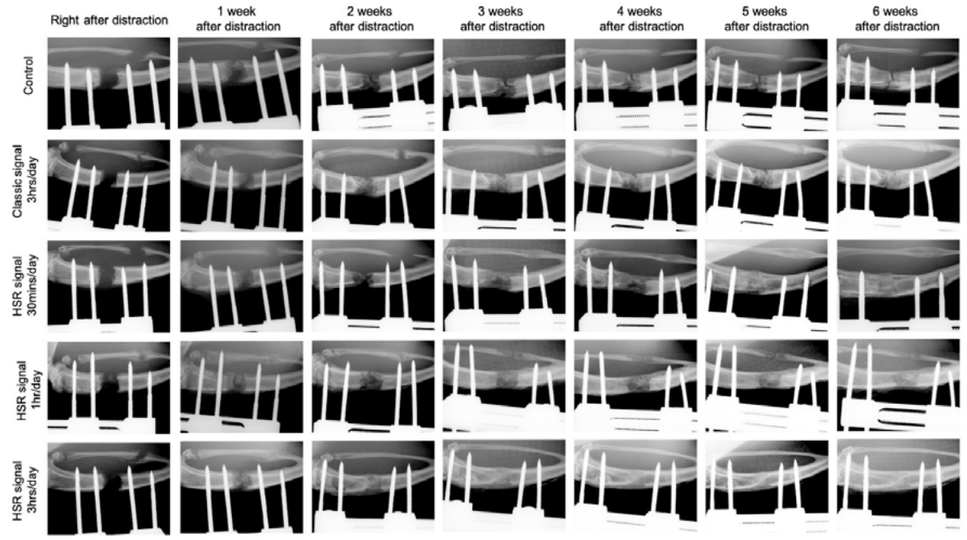
12. Li Q, Wang H, Zhang J, Kong APS, Li G, Lam TP, Cheng JCY, Lee WYW. Deletion of SIRT3 inhibits osteoclastogenesis and alleviates aging or estrogen deficiency-induced bone loss in female mice. *Bone*. 2021;144. doi:10.1016/j.bone.2020.115827.

13. Feng L, Yang ZM, Li YC, Wang HX, Lo JHT, Zhang XT, Li G. Linc-ROR promotes mesenchymal stem cells chondrogenesis and cartilage formation via regulating SOX9 expression. *Osteoarthritis and Cartilage.* 2021;29(4):568-578. doi: 10.1016/j.joca.2020.12.020.

14. Luo S, Kong L, Wang J, Nie H, Luan B, Li G. Development of modified Ilizarov hip reconstruction surgery for hip dysfunction treatment in adolescent and young adults. *Journal of Orthopaedic Translation.* 2021;27:90-95. doi:10.1016/j.jot.2020.11.002.

15. Pan Q, Li Y, Li Y, Wang H, Kong L, Yang Z, Zhang X, Bai S, Zong Z, Chen G, Lin S, Li G. Local administration of allogeneic or autologous bone marrow-derived mesenchymal stromal cells enhances bone formation similarly in distraction osteogenesis. *Cytotherapy*. 2021;23(7):590-598. doi: 10.1016/j.jcyt.2020.12.005.

16. Yu J, Xia X, Dong Y, Gong Z, Li G, Chen GG, San Lai PB. CYP1A2 suppresses hepatocellular carcinoma through antagonizing HGF/MET signaling. *Theranostics*. 2021;11(5):2123-2136. doi: 10.7150/thno.49368.



Radiological assessment results. At the end of lengthening, a weekly anteroposterior radiograph including the distraction zone was taken until termination. Representative series of radiographs across the duration of distraction osteogenesis (DO) showed the progression of bone consolidation. All pulsed electromagnetic field (PEMF) treatments had different levels of promoting effects on callus formation. GHSR3h group appeared to have the best bone-healing outcome with earlier continuous callus formation and better consolidation. Gclassic3h and GHSR1h groups appeared to have a similar healing outcome, which was better than those of GHSR1/2h and Gcon groups, but not as good as GHSR3h. HSR, high slew rate groups.

Source: Li Y, Yang Y, Wang M, Zhang X, Bai S, Lu X, Li Y, Waldorff EI, Zhang N, Lee WYW, Li G. High slew rate pulsed electromagnetic field enhances bone consolidation and shortens daily treatment duration in distraction osteogenesis. Bone & Joint Research. 2021;10(12):767-779. doi:10.1302/2046-3758.1012.bjr-2021-0274.r1.







呂愛蘭

KATHY LUI

10 STEM CELLS AND TISSUE REGENERATION

Stem Cell and Vascular Regeneration



Principal Investigator

Kathy Lui

Team members

Kevin Yang, Wenchu Ye, Di Liu, Zhangjing Ma, Peng Ye, Wentao Gao, Danny Wong, Kathleen Chan

Research Progress Summary

During the past years, Kathy Lui and her team have been uncovering the potential of using human pluripotent stem cells for cell therapy, disease modeling, and drug screening. The below two research projects are examples of this effort:

Research on pancreatic beta cell therapy and functional regeneration

There has been a continuous debate over whether there is an adult progenitor or stem cell for the generation of pancreatic beta cells to treat diabetes particularly insulin-dependent diabetes. Compared to insulin therapy, pancreatic beta cell therapy is more appealing given that these cells can respond to the changing blood glucose levels to prevent complication such as hypoglycemia. However, pancreatic beta cells were not able to regenerate after injury. In 2021, the team has reported that there is no endogenous adult stem cell for beta cell (re)generation as demonstrated by a new genetic lineage tracing mouse model (*Nature Metabolism*, 2021; *Cell Metabolism*, 2021). Adult beta cells are mainly derived from the rare process of pre-existing beta cell replication. Therefore, additional therapeutic approaches should be developed to replenish adult beta cells after injury. In 2020, they have reported a new differentiation protocol for generating human pancreatic beta-like cells from human pluripotent stem cells, and uncovered a cell surface marker for negative purification of the mature and functional human beta-like cells (*Stem Cell Reports*, 2020). Recently, pharmaceutical companies such as Semma Therapeutics, Viacyte, Inc, etc have reported FDA approval to launch clinical trials for testing the safety and therapeutic efficacy of human stem cell derived pancreatic progenitor cells. These mark the beginning of using human

stem cell derived beta cells as personalized cell based therapies to treat diabetes. Besides making new beta cells from human pluripotent stem cells, they have further studied the endogenous regulatory pathways to understand how insulin is produced, facilitating the search for the pathophysiological origin of diabetes.

Research on COVID-19 related vascular disease and dysfunction

In view of the unknown impact of the SARS-CoV-2 virus on vascular function in COVID-19 patients, the team has also investigated whether the virus has a direct effect in impairing endothelial cell function or a secondary effect in inducing the dysfunction through immune over-reaction. They have written a concise review to summarise the arguments on both sides of this topic (*Journal of Molecular and Cellular Cardiology*, 2021). Moreover, they have also collaborated with Leo Poon's team at The University of Hong Kong to study the effect of SARS-CoV-2 on the infectivity, function and inflammation of vascular cells. Importantly, they model SARS-CoV-2 infection in these cells by generating human pluripotent stem cell derived endothelial cells for *in vitro* disease modeling and drug screening. While ACE2 is indispensable for SARS-CoV-2 infection in these cells, they found that the virus can directly induce endothelial inflammation and dysfunction independent of ACE2 expression.

Conference presentation

Despite that the pandemic has not ended, Kathy has been invited to give several virtual lectures in some international and regional conferences, including a lecture for the Federation of Immunological Societies of Asia-Oceania (FIMSA) in Korea; a lecture for the Immunity and Infection Seminar in University of Freibury, Germany; a lecture for the exchange programme between The Chinese University of Hong Kong and Monash University, Australia; a lecture for the 24th Annual Scientific Meeting of Institute of Cardiovascular Science and Medicine, Hong Kong. The scientific meeting for the Hong Kong Society for Immunology (HKSI) has been organised by the team in 2021 as she has been serving as the chairman of HKSI.

Research and Scholarship

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Kathy Lui	Young Researcher Award 2020	The Chinese University of Hong Kong
	Young Investigator Award	The Chinese University of Hong Kong
	2021 Circulation Research Extraordinary Reviewer	American Heart Association, U.S.A.

Fellowships

Member's Name	Details	
	Fellowship	Organisation
Wenchu Ye	RC Postdoc Fellowship	The Chinese University of Hong Kong

Academic Editorship

Member's Name	Details	
	Role	Journal
Kathy Lui	Editorial Member	Circulation Research
		Cardiovascular Research
		Frontiers in Immunology
		Scientific Reports
	Associate Editor	Stem Journal
		Journal of Immunology and Regenerative Medicine

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Kathy Lui	Grant Reviewer	Sir Henry Dale Fellowship, Wellcome Trust, United Kingdom
		Spark Funding Scheme, Swiss National Science Foundation, Switzerland
		New Talent Programme, Dutch Research Council, Netherland
	Journal Reviewer	Circulation Research
		Diabetes
		Theranostics
		Acta Pharmaceutica Sinica B
		Pharmacological Research
		China Science Life Science
Kevin Yang	Journal Reviewer	Immunology Letters

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Kathy Lui	Vascular Diseases and Regeneration	National Natural Science Foundation of China – Excellent Young Scientist Fund	01/01/2020	31/12/2022	RMB 1,300,000
	Studying the Functional Mechanism of Endothelial YY1 in Postischemic Angiogenesis	Research Grants Council – General Research Fund	01/01/2021	31/12/2023	1,195,542
	Studying the Role of m6A RNA Modification in Vascular Diseases and Regeneration	National Natural Science Foundation of China – Research Fund	01/01/2021	31/12/2023	RMB 550,000
	Aging, Skeletal Degeneration and Regeneration	Research Grants Council – Areas of Excellence Scheme	01/05/2021	30/04/2029	64,889,000
Wenchu Ye	平滑肌細胞焦亡在動脈粥樣硬化中的作用及機制研究	National Natural Science Foundation of China – Excellent Young Scientist Fund	01/01/2021	31/12/2023	RMB 240,000

Publications

A. Journal Papers

1. Yan Y, Tang R, Li B, Cheng L, Ye S, Yang T, Han YC, Liu C, Dong Y, Qu LH, Lui KO, Yang JH, Huang ZP. The cardiac translational landscape reveals that micropeptides are new players involved in cardiomyocyte hypertrophy. *Molecular Therapy*. 2021;29(7):2253-2267. doi:10.1016/j.ymthe.2021.03.004.

2. Zhao H, Huang X, Liu Z, Pu W, Lv Z, He L, Li Y, Zhou Q, Lui KO, Zhou B. Pre-existing beta cells but not progenitors contribute to new beta cells in the adult pancreas. *Nature Metabolism*. 2021;3(3):352-365. doi:10.1038/s42255-021-00364-0.

3. Han DSC, Ni M, Chan RWY, Wong DKL, Hiraki LT, Volpi S, Jiang P, Lui KO, Chan KCA, Chiu RWK, Lo YMD. Nuclease deficiencies alter plasma cell-free DNA methylation profiles. *Genome Research*. 2021;31(11):2008-2021. doi:10.1101/gr.275426.121.

4. Weng W, Liu X, Lui KO, Zhou B. Harnessing orthogonal recombinases to decipher cell fate with enhanced precision. *Trends in Cell Biology*. Published online 2021. doi:10.1016/j.tcb.2021.09.007. (Review, Epub ahead of print)

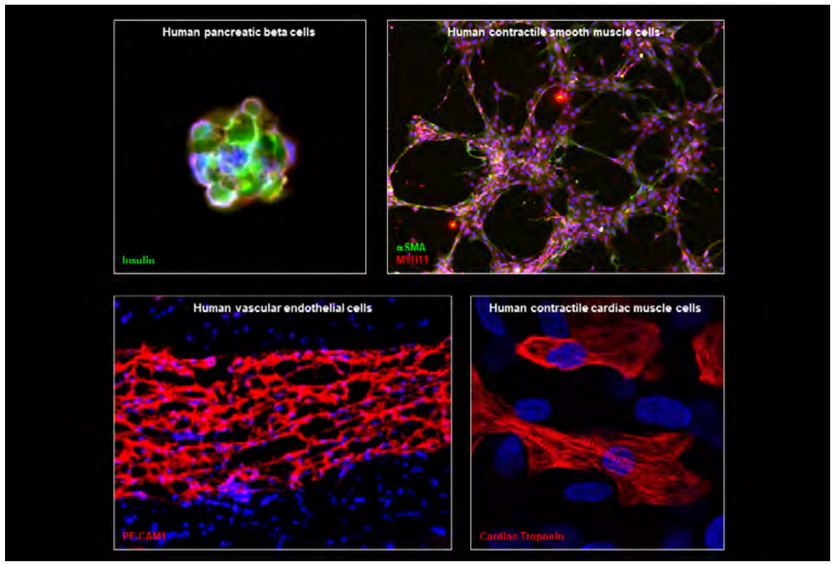
5. Lui KO, Huang Y. Chaperone mediated autophagy regulates eNOS uncoupling in cardiovascular events. *Circulation Research*. 2021;129(10):946-948. doi:10.1161/CIRCRESAHA.121.320212. (Editorial)

6. Zhao H, Lui KO, Zhou B. Pancreatic beta cell neogenesis: Debates and updates. *Cell Metabolism*. 2021;33(11):2105-2107. doi:10.1016/j.cmet.2021.10.007. (Editorial)

7. Zhang S, Li Y, Huang X, Liu K, Wang QD, Chen AF, Sun K, Lui KO, Zhou B. Seamless genetic recording of transiently activated mesenchymal gene expression in endothelial cells during cardiac fibrosis. *Circulation*. 2021;144(25):2004-2020. doi:10.1161/circulationaha.121.055417. (Epub ahead of print)

8. Li Y, Zhu H, Zhang Q, Han X, Zhang Z, Shen L, Wang L, Lui KO, He B, Zhou B. Smooth muscle-derived macrophage-like cells contribute to multiple cell lineages in the atherosclerotic plaque. *Cell Discovery*. 2021;7(1):1-4. doi:10.1038/s41421-021-00328-4. (Letter)

9. Ma Z, Yang KY, Huang Y, Lui KO. Endothelial contribution to COVID-19: An update on mechanisms and therapeutic implications. *Journal of Molecular and Cellular Cardiology*. 2022;164:69-82. doi:10.1016/j.yjmcc.2021.11.010. (Epub ahead of print)



Functional organoids generated from human pluripotent stem cells from Kathy Lui and her team's laboratory

Source: Kathy Lui and her team

李郁偉

WAYNE LEE



10 STEM CELLS AND TISSUE REGENERATION



Principal Investigator

Wayne Lee

Team members

Dorsa Dehghan-Baniani, Rachel Shiu, Tsz-lam Yiu, Ericsson Fung, Allen Hsiao, Belle Wang, Kenneth Yang, Jessica Lo, Rongliang Wang, Zhe Zhang

Research Progress Summary

Wayne Lee and his research team work on the role of osteocytes in musculoskeletal diseases by using advanced imaging and mechanical stimulation devices on 3D cell culture and transgenic animal models. They established primary osteocyte culture model derived from patients with adolescent idiopathic scoliosis (AIS), allowing them to identify abnormal expression of several miRNAs and lncRNAs which disrupt osteocytogenic differentiation. Based on these pre-clinical studies, they proposed a composite model consisted of clinical data and circulating biomarkers for the prediction of curve progression in AIS. The team has continued to search for factors associated with the onset and progression of AIS. They have deepened their studies to investigate the metabolomic and proteomic changes in AIS patients with high risk to curve progression. Osteocytes are the major mechanosensing cells in skeleton and transduce mechanical stimuli into biochemical signals through highly specialized dendritic processes and lacunocanalicular network (LCN). Recently, they have extended their osteocyte research platform to investigate the role of osteocytes in other musculoskeletal diseases such as osteoarthritis and osteoporosis. Their recent findings provide new insights into the development of potential treatments targeting osteocytes to prevent age-related bone loss and augment the benefits of exercise on senescent skeleton. Furthermore, with the generous support from Li Ka Shing (Canada) Foundation and the Matching Grant Scheme, the team and their clinical colleagues and industrial collaborator reported how a state-of-the-art multi-energy spectral photon-counting computed tomography (MARS) can imagine orthopedic implant failure not detected by standard current imaging techniques. This system has a potential clinical application in orthopedic patients.

Research and Scholarship

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Yujia Wang	Top Podium Presentation Award	The International Research Society of Spinal Deformities
Allen Hsiao	Young Investigator Poster Presentation Award First Place	Hong Kong Institute of Diabetes and Obesity

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Wayne Lee	Editor and Reviewer	Journal of Orthopaedic Translation
	Reviewer	Biomaterials
		Scientific Reports
		Stem Cells International
		The Journal of Frailty & Aging
		BMC Musculoskeletal Disorders

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Wayne Lee	Decellularized Scaffolds for Bone and Cartilage Regeneration	Innovation and Technology Commission – Innovation and Technology Fund	01/08/2021	31/01/2024	2,081,500
	Is Vitamin D Playing a Role in the Pathogenesis of AIS?	American Society for Bone and Mineral Research	01/10/2020	30/09/2023	468,000
	Bone Aging and Osteocyte Biology	The Chinese University of Hong Kong – Improvement on Competitiveness in Hiring New Faculties' Funding Scheme	01/08/2020	31/07/2023	1,106,667
	For the Acquisition and Maintenance of MARS Preclinical Spectral CT System to Facilitate the Research Projects	University Grants Committee – Research Matching Grant Scheme	01/01/2020	31/12/2025	1,849,650
	Research Study on Muscle Loss in Aged Mice	University Grants Committee – Research Matching Grant Scheme	01/10/2020	31/07/2023	60,000
	Novel Biological Action of Long Noncoding RNA LBX1-AS1 on Osteocytogenesis and Osteocyte Function in Adolescent Idiopathic Scoliosis	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	861,601
	Exploration of Effects and Molecular Mechanism of Ginkgolide B in Treating Ageing-related Osteoporosis	Research Grants Council – General Research Fund	01/08/2020	31/07/2022	920,567
	Pathological Implication and Functional Characterization of a Novel Long Non-Coding RNA LBX1-AS1 in Adolescent Idiopathic Scoliosis	Health and Medical Research Fund – Research Fellowship Scheme	01/08/2019	31/07/2022	971,760
	Development of Staphylococcal Enterotoxins C2 (SEC2) as a Drug to Promote Osteoporotic Fracture Healing	The Chinese University of Hong Kong – Improvement on Competitiveness in Hiring New Faculties' Funding Scheme	01/04/2020	30/09/2022	2,268,318
	Aging, Skeletal Degeneration and Regeneration	Research Grants Council – Areas of Excellence Scheme	01/05/2021	30/04/2029	64,889,000

Publications

A. Journal Papers

1. Yang KG, Lee WYW, Hung ALH, Hung VWY, Tang MF, Leung TF, Kong APS, Cheng JCY, Lam TP. Decreased cortical bone density and mechanical strength with associated elevated bone turnover markers at peri-pubertal peak height velocity: A cross-sectional and longitudinal cohort study of 396 girls with adolescent idiopathic scoliosis. *Osteoporosis International*. 2021;1:1-11. doi:10.1007/s00198-021-06200-1.

2. Yang G, Lee WYW, Hung ALH, Tang MF, Li X, Kong APS, Leung TF, Yung PSH, To KKW, Cheng JCY, Lam TP. Association of serum 25(OH)Vit-D levels with risk of pediatric fractures: A systematic review and meta-analysis. *Osteoporosis International*. 2021;32(7):1287-1300. doi:10.1007/s00198-020-05814-1. (Review)

3. Xu L, Feng Z, Dai Z, Lee WYW, Wu Z, Liu Z, Sun X, Tang N, Cheng JCY, Qiu Y, Zhu Z. A functional SNP in the promoter of LBX1 is associated with the development of adolescent idiopathic scoliosis through involvement in the myogenesis of paraspinal muscles. *Frontiers in Cell and Developmental Biology*. 2021;9:3256. doi:10.3389/fcell.2021.777890. (Review)

4. Wang Y, Chen H, Zhang J, Lam TP, Hung ALH, Cheng JCY, Lee WYW. Potential muscle-related biomarkers in predicting curve progression to the surgical threshold in adolescent idiopathic scoliosis — A pilot proteomic study comparing four non-progressive vs. four progressive patients vs. a control cohort. *Journal of Clinical Medicine*. 2021;10(21):4927. doi:10.3390/jcm10214927.

5. Lin W, Chen S, Wang Y, Wang M, Lee WYW, Jiang X, Li G. Dynamic regulation of mitochondrial-endoplasmic reticulum crosstalk during stem cell homeostasis and aging. *Cell Death & Disease*. 2021;12(9):1-8. doi:10.1038/s41419-021-03912-4. (Review)

6. Li Y, Yang Y, Wang M, Zhang X, Bai S, Lu X, Li Y, Waldorff EI, Zhang N, Lee WYW, Li G. High slew rate pulsed electromagnetic field enhances bone consolidation and shortens daily treatment duration in distraction osteogenesis. *Bone & Joint Research*. 2021;10(12):767-779. doi:10.1302/2046-3758.1012.BJR-2021-0274.R1. (Epub ahead of print)

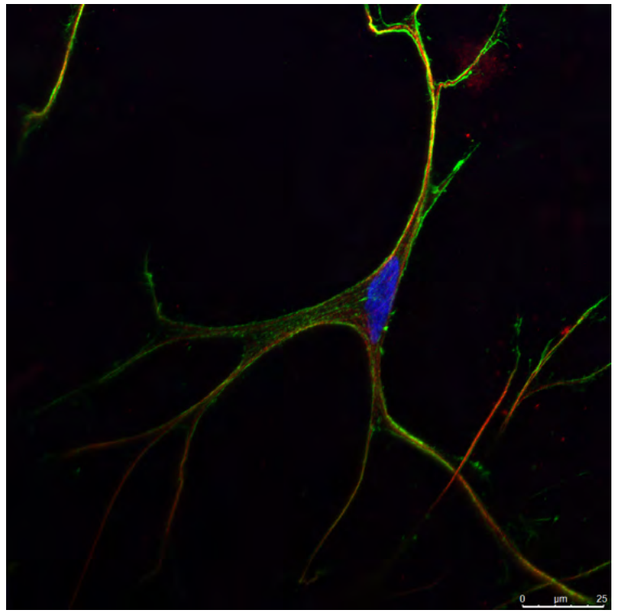
7. Li Q, Yang G, Xu H, Tang S, Lee WYW. Effects of resveratrol supplementation on bone quality: A systematic review and meta-analysis of randomized controlled trials. *BMC Complementary Medicine and Therapies*. 2021;21(1):1-15. doi:10.1186/s12906-021-03381-4.

8. Li Q, Wang H, Zhang J, Kong AP shan, Li G, Lam T ping, Cheng JC yiu, Lee WYW. Deletion of SIRT3 inhibits osteoclastogenesis and alleviates aging or estrogen deficiency-induced bone loss in female mice. *Bone*. 2021;144:115827. doi:10.1016/j.bone.2020.115827.

9. Li Q, Cheng JC yiu, Jiang Q, Lee WYW. Role of sirtuins in bone biology: Potential implications for novel therapeutic strategies for osteoporosis. *Aging Cell.* 2021;20(2):e13301. doi:10.1111/acel.13301. (Review)

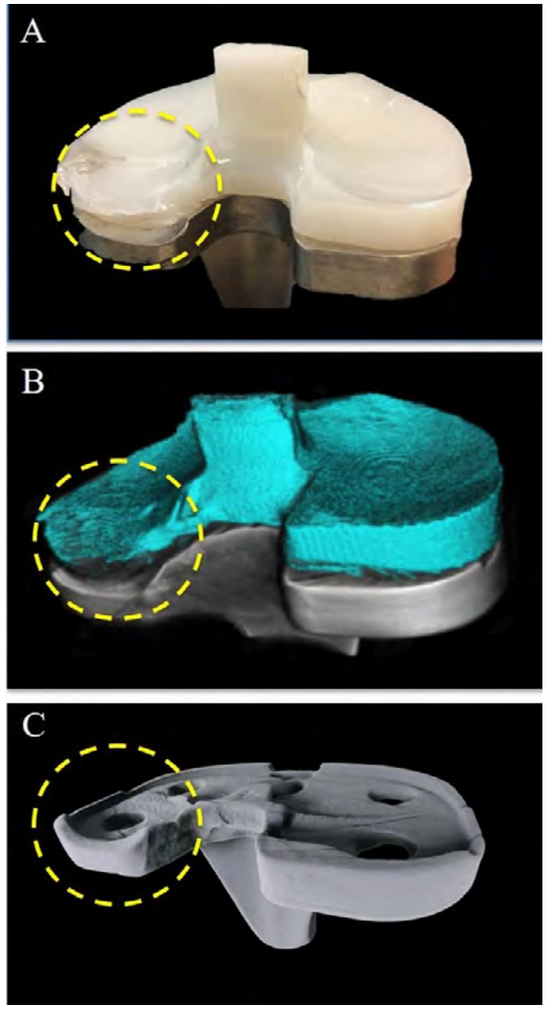
10. Lau LCM, Lee WYW, Butler APH, Chernoglazov AI, Chung KY, Ho KKW, Griffith J, Butler PH, Yung PSH. Multi-energy spectral photon-counting computed tomography (MARS) for detection of arthroplasty implant failure. *Scientific Reports.* 2021;11(1):1-6. doi:10.1038/s41598-020-80463-2.

11. Kong L, Wang Y, Wang H, Pan Q, Zuo R, Bai S, Zhang X, Lee WY, Kang Q, Li G. Conditioned media from endothelial progenitor cells cultured in simulated microgravity promote angiogenesis and bone fracture healing. *Stem Cell Research and Therapy*. 2021;12(1):1-14. doi:10.1186/s13287-020-02074-y.



Representative co-immunofluorescent staining demonstrates structural features of 3D culture of primary osteocytes derived from non-scoliosis adolescent requiring orthopedic surgery (cytoskeletal F-actin in green; dendrites E11 in red; and nucleus in blue). Scale bar, 25 µm.

Source: Zhang J, Chen H, Leung RKK, Choy KW, Lam TP, Ng BKW, Qiu Y, Feng JQ, Cheng JCY, Lee WYW. Aberrant miR-145-5p/b-catenin signal impairs osteocyte function in adolescent idiopathic scoliosis. FASEB Journal. 2018;32(12):6537-6549. doi:10.1096/fj.201800281.



(A) Photograph of an extracted arthroplasty implant, (B) MARS-CT image and (C) MARS-CT image with ultra-high molecular weight polyethylene digitally removed. The wear at the posteromedial aspect of the polyethylene implant and tibial metallic tray is clearly visible (dotted yellow circle).

Source: Lau LCM, Lee WYW, Butler APH, Chernoglazov AI, Chung KY, Ho KKW, Griffith J, Butler PH, Yung PSH. Multi-energy spectral photon-counting computed tomography (MARS) for detection of arthroplasty implant failure. Scientific Reports. 2021;11(1):1-6. doi:10.1038/s41598-020-80463-2.



秦嶺

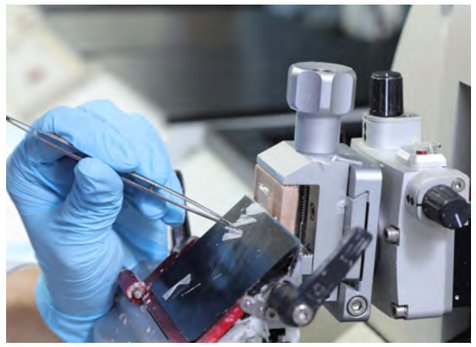
LING QIN

11 BIOMATERIAL AND DRUG TRANSLATIONAL RESEARCH

Innovative Orthopaedic Biomaterial and Drug Translational Research

Research Progress Summary

The team led by Ling Qin focuses on the development of orthopaedic implants/devices with innovative biomaterial or hybrid systems and medical drugs/nutrition supplements for orthopaedics diseases or injuries, such as osteoporosis, osteoporotic fractures, osteonecrosis. By integrating medical science, life science, material science, pharmacological science, imaging technology, and biomechanics, they identify the potential solutions for clinical problems. Then, they collaborate with their industrial partners to transform their research into medical products that benefits patients. The feedback from patients and clinicians would refine future R&D and improve the quality of innovative products.





With collective efforts and endeavors, Ling's R&D programme has secured significant R&D and scientific competitive grants, including the Areas of Excellence Scheme, the Theme-based Research Scheme and the Collaborative Research Fund, which are the most competitive grants schemes given by the Research Grants Council of the Hong Kong Special Administrative Region. In 2021, they have also got two General Research Fund proposals funded and run a company under the Technology Start-up Support Scheme for Universities. In 2021, Ling published 35 papers (6 of them with impact factor above 10).



Research Progress Summary



Principal Investigator

Ling Qin

Team members

Jiankun Xu, Dick Chow, Le Huang, Wenxue Tong, Lizhen Zheng, Hao Yao, Bingyang Dai, Ye Li, Li Zou, Hongtao Xu, Liangbin Zhou, Xuan He, Xiaodan Chen, Xu Li, Ziyi Chen, Zhi Yao, Liang Chang, Shunxiang Xu, Yuantao Zhang, Xin Chen, Haozhi Zhang, Yuanming An, Tongzhou Liang, Jiaxin Guo, Shian Zhang

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Weihao Yuan Zhi Yao Jiaxin Guo Shunxiang Xu	Professor Charles K.KAO Student Creativity Awards 2021 Second Runner-up	The Chinese University of Hong Kong
	The 7th Hong Kong University Student Innovation and Entrepreneurship Competition Second Prize of Life Sciences	Hong Kong New Generation Cultural Association Innovation and Technology Commission
Zhi Yao	2021 Virtual Student Paper Competition Gold Award	The Tissue Engineering and Regenerative Medicine International Society, Inc. – Asia Pacific
Jiaxin Guo	2021 Virtual Student Paper Competition Royal Society of Chemistry Award	The Tissue Engineering and Regenerative Medicine International Society, Inc. – Asia Pacific
Le Huang Shunxiang Xu	The 7th Hong Kong University Student Innovation and Entrepreneurship Competition Third Place Award of Startup	Hong Kong New Generation Cultural Association Innovation and Technology Commission

Research and Scholarship

Member's Name	Details	
	Award	Organisation
Le Huang Shunxiang Xu Jiankun Xu Yuantao Zhang Jiaxin Guo	The 7th China International "Internet+" College Students Innovation and Entrepreneurship Competition – Hong Kong Chapter Silver Award	Hong Kong New Generation Cultural Association Innovation and Technology Commission
Le Huang Shunxiang Xu	Intellectual Property Innovation and Entrepreneurship Contest: Hong Kong Chapter Top Ten	Cyberport, Hong Kong

Academic Editorship

Member's Name	Details	
	Role	Journal
Ling Qin	Editor-in-Chief	Journal of Orthopaedic Translation
	Editorial Advisory Board Member	Recent Patents on Biomedical Engineering
	Member	International Society of Musculoskeletal and Neuronal Interactions
		World Journal of Rheumatology
	第三屆編委	《中華創傷骨科雜誌》
	Associate Editor	Orthopaedic Surgery
	International Review Panel	European Cells & Materials Journal European Cells & Materials Journal
	Editorial Board Member	Current Osteoporosis Reports
Jiankun Xu	Editoral Board Member	Journal of Orthopaedic Translation

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Dick Chow	Reviewer	Orthopaedic Research Society 2022 Annual Meeting

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Ling Qin	Multifunctional Bioactive 3D-Printed Scaffold as an All-in-One Platform for Postsurgical Osteosarcoma Treatment and Bone Defect Repair	Innovation and Technology Fund – Mainland-Hong Kong Joint Funding Scheme	01/11/2021	31/10/2023	2,162,000
	Aging, Skeletal Degeneration and Regeneration	Research Grants Council – Areas of Excellence Scheme	01/05/2021	30/04/2029	64,889,000
	Identification of a Central to Sympathetic Neural Circuit in Magnesium-promoted Bone Regeneration Using Retrograde Tracing and Single-cell RNA-seq	Research Grants Council – General Research Fund	01/01/2021	31/12/2023	1,126,379
	Calcitonin Gene-related Peptide Induced by Electrical Stimulation at Single Dorsal Root Ganglion Accelerates Osteoporotic Fracture Healing	Research Grants Council – General Research Fund	01/01/2020	31/12/2022	1,115,145
	Further Development and Translation of Innovative Titanium-Magnesium Plate-screw Hybrid Fixation System for Osteoporotic Fracture Fixation and Healing Enhancement	Innovation and Technology Fund – Innovation and Technology Support Programme	01/01/2019	31/12/2022	2,449,000
	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

Publications
A. Journal Papers

1. Wang J, Xu J, Wang X, Sheng L, Zheng L, Song B, Wu G, Zhang R, Yao H, Zheng N, Yun Ong MT, Yung PS hang, Qin L. Magnesium-pretreated periosteum for promoting bone-tendon healing after anterior cruciate ligament reconstruction. *Biomaterials*. 2021;268. doi:10.1016/j.biomaterials.2020.120576.

2. He X, Li Y, Guo J, Xu J, Zu H, Huang L, Ong MTY, Yung PSH, Qin L. Biomaterials developed for facilitating healing outcome after anterior cruciate ligament reconstruction: Efficacy, surgical protocols, and assessments using preclinical animal models. *Biomaterials*. 2021;269. doi:10.1016/j.biomaterials.2020.120625. (Review)

3. Zu H, Chau K, Olugbade TO, Pan L, Dreyer CH, Chow DHK, Huang L, Zheng L, Tong W, Li X, Chen Z, He X, Zhang R, Mi J, Li Y, Dai B, Wang J, Xu J, Liu K, Lu J, Qin L. Comparison of modified injection molding and conventional machining in biodegradable behavior of perforated cannulated magnesium hip stents. *Journal of Materials Science and Technology*. 2021;63:145-160. doi:10.1016/j.jmst.2020.02.057.

4. Liu Y, Li H, Xu J, TerBush J, Li W, Setty M, Guan S, Nguyen TD, Qin L, Zheng Y. Biodegradable metal-derived magnesium and sodium enhances bone regeneration by angiogenesis aided osteogenesis and regulated biological apatite formation. *Chemical Engineering Journal*. 2021;410:127616. doi:10.1016/j.cej.2020.127616.

5. Cheng W, Gan D, Hu Y, Zheng Z, Zeng Q, Li L, Wang X, Zhang Y, Xu Z, Qin L, Zhang P. The effect and mechanism of QufengZhitong capsule for the treatment of osteoarthritis in a rat model. *Journal of Orthopaedic Translation*. 2021;28:65-73. doi:10.1016/j.jot.2020.10.013.

6. Yao H, Xu J, Wang J, Zhang Y, Zheng N, Yue J, Mi J, Zheng L, Dai B, Huang W, Yung S, Hu P, Ruan Y, Xue Q, Ho K, Qin L. Combination of magnesium ions and vitamin C alleviates synovitis and osteophyte formation in osteoarthritis of mice. *Bioactive Materials*. 2021;6(5):1341-1352. doi:10.1016/j.bioactmat.2020.10.016.

7. Zheng L, Huang L, Chen Z, Cui C, Zhang R, Qin L. Magnesium supplementation alleviates corticosteroid-associated muscle atrophy in rats. *European Journal of Nutrition*. 2021;60(8):4379-4392. doi:10.1007/s00394-021-02598-w.

8. Wan P, Wang W, Zheng L, Qin L, Yang K. One-step electrodeposition synthesis of bisphosphonate loaded magnesium implant: A strategy to modulate drug release for osteoporotic fracture healing. *Journal of Materials Science and Technology*. 2021;78:92-99. doi:10.1016/j.jmst.2020.10.055.

9. Li Y, Xu J, Mi J, He X, Pan Q, Zheng L, Zu H, Chen Z, Dai B, Li X, Pang Q, Zou L, Zhou L, Huang L, Tong W, Li G, Qin L. Biodegradable magnesium combined with distraction osteogenesis synergistically stimulates bone tissue regeneration via CGRP-FAK-VEGF signaling axis. *Biomaterials*. 2021;275:120984. doi:10.1016/j.biomaterials.2021.120984.

10. Dai B, Li X, Xu J, Zhu Y, Huang L, Tong W, Yao H, Chow DHK, Qin L. Synergistic effects of magnesium ions and simvastatin on attenuation of high-fat diet-induced bone loss. *Bioactive Materials*. 2021;6(8):2511-2522. doi:10.1016/j.bioactmat.2021.01.027.

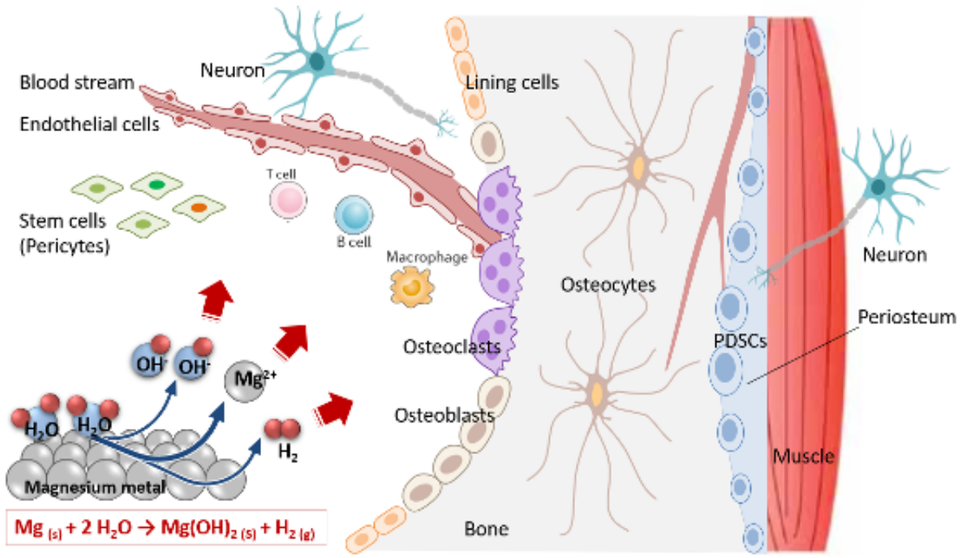
11. Chang L, Yao H, Yao Z, Ho KKW, Ong MTY, Dai B, Tong W, Xu J, Qin L. Comprehensive analysis of key genes, signaling pathways and miRNAs in human knee osteoarthritis: Based on bioinformatics. *Frontiers in Pharmacology*. 2021;12:1-17. doi:10.3389/fphar.2021.730587.

12. Mi J, Xu JK, Yao Z, Yao H, Li Y, He X, Dai BY, Zou L, Tong WX, Zhang XT, Hu PJ, Ruan YC, Tang N, Guo X, Zhao J, He JF, Qin L. Implantable electrical stimulation at dorsal root ganglions accelerates osteoporotic fracture healing via calcitonin gene-related peptide. *Advanced Science*. 2021;2103005:1-14. doi:10.1002/advs.202103005. (Epub ahead of print)

13. Liu Y, Peng L, Li L, Huang C, Shi K, Meng X, Wang P, Wu M, Li L, Cao H, Wu K, Zeng Q, Pan H, Lu WW, Qin L, Ruan C, Wang X. 3D-bioprinted BMSC-laden biomimetic multiphasic scaffolds for efficient repair of osteochondral defects in an osteoarthritic rat model. *Biomaterials*. 2021;279:121216. doi:10.1016/j.biomaterials.2021.121216.

14. Chow DHK, Wang J, Wan P, Zheng L, Ong MTY, Huang L, Tong W, Tan L, Yang K, Qin L. Biodegradable magnesium pins enhanced the healing of transverse patellar fracture in rabbits. *Bioactive Materials*. 2021;6(11):4176-4185. doi:10.1016/j.bioactmat.2021.03.044.

15. Li X, Dai B, Guo J, Zheng L, Guo Q, Peng J, Xu J, Qin L. Nanoparticle–cartilage interaction: Pathology-based intra-articular drug delivery for osteoarthritis therapy. *Nano-Micro Letters*. 2021;13(1). doi:10.1007/S40820-021-00670-Y. (Review)



Ling Qin and his team's research area is on further understanding of bioactive effects of the implant byproducts (i.e. Mg^{2+} , OH^- and H^2) in bone regeneration via exogenous and endogenous growth factors.

Source: Ling Qin and his team

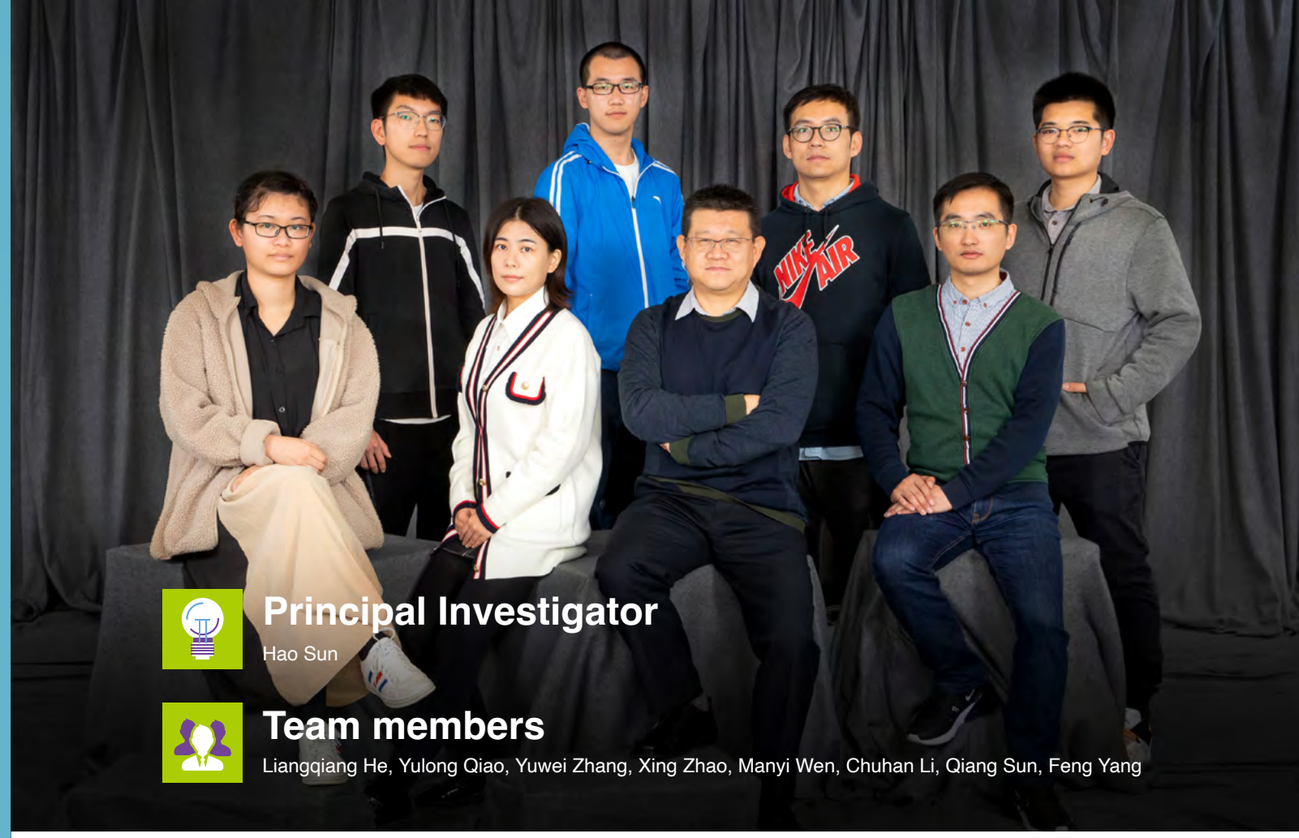
孫昊

HAO SUN



AGCT
TCGA

12 GENOMICS AND BIOINFORMATICS



Principal Investigator

Hao Sun

Team members

Liangqiang He, Yulong Qiao, Yuwei Zhang, Xing Zhao, Manyi Wen, Chuhan Li, Qiang Sun, Feng Yang

Research Progress Summary

In the reporting period, Hao Sun and his team has 8 ongoing grants funded by the Research Grants Council – General Research Fund, the National Natural Science Foundation of China/ Research Grants Council Joint Research Scheme, the Food and Health Bureau – Health and Medical Research Fund, and the Research Grants Council – Theme-based Research Scheme, for studying of transcriptional regulation mechanisms in muscle stem cells as well as next generation data analysis for plasma DNA/RNA sequencing. The team also published 5 papers on some high impact journals such as *Nature Communications* et al.

Research and Scholarship

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Hao Sun	Reviewer	Bioinformatics
		Clinical Biochemistry
		Nature Communications
		RNA Biology

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Hao Sun	Elucidation of Intrinsic and Extrinsic Alterations Regulating Skeletal Muscle Stem Cell Aging: Mechanisms for Sarcopenia	Food and Health Bureau – Health and Medical Research Fund	12/02/2021	01/12/2024	1,496,150
	Study on the Mechanism Underlying BMAL1/CLOCK-mediated Regulation of Human Stem Cell Homeostasis and Aging	National Natural Science Foundation of China/Research Grants Council – Joint Research Scheme 2018/19	01/01/2019	31/12/2022	1,166,714
	Genome-wide Computational Identification and in Vivo CRISPR Screen of Key Transcription Factors (TFs) and TF Hotspots Governing Muscle Satellite Cell Lineage Progression	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	1,136,632
	Mechanistic Investigation of Linc-p27 Function in Skeletal Muscle Satellite Cell and Muscle Regeneration	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	970,697
Hao Sun	Plasma DNA as a Platform Technology for Cancer Detection	The Chinese University of Hong Kong – Focused Innovations Scheme C	01/12/2016	30/11/2021	2,093,500
		The Chinese University of Hong Kong Matching Fund for Research Grants Council – Theme-based Research Scheme	01/12/2016	30/11/2021	4,444,000
	To Investigate 3D Genome Dynamics During the Muscle Satellite Cell Lineage Progression	The Chinese University of Hong Kong Research Committee – Direct Grant	30/06/2020	29/05/2021	62,000



Publications

A. Journal Papers

1. Chen X, Yuan J, Xue G, Campanario S, Wang D, Wang W, Mou X, Liew SW, Umar MI, Isern J, Zhao Y, He L, Li Y, Mann CJ, Yu X, Wang L, Perdiguero E, Chen W, Xue Y, Nagamine Y, Kwok CK, Sun H, Muñoz-Cánoves P, Wang H. Translational control by DHX36 binding to 5'UTR G-quadruplex is essential for muscle stem-cell regenerative functions. *Nature Communication*. 2021;12(1). doi:10.1038/S41467-021-25170-w.

2. He L, Ding Y, Zhao Y, So KK, Peng XL, Li Y, Yuan J, He Z, Chen X, Sun H, Wang H. CRISPR/Cas9/AAV9-mediated *in vivo* editing identifies MYC regulation of 3D genome in skeletal muscle stem cell. *Stem Cell Reports*. 2021;16(10):2442-2458. doi: 10.1016/j.stemcr.2021.08.011.



Noncoding Assessment of long RNAs in Magnoliophyta Species.

Source: Sun K, Wang H, Sun H. NAMS webserver: Coding potential assessment and functional annotation of plant transcripts. Briefing in Bioinformatics. 2021;22(3). doi:10.1093/bib/bbaa200.







12 GENOMICS AND BIOINFORMATICS



Principal Investigator

Peiyong Jiang

Team members

Ze Zhou, Wenlei Peng, Olivia Tse, Harry Chan, Jiaen Deng, Yuwei Gao, Xi Hu, Yuwei Shi, Xingqian Li

Research Progress Summary

Peiyong Jiang and his team continue the efforts to identify new biological properties of cell-free DNA such as plasma DNA end motifs, jagged ends, and circular cell-free DNA molecules, and develop new diagnostic tools based on sequencing technologies. They established the academic collaboration with the Broad Institute of MIT and Harvard, published a study related to single-cell meta-analysis of SARS-CoV-2 entry genes across tissues and demographics in Nature Medicine. They continue the collaboration with Wayne Luk, from the Department of Computing at Imperial College London. They filed two patent applications in 2021.



Research and Scholarship

Fellowships

Member's Name	Details	
	Fellowship	Organisation
Peiyong Jiang	Senior Member	National Academy of Inventors

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Peiyong Jiang	Centre for Novostics	Innovation and Technology Commission – Innovation and Technology Fund	01/05/2020	01/05/2025	Amount not to be disclosed

Publications

A. Journal Papers

1. Yu SCY, Jiang P, Peng W, Cheng SH, Cheung YTT, Tse OYO, Shang H, Poon LC, Leung TY, Chan KCA, Chiu RWK, Lo YMD. Single-molecule sequencing reveals a large population of long cell-free DNA molecules in maternal plasma. *Proceedings of the National Academy of Sciences*. 2021;118(50):e2114937118. doi:10.1073/pnas.2114937118.

2. Vong JSL, Ji L, Heung MMS, Cheng SH, Wong J, Lai PBS, Wong VWS, Chan SL, Chan HLY, Jiang P, Chan KCA, Chiu RWK, Lo YMD. Single cell and plasma RNA sequencing for RNA liquid biopsy for hepatocellular carcinoma. *Clinical Chemistry*. 2021;67(11):1492-1502. doi:10.1093/clinchem/hvab116.

3. Sin STK, Ji L, Deng J, Jiang P, Cheng SH, Heung MMS, Lau CSL, Leung TY, Chan KCA, Chiu RWK, Lo YMD. Characteristics of fetal extrachromosomal circular DNA in maternal plasma: Methylation status and clearance. *Clinical Chemistry*. 2021;67(5):788-796. doi:10.1093/clinchem/hvaa326.

4. Lo YMD, Han DSC, Jiang P, Chiu RWK. Epigenetics, fragmentomics, and topology of cell-free DNA in liquid biopsies. *Science*. 2021;372(6538). doi:10.1126/science.aaw3616. (Review)

5. Zhou Z, Cheng SH, Ding SC, Heung MMS, Xie T, Cheng THT, Lam WKJ, Peng W, Teoh JYC, Chiu PKF, Ng CF, Jiang P, Chan KCA, Chiu RWK, Lo YMD. Jagged ends of urinary cell-free DNA: Characterization and feasibility assessment in bladder cancer detection. *Clinical Chemistry*. 2021;67(4):621-630. doi:10.1093/clinchem/hvaa325.

6. Gai W, Zhou Z, Agbor-Enoh S, Fan X, Lian S, Jiang P, Cheng SH, Wong J, Chan SL, Jang MK, Yang Y, Liang RHS, Chan WK, Ma ESK, Leung TY, Chiu RWK, Valantine H, Chan KCA, Lo YMD. Applications of genetic-epigenetic tissue mapping for plasma DNA in prenatal testing, transplantation and oncology. *eLife*. 2021;10. doi:10.7554/elife.64356.

7. Tse OYO, Jiang P, Cheng SH, Peng W, Shang H, Wong J, Chan SL, Poon LCY, Leung TY, Chan KCA, Chiu RWK, Lo YMD. Genome-wide detection of cytosine methylation by single molecule real-time sequencing. *Proceedings of the National Academy of Sciences of the United States of America*. 2021;118(5). doi:10.1073/pnas.2019768118.

8. Ma MJL, Yakovenko S, Zhang H, Cheng SH, Apryshko V, Zhavoronkov A, Jiang P, Chan KCA, Chiu RWK, Lo YMD. Fetal mitochondrial DNA in maternal plasma in surrogate pregnancies: Detection and topology. *Prenatal Diagnosis*. 2021;41(3):368-375. doi:10.1002/pd.5860.

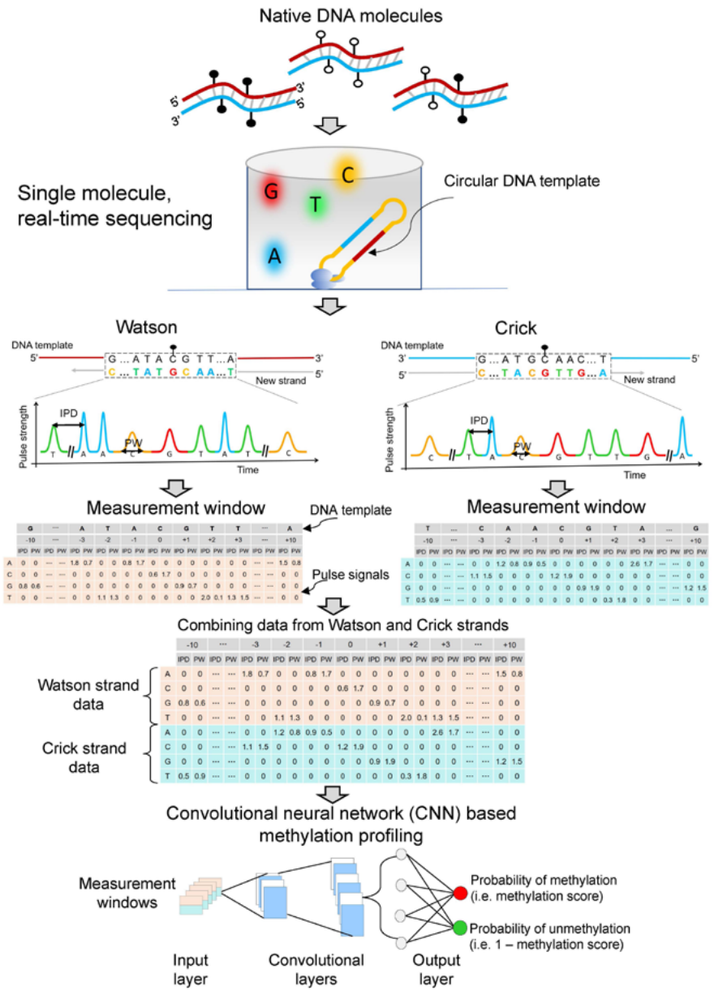


Fig. 1

Schematic 5mC detection using single molecule sequencing and the HK model

Source: PNAS (https://www.pnas.org/content/118/5/e2019768118)

王華婷

HUATING WANG



13 NON-CODING RNAS AND CELLULAR SIGNALLING



Principal Investigator

Huating Wang

Team members

Xiaona Chen, Liangqiang He, Suyang Zhang, Yang Li, Yulong Qiang, Zhiming He, Qin Zhou

Research Progress Summary

During the past year, the team led by Huating Wang continued the work on gene regulatory mechanisms centered on transcription factors (TFs) and RNA binding proteins (RBPs) in skeletal muscle stem cells and muscle regeneration. Specifically, they have been focusing on the following projects: (1) to characterise the previously unknown function of RBPs in 3D genome organisation; (2) to investigate key TF function in early regulatory events during satellite cell activation in muscle regeneration; (3) to study the functional roles of DHX36 in skeletal muscle stem cells and muscle regeneration; (4) to characterise 3D genome organisation in muscle stem cell lineage progression as well as sarcopenia, a muscle weakening condition associated with aging. Findings from their research were published on Stem Cell Reports, Nature Communications, Briefings in Bioinformatics and well accepted by the peers from the scientific communities. As a result, Huating and her research team were invited to present their work at international and regional conferences such as China Muscle Society Annual Meeting, Annual Meeting of RNA Society etc. In addition, fruitful collaborations have been established with peer scientists from Hong Kong, China, U.S.A. and Europe.

Research and Scholarship

Fellowships

Member's Name	Details	
	Fellowship	Organisation
Liangqiang He	Postdoc Fellowship	Faculty of Medicine, The Chinese University of Hong Kong
Suyang Zhang	Postdoc Fellowship	Faculty of Medicine, The Chinese University of Hong Kong

Academic Editorship

Member's Name	Details	
	Role	Journal
Huating Wang	Editorial Board Member	Skeletal Muscle

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Huating Wang	Reviewer	Science Translational Medicine
		EMBO Reports
		Nucleic Acid Research
		Molecular Therapy
		Cell Regeneration

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Huating Wang	Functional Characterization of ATF3 in Skeletal Muscle Stem Cells and Muscle Regeneration	Research Grants Council – General Research Fund	01/01/2021	31/12/2023	1,394,799
	Elucidation of Intrinsic and Extrinsic Alterations Regulating Skeletal Muscle Stem Cell Aging: Mechanisms for Sarcopenia	Food and Health Bureau – Health and Medical Research Fund	02/12/2021	01/12/2023	1,496,150
	Aging, Skeletal Degeneration and Regeneration	Research Grants Council – Areas of Excellence Scheme	01/05/2021	30/04/2029	64,889,000
	Molecular Regulation of Quiescence and Early Activation in Muscle Stem Cells	Research Grants Council – Collaborative Research Fund	30/06/2020	29/06/2023	6,969,211
	3D Genome Rewiring during Muscle Stem Cell Linage Development and Aging	Research Grants Council – General Research Fund	01/01/2021	31/12/2023	1,194,637
	Investigating the Functional Significance of Three-dimensional Structures of Topologically Associating Domains	Research Grants Council – General Research Fund	01/01/2021	31/12/2023	1,195,542
	Studying the Functional Mechanism of Endothelial YY1 in Postischemic Angiogenesis	Research Grants Council – General Research Fund	01/01/2021	31/12/2023	1,195,542
	Elucidation of Post-Transcriptional Regulatory Functions of DHX36 in Skeletal Muscle Stem Cells and Muscle Regeneration	Research Grants Council – General Research Fund	01/01/2020	31/12/2022	1,111,376
	Large Scale Interaction Analysis of RNA Binding Proteins/LncRNAs to Identify LncRNA Nuclear Localization Mechanisms	Research Grants Council – General Research Fund	01/01/2020	31/12/2022	1,115,175
	長鏈非編碼RNA Linc-Cdkn1b對骨骼肌幹細胞及肌肉再生的的調控及其分子機制研究	National Natural Science Foundation of China	01/01/2019	31/12/2022	RMB 600,000
	Epigenetic Mapping in Human Skeletal Muscle Stem Cells	The Hong Kong Epigenomics Project	01/08/2018	31/12/2022	1,000,000

Publications

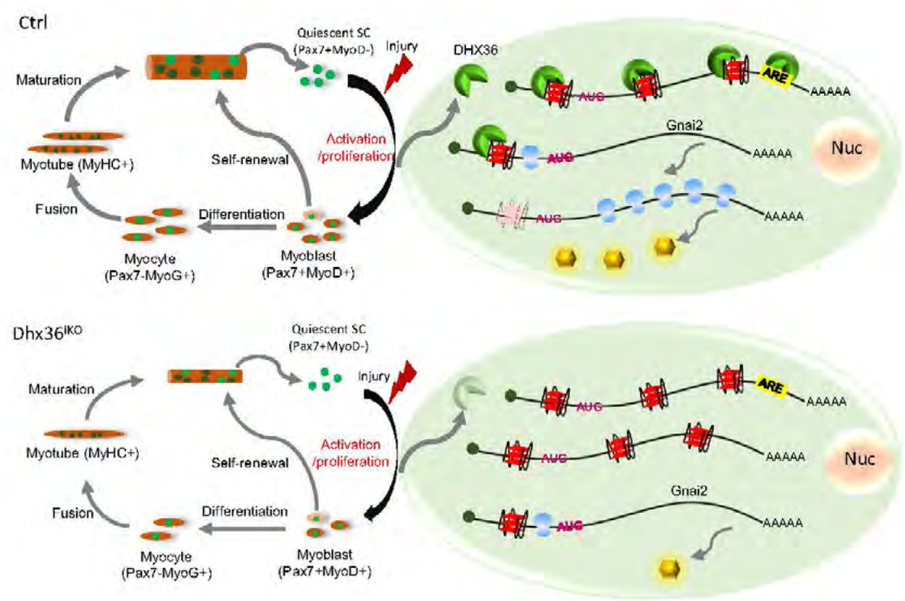
A. Journal Papers

1. He L, Ding Y, Zhao Y, So KK, Peng XL, Li Y, Yuan J, He Z, Chen X, Sun H, Wang H. CRISPR/Cas9/AAV9-mediated in vivo editing identifies MYC regulation of 3D genome in skeletal muscle stem cell. *Stem Cell Reports*. 2021;16(10):2442-2458. doi:10.1016/j.stemcr.2021.08.011.

2. Chen X, Yuan J, Xue G, Campanario S, Wang D, Wang W, Mou X, Liew SW, Umar MI, Isern J, Zhao Y, He L, Li Y, Mann CJ, Yu X, Wang L, Perdiguero E, Chen W, Xue Y, Nagamine Y, Kwok CK, Sun H, Muñoz-CY, Kwo P, Wang H. Translational control by DHX36 binding to 5'UTR G-quadruplex is essential for muscle stem-cell regenerative functions. *Nature Communications*. 2021;12(1):5043. doi:10.1038/s41467-021-25170-w.

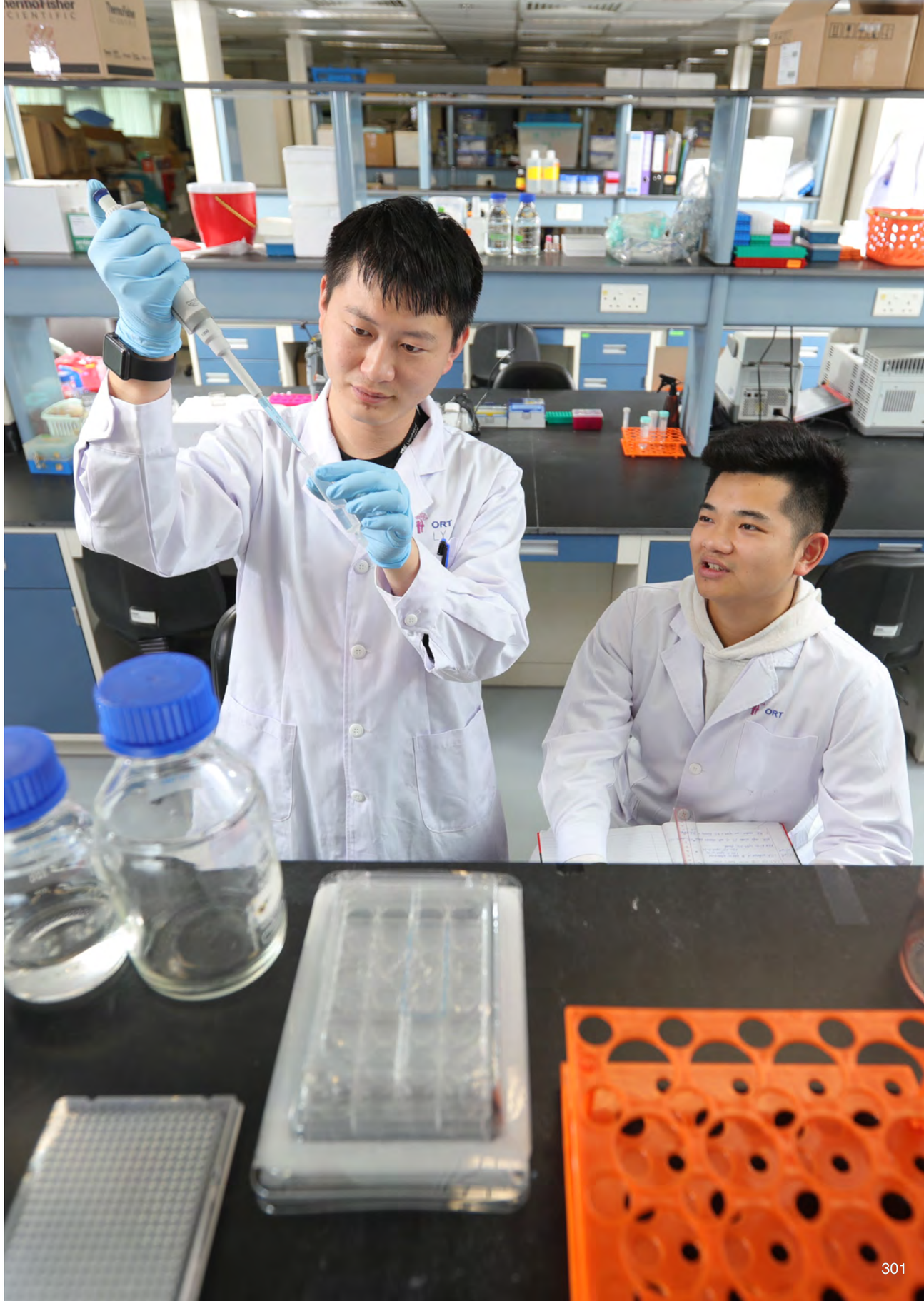
3. Huang Y, Qiao Y, Zhao Y, Li Y, Yuan J, Zhou J, Sun H, Wang H, Li Ka Shing A. Large scale RNA-binding proteins/LncRNAs interaction analysis to uncover lncRNA nuclear localization mechanisms. *Briefings in Bioinformatics*. 2021;22(6):1-15. doi:10.1093/bib/bbab195.

4. Wang H, Huang Y, Yu M, Yu Y, Li S, Wang H, Sun H, Li B, Xu G, Hu P. Muscle regeneration controlled by a designated DNA dioxygenase. *Cell Death & Disease* 2021 12:6. 2021;12(6):1-14. doi:10.1038/s41419-021-03817-2.



Schematic illustration of the functional mechanism of DHX36 in regulating SC proliferation and muscle regeneration.

Source: Chen X, Yuan J, Xue G, Campanario S, Wang D, Wang W, Mou X, Liew SW, Umar MI, Isern J, Zhao Y, He L, Li Y, Mann CJ, Yu X, Wang L, Perdiguero E, Chen W, Xue Y, Nagamine Y, Kwok CK, Sun H, Muñoz-CY, Kwo P, Wang H. Translational control by DHX36 binding to 5'UTR G-quadruplex is essential for muscle stem-cell regenerative functions. Nature Communications. 2021;12(1):5043. doi:10.1038/s41467-021-25170-w.





胡嘉麒

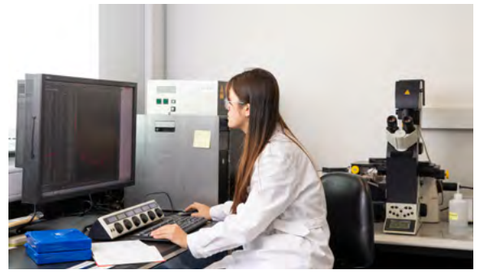
WILLIAM WU

13 NON-CODING RNAS AND CELLULAR SIGNALLING

Research Progress Summary

Cancer – The team led by William Wu discovered that *Streptococcus thermophilus*, a probiotic bacterium depleted in patients with colorectal cancer, can suppress intestinal tumourigenesis in mice. The tumour-suppressive effect of *S. thermophilus* is mediated, at least in part, by the secretion of β-galactosidase. These findings support this probiotic could be a potential prophylactic for preventing colorectal cancer in humans (*Gastroenterology*, 2021).

COVID-19 – Their bioinformatic analysis indicated that augmented T helper 17 cell differentiation and cytokine response may explain the increased incidence of Guillain-Barré syndrome among COVID-19 patients (*Cell proliferation*, 2021).



Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Huarong Chen	Poster of Distinction	Digestive Disease Week 2021, American Gastroenterological Association

Fellowships

Member's Name	Details	
	Fellowship	Organisation
Qing Li	Research Grant Council Postdoctoral Fellowship 2021/2022	Hong Kong Research Grants Council

Academic Editorship

Member's Name	Details	
	Role	Journal
William Wu	Guest Editor	Frontiers in Cell and Developmental Biology
	Associate Editor	Frontiers in Oncology
	Editorial Board Member	Journal of Pharmacy and Pharmacology
Xiaodong Liu	Guest Associate Editor	Frontiers in Molecular Neuroscience
	Review Editor	Frontiers in Pain Research
Huarong Chen	Guest Editor	Diagnostics

Research Progress Summary



Principal Investigator

William WU

Team members

Matthew Chan, Lin Zhang, Xiaodong Liu, Huarong Chen, Idy Ho, Chuan Xie, Qing Li, Xiao Sun, Judeng Zeng, Xiaoting Zhang, Xiansong Wang, Dan Huang, Hung Chan, Zidan Zou, Wenyi Zhu, Tingting Jin, Hongbin Liu, Qian Li, Hao Su, Yingzhi Liu, Yanjun Jiang, Tsui Ping Tam, Dongjiao Chen

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
William Wu	Peer Reviewer	Gut
		Science Advances
		Theranostics
		Oncogene
Xiaodong Liu	Peer Reviewer	Proceedings of the National Academy of Sciences of the United States of America
Huarong Chen	Peer Reviewer	Molecular Cancer
		Theranostics
		Oncogene
		Frontiers in Immunology

Member's Name	Details	
	Role	Journal / Conference
Huarong Chen	Peer Reviewer	Cells
Lin Zhang	Peer Reviewer	Gut
		Journal of Pathology
	Reviewer	AGA Abstract Review Committee (Pre-clinical Treatment of Intestinal Inflammation)

Research and Scholarship

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
William Wu	Mechanism of VitD3 Targeting Autophagy-lysosomal Pathway Inhibiting C. *difficile*-related Inflammation	National Natural Science Foundation of China	01/01/2021	31/12/2024	RMB 550,000
	m6A Modification Controls the Autophagic Response to *Helicobacter pylori* Infection	Research Grants Council – General Research Fund	01/01/2021	31/12/2023	1,195,290
	A Mechanistic Study on the Influence of Cancers on Human Genome Evolution	Shenzhen Science and Technology Programme, Shenzhen Science and Technology Innovation Commission	18/03/2019	31/03/2022	RMB 3,000,000
	A Mechanistic Study of the Therapeutic Effect of Butyrate in Nonalcoholic Steatohepatitis: Involvement of Autophagy	Research Grants Council – General Research Fund	01/01/2019	31/12/2021	971,635
	Molecular Characterization of the Ubiquitin-proteasome System as a Host Defense Mechanism against Intracellular Helicobacter pylori Infection	The TUYF Charitable Trust	01/09/2019	31/08/2022	2,851,800
	Molecular Characterization of the Ubiquitin-proteasome System as a Host Defense Mechanism against Intracellular *Helicobacter pylori* Infection - RMG01	Research Grants Council – Research Matching Grant	01/06/2020	31/05/2023	1,419,234
Matthew Chan	Butyrate for the Prevention and Treatment of Chemotherapy-Induced Neuropathic Pain	Project Grant, Australian and New Zealand College of Anaesthetists	01/04/2020	31/03/2021	279,240
Lin Zhang	Targeting H3K27me3 by EZH2 Inhibitors in Control of Drug-resistant Helicobacter pylori Colonization	Food and Health Bureau – Health and Medical Research Fund	01/09/2020	31/08/2023	1,494,292
	A Mechanistic Study of the Therapeutic Effect of Butyrate in *Helicobacter pylori* Colonization and its Associated Gastritis: Involvement of Autophagic-lysosomal Pathway	National Natural Science Foundation of China	01/01/2019	31/12/2022	RMB 580,000
	Effects of Ketamine and Cannabis on Antimicrobial Peptide Expression and Infection Susceptibility	Narcotics Division, Security Bureau – Beat Drugs Fund	01/08/2019	31/07/2022	3,086,761
	Elucidation of the Role of Cathelicidin in Protection against Multi-drug Resistant *Acinetobacter baumannii* Associated Pneumonia	Food and Health Bureau – Health and Medical Research Fund	20/09/2019	19/09/2022	1,499,800
	Translation Medical Research on Autophagy for Helicobacter pylori Eradication	Shenzhen Science and Technology Programme, Shenzhen Science and Technology Innovation Commission	19/03/2019	18/03/2022	RMB 500,000
Huarong Chen	RNA N6-methyladenosine Methyltransferase-like 3 (METTL3) is a Potential Therapeutic target for Immunotherapy in Colorectal Cancer	Food and Health Bureau – Health and Medical Research Fund	01/09/2021	31/08/2023	1,475,400
Xiaodong Liu	Screening of Botanic Ingredients for the Prevention or Treatment of Gout and the Mechanistic Study	Amway R&D China	28/04/2020	27/04/2023	RMB 600,000
	Screening of Botanic Ingredients for the Prevention or Treatment of Gout and the Mechanistic Study	Research Grants Council – Research Matching Grant	01/09/2020	27/04/2023	277,688.42

Publications

A. Journal Papers

1. Li Q, Hu W, Liu WX, Zhao LY, Huang D, Liu XD, Chan H, Zhang Y, Zeng JD, Coker OO, Kang W, Ng SSM, Zhang L, Wong SH, Gin T, Chan MTV, Wu JL, Yu J, Wu WKK. Streptococcus thermophilus Inhibits Colorectal Tumorigenesis through Secreting β-Galactosidase. *Gastroenterology*. 2021;160(4):1179-1193.e14. doi:10.1053/j.gastro.2020.09.003.

2. Li Z, Li X, Shen J, Tan H, Rong T, Lin Y, Feng E, Chen Z, Jiao Y, Liu G, Zhang L, Chan MTV, Wu WKK. Bioinformatic analysis of SMN1-ACE/ACE2 interactions hinted at a potential protective effect of spinal muscular atrophy against COVID-19-induced lung injury. *Briefing in Bioinformatics*. 2021;22(2):1291-1296. doi:10.1093/bib/bbaa285.

3. Li Z, Huang Z, Li X, Huang C, Shen J, Li S, Zhang L, Wong SH, Chan MTV, Wu WKK. Bioinformatic analyses hinted at augmented T helper 17 cell differentiation and cytokine response as the central mechanism of COVID-19–associated Guillain-Barré syndrome. *Cell Proliferation*. 2021;54(5). doi:10.1111/cpr.13024.

4. Yu X, Li L, Chan MTV, Wu WKK. Bioinformatic analyses suggest augmented interleukin-17 signaling as the mechanism of COVID-19-associated herpes zoster. *Environmental Science and Pollution Research*. 2021;28(46):65769-65775. doi:10.1007/s11356-021-15567-x.

5. Liu Y, Ling L, Wong SH, Wang MH, Fitzgerald JR, Zou X, Fang S, Liu X, Wang X, Hu W, Chan H, Wang Y, Huang D, Li Q, Wong WT, Choi G, Zou H, Hui DS, Yu J, Tse G, Gin T, Wu WKK, Chan MT, Zhang L. Outcomes of respiratory viral-bacterial co-infection in adult hospitalized patients. *EClinicalMedicine*. 2021;37. doi:10.1016/j.eclinm.2021.100955.

6. Ho IHT, Ng LHL, Cheng X, Gin T, Chan CS, Sun W, Xiao L, Zhang L, Chan MTV, Wu WKK, Liu X. Annexin a2 traps mu-opioid receptors in recycling endosomes upon remifentanil-induced internalization. *Neurobiology of pain* . 2021;10. doi:10.1016/j.ynpai.2021.100071.

7. Zhou J, Lee S, Wang X, Li Y, Wu WKK, Liu T, Cao Z, Zeng DD, Leung KSK, Wai AKC, Wong ICK, Cheung BMY, Zhang Q, Tse G. Development of a multivariable prediction model for severe COVID-19 disease: A population-based study from Hong Kong. *NPJ Digital Medicine*. 2021;4(1). doi:10.1038/s41746-021-00433-4.

8. Ouyang Y, Zhu Z, Huang L, Zeng C, Zhang L, Wu WKK, Lu N, Xie C. Research trends on clinical helicobacter pylori eradication: A bibliometric analysis from 1983 to 2020. *Helicobacter*. 2021;26(5). doi:10.1111/hel.12835.

9. Zhou J, Li H, Chang C, Wu WKK, Wang X, Liu T, Cheung BMY, Zhang Q, Lee S, Tse G. The association between blood pressure variability and hip or vertebral fracture risk: A population-based study. *Bone*. 2021;150. doi:10.1016/j.bone.2021.116015.

10. Lau WKW, Ngan LHM, Chan RCH, Wu WKK, Lau BWM. Impact of COVID-19 on pornography use: Evidence from big data analyses. *PLoS One*. 2021;16(12):e0260386. doi:10.1371/journal.pone.0260386.

11. Lee S, Zhou J, Wong WT, Liu T, Wu WKK, Wong ICK, Zhang Q, Tse G. Glycemic and lipid variability for predicting complications and mortality in diabetes mellitus using machine learning. *BMC Endocrine Disorders*. 2021;21(1). doi:10.1186/s12902-021-00751-4.

12. Chen X, Li Z, Zhang X, Yan J, Ding L, Song Y, Huo Y, Chan MTV, Wu WKK, Lin J. A new robotically assisted system for total knee arthroplasty: A sheep model study. *The International Journal of Medical Robotics and Computer Assisted Surgery*. 2021;17(4). doi:10.1002/rcs.2264.

13. Li Z, Zhang X, Ding L, Du K, Yan J, Chan MTV, Wu WKK, Li S. Deep learning approach for guiding three-dimensional computed tomography reconstruction of lower limbs for robotically-assisted total knee arthroplasty. *The International Journal of Medical Robotics and Computer Assisted Surgery*. 2021;17(5):e2300-n/a. doi:10.1002/rcs.2300.

14. Ng Y, Lo MCK, Lee K, Xie X, Kwong TNY, Ip M, Zhang L, Yu J, Sung JJY, Wu WKK, Wong SH, Kwok K. Development of an open-access and explainable machine learning prediction system to assess the mortality and recurrence risk factors of clostridioides difficile infection patients. *Advanced Intelligent Systems*. 2021;3(1):2000188. doi:10.1002/aisy.202000188.

15. Li Z, Li X, Shen J, Chan MTV, Wu WKK. Miller fisher syndrome associated with COVID-19: An up-to-date systematic review. *Environmental Science and Pollution Research*. 2021;28(17):20939-20944. doi:10.1007/s11356-021-13233-w. (Review)

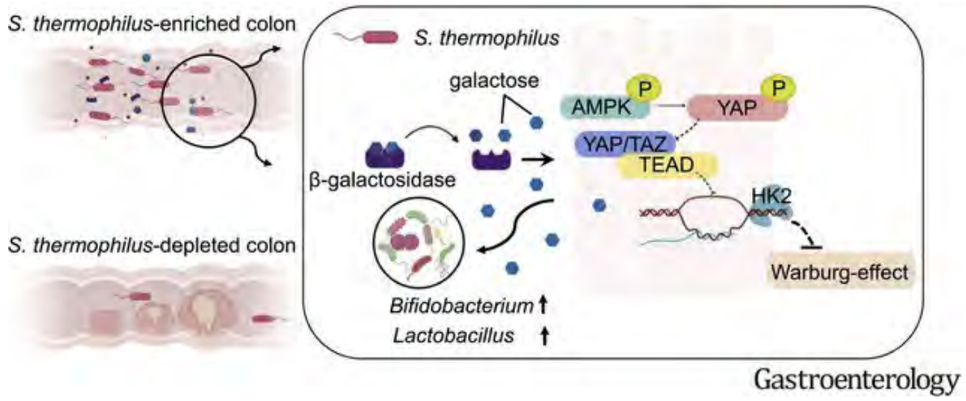
16. Xu D, Ma X, Sun C, Han J, Zhou C, Chan MTV, Wu WKK. Emerging roles of circular RNAs in neuropathic pain. *Cell Proliferation*. 2021;54(12). doi:10.1111/cpr.13139. (Review)

17. Li Z, Li X, Xu D, Chen X, Li S, Zhang L, Chan MTV, Wu WKK. An update on the roles of circular RNAs in osteosarcoma. *Cell Proliferation*. 2021;54(1). doi:10.1111/cpr.12936. (Review)

18. Kang X, Zhang R, Kwong TN, Lui RN, Wu WKK, Sung JJ, Yu J, Wong SH. Serrated neoplasia in the colorectum: Gut microbiota and molecular pathways. *Gut Microbes*. 2021;13(1):1-12. doi:10.1080/19490976.2020.1863135. (Review)

B. Letter

1. Zhou J, Wang X, Lee S, Wu WKK, Cheung BMY, Zhang Q, Tse G. Proton pump inhibitor or famotidine use and severe COVID-19 disease: A propensity score-matched territory-wide study. *Gut*. 2021;70(10):2012-2013. doi:10.1136/gutjnl-2020-323668.



Streptococcus thermophilus is a potential prophylactic for colorectal cancer prevention. The tumour-suppressive effect of S. thermophilus is mediated at least by the secretion of β-galactosidase.

Source: Li Q, Hu W, Liu WX, Zhao LY, Huang D, Liu XD, Chan H, Zhang Y, Zeng JD, Coker OO, Kang W, Ng SSM, Zhang L, Wong SH, Gin T, Chan MTV, Wu JL, Yu J, Wu WKK. Streptococcus thermophilus Inhibits Colorectal Tumorigenesis through Secreting β-Galactosidase. Gastroenterology. 2021;160(4):1179-1193.e14. doi:10.1053/j.gastro.2020.09.003.



司徒卓俊

CHEUK CHUN SZETO

14 NEPHROLOGY

Biomarker and Translational Research

Research Progress Summary

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

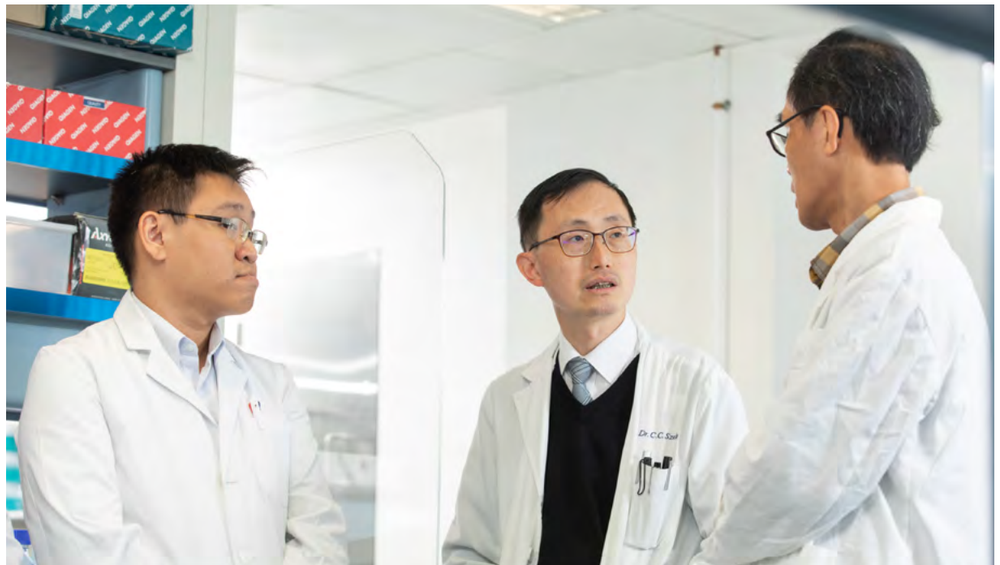
Efforts made to attract private funds for research

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

Opportunities and difficulties in inter-institutional collaboration in research activities

Over the past year, they had increasing collaboration with academic institutes and pharmaceutical companies. Here are a few recently completed or on-going collaboration with international and regional organisations:

1. With Stanley Fan, Barts Health NHS Trust, London, United Kingdom on: Polymerase Chain Reaction/Electrospray Ionisation-Mass Spectrometry (PCR/ESI-MS) for rapid bacterial identification in peritoneal dialysis effluent.
2. With Chris McIntyre, Division of Nephrology, Schulich School of Medicine and Dentistry, University of Western Ontario, Canada on: Endotoxemia in chronic kidney disease.
3. With Daniel March, Department of Infection, Immunity & Inflammation, University of Leicester, United Kingdom on: Endotoxemia and cardiovacular disease in dialysis patients.
4. With Christoph Aufricht, Medical University of Vienna, Austria on: Alanyl-Glutamine in Peritoneal Dialysis Fluids Improves Peritoneal Health and Systemic Inflammation.





Principal Investigator

Cheuk Chun Szeto

Team members

Peter Poon, Ka Bik Lai, Cathy Luk, Dineal Than, Lingfeng Zeng, Phyllis Cheng, Jack Ng, Winston Fung, Gordon Chan

Promotion of research collaboration with industry and other outreaching activities

Their patient population represents a wealth of resources for clinical research. They are actively exploring opportunities to collaborate with industrial and biotechnological establishments in the field of peritoneal dialysis for product development and validation.

Ongoing and upcoming collaborative work with biotechnological establishments (not including pharmaceutical company sponsored clinical trials) include:

1. Ethos Biosciences, Philadelphia, USA on: Novel urinary biomarkers for chronic kidney disease.
2. LiberDi, The Trendlines Group, Israel on: The liberDi dialysis system.
3. Zytoprotec GmbH, Germany on: Alanyl-Glutamine in Peritoneal Dialysis Fluids Improves Peritoneal Health and Systemic Inflammation.



Research and Scholarship

Fellowships

Member's Name	Details	
	Fellowship	Organisation
Winston Fung	Emerging Leaders Program	International Society of Nephrology

Academic Editorship

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

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Cheuk Chun Szeto	Chair of Nephrology Annual Review Course	World Congress of Nephrology 2021
	Co-Chair of Scientific Committee (Dialysis Sub-theme)	16th Asia Pacific Congress of Nephrology
	Member of Grant Review Board	National Science Centre (Narodowe Centrum Nauki – NCN), Poland
		Marsden Fund, Royal Society Te Apārangi, New Zealand

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Cheuk Chun Szeto	A Phase 2 Study to Evaluate the Safety and Effect on Proteinuria of OMS721 in Subjects with IgA Nephropathy, Lupus Nephritis, Membranous Nephropathy, or C3 Glomerulopathy including Dense Deposit Disease	Omeros Corporation	10/2018	02/2022	179,250
	A Randomized, Multicenter, Double-blind, Parallel-group, Active-control Study of the Efficacy and Safety of Sparsentan for the Treatment of Immunoglobulin a Nephropathy	Retrophin, Inc.	11/2018	06/2023	358,147
	Role of TGF-beta/Smad3 Signaling in Lupus Nephritis	Research Grants Council – General Research Fund	06/2019	08/2022	1,064,682
	Translating Multi-omic Discoveries to Transform Diabetes Care and Reduce Diabetic Complications	Research Grants Council – Research Impact Fund	01/2019	12/2023	12,000,000
	Randomized, Double-blind (Within Dose Groups), Placebo-controlled and Parallel Group Trial to Investigate the Effects of Different Doses of Oral BI 685509 Given Over 20 Weeks on UACR Reduction in Patients with Non-diabetic Kidney Disease	Boehringer Ingelheim International GmbH	06/2021	01/2023	358,988

Publications

A. Journal Papers

1. Szeto CC, Ng JKC, Wing-Shing Fung W, Chan GCK, Cheng PMS, Lai KB, Pang WF, Chow KM, Leung CB, Li PKT. Extended antibiotic therapy for the prevention of relapsing and recurrent peritonitis in peritoneal dialysis patients: A randomized controlled trial. *Clinical Kidney Journal*. 2021;14(3):991-997. doi:10.1093/ckj/sfaa256.

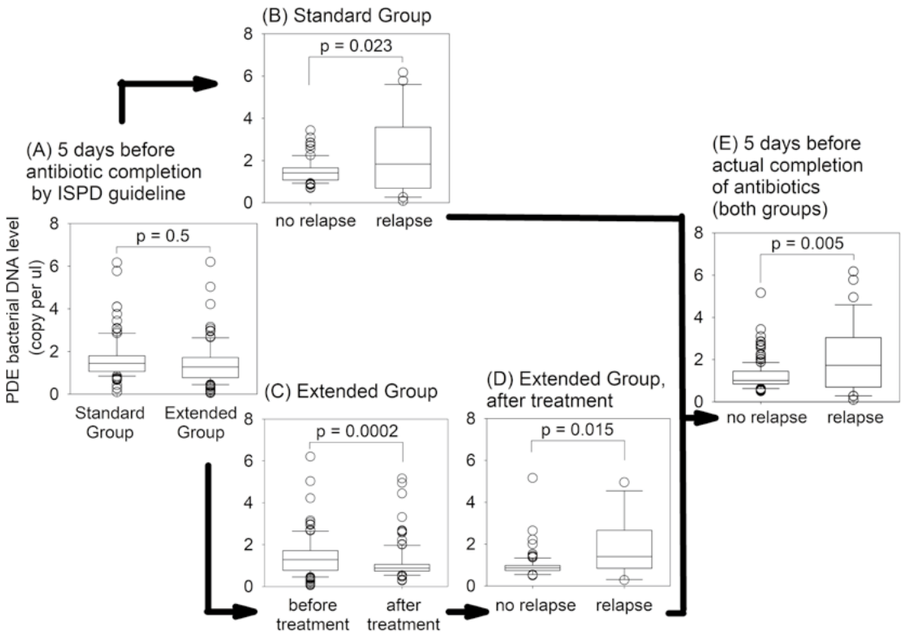
2. Zeng L, Szeto CC. Urinary podocyte markers in kidney diseases. *Clinica Chimica Acta*. 2021;523:315-324. doi:10.1016/j.cca.2021.10.017. (Review)

3. Fung WWS, Chow KM, Li PKT, Szeto CC. Clinical course of peritoneal dialysis-related peritonitis due to non-tuberculosis mycobacterium – A single centre experience spanning 20 years. *Peritoneal Dialysis International: Journal of the International Society for Peritoneal Dialysis*. 2022;42(2):204-211. doi:10.1177/08968608211042434. (Epub ahead of print)

4. Fung WWS, Chow KM, Szeto CC. Bilious peritoneal dialysate in a peritoneal dialysis patient. *Kidney International*. 2021;100(2):485. doi:10.1016/j.kint.2020.12.018. (Editorial)

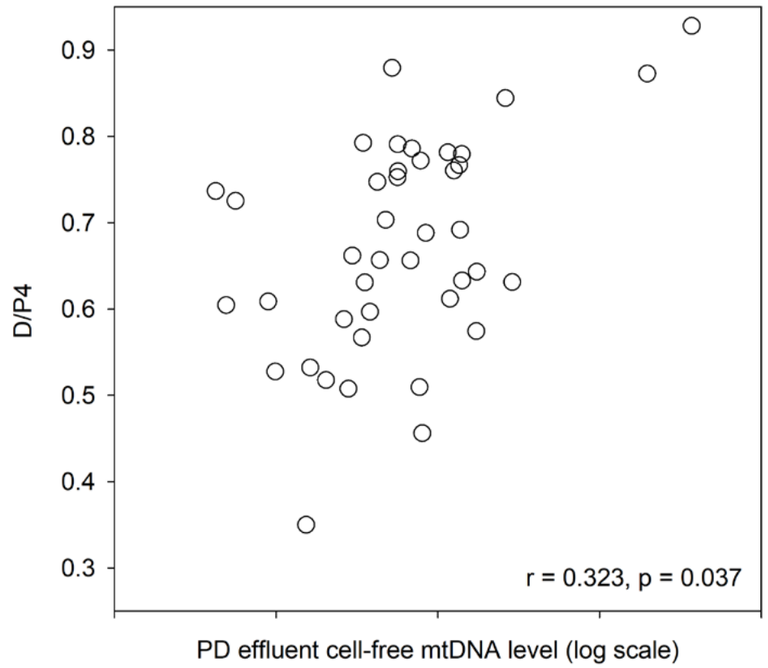
5. Than WH, Ng JKC, Fung WWS, Chan GCK, Lai KB, Luk CCW, Cheng PMS, Chow KM, Szeto CC. Prognostic significance of peritoneal dialysis effluent mitochondrial DNA level. *Clinica Chimica Acta*. 2021;519:1-9. doi:10.1016/j.cca.2021.03.028.

6. Szeto CC, Ng JKC, Fung WWS, Lai KB, Chow KM, Li PKT, Massiah A, Alcolea-Medina A, Wilks M, Fan SL. Polymerase chain reaction/electrospray ionization–mass spectrometry (PCR/ESI-MS) is not suitable for rapid bacterial identification in peritoneal dialysis effluent. *Peritoneal Dialysis International: Journal of the International Society for Peritoneal Dialysis*. 2021;41(1):96-100. doi:10.1177/0896860820917845.



Peritoneal dialysis effluent (PDE) bacterial DNA fragment level: (A) comparison between the Standard and Extended Group at the time of randomisation, i.e. 5 days before antibiotic completion according to the International Society for Peritoneal Dialysis (ISPD) guideline; (B) for the Standard Group, comparison between patients with and without relapsing or recurrent peritonitis episodes; (C) for the Extended Group, change in PD effluent bacterial DNA level after an extra week of antibiotic therapy; (D) for the Extended Group, comparison between patients with and without relapsing or recurrent peritonitis episodes; and (E) comparison between patients with and without relapsing or recurrent peritonitis episodes, 5 days before the actual completion of antibiotics for the entire study population. (All data were compared by the Mann Whitney U test, except that part (C) was by the Wilcoxon signed rank test.)

Source: Szeto CC, Ng JKC, Wing-Shing Fung W, Chan GCK, Cheng PMS, Lai KB, Pang WF, Chow KM, Leung CB, Li PKT. Extended antibiotic therapy for the prevention of relapsing and recurrent peritonitis in peritoneal dialysis patients: A randomised controlled trial. Clinical Kidney Journal. 2021;14(3):991-997. doi:10.1093/ckj/sfaa256.



Relation between dialysate-to-plasma creatinine concentration at 4 hours (D/P4) and cell-free mtDNA level in dialysis effluent.

Source: Szeto CC, Ng JKC, Wing-Shing Fung W, Chan GCK, Cheng PMS, Lai KB, Pang WF, Chow KM, Leung CB, Li PKT. Extended antibiotic therapy for the prevention of relapsing and recurrent peritonitis in peritoneal dialysis patients: A randomised controlled trial. Clinical Kidney Journal. 2021;14(3):991-997. doi:10.1093/ckj/sfaa256.





李錚

ZHENG LI

15 ROBOTICS & AI



Principal Investigator

Zheng Li

Team members

Tianle Pan, Wing Yin Ng, Jixu Li, Yehui Li, Chi To Chan, Wenci Xin

Research Progress Summary

In the past year, Zheng Li's team focused his research in intelligent flexible endoscope robot, magnetic anchored and guided endoscope (MAGS) robot, electromagnetically actuated soft-tethered (EAST) colonoscope robot and soft hand rehabilitation robot. These research yield publications in leading journals/conferences in the robotics field as listed in the report, as well as wide media coverage. The MAGS endoscope received the Bronze of International Exhibition of Inventions of Geneva and was showcased in the CUHK Innovation Day and the Hong Kong International Medical and Healthcare Fair. The EAST colonoscope robot received the Champion and Special Award of PCKKSCA and was exhibited during the InnoCarnival organised by Science Park. The soft hand rehabilitation robot received the support from TSSSU and TBF for technology transfer. The system showcased in the Hong Kong International Medical and Healthcare Fair and the Asia Summit on Global Health held in Hong Kong Convention and Exhibition Centre. In terms of academic conferences and public forums, most of the conferences were held online due to the pandemic. His team joined the organisation of the EMedic summit and actively participated in the leading technical conferences, such as ICRA, IROS, ROBOSoft, etc. In terms of research collaboration, the team has deepened the collaboration with Johns Hopkins University, Imperial College London, and ETH Zurich under the multiscale medical robotics centre. Besides, the team also established the collaboration with Harbin Institute of Technology (Shenzhen) on soft robot research. Last but not least, Zheng's team will continue their collaboration with Monash University on the flexible endoscope robot development.

Research and Scholarship

Research Awards and Recognitions

Member's Name	Details	
	Award	Organisation
Truman Cheng Zheng Li Calvin Ng Philip Chiu Joseph Sung	Bronze – International Exhibition of Inventions of Geneva 2021	International Exhibition of Inventions of Geneva
Yuehui Li Tianle Pan Wenci Xin	Champion - Prof. Charles K.Kao Student Creativity Awards	The Chinese University of Hong Kong
Yuehui Li Tianle Pan Wenci Xin	Special Award - Prof. Charles K.Kao Student Creativity Awards	The Chinese University of Hong Kong

Academic Editorship

Member's Name	Details	
	Role	Journal
Zheng Li	Associate Editor	Robotics and Automation Letters
		International Conference on Robotics and Automation
		IEEE/RSJ International Conference on Intelligent Robots and Systems
		International Conference on Soft Robotics
	Topic Editor	Frontiers in Robotics and Artificial Intelligence

Reviewer of Journal / Conference

Member's Name	Details	
	Role	Journal / Conference
Tianle Pan	Reviewer	RoBoSoft Conference
Yehui Li	Reviewer	Robotics and Automation Letters
Zheng Li	Reviewer	Soft Robotics
		IEEE Transactions on Robotics
		IEEE/ASME Transactions on Mechatronics
		Robotics and Automation Letters
		Journal of Mechanisms and Robotics
		Mechanism and Machine Theory
		IEEE Transactions on Medical Robotics and Bionics
		International Conference on Robotics and Automation
		IEEE/RSJ International Conference on Intelligent Robots and Systems
		International Conference on Soft Robotics

Grants and Consultancy

Name	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Zheng Li	Hopebotics Limited	Technology Start-up Support Scheme for Universities	01/04/2021	31/03/2022	400,000
	Hopebotics – Soft Wearable Robotic Hand for Stroke Rehabilitation	Technology and Business Development Fund	01/08/2021	31/07/2022	200,000
	Soft Robotic Exosuit for Lower Limb Rehabilitation	Innovation and Technology Support Programme	01/09/2021	31/08/2023	2,948,600

Publications

A. Journal Papers

1. Cheng T, Li W, Ng WY, Huang Y, Li J, Ng SH, Chiu PWY, Li Z. Deep learning assisted robotic magnetic anchored and guided endoscope for real-time instrument tracking. *IEEE Robotics and Automation Letters*. 2021;6(2):3979-3986. doi:10.1109/lra.2021.3066834.

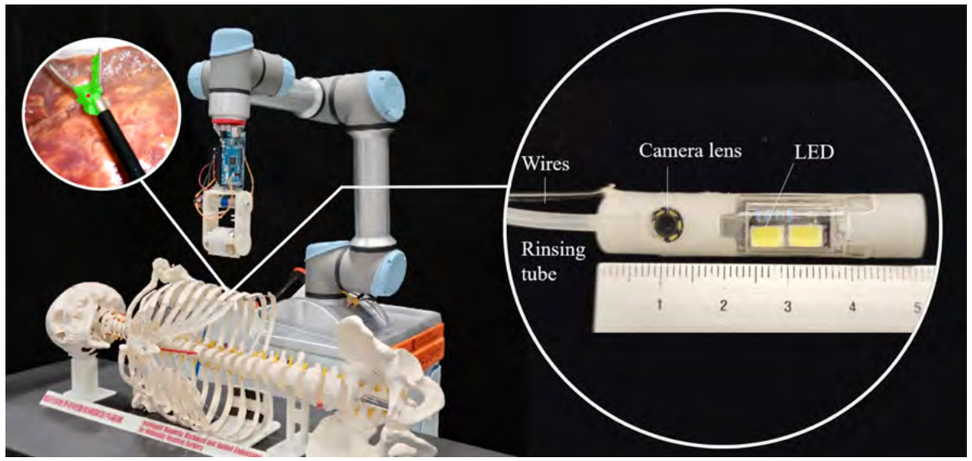
2. Pan TL, Lei MC, Ng WY, Li Z. Analytical modeling of the interaction between soft balloon-like actuators and soft tubular environment for gastrointestinal inspection. *Soft Robotics*. Published online June 18, 2021. doi:10.1089/soro.2020.0159. (Epub ahead of print)

3. Li Y, Guo C, Xin W, Pan T, Li W, Chiu PWY, Li Z. Design and preliminary evaluation of an electromagnetically actuated soft-tethered colonoscope. *IEEE Transactions on Medical Robotics and Bionics*. 2021;3(2):402-413. doi:10.1109/tmrb.2021.3063844.

4. Li W, Chiu PWY, Li Z. A novel neural approach to infinity-norm joint-velocity minimization of kinematically redundant robots under joint limits. *IEEE Transactions on Neural Networks and Learning Systems*. Published online 2021. doi:10.1109/tnnls.2021.30. (Epub ahead of print)

B. Conference Paper

1. Li Y, Li W, Xin W, Zhang X, Xian Y, Chiu PWY, Li Z. Orientation control of an electromagnetically actuated soft-tethered colonoscope based on 2OR pseudo-rigid-body model. *2021 IEEE International Conference on Robotics and Automation (ICRA)*. 2021:1191-1197. doi:10.1109/icra48506.2021.9561742.



Magnetic Anchored and Guided Endoscope (MAGS) System: the system contains an internal magnetic capsule endoscope module and an external permanent magnet held by a robot arm with an intelligent controller. Compared with existing endoscopes, the MAGS can be placed inside the body cavities and does not require a dedicated incision port. The view could be controlled autonomously by tracking the surgical instruments and ease the endoscope manipulation.

Source: Zheng Li and his team

INTERVIEW OF PRINCIPAL INVESTIGATORS

與首席研究員對話



Interview of Principal Investigator

與首席研究員對話



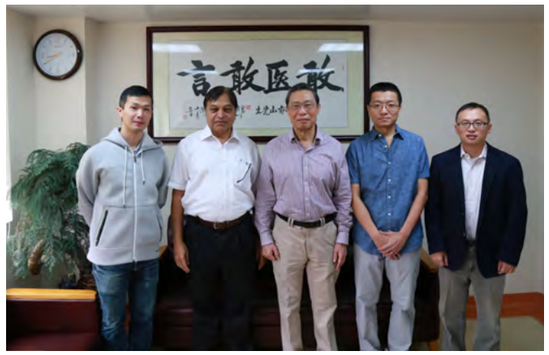
Chris Mok
莫家斌

Chris Mok received his BSc in Chemistry from The Hong Kong University of Science and Technology in 2002. He furthered his studies at The University of Hong Kong where he obtained his MPhil in 2005 and PhD in 2010. In 2021, he joined CUHK as an Assistant Professor. His research focuses on understanding the interplay between the host adaptive immunity and the viral determinants of respiratory viruses such as influenza viruses and coronaviruses using a combination of clinical, virological, immunological, and structural approaches. He is particularly interested in studying how adaptive immunity is influenced by the evolution of respiratory viruses that will help to improve the current vaccines.

01

You were first trained in chemistry in your undergraduate study. When did you start developing your interest in medical research, in particular microbiology and infectious diseases? Why?

A: I was planning to pursue my career in drug discovery research after my graduation from bachelor degree, but I realised that there were indeed very few pharmaceutical companies in Hong Kong at that time. Luckily, I met a professor at the HKU Research Open Day who later became the mentor of my MPhil study. I was recruited to his infectious disease research team and my project was to study cell biology related to avian influenza (H5N1) virus. Switching from chemistry to virology was really not easy. I still recall that I spent half a year self-studying to catch up my knowledge. After I completed my MPhil, I joined Prof Malik Peiris's team for the PhD degree and continued my exploration on viruses.



A photo of Chris with Nanshan Zhong (middle) and Malik Peiris (left two).



Chris was conducting MERS research in Nigeria in 2018.

02

Among all infectious diseases, your work focuses on understanding the interplay between the host adaptive immunity and the viral determinants of respiratory viruses. Is there any reason behind this choice?

A: Research on emerging pathogens such as H5N1 and SARS-CoV are the traditional strength of the team where I received my training. Though our understandings of these zoonotic viruses are much deeper than before, how they can jump over the species barrier and cause disease in humans is still not very well understood. I have been in particular fascinated by the question of how our adaptive immunity reacts to the infection of these deadly organisms. In addition, it is believed that we all keep being infected by different seasonal influenza or coronaviruses throughout our entire life. Whether our immune history may play a role to determine the outcomes from the infection of zoonotic virus is an interesting question.

03 Compared with the SARS pandemic in 2003, the research in COVID-19 and subsequent vaccine development are advancing at a much faster pace. Would you please share with us how research in emerging infectious diseases benefits from modern technology?

A: The advancement in technology over the past two decades greatly contributes to our responses to the COVID-19. One big jump is on the pathogen identification and diagnosis. Back in the SARS outbreak, it took almost 1.5 months to sequence and identify the pathogen. The PCR (polymerase chain reaction) and point of care test for quick diagnosis were invented but not quite common. On the contrary, it took only 1 week to identify the causative agent of COVID-19 with the help of next-generation sequencing technology. Nucleic acid and antigen detection are almost like a routine approach nowadays. They help us to control the COVID-19 outbreak effectively. In addition, we have learnt a lot from the studies of SARS-CoV and MERS-CoV, which both are belonged to the coronavirus family. With these precedent studies, we can instantly apply the knowledge to understand the mode of transmission or develop novel therapeutic strategies as well as vaccines for COVID-19.

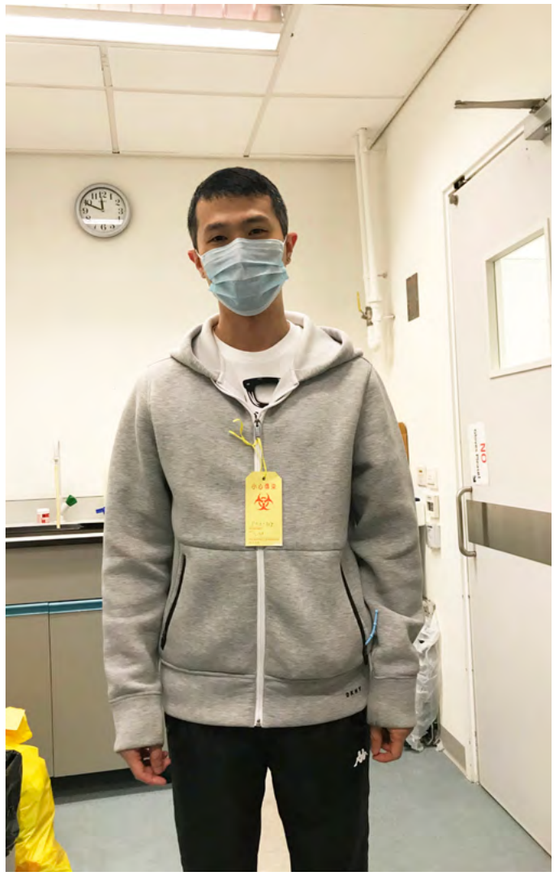
04 When there is a pandemic, we always see microbiologists working hand in hand with public health specialists to fight against the disease. What are the differences in their roles and how do they work together to achieve a common goal?

A: Microbiologists may pay more attention to understanding the basic science related to the pathogens. Their focuses will be on the properties of the virus, the impact of the mutations or the immune responses from the host. Public health specialists instead apply this knowledge and "translate" them into a practical approach for controlling the disease at the population level. I think both of them are playing crucial roles during an outbreak.

For instance, colleagues in CUHK and I have set up a longitudinal cohort to investigate the effect of BioNTech and Sinovac vaccines across time. We, as microbiologists, study the immune response of these vaccinees in detail through a head-to-head comparison. Public health experts then integrate our data into their epidemiological model to predict the upcoming outbreak situation and recommend policies to the government.

We also identified specific vaccine strategies through this cohort that can boost specific antibodies against the Omicron variant. But who is at a higher risk that should be received first? How to arrange the limited resource in order to maximise the overall protection rate? These problems are exactly what our public health experts can help to solve. With this good bridging between microbiology and public health, it can provide a better fit vaccine strategy for the public.

05 The development of mRNA vaccines can be dated back to 1989, but it is not widely used until the COVID pandemic. Would you please explain to us the mechanism of mRNA vaccines, and how they are different from traditional vaccines?



A: Messenger RNA (mRNA) vaccine was first designed as a novel therapeutic strategy for cancer patients. The technology has been widely used for producing vaccines against COVID-19. While traditional vaccines are mainly made from microbial protein or inactivated microbe, mRNA vaccines trigger the immunity through direct delivery of antigen-encoding mRNAs into the recipients. These mRNAs will express the spike protein which is located on the surface of the SARS-CoV-2 in our body hence stimulating T and B cell immune responses against the virus.

The mRNA vaccines have several advantages compared to traditional vaccines. Firstly, the mRNA vaccines are not constructed by neither active nor inactivated pathogen. High level of biosafety facility and containment are not required during the manufactory process. Secondly, the only required resource for producing the mRNA vaccines are the genomic sequence of the viral antigen. Vaccines can thus be produced much earlier without waiting the virus seed delivered from the outbreak zone.

However, the experience of the COVID-19 outbreak demonstrated that the vaccines produced by traditional approaches are still very important. Taking BioNTech as an example, we have observed that a small proportion of people may have allergic reactions due to the vigorous immune response triggered by the mRNA vaccines. Preservation is another major issue for the mRNA vaccines. While the vaccines are required to store at -80°C, many developing countries may not be able to afford the ultra-low freezers. Finally, the mRNA vaccines so far can only express one protein at a time while the virus-inactivated vaccines are composed of different viral antigens that can trigger a broader immunity than the mRNA vaccines.

06 Can you share with us the main challenges that you encountered during your research journey as a microbiologist?

A: As a microbiologist who works at the frontline during outbreak every time, it is true that there are so much different challenges in the course of my research. For example, the results from my experiment may not fit or even contradict to my hypothesis. However, I have learnt to be very patient and optimistic throughout many years of my research life. My experience is to first break down the big question into small pieces and solve it bit by bit. I am satisfied that such approach works well in my case.

Racing against time is another challenge for me who work in the infectious disease research area. Sometimes, I need to compete with other scientists around the world on the same research question. Knowing that my work will be influential to millions of people worldwide, I would expect my findings to be fast, accurate and impactful. Good stress management is thus essential for me as well.

07 Among the many research projects you have conducted, would you please share with us one or two projects that you consider the most significant or interesting?

A: One of my favourite studies was to demonstrate the high risk of occupational infection of Middle East respiratory syndrome (MERS) in Africa. Though people may think that transmission of MERS-CoV from camels to human is mainly occurred in the Middle East, in fact only 4% of the camels is living in that area while over 77% of them can be found in Africa and many of them have been infected by the MERS-CoVs. Surprisingly, no human zoonotic MERS had been reported in Africa. Our study found that one-third of the camel workers who work in a slaughterhouse in Nigeria were found to be infected with MERS-CoV. Our findings suggest that the MERS-CoV is posing a potential risk of outbreak in Africa but the strains that are circulating may differ in the pathogenicity from those circulating in the Arabian Peninsula. We have published our findings in *The Lancet Infectious Diseases* in 2021 (Mok CKP, et al. 2021;21(3):385-395). I am actually very delighted with this publication as most of the fieldwork was mainly done by myself in Nigeria.

Another important project is our ongoing study on COVID-19 vaccines. We are currently being supported by the Hong Kong Government to evaluate the immunogenicity of two COVID-19 vaccines, CoronaVac and BNT162b2. We obtain data in a timely manner and feedback our recommendations on vaccination strategies to the government. This study serves as an excellent example of what I explained before these findings from basic science can be translated into the public health policy. Our findings have been published in the *Respirology* (Mok CKP, et al. 2021), *American Journal of Respiratory and Critical Care Medicine* (Mok CKP, et al. 2022) and *Nature Medicine* (Cheng SMS, et al. 2022)

08 What are your personal interests outside medicine?

A: I love sports a lot as I enjoy the power and the speed. I used to be an athlete, badminton and handball player. I feel honoured that I had opportunities to represent Hong Kong in international handball events. I started playing ice hockey in recent years and used to play as a goalie on weekly basis before the COVID-19 pandemic.



▲ Chris was playing as a goalie in an ice hockey match. Ice hockey becomes one of his favourite sports in recent years.

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

A: I look forward to contributing to the infectious diseases research in CUHK. Firstly, I am happy to participate in the setup of the new animal biosafety level II (ABSL2) and biosafety level III (BSL3) facilities in the Faculty. Secondly, I hope I may help to promote a synergistic atmosphere in infectious disease research by coordinating different research groups in our faculty. Last but not least, I shall seek opportunities to strengthen the collaboration in infectious diseases research between CUHK and the institutes in China, in particular those within the Greater Bay Area. I truly believe that these goals can only be achieved together with the colleagues in our university.

Interview of Principal Investigator

與首席研究員對話



Hei Ming Lai
黎曦明

Hei Ming Lai has graduated from MBBS, The University of Hong Kong in 2018. He is a psychiatrist-neuroscientist in training. He joined the Department of Psychiatry at The Chinese University of Hong Kong as a Clinical Lecturer in 2019 and became an Assistant Professor (Clinical) in 2021. He has been involved in the development of neuroscientific research tools for 6 years, with his foundational work published in leading journals as first and corresponding authors since his undergraduate years. His work has been awarded a Gold Medal in the 46th International Exhibitions of Inventions Geneva and Honourable Mention in Nikon Small World Photomicrography Competition. His current research interests include neuroscientific research tool development, the neural correlates of mental phenomena and neuropsychopharmacology.

01 **The brain is arguably the most complex organ in the human body. Why did you choose neuroscience and psychiatry as your specialty? When did you start your interest in this field?**

A: I started to study neuroanatomy since my undergraduate degree, and I felt increasingly affectionate to this field during my teaching life. Psychiatry is a belief and an abstractive subject, which links matter to mind. I was very interested to learn how the brain structure affects the abstract details such as our thinking and emotions and how mental problems can be solved scientifically.

02 **Stress and anxiety are one of the most common health issues for people who live in fast-moving cities like Hong Kong. How would you see this trend of psychiatric problems?**

A: I see the trend of psychiatric disorders is growing because the development of modern medicine and technology extends the human lifespan. Nevertheless, it raised the problem that how to add life to years instead of how to add years to life. Many diseases could be cured by medical advance, but the quality of life seems not, especially in such fast-moving cities. It is getting more and more discoveries on the mental health problem eventually so the awareness and demand on this subject arise. And therefore, this situation forced us to further study in this field and to solve the mental health disorder.

03 **What is the most impressive research that you have done? Is there any inspiration learning from it?**

A: Since I studied in undergraduate degree, I have been thinking the way how to image the brain structure at a microscopic scale, in contrast to magnetic resonance imaging (MRI) as a clinical method which is on a larger scale. I have been focusing on studying the smaller size of structure such as how neuron overlaps, because it is directly related to human memory and thinking systems. Currently it has no tool to map such a small structure so I would like to focus on the development of technologies for understanding and tackling neuropsychiatric disorders.

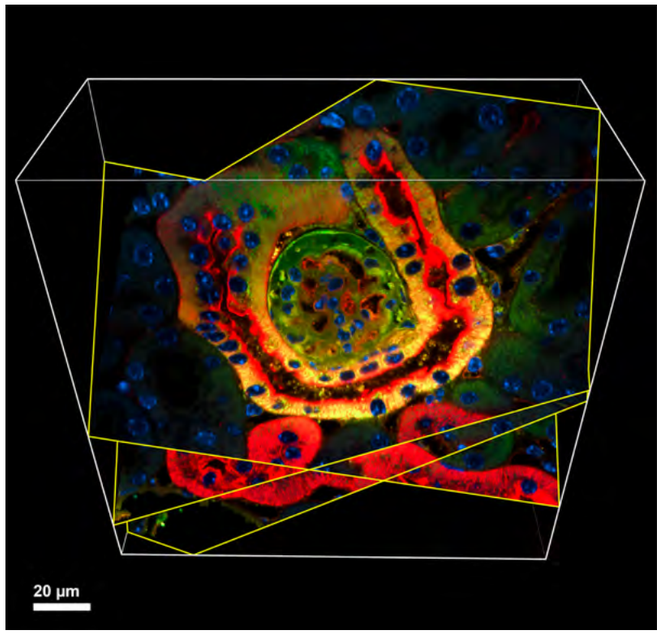
For example, we have researched about the nano material recently, in which we would like to support a clearer understanding on the neuron network mapping. Unfortunately, we found that this material cannot be utilised in medicine but LED panel or solar panel instead. It is not the first time that our experiment cannot be used on medicine. In other words, we have faced many failures and errors but it inspired us to solve problems next time by trying a number of different methods and learning from the mistakes.

04 Would you mind introducing to us the techniques of the 3D visualisation of neural tissue microstructure? How does it utilise this technique on human brain material?

A: Human brain is non-transparent. It is like a tofu with wires inside which across all sections. We would like to see how wires cross inside the tofu, similar to how neural cells connect to each other in a human brain in order to connect and communicate with each other.

Traditionally, to understand the structural and functional connections within the brain, scientists cut brain tissues into slices, and trace the nerve fibres sections by sections. The method was time consuming and not cost-effective. My team has developed a new visualisation technique for human brain tissues.

The technique includes 3 stages - sectioning, staining, and seeing. Sectioning is the tissue clearing stage where brain tissues are made to be “transparent”. A clearing solution, OPTIClear, is used to adjust the optical properties of the brain tissue. Hydrophobic parts (e.g., lipid membranes and lipid droplets) and hydrophilic parts (e.g., extracellular space, cytosol and nucleus) of the brain tissue have significant difference in refractive index, making the brain tissue translucent. OPTIClear reduces inhomogeneity within tissues and allows matching of refractive indices, resulting in the minimisation of scattering of light. Fluorescent dyes are then added to the transparent brain tissue in the staining process. 3D microscopic structures in the human brain can then be studied in the seeing stage. Recently, we are building a new generation of microscopes to have a better imaging of the tissue.

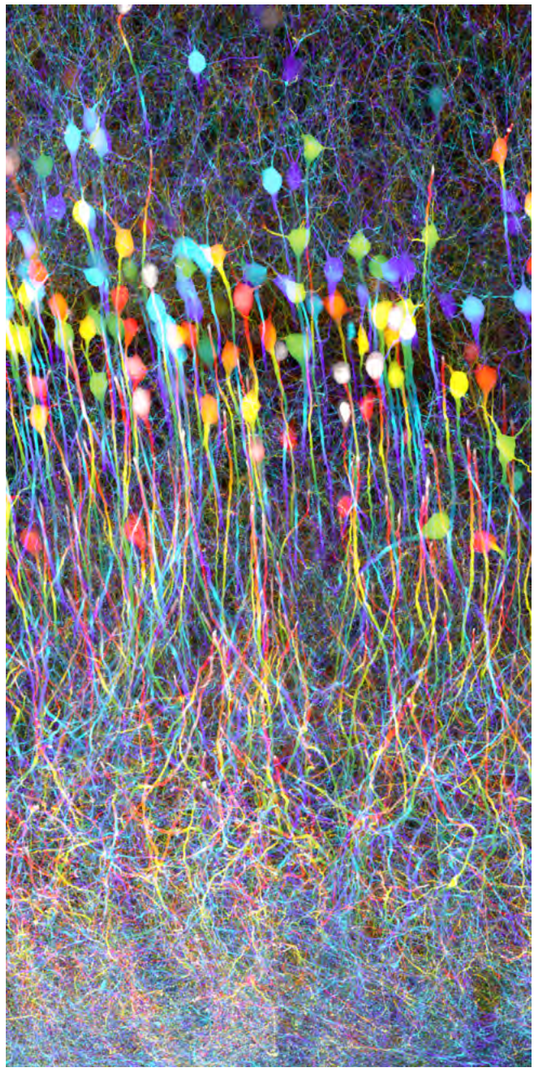


◀ Oblique sections of a mouse glomerulus with its associated distal convoluted tubule (red) found wrapping around itself, imaged using our in-house developed clearing and staining techniques.

05 You have developed a new tissue clearing solution OPTIClear and you have received several awards for this development. Would you mind introducing to us the latest development of this technology and what are the impacts on neuroscience?

A: In terms of achievement, the solution of OPTIClear has been patented and filed in the U.S. and China, and European countries (in progress). This solution became a standard tool to map the brain and neuron connections. This is to optimise the study of neuro and to speed up the way of treatment. This solution also became a daily usage, which helped to understand the structural and functional connections within the brain. Many users have asked us for the recipe of this method for their further studies.

For the development of “staining”, it is in progress at around 50% while we have to solve more issues as it is difficult to fully stain the brain due to its large size and complexity. Therefore, this subject has not been published yet.



▲ A color-coded 3D image of a mouse hippocampus using the team's in-house developed clearing reagent OPTIClear.

06 Would you please share with us some of the challenges you have encountered during the journey of the development of OPTIClear?

A: The concept was easy to understand but it encountered many challenges when it came to practical as we still did not fully understand how to transfer the brain into a visible structure.

Refractive index homogenisation is a crucial step in tissue clearing. We have tried to perform screening experiments for more than 8-9 hours per day for few months and still could not find the appropriate refractive index-adjusting agents. It felt like we went into a dead-end road and could not move further without directions. Ended up we found the proper chemical by luck. We trusted that the negative results or failures from our researches have finally led us to the current OPTIClear.

07 You started training in medicine but at the same time you are very knowledgeable in physics and chemistry. How did you gain so much information from different perspectives? As you are involved in several roles in teaching, research and clinical, could you please share with us more on your time management?

A: I think it might be because I study in neuroscience, I am able to manage my mentality. If I think everything is easy, there is nothing that I cannot learn from. I indeed gained all of these knowledge including physics, chemistry, mathematics, programming, etc from Google or YouTube.

In view of time management, I am a hard-working person, yet I think self-awareness is more important. I always agree that passion driven is more important, instead of pressure driven. My efficiency would get lower if I am burnt out. In such case, I would stop it when proper and go for a short break. “Taking a break is for accomplishing a longer journey.”



◀ Hei Ming's leisure activity of going hiking with his cat Durian (Instagram account: durianissupernaughty)

08 What are your personal interests outside medicine?

A: I am a cat lover. My family has 3 cats (female). My leisure activity is going hiking with two of my cats; while one of them does not like hiking so she stays home usually.

09 As a clinician-scientist, what advice(s) would you like to give to fellow students who are interested in pursuing a career in medical science?

A: Instead of thinking that is difficult and hard to understand, we should enjoy learning and find its interest. Once we overcome our mental obstacle, we would find learning is actually not that difficult. Passion driven is very important.

I would encourage our students to explore any methods that you can think of. Do not be afraid of failure and do not back off when you are facing challenges because every failure makes the next trial better.

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

A: I hope the technology that we have developed can be more mature so that we can utilise it to further study on how the human brain operates which we have been working on. The brain is the most complicated organ in the human body, in which we still do not fully understand it now. Based on previous data, I will keep being creative to further explore different methods and keep trying and learning from failure. At the same time, I will keep my passion to drive my interest and to avoid burn out.

Interview of Principal Investigator

與首席研究員對話



Peter Cheung
張栢恒

Peter Cheung completed his Bachelor's and Master's Degrees in Science in Canada before he relocated to Hong Kong to further his doctoral studies. He joined The Chinese University of Hong Kong as Assistant Professor in May 2021 and has recently been appointed as Assistant Dean (Research). With a research interest in the gene transcription of ribonucleic acid (RNA) viruses emphasising influenza virus and coronavirus, he developed a novel genomics platform to understand the virus replication machinery that is pivotal in the development of antiviral medication and vaccines for infectious diseases. Apart from research, Peter is passionate about teaching and has become a member of the Community of Practice entitled "The Innovation and the Future of STEM Education" in the hope to enhance students' learning outcomes through innovative pedagogies and technologies.

01 **Why did you choose to study influenza virus and coronavirus, among other viruses, as your research emphasis? What has driven your interest in the gene transcription of RNA viruses?**

A: As a travel hub situated at an epicenter of zoonotic and pandemic emergence, Hong Kong is particularly challenged by emerging and re-emerging infectious diseases. I chose to study the influenza virus and coronavirus because these two respiratory viruses have been a significant threat to global public health. Seasonal influenza viruses cause annual epidemics with substantial morbidity and mortality. COVID-19 recently has unleashed a pandemic with damages on a meteoritic scale. Existing vaccines for influenza virus and SARS-CoV-2 are not optimal. In general, pandemics resulting from these viruses arise at unpredictable intervals but spread worldwide within weeks or months. Conventional vaccines cannot be deployed in time to contain initial epidemics.

The virus needs to replicate to make many copies of itself. One critical step is to copy its genetic material. The RNA viral polymerase is the copying machine that copies the genetic material in the form of RNA to make new viruses. The accuracy of this genome-copying machine becomes critical because any errors made would be passed on to new progeny viruses. The curiosity drove my interest in understanding the mechanics of how the replication machinery makes errors and how errors would affect the virus to adapt to the new environment and survive in one host and the entire community. The health consequences of mutations are enormous, including the jumping of an animal virus to humans and the emergence of new virus variants, such as in the case of COVID-19, the Omicron and Delta, and drug- and vaccine-resistant viruses.

02 **Severe Acute Respiratory Syndrome (SARS) devastated the Asian countries in 2003, followed by influenza and COVID-19 affecting countries around the globe. Would a better understanding of gene transcription foresee the virus evolution and the variation of disease severity among individuals? In addition, how would it impact the application in diagnostic tests, vaccines, and medication?**

A: Absolutely, gene replication is essential to the virus; hence, if antivirals can inhibit the machinery responsible for this process, this could be a promising drug target, as shown in the clinical trials for influenza and COVID-19. Besides being a promising target for the development of antivirals, the replication machinery or polymerase of the virus is the driving engine for mutations. By understanding how errors are made, we can predict the virus's capacity to evolve and know how antiviral drugs that target the polymerase protein resist mutations, such as Molnupiravir and Remdesivir. We are also working on predicting new mutations that may emerge in the future and predicting the best sites on the viral protein for the development of vaccines. The virus and host are a constant interplay that drives viral evolution. There are specific mutations in the viral protein, such as the famous surface protein, Spike protein, that contributes to the incubation period of the virus and transmissibility from one person to another.

03 What tools are you developing to study gene transcription? How would it help understand the gene transcription and virus evolution using Cryogenic Electron Microscopy (Cryo-EM)?

A: We recently developed a genomic platform that can map the replication machinery along the genomic tracks, just like installing a GPS system on the polymerase. If you can imagine, the polymerase is like a car, and there are many road signs and traffic lights. In the world of coronavirus, we have no clue how to read these road signs and traffic lights. So, we wanted to develop a genomics and bioinformatics platform that can understand the movement of these cars in response to the road signs and traffic lights so we can have an idea of what these instructions are. This information would be critical because the interaction between the regulatory signals and polymerase has recently been explored for drug targets. Also, it seems that one of these signals involves asking the polymerase to hop around the genome, leading to a type of mutation called recombination, which may be able to explain the origin of the Omicron variants where as many as 37 mutations can occur at once.

The SARS-CoV-2 polymerase is the central machinery for viral transcription and replication critical to the evolution, transmission, and pathogenesis, rendering it a suitable therapeutic target. The fast rate at which structural information on the polymerase complex and associated non-structural proteins has been discovered in recent months, has led to a leap in our molecular knowledge of SARS-CoV-2 replication. However, one great challenge in structural biology is purifying both the SARS viral polymerase and proofreading enzyme together in one complex. This is a holy grain in structural biology that can provide invaluable insight on the coordination between elongation and proofreading. Understanding the interactions between the two fundamental processes by obtaining the Cryo-EM structure of our purified polymerase complex allows quick identification of antivirals that can inhibit the tightly integrated processes recapitulating the real enzymology without separation and transform drug development research. Also, it unleashes a wealth of information as to the dynamics of how SARS-CoV-2 replication-transcription complex (RTC) edits its genome and how the proofreading machinery overlooks some mutations. With genomics and Cryo-EM, we can begin to answer how a virus with the unique ability to proofread replication can generate so many deadly and transmissible variants of concerns devastating the world.

04 Your research focuses on the structural basis of gene transcription in RNA viruses and the biological consequences of transcriptional errors. As a scientist, how do you see the role of non-biological factors (e.g. environment, human behavior, etc.) in virus replication? How should we best protect ourselves from getting infected by the virus?

A: Respiratory viruses are highly contagious, so it is essential to understand that the viruses replicate their genome from different angles. From the genome perspective, we can understand how genetic changes in the virus can help the virus transmit and evolve remain active and replicative in the harsh environment. Structurally, we can understand how the virus regulates its replication process for identifying new drug targets. My research focuses relevant to public health lie in diagnostics, vaccine effectiveness, and antivirals. Of course, there are other preventative measures for emerging infectious diseases. The primary non-biological factors contributing to the evolution of virus replication lie in human traveling and social distancing.



▲
Pictured from left to right: Zhitong Zhu (RA), Xinzhou Xu (Postdoc), Peter Cheung (PI), Zhibin Liang (RA) and Wing Ying Angela Au (Mphil Student)

05

Referring to the article you published in an internationally prestigious journal, *Lancet Microbe*, you have found that the experimental setups for diagnostic tests (e.g. specimen type, RNA extraction methods) play a critical role in optimizing the testing performance. How would your findings help in fighting against the recent COVID-19 pandemic? Aiming to alleviate the burden on the medical system, would your conclusions also apply to the COVID-19 rapid antigen testing, which is becoming popular?

A: Due to their increased sensitivity and specificity, nucleic acid tests are preferred in clinical testing over antigen tests. Quantitative polymerase chain reaction (qPCR) is the most frequently used diagnostic technique in humans. However, the loop-mediated isothermal amplification (LAMP) assay has emerged as a preferred alternative to qPCR at many international airports, hospitals, and testing centers worldwide. Digital polymerase chain reaction (dPCR) is a breakthrough tool designed to aid in diagnosing COVID-19 that enables the absolute measurement of nucleic acids in hospitals and diagnostic centers. Although dPCR is less popular than qPCR and LAMP, it is gaining popularity because of its high sensitivity.

The type of diagnostic tests and the optimal conditions to perform the tests are critical for efficient disease control and prevention. A standardized experimental design across many institutions is essential to ensure the accuracy and consistency of COVID-19 nucleic acid test results. Therefore, we conducted a comprehensive review and meta-analysis on dPCR, qPCR, and LAMP. Our research, which comprised the most significant number of more than 15,000 samples obtained from hospitals and clinics, revealed that dPCR is the most sensitive method, followed by qPCR and LAMP. Due to its increased sensitivity, dPCR will benefit clinicians in diagnosing and reporting COVID-19 infections.

Additionally, we determined that when experimental variance is controlled, the accuracy of nucleic acid-based COVID-19 detection is comparable across different testing types. Further, we demonstrated that assay accuracy is more strongly reliant on the experimental design than the test type. Thus, our findings add to the body of knowledge that, in order to get the highest performance, optimizing the experimental setup is more critical than the test type selection.

Even though rapid antigen tests are becoming very popular due to their simplicity and rapidness in performing the test, nucleic acid-based tests remain the most reliable method. This is why a confirmation diagnosis must involve at least one nucleic acid-based test. Antigen tests and PCR help detect disease early in around three days, even though PCR tests are more accurate with fewer false positive or negative results than rapid antigen tests.

06

What achievements do you have within this year? Being a new Principal Investigator of the Institute, what are your visions and goals in the coming five years?

A: This year, our students have performed very well. We have one undergraduate student who published a *Lancet Microbe* paper as the first author. We also have a Ph.D. student who recently published a high-quality article in *Nucleic Acids Research*. These are top journals in their respective fields. Our team has also secured a highly competitive collaborative grant, which is essential to lay a foundation for our new laboratory. Our research goal is to establish a team that can lead internationally on a novel technological platform in structural and genomic biology. I also place training students and staff as a top priority, allowing them to pursue their interests and harness their strengths. Before assigning a project to my students, the first question is what their interests are but not how they can help with my projects. I also wanted in the five years to build a tight collaborative network with my fellow CUHK colleagues that can address significant global challenges such as COVID-19.

07

What are your personal interests outside science?

A: I love to hike and explore the wildlife. Many insights and new ideas are gained from learning about nature, such as organisms and plants, to understand how evolution plays a role in their adaptations to nature in much the same way a virus adapts to the hosts. I also love to play sports such as soccer and basketball that emphasise teamwork and friendships.



◀ Hiking with team members and exploring the wildlife

08 Would you mind sharing some excitements and challenges you have had in your research journey? Virus evolution changes unpredictably and rapidly, while it could be a long journey to understand virus evolution and the development of effective vaccines and medication. How do you usually adapt to the change during the process of related research?

A: I think a great excitement would always be the eureka moments, such as when we first isolated a mutant influenza virus that does not mutate. I also love to develop and build novel methods that can provide us with information to open a new realm of research. I remember trying to develop a type of sequencing technology that requires much higher precision and accuracy in reading DNA sequences than current technology allows. The little things that worked by problem-solving give me the rewards and keep us going.

09 What advice would you give to younger generations who are interested in pursuing their career in medical research?

A: My number one advice is to explore the topics you are interested in and to do what you love to do. In pursuing science, experiments do not work most of the time, so it would be your passion fueling you and keeping you on. If you are a biomedical engineer, the great delight that comes with anything successful can be your fuel. If you are a pure biologist, you should take enjoyment from discovering something that no one has observed. These would make all previous failures worthwhile.



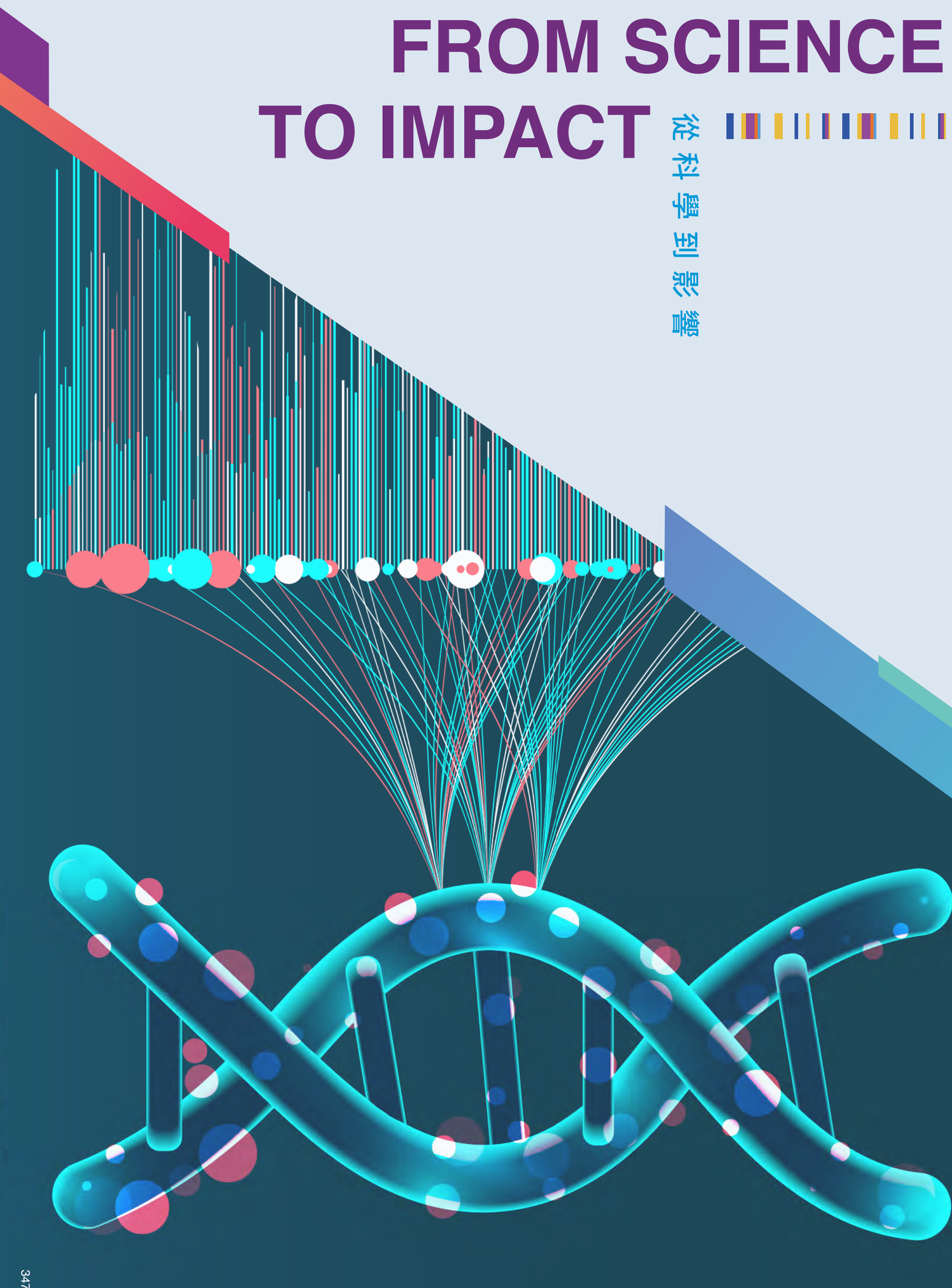
▲ Group dinner for celebration of the Chinese New Year



▲ Delivering a STEM education lecture for high school students

FROM SCIENCE TO IMPACT

從科學到影響



From Science to Impact

從科學到影響



Jun Yu
于君

01 **Since your discovery of biomarker miR-92, your team has further identified miR-135b. What is the potential? How does it compare to miR-92 in terms of sensitivity, specificity and reproducibility?**

A: Colorectal cancer (CRC) has become the number one cancer in Hong Kong and is a major public health issue. The stool-based early screening and diagnostic molecular marker is still not available. Early diagnosis of precancerous adenoma and CRC is fundamental to reducing CRC incidence and improve prognosis. Being the gastrointestinal (GI) disease team and the State Key Laboratory of Digestive Disease, our team predominantly focuses on researches on colorectal, liver and gastric cancer, which account for around 50% of all cancer types in Chinese. We have been working for over 10 years to develop non-invasive diagnostic biomarkers for sensitive and specific detection of colorectal adenoma and CRC. We pioneered the application of stool microRNA detection for CRC diagnosis and showed microRNA are good markers of CRC (*Gut* 2009, 2012; *Clinical Cancer Research* 2014), which has been shown to outperform widely used faecal immunochemical test (FIT) for colorectal adenoma and CRC screening. These markers are based on quantitative PCR platform, which is rapid, inexpensive and reliable.

In terms of sensitivity and specificity, miR-135b is comparable to miR-92a. Similar to miR-92a, it is highly reproducible as independent groups has already published follow-up work in peer-reviewed papers. We have also verified in multiple CRC cohorts that miR-135b is a sensitive and specific marker for CRC and also adenoma diagnosis. We are now investigating whether combination of miR-92a and miR-135b, and other miRNAs could further improve the diagnostic the performance for CRC. Stool-based miR-92a biomarker was licensed to external company and developed into marketed product. In this connection, a stool-based miR-92a detection kit for CRC was approved by China FDA in 2018 for clinical practice.



02 In addition to biomarker detection, your team has also focused on metagenomics analysis using faecal bacteria. What are the advantages over the conventional detection method?

A: Dysbiosis of gut microbiome has been identified to be a potentially important etiological factor in the initiation and progression of CRC. Faecal bacteria have recently emerged as a new class of biomarkers for the diagnosis of colorectal adenoma and CRC. Our pioneering work in metagenomic analysis of colorectal adenoma and CRC in around 600 stool samples by shotgun metagenomic sequencing, has catalogued shifts in microbial communities in human gut during colorectal carcinogenesis. Comparison of the faecal microbiome of CRC patients, adenoma patients and healthy subjects of Hong Kong Chinese population, we have identified bacterial gene markers as non-invasive, stool-based biomarker for diagnosis of CRC and adenoma with high sensitivity and specificity (*Gut* 2016, 2017, 2019; *Clinical Cancer Research*, 2017). Bacterial gene markers have several advantages with regards to CRC detection: 1) they can be readily detected in stool, which is less invasive compared to other methods; 2) we have designed very simple, fast assay formats for the cost-effective detection of CRC and adenoma; and 3) the key advantage is that since bacterial changes are involved in the early stages of cancer, it has a better sensitivity for detection of colorectal adenomas compared to miRNA markers.

Source: Jun Yu

03 Is there a specific type of colorectal cancer that your methods of biomarker detection and metagenomics analysis using faecal bacteria would be more effective in identifying? For example, familial and heredity cancer? And the stages of cancer by which the detection methods would be most effective?

A: Bacteria marker identification is better based on large scale samples as discovery cohort for deep metagenomics sequencing of stool samples and on different population samples for multiple validations so as to prove their sensitivity and specificity and the potential usefulness in variant populations. Although alterations in certain microbes might be associated with molecular features of CRC, such as KRAS-mutation and microsatellite instability, we have been focusing on markers that apply to all subtypes of sporadic CRC patients, which accounts for a majority of CRC. Familial and heredity are relatively rare (<10%). Studies with larger patient populations incorporating will be required to further elucidate the changes in microbiome in these populations. So far, detection is most effective on stage II-IV cancer (>85%), followed by stage I cancer (>75%) and adenoma (>50%), which is superior to the conventional FIT test (stage I: 40%, adenoma: <10%). However, we always strive to further improve detection rate at early stages, as it is very important to identify colorectal adenoma and the early stage of CRC. This will enable risk stratification of asymptomatic subjects for evaluation by endoscopy, and is of major impact to the public health.

04 In your study conducted and published in 2018, your team has performed metagenome-wise study on faecal samples in both Asian and European populations. What are your main observations on the differences and similarities in both populations?

A: In this study (*Microbiome* 2018), we observed that there are consistent alterations in the gut microbiome in CRC. Across Asian, European and America populations, we identified four common bacterial gene markers (one from *Fusobacterium nucleatum*; two from *Peptostreptococcus anaerobius*; and one from *Parvimonas micra*) that can serve as faecal biomarkers to differentiate CRC patients from normal individuals in Hong Kong, Germany, French/Austrian and American cohorts. These similar alterations in the gut microbiome largely represent pathogenic bacteria that plays casual role in CRC. On the other hand, we also observed some differences with other species, e.g. *P. stomatis*, *S. moorei*, etc, that is only unique to 1 or 2 cohorts. I think it is great to have consistent changes across different populations from a biomarker viewpoint – and our subsequent studies showed that these bacteria are good predictive markers in CRC patients.



05 With your novel findings on these novel biomarkers and faecal bacteria for disease detection, what would be your next steps and future directions?

A: Based on our novel findings on these novel biomarkers, we have published a series of papers that highlight the use of faecal bacterial biomarkers that could be used for diagnosis of CRC or adenoma patients (*Gut*, 2017, 2020; *Clinical Cancer Research*, 2017). We have shown that the combination of gut bacterial markers in stool have superior sensitivity compared to the conventional FIT test. Based on these discoveries, we have applied and filed patents for novel diagnostics for CRC and adenoma. We have licensed our bacteria marker work to GenieBiome ltd, and a diagnostic kit has been put on the market in Hong Kong.

Our future directions will include 1) using the combination of biomarkers to construct a multitarget test for the non-invasive CRC/adenoma diagnosis with superior specificity and sensitivity when compared to conventional tests; 2) validating the performance of our bacterial markers across different populations to expand our applications territory-wide and worldwide; 3) developing bacterial predictive markers and efficacy-enhancing probiotics for chemotherapy in CRC. We have just obtained a UGC-RIF funding support for this study; and 4) developing bacterial predictive markers and efficacy-enhancing probiotics for immunotherapy in gastrointestinal cancers.





06 With your past experience and collaborations with biotechnology companies, would it pose advantages for you to translate your recent research to impact for the society and even to the world? Have you faced any hurdles or obstacles in your past experiences and how did you overcome that?

A: My past experiences and collaborations with biotechnology companies are vital to translation of our research to impact the society. In our group, we focused on innovation and science behind our discoveries. By collaborating with companies, we can bring together the expertise of academic research and commercialisation, to better develop our discoveries into commercial products. I have accomplished translating scientific discovery into commercialisable products. The stool-based detection kit of biomarker miRNA92a for the early diagnosis and screening of CRC was approved by China FDA in 2018 (approval #20183400108); the gastric cancer plasma detection kit (methylated RNF180) was approved by China FDA in 2020 (approval #20203400447). Each of these two detection markers/kits was the first China FDA approved molecular detection biomarker which has been applied for clinical practice for the early detection of CRC and gastric cancer respectively. The faecal bacteria gene marker “M3 test” has been clinically used in Hong Kong for early diagnosis of CRC. These benefit patient care by improving early diagnosis and guiding the management of gastrointestinal cancers.

07 How would you advise our young scientists in the research field? What are the experiences you would like to share with them about translating scientific research findings to giving impacts to the society?

A: It is important for young scientists to cultivate scientific curiosity, to choose a good project, and to take pride in doing research well with a series of basic skills and a broad knowledge base. Curiosity and interest in a given topic as well as a strong passion for science are the main drivers for success.

It is widely accepted that research can lead to improved health outcomes. Translating research into meaningful impacts in peoples’ wellness requires actions that stretch well beyond basic research. You may start with a research project which is expected to generate valuable knowledge and intellectual property, that will drive the downstream development of commercial products, and pave the way for clinical trials, strengthening Hong Kong’s position as an innovation hub.

All rights reserved.
Copyright © 2021 by Li Ka Shing Institute of Health Sciences,
The Chinese University of Hong Kong

版權所有
出版：香港中文大學李嘉誠健康科學研究所

Address 地址：	CUHK Li Ka Shing Medical Sciences Building, Prince of Wales Hospital, Shatin, the New Territories, HKSAR, The People's Republic of China 中華人民共和國香港特別行政區 新界 沙田 威爾斯親王醫院 香港中文大學李嘉誠醫學大樓
Tel 電話：	(852) 3763 6003
Fax 傳真：	(852) 3763 6333
Home Page 網址：	www.lihs.cuhk.edu.hk
Photography 攝影：	Mr. Gary Mak, Mad Production
Design 設計：	dige2.com, DIGE2 Limited
Production 印刷：	High Technology Printing Group Limited 高科技印刷集團有限公司
Print Run 版次：	May 2022 2022 年 5 月
Quantity 印數：	500 Copies 500 本