Food and Health Bureau
The Government of the Hong Kong Special Administrative Region

Health Research Symposium 2021

23 November 2021

Hybrid Conference

Implementing evidence-based research in the era of COVID-19 and other global health challenges

The 10th Anniversary of the Establishment of the Health and Medical Research Fund

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Message from the Secretary for Food and Health

I am delighted to welcome you to the Health Research Symposium 2021. This year, the Symposium marks an important milestone and commemorates the 10th anniversary of the establishment of the Health and Medical Research Fund (HMRF).

Over the past 30 years, the Food and Health Bureau (FHB), through the HMRF and its former funds, has taken the lead in supporting health-related research, developing the infrastructure and building research capacity necessary to address public health threats caused by emerging infectious diseases and the increase in non-communicable diseases in order to advance scientific knowledge, enhance clinical practice and improve population health. The central theme of this year's Symposium, "Implementing evidence-based research in the era of COVID-19 and other global health challenges", aims to understand how the challenges to the healthcare system resulting from the global COVID-19 pandemic can be mitigated through application of evidence-based research findings, and well reflects the HMRF's objectives. This year's Symposium, for the first time, is being held in hybrid mode with the presentations being made both virtually and in person.

During the present COVID-19 epidemic, Hong Kong has demonstrated that its evidence-based public health measures are able to bring the outbreak under control. The Government's prompt reactions to this public health crisis are, in part, due to its foresight and considerable support to enhance Hong Kong's preparedness for the control of emerging and re-emerging infectious diseases over many years since the outbreak of Severe Acute Respiratory Syndrome in 2003 by setting up the Research Fund for the Control of Infectious Diseases with an approved commitment of $450 million, which provided extensive support to epidemiologists, researchers and clinicians up to its consolidation into the HMRF established in 2011 with an injection of $1,000 million. In 2021, the approved commitment of the HMRF has been increased to $4,223 million.

Since April 2020, FHB and HMRF have awarded a total of $513 million to 67 COVID-19 research studies to address important research areas in transmissibility and infectability of the virus; effective surveillance and prevention strategies of the disease; development of treatments and therapies; evaluation of vaccine-induced immune response and reactogenicity to different groups including young adolescents, adults, the elderly and cohorts receiving booster vaccinations, as well as comparison of the immune status in convalescent and vaccinated cohorts; the role of gut microbiota in enhancing immune response to vaccination; and knowledge, confidence and acceptance of vaccination, and social and behavioural interventions to reduce the spread of novel coronavirus in different community groups. Many of these studies have already published their findings in the world's leading medical journals, and these new evidence are crucial in informing Government's policy on COVID-19 preparedness and control.

While COVID-19 may have been at the forefront of our thoughts for most of the past two years, HMRF has also committed extensive resources to support research on primary healthcare and non-communicable diseases including tobacco control, cancer, diabetes and mental health, among others. The increasing ageing population means that the number of people living with chronic diseases in particular will increase and research on ameliorating these long-term conditions is required. Several studies, for example, those on tobacco control and cancer screening, have had a positive impact on the quality of life and overall population health through informing health policy and decision making as well as enhancing clinical practice and health services. The significant reduction in smoking and tobacco use in Hong Kong in recent years and the implementation of the Breast Cancer Screening Pilot Programme are two examples of the application of findings from HMRF-funded research projects.

I am very pleased that we shall be honouring the many excellent researchers who have contributed their efforts to improving the health of the Hong Kong population through an award ceremony today. In addition, to recognise the excellent research efforts on COVID-19 and celebrate the 10th anniversary of the establishment of the HMRF, two categories of special award, namely, "Outstanding Project Team on COVID-19 Research Award" and "10th HMRF Anniversary Award" will be presented during the Symposium.

Finally, this Symposium is a remarkable platform to facilitate academic exchange, bringing together researchers, health service providers, and policy makers to share with a view to advancing science in health. I expect to see more excellent research projects supported by HMRF in the years to come. It is with immense pleasure that I acknowledge the contribution of our renowned overseas speakers and our many local experts for joining us today and for sharing their knowledge and experience with us all. I look forward to a stimulating and rewarding event.

Prof. Sophia Siu Chee CHAN, *JP*
Secretary for Food and Health of the Hong Kong Special Administrative Region

Message from the Permanent Secretary for Food and Health (Health)

I am delighted to welcome our distinguished speakers and all participants to the Health Research Symposium 2021.

The Food and Health Bureau (the Bureau) is dedicated to creating and sustaining a healthy Hong Kong. The results obtained from our continuing support to cutting-edge health and medical research play an important role in informing our health policies.

In 2011, the Health and Medical Research Fund (HMRF) was established with an initial commitment of $1,415 million by consolidating the Health and Health Services Research Fund and the Research Fund for the Control of Infectious Diseases. The Bureau has further increased its funding support in 2016 and again in 2021, while incorporating the functions of the Health Care and Promotion Fund under the HMRF. The funding commitment now stands at a total of $4,223 million.

To date, the HMRF has supported nearly 2,000 investigator-initiated research projects, 333 health promotion projects, 30 commissioned programmes, as well as 44 research fellowship awards. These projects cover a wide range of topics including control of infectious diseases and management and prevention of major non-communicable diseases (such as mental health, cardiovascular illnesses, cerebrovascular diseases, cancers and diabetes), research and health promotion activities on modifiable lifestyle factors (including tobacco control, use of alcohol, injury prevention, healthy diet and physical activity), health services, elderly care, Chinese medicine, and many others.

The HMRF also commissioned research in key areas to fill knowledge gaps, inform health policy and address public health threats. Undoubtedly, the most significant global health threat in recent years has been the COVID-19 pandemic, and the HMRF has commissioned research programmes to generate important new knowledge on this disease, including its causes, diagnosis, treatment and prevention. These research projects are made possible through the Bureau's commitment over many years in supporting research on emerging and re-emerging infections. This support stands us in good stead when it comes to addressing other public health threats like avian influenza, swine influenza and Middle East Respiratory Syndrome. Hong Kong is now one of the few places in the world where COVID-19 is under control.

Research findings of HMRF-funded projects have contributed to promote clinical excellence, enhance health services and inform health policies. As part of the Government's strategy of developing Hong Kong into a biotechnology and biopharmaceutical hub, two Phase 1 Clinical Trials Centres have been supported to conduct safety, pharmacology and efficacy of various treatments for a range of cancers since 2014. And in the strengthening of tobacco control policy towards a smoke-free Hong Kong, an evaluation of various tobacco control policies is ongoing and the results are expected to further inform policy in this area. Following the first comprehensive Hong Kong Mental Morbidity Survey on the prevalence, risk factors and health service utilisation for common mental disorders of adults in 2010, the HMRF has commissioned a wider series of mental health surveys covering young children, youth, adults and elderly, which are still underway. In September 2021, the Breast Cancer Screening Pilot Programme was launched taking into consideration the research findings of a recently completed HMRF-commissioned study on the risk of breast cancer in Hong Kong.

With the Government's continuing and unfailing support, I very much hope our research community will continue to excel and contribute to the health and well-being of our society.

The Health Research Symposium this year will again showcase the rich knowledge generated by researchers funded by the HMRF. I wish all participants an insightful experience at this Symposium.

Mr. Thomas Chan, *JP*
Permanent Secretary for Food and Health (Health) of the Hong Kong Special Administrative Region

Organising Committee of the Health Research Symposium 2021

Chairperson

Dr CHUI Tak-yi, *JP*

Under Secretary for Food and Health of the Hong Kong Special Administrative Region

Members

Prof Paul CHAN Kay-sheung

Professor and Chairman
Department of Microbiology
The Chinese University of Hong Kong

Prof Benjamin John COWLING

Professor and Division Head
Division of Epidemiology and Biostatistics
School of Public Health
The University of Hong Kong

Prof LAU Chak-sing, *JP*

Chair and Daniel CK Yu Professor in Rheumatology and Clinical Immunology
Head, Department of Medicine
The University of Hong Kong

Prof David SHUM Ho-keung

Dean
Faculty of Health and Social Sciences
The Hong Kong Polytechnic University

Prof Agnes TIWARI

Chairperson
Nursing Council of Hong Kong

Dr Thomas TSANG Ho-fai

President
Hong Kong College of Community Medicine

Prof Martin WONG Chi-sang

Professor and Associate Director (General Affairs)
The Jockey Club School of Public Health and Primary Care
The Chinese University of Hong Kong

Prof Samuel WONG Yeung-shan

Director
The Jockey Club School of Public Health and Primary Care
The Chinese University of Hong Kong

Review Panel of the Health Research Symposium 2021

Chairperson

Dr CHUI Tak-yi, *JP*

Under Secretary for Food and Health of the Hong Kong Special Administrative Region

Members

Dr Tony HA

Deputizing Director (Strategy and Planning)
Hospital Authority
(Representative from Hospital Authority)

Dr Thomas TSANG Ho-fai

President, Hong Kong College of Community Medicine
(Chairperson of the Assessment Panel on the Commissioned Research on COVID-19)

Dr WONG Ka-hing, *JP*

Head, Public Health Services Branch,
Department of Health
(Representative from Department of Health)

Poster Judges

Prof Paul CHAN Kay-sheung
Professor and Chairman
Department of Microbiology
The Chinese University of Hong Kong

Prof Benjamin John COWLING
Professor and Division Head
Division of Epidemiology and Biostatistics
School of Public Health
The University of Hong Kong

Prof Alexandros MOLASIOTIS
Angel S.P. Chan Lau Professor in Health and Longevity
Chair Professor and Head
School of Nursing
The Hong Kong Polytechnic University

Prof Martin WONG Chi-sang
Professor and Associate Director (General Affairs)
The Jockey Club School of Public Health and Primary Care
The Chinese University of Hong Kong

Prof YIP Shea-ping
Professor and Head
Department of Health Technology and informatics
The Hong Kong Polytechnic University

Awards

Outstanding Project Team on COVID-19 Research Awards

Outstanding Project Team on COVID-19 Research Awards aim to commemorate exemplary project teams working on COVID-19 commissioned studies which were approved in 2020. Since some projects are still on-going and their impact would need to be confirmed after project completion, higher priority will be given to projects with immediate impact to the Government's policy/clinical practice to combat the COVID-19 pandemic this time. The selection in the next Symposium will extend to the new COVID-19 studies commissioned in 2021.

Principal Applicant	**Project Title (Project No.)**
Prof Benjamin John COWLING The University of Hong Kong	Nowcasting COVID-19 transmission dynamics, severity, and the effectiveness of control measures (COVID190118)
Prof NG Siew-chien The Chinese University of Hong Kong	Role of Gastrointestinal Tract and Gut Microbiota in Pathogenesis of Coronavirus Disease 2019 (COVID-19): A Missing Site for Viral Replication & Transmission (COVID190111)
Prof Leo POON Lit-man The University of Hong Kong	Molecular epidemiological study of COVID-19 cases in Hong Kong (COVID190205)
Dr Gilman SIU Kit-hang The Hong Kong Polytechnic University	Whole-genome sequencing of COVID-19 cases in Hong Kong: development of a geo-phylogenetic database and characterisation of SARS-CoV-2 variants circulating in the community (COVID190204)
Prof ZHANG Tong The University of Hong Kong	Grid monitoring of SARS-CoV-2 in sewage for an early-warning sign of community outbreak (COVID190209)

Awards

The 10th HMRF Anniversary Awards

The 10th HMRF Anniversary Awards aim to recognise longstanding achievements in projects funded by the HMRF and these projects received specific HMRF project awards (except Best Poster Award) in any previous Symposium from 2011 onwards.

A. Breakthrough research

Principal Applicant	Project Title (Project No.)
Prof Alfred CHENG Sze-lok The Chinese University of Hong Kong	Elucidating gene regulatory networks of HBx isolated from novel HBV subgenotype/ mutants associated with increased risk of hepatocellular carcinoma (08070332)
Prof Richard CHOY Kwong-wai The Chinese University of Hong Kong	Clinical Application of an Established Target-enrichment Massively Parallel Sequencing Method for Genetic Screening and Diagnosis of Hereditary Hearing Loss Patients with Normal arrayCGH Result (01120256)
Prof JIN Dong-yan The University of Hong Kong	Roles of Epstein-Barr virus-encoded miR-BART microRNAs in viral persistence and transformation of epithelial cells (12110962)

B.Public health, clinical and health services research

Principal Applicant	Project Title (Project No.)
Prof Cindy LAM Lo-kuen The University of Hong Kong	A Study on Health-related Quality of Life of patients with Colorectal Neoplasm and Cost-Effectiveness Analysis of Colorectal Cancer Screening in Hong Kong (08090851)
Dr Wendy LAM Wing-tak **The University of Hong Kong**	A longitudinal study of psychosocial needs, physical symptom distress, and psychological distress of Chinese patients with colorectal cancer (08090921)
Prof Vincent MOK Chung-tong The Chinese University of Hong Kong	Amyloid Burden in Poststroke Dementia (07080411)

C. Health promotion

Principal Applicant	Project Title (Project No.)
Prof LAM Tai-hing The University of Hong Kong	Youth Quitline: An accessible telephone-based smoking cessation hotline for youth (18040084)
Prof Albert LEE The Chinese University of Hong Kong	Community Development Approach to create better health of our young generation within the settings of their daily life (18040564)
Prof Vivian LEE Wing-yan The Chinese University of Hong Kong	Joint Nursing-Pharmacy Health Promotion Programme for Hidden Elders in the Community (22080564)
Prof Agnes TIWARI Fung-yee The University of Hong Kong	'Becoming Parents': A hospital-community partnership to enhance transition to parenthood (03100105)

Awards

Excellent Research Awards

Principal Applicant	Project Title (Project No.)
Prof Richard CHOY Kwong-wai The Chinese University of Hong Kong	Whole genome sequencing analysis of genetically undiagnosed euploid fetuses with increased nuchal translucency (04152666)
Prof Ava KWONG The University of Hong Kong	Screening of founder and recurrent BRCA mutations in Hong Kong and US Chinese populations (01121376)
Prof LAU Chak-sing The University of Hong Kong	Validation of a new definition of lupus low disease activity state (LLDAS): Clinical and management implications (12132961)
Prof LI Miao-xin [Administering Institution: The University of Hong Kong]	Development of multivariate gene-based association analysis approaches for endophenotypes of complex diseases and their application to genetic mapping in a Chinese schizophrenia sample (02132236)
Prof Winnie MAK Wing-sze The Chinese University of Hong Kong	Mobile self-compassionate programme for the promotion of public mental health: Randomised controlled trial (11121081)
Prof NG Ho-keung The Chinese University of Hong Kong	Molecular stratification of lower grade gliomas in routine practice in Hong Kong (02133146)

Excellent Health Promotion Project Awards

Principal Applicant	Project Title (Project No.)
Ms Vicky CHUNG Wai-yin Life Education Activity Programme	"A Healthy Me Is Alcohol Free"- Helping students to avoid alcohol and develop a healthy life (健康不要「酒」) (30160274)
Prof Angela LEUNG Yee-man The Hong Kong Polytechnic University	Changing the way we prevent diabetes: the use of mobile application (29150794)

The Most Promising Young Researcher Awards

Principal Applicant	Project Title (Project No.)
Dr CHEUNG Ching-lung The University of Hong Kong	The role of Vitamin D and bone metabolism in cardiovascular events risk, an interaction or mediation? An 11 year follow-up study (12132451)
Prof LI Miao-xin [Administering Institution: The University of Hong Kong]	Development of multivariate gene-based association analysis approaches for endophenotypes of complex diseases and their application to genetic mapping in a Chinese schizophrenia sample (02132236)

Programme

<table>
<tr><th>Time</th><th colspan="2">Programme</th></tr>
<tr><td>08:20 – 08:50</td><td colspan="2">Registration / Login</td></tr>
<tr><td>08:50 – 09:15</td><td colspan="2">Welcoming Remarks
Prof Sophia CHAN Siu-chee, JP, Secretary for Food and Health

Presentation of Special Awards</td></tr>
<tr><td>09:15 – 10:35</td><td colspan="2">Keynote Lectures I & II:
Control and prevention of emerging infectious diseases
Moderator: Prof Gabriel Matthew LEUNG, GBS, JP, Research Council

K1 - Innovation in design and implementation of primary care clinical trials to generate evidence for community therapeutics for COVID-19: The UK National Urgent Public Health PRINCIPLE Trial example
Prof Chris BUTLER
Professor of Primary Care, Nuffield Department of Primary Care Health Sciences
University of Oxford, United Kingdom

K2 - Infectious disease dynamics as a tool for decision makers during pandemics
Prof Steven RILEY
Professor, Infectious Disease Dynamics, School of Public Health, Faculty of Medicine
Imperial College London, United Kingdom

Panel Discussion</td></tr>
<tr><td>10:35 – 11:00</td><td colspan="2">Coffee Break / Poster Session</td></tr>
<tr><td>10:35 – 10:50</td><td colspan="2">Sharing Session on Research Fellowship Scheme</td></tr>
<tr><td></td><td>F1 - Income inequality and cardiovascular health in China (02160107)
Dr KWOK Man-ki
The University of Hong Kong</td><td>F2 - Evaluation of uptake and impact of Physical Activity Guidelines for preschool children in Hong Kong (02160127)
Dr Wendy HUANG Yajun
Hong Kong Baptist University</td></tr>
<tr><td>11:00 – 13:00</td><td>Parallel Session 1:
Combating COVID-19
Moderator: Dr Thomas TSANG Ho-fai
Grant Review Board Executive

T1a - Comparing immunogenicity against SARS-CoV-2 in COVID19 vaccinees and convalescent patients (COVID1903010 – Project 2)
T1a - Clinical study of flu-based and PD1-based vaccines for the SARS-CoV2 (COVID190123)
Prof Ivan HUNG Fan-ngai
The University of Hong Kong

T1b - To compare the reactogenicity and immunogenicity of the recommended COVID-19 vaccines in young adolescents in Hong Kong (COVID19F02)
Prof LAU Yu-lung
The University of Hong Kong

T1c - Long-term longitudinal comparisons of health status and immune responses in convalescent COVID-19 and vaccinated cohorts in Hong Kong (COVID1903003)
Prof David HUI Shu-cheong
The Chinese University of Hong Kong

T1d - Comprehensive assessment of longitudinal vaccine-induced immune responses, safety and potential effectiveness of COVID-19 vaccines (COVID1903001)
T1d - Randomized trial of COVID-19 booster vaccinations (Cobovax trial) (COVID19F09)
Prof Benjamin John COWLING
The University of Hong Kong

T1e - COVID-19 vaccines Adverse events Response and Evaluation (CARE) Programme (COVID19F01)
Prof Ian WONG Chi-kei
The University of Hong Kong

Panel Discussion</td><td>Parallel Session 2:
Implementing research findings in clinical practice
Moderator: Prof LAU Chak-sing JP
Research Council

T2a - Role of Gastrointestinal Tract and Gut Microbiota in Pathogenesis of Coronavirus Disease 2019 (COVID-19): A Missing Site for Viral Replication & Transmission (COVID190111)
T2a - Novel strategies to facilitate early detection, prevention and Intervention for long-Term Health problems related to COVID-19 (NovITor-COVID study) (COVID1903002)
T2a - Modulation of gut microbiota to enhance health and immunity in vulnerable individuals during COVID-19 pandemic (COVID19F07)
Prof NG Siew-chien
Dr Joyce MAK Wing-yan
The Chinese University of Hong Kong

T2b - Comprehensive clinical, virological, microbiological, immunological and laboratory monitoring of patients hospitalized with Coronavirus Diseases (COVID-19) (COVID190107)
T2b - 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 (COVID19F06)
Prof Paul CHAN
The Chinese University of Hong Kong

T2c - Risk assessment of hereditary breast and ovarian cancer syndrome in Chinese population by multiple-gene sequencing (03143406)
Prof Ava KWONG
The University of Hong Kong

T2d – Enhancing the Clinical Management in Kidney Transplant Patients with Unknown Donor HLA Typing by a Modified Urine Typing Technology (13142121)
Dr Janette KWOK Siu-yin
Queen Mary Hospital</td></tr>
</table>

Programme

<table>
<tr><td>13:00 – 14:00</td><td colspan="2">Lunch Break / Poster Session</td></tr>
<tr><td>14:00 – 16:00</td><td>Parallel Session 3:
Preparedness for the next pandemic
Moderator: Prof Keiji FUKUDA
The University of Hong Kong

T3a - Grid monitoring of SARS-CoV-2 in sewage for an early-warning sign of community outbreak (COVID190209)
Prof ZHANG Tong
The University of Hong Kong

T3b - Molecular epidemiological study of COVID-19 cases in Hong Kong (COVID190205)
Prof Leo POON Lit-man
The University of Hong Kong

T3c - Whole-genome sequencing of COVID-19 cases in Hong Kong: development of a geo-phylogenetic database and characterisation of SARS-CoV-2 variants circulating in the community (COVID190204)
Dr Gilman SIU Kit-hang
The Hong Kong Polytechnic University

T3d - Community based sero-epidemiological study of COVID19 to provide data in real time on age-stratified infection attack rates, disease severity and population-immunity, for guiding intervention policy (COVID190126)
Prof Joseph Sriyal Malik PEIRIS
The University of Hong Kong

T3e - Investigation of Hong Kong's early detection, assessment and response (S-EDAR) system to the new emerging infectious disease outbreak COVID-19 (COVID190105)
Prof YEOH Eng-kiong
The Chinese University of Hong Kong

Panel Discussion</td><td>Parallel Session 4:
Translating knowledge to primary healthcare
Moderator: Prof Cindy LAM Lo-kuen
Grant Review Board

T4a - The Hong Kong Mental Morbidity Survey for Older People (MHS-P1(Part 3)
T4a - A 9-year follow up of the Hong Kong Mental Morbidity Survey (HKMMS) on Chinese adults with Depressive and Anxiety symptoms (CFS-CUHK4)
Prof Linda LAM Chiu-wa
The Chinese University of Hong Kong

T4b - In-depth study of the cost-effectiveness of the Risk Assessment and Management Programme for Hypertension (RAMP-HT) (慢性疾病管理計劃 – 風險評估及治理) for patients with uncontrolled hypertension in primary care in Hong Kong (13142471)
Dr Esther YU Yee-tak
The University of Hong Kong

T4c - Effectiveness of auriculotherapy on older people with insomnia (13144061)
Prof Lorna SUEN Kwai-ping
Tung Wah College

T4d - Use of nicotine replacement therapy (NRT) sample and brief smoking cessation advice for recruiting smokers to smoking cessation services and motivating quit attempts (01170418)
Dr Derek CHEUNG Yee-tak
The University of Hong Kong

T4e - 「乳妳同盟」母乳餵哺社區支援計劃 (30160474)
Ms YIP Wing-foon
The Hong Kong Sheng Kung Hui Lady MacLehose Centre</td></tr>
<tr><td>16:00 – 16:30</td><td colspan="2">Coffee Break / Poster Session</td></tr>
<tr><td>16:00 – 16:15</td><td colspan="2">Sharing Session on Research Fellowship Scheme</td></tr>
<tr><td></td><td>F3 - Establishing a best panel of stool-based detection for non-invasive colorectal neoplasm screening (02160037)
Dr Jessie LIANG Qiaoyi
The Chinese University of Hong Kong</td><td>F4 - The cost-effectiveness of Prostate Health Index for prostate cancer detection in Chinese men (02160047)
Prof Jeremy TEOH Yuen-chun
The Chinese University of Hong Kong</td></tr>
<tr><td>16:30 – 17:50</td><td colspan="2">Keynote Lectures III & IV:
Developing strategies to implement research findings into clinical practice
Moderator: Prof YEOH Eng-kiong, Grant Review Board Executive

K3 - Introducing Implementation Science – Linking Research and Practice
Prof Per NILSEN
Professor, Department of Health Medicine and Caring Science
Linköping University, Sweden

K4 - Better Research and better uptake: lessons from the pandemic
Prof Paul GLASZIOU
Director, Institute for Evidence-Based Healthcare, Faculty of Health Sciences & Medicine
Bond University, Australia

Panel Discussion</td></tr>
<tr><td>17:50 – 18:00</td><td colspan="2">Award Ceremony</td></tr>
<tr><td>18:00 – 18:10</td><td colspan="2">Closing Remarks
Dr CHUI Tak-yi, JP, Under Secretary for Food and Health</td></tr>
</table>

Venue: Hong Kong Academy of Medicine Jockey Club Building
99 Wong Chuk Hang Road, Aberdeen, Hong Kong

( ): Project Number

Run Run Shaw Hall (1/F)
Virtual Room 1

Pao Yue Kong Auditorium (G/F)
Virtual Room 2

Keynote Lectures

K1 – Innovation in Design and Implementation of Primary Care Clinical Trials to Generate Evidence for Community Therapeutics for COVID-19: The UK National Urgent Public Health PRINCIPLE Trial example

Prof Chris BUTLER

Professor of Primary Care, Nuffield Department of Primary Care Health Sciences, University of Oxford, United Kingdom

Professor Butler trained in medicine at the University of Cape Town, did doctoral work at The University of Wales College Of Medicine, and studied Clinical Epidemiology at The University of Toronto. He is now a Professorial Fellow at Trinity College, Oxford, and a Professor of Primary Care at the Nuffield Department of Primary Care Health Sciences at the University of Oxford. Professor Butler's main research interests are in common infections (especially the appropriate use of antibiotics and antivirals, diagnostics, and antimicrobial resistance), and health behaviour change (especially motivational interviewing in health care). He has expertise in clinical trials, cohort studies, qualitative research and analysis of routinely collected data. He chairs the Longitude Prize Advisory Panel and is a Fellow of the Academy of Medical Sciences. He was the patient-nominated Royal College of General Practitioners Wales General Practitioner or the Year in 2019, and won the Royal College of GPs Research Paper of the year in 2020. He has published >400 scientific papers. He currently co-leads the UK National Urgent Public Health Priority Platform Randomised Trial of community treatments for Covid-19 (PRINCIPLE: https://www.principletrial.org)

There were no randomised trials of oseltamivir in the H1N1 pandemic, even though this drug was given out in large quantities, so we will never know if we did more good than harm with that treatment. COVID-19 has demanded the rapid generation and implementation of evidence to better support primary care. Evidence generated during the pandemic in the context where it is to be used is urgently needed, as evidence from hospital trials does not necessarily apply to early treatment in the community, for example. Using traditional approaches, pandemics are often over before relevant trials can be set up, let alone generate evidence to guide care during the pandemic itself. Traditional trial design and implementation takes a long time and is usually limited to the evaluation of a small number of candidate treatments in any one study, and so may not be suited to pandemic circumstances where many candidate interventions may need to be rapidly evaluated and with more interventions emerging subsequent to the start of a trial, thus limiting the changes of enhancing the quality of clinical care during the pandemic itself.

There are few specific treatments for COVID-19 that have been proven in rigorous clinical trials to be effective. Most cases are being managed in the community. It is essential that we urgently identify therapeutics that speed recovery and prevent the need for hospital admission. An ideal intervention would be one that is safe, with few side-effects, helps prevent disease progression, and can be administered in the community using existing processes and capability.

This talk covers an example of the rapid initiation and implementation of a novel clinical trial in the community, with findings generated rapidly enough to be implemented during the pandemic itself.

The Platform **R**andomised trial of treatme**N**ts in the **C**ommunity for ep**I**demic and **P**andemic i**L**l**n**E**s**ses (**PRINCIPLE**) is a multicentre, open-label, multi-arm, response-adaptive platform randomized controlled trial of community treatments for COVID-19.

Innovation in trial design: PRINCIPLE operates under a master protocol that allows the addition of further interventions into the trial while the trial is already in progress, so a new trial does not need to be started afresh each time an additional suitable intervention becomes available, and it also means that existing controls can be used efficiently to give rapid answers about the effectiveness of new interventions. Response adaptive randomisation allows the proportion of participants allocated to each intervention to be adjusted, based on emerging data from the trial to increase efficiency and shorten time to results.

Innovation in trial Implementation: We recruit through our traditional route general practice as well as being a paperless 'online' trial, using approaches where the 'patient comes to research' as well as the trial 'taking research to the patient.'

Innovation in the evidence base: Clinical alerts can be sent out to all clinicians in the NHS around the implications of the findings. Readouts for **azithromycin, doxycycline, inhaled budesonide and colchicine** will be presented, with a focus on detailing the benefits from inhaled budesonide treatment.

Keynote Lectures

K2 – Infectious Disease Dynamics as a Tool for Decision Makers During Pandemics

Prof Steven RILEY
Professor, Infectious Disease Dynamics, School of Public Health, Faculty of Medicine, Imperial College London, United Kingdom

Steven is a Professor of Infectious Disease dynamics at Imperial College in London. He completed a PhD in mathematical epidemiology at Oxford University in the group that later became the MRC Centre for Global Infectious Disease Analysis at Imperial College. Steven collaborated with The University of Hong Kong (HKU) on studies of SARS-CoV-1 before joining HKU in 2004 just as the School of Public Health was established. While at HKU, he worked on the disease dynamics of influenza and other respiratory viruses before returning to Imperial in 2010. Steven has contributed to the UK response to COVID-19 as a member of: the COVID-19 Response Team at Imperial College, the Scientific Pandemic Influenza - Modelling (SPI-M) committee for the UK government, and the Imperial College REal-time Assessment of Community Transmission (REACT) study team.

Many infectious diseases spread quickly from person to person. This makes them fundamentally different to other health threats because the amplitude of the threat they pose can accelerate exponentially, forcing leaders to make very difficult decisions in a short space of time with imperfect information. The emergence of SARS-CoV-2 illustrated clearly how leaders can reach very different conclusions. In this talk, I will give examples of how the science of infectious disease dynamics can help reduce uncertainty when used to help with planning, responding and learning from pandemics. As the world transitions from low to high immunity against SARS-CoV-2 with as little health impact as possible, we have the opportunity to revise our plans to reduce greatly the impact of the next similar emergent virus. At the end of the talk, I will give a personal view of how we can prioritize the science of improving our response.

Keynote Lectures

K3 – Introducing Implementation Science – Linking Research and Practice

Prof Per NILSEN
Professor, Department of Health Medicine and Caring Science, Linköping University, Sweden

Professor Per Nilsen is a Professor in Department of Medicine and Caring Sciences at Linköping University, Sweden. He has developed a doctoral-level implementation course, which has run annually since 2011, attracting PhD students from all over world. Nilsen visited the Chinese University of Hong Kong one semester in 2017, giving implementation lectures and seminars. He takes particular interest in issues concerning behaviour and practice change and the use of theories, models and frameworks for improved understanding of implementation. His research interests can be traced to his varied background, including behavioural economy at the Stockholm School of Economics and systems development.

The word "implement" is derived from the Latin "implere", meaning "to fulfil" or "carry into effect". This provides a basis for a broad definition of implementation science as the scientific inquiry into questions concerning how to carry intentions into effect. The intentions may be formulated in policies, clinical guidelines or other recommendations; they can be manifested in specific interventions; and they can relate to the use of research in decisions by individuals and organizations.

The birth of implementation science is usually linked to the emergence of the evidence-based movement in the 1990s, which popularized the notion that research findings and empirically supported ("evidence-based") interventions should be more widely implemented in healthcare and other settings for improved health and welfare of populations. The field of implementation science has identified many challenges that exist when translating research into practice and investigated strategies to address these obstacles.

The keynote lecture by Professor Per Nilsen from Linköping University, Sweden, provides an overview of the implementation science field and summarizes knowledge about barriers to implementation and facilitators and strategies to overcome challenges to achieve a more evidence-based healthcare practice.

Keynote Lectures

K4 - Better Research and Better Uptake: Lessons from the Pandemic

Prof Paul GLASZIOU
Director, Institute for Evidence-Based Healthcare
Faculty of Health Sciences & Medicine, Bond University, Australia

Paul is Professor of Evidence-Based Practice at Bond University and the Director of the Institute for Evidence Based Healthcare. He was the Director of the Centre for Evidence-Based Medicine in Oxford from 2003-2010. His key interests include identifying and removing the barriers to using high quality research in everyday clinical practice. He is a leader within the Reward Alliance, investigating research waste and promoting better prioritisation, design, conduct, regulation, management and reporting of health research. Other interests include overdiagnosis and overtreatment, general practice, uptake of evidence for non-drug interventions, and automation of systematic review processes.

Jeremy Farrar, Director of Wellcome and Chair of the World Health Organization R&D Blueprint Scientific Advisory Group, has said "It's critical that the global research effort is rapid, robust and is conducted at scale and co-ordinated across multiple countries." The record setting speed of development and testing of vaccines was built on the work of CEPI - Coalition for Epidemic Preparedness Innovations, and has begun to halt the pandemic, though slowed by vaccine hesitancy.

Similarly, the rapid clear answers to treatment questions have saved hundreds of thousands of lives during the course of the COVID-19 pandemic. In previous pandemics, large-scale randomized trials were generally not set up in time. Many of the >2,000 planned drug studies examining COVID-19 treatments (www.covid-trials.org), most have delivered little or no directly useful information. However, there are some important exceptions, with trials such as RECOVERY, REMAP-CAPS and SOLIDARITY setting new standards and showing that a combination of old-fashioned randomization, established clinical-trials networks and imaginative use of modern information technology can provide many rapid and reliable therapeutic answers. The speed of the RECOVERY trial was record-breaking: the period from protocol to first patient recruitment was nine days, with the 176 UK hospitals recruiting >12,000 hospitalized patients (15% UK COVID-19 cases), and it provided clear answers within a few months on the effectiveness of dexamethasone and the ineffectiveness of hydroxychloroquine and lopinavir–ritonavir.

While the pandemic has seen remarkable trials for vaccines and drug treatments, much less has been done to evaluate the effects of Public Health and Social Measures (also known as non-pharmaceutical' interventions - NPIs - or Behavioural, Environmental, Social and Systems Interventions – BESSIs. Only a handful of trials have been registered and few completed in time to influence practice and policy. Important lessons can be learned from examining both the successes and failures of research during this pandemic, both in research and in its implementation.

Parallel Session 1: Combating COVID-19

T1a - Comparing Immunogenicity against SARS-CoV-2 in Covid-19 Vaccinees and Convalescent Patients

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Background: Vaccinating COVID-19 recovered patients with mRNA vaccines boosts their immune response against wild type viruses (WT), in view of increasing prevalence of virus variants, we aimed to investigate whether vaccine platform and time of vaccination affects the immunogenicity against SARS-CoV-2 wild type and delta variant strains.

Methods: Convalescent COVID-19 patients aged above 18 years were recruited and blood samples were taken at after discharged, one month, three months, six months post-recovery. Then, COVID-19 recovered subjects received one dose of BNT162b2 (PC-B) or CoronaVac (PC-C) vaccines, and their sera samples were collected before vaccination as baseline and at day 28 post-vaccination. Furthermore, SARS-naïve volunteers were administrated two doses of BNT162b2 (CN-B) or CoronaVac (CN-C) vaccines and taken blood at baseline, day 21 (CN-B) or day 28 (CN-C), and day 56 post-primer dose. The neutralizing antibody in sera against SARS-CoV-2 HKU-001a (WT) and B.1.617.2 (delta variant, DV) was determined with live virus neutralization assay (vMN).

Findings: vMN geometric mean titre (GMT) against WT in COVID-19 recovered individuals decreased to 26·9 [95% confidence interval (CI), 22·9-31·5] from 73·6 (95%CI, 63·8-84·8) at 6 months post-recovery. After receiving one dose of BNT162b2, subjects in PC-B group, one dose of BNT162b2 enhanced antibody response against WT with 22·3 folds increase, and induced 20·4 folds increase of GMT against DV which was significantly higher than that after a booster vaccination in CN-B group (11·1 folds) (p=0·007). Similarly, recovered subjects in PC-C group showed significant increase of GMT against DV after primer vaccination than SARS-CoV-2 naïve subjects in CN-C group after booster vaccination (2·2 vs 1·3) (p=0·029). In both PC-B and PC-C groups, there was no difference between GMT against WT and DV after vaccination. Subjected showed inferior GMT against delta variant compared to GMT against wild type in CN-C and CN-B groups on day 56.

Interpretation: One dose of COVID-19 vaccines enhanced the pre-existing neutralizing activity in recovered subjects. The antibody response to DV was non-inferior to that against wild type in recovered subjects after vaccination, while SARS-naïve subjects showed a significantly lower antibody activity against DV than against WT. Long term follow-up should be performed to determine the duration of antibody response in COVID-19 recovered people after vaccination.

Project Number: COVID1903010 – Project 2

Parallel Session 1: Combating COVID-19

T1a - Clinical Study of Flu-based and PD1-based Vaccines for the SARS-CoV2 [Title of presentation: A Phase 1, Randomized, Double-blinded, Placebo-controlled, Dose-escalation and Dose-expansion Study to Evaluate the Safety and Immunogenicity of DelNS1-nCoV-RBD LAIV for COVID-19 in Healthy Adults]

Ivan HUNG Fan-ngai[1], CHEN Honglin[2], CHEN Zhiwei[2], Ricky ZHANG Ruiqi[1], CHAN Kwok-hung[1], Kelvin TO Kai-wang[2] and YUEN Kwok-yung[2]

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Background: In response to the outbreak of SARS-CoV-2 in late-2019, a panel of DelNS1-based RBD vaccines composed of H1N1 subtype (HA and NA derived from strain of 2009) – namely DelNS1-nCoV-RBD LAIV – have been made. The vaccine is delivered intranasally. The purpose of this study is to evaluate the safety and immunogenicity of DelNS1-nCoV-RBD LAIV for COVID-19 in healthy adults.

Methods: We conducted a phase 1 randomized, double-blinded, placebo-controlled study on healthy subjects between the age of 18 to 55 and COVID-19 vaccines naïve, between March 2021 to September 2021. Subjects were enrolled and randomly assigned (4:1) into DelNS1-nCoV-RBD LAIV (low/ high dose) or placebo group. The low-dose vaccine composed of 1x 107 EID50/ dose in 0.2mL and the high-dose vaccine composed of 1x 107.7 EID50/ dose in 0.2mL and the placebo vaccine composed of 0.9% normal saline/dose in 0.2mL. Recruited subjects were administered the vaccine intranasally on day 1 and day 29. All recruited subjects were monitored from day 1 to day 56. The primary end-point was the safety of the vaccine and the secondary end-points included the mucosal total Ig in saliva against the SARS-CoV-2 RBD, microneutralization neutralization against the live SARS-CoV-2, anti SARS-CoV-2 RBD IgG and the T-cell responses against the SARS-CoV-2 spike peptide.

Findings: Twenty-nine healthy Chinese subjects were recruited of which 11 subjects were recruited into the low-dose group, 12 subjects were recruited into the high-dose group and 6 subjects recruited into the placebo group. Twenty subjects (69%) were male. No subject was discontinued due to an adverse event. No adverse events of special interest or severe adverse events were reported within 56 days after the first vaccination in all three groups. There was no significant difference in the incidence of any reactogenicities (p=0.595) or unsolicited adverse events (p=0.620) within 56 days after the first vaccination among all the groups. Although statistically not significant, there was a trend that the total mucosal Ig fold increase after the first dose at day 4 were higher in the high-dose group when compared to the low-dose and placebo groups (day 4: 5.2 vs. 3.3 vs. 3.6; p=0.64), and after the second dose at day 32 in both the low-dose and the high-dose group when compared to the placebo group (day 32: 3.1 vs. 4.5 vs. 1.58; p=0.52). The T-cell response was also higher in the high-dose group than the low-dose and placebo groups on day 15 and day 43 after the first vaccination (day 15: 15 vs. 1 vs. 1; p=0.24 and day 43: 12.5 vs.1 vs. 5; p=0.55).

Conclusion: The intranasal DelNS1-nCoV-RBD LAIV is safe and immunogenic. A phase-2 clinical trial with larger sample size is warranted.

Project Number: COVID190123

Parallel Session 1: Combating COVID-19

T1b - To Compare the Reactogenicity and Immunogenicity of the Recommended COVID-19 Vaccines in Young Adolescents in Hong Kong

Prof LAU Yu-lung
Doris Zimmern Professor in Community Child Health, Chair Professor of Paediatrics
Department of Paediatrics and Adolescent Medicine
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Introduction and Project Objectives: Adolescents remain at risk of severe COVID-19 and atypical presentations such as multisystem inflammatory syndrome in children (MIS-C). Safety and immunogenicity of mRNA and inactivated COVID-19 vaccination need to be understood, including in healthy adolescents and those with severe immune compromise, which may alter the safety profile and immune response of the vaccines.

Methods: Healthy adolescents are recruited for vaccination with 2 doses of CoronaVac or BNT162b2, with antibody and T cell response assessment for 3 years, and compared against their parents. Reactogenicity is solicited for 7 days and severe adverse events are monitored for 3 years. Patients with primary (monogenic) and secondary immune compromise are also recruited and compared against healthy adolescents.

Results: Both CoronaVac and BNT162b2 are associated with favourable reactogenicity profile. No severe adverse events were recorded in adolescent participants with good past health or allergic history to PEG-containing drugs and first dose of BNT162b2 during the data observation period. Anti-Spike-RBD and surrogate neutralizing antibody responses and T cell responses are non-inferior in healthy adolescents compared with adults for either vaccines. Both vaccines induced antibody response and helper and cytotoxic T cell response in healthy adolescents. Patients with severe immune compromise have attenuated responses to vaccination.

Conclusion and Discussion: Both vaccines appear safe and immunogenic in healthy adolescents. Three doses of vaccine may be beneficial in those receiving CoronaVac and those with immune compromise. Vaccination is safe in those with PEG-containing drug allergies or hypersensitivity reactions to first dose of BNT162b2.

Project Number: COVID19F02

Parallel Session 1: Combating COVID-19

T1c - Long-term Longitudinal Comparisons of Health Status and Immune Responses in Convalescent COVID-19 and Vaccinated Cohorts in Hong Kong

Prof David HUI Shu-cheong
Chairman, Department of Medicine & Therapeutics, Stanley Ho Professor of Respiratory Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China

Objectives: 1. To examine the health status and immune responses of COVID-19 patients who have recovered from different levels of disease severity. 2a. To investigate the SARS-CoV-2 specific cellular and humoral immune responses and 2b. To identify the early signatures associate to these responses from community subjects who have received different types of COVID-19 vaccines. 3. A booster study also conducted for subjects who have had poor antibody response despite having received 2 doses of CoronaVac.

Methodology: The health conditions of adults (N=400) who recovered from varying severity of COVID-19 are being assessed and their blood are collected at 6, 12, 24 and 36 months after discharge. The assessment package includes: lung function tests, 6-min walk distance (6MWD), chest radiographs/CT, and SF36 questionnaire. Blood samples from community cohorts are collected from before and serially up to 36 months after receiving one of the 2 COVID-19 vaccines (N=350 in each group of Biontech vs CoronaVac). The kinetics of SARS-CoV-2 specific humoral and cellular immune responses from both convalescent and vaccinated cohorts are determined by neutralization assay and by measuring specific T cell responses upon stimulation of SARS-CoV-2 specific peptide library respectively. The antiviral level of the human plasma with various neutralization titer collected from different vaccinated cohorts will be tested in mouse model and ADCC assay.

Results:

a) The majority of patients have normal spirometry but their 6MWD and SF 36 response were lower than the general population. Because the rate of antibody waning slows with time, we fitted lines of decay to 115 sera from 62 convalescent patients collected beyond 90 days after symptom onset and estimate that PRNT50 antibody will remain detectable for around 1,717 days after symptom onset and that levels conferring 50% protection will be maintained for around 990 days post-symptom onset, in symptomatic patients (Lau E, et al. EClinicalMed 2021).
b) Through the head-to-head comparison, vaccination with BNT162b2 (n=49) induces significantly higher levels of SARS-CoV-2 specific binding and neutralizing antibody responses when compared to CoronaVac (n=49) at 1 month post second dose. CoronaVac induces higher CD4+ and CD8+ T cell responses to the structural protein than BNT162b2 (Mok C, et al. Respirology 2021).
c) Our RCT study has shown that BNT162b2 booster dose (n=40) for 80 community subjects who have poorly responded to 2 doses of CoronaVac is significantly more immunogenic than a CoronaVac booster (n=40). BNT162b2 also elicits high level of SARS-CoV-2 specific neutralizing antibody to different variants of concern. The adverse reactions were only mild and short-lived (to be submitted).

Project Number: COVID1903003

Parallel Session 1: Combating COVID-19

T1d - Comparison of Inactivated and mRNA Vaccines for COVID-19

Project 1: Comprehensive assessment of longitudinal vaccine-induced immune responses, safety and potential effectiveness of COVID-19 vaccines
Project 2: Randomized trial of COVID-19 booster vaccinations (Cobovax trial)

Prof Benjamin John COWLING
Professor and Division Head, Division of Epidemiology and Biostatistics, School of Public Health,
The University of Hong Kong, Hong Kong SAR, China

Introduction: In early 2020, Hong Kong was one of the first-affected locations by the COVID-19 pandemic outside of mainland China. However, timely public health measures have successfully controlled a number of surges in daily case numbers, and fewer than 12,000 confirmed cases were recorded in the first 18 months of the pandemic. The objective of these studies is to assess the immune responses to COVID-19 vaccines and inform vaccination strategies.

Methods: In COVID1903001, two observational cohorts have been established to study immune responses to COVID-19 vaccines in Hong Kong. The first cohort includes up to 1500 individuals of all ages, followed for up to 4 years after receiving a first dose of COVID-19 vaccination. The second cohort includes up to 1000 older adults, followed for up to 4 years from April 2021. In both cohorts blood samples are collected every 6 months, and the first cohort includes additional blood draws after any dose of vaccination. In COVID19F01, 400 adults who have received two doses of COVID-19 vaccine will be randomly allocated to receive a third dose of either inactivated or mRNA vaccine, with blood samples collected at 1, 6 and 12 months after the 3rd dose. In both studies samples will be tested for antibodies and cellular responses against SARS-CoV-2 to allow quantification of the strength and duration of immune responses to vaccination.

Results: Antibody responses to two doses of mRNA vaccines were on average 10 times higher than antibody responses to two doses of inactivated vaccine. Immediate reactions to inactivated vaccine were milder. Antibody levels declined faster in recipients of the inactivated vaccine, to low levels by 3-6 months.

Conclusion: mRNA vaccines conferred higher antibody titers than inactivated vaccines, but both vaccine technologies improved immunity against COVID-19. Vaccination provides a pathway back to a new normal, by replacing the public health and social measures that have so far prevented large epidemics. However any relaxation of public health measures will only be safe once we can achieve a high level of population immunity, and third doses will likely be required within the next 6 months particularly in individuals who initially received two doses of inactivated vaccine.

Project Number: COVID1903001
Project Number: COVID19F01

Parallel Session 1: Combating COVID-19

T1e - COVID-19 Vaccines Adverse Events Response and Evaluation (CARE) Programme [Title of presentation: Bell's palsy following Vaccination with mRNA (BNT162b2) and Inactivated (CoronaVac) SARS-CoV-2 vaccines: a Case Series and Nested Case-control Study.]

Prof Ian WONG Chi-kei
Lo Shiu Kwan Kan Po Ling Professor in Pharmacy, Head of Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong SAR, China

Background: Bell's palsy is a rare adverse event reported in clinical trials of COVID-19 vaccines. However, to our knowledge no population-based study has assessed the association between the inactivated SARS-CoV-2 vaccines and Bell's palsy. The aim of this study was to evaluate the risk of Bell's palsy after BNT162b2 and CoronaVac vaccination.

Methods: In this case series and nested case-control study done in Hong Kong, we assessed the risk of Bell's palsy following vaccination with BNT162b2 (Fosun-BioNTech [equivalent to Pfizer-BioNTech]) or CoronaVac (from Sinovac Biotech, Hong Kong) using data from the Department of Health and Hospital Authority's territory-wide electronic health records (the Clinical Data Analysis and Reporting System -CDARS). We described reported cases of Bell's palsy among vaccine recipients. We compared the estimated age-standardised incidence of clinically confirmed cases among individuals who had received the CoronaVac or BNT162b2 vaccination (up to 42 days before presentation) with the background incidence in the population. A nested case-control study was also done using conditional logistic regression to estimate the odds ratio (OR) for risk of Bell's palsy and vaccination. Cases and controls were matched (1:4) by age, sex, admission setting, and admission date.

Results: Between February 23 and May 4, 2021, 451 939 individuals received the first dose of CoronaVac and 537 205 individuals received the first dose of BNT162b2. 28 clinically confirmed cases of Bell's palsy were reported following CoronaVac and 16 cases were reported following BNT162b2. The age-standardised incidence of clinically confirmed Bell's palsy was 66·9 cases per 100 000 person-years (95% CI 37·2 to 96·6) following CoronaVac vaccination and 42·8 per 100 000 person-years (19·4 to 66·1) for BNT162b2 vaccination. The age-standardised difference for the incidence compared with the background population was 41·5 (95% CI 11·7 to 71·4) for CoronaVac and 17·0 (-6·6 to 40·6) for BNT162b2, equivalent to an additional 4·8 cases per 100 000 people vaccinated for CoronaVac and 2·0 cases per 100 000 people vaccinated for BNT162b2. In the nested case-control analysis, 298 cases were matched to 1181 controls, and the adjusted ORs were 2·385 (95% CI 1·415 to 4·022) for CoronaVac and 1·755 (0·886 to 3·477) for BNT162b2.

Conclusion: Our findings suggest an overall increased risk of Bell's palsy after CoronaVac vaccination. However, the beneficial and protective effects of the inactivated COVID-19 vaccine far outweigh the risk of this generally self-limiting adverse event. Additional studies are needed in other regions to confirm our findings. (Lancet Infect Dis. 2021 Aug 16;S1473-3099(21)00451-5.)

Project Number: COVID19F01

Parallel Session 2: Implementing Research Findings in Clinical Practice

T2a - Role of Gastrointestinal Tract and Gut Microbiota in Pathogenesis of Coronavirus Disease 2019 (COVID-19): A Missing Site for Viral Replication & Transmission

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The role of gut microbiota in pathogenesis of COVID-19 is largely unknown. We evaluated gut bacterial and viral microbiota in COVID-19 patients and its association with disease severity and outcomes and determined the effect of SARS-CoV-2 on gut inflammation and ACE2 expression by a prospective case control studies including 50 hospitalised patients with laboratory-confirmed SARS-CoV-2 infection, 30 patients hospitalized with community-acquired pneumonia, and 30 healthy individuals. 73.3% of COVID-19 patients had SARS-CoV-2 nucleic acid detected in faeces during hospitalization (median 3.86×103 copies per mL inoculum). 46.7% showed active SARS-CoV-2 infection with strikingly higher coverage the 3' vs 5' end of SARS-CoV-2 genome in faecal viral metagenome profile, even after disease resolution. Patients with COVID-19 had altered bacterial and viral microbiota, compared with healthy controls ($P < 0.05$), which persisted up to 6 months after recovery. Several gut commensal bacteria with known immunomodulatory potential e.g. Faecalibacterium prausnitzii, Eubacterium rectale and bifidobacteria and two Pepper-derived RNA virus species (RNA virus) were underrepresented in COVID-19 patients. Depletion of these bacterial and viral taxa was associated with more severe disease as well as elevated concentrations of inflammatory cytokines and blood markers ($P < 0.05$).

Our study showed that there was prolonged and active SARS-CoV-2 virus in the faeces of COVID-19 patients, even after recovery, which highlights the threat of potential fecal-oral viral transmission. We, for the first time, identified several biomarkers of gut bacterial and viral microbiota specific to COVID-19, and elucidate their associations with disease severity and host immune response. This will allow potential therapeutics to modulate the gut microbiota to reduce severity and complication of COVID-19.

Project Number: COVID190111

Parallel Session 2: Implementing Research Findings in Clinical Practice

T2a - Novel Strategies to Facilitate Early Detection, Prevention and Intervention for Long-term Health Problems Related to COVID-19 (NovITor-COVID Study)

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In order to study the effect of COVID-19 on the development of co-morbidities (**Programs 1-2**) and to examine the impact of a novel digital mental health (DMH) platform on neuropsychiatric disorders (**Program 3**); and evaluate the role of a novel oral microbiome replacement therapy on reducing chronic comorbidities in COVID-19 survivors; and the impact of gut microbiota on immunity to COVID-19 vaccination (**Program 4**), we performed a total of 4 studies: prospective cohort studies (**Programs 1-2**); (ii).Prospective cohort and pre-post observational study (**Program 3**); (iii).a mixed randomized, placebo-controlled (**Program 4a**) and prospective cohort design (**Program 4b**) including COVID-19 survivors, healthy controls and subjects going to receive COVID-19 vaccines. We hoped to evaluate the incidence and trajectory of various COVID-19 complications and neuropsychiatric disorders, the effect of modulation of gut microbiota on long-term complications associated with COVID-19 and the seroprevalence of SARS-CoV-2 specific antibodies after COVID-19 vaccines.

Project Number: COVID1903002

Parallel Session 2: Implementing Research Findings in Clinical Practice

T2a - Modulation of Gut Microbiota to Enhance Health and Immunity in Vulnerable Individuals During COVID-19 Pandemic

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Elderlies and patients with type 2 diabetes mellitus (DM) have a higher risk of developing severe COVID-19 infection and mortality. Gut microbiota has been linked to the pathogenesis of COVID-19 and to our immune function. We aimed to evaluate the efficacy of modulating gut microbiota with a microbiome immunity formula in vulnerable subjects (patients with underlying type 2 DM and elderlies) in improving immune functions, reducing adverse events associated with COVID-19 vaccines, and reducing hospitalisation in susceptible individuals during the COVID-19 pandemic. A 12-month double-blinded, randomised controlled trial on the use of a microbiome immunity formula vs. Placebo in enhancing health and immunity in patients with Type 2 DM and a 12-month, open-labelled, randomised controlled comparing 3-month vs. 6-month regimen of microbiome immunity formula in elderly individuals will be performed to assess the proportion of subjects achieving restoration of gut dysbiosis at 6 months, adverse events associated with COVID-19 vaccines and number of unplanned hospitalisation and clinic visits.

Project Number: COVID19F07

Parallel Session 2: Implementing Research Findings in Clinical Practice

T2b - Comprehensive Clinical, Virological, Microbiological, Immunological and Laboratory Monitoring of Patients Hospitalized with Coronavirus Diseases (COVID-19)

Prof Paul CHAN
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Introduction and Project Objectives: The SARS-CoV-2 emerged in late 2019 and became a pandemic of devastating disease (COVID-19). Our project aimed at: (i) Evaluating the diagnostic performance of various specimen types; (ii) Delineating the profiles of virological and immunological markers; and (iii) Exploring alternative detection methods targeting different gene regions.

Methods: Prospective studies were performed on hospitalized COVID-19 patients. Diagnostic performance of self-collected samples was evlauted. Cytokine profile in association with clinical outcome was delineated. Clinical value of subgenomic viral RNA profiling from serial respiratory and stool specimens was examined.

Diagnostic value of self-collect samples: Deep throat saliva (DTS) had the lowest PCR positive rate (68.7% vs 89.4% [sputum] and 80.9% [pooled nasopharyngeal and throat swabs, NPSTS]), and the lowest viral RNA concentration (mean log copy/mL 3.54 vs 5.03 [sputum] and 4.63 [NPSTS]).

Mouth gargle (MG) was not different from DTS in the positive rates across test platforms (ranged from 89.9% to 96.3%, p=0.46 to 1.00). A positive correlation between the paired MG and DTS was observed (Spearman's correlation: 0.662-0.727).

Nasal strip showed significant correlation with NPSTS (p=0.0003) and DTS (p=0.01). Nasal strip and NPSTS showed 94% and 100% agreement for NPSTS-positive and -negative samples, respectively.

Cytokine/chemokine immune response: IL-38 showed a regulatory and protective role in SARS-CoV-2 infection. Proinflammatory Th1 helper (IL-18, IP-10, MIG, IL-10) and ARDS-associated cytokines (IL-6, MCP-1, IL-1RA and IL-8) were enhanced progressively with severity. Furthermore, 11 cytokines were consistently different in both early and late phases, including 7 (GROα, IL-1RA, IL-6, IL-8, IL-10, IP-10, MIG) that increased and 4 (FGF-2, IL-5, MDC, MIP-1α) that decreased from mild to severe/critical patients.

Subgenomic viral RNA profile: While conventional diagnostic PCR targeting genomic viral RNA often remained positive for 3-4 weeks, it was rare to have PCR targeting subgenomic viral RNA remained positive beyond 10 days after illness onset. Most stool specimens tested positive by diagnostic PCR were negative by subgenomic PCR, suggesting non-viable viruses.

Conclusion: DTS is suboptimal in diagnostic yield, whereas mouth gargle can be applied for massive screening. Nasal strip provides a good diagnostic yield and is particularly feasible for children. Th1 helper response and ARDS-associated cytokines correlate with severity. MCP-1 predicts day of mechanical ventilation, vasopressor requirement and length of ICU stay. PCR targeting subgenomic viral RNA and does not require a high biosafety containment facilities, and is a feasible and reliable tool to monitor infectivity.

Project Number: COVID190107

Parallel Session 2: Implementing Research Findings in Clinical Practice

T2c - Risk Assessment of Hereditary Breast and Ovarian Cancer Syndrome in Chinese Population by Multiple-gene Sequencing

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Differences in the mutation spectrum across ethnicities suggest that it is important to identify genes in addition to common high penetrant genes to estimate the associated breast cancer risk in Chinese. A total of 1,338 high-risk breast cancer patients who tested negative for germline BRCA1, BRCA2, TP53 and PTEN mutations between 2007-2017 were selected from the Hong Kong Hereditary Breast Cancer Family Registry. Patient samples were subjected to next-generation DNA sequencing using a multigene panel. All detected pathogenic variants were validated by bi-directional DNA sequencing. The sequencing data was co-analyzed by our in-house developed bioinformatics pipeline. Sixty-one pathogenic variants (4.6%) were identified in 11 cancer predisposition genes. The majority of the carriers (77.1%) had early-onset of breast cancer (age <45), 32.8% had family members with breast cancer and 11.5% had triple-negative breast cancer (TNBC). The most common mutated genes were PALB2 (1.4%), RAD51D (0.8%) and ATM (0.8%). A total of 612 variants of unknown significance (VUS) were identified in 494 patients, and 87.4% of the VUS were missense mutations. An additional 4.6% of the patients were identified in patients who tested negative for germline BRCA1, BRCA2, TP53 and PTEN mutations using the multigene test panel.

Project Number.: 03143406

Parallel Session 2: Implementing Research Findings in Clinical Practice

T2d - Enhancing the Clinical Management in Kidney Transplant Patients with Unknown Donor HLA Typing by a Modified Urine Typing Technology

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Introduction and Project Objectives: Kidney transplantation is the most cost-effective treatment modality for end stage kidney diseases. However, around 9% of the transplanted patients suffer from transplant failure and require re-transplantation. Antibody-mediated rejection (AMR) is one of the main causes of graft failure after kidney transplantation, therefore prevention and management of AMR is crucial in prolonging allograft survival. Donor-specific antibodies (DSA) play a pivotal part in AMR, however, the diagnosis of the presence of DSA requires donor's HLA information, which is lacking in the majority of kidney transplant patients who have received transplantations outside of Hong Kong. We employed a simple and non-invasive approach for determining donor HLA typing from recipients' urine samples to facilitate the correlation of DSA.

Methods: 700 urine samples were collected from patients who received kidney transplantations outside Hong Kong with unknown donor HLA information. PCR-sequence-specific primers (PCR-SSP) were used to deduce the donor mismatched HLA antigens. Due to the low resolution of the conventional PCR-SSP, the application of Next Generation Sequencing (NGS) to deduce donor mismatched HLA typing in high resolution was also investigated.

Results: Using PCR-SSP and NGS, the deduction success rate of donor mismatched HLA antigens was nearly 80.0%. Other than in the HLA-A, -B, and -DR loci, mismatched HLA typing was also deduced in the DQ loci. Anti-HLA IgG antibodies against HLA Class I and Class II antigens were detected in 27.9% of the patients. DSA was found in 11.1% of the patients, which was comparable to patients who received their transplantations in Hong Kong with known donor typing. With the results of DSA, 88.5% of AMR could be managed in patients with surviving allografts transplanted between 2013 and 2018. Allograft failure with histologic proven AMR was found in 11.5% of patients before the commencement of this study. This highlighted that the availability of donor HLA typing information is crucial for the early diagnosis of AMR, allowing prompt medical intervention to salvage graft failure.

Conclusion and/or Discussion: Recipients' urine samples have proven to be a valuable non-invasive source for deducing donor HLA typing with PCR-SSP and NGS. Deduction of donor mismatched HLA typing could enhance clinical management of post-transplant patients with unknown donor information.

Project Number: 13142121

Parallel Session 3: Preparedness for the Next Pandemic

T3a - Grid Monitoring of SARS-CoV-2 in Sewage for an Early-warning Sign of Community Outbreak

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Introduction and Project Objectives: Sewage surveillance, which tests the collection of faecal samples in a given sewershed, could offer a scalable, cost-effective strategy for measuring population-level infections. This project objectives are to test SARS-CoV-2 virus in community sewage collected from various sites of Hong Kong using methods established by the HKU team, to provide early-warning signals for the re-emergence of COVID-19 in local communities as a supplementary part for the clinical tests.

Methods: Sewage testing method for SARS-CoV-2 includes three steps: virus concentration, viral genetic material (RNA) extraction and quantification via Reverse transcription qPCR.

Results: The initial trial was conducted in early October 2020 as a response to an infection cluster at Kwai Chung. Initial findings of the trial indicated that sewage testing data were largely consistent with the clinical tests, and the sewage test was a useful tool to provide additional information for assessing the risk associated with outbreak in an area. We then applied our approach to monitor the re-emergence of SARS-CoV-2 circulation in local community by testing sewage samples collected from 26 stationary sites in Hong Kong. The sewage surveillance in this stage has effectively caught the rising trend of clinical cases in the fourth wave starting from the middle of November 2020.

From December 2020 to February 2021, routine sewage analysis at the 26 stationary sties were shifted to the monitoring of estates with infection clusters. Sewage testing results provided a basis for statutory public health action in identifying buildings and places for compulsory testing operations to uncover the infected individuals in local community. More than 50 confirmed cases were found, cutting off hidden transmission chains in these communities.

As the fourth wave of COVID-19 in Hong Kong begun to subside from February 2021, we resumed the routine monitoring of the 26 stationary sties for this HMRF project. Sewage testing results at this stage indicated the downward trend of the fourth outbreak.

Conclusion: The above results about sewage surveillance for SARS-CoV-2 in Hong Kong have demonstrated that the sewage surveillance could be used for the following purposes: (1) Providing early warning signals for COVID-19 outbreak; (2) Tracking the development trend of community outbreak; and (3) Complementing the monitoring of estates with infection clusters.

Since December 2020, daily sewage testing results have been incorporated into local monitoring scheme as an essential part of the whole control strategy of COVID-19. The systematic routine sewage monitoring programme now covers over 112 stationary sampling sites in Hong Kong, providing early warning signal of COVID-19 re-emergence for over 5.4 million people.

Project Number: COVID190209

Parallel Session 3: Preparedness for the Next Pandemic

T3b - Molecular Epidemiological Study of COVID-19 Cases in Hong Kong

Prof Leo POON Kit-man
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Introduction/Objectives: Molecular epidemiology can track the spread of epidemics. As a WHO COVID-19 Reference Laboratory, we attempted to use next generation sequence (NGS) technology to understand the viral dynamic of SARS-CoV-2 in Hong Kong. Findings from our analyses were reported to the Hong Kong Government on a weekly basis to inform field investigations, epidemiological studies and public health response.

Methods: We obtained SARS-CoV-2 positive respiratory samples from Centre for Health Protection and deduced full-length viral genomes using various NGS platforms (Illumina and Nanopore).

Results and Discussion: Hong Kong has experienced 4 major waves of COVID-19. Thus far, we have sequenced about 25% of all COVID-19 cases in Hong Kong. Although there were numerous importations of SARS-CoV-2 variants, including variants of concern (VOC), only three variant introductions were responsible for 90% of locally acquired cases. We also demonstrated that SARS-CoV-2 transmission patterns in these waves were very different from each others. In addition, we observed that non-adherence to prolonged preventative measures may lead to sustained local transmission in Hong Kong. We will discuss a few representative super-spreading events as examples.

We provided genetic evidence to demonstrate the world's first reverse zoonotic transmission (humans to pets), SARS-CoV-2 reinfection, and inflight transmission. We also identified certain settings (e.g., hotels and airport) and environmental conditions (e.g., poor ventilation) are potential hotspots for SARS-CoV-2 transmission. Our investigations also revealed possible virus sources, previously unknown transmission chains and misdiagnosed cases. These findings helped to develop or refine evidence-based control policy against COVID-19.

We also studied a substantial number of imported cases, thereby identifying countries seriously affected by VOC. Such information is critical to policy makers for revising travel restriction policy on incoming travellers. We also reasoned that travel hubs like Hong Kong can be used as surveillance sites to monitor SARS-CoV-2 sequence diversity at regional level.

In addition to local impacts, we used our experiences to draft WHO guidelines for genomic surveillance of SARS-CoV-2 and use our sequencing pipelines to analysis cases for overseas countries.

Conclusion: Hong Kong uses an elimination strategy to control COVID-19 and a close monitoring of SARS-CoV-2 sequence dynamic within Hong Kong is one of the essential components to achieve this. Our work has provided scientific underpinning to develop COVID-19 control strategies.

Project Number: COVID190205

Parallel Session 3: Preparedness for the Next Pandemic

T3c - Whole-genome Sequencing of COVID-19 Cases in Hong Kong: Development of a Geophylogenetic Database and Characterisation of SARS-CoV-2 Variants Circulating in the Community

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Background: In spite of stringent public health measures, Hong Kong experienced four epidemic waves of COVID-19, resulting in 12,348 infected cases and 213 deaths as of October 2021. Our team established Nanopore GridION and Illumina Miseq platform for whole-genome sequencing of SARS-CoV-2 at the early stage of the pandemic (in February 2020).

Objective: We aim to develop a phylogenomic database coupled with geospatial information system to unveil the transmission linkage of COVID-19 cases in Hong Kong.

Result: Phylogenomic analysis enabled us to identify an asymptomatic patient as the source of the first superspreading event of COVID-19 (Buddhist worship hall cluster) happened in late February 2020. After months of relative quiescence, a large COVID-19 outbreak (third wave) occurred in Hong Kong in July 2020. The phylogeny of some early cases indicated that the outbreak was attributed to a single lineage B.1.1.63, which was identical to viral genomes isolated from marine crew and aircrew who were exempted from mandatory quarantine.

In early October 2020, before the onset of the fourth wave, we identified a novel viral genome (lineage B.1.36.27) among local cases, which was most closely related to imported cases from Nepal. We highlighted flaws in hotel quarantine arrangements, under which travellers could still receive visitors. The Government later implemented the policy that inbound travellers should be quarantined at designated hotels and not be allowed visitors.

In December 2020, the United Christian Hospital experienced a large outbreak of SARS-CoV-2 in a palliative care and medicine ward. Later in January 2021, two healthcare workers from North District Hospital tested positive after taking care of COVID-19 patients. In both cases, we conducted phylogenomic analysis, enabling the hospitals to trace the transmission chain and prevent further cases.

In April 2021, we used rapid phylogenomic analysis to identify the transmission link between Filipino domestic helpers and an Indian businessman who had travelled from Dubai and tested positive for a SARS-CoV-2 VOC Beta. The genomic data enabled us to trace the entire transmission chain and their close contacts. Eventually, we identified an inbound traveller, who had stayed in the adjacent hotel room to the Indian businessman during quarantine, was the source of the transmission.

Recently we developed a phylogeographical information system which integrated the genomic, epidemiological, spatial and temporal information of COVID-19 cases in Hong Kong. Data visualizations are combined with the cartographic display to yield a clear view of the genomic diversity of SARS-CoV-2 variants and their distributions across Hong Kong districts, with a focus on the clustering of cases based on phylogenetic proximity.

Conclusion: Continued genomic surveillance of the imported cases is pivotal in detecting novel lineages that enters Hong Kong.

Project Number: COVID190204

Parallel Session 3: Preparedness for the Next Pandemic

T3d - Community Based Sero-epidemiological Study of COVID19 to Provide Data in Real Time on Age-stratified Infection Attack Rates, Disease Severity and Population-immunity, for Guiding Intervention Policy

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Introduction and Project Objectives: During an epidemic, diagnosed cases represent a tip-of-the-iceberg of infection taking place in the community. Sero-epidemiological studies provide an effective means to assess true infection attack rates in a community to inform control strategies. The aim of the study was to define infection attack rates, development and duration of population immunity to SARS-CoV-2 through population based serial cross sectional and longitudinal sero-epidemiology studies.

Methods: Venous blood samples were collected from volunteers from four study cohorts chosen to provide different levels of exposure risk and one of RT-PCR confirmed cases. These were Cohort A) Community-based longitudinal cohort; Cohort B) Serial age-stratified cross-sectional sampling of blood donors; Cohort C) Individuals working in occupations associated with increased social contacts who are at increased risk of infection; Cohort D) Individuals discharged from quarantine. Cohort E: Cohort E) was a longitudinal follow up of a cohort of RT-PCR confirmed COVID-19 infections to define the duration of immunity following natural infection. Sera were tested by for SARS-CoV-2 specific antibody and a subset tested for T cell responses.

Results: Total numbers of sera collected from Cohorts A, B, C and D as of end of August 2021 was 4599, 13,968, 2,066 and 4,296 respectively. Virus neutralization confirmed sero-prevalence in the unvaccinated individuals in the four cohorts were 1.3% (95% CI 0.9-1.9), 0.12% (95% CI 0.06-0.19), C 0.16% (95% CI 0.02-0.57) and 9.92% (95% CI 8.92-10.9) respectively. Cohort A is the most representative cohort for estimating population sero-prevalence. From this data we estimate a total of 61,000 (95% CI 18,000 to 128,000) infections which is age-adjusted incidence of 0.8%. Thus, case detection captured 29 % of overall infections occurring in Hong Kong. Blood donors under-estimated population sero-prevalence, likely because blood-donors are a more "health conscious" subgroup of the population and because blood donation is deferred for 180 days for anyone with confirmed COVID-19, likely excluding most of those with known infection.

Follow up of RT-PCR confirmed SARS-CoV infections showed that neutralizing antibody will remain detectable for around 1,717 days after symptom onset and that levels conferring 50% protection will be maintained for around 990 days post-symptom onset, in symptomatic patients. PRNT titres wane faster in children.

Discussion and Conclusion: Population based infection attack rate in the community remains low and 29% of infections are detected. Symptomatic COVID-19 disease is followed by relatively long-lived protection from re-infection by antigenically similar viruses.

Project Number: COVID190126

Parallel Session 3: Preparedness for the Next Pandemic

T3e - Investigation of Hong Kong's Early Detection, Assessment and Response (S-EDAR) System to the New Emerging Infectious Disease Outbreak COVID-19

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Introduction and Project Objectives: Our study aims to inform policy makers how Hong Kong's system of early detection, assessment and response (S-EDAR) to COVID-19 can be enhanced for control during the course of the pandemic at different transmission scenarios, and to inform future preparedness and response plans.

Methods: Relevant documents from WHO and other international public health organizations and scoping review of the international literature are used to evaluate the effectiveness and implementation of S-EDAR in Hong Kong with input from policy-makers and relevant stakeholders and comparative case study of government responses to provide real-time input for adjustments in pandemic control (Stage 1); and for an enhanced S-EDAR informed by international and local experts, and a Delphi survey for the feasibility and applicability (Stage 2). Inputs from:

- Comparative case studies of government responses in Hong Kong, Japan, Malaysia, South Korea, Shanghai, and Singapore;
- 35 local key informants including policy-makers, healthcare administrators and professionals in public and private sectors, business organizations, and general public/patients;
- 17 local and international experts;
- Analysis of infection surveillance and control data from Centre of Health Protection and Hospital Authority, and assessing effectiveness of screening strategies for inbound travellers

Results:

1. Comparative case studies
   The key lessons from the six jurisdictions highlighted the need for an on-going surveillance system, broaden screening, comprehensive preparedness plans and regular drills, information technology, capacity for testing, contact tracing, isolation and quarantine. Measures should be proportionate to the stages of the outbreak to reduce socio-economic impacts. Relaxation of measures should be based on risk assessment stratified by environmental settings, implemented in stages, and reversible when needed.

2. System dynamics modelling
   The simulation suggested that both PCR-polymerase chain reaction test (with a 7-day quarantine) and rapid antigen test screening for inbound travelers is insufficient to control local transmissions at travel volumes in 2019. However, travel volumes at the lower level 1 month before the entry ban of all countries can be controlled.

3. Development of an Enhanced S-EDAR for Hong Kong
   From findings of key informant interviews and expert workshops, an Enhanced three component S-EDAR has been developed 1) "Preparedness plan and resilience system", 2) "Readiness system" to mobilize resources, enhance surge capacities and scale-up response, and 3) "Response system" with implementation strategies at government, healthcare and community levels for response actions to be taken by different sectors.

Conclusion: The Enhanced S-EDAR will be a robust evolutionary system to enable preparedness, readiness and timely response to the rapidly changing transmission scenarios and dynamic context in the control of COVID-19 and emerging infectious diseases. Its feasibility and applicability will be scrutinized in the Delphi survey of local experts.

Project Number: COVID190126

Parallel Session 4: Translating Knowledge to Primary Healthcare

T4a - The Hong Kong Mental Morbidity Survey for Older People

Prof Linda LAM Chiu-wa
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Background: Population ageing is a major public health concern. Dementia and mental disorders in late life not only affect independent functioning, but also pose significant burden to the elders and their caregivers.

Aims and Objectives: The Hong Kong Mental Morbidity Survey for Older People (HKMMSOP) is a commissioned HMRF project which aims to evaluate current prevalence of neurocognitive and/or mental disorders in Hong Kong adults aged 60 or over.

Methods: Older adults, living either in the community or residential facilities would be randomly recruited through residential addresses over Hong Kong.

Major findings: In November 2021, over 2,500 participants have been assessed. The unweighted prevalence of mild and major neurocognitive disorders was 26.8% and 5.1% respectively. 10.4% of participants had diagnosable anxiety and depressive disorders. Older age, lower educational attainment, higher level of chronic physical morbidity were associated with higher risks of cognitive impairment and mental health problems. We also found that participation of a wider range of leisure based cognitive, mental and social activities were associated with higher cognitive function and lower level of mood symptoms.

Discussion: We observed a relatively high prevalence of mild neurocognitive disorder, while the prevalence of major neurocognitive disorder did not appear to exhibit great leap over the years. From the perspective of early intervention for cognitive and mental health, we should further explore the pragmatics of introducing client based healthy lifestyles.

Project Number: MHS-P1 Part 3

Parallel Session 4: Translating Knowledge to Primary Healthcare

T4a - A 9-year Follow Up of the Hong Kong Mental Morbidity Survey (HKMMS) on Chinese Adults with Depressive and Anxiety Symptoms

Prof Linda LAM Chiu-wa
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Background: Mental disorders are important causes of morbidity and loss of productivity in adulthood. The Hong Kong Mental Morbidity Survey (HKMMS), conducted from 2010 to 2013 (T0), reported that the one-week weighted prevalence of common mental disorders (CMD) was 13.3% in the Hong Kong adult population.

Aims and Objectives: The current study aims to evaluate the long-term trajectories of CMDs in the Hong Kong community.

Methods: Participants assessed at the HKMMS were invited for 7 year follow up. Clinical Interview Schedule – Revised (CISR) were assessed for CMD. Information on psychosocial and physical health status were obtained through structured questionnaires.

Results: In June 2021, 1,500 participants were assessed for 7 year follow up (Baseline: normal – 890, subsyndromal group – 360, CMD group -250) For the baseline normal group, 69 % remained well; 8% had episode onset of CMD at 7 years. For the baseline subsyndromal group, 37% achieved normal level; and 29% had episode onset of CMD. For the Baseline CMD group, 16% had remission; 22% improved to subsyndromal group and 61% remained with significant depressive and anxiety at 7 years. A higher level of baseline mood symptoms and physical health problems, current poor perceived social support and life events in recent years were associated with high level of mood symptoms at 7 years.

Discussion: The findings suggested that while depressive and anxiety disorders persisted in a proportion of people, there are some people whose symptoms attenuated or remitted. With the recognition that policy should target on the adverse psychosocial factors, there may be a room to booster pro-mental well being factors as part of community based mental health interventions.

Project Number: CFS-CUHK4

Parallel Session 4: Translating Knowledge to Primary Healthcare

T4b - In-depth Study of the Cost-effectiveness of the Risk Assessment and Management Programme for Hypertension (RAMP-HT) for Patients with Uncontrolled Hypertension in Primary Care in Hong Kong

Dr Esther YU Yee-tak
Department of Family Medicine and Primary Care, The University of Hong Kong, Hong Kong SAR, China

Introduction: The Risk Assessment and Management Programme for Hypertension (RAMP-HT) of the Hospital Authority is an evidence-based, structured multi-component intervention incorporating team-based risk-guided management strategies focusing on total cardiovascular disease (CVD) risk control. RAMP-HT improved blood pressure control of patients with uncontrolled hypertension after 1-year compared to those receiving usual public primary care. This project evaluated the long-term effectiveness on reducing cardiovascular complications and mortality, and the 5-year and estimated lifetime cost-effectiveness of RAMP-HT.

Methods: This is a prospective cohort study on adult patients with hypertension without complications or diabetes mellitus receiving public primary care in Hong Kong. A total of 79,161 RAMP-HT participants were matched one-to-one with patients receiving usual care in 2011-2013. Effects of RAMP-HT on CVD and all-cause mortalities were evaluated using Cox proportional hazards regression. The number-needed-to-treat to prevent one CVD event/mortality event was determined. Programme cost of RAMP-HT was collected from the Hospital Authority using costing questionnaires. Public medical costs were estimated based on public health services utilization rates, while a subset of 486 patients completed a survey on private medical costs. Cost-effectiveness of RAMP-HT per CVD and all-cause mortality prevented, and event-free year gained were calculated. A Monte-Carlo simulation model was developed using empirical data to evaluate the lifetime cost-effectiveness of RAMP-HT.

Results: After a median follow-up of 5.3 years, RAMP-HT participants had significantly lower cumulative incidences of CVD (9.14%vs.14.95%, $p<0.001$) and all-cause mortality (5.04%vs.10.99%, $p<0.001$) compared to usual care patients, corresponding to a 5.81% and 5.95% absolute risk reduction, respectively. The number-needed-to-treat was 17 to prevent one CVD event and 20 for all-cause death. The total programme cost over 5 years per RAMP-HT patient was HK$521. RAMP-HT participants had significantly lower direct public medical costs over 5 years than usual care patients (RAMP-HT: HK$61,904; Usual care: HK$91,561) but similar annual private medical costs (RAMP-HT: HK$3,347; usual care: HK$3,588). The cost invested on RAMP-HT to prevent/ gain 1 event-free-year was HK$9,058/HK$1,905 for CVD and HK$10,345/HK$3,490 for all-cause mortality. RAMP-HT was estimated to be cost-saving, saving HK$5,569 per RAMP-HT participant compared to patients receiving usual care over lifetime.

Conclusion and Implications: The team-based RAMP-HT, through coordinated use of each healthcare professional's expertise to deliver quality hypertension management, was highly effective in preventing hypertension-related complications and mortality, and saving public healthcare cost. The benefits of integrating such model of care in busy naturalistic primary care were sustainable and could alleviate the burden of public healthcare system.

Project Number: 13142471

Parallel Session 4: Translating Knowledge to Primary Healthcare

T4c - Effectiveness of Auriculotherapy on Older People with Insomnia

Prof Lorna SUEN Kwai-ping
Tung Wah College, Hong Kong SAR, China

Introduction and Project Objectives: Insomnia is common among the elderly. Given the adverse effects of prolonged use of hypnotics, three minimally invasive procedures, namely, laser auriculotherapy (LAT), magneto-auriculotherapy (MAT), and their combination, were investigated to determine the desirable treatment modality to improve the sleep conditions of elderly. This study aims to determine the optimum treatment protocol of AT for improving sleep conditions and quality of life in elderly with insomnia.

Methods: This is a three-arm double-blinded randomised trial. A total of 145 eligible subjects were randomised into (1) placebo LAT and MAT; (2) LAT and placebo MAT; and (3) LAT plus MAT. Seven auricular points namely 'shenmen', 'heart', 'liver', 'spleen', 'kidney', 'occiput' and 'subcortex' were used. Treatment was delivered three times a week, for six weeks. The subjects were assessed at baseline, 6 weeks, and follow-up after 6 weeks, 3 months and 6 months. Generalised Estimating Equations were used for evaluating interactions among the groups over time on the primary outcome – Pittsburgh Sleep Quality Index (PSQI), and secondary outcomes (sleep parameters using actigraphic monitoring, quality of life using SF-12, and Patient Health Questionnaire (PHQ-9) for assessing depression status).

Results: The treatment effects of the three protocols were comparable. Significant improvements in all the subjective measures (PSQI, health-related quality of life, depression status) for individual groups over time were indicated. Significant deduction in the awakening time after sleep onset and increase in sleep efficiency were detected in subjects who received MAT but not in those who received LAT alone. The combined MAT and LAT approach did not show any advantage over MAT alone.

Conclusion and Discussions: The findings of this meticulous RCT can provide valuable information and increase the understanding of the therapeutic effect of AT, either combined MAT, and LAT or MAT alone. It is suggested that a longer therapeutic course and more frequent administration of LAT may be considered in future trials to achieve the optimal treatment effect. In general, AT was demonstrated to be a well-received treatment modality with minimal adverse effects, and effective in improving sleep conditions of the elderly. This project addresses the thematic priority of Chinese Medicine under the Health and Health Services Theme of HMRF. The findings can offer insights in future research directions, and to translate knowledge to primary healthcare in the community.

Trial Registration: ClinicalTrials.gov: NCT02970695

Project Number: 13144061

Parallel Session 4: Translating Knowledge to Primary Healthcare

T4d - Use of Nicotine Replacement Therapy (NRT) Sample and Brief Smoking Cessation Advice for Recruiting Smokers to Smoking Cessation Services and Motivating Quit Attempts

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Introduction and Project Objectives: Nicotine replacement therapy (NRT) sampling is effective to increase use of smoking cessation service use and tobacco abstinence in primary care settings. This study promoted the delivering of NRT sampling and brief smoking cessation advice to smokers and the effects of this strategy on smokers' recruitment and cessation outcomes when it was applied at outdoor smoking hotspots.

Methods / Implementation: This is a pragmatic two-arm cluster-randomized trial which was conducted in 4 phases: (1) Training of smoking cessation (SC) ambassadors (SCAs) for the SC promotion; (2) SC promotion sessions to deliver the quitting advice and NRT sampling (experimental group), or the quitting advice only (control group); (3) Follow-up of the recruited smokers; (4) Evaluation of the effectiveness of promotion, quit outcomes, and use of NRT sampling.

Results / Outcome: This project trained 59 SCAs, held 244 smoking cessation promotion sessions, approached 9224 smokers and offered SC counseling to 1427 (15.5% of all approached smokers) smokers onsite. This project helped 299 (21.0% of smokers received counseling) smokers to quit successfully. By intention to treat, the NRT sample significantly attracted more participants to receive nurses' onsite counseling (Adjusted incident rate ratio=1.35, 95%CI, 1.12-1.62, p<0.01). Group differences in other recruitment outcomes were not significant. The two trial groups showed similar quit attempts (RR (risk ratio) =1.02 and 0.90 at the 1-, and 3-month follow-up, respectively, all p-values > 0.05), but the experimental group reported lower use of cessation service (RR=0.72, and 0.85 at the 1-, and 3-month follow-up, respectively, all p-value < 0.05). Tobacco abstinence at 6-month was similar in both groups. At 1-month follow-up, in the experimental group who received NRT sample, 51.7% had ever used the NRT sample and 34.1% completed the full course of the NRT samples. At 1-month follow-up, no significant group difference in the use of any NRT in the past month was detected (39.8% and 34.4%, p>0.05).

Conclusion: Delivery of NRT sample at outdoor smoking hotspots increased uptake of onsite nurses' brief counseling. This strategy reduced enrolment of smoking cessation services, but it did not alter quit attempts and long-term tobacco abstinence.

Project Number: 01170418

Parallel Session 4: Translating Knowledge to Primary Healthcare

T4e - 「乳妳同盟」母乳餵哺社區支援計劃

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Introduction:
本計劃旨在集結跨界別力量，如：護理專業人士、具母乳餵哺或具陪月經驗的婦女等，為準新手父母及母乳餵哺家庭提供支援服務，讓媽媽及其家庭成員在知識及照顧技巧層面獲得正確的資訊，同時承托媽媽在情緒層面上的需要，正面鼓勵及支持新生嬰兒媽媽以母乳餵哺孩子，增強她們對母乳餵哺的信心及延長母乳餵哺期。

Project Objectives:
(i) 提升新手父母的能力及信心；
(ii) 集結跨界別力量，建立協作平台；
(iii) 推動關愛精神，支援有需要的家庭；
(iv) 提升家庭關係，以助延長母乳媽媽的餵哺期；
(v) 加強公眾對母乳餵哺的認識。

Methods / Implementation:
舉行「母乳好處及餵哺技巧」工作坊、「乳妳同盟」大使（指導員）訓練、「為母則強」社區互助小組、「乳妳同盟」大使支援服務及社區教育活動。

Results / Outcome:
本計劃接觸到：
(i) 126 位母乳餵哺的母親；
(ii) 30 名母乳餵哺指導員；
(iii) 84 名家庭成員；
(iv) 8 個合作伙伴，包括：香港大學護理學院、香港助產士學院、廣華醫院產科門診部、瑪嘉烈醫院婦產科、葵青及荃灣區母嬰健康院、媽媽牌同盟、明愛綠色小腳板及社會福利署。及
(v) 420 位公眾人士。

Conclusion:
本計劃旨在集結跨界別力量，為準新手父母及母乳餵哺家庭提供支援服務，為媽媽及其他家庭成員在餵哺的知識及照顧嬰兒技巧層面提供正確的資訊，同時亦承托媽媽在情緒層面上的需要，正面鼓勵及支持母乳餵哺媽媽，增強她們的信心，並鼓勵延長母乳餵哺期。

是次項目計劃共有 126 位新手父母及母乳餵哺家庭參加，計劃團隊同時招募了 30 名母乳餵哺指導員，透過不同的專業團體，為計劃參加者提供訓練及支援服務。當中有 90% 母親認同工作坊能增加對母乳餵哺的知識及技巧，並增強其餵哺母乳的信心，延長母乳餵哺期。此外，70% 母親滿意「母乳餵哺指導員」所提供支援服務。她們認同當遇上疑問及困難時，能夠有平台可以查詢，甚至有婦女義工進行家庭探訪，能協助改善母乳餵哺的實踐情況，有助她們舒緩身心壓力。另一方面，80% 指導員認同訓練內容實用，有助她們為計劃參與母親提供指導；而且她們所得的知識及技巧，能於日常生活中學以致用，甚至協助自己的親友，有助提升其自信心，同時加強人際關係。

是次項目計劃邀請到不同的單位共同協作，如：廣華醫院產科門診部、瑪嘉烈醫院婦產科提供平台，讓計劃團隊招募新手父母、母乳餵哺家庭參與計劃；同時邀請到香港大學護理學院、香港助產士學院的專業團隊，為計劃參加者提供工作員及訓練活動等。80% 合作伙伴認同社區支援計劃能支援母乳餵哺的母親，願意繼續共同協作，於社區內推動母乳餵哺的工作。與坊間其他團體稍為不同的一點，是計劃團隊致力鼓勵及邀請家庭成員一同參與活動，包括新手爸爸及祖父母。工作員希望增強家庭成員們的能力和參與，能為母乳餵哺媽媽提供正面的支持甚至是正確的支援。90% 家庭成員認同透過講座能認識母乳餵哺的好處，表示願意支持母親以母乳餵哺嬰兒，並協助及鼓勵其延長母乳餵哺期。

計劃團隊年度性地於社區內舉行社區教育活動，安排母乳餵哺大使於活動內協助向準新手父母推廣及宣傳母乳餵哺好處，同時向公眾人士推廣及宣傳母乳餵哺的資訊，以提升公眾人士對母乳餵哺的接受性。70% 回應的公眾人士認同增加對母乳餵哺的認識，表示支持及鼓勵身邊女性以母乳餵哺嬰兒。

Project Number: 30160474

Research Fellowship Scheme

F1 - Income Inequality and Cardiovascular Health in China

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Introduction and Project Objectives: Whether absolute income (income per se) or relative income (social comparisons of income) at the household or neighbourhood level affects cardiovascular disease (CVD) risk in China is understudied. Relative income have been hypothesized to affect health via material and/or psychosocial stress pathways. However, it remains unclear whether stress biomarkers, such as cortisol, are on the pathway from income to CVD risk. This project aimed to examine the associations of absolute and relative household and neighbourhood income with CVD risk, and the mediating role of cortisol, in Hong Kong Chinese, and to assess whether cortisol, a major stress hormone, plays a potential causal role in CVD and its risk factors in Westerners and Hong Kong Chinese.

Methods: Complementary designs with an observational study and two Mendelian randomization (MR) studies were used. Based on Hong Kong's FAMILY Cohort, 17,607 adults (recruited from 2009 to 2014) were included for the observational study to examine the associations of income with CVD risk, and 1,562 adults (attended clinical follow-up started in 2016) were used to assess the mediating role of cortisol and for the MR study in Hong Kong Chinese. Publicly available genome-wide association studies (GWAS) with large sample size and extensive genotyping for cortisol and CVD and its risk factors were included for the MR study in Westerners.

Results: In the observational analysis in Hong Kong Chinese, relative household income deprivation was associated with higher systolic blood pressure but lower body mass index, whereas it was unrelated to self-reported CVD and diabetes. Neighbourhood income inequality was generally unrelated to CVD risk, nor was absolute income. Cortisol did not clearly mediate the association of relative household income deprivation with systolic blood pressure. Using the MR analysis, genetically predicted cortisol was unrelated to ischemic heart disease, ischemic stroke, diabetes or other CVD risk factors in Westerners, nor CVD risk in Hong Kong Chinese.

Conclusion and/or Discussion: Relative household income deprivation was not consistently associated with cardiovascular health in Hong Kong Chinese adults, nor was neighbourhood income inequality or absolute income. Relevance of relative and absolute income to cardiovascular health may be context specific. Cortisol unlikely plays a role in cardiovascular risk, casting doubts on the cortisol-related pathway to CVD. Better understanding of complex psychosocial mechanisms and alternative mediating pathways would inform more effective preventive strategies to close the income gap in cardiovascular health in China.

Research Fellowship Number: 02160107

Research Fellowship Scheme

F2 - Evaluation of Uptake and Impact of Physical Activity Guidelines for Preschool Children in Hong Kong

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Introduction and Project Objectives: The first guidelines for physical activity and sedentary behaviour for children aged 2 to 6 years was first released in 2012 by the Department of Health and a revised version was published in 2018. This study investigated the awareness and knowledge of the guidelines among parents and preschool teachers, examined the associations of awareness and knowledge with beliefs, intention, and children's physical activity and sedentary behaviour as suggested by health communication theory, and identified perceived barriers and facilitators to implementation and develop messages recommendations supplementing the guidelines through focus group interviews.

Methods: A complementary (quantitative and qualitative) research approach was applied. 351 children and their parents were recruited from 8 kindergartens. Children worn an activPAL accelerometer for seven consecutive days to measure physical activity and sedentary time. Parents reported their child's sedentary screen time and sociodemographic information, and responded to questions assessing their awareness, knowledge, belief and intention of the guidelines. Focus group interviews were conducted among a group of parents and teachers to gauge their feedback on the guidelines.

Results: Very few children (14.6%) met the physical activity guidelines and 41.6% of them met the screen time recommendations. Awareness and knowledge of the guidelines was low within parents. Being aware of the having better knowledge was associated with better belief of the guidelines and higher intention of the guidelines' adoption. Parents' awareness of the guidelines was positively related with children's physical activity, while better knowledge and higher intention within parents were favourably correlated with children's sedentary behaviour. Parents and teachers generally agreed with the recommendations, however, they identified various barriers for implementation. They also suggested using innovative mediums for dissemination and communication.

Conclusion and Discussion: Compliance with the PA guidelines is low for preschool children in Hong Kong. There is a lack of awareness and adequate knowledge of the physical activity guidelines among parents. The guidelines should be supplemented with clear messages catering for local needs and to ensure that precursors to behaviour change could be motivated. Certain segments of the populations should be targeted in future health promotion. Increasing stakeholders' awareness and knowledge of the guidelines may be helpful to enhancing belief and intention of adopting the guidelines.

Research Fellowship Number: 02160127

Research Fellowship Scheme

F3 - Establishing a Best Panel of Stool-based Detection for Non-invasive Colorectal Neoplasm Screening

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Introduction and Project Objectives: Colorectal cancer (CRC) screening can facilitate successful treatment and reduce cancer incidence. We aimed to establish stool-based multitarget tests to improve colorectal neoplasm screening by involving our previously identified CRC-associated miRNAs (reflecting changes in host cells) and bacterial markers (reflecting environmental risk factors).

Methods: Multiplex TaqMan probe-based qPCR for bacterial markers (Fusobacterium nucleatum (Fn), Bacteroides clarus (Bc), Clostridium hathewayi (Ch), a Lachnoclostridium sp. 'm3' and an undefined species 'm7') and multiplex MGB probe-based RT-qPCR for miRNAs (miR92a, miR135b, miR21, miR145 and miR133a) were established. Stool samples from 698 subjects, consisting of 203 patients with CRC, 207 patients with adenoma (120 advanced adenoma (AA) and 87 non-advanced adenoma (NAA)) and 288 normal controls, were tested. Statistical modelling to employ these markers with/without fecal immunochemical test (FIT) was conducted using logistic regression (LR), multinomial logistic regression (mLR) and random forest classification, with best subsets regression and cross validation where appropriate. Diagnostic performance of the new models were assessed.

Results: With conventional cutoff at 100 ng Hb/mL, FIT detected 72.3%, 17.9% and 0% of CRC, AA and NAA respectively although at superior specificity of 99.5%. Without FIT, combining 4Bac (Fn, m3, Bc and Ch) and 3 miRNAs (miR92a, miR145 and miR135b) by mLR model showed sensitivities of 89.9%, 44.6% and 45.6% for CRC, AA and NAA respectively at 84.8% specificity. Bacterial markers (Fn, m3, Bc, Ch) combined with FIT by LR model showed sensitivities of 94.4%, 44.1% and 38.4% for CRC, AA and NAA respectively at 84.7% specificity. miRNAs (all five) combined with FIT by LR model showed sensitivities of 90.2% for CRC and 43.3% for AA at 80.3% specificity, although not satisfactory for NAA. Models involving all three types of markers showed further improved diagnostic performances. The mLR model involving 4Bac (Fn, m3, Bc, Ch), 3 miRNAs (miR92a, miR145, miR135b) and FIT detected 96.9%, 48.2% and 43.0% of CRC, AA and NAA respectively at 84.8% specificity. The random forest classifier involving 2Bac (Fn, m3), 4 miRNAs (miR92a, miR21, miR135b, miR133a) and FIT showed sensitivities of 94.3%, 46.4% and 46.8% for CRC, AA and NAA respectively at 84.8% specificity.

Conclusion: The combination of fecal bacterial and miRNA markers increases the sensitivity for colorectal neoplasm detection, and could be easily implemented with FIT. This study provides marker panels and corresponding modelling methods, involving fecal bacterial and miRNA markers with or without FIT, for clinical implementation to improve colorectal neoplasm screening.

Research Fellowship Number: 02160037

Research Fellowship Scheme

F4 - The Cost-effectiveness of Prostate Health Index for Prostate Cancer Detection in Chinese Men

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Introduction and Project Objectives: Prostate-specific antigen (PSA) and prostate health index (PHI) have been used as biomarkers for prostate cancer detection. In this study, we aimed to evaluate the cost-effectiveness of PHI for prostate cancer detection in Chinese men.

Method: We developed a Markov model for Chinese male patient aged 50-75 years old. The PSA strategy was to offer TRUS-PB for all patients with elevated PSA of 4-10 ng/mL. The PHI strategy was to offer PHI for patients with elevated PSA of 4-10 ng/mL. TRUS-PB would only be offered for patients with PHI >35.0. Model inputs were extracted from local data when available. The cost per quality-adjusted life years gained for both strategies were calculated. The incremental cost-effectiveness ratios in relation to the willingness-to-pay (WTP) threshold were compared. One-way sensitivity analysis and probabilistic sensitivity analysis were performed. Cost-effectiveness acceptability curves were also constructed.

Results: With a Markov model of 25 screening cycles from age 50 to 75 years, the mean total costs per man were estimated to be USD 27,439 in the PSA strategy and USD 22,877 in the PHI strategy. The estimated effects were estimated to be 15.70 in the PSA strategy and 16.05 in the PHI strategy. The PHI strategy was associated with an expected decrease in cost of USD 4562 and an expected gain of 0.35 QALY, resulting in an ICER of USD -13056.56. The results were shown to be robust upon one-way sensitivity analysis. Upon Monte Carlo simulation, the PHI strategy was more cost-effective for 100% of the iterations. The PHI strategy demonstrated dominance over the PSA strategy regardless of what WTP threshold we use.

Conclusion: A PHI-based screening strategy may be more cost-effective than a PSA-based strategy for prostate cancer detection in Chinese men. These results support consideration of a PHI-based approach for prostate cancer in Hong Kong.

Discussion: Our study showed that the PHI strategy could reduce the need of prostate biopsy, prostate biopsy-related complications, and was much more cost-effective than the PSA strategy. The study results had huge implications in the management of patients with elevated PSA in Hong Kong. Currently, PHI has been adopted for routine use by urology specialists in the public system in Hong Kong.

Research Fellowship Number: 02160047

Abstracts for Poster Presentation: Advanced Medical Research

AMR-1-21

Eradication of Hepatocellular Carcinoma by Augmenting Immunotherapy Efficacy via Cell Cycle Related Kinase (CCRK) Inhibition

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Introduction and Project Objectives: Hepatocellular carcinoma (HCC) is a sexually dimorphic cancer associated with elevated male hormone androgen, inflammation and obesity. Obesity-promoted HCC was reported to be dependent on the enhanced production interleukin 6 (IL-6) that also play roles in linking oncogenic pathways and tumor-associated immunosuppression. Our previous study demonstrated that androgen receptor (AR)/cell cycle-related kinase (CCRK) signaling can activate β-catenin which has been shown to trigger inflammation and promote immune escape in HCC. However, the role of CCRK in immunoregulation remains undefined.

Methods: The role of CCRK was determined in a carcinogen-dietary induced non-alcoholic-fatty-liver-disease (NAFLD)- and orthotopic-HCC mouse models followed by tumorigenicity and immunophenotype analysis. Mechanistic studies on the relationship of CCRK/IL-6 and myeloid-derived suppressor cell (MDSC) were determined by flow cytometry, expression/correlation analyses in co-culture system. Further studies were conducted in liver-specific CCRK-inducible transgenic (TG) mice and orthotopic HCC models using CRISPR/Cas9-mediated Ccrk depletion to determine the role of CCRK/IL-6/MDSC in tumorigenicity.

Results: Our results showed that lentivirus-mediated CCRK ablation in liver of male mice fed with high-fat-high-carbohydrate(HFHC) diet abrogated obesity-related HCC development associated with reduced polymorphonuclear (PMN)-MDSC expansion. Mechanistically, hepatoma CCRK stimulated immunosuppressive CD11b+CD33+HLA-DR− MDSC expansion through upregulating IL-6. At molecular level, CCRK activated nuclear factor-κB (NF-κB) via enhancer of zeste homologue 2 (EZH2) and facilitated NF-κB-EZH2 co-binding to IL-6 promoter. Consistently, hepatic CCRK induction in TG mice activated the EZH2/NF-κB/IL-6 cascade, leading to accumulation of PMN-MDSCs with potent T-cell suppressive-activity. In contrast, inhibiting tumorous CCRK or hepatic IL-6 increased interferon (IFN)-γ+tumour necrosis factor(TNF)-γ+CD8+T-cell infiltration and impaired tumorigenicity, which was rescued by restoring PMN-MDSCs.

Conclusion: Our results delineate an immunosuppressive mechanism of the hepatoma-intrinsic CCRK signaling and highlight an overexpressed kinase target whose inhibition might suppress hepatocellular carcinogenesis. By taking both cancer biology and tumor immunology into consideration, CCRK is an exploitable druggable target for cancer therapy.

Acknowledgements: This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (#03141376).

Project No. : 03141376

AMR-2-40

Impact of Haemostatic Sealant versus Electrocoagulation on Ovarian Reserve After Laparoscopic Ovarian Cystectomy of Ovarian Endometriomas: A Randomised Controlled Trial

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Introduction and Project Objectives: Bipolar coagulation is used for haemostasis in laparoscopic ovarian cystectomy of endometrioma, but it may damage the ovarian reserve. This study was designed to determine the effect of a haemostatic sealant, FloSeal©, compared to bipolar coagulation on the ovarian reserve after laparoscopic cystectomy for endometriomas.

Methods: This was a prospective, patient-blinded, randomised controlled trial conducted in a university-affiliated tertiary hospital. Women aged 18 to 40 years with clinical and ultrasound diagnosis of 3-8cm unilateral or bilateral endometriomas, with no previous ovarian surgery, were randomised to haemostasis by the application of haemostatic sealant, FloSeal©, or standard care. Primary outcome was the effect on the antral follicular count (AFC) 6 months after the operation as it captures the effect in the ovary subjected to treatment. Secondary outcomes included the change in anti-mullerian hormone (AMH), follicular-stimulating hormone (FSH), peak systolic velocity, normal ovarian volumes and peri-operative outcomes, including haemostasis, complications, pain and satisfaction scores. Repeated measure analysis of variance was used to analyse between the two groups.

Results: A total of 94 patients aged 32.36 ± 4.92 years underwent laparoscopic cystectomy for ovarian endometriomas. The average diameter of the endometrioma was 4.21± 1.38 cm. The increase in AFC of the affected ovaries at 6 months in the intervention group was significantly ($p=0.018$) higher than that in the control group. Repeated measures analysis of variance revealed significant effect with time ($p=<0.001$) and of interaction of group x time ($p=0.028$) for affected ovary AFC. No significant difference was noted between the two groups with regards to other the secondary outcomes.

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Conclusion: Applying FloSeal© after laparoscopic cystectomy of ovarian endometriomas produced a greater increase in AFC 6 months after surgery than the control group. FloSeal© should be considered for haemostasis during laparoscopic ovarian cystectomy in those women who wish to preserve fertility.

Project No.: 04152656

AMR-3-41

Secreted Stanniocalcin 1 Fosters Metastasis of Hepatocellular Carcinoma via the JNK Pathway

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Introduction and Project Objectives: The hypoxic microenvironment of hepatocellular carcinoma (HCC) is a key contributor to aggressive phenotypes of the tumor. Identification of functional hypoxia-responsive molecular targets is pivotal to understand the tumor biology of HCC. Stanniocalcin 1 (STC1) is a glycoprotein that acts in autocrine, paracrine and endocrine manners. It was found upregulated by hypoxia in some cancer cell lines. In this study published in Cancer Letters, we investigated the significance of secreted STC1 in HCC [1].

Methods: Clinical HCC tissue and serum samples were used to analyze the expression of STC1. Cell motility assay and Matrigel invasion assays were employed to examine the functional effects of STC1 in vitro. Effect of STC1 on metastasis in vivo was investigated by orthotopic injection model with nude mice.

Results: Hypoxia upregulated STC1 mRNA expression and induced the secretion of STC1 protein in HCC cells. Functionally, recombinant human STC1 protein (rhSTC1) enhanced cell migratory and invasive abilities in vitro. The pro-metastatic effects were abrogated by co-treatment with anti-STC1 antibody. Furthermore, silencing of STC1 in HCC cells attenuated extracellular STC1 protein secretion and suppressed lung metastasis in vivo. Mechanistically, secreted STC1 activated the JNK pathway in HCC cells by altering the expression of pJNK and p-cJun. The in vitro functional effects of rhSTC1 could be abolished by JNK inhibitor. From our clinical samples, STC1 mRNA level was upregulated in HCC tissues when compared to the paired non-tumoral liver tissues. The clinical relevance was substantiated by a higher STC1 protein level in the serum of HCC patients. Moreover, a higher serum STC1 level was associated with and worse survival outcome.

Conclusion: Our findings illustrated that secreted STC1 promotes metastasis of HCC through JNK signaling. STC1 is a potential prognostic biomarker and a therapeutic target for HCC.

1. Chan KK, et al…& Lo RC. Secretory Stanniocalcin 1 promotes metastasis of hepatocellular carcinoma through activation of JNK signaling pathway. Cancer Lett. 2017 Sep 10;403:330-338.

Project No.: 03142766

AMR-4-47

Clinical Application of Enumeration and Genomic Characterization for Non-invasive Detection and Real-time Monitoring of Circulating Tumor Cells for Esophageal Carcinoma

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Introduction: Esophageal squamous cell carcinoma (ESCC) is deadly cancer with its highest incidence worldwide amongst Chinese. Despite current upfront chemoradiotherapy (CRT) plus surgical approaches, ESCC patient survival rates are dismal. There is still a need for early predictive markers to track treatment responses. Advances in enrichment and identification of circulating tumor cells (CTCs), which can escape from both primary and metastatic tumors into the blood of cancer patients, allows real-time monitoring of CTC levels at diagnosis/during/after treatment to assess treatment efficacy.

Project Objectives: • Determine the clinical usefulness of non-invasive real-time monitoring of CTCs in ESCC patients during treatment in comparison to current CT/PET imaging • Utilize next-generation sequencing (NGS) targeted gene sequencing to examine genetic changes before/during/after treatment to identify useful biomarkers for metastasis and drug resistance

Identification of key driver genes for metastasis and druggable targets from CTC analysis is expected to improve diagnosis and targeted treatment of metastatic ESCC and improve patient precision care. We investigated the prognostication and risk stratification role of liquid biopsy serial monitoring for ESCC.

Methods: CTCs and plasma cell-free DNA (cfDNA) were isolated from 199 blood samples of 103 advanced ESCC patients treated by CT or CRT/surgery at serial treatment timepoints. CTCs were isolated using size separation on microfluidic chips and enumeration by immunofluorescent staining with antibody cocktails of CD45/EpCAM/CK/MUC1. Kaplan Meier curve, log-rank test, and COX regression analysis were used for statistical analysis of disease relapse and survival.

Results: In 57 ESCC patients receiving palliative CT, high CTC counts at CT pre-cycle III is independently associated with

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response at interim reassessment and progression-free survival (PFS) in multivariate COX analysis. Integration of changes of both baseline pre-cycle III CTC and cfDNA into four risk groups based on the number of favorable/unfavorable changes of CTC/cfDNA, were independently associated with overall survival (OS) by multivariate COX analysis. In 43 loco-regionally advanced ESCC treated by CRT/surgery, high CTC counts at end of CRT/pre-operation significantly associated with early-progression at 10-month PFS.

Conclusion: CTC counts at pre-cycle III and combined changes of CTC/cfDNA are independent prognostic markers for ESCC patients receiving palliative CT. CTC counts at post CRT is predictive for early disease progression for CRT/surgery-treated ESCC patients.

Implications: Longitudinal liquid biopsy serial monitoring provides complementary information for prediction/prognosis for CT responses in advanced ESCC. The CTC/cfDNA blood-based diagnostics have potential clinical utility for non-invasive monitoring of minimal disease burden to better guide clinical treatment.

Project No.: 05160926

AMR-5-59

Translating Functional Tumour Volume and Biology of Peritoneal Carcinomatosis to Identify Suitable Candidate for Cytoreductive Surgery in Ovarian Carcinoma

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Introduction and Project Objectives: In ovarian carcinoma (OC), cytoreductive surgery (CRS) is the primary treatment strategy; however, peritoneal carcinomatosis (PC) may prevent complete CRS. PC burden is quantified using the surgical peritoneal cancer index (sPCI) determined by laparotomy or laparoscopy and is correlated with reduced likelihood of achieving complete CRS. One disadvantage of sPCI is the invasive nature. Diffusion-weighted imaging (DWI) is a functional magnetic resonance imaging (MRI) sequence which has been shown to improve OC tumour characterisation and PC detection [1]. DWI is quantified with apparent diffusion coefficient (ADC) which reflects tumour cellularity and aggressiveness. Previous work has shown that a semi-automated quantification method based on ADC could accurately demarcate functional tumour volumes [2]; this could aid in quantifying PC burden and thus predicting the likelihood of achieving complete CRS. The objectives of our study were: (1) to develop a non-invasive method of assessing PC burden; and (2) to evaluate its predictive value in determining incomplete tumour debulking in patients with advanced or recurrent OC.

Methods: Patients with advanced (International Federation of Gynecology and Obstetrics [FIGO] stage III/IV) or recurrent OC were recruited for DWI prior to surgery. Clinicopathological factors including age, FIGO stage, and pre-surgical serum cancer antigen (CA125) levels were also collected. PC lesions were semi-automatically segmented with a clustering algorithm on DWI which retained voxels associated with solid tumour components. Functional peritoneal cancer index (fPCI) is based on the segmentation results of tumour volume in 13 abdominopelvic regions with additional points given to the involvement of critical sites. The ADC values of the largest PC lesion of each patient were also recorded. fPCI was then correlated with sPCI and surgical complexity and was also assessed on its ability to predict incomplete CRS.

Results: Fifty-three patients (mean age: 56.1 years) were prospectively recruited. Complete CRS was achieved in 38 patients. Significant correlations were found between fPCI and sPCI ($r > 0.757$, $p < 0.001$). fPCI was found to be correlated with surgical complexity scores ($p = 0.043$), and that patients who achieved CRS had significantly lower fPCI compared to patients with incomplete debulking ($p < 0.001$). A predictive model combining fPCI, ADC, and FIGO stage achieved an AUC of 0.947 in predicting incomplete CRS.

Conclusion: fPCI, a non-invasive DWI-based scoring system, offers a semi-automated method of quantifying PC burden. Furthermore, a predictive model including fPCI, ADC, and FIGO could predict the likelihood of incomplete CRS with high accuracy.

Project No.: 03143616

AMR-6-69

A Comprehensive Study on the Effects of Antioxidant Supplements in Liver Cancer Development and Treatment

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Introduction and Project Objectives: Controversy over the benefits of antioxidants supplements in cancers persists for long. Using hepatocellular carcinoma (HCC) as a model, we investigated the effects of exogenous antioxidants N-acetylcysteine (NAC) and glutathione (GSH) on tumor initiation and growth.

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Methods: Multiple mouse models, including diethylnitrosamine (DEN)-induced and Trp53KO/C-MycOE-induced HCC models, mouse hepatoma cell and human HCC cell xenograft models with subcutaneous or orthotopic injection were used. In vitro assays including ROS assay, colony formation, sphere formation, proliferation, migration and invasion, apoptosis, cell cycle assays were conducted. Western blot was performed for protein expression and RNA-sequencing to identify potential gene targets.

Results: In these multiple different mouse and cell line models, we observed that NAC and GSH promoted HCC tumor initiation and growth, accompanied with significant reduction of intracellular reactive oxygen species (ROS) levels. Moreover, NAC and GSH promoted cancer stemness, and abrogated the tumor-suppressive effects of Sorafenib both in vitro and in vivo. Exogenous supplementation of NAC or GSH reduced the expression of NRF2 and GCLC, suggesting the NRF2/GCLC-related antioxidant production pathway might be desensitized. Using transcriptomic analysis to identify potential gene targets, we found that TMBIM1 was significantly upregulated upon NAC and GSH treatment. Both TCGA and in-house RNA-sequence databases showed that TMBIM1 was overexpressed in HCC tumors. Stable knockdown of TMBIM1 increased the intracellular ROS; it also abolished the promoting effects of the antioxidants in HCC cells. On the other hand, BSO and SSA, inhibitors targeting NAC and GSH metabolism respectively, partially abrogated the pro-oncogenic effects induced by NAC and GSH in vitro and in vivo.

Conclusion: Our data implicate that exogenous antioxidants NAC and GSH, by reducing the intracellular ROS levels and inducing TMBIM expression, promoted HCC initiation and tumor growth, and counteracted the therapeutic effect of Sorafenib. Our study provides scientific insight regarding the use of exogenous antioxidant supplements in cancers.

Project No.: 04152336

AMR-7-97

Characterization of Anti-CCL28 as a Novel Therapy to Overcome Sorafenib Resistance in HCC

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Introduction and Project Objectives: Sorafenib is the first molecular drug approved for and remains as an alternative first-line drug treatment advanced hepatocellular carcinoma (HCC). However, the efficacy of sorafenib treatment is only modest. Therefore, there is need to investigate the key mechanisms by which sorafenib resistance develops in HCC patients. Here, we aimed to provide experimental evidence that targeting chemokine (C-C motif) ligand 28 (CCL28) is an efficient therapeutic approach in sorafenib-resistant (SR) HCC.

Methods: Transcriptome sequencing was performed in 41 cases of HKU-QMH patient cohorts and TCGA database was also applied to examine the top upregulated members of cytokines family. The mRNA expression of CCL28 was further validated in human HCCs by real-time PCR. Expression changes of CCL28, HIF-1α and HIF-1α target genes upon hypoxic or sorafenib treatments were assessed by real-time PCR, ELIZA, or Western Blotting. The resistance to sorafenib in HCC cells was examined by annexin-V apoptosis assay. Regulatory T (Treg) cell infiltration was assessed using migration chambers and by flow-cytometric analysis. Orthotopic liver xenograft model in nude mice was used to investigate the efficacy of combination treatment of sorafenib and anti-CCL28 antibody in HCC.

Results: Here we report that CCL28 was the top three most upregulated cytokines in HCC in HKU-QMH cohorts and TCGA. It was overexpressed in human HCCs and its upregulation was correlated with a metastatic phenotype in HKU-QMH clinical cohort. CCL28 expression was significantly induced upon hypoxic treatment (1% O2) in HCC cells and was dramatically attenuated upon HIF-1α knockdown or digoxin treatment. Sorafenib treatment upregulated CCL28 expression in HCC cells and CCL28 overexpression was also seen in the SR HCC cells. In SR HCC cells, we observed that HIF-1α target genes, such as CA9, LOX, VEGF, and CCL28, were significantly upregulated upon sorafenib treatment as compared to the corresponding mock control. However, our results did not support that CCL28 induced Treg cell infiltration in HCC both in vitro and in vivo. Of note, combination treatment with sorafenib and anti-CCL28 neutralizing antibody showed significant tumor regression in orthotopic liver xenograft model in nude mice.

Conclusion: CCL28 may play a role in tumor progression and sorafenib resistance in HCC, likely via a non-Treg cell regulatory pathway, and HIF-1α is a major determinant of CCL28 expression in SR HCC cells. Combination treatment with sorafenib and anti-CCL28 neutralizing antibody may act a novel and efficient therapeutic approach in HCC.

Project No.: 03142966

AMR-8-131

Intestinal Organoid Cultures of Early Onset Colorectal Cancer in Hong Kong

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Abstracts for Poster Presentation: Advanced Medical Research

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Introduction and Project Objectives: The incidence of sporadic early-onset colorectal cancer (EOCRC) has been increasing worldwide, and has been especially high in Hong Kong for over three decades. However, the underlying pathogenic mechanism remains poorly understood due to the lack of a comprehensive study to delineate the molecular alterations, as well as a representative cell model for biological studies. Aims and Objectives: We aimed to generate a living biobank of CRC with paired normal, particularly for sporadic EOCRC, and to document the key drivers in this cohort and the maintenance of genomic stability over long-term culture.

Methods: We established organoids from colectomy samples, with priority given to young CRC patients (≤50). Organoid and frozen tissue genomic profiles were studied in parallel. We also continuously cultured 10 paired tumour-normal organoids in vitro for 6 months and evaluated the changes in genomic profile. Methods: DNA and RNA were extracted from organoids and frozen tissues for whole-exome sequencing (WES) and RNA sequencing. Somatic variants were identified and compared between organoid and frozen tissues, early and late passage organoids.

Results: We established an organoid biobank from 20 CRC patients, with 11 being sporadic EOCRC. This biobank captured tumours evolved from both the conventional adenoma carcinoma sequence and the serrated neoplasia pathway. Five tumour organoids derived from 2 patients carried a PTPRK-RSPO3 fusion, representing the first in vitro 3D cell model of its kind. After long-term culture, the number of variants, their mutant allelic fractions and inferred copy number alterations were well preserved in tumour organoids. However, we observed clonal dominance in normal organoids.

Conclusion: We established a CRC biobank with distinct clinical features and genomic profiles. Heterogeneous tumour organoids are genomically stable, while subclones in normal organoids evolved and dominated during long-term cultures. **Implications:** This biobank is a valuable resource for biological studies and drug sensitivity screening.

Publications: The results of this study were included in a paper published in GUT: Yan HHN, Siu HC, Ho SL, Yue SSK, Gao Y, Tsui WY, Chan D, Chan AS, Wong JWH, Man AHY, Lee BCH, Chan ASY, Chan AKW, Hui HS, Cheung AKL, Law WL, Lo OSH, Yuen ST, Clevers H, Leung SY. Organoid cultures of early-onset colorectal cancers reveal distinct and rare genetic profiles. Gut Epub ahead of print: [26 March 2020]. doi:10.1136/gutjnl-2019-320019. The publication is available at BMJ journal through http://dx.doi.org/10.1136/gutjnl-2019-320019.

Project No.: 02132886

AMR-9-141

MiR-199a-3p as a Key Target in Stemness and Chemoresistance in Ascitic Ovarian Cancer Cells

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Introduction and Project Objectives: Overcoming drug resistance is an inevitable challenge to the successful treatment of cancer. The functional role of abiotic factors in tumor progression is becoming increasingly clear.

Method and Results: Here, we show that ascitic fluid-induced shear stress in conjunction with growth factors in the tumor microenvironment endow ovarian cancer cells with stem-like and drug resistant properties. Notably, among several microenvironmental factors tested, hepatocyte growth factor (HGF), which is abundantly present in the ascites, significantly downregulated miR-199a-3p in a similar pathway as shear stress through transcriptional downregulation of primary miR-199a-1, but not miR-199a-2, through a c-Met/PI3K/Akt signaling pathway through a positive feedback loop. This is accompanied with a decrease in miR-199a-3p expression and upregulation of stemness CD44, ALDH3 and chemoresistance markers ABCG2 and P-gp. Low expression miR-199a-3p expression and Akt activation were associated with platinum resistance of ovarian cancer and confer poorer progression-free survival. miR-199a-3p mimic significantly suppressed ovarian tumor metastasis and its ectopic expression in combination with cisplatin or paclitaxel further decreased the peritoneal dissemination of ovarian cancer in vivo. Our results also confirmed successful miR-199a-3p overexpression and its downstream effectors including a reduction of Oct4, CD44 and as well as ABCG2 and P-gp expression.

Conclusion: Together, these findings unveil the regulation of miR-199a-3p under ascitic shear flow and highlight its importance in ovarian cancer chemoresistance. The novel approach using miR-199a-3p mimic may serve as an effective therapeutic option to resensitize ovarian tumor cells to standard chemotherapy.

Project No.: 05163536

Abstracts for Poster Presentation: Advanced Medical Research

AMR-10-165

The Role of Regulatory B Cells (Bregs) in Tumor Recurrence after Liver Transplantation for Liver Cancer Patients

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Introduction: Liver transplantation (LT) is the only promising treatment option for selected patients with hepatocellular carcinoma (HCC). However, tumor recurrence after LT remains a critical issue. Regulatory B cells (Bregs) promote cancer recurrence in various human cancers. Early graft injury may recruit lymphocytes to promote tumor recurrence after liver transplantation.

Project Objective: We aimed to investigate the role of regulatory B cells (Bregs) in tumor recurrence after liver transplantation and further to explore the underlying mechanisms through a series of clinical association study, in vitro functional experiments and animal models.

Methods: The association among graft injury, Bregs and tumor recurrence was evaluated both in clinical cohort and rat LT models. The role of CXCL10/CXCR3 signaling in Breg mobilization was further studied in CXCL10-/- and CXCR3-/- mice model simulating post-transplantation liver graft injury (hepatic ischemia/ reperfusion (IR) followed by major hepatectomy).

Results: Clinically, the percentage of circulating Bregs in recipients with graft weight ratio (GWR)<60% was higher compared to the recipients with GWR≥60% after LT. Recipients with high percentage of circulating Bregs on day 7 after LT showed a higher incidence of tumor recurrence (recurrence vs. non-recurrence, 0.62±0.08 vs. 0.34±0.02% of PBMCs, $p<0.05$). The association among liver graft injury, Bregs mobilization and tumor recurrence was further confirmed in rat LT models. Functional study demonstrated that Bregs induced tumor recurrence by promoting HCC proliferation and invasion through NF-κB/MMPs signaling pathway. And mobilization and recruitment of Bregs was CXCL10/CXCR3 signaling dependent.

Conclusion: CXCL10/CXCR3 signaling during liver graft injury mobilized circulatory Bregs to promote tumor recurrence after liver transplantation. Circulatory Bregs may serve as a novel marker to predict and monitor cancer recurrence in the scenario of liver transplantation for liver cancer patients.

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Authors: Yan Shao, Xiao Bing Liu, Chung Mau Lo,, Xiang Qi, Jiang Liu, Chang Xian Li, Chang Chun Ling, Wai Ho Yeung, Hui Liu, Yuen Yuen Ma, Kevin Tak-Pan Ng, Kwan Man*

Project No.: 03143336

AMR-11-201

Targeting Human Papillomavirus (HPV) Negative Cervical Cancer

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Introduction and Project Objectives: While the great majority of cervical cancer is associated with persistent infection by oncogenic human papillomavirus (HPV), a small fraction of HPV negative cervical cancer is consistently identified, and little is known about their oncogenesis mechanism. Previous genomic studies suggested most HPV negative cervical cancer carry mutations in the gene ARID1A encoding one of the components of the SWI/SNF chromatin remodeling complex. Many drugs targeting ARID1A are under development as ARID1A mutations are common in many malignancies. This study aims to examine the hypothesis that most HPV negative cervical cancer are genetically associated with mutated SWI/SNF complex components; and to explore the utility of ARID1A targeting agents in treating HPV negative cervical cancer.

Methods: DNA was extracted from paraffin fixed formalin embedded (FFPE) and frozen archival cervical cancer tissues and tested with a sensitive HPV line blot assay INNO-LiPA. Immunohistochemical staining of ARID1A was performed on the FFPE tissues. Targeted sequencing was performed on 36 samples consisting of 24 HPV positive and 12 HPV negative samples. Indels in the coding sequences of SWI/SNF complex genes and PI3K-Akt signalling genes were examined. Efficacy of GSK126 and MK2206 on suppressing growth of HPV negative cervical cancer cell model C33A and HPV positive cell model HeLa, SiHa, and CaSki was assessed in 3D culture and nude mice xenograft models.

Results: The overall survival of HPV negative cancer patients was shorter than that of HPV positive cancer patients, although statistical significance was not reached. ARID1A protein expression was not significantly different in HPV positive and HPV negative tumours. This is consistent with the finding in targeted sequencing that in our cohort, ARID1A mutations were not common. Instead, ARID1B and BCL1111B were the most commonly mutated SWI/SNF complex genes in HPV negative tumours. GSK126 could effectively suppress the growth of C33A and HeLa spheroids, but not SiHa and CaSki spheroids. Similarly, GSK126 could inhibit the growth of C33A and HeLa xenograft.

Conclusion: Our results suggest that ARID1A is not always commonly mutated in HPV negative cervical cancer.

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Nevertheless, the SWI/SNF complex is still likely dysfunctional and can be targeted using EZH2 methyltransferase inhibitors such as GSK126. GSK126 is a promising candidate for treating HPV negative cervical cancer.

Project No.: 05162176

AMR-12-202

p21-activated Kinase 4 in Ovarian Cancer Chemoresistance

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Introduction: p21-activated kinase 4 (PAK4) is an oncogenic serine/threonine kinase associated with chemoresistance in ovarian cancer. As a nucleo-cytoplasmic shuttling protein, nuclear PAK4 is known to facilitate gene transactivation in cancer cells. Concerted EGFR-PAK4 signaling is important for ovarian cancer cell growth and EGFR activation promotes nuclear localization of PAK4.

Project Objectives: This study aims to elucidate the mechanism of PAK4-mediated chemoresistance in ovarian cancer through gene transcription; and to explore the possibility of enhancing the anti-tumour efficacy of chemotherapy and EGFR inhibitors by targeting PAK4.

Methods: Ovarian cancer cell lines A2780s and SKOV3 stably expressing PAK4-WT (Wild type PAK4) or PAK4-ΔNLS1 (nuclear localization signal mutant PAK4) were established. The transcriptomes of SKOV3-PAK4-WT and SKOV3-PAK4-ΔNLS1 were compared by microarray analysis using an Affymetrix Genechip. MTT assay was performed to generate dose-response curves of a PAK4 inhibitor PF-3758309 in combination with cisplatin or gefitinib in ovarian cancer cell lines OVCAR3 and TUOS3. Expression and phosphorylation status of group II PAKs members and ErbB family members before and after drug treatment were profiled by western blotting in OVCAR3 and TUOS3. Apoptosis was evaluated by cell cycle analysis with PI staining. Anti-tumourigenic effects of the drug combinations in vivo was evaluated using cell line and patient-derived xenografts.

Results: Expression of nuclear PAK4 led to significant downregulation of genes involved in DNA damage repair. BAG2 was found to be a downstream target of nuclear PAK4 to reduce chemosensitivity in ovarian cancer cells. Inhibition of PAK4 by PF-3758309 enhanced the anti-tumoural effect of cisplatin and EGFR inhibitor gefitinib in both cell line and patient-derived xenograft models.

Conclusion: PAK4 contributes to chemoresistance through transcriptional regulation of BAG2 in ovarian cancer. Targeting PAK4 in ovarian cancer may enhance the anti-tumourigenic effect promoted by cisplatin and EGFR inhibitors.

Project No.: 03143006

AMR-13-221

Targeting Stearoyl-CoA Desaturase-1 (SCD1) in Combination with Sorafenib for the Treatment of Hepatocellular Carcinoma

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Introduction and Project Objectives: We investigated the functional role and clinical significance of Stearoyl CoA desaturase-1 (SCD1) mediated endoplasmic reticulum (ER) stress in regulation of liver tumor-initiating cells (T-ICs) and sorafenib resistance, aiming to develop a novel therapeutic strategy against hepatocellular carcinomas (HCCs).

Methods: We evaluated the clinic-pathological relevance of SCD1 and its correlation with sorafenib resistance in large cohorts of HCC clinical samples by qPCR and immunohistochemical analyses. Lentiviral-based overexpression and knockdown approaches were performed to characterize functional roles of SCD1 in regulation of liver T-ICs and sorafenib resistance. Molecular pathways mediating the phenotypic alterations was identified through RNA sequencing analysis and functional rescue experiments. The combinatorial effect of SCD1 inhibitor and sorafenib was tested using our patient-derived tumour xenograft (PDTX) model.

Results: SCD1 overexpression was found in HCC which was associated with shorter disease free survival. SCD1 was found to regulate the populations of liver T-ICs; while its suppression by SCD1 inhibitor suppressed liver T-ICs and sorafenib resistance. Interestingly, SCD1 was markedly upregulated in our established sorafenib-resistant PDTXs, and its overexpression predicts the clinical response of HCC patients to sorafenib treatment. Suppression of SCD1 forces liver T-ICs to differentiate via ER stress induced unfolded protein response (UPR), resulting in their enhanced sensitivity to sorefenib. Using a patient-derived xenograft model (PDTX#1), we found that a novel SCD1 inhibitor (SSI-4) demonstrated maximal growth suppressive effect when combined with sorafenib treatment.

Conclusion: SCD1 mediated ER stress regulates liver T-ICs and sorafenib sensitivity. Targeting SCD1 alone or in combination with sorafenib might be a novel personalized medicine against HCC.

Project No.: 03142736

Abstracts for Poster Presentation: Advanced Medical Research

AMR-14-222

Interleukin-1 Receptor Associated Kinase 1 (IRAK1) is a Target that Drives Liver Tumor Initiating Cells and Sorafenib Resistance in Hepatocellular Carcinoma

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Introduction and Project Objectives: Frequent relapse and drug resistance can be attributed to the existence of tumor-initiating cells (T-ICs) within the tumor bulk. From transcriptome sequencing of 16 pairs of clinical HCC samples, we found that Interleukin-1 receptor-associated kinase 1 (IRAK1) in the TLR/IRAK pathway was significantly upregulated in hepatocellular carcinoma (HCC). In this study, we aim to characterize and delineate the regulatory mechanism of IRAK1 on liver T-ICs, evaluate the correlation of IRAK1 expression with liver T-IC markers and sorafenib resistance in human HCC, and ultimately evaluate the therapeutic efficacy of IRAK1/4 inhibitor in combination with sorafenib in the treatment of HCC.

Methods: In this study, we evaluated the clinic-pathological relevance of IRAK1 in large cohorts of HCC clinical samples by qPCR, western blot and immunohistochemical analyses. Lentiviral-based overexpression and knockdown approaches were performed to characterize functional roles of IRAK1 in regulation of liver T-ICs including self-renewal, tumorigenicity, chemoresistance, drug resistance to sorafenib, migration and expression of liver CSC markers and sorafenib resistance. Molecular pathways mediating the phenotypic alterations was identified through RNA sequencing analysis and functional rescue experiments. Lastly, the combinatorial effect of IRAK1/4 inhibitor and sorafenib was tested using HCC xenograft models.

Results: IRAK1 overexpression was observed in HCC at the mRNA and protein levels and correlated with advanced tumor stages and poor patents survival. Interestingly, IRAK4, an upstream regulator of IRAK1, was also found to be consistently upregulated. We demonstrated that IRAK1 regulates liver T-IC properties, including self-renewal, tumorigenicity and liver T-IC marker expression. IRAK1 inhibition sensitized the HCC cells to doxorubicin and sorafenib treatment in vitro through the suppression of the apoptotic cascade. Pharmacological inhibition of IRAK1 with a specific IRAK1/4 kinase inhibitor consistently suppressed liver T-IC populations. Through RNA sequencing analysis by comparing gene expression profiles between IRAK1-knockdown and control cells, we identified Aldo-Keto Reductase Family 1 Member 10 (AKR1B10) as a novel downstream target of IRAK1. Clinically, AKR1B10 was found to be overexpressed in HCC, which was significantly correlated with IRAK1 expression. Functional analysis demonstrated that knockdown of AKR1B10 negated the IRAK1-induced T-IC functions via modulation of the AP-1 complex. Using an HCC xenograft model, we found that an IRAK1/4 inhibitor in combination with sorafenib synergistically suppressed the tumor growth.

Conclusion: Our data suggests that targeting the IRAK4/IRAK1/AP-1/AKR1B10 signaling pathway may be a potential therapeutic strategy against HCC.

Project No.: 04150266

AMR-15-48

Early Growth Genetics and Cardiometabolic Risk in Chinese Adolescents

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Introduction and Project Objectives: Accumulating evidence suggested a genetic link between prenatal growth and cardiometabolic diseases later in life. This study aims to: 1) discover novel common genetic variants associated with birthweight (a proxy for measuring prenatal growth) in Chinese adolescents and also in multiple cohorts of Chinese population; 2) explore the long-term influence of birthweight-related variants on cardiometabolic traits measured during adolescence.

Methods: In the discovery stage, we performed genome-wide association study (GWAS) in 3,772 Chinese-ancestry individuals from four independent sources: a) 1872 adolescents from a community-based school survey for risk factor assessment; b) 915 children from the Hyperglycaemia and Adverse Pregnancy Outcomes study at the Hong Kong centre; c) 452 adults from hospital staff and a territory-wide health screening program; and d) 533 related individuals from the Hong Kong Family Diabetes Study. Within each cohort, around 4.8 million high-quality SNPs were tested for the association with birthweight using either a linear regression or a linear mixed model, with adjustments for gender, gestational age (if available) and principal components (PCs). Results of individual studies were combined by meta-analysis under a fixed-effects model. Samples for in silico replication were taken from the published trans-ancestry meta-analysis of birthweight in up to 321,223 individuals, contributed by the EGG Consortium. We tested the association between our top hits for birthweight and cardiometabolic traits (including the obesity traits, fasting glucose and insulin levels, HOMA-IR, HOMA-β, blood pressure, lipid profiles and albumin-creatinine ratio) in the cohort of adolescents using a linear regression with adjustments for PCs,

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sex, age, and/or body mass index.

Results: In the GWAS for birthweight, we have identified 15 suggestive loci for birthweight in adolescents using a standard threshold of P<10^-5; but none was previously reported and was replicated in independent cohorts. In the meta-analysis of GWAS using multiple Chinese cohorts, a total of 20 distinct genomic regions were prioritized (P<1×10^-5), including a reported locus GCK and 19 suggestive novel loci. Using the data contributed by the EGG Consortium, we observed replication of associations for two signals located at GCK (P=4.5×10^-3) and DLGAP2 (P=5.0×10^-3) loci. Moreover, the birthweight-lowering allele of the GCK variants was significantly associated with higher fasting glucose level measured during adolescence (1.1×10^-4 < P < 3.5×10^-3).

Conclusion: We have identified novel associations between the fetal glucose-raising alleles at GCK loci and reduced birthweight in Chinese population. This study demonstrated evidence of shared genetic determinants between early growth phenotype and cardiometabolic risk factors.

Project No.: 05161386

AMR-16-54
Evaluating the Clinical Utility of Genome Sequencing for Cytogenetically Balanced Chromosomal Abnormalities in Prenatal Diagnosis

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Introduction and Project Objectives: Balanced chromosomal abnormalities (BCAs) are changes in the localization or orientation of a chromosomal segment without visible gain or loss of genetic material. BCAs occur at a frequency of 1 in 500 newborns and are associated with an increased risk of multiple congenital anomalies and/or neurodevelopmental disorders, especially if it is a de novo mutation. As GS sequencing cost continues to be reduced, it is foreseeable that GS will become more affordable for clinical use in the near future. In order to judge the feasibility and clinical utility of GS in the evaluation of BCAs, the clinical implications will be examined.

Methods: In this pilot project, we used short read genome sequencing (GS) to retrospectively re-sequence ten prenatal subjects with de novo BCAs and compared the performance of GS with the original karyotyping. To detect all chromosomal abnormalities, including cryptic genomic imbalances, GS data were analyzed by in-house bioinformatics pipeline customized for structural variants (SV) and copy number variants (CNV) detection.

Results: GS characterized all BCAs found by conventional karyotyping with the added benefit of precise sub-band delineation. In nine out of ten cases in this study (90%), the conventional karyotype results were revised by at least one sub-band. By identifying BCA breakpoints at the nucleotide level using GS, we found disruption of OMIM genes in three cases and identified cryptic gain/loss at the breakpoints in two cases. Of these five cases, four cases reached a definitive genetic diagnosis and were classified as pathogenic under the ACMG pathogenicity framework while the other one case had a BCA interpreted as unknown clinical significance. The additional information gained from GS can change the interpretation of the BCAs and has the potential to improve the genetic counselling and perinatal management by providing a more specific genetic diagnosis.

Conclusion: To conclude, the findings from this study demonstrated the advantages of GS over conventional karyotyping on the detection of BCAs. GS allows the precise detection of BCA breakpoints and cryptic genomic imbalances surrounding the regions of BCAs. This results in better evaluation on the risk of congenital anomalies in BCA on a case-by-case basis.

Project No.: 05162986

AMR-17-93
Genetic Study of the SNARE Gene Family in Hong Kong Chinese with Bipolar Disorder

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Introduction and Project Objectives: Bipolar disorder is a mood disorder with extreme mood swings previously known as "manic-depression". It was estimated to be 2.5% among Hong Kong's general population. The hereditability is estimated to be 80%–85%.3 Genetic research has the power to explain significant aspects of mental illness by identifying genetic factors that can explain substantial components in the variation of human behavior. SNARE complex proteins are necessary for

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vesicular neurotransmission and could be an important class of proteins associated with susceptibility to bipolar disorder. This project aims to study the association of genetic variants that associate with the susceptibility of bipolar disorder in Hong Kong Chinese patients with a special focus on SNARE genes and their interaction partners.

Methods: We used firstly a candidate gene targeted deep resequencing approach (N=30) to examine potential damaging mutations in SNARE complex and associated proteins. Then we use a bigger sample with the rest of our subjects for genotyping analyses. Our target is a group of BPD patients of Han Chinese ethnicity in Hong Kong (a total of 628 subjects, including BPD, some other psychiatric patients and healthy controls).

Results: We found a risk allele of LONRF1 (LON peptidase N-terminal domain and ring finger 1) that associated with BPD. Regarding dominant model, two SNPs in LONRF1 gene rs12678448 and rs3802268 were found to be associated with psychiatric disorders. Besides LONRF1, several genes with potentially damaging risk alleles are — USO1, UNC13B, STX2 and SNAP29. Two genes were found to have potentially damaging Insertion/Deletion mutations NAPA and PI4KA. SCFD1 gene has a potential splicing mutation.

Conclusion: In summary these SNARE related genes that associated with BPD could be targets for novel drug therapy. The finding of circadian rhythm gene polymorphism in LONRF1 may imply that some subjects having a particular variant may benefit more than others by light therapy which has been shown to be effective in some cases of bipolar disorder.

Project No.: 03144526

AMR-18-147

Whole Genome Sequencing Analysis of Genetically Undiagnosed Euploid Fetuses with Increased Nuchal Translucency

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Introduction: Increased nuchal translucency (NT) detected during the first trimester is a well-known and widely accepted marker for chromosomal aneuploidies or genomic disorders. The risk of having major fetal anomalies, miscarriage, and fetal death increases markedly in relation to the thickness. Chromosomal microarray studies revealed that ~8% of these fetuses carry pathogenic copy number variants (CNVs). However, the genetic etiologies yet to be discovered may be diverse in terms of genes and variant types. A holistic and comprehensive approach to uncover CNVs, single nucleotide variants (SNVs), structural variants (SVs) is imperative for the investigation of this patient group.

Project Objectives: In this study we propose to (i) study the genome wide spectrum and frequency of genetic variants and spatial genomic organization during early fetal development, (ii) investigate the variability of genomic variants associating with the increased NT related birth defects, (iii) discuss the feasibility of application of WGS in the prenatal setting.

Methods: Fetuses with increased nuchal translucency (>3.5mm) with structural abnormalities previously undiagnosed by karyotype and chromosomal microarray were recruited for whole genome sequencing at >100X depth to detect SNVs, indels, structural variations (including inversions, translocations), noncoding variants, and mosaicisms. Results were integrated for interpretation in accordance with the guidelines of the American College of Medical Genetics and Genomics. Pathogenic or likely pathogenic (P/LP) variants were selected for molecular validation.

Results: Overall, 15 trios were enrolled in this study, including ten cases with isolated increased NT and five cases with additional structural malformations. Whole Genome sequencing detected additional diagnostic findings in 5 trios (33%), including four cases with P/LP single-nucleotide variants in the genes COL2A1, ANKRD11, ARMC4, GATA4, and one mosaic (40%) turner syndrome. In one fetus, a cryptic complex structural rearrangement was detected which involved a 150.1kb insertion seq[hg19]ins(2;12)(q33.2;q24.31). The insertion segment was divided into 11 sub segments, of which five were inserted to chromosome 2q33.2. This complex rearrangement disrupted the BMPR2 gene and could be associated with Primary Pulmonary Hypertension and/or Venoocclusive Disease 1.

Conclusion: Our study demonstrates high read-depth genome sequencing can facilitate diagnosis of euploid fetuses with increased nuchal translucency. The diagnostic findings across different mutation types detected by genome sequencing were important for clinical management and decision making. GS could be suggested to be a more comprehensive prenatal genetic test. Recently, we have implemented genome sequencing in prenatal care in Hong Kong to bridge the gap between clinical phenotypes and underlying undiagnosed genetic etiologies.

Project No.: 04152666

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AMR-19-166

Oligodendrocyte Pathology in Ataxia-Telangiectasia - The Cellular Basis of Myelin Abnormality in a Rare Genetic Disease

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Introduction and Project Objectives: The early loss of myelination in the cerebral cortex is a common pathology in the aging brain. In rare diseases with distinct genetic deficits in DNA double strand breaks repairs, Ataxia Telangiectasia (A-T), premature myelin loss was commonly observed. We hypothesized that the compromised DNA repair in the oligodendrocyte (OL) lineage may be associated with age-related myelin loss. To investigate if DSB repair mediated by A-T mutated protein (ATM) is critical to myelination, we compared the histopathology of OLs in the human A-T brain tissues.

Methods: The post-mortem human frontal cortex and cerebellar cortex specimens of normal control (n = 18, mean age =18.5 years), A-T (n = 10, mean age = 26.2 years) were obtained from NeuroBioBank, National Institute of Health. The genomic mutations in each A-T case were confirmed by TruSight Inherited Disease Sequencing Panel on an Illumina platform. The histological changes of OL lineage and their DNA damage burden were examined by immunohistochemistry with the corresponding gene expression profiled by an array of real-time polymerase chain reaction analysis. The pathological data were collated with the targeted genomic sequencing analysis followed by in silico modelling.

Results: Consistent with clinical ataxia, immunohistochemistry revealed a significant reduction of OLs in the cerebellar cortex, but not frontal cortex, of A-T tissues. Such cerebellar OL degeneration was strongly associated with frameshift ATM mutations but appeared to be independent of neuronal loss. Importantly, our structural analysis, three-dimensional modelling and docking experiments of the mutant ATM proteins in silico indicated that key OL-specific proteins MBP and MyRF are putative substrate of ATM kinase activity. Particularly, when the ATM structure is prematurely terminated at the spiral/pincer regions (1-1892 aa), these putative interactions are compromised and likely to related to the different severity of OL loss in A-T patients.

Conclusion: Our findings suggested that the cerebellar but not cortical OL population in the A-T brain. While such regional specificity warrants further investigations, this study suggested that the vulnerability of OL to ATM dysfunction may be the cellular basis of myelin loss in A-T and the aging brain.

Project No.: 04151436

AMR-20-174

Diagnostic Value of Whole Exome Sequencing in Chinese Patients with Rare Pediatric Onset Neuromuscular Diseases Having Diagnostic Challenges

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Introduction and Project Objectives: Neuromuscular disorders (NMDs) comprise a group of rare heterogeneous genetic diseases with a broad spectrum of overlapping clinical presentations that makes diagnosis challenging. Notably, the recent introduction of whole-exome sequencing (WES) is introducing rapid changes on the genetic diagnosis of NMDs. We aimed to investigate the diagnostic value of WES for rare pediatric-onset NMDs.

Methods: We applied integrated diagnostic approach and performed WES in 50 Chinese subjects (30 males, 20 females) with undiagnosed pediatric-onset NMDs despite previous comprehensive diagnostic tests. The patients were categorized in four subgroups according to phenotyping and investigation findings. Variants on NMDs gene list and open exome analysis for those with initial negative findings were identified.

Results: WES identified causative variants in ACTA1 (n = 2), POMT1, COL6A1 (n = 2), MTMR2, LMNA, SELENON, DNM2, TGFB1, MPZ, IGHMBP2, and LAMA2 in 13 patients. We identified the first reported case of MTMR2 in Chinese. Two subjects have variants of uncertain significance (VUSs) in TTN and SCN11A, unlikely to be pathogenic due to incompatible phenotypes. The mean interval time from symptom onset to genetic diagnosis was 10.4 years (range from 1 month to 33 years). The overall diagnostic yield of WES in our cohort was 26% with findings comparable to overseas studies. Open exome analysis was necessary to identify the pathogenic variant in TGFB1 that caused skeletal dysplasia with neuromuscular presentation.

Conclusion: Our study shows a clear role of WES in the pathway of integrated diagnostic approach to shorten the diagnostic odyssey in patients with rare NMDs. WES is recommended as the first-tier genetic testing for rare NMDs.

Project No.: 03142176

Abstracts for Poster Presentation: Advanced Medical Research

AMR-21-196

Parental Expectations of Raising a Child with Disability in the Decision-Making for Prenatal Testing and Termination of Pregnancy: The Local Needs for Genetic Counselling and Public Education

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Introduction and Project Objectives: Prenatal testing is widely available in clinical practice in Hong Kong. The study aimed to examine attitudes toward prenatal testing and termination of pregnancy (TOP) among parents and obstetric providers in relation to their views on raising a child with disability.

Methods: An explanatory sequential mixed-methods study was conducted. A survey among 274 parents and 141 providers was followed by interviews with 26 parents and 10 providers. Using multivariate analysis, the relationships between attitudes were examined. Thematic analysis was used to identify the reasons behind the attitudes.

Results: Parents and providers reported different expectations of a child with disability, of which affecting their attitudes of termination of pregnancy. Parents reported more positive attitudes toward raising a child with disability and more moral views about TOP. In contrast, providers reported more variations in attitudes toward offering prenatal testing and TOP. Significant associations were found between attitudes toward prenatal testing, raising a child with disability, reproductive autonomy, and TOP. Three major themes were identified: (1) meanings of parenthood from genetic tests; (2) views toward TOP and parental responsibility; and (3) implications of advanced extended prenatal genetic testing.

Conclusion: Perceived social-cultural norms of disabilities and parental expectations of raising a child with disability influence decision-making regarding TOP. Providers need to explore parental values in disability and TOP rather than assume parents share their views. As more conditions of the fetus are able to be detected, the implications of the technology and disabilities need to be addressed in antenatal care.

Project No.: 03144536

AMR-22-230

Risk Assessment of Hereditary Breast and Ovarian Cancer Syndrome in Chinese Population by Multiple-Gene Sequencing

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Introduction: Differences in the mutation spectrum across ethnicities. suggest that it is important to identify genes in addition to common high penetrant genes to estimate the associated breast cancer risk.

Project Objective: To assess the prevalence of other breast cancer associated genes in Chinese high-risk breast and/or ovarian cancer patients.

Methods: A total of 1,338 high-risk breast cancer patients who tested negative for germline BRCA1, BRCA2, TP53 and PTEN mutations between 2007-2017 were selected from the Hong Kong Hereditary Breast Cancer Family Registry. Patient samples were subjected to next-generation DNA sequencing using a multigene panel. All detected pathogenic variants were validated by bi-directional DNA sequencing. The sequencing data was co-analyzed by our in-house developed bioinformatics pipeline.

Results: Sixty-one pathogenic variants (4.6%) were identified in 11 cancer predisposition genes. The majority of the carriers (77.1%) had early-onset of breast cancer (age <45), 32.8% had family members with breast cancer and 11.5% had triple-negative breast cancer (TNBC). The most common mutated genes were PALB2 (1.4%), RAD51D (0.8%) and ATM (0.8%). A total of 612 variants of unknown significance (VUS) were identified in 494 patients, and 87.4% of the VUS were missense mutations.

Conclusion: An additional 4.6% of the patients were identified in patients who tested negative for germline BRCA1, BRCA2, TP53 and PTEN mutations using the multigene test panel.

Project No.: 03143406

AMR-23-23

Behavioural Dysexecutive Syndrome after Stroke

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Introduction and Project Objectives: Behavioural dysexecutive syndrome (BDES), a common phenomenon in stroke patients, usually manifests as agitation/aggression, euphoria and apathy. This study aimed to evaluate the clinical course, prevalence

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and clinical and brain imaging correlates of BDES in a cohort of Hong Kong stroke survivors.

Methods: This longitudinal study enrolled a cohort of 369 stroke survivors and 237 healthy controls. For stroke survivors, baseline measurements were obtained at 3 months after the index stroke and follow-up measurements were obtained at an average of 38 months post-stroke. Healthy controls were assessed once only upon recruitment. BDES was assessed using the Chinese version of the Dysexecutive Questionnaire (self-version). The stroke severity, disability in daily activities, global cognitive and executive function, anxiety and depressive symptoms and other clinical information were obtained. The presence and location of infarcts were evaluated via magnetic resonance imaging (MRI).

Results: At 3 months post-stroke, the prevalence of BDES was 18.7%. The Hospital Anxiety Depression Scale anxiety subscale score (odds ratio [OR]=1.184, 95% confidence interval [CI]=1.083-1.295, p<0.001), presence of current depression (OR=4.055, 95%CI=2.060-7.983, p<0.001) and Mini-Mental State Examination score (OR=0.805, 95%CI=0.705-0.906, p<0.001) were identified as significant predictors of the presence of post-stroke BDES in a multivariate logistic regression. No significant MRI correlate was identified. The BDES group exhibited poorer performances on the Chinese version of Frontal Assessment Battery (compared with the non-BDES and healthy control groups, respectively: 10.1±2.5 vs 12.8±2.4 and 12.5±2.8, p=0.001 and 0.016), Colour Trails Test (error: 4.9±4.9 vs 0.6±1.7 and 0.3±0.7, p<0.001 for both; nearly-missed response: 6.2±7.3 vs 0.6±2.5 and 0.1±0.4, p<0.001 for both; prompts: 7.2±7.4 vs 1.1±2.8 and 0.4±1.3, p<0.001 for both; and time required to complete CTT2: 215.0±80.4 vs 162.5±76.8 and 127.6±87.2 seconds, p=0.040 and 0.001), Category Fluency Test (intrusion response: 1.4±1.8 vs 0.4±1.0 and 0.3±0.6, p<0.001, for both and total correct response: 33.0±11.3 vs 41.3±10.6 and 46.6±11.8, p=0.025 and <0.001) and Arrow Test (response time: 47.5±27.1 vs 24.6±10.5 and 20.4±5.4 seconds, p<0.001 for both and interference score: 104.6±101.0 vs 24.8±36.2 and 13.2±7.3, p<0.001 for both).

Conclusion: Many stroke survivors develop BDES within 3 months post-stroke. The study results indicate that anxiety symptoms, current depression and poor cognitive functioning predict BDES at 3 months after the index stroke. BDES was related to poor performance during executive functioning tasks such as conceptualisation, category fluency and motor programming.

Project No.: 02130726

AMR-24-25

Development of 3D DNA Nanocages as Safe and Cost-effective Nanocarriers for BBB Penetration and Potential Use in Targeted Drug Delivery in the Brain System

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Introduction and Project Objectives: Millions of people worldwide are being affected by neurodegenerative diseases including brain tumor, stroke, Parkinson's disease and Alzheimer's disease, etc. The clinical applications of chemotherapy in brain have been severely limited due to the restricted transport of sufficient amount of active therapeutic agents across the blood-brain barrier (BBB) for disease treatment in the central nervous system (CNS). So far, typical two strategies including invasive and noninvasive drug delivery have been investigated to enhance therapeutic efficacy in the brain system. However, they still suffers from several drawbacks including high cost, high risk and high level of discomfort in patients, loss of drug activity after chemical modification, and complicated preparation steps. To ameliorate this problem, scientists have been gradually explored the use of nanocarriers including liposomes, albumin nanoparticles, polymeric nanoparticles, metallic nanoparticles or synthetic dendrimers for drug delivery to brain systems. They have been functionalized with a variety of targeting moieties in order to facilitate the penetration across the BBB. However, some studies indicated that drug loading efficiency of polymeric nanoparticles is not very high (~ 10%) and some drugs such as paclitaxel could dissociate from albumin nanoparticles very shortly after administration in the blood stream. In addition, it is well-known that polymeric or metallic nanoparticles induce cytotoxicity under a high concentration of accumulation in a living system. Thus, development of alternative nanocarrier systems which would exhibit efficient drug loading, substantial cellular uptake, low cytotoxicity and BBB penetration is still of great research and clinical interest for targeted drug delivery to the brain tumor.

Methods: In this work, we have successfully assembled 3D DNA nanocages and functionalized them with BBB penetration peptides.

Results: We showed that self-assembled DNA nanocages are promising tools for delivery applications because of their substantial cellular uptake, low cytotoxicity, high bio-stability and biocompatibility.

Conclusion: The fully double-stranded feature of nanocages is favorable for different cargo loading mechanisms such

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as intercalation and minor groove binding. Therapeutic agents such as anticancer drugs could be efficiently loaded onto functionalized 3D DNA nanocages and then carried to specific sites of interests in cellular environment. Importantly, self-assembled DNA nanocages with/without peptide functionalization are able to pass through the BBB and get into the brain system in vivo.

Project No.: 03141076

AMR-25-34

Massively Parallel Discovery of Combination Therapies for Parkinson's Disease

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Introduction and Project Objectives: Multigenic perturbations lead to many human diseases including Parkinson's disease (PD), which is the second most common neurodegenerative disease. Discovering synergistic drug combinations that target the perturbed genes could improve motor symptoms and suppress neurodegeneration in PD. However, conventional methods in identifying promising drug combinations are labor intensive and cost-ineffective. Our newly developed screening platform, combinatorial genetics en masse (CombiGEM)-CRISPR enables rapid assembly of barcoded combinatorial genetic libraries for high-throughput functional characterization of genetic perturbations. To facilitate the discovery of effective drug combinations, this project aims to perform massively parallel studies with CombiGEM-CRISPR to isolate druggable gene combinations that suppress PD-associated cytotoxicity in rotenone- and MPP+-induced models, and to validate genetic hits and the matching drug combination effects in in vitro and in vivo models of PD.

Methods: Combinatorial CRISPR-Cas9 screens were performed using pairwise guide RNA library comprising 7,569 combinations, targeting 28 druggable genes.

Results: Specific druggable gene knockouts and the matching drugs that rescue cells from rotenone- and MPP+-induced toxicities were identified. We validated the effect of the top hit HSP90B1 + HDAC2 identified from the screens on suppressing PD-associated cytotoxicity. To translate the genetic combinations to therapeutic candidates, we applied drug combinations that correspond to the druggable targets and measure their effects on rotenone- and MPP+-induced cell death in SK-N-MC cells using MTT activity assays. (17-(Dimethylaminoethylamino)-17-demethoxygeldanamycin (17-DMAG) and vorinostat were used as the drugs to target HSP90B1 and HDAC2, respectively. Our results indicated that 17-DMAG and vorinostat act synergistically to enhance cell survival against rotenone- and MPP+- induced toxicity when compared to single-drug treatments in SK-N-MC cells. In addition, we observed this drug combination reduced toxicity induced by alpha-synuclein expression in transgenic flies, another well-characterized model of PD.

Conclusion: We have successfully carried out large-scale profiling studies to evaluate the effect of druggable gene combination en masse, and identified the simultaneously knockout of HSP90B1 and HDAC2 protects cells from rotenone- and MPP+-induced toxicities. We further validated the protective effect of the matching drug combination regimen (17-DMAG + vorinostat) using multiple in vitro and in vivo models of PD. Our work paves the way for further exploring the efficacy of the identified combination regimen for therapeutic use.

Project No.: 04151416

AMR-26-56

Activation of Hedgehog Signaling Promotes Development of Mouse and Human Enteric Neural Crest Cells, Based on Single-cell Transcriptome Analyses

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Introduction and Project Objectives: It has been a challenge to develop fully functioning cells from human pluripotent stem cells (hPSCs). We investigated how activation of hedgehog signaling regulates derivation of enteric neural crest (NC) cells from hPSCs.

Methods: We analyzed transcriptomes of mouse and hPSC-derived enteric NCs using single-cell RNA sequencing (scRNA-seq) to identify changes in expression associated with lineage differentiation. Intestine tissues were collected from Tg(GBS-GFP), Sufuf/f; Wnt1-cre, Ptch1+/- and Gli3Δ699/Δ699 mice and analyzed by flow cytometry and immunofluorescence for levels of mRNAs encoding factors in the hedgehog signaling pathway during differentiation of enteric NCs. Human NC cells (HNK-1+ p75NTR+) were derived from IMR90 and UE02302 hPSC lines. hPSC were incubated with hedgehog agonists (SAG) and antagonists (cyclopamine) and analyzed for differentiation. hPSC-based innervated colonic organoids were derived from these hPSC lines and analyzed by immunofluorescence and neuromuscular coupling assay for expression of neuronal subtype markers and for assessing the functional maturity of the hPSC-derived neurons, respectively.

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Results: scRNA-seq analysis revealed that neural fate acquisition by human and mouse enteric NCs requires reduced expression of NC- and cell cycle- specific genes and upregulation of neuronal- or glial-lineage specific genes. Activation of the hedgehog pathway was associated with progression of mouse enteric NCs to the more mature state along the neuronal and glial lineage differentiation trajectories. Activation of the hedgehog pathway promoted development of cultured hPSC into NCs of greater neurogenic potential by activating expression of genes in the neurogenic lineage. The hedgehog agonist increased differentiation of hPSCs into cells of the neuronal lineage by upregulating expression of GLI2 target genes, including INSM1, NHLH1, and various bHLH family members. The hedgehog agonist increased expression of late neuronal markers and neuronal activities in hPSC-derived neurons.

Conclusion: In enteric NCs from humans and mice, activation of hedgehog signaling promotes differentiation into neurons by promoting cell-state transition, expression of genes in the neurogenic lineage, and functional maturity of enteric neurons.

Project No.: 03143236

AMR-27-75

Ketamine Inhibits Stress-Induced Dendritic Spine Elimination through Activation of Parvalbumin Interneurons

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Introduction and Project Objectives: Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist that is commonly used for anaesthesia. Recent studies show that a single subanaesthetic dose of ketamine exerts robust antidepressant effects on treatment-resistant depressive disorder patients. Animal studies also show that ketamine exerts antidepressant-like effects and increases dendritic spine density. Nevertheless, it is unclear how ketamine affects dendritic spine dynamics under stressed condition in vivo.

Methods: To investigate the underlying mechanism of ketamine antidepressant effects, we used in vivo two-photon transcranial imaging microscopy to examine the effects of ketamine on dendritic spine plasticity in the frontal association cortex (FrA) in 1-month-old chronic restraint stressed mice.

Results: We found that restraint stress induced dendritic spine loss by decreasing the rate of spine formation and increasing the rate of spine elimination. Ketamine inhibited stress-induced spine loss mainly by protecting mushroom spines from elimination. Ketamine also induced re-formation of spines in close proximity to previously stress-eliminated spines. Electrophysiological and in vivo imaging experiments showed that ketamine enhanced activity of parvalbumin (PV) interneurons under stress condition and counterbalanced the stress-induced net loss of PV axonal boutons. In addition, selective chemogenetic excitation of PV interneurons mimicked the protective effects of ketamine on dendritic spines against stress.

Conclusion: Chronic stress exposure has been reported to induce dendritic spine loss and reduce dendritic arborization in prefrontal cortex and hippocampus. Previous studies reported that ketamine increased dendritic spine density in naive or stressed animals using fixed brain tissues. However, it is unclear whether the increase in dendritic spine density is owing to the promotion of spinogensis or inhibition of spine elimination. By using in vivo two-photon imaging, we traced how repeated stress affected synaptic structure dynamics in the FrA and how ketamine counteracted stress effects in 1-month-old mice. We showed that stress-induced loss of dendritic spines was the result of reduced spine formation and enhanced spine elimination. We also found that ketamine counteracted the loss of dendritic spines by preventing stress-induced spine elimination, while having minimal effect on spine formation. In addition, ketamine increased the activity of genetically labelled PV interneurons in the FrA of mice under acute stress in vivo. Furthermore, data from chemogenetic experiments showed that selective activation of PV interneuron prevented stress-induced spine elimination, whereas inhibition of PV interneuron abolished the protective effect of ketamine against stress-induced spine elimination, suggesting the involvement of PV interneuron activity in the modulation of dendritic spines by ketamine. Taken together, our data provide new insights on the effects of ketamine on synaptic circuitry under stress and a possible mechanism to counteract stress-induced synaptic impairments through PV interneurons activation.

Project No.: 03143096

AMR-28-76

Human Pluripotent Stem Cell-derived Ectomesenchymal Stromal Cells Promote More Robust Functional Recovery than Umbilical Cord-derived Mesenchymal Stromal Cells after Hypoxic-ischaemic Brain Damage

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Introduction and Project Objectives: Hypoxic-ischaemic encephalopathy (HIE) is one of the most serious complications in neonates and infants. Mesenchymal stromal cell (MSC)-based therapy is emerging as a promising treatment avenue for HIE. However, despite its enormous potential, the clinical application

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of MSCs is limited by cell heterogeneity, low isolation efficiency and unpredictable effectiveness. In this study, we aimed to examine the therapeutic effects and underlying mechanisms of human pluripotent stem cell-derived ectomesenchymal stromal cells (hPSC-EMSCs) in a rat model of HIE.

Methods: hPSC-EMSCs were induced from either human embryonic stem cells or induced pluripotent stem cells. Stem cells or the conditioned medium (CM) derived from stem cells were delivered intracranially or intranasally to neonatal rats with HIE. Human umbilical cord-derived MSCs (hUC-MSCs) were used as the therapeutic comparison control and phosphate-buffered saline (PBS) was used as a negative control. Lesion size, apoptosis, neurogenesis, astrogliosis and microgliosis were evaluated. The rotarod test and Morris water maze were used to determine brain functional recovery. RNA-seq and ELISA assays were used to determine the secretory factors that were differentially expressed between hPSC-EMSCs and hUC-MSCs.

Results: hPSC-EMSCs showed a higher neuroprotective potential than hUC-MSCs, as demonstrated by a more significant reduction in lesion size and apoptosis in the rat brain following hypoxia-ischaemia (HI). Compared with PBS treatment, hPSC-EMSCs promoted endogenous neurogenesis and alleviated astrogliosis and microgliosis. hPSC-EMSCs were more effective than hUC-MSCs. hPSC-EMSCs achieved a greater recovery of brain function than hUC-MSCs and PBS in rats with HIE. CM derived from hPSC-EMSCs had neuroprotective and neurorestorative effects in vitro through anti-apoptotic and neurite outgrowth- and neurogenesis-promoting effects. Direct comparisons between hPSC-EMSCs and hUC-MSCs revealed the significant enrichment of a group of secretory factors in hPSC-EMSCs, including nerve growth factor (NGF), platelet-derived growth factor-AA and transforming growth factor-β2, which are involved in neurogenesis, synaptic transmission and neurotransmitter transport, respectively. Mechanistically, the CM derived from hPSC-EMSCs was found to potentiate NGF-induced neurite outgrowth and the neuronal differentiation of NPCs via the ERK/CREB pathway. Suppression of ERK or CREB abolished CM-potentiated neuritogenesis and neuronal differentiation. Finally, intranasal delivery of the CM derived from hPSC-EMSCs significantly reduced brain lesion size, promoted endogenous neurogenesis, mitigated inflammatory responses and improved functional recovery in rats with HIE.

Conclusion: hPSC-EMSCs promote functional recovery after HI through multifaceted neuromodulatory activities via paracrine/trophic mechanisms. We propose the use of hPSC-EMSCs for the treatment of HIE, as they offer an excellent unlimited cellular source of MSCs.

Project No.: 03140496

AMR-29-79

FGF21 Mediates the Anti-Depressant Effects of Exercise by Coordinating the Crosstalk between Brain and Peripheral Organs

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Introduction and Project Objectives: Major depression is a common psychiatric disease affecting a large percentage of people worldwide. Increasing evidence suggests that diabetes and obesity are major risk factors for depression and that lifestyle intervention, especially physical exercise, is one of the most effective strategies to prevent depression. Fibroblast growth factor (FGF) 21 is a metabolic hormone critically involved in energy metabolism, and it is also a potential drug for treating obesity-related metabolic disorders. Circulating FGF21 level is markedly elevated in both rodents and humans with physical exercise. This study aims to investigate the role of FGF21 in mediating the antidepressant effects of exercise, and to test our hypothesis that FGF21 exerts its anti-depressant effects by mediating the multi-organ crosstalk between liver, muscle and brain.

Methods: Both global and conditional genetic knockout (KO) mice were employed to explore the role of FGF21 in exercise-induced alleviation in depression-like behaviors and the underlying mechanisms. Furthermore, the modulatory effects of FGF21 on the tryptophan-kynurenines pathway were evaluated using both gain- and loss-of-functional experiments.

Results: Exercise training significantly alleviated depressive symptoms in wild-type (WT) mice, however, these anti-depressive effects of exercise were largely diminished in FGF21 KO mice. Replenishment with recombinant mouse FGF21 alone was sufficient to reverse obesity-induced depression through alleviation in neuroinflammation and improvement in neurogenesis and plasticity. Muscle-specific depletion of the FGF21 co-receptor β-Klotho further demonstrated that the anti-depressant effects of FGF21 were attributed in part to its direct actions in skeletal muscle by controlling the tryptophan-kynurenine axis. Furthermore, adiponectin served as a downstream mediator of FGF21 to confer the anti-depression effects of physical exercise.

Conclusion: Collectively, these data identify FGF21 as an important mediator for the anti-depressant effects of exercise through suppressing hippocampal neuroinflammation and promoting neurogenesis and plasticity. The anti-depressant effect of FGF21 was partially dependent on its ability to induce

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adiponectin secretion in adipocyte and to modulate the tryptophan-kynurenine axis in skeletal muscle. The findings shed new light on how physical exercise prevents major depression and protect neuronal functions by modulating hormone-mediated multi-organ crosstalk and also raise the possibility that FGF21 and its agonist may represent a promising therapeutic agent for depression.

Project No.: 03144516

AMR-30-104
Local Infusion of Cholecystokinin in the Auditory Cortex and Successive Sound Stimuli Lead to Epileptic Seizures

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Introduction and Project Objectives: Epileptic seizures represent an imbalance between neural excitation and inhibition that result from an abnormal synaptic plasticity. Cholecystokinin (CCK), an extremely abundant neuropeptide in central nervous system, has indispensable role in regulating neural excitatory and inhibitory balance. Our previous results proved that CCK-positive neurons from entorhinal cortex (EC) determine neocortical plasticity. In this project, we sought to develop an epilepsy model through electrical activation of the EC, develop an audiogenic model of epilepsy through the administration of CCK-4, and also to test CCK-B receptor (CCK-BR) antagonists as potential anti-epileptic drugs so as to extend our understanding of the role of CCK in the development of epilepsy.

Methods: In order to evoke seizure activities through electrical kindling, a chronic microelectrode was implanted in the EC followed by daily application of a high-frequency electrical stimulus in CCK-A and –B receptor knockout (CCK-ABR-KO) and wildtype mice. Audiogenic epilepsy model was developed by intraperitoneally injecting mice with CCK-4 or long-acting CCK-4 analogue followed by pairing with low-intensity noise (~50 dB), myoclonic jerks of the head and neck in response to noise or light (control) stimulus after pairing was analysed using MATLAB custom algorithm. A fast-screening of CCK-BR antagonists based on whether they can block long term potentiation in cortical brain slices was carried out by applying theta burst stimulation (TBS) in the presence of selected CCK-BR antagonists and kainic acid (KA) model of temporal lobe epilepsy was adopted to test the efficacy of these antagonists against epileptic seizures.

Results: Local electrographic seizure known as afterdischarge was evident in EC kindled mice. CCK-ABR-KO mice showed a higher afterdischarge threshold and prolonged period of post-ictal depression compared with wildtype. After pairing with noise, CCK-4 injected mice showed myoclonic jerks of the head and neck with brief twitching movement which rhymed in oscillation of noise. Different from classic audiogenic seizure model that uses high-intensity noise (~100 dB) to induce seizure, our mouse model shows synchronized movement in the presence of low intensity noise (~50 dB) that the mouse showed no response previously. Also, administration of CCK-BR antagonists (YF476 or YM022) reduced the frequency of spontaneous convulsive seizures in our KA epileptic mice model.

Conclusion: Our results reveal that CCK-ABR-KO mice are resistant to induction of convulsive seizure, CCK-4 administration can evoke audiogenic seizure and blocking CCKB-receptor can alleviate epilepsy in KA model. Our findings therefore suggest the role of CCK in epilepsy and the anti-epileptic effects of CCKB-receptor antagonists.

Project No.: 03141196

AMR-31-138
High-throughput Brain Activity Mapping and Machine Learning as a Foundation for Systems Neuropharmacology

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Introduction and Project Objectives: The development of next-generation technologies for mapping dynamic patterns of neural activity has the potential to revolutionize understanding of brain function in both health and disease. One critical application of these technologies is the systematic characterization of existing pharmacological agents used to treat brain disorders along with novel experimental therapeutics in order to advance the development of next-generation therapies.

Methods: In this project, we describe a high-throughput, in vivo drug screening strategy that combines automated whole-brain activity mapping with computational bioinformatics analysis. Our strategy utilizes functional brain physiology phenotypes derived from live, non-anesthetized zebrafish that have been treated with compounds of interest as an input for predicting the therapeutic potential of neuroactive compounds. This technology relies on an autonomous robotic system capable of manipulating awake zebrafish larvae for rapid microscopic imaging of their brains at the level of cellular resolution, which allows for rapid assessment of action potential firing across a whole zebrafish brain; as a result, a large number of whole-brain activity maps (BAMs) can be acquired for a compound library.

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Results: Our study was performed in two phases. The first phase utilized a 179 compound "training set" of clinical used approved drugs, which were used to generate information-rich BAMs. Next, the intrinsic coherence among the BAMs for drugs in the training set was determined by a consensus clustering algorithm. This analysis revealed that certain BAM drug clusters were associated statistically with the drugs' therapeutic categories as determined by the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system. Using the test case of anti-epileptic drugs, in the second phase of the study the clustering results were used to build a functional classifier along with a ranking mechanism, which successfully predicted anti-epileptic candidates from a library of 121 non-clinical compounds. Excitingly, this analysis provided novel insights in the form of specific compounds and processes, for example epigenetic mechanisms, that have the potential to help guide development of next-generation anti-epileptic agents with novel mechanisms of action.

Conclusion: Take as a whole, the HT-BAMing technology, computational approaches, and foundational dataset for systems neuropharmacology we describe has the potential to provide insight into mechanisms of action of poorly understood pharmacological agents and novel compounds. Future applications of this strategy in conjunction with genetically engineered zebrafish models of CNS disorders has tremendous potential to assist in the discovery of novel disease-modifying pharmacological agents to expand the treatment options available to patients with CNS disorders.

Project No.: 03141146

AMR-32-157
Striatal Dopamine Transmission in Individuals with Isolated Rapid Eye Movement Sleep without Atonia: A Search for Precursor Biomarker for Neurodegeneration

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Introduction and Project Objectives: REM sleep behaviour disorder (RBD) is a specific precursor of synucleinopathic neurodegeneration. However, neurodegenerative implication of isolated REM sleep without atonia (RSWA) in the absence of dream enactment behavior is unclear. The current study aimed to examine the neurodegenerative implication of isolated RSWA among first-degree relatives (FDRs) of RBD patients, as reflected by their loading of neurodegenerative risk factors and prodromal markers and stratal dopamine transmission function.

Methods: This case-control study recruited a total of 50 age and sex-matched subjects (Mean age = 58.6±9.1 years. 34% female) into three arms: FDRs of RBD patients with isolated RSWA (n=16), FDRs of RBD patients without isolated RSWA (n=18) and controls who did not have any RWSA and family history of RBD (n=15). Subjects underwent comprehensive clinical and polysomnographic assessment. Striatal dopaminergic transmission function of the subjects was assessed by triple-tracer (18F-DOPA, 11C-Raclopride and 18F-FDG) PET/CT scan.

Results: The three groups did not differ in their striatal dopaminergic transmission function as measured by triple-tracer PET/CT scan. While they did not differ in their Prodromal Parkinson's Disease likelihood ratio by MDS Research Criteria, they differed significantly in their prevalence of a family history of clinically diagnosed synucleinopathies (Parkinson's disease (PD) or dementia of Lewy bodies (DLB)) among their FDRs (Fischer exact test: FDRs with RSWA vs FDRs without RSWA vs non-RBD FDRs controls = 58.8% vs 22.2% vs 0%, p = 0.001).

Conclusion: Using GEE analysis, RSWA is a significant predictor of having a family history of clinically diagnosed synucleinopathies (B=1.61, Wald 95% CI= 0.14 – 3.08, Wald chi-square = 4.59, d.f. = 1, P = 0.032).

Project No.: 04153036

AMR-33-192
Alleviation of Early High Mortality and Aggravated Brain Pathology by Lutein in a Genetic Type I Diabetic Mouse Model after Experimental Stroke

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Introduction: Type 1 diabetic patients experienced a higher mortality and shortened median survival after stroke.

Project Objectives: to understand the mechanisms of earlier mortality and aggravated brain damage in type I diabetic patients after ischemic stroke using a genetic mouse model of type I diabetes (Ins2Akita/+ mice) and to identify the

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therapeutic potential of lutein treatment.

Study Design: male Ins2Akita/+ mice as a type I diabetic animal model with their age-matched littermates (11-12 weeks old) will be challenged with experimental stroke induced by middle cerebral artery occlusion with or without lutein treatment.

Methods: Hyperglycemic Ins2Akita/+ mice were challenged with transient middle cerebral artery occlusion to induce experimental stroke

Results: After 2h of long ischemia, hyperglycemic Ins2Akita/+ mice exhibited aggravated neurological deficits, increased infarct size and hemorrhagic transformation as early as 2h after reperfusion. Earlier death and higher mortality rate were observed in Ins2Akita/+ mice with a longer duration of reperfusion and hemorrhagic transformation further exaggerated at 22h of reperfusion in those survived. Since 2h after reperfusion, decreased ZO-1 and increased MMP-9 immunoreactivities in the infarct cores, down-regulation of ZO-1 but up-regulation of VEGF, p-Erk1/2 and p-p38 at protein level, and elevated mRNA expression of ER stress-related CHOP were seen in Ins2Akita/+ ipsilateral brains. After 0.5h of ischemia, infarcts similar to those induced by 2h long ischemia were observed in Ins2Akita/+ mice at 23.5h after reperfusion but with milder neurological deficits. Administration of lutein, an anti-inflammatory and anti-oxidative agent, was successful in reducing neurological deficits in Ins2Akita/+ mice subjected to 0.5h of ischemia, although the suppression of infarct aggravation was not statically significant.

Conclusion: Results of 2h long ischemia suggested that hyperglycemia plays an important role in the exacerbation of stroke at an early stage by compromising blood vessel integrity and exerting inflammatory response, while results of 0.5h short ischemia showed the neuroprotective effect of lutein against ischemia/reperfusion injury.

Implications (for health care services, health care delivery, health policy in Hong Kong): Lutein is neuroprotective and may act as a safe potential treatment after stroke attack in diabetic patients.

Project No.: 03142256

AMR-34-220

Investigating the Impact of Periodontitis on Neuroinflammation, Neuropathology and Neurodegeneration in Alzheimer's Disease

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Introduction: Periodontitis, a source of chronic systemic inflammation, is a pathological inflammatory condition of the gum that leads to progressive destruction of the periodontium. Given that inflammation plays a pivotal role linking periodontal infections and various systemic diseases, increasing lines of evidence also indicated that periodontitis might participate in the progression of neurodegenerative diseases such as Alzheimer's disease (AD).

Project Objectives: As inflammation within the brain is a prominent feature of AD, chronic, low-grade inflammatory conditions such as that seen in periodontitis may thus exacerbate neuroimmune responses and AD progression. Our present study aimed to apply two different experimental models of periodontitis (bacterial-induced periodontitis and ligature-induced periodontitis) in 3xTg-AD mice and examine cognitive dysfunctions and neuropathology

Methods: For bacterial-induced periodontitis, female 3xTg mice at 6 months of age were injected with heat-killed P. gingivalis bacteria into their buccal mucosa 3 times per week every other week for a total of 5 weeks. For ligature-induced periodontitis, another group of mice had silk sutures tied around the maxillary second molars for the same duration of time. Effects of periodontitis on sickness behavior and cognitive functions were assessed by open field, spontaneous Y-maze, and puzzle box test. Following behavioral testing, the jaws and gums were harvested for the evaluation of periodontal status. Different brain regions were harvested for further biochemical and immunohistochemical analysis.

Results: Both models of periodontitis led to a significant loss of periodontal bone level, which was accompanied by increased gene expression levels of IL-1β and TNF-α in the gums. Results from the behavioral tests revealed that bacterial injection exacerbated both short- and long-term memory function, while ligature placement reduced exploratory motivation and exacerbated long-term memory function in AD mice. When assessing for tau pathology, significantly higher levels of phosphorylated tau proteins were detected in the brains of AD mice following induction of periodontitis. Concomitant with the increase in phosphorylated tau proteins, our findings also showed that AD mice injected with heat-killed bacteria were presented with elevated microglial and astrocytes immunoreactivity in the brain.

Conclusion: Findings from the present study confirmed that experimental periodontitis could enhance the brain inflammatory response and subsequently exacerbate AD tau

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pathology and cognitive functions in 3xTg mice.

Project No.: 04151216

AMR-35-27

Effects of RANKL Inhibition on Promoting Healing of Bone Erosion in Rheumatoid Arthritis Using HR-pQCT: A 2-year, Randomised, Double-blind, Placebo-controlled Trial

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Introduction and Project Objectives: Partial repair of bone erosions in rheumatoid arthritis (RA) is known from high-resolution peripheral quantitative CT (HR-pQCT) studies in patients with moderate to high disease activity using anti-tumour necrosis factors and anti-IL-6 biological therapies. Whether receptor activator of nuclear factor kappa B ligand (RANKL) inhibition by denosumab is superior to placebo in healing of existing erosions in patients with RA with low disease activity or in remission on conventional synthetic disease-modifying antirheumatic drugs is uncertain. The aim of the study was to evaluate the effects of denosumab on erosion healing at 2–4 metacarpophalangeal (MCP) head as determined by HR-pQCT in patients with RA with stable disease.

Methods: This was a randomised, placebo-controlled, double-blind study. Patients with RA with disease activity score 28 joints (DAS28) ≤5.1 were randomised (1:1) to subcutaneous denosumab 60 mg or placebo once every 6 months for 24 months. Patients were treated to the target of DAS28 remission or LDA throughout the study period according to a standard protocol. The primary outcome was erosion healing at MCP 2–4 on HR-pQCT at 12 months. The effects of denosumab on erosion and joint space parameters on HR-pQCT and radiographs, disease activity and health assessment questionnaire-disability index (HAQ-DI) were also examined.

Results: At 24 months, HR-pQCT images were analysed in 98 patients. One-third of the patients achieved sustained low disease activity throughout the study. At 12 months, changes in erosion parameters on HR-pQCT were similar between the two groups. At 24 months, new erosions (19% vs 9%, p=0.009) and erosion progression (18% vs 8%, p=0.019) were more common in the placebo group than the denosumab group. Erosion healing was seen in a significantly higher proportion of patients in the denosumab group (20% vs 6%, p=0.045) at 24 months. Logistic regression analysis revealed that the use of denosumab was associated with erosion healing (OR 3.39, 95% CI 1.08 to 10.63) after adjustment for covariates. No significant changes in joint space parameters on HR-pQCT, van der Heijde-Sharp erosion score, DAS28 and HAQ-DI were observed in the two groups at 12 and 24 months. The treatments were well tolerated.

Conclusion: Although no differences in erosion parameters were observed at 12 months, denosumab was more efficacious than placebo in erosion repair on HR-pQCT after 24 months. It could be considered a treatment option for retarding bone damage progression independent of the disease activity control.

Project No.: 04152616

AMR-36-45

The Efficacy of Buscopan® in Reducing Pain during Ultrasound-guided Manual Vacuum Aspiration (MVA): A Randomized Controlled Trial

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Introduction and Project Objectives: Patients undergoing ultrasound-guided manual vacuum aspiration (USG-MVA) for early pregnancy loss complains of moderate pain from uterine spasms. The current pain control regimen includes the use of oral non-steroidal anti-inflammatory drugs (NSAIDs) taken an hour before the procedure, paracervical block (PCB) and topical lidocaine gel applied just before the insertion of the catheter. We hypothesized that the addition of Buscopan®, an anti-spasmodic drug, may improve the pain control during USG-MVA.

Methods: This was a prospective, double-blinded, randomized controlled trial conducted between February 2018 and January 2020 in Prince of Wales Hospital. 111 women were assigned to receive a 1ml intravenous injection containing either a 20mg Buscopan® (n = 55) or saline (n = 56) as placebo immediately before the USG-MVA procedure. Primary outcome was the pain scores immediately and 2 hours after the USG-MVA. Secondary outcomes were complications, side effect profiles, psychological states, physiological stress (saliva alpha-amylase, sAA) and client satisfaction. Two-way mixed ANOVA was used to evaluate for main effects and interactions.

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Results: For the 'Buscopan®' group, median abdominal pain scores were 15% lower immediately post-procedure and 21% lower 2 hours post-procedure, though not statistically significant. Repeated measures ANOVA indicated that the both vaginal and abdominal pain scores improved significantly with the time (Vaginal: $F(1,108) = 180.10$, $p < 0.0001$; Abdominal: $F(1,108) = 83.41$, $p < 0.001$) but were independent of randomization group (Vaginal: $F = 0.32$, $p = 0.320$; Abdominal: $F = 1.41$, $p = 0.650$). No difference was noted for the complications and side effect profiles between the two groups. Measured Log10 sAA levels reduced significantly with time ($F(2.8, 286.1) = 6.30$, $p < 0.001$) but not with group ($F = 0.10$, $p = 0.960$). However, the 'Buscopan®' group reported significantly higher ($p = 0.032$) mean VAS satisfaction scores compared to the placebo group (79.0 ± 17.3 vs 73.4 ± 24.1).

Conclusion: Ultrasound-guided manual vacuum aspiration is associated with a moderate amount of uterine contraction pain. Women receiving Buscopan® for pain relief were, in general, more satisfied with the procedure than those who received a placebo. Higher satisfaction scores in those receiving Buscopan® may be related to the slight reduction in immediate post-procedure abdominal cramping pain, rather than vaginal pain. Anti-spasmodics can be helpful in the reduction of USG-MVA associated abdominal cramping pain. Further studies with larger doses or alternative anti-spasmodics are warranted.

Project No.: 05160406

AMR-37-50

Commissioned Programme on the CUHK Phase 1 Clinical Trial Centre at the Prince of Wales Hospital

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Introduction and Project Objectives: Phase 1 clinical trial is the foundation of translational research, bridging advances in basic science to clinical application. The objectives of the CUHK Phase 1 Clinical Trial Centre (P1CTC) are to: 1) develop an internationally recognized centre for conducting phase 1 clinical trials, 2) build a specialized team and infrastructure to support phase 1 clinical trials, 3) promote knowledge transfer among stakeholders in drug development and 4) provide pharmacokinetic (PK)/ pharmacodynamic platform to support the development of investigational medicinal products (IMP), Traditional Chinese Medicine (TCM) and other complementary products

Methods: The entire 11/F (EF block) of the Prince of Wales Hospital was converted into a P1CTC that comprises of 24 beds equipped with facilities for resuscitation and safety monitoring devices, 2 consultation rooms, recreational space, drug storage room, specimen-processing area, nurses stations and offices. Two liquid chromatography mass spectrometry machines were acquired to support PK work.

The Centre was supported by a clinical team (physicians, nurses, pharmacist, research assistant and workman) and an operation/ business development team. The Chief Director, 2 Medical Directors and 2 Deputy Medical Directors supervised the operation, research activities and strategic direction.
The Centre was governed by the Faculty of Medicine, Clinical Research Management Office and Clinical Research Ethics Committee for adherence to Standard Operating Procedures and other practice policies. This safeguards accuracy and integrity of scientific output and ensured subject safety.

Results: From 2014 to 2019, the Centre completed 46 phase 1 clinical trials and recruited over 600 subjects. Thirty percent of these studies involved IMPs in oncology and 70% in hepatology, endocrinology , TCM and other disciplines. In August 2016, the Centre was recognised by China Food and Drug Administration (CFDA) for conducting clinical testing of pharmaceutical compound and 7 CFDA studies were completed. Other notable achievements included the establishment of a precision oncology program to molecularly match patients to anti-cancer drug trials, formation of the Asia-One Phase 1 Research Consortium in oncology and the launch of a webpage and e-platform for facilitating recruitment of healthy volunteers. The Centre hosted educational observerships for overseas visitors and masterclasses in Methods of Cancer Research.

Conclusion: The Centre was established in accordance to the objectives of the commissioned programme to support early phase evaluation of novel compounds. In our commitment to promote biotechnology development in Hong Kong, the Centre will continue to expand capacity and facilitate support to key stakeholders in drug development.

Project No.: CTC-CUHK

AMR-38-55

Using Ultrasound for Screening Scoliosis to Reduce Unnecessary Radiographic Radiation - A Prospective Diagnostic Accuracy Study on 442 Schoolchildren from the Scoliosis Screening Program in Hong Kong

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Introduction and Project Objectives: Angle of Trunk Rotation (ATR) and Moiré Topography are used in screening scoliosis in Hong Kong. Those screened positive for suspected scoliosis will have x-ray assessment. Subjects with Cobb angle ≥ 20° are referred for specialist care. There were cases with Cobb angle < referral threshold of 20° thus being subjected to unnecessary x-ray exposure. Our objective is to determine if ultrasound can identify subjects "not for specialist referral" to reduce unnecessary x-ray exposure.

Methods: Schoolchildren screened positive for suspected scoliosis were prospectively recruited from the scoliosis screening program. In addition to whole spine radiography, ultrasound of the spine was independently performed on the same day. X-ray-based referral status, i.e. "Cobb≥20°-for specialist referral" or "Cobb<20°-not for specialist referral", was the gold standard. The ultrasound-based referral status was determined with the ultrasound spinous process angle (SPA). ATR was also measured.

Results: 442 subjects (243 females and 199 males, mean age 13.2±1.8 years) with various degrees of coronal curvatures (mean Cobb angle of major curve 14.0°±6.6°, range 0-39.0°) were studied. 78 subjects (17.6%) had Cobb angles ≥ 20°. Patient-based analysis showed that area under the ROC curve was 0.735 ($p<0.001$) with ultrasound-derived SPA alone for predicting the referral status, and improved to 0.832 ($p<0.001$) when ATR was incorporated into the prediction model. The sensitivity and specificity were 92.3% and 51.6% respectively at a probability cut-off of 0.11. The positive and negative predictive values were 29.0% and 96.9% respectively.

Conclusion: This study provided strong evidence that ultrasound together with ATR measurement was useful for identifying schoolchildren who did not require specialist referral with Cobb angle < 20°. This helped to reduce unnecessary X-ray exposure in the referral workflow of the scoliosis screening program. In the present study, 42.5% of subjects who would have been subjected to whole spine radiography could avoid taking x-ray with incorporation of ultrasound into the screening program. On the other hand, 1.4 % of subjects had false negative results among whom only 3 (0.7%) had major Cobb > 25°. Ultrasound could therefore be considered for incorporation into the scoliosis screening program to minimize radiographic exposure in line with the "As Low As Reasonably Achievable" (ALARA) principle of radiation safety especially for immature subjects.

Project No.: 04152896

AMR-39-74

Deciphering the Molecular Mechanism of Protein Arginine Methyltransferase (PRMT) 1 in the Regulation of Hepatic Glucose and Lipid Metabolism

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Introduction and Project Objectives: Non-alcoholic fatty liver disease (NAFLD) is strongly associated with obesity and type 2 diabetes and it is an increasingly prevalent liver disease characterized by high intrahepatic triglyceride accumulation due to various causes other than excessive alcohol consumption. Despite of an accumulating number of studies have revealed the complex mechanism behind NAFLD, there is still no pharmacological therapy available to treat this disease in the clinic. In this study, we investigated a novel role of protein arginine methyltransferases (PRMT) 1 in the activation of fatty acids β-oxidation in NAFLD.

Methods and **Results:** In the mice with adeno-associated virus (AAV)-facilitated over-expression of PRMT1, it dramatically attenuated hepatic steatosis upon 4-month high-fat diet (HFD) feeding with improved liver function. Meanwhile, we observed an accelerated fatty acids β-oxidation rate in the liver lysate with PRMT1 over-expression upon HFD when compared to HFD control group. Along with the activation of fatty acid β-oxidation, we found that the expression of PGC-1α was increased at both mRNA and protein levels in PRMT1 over-expression mice. Thus, we hypothesised that, despite of the methylation of PGC-1α at protein level, PRMT1 regulated it at transcriptionally level as well. By using methyltransferase inactive PRMT1 mutant (G80R), we identified the binding site of HNF-4α, which is a transcription factor regulated by PRMT1 and served as co-activator of PGC-1α with PRMT1 using luciferase reporter assay.

Conclusion: Taken together, these data suggested a novel role of PRMT1 in the regulation of fatty acid β-oxidation upon long-term HFD feeding through the activation PGC-1α at transcriptional level.

Project No.: 03143966

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AMR-40-121

Cardiovascular Disease Risk Factors in Late Adolescence of Late Preterm and Early Term Births: A Prospective Observation from the "Children of 1997" Birth Cohort

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Introduction: Evidence from Western settings suggests that individuals born preterm have higher blood pressure. The association of late preterm and early term birth with cardiovascular disease risk factors, and whether infant growth mediates these associations, is however less clear.

Project Objectives: To assess the associations of late preterm and early term birth with cardiovascular disease risk factors in young adulthood and to assess whether any of the associations are mediated by accelerated infant weight growth.

Methods: In the prospective Hong Kong birth cohort "Children of 1997" (n=4857, 60% follow-up), we used multivariable linear regression, with multiple imputation and inverse probability weighting, to examine the associations of gestational age, i.e. late preterm (34 0/7 to 36 6/7 weeks), early term (37 0/7 to 38 6/7 weeks) and term birth (39 0/7 to 42 6/7 weeks), with cardiovascular disease risk factors at 17.5 years. We tested whether any association was mediated by accelerated weight gain from birth to 12 months, defined as an increase in weight z-score ≥0.67, using the Pearl's mediation formula.

Results: Among the included cohort participants born at ≥34 week gestation, 183 (3.8%) were late preterm births, 1419 (29%) early term births and 3198 term births (67%). Compared to term births, late preterm births had higher BMI z-score (0.27, 95% CI 0.01,0.44), waist-to-hip ratio z-score (0.29, 95% CI 0.11, 0.47), waist-to-height ratio z-score (0.31, 95% CI 0.12, 0.49), fat mass index (0.47, 95% CI 0.05, 0.90), lean mass index (0.38 95% CI 0.10, 0.65) and systolic blood pressure (2.92 mmHg, 95% CI 1.27, 4.57), but not % body fat (0.88, 95% CI -0.23, 2.02) at 17.5 years. The associations with higher weight to height indices but not with higher waist ratios or blood pressure were partially mediated by accelerated weight gain from birth to 12 months. Fasting lipid profile and HbA1c levels did not differ by gestational age.

Conclusion: Young adults born late preterm without in-utero growth restriction or postnatal growth faltering had elevated systolic blood pressure, suggesting a full-term gestation is beneficial to cardiovascular health and should be encouraged. Accelerated infant growth partially mediated the higher fat mass and lean mass but not higher waist ratios or blood pressure in adults born late preterm, implicating different pathways to different markers of cardiovascular health and avoiding rapid infant growth in such late preterm births cannot prevent the adverse impact of shorter gestational age on subsequent blood pressure.

Project No.: 03143766

AMR-41-122

Serum Interleukin 6 and Insulin Resistance – A Mendelian Randomization Study

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Introduction: Low grade inflammation, as characterised by a higher interleukin 6 (IL-6) level, is associated with insulin resistance and type II diabetes. However it is unclear whether the previous observed association is causal or due to confounding or reverse cauality.

Project Objectives: To assess whether higher IL-6 level causally associates with insulin resistance using Mendelian randomisation.

Methods: In a prospective Hong Kong birth cohort "Children of 1997" (3498 participants), we used multivariate linear regression with multiple imputation to examine associations of IL-6 concentrations with insulin resistance assessed from homeostasis model assessment-insulin resistance (HOMA-IR). To examine the causal relations of IL-6 with HOMA-IR using Mendelian randomisation, we used genetic predictors of IL-6 from the Magnetic Consortium to assess effects on HOMA-IR in "Children of 1997" and in the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC). We combined the genetic variant specific Wald estimates using inverse-variance weighted (IVW). We evaluated the heterogeneity in the IVW estimate using the MR-Egger regression.

Results: Genetically predicted IL-6 was significantly associated with HOMA-IR in MAGIC consortium, however the association was weakened when a SNP associated with body mass index was removed. The same direction of the associations between IL-6 and HOMA-IR was seen in the Mendelian randomisation analysis in the "Children of 1997" birth cohort, however some associations did not reach statistical significance, partly attributed to the weaker genetic instruments and smaller sample size.

Conclusion: Some of our findings support a potential causal role of IL-6 in the development of insulin resistance. However, given the limitation of the present Mendelian randomisation analysis, including weak instrument and potential pleiotropic effects, further studies using stronger genetic instruments are warranted to confirm whether IL-6 is a therapeutic target to

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improve insulin sensitivity and avert the progression to type II diabetes.

Project No.: 03143776

AMR-42-130
Selective Overexpression of SIRT1 in Adipose Tissue Protects Adiponectin Deficiency Induced Liver Injury

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Introduction and Project Objectives: SIRT1 is a metabolic sensor regulating energy homeostasis in mammals. Previous results demonstrate that overexpression of human SIRT1 selectively in adipose tissue of mice (Adipo-SIRT1) enhances insulin sensitivity and prevents metabolic ageing. Preliminary results indicated that clusterin, a molecular chaperone, was up-regulated by SIRT1 in adipose tissue. The present study investigated the role of adipose SIRT1 in the prevention of obesity-induced NAFLD.

Methods: Mice including those with adipose overexpression of human SIRT1 (Adipo-SIRT1) or their wild type (WT) littermates, and those lacking clusterin expression without (CKO) or with adipose overexpression of human SIRT1 (CKOAdipo-SIRT1) were fed with a high fat diet (HFD) for 12-weeks, starting from the age of five-weeks. Body weight and fat mass, circulating glucose, lipid and insulin levels, systemic insulin sensitivity and energy expenditure were monitored on a regular basis. At the end of treatment, serum samples were collected for analyzing the lipid contents, fatty acid composition and lipoprotein particles. Liver and adipose tissues were subjected to histological staining, biochemical and molecular analyses. Mitochondria and mitochondria-endoplasmic reticulum contacting sites (MERCs) were isolated from adipose tissue for structural and functional comparisons.

Results: The present study revealed that overexpression of adipose SIRT1 prevented dietary obesity-induced metabolic abnormalities [insulin resistance, glucose intolerance and dyslipidemia] and obesity-induced NAFLD. SIRT1 was enriched at MERCs to trigger mitohormesis and unfolded protein response, in turn preventing HFD-induced ER stress. Clusterin was significantly upregulated and acted together with SIRT1 to regulate the protein and lipid compositions at MERCs in adipose tissue of Adipo-SIRT1. The results demonstrated that adipose SIRT1 enhanced the clusterin presence and omega-3 polyunsaturated fatty acids (PUFA) during HDL biogenesis in adipose tissue. The latter facilitated the transportation of omega-3 PUFA from adipose to liver.

Conclusion: The present study demonstrated that adipose SIRT1 enhanced the transportation of omega-3 PUFA via clusterin-containing HDL to liver, in turn eliciting the protective functions against NAFLD.

Project No.: 04151796

AMR-43-136
Dragon Protein Ameliorates Acute Kidney Injury by Inhibiting Necroptosis in Proximal Tubular Cells

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Introduction and Project Objectives: Acute kidney injury (AKI) is increasingly prevalent in Hong Kong and worldwide, and it associates with high morbidity, mortality and cost. AKI also increases the risk of developing chronic kidney disease (CKD) and exacerbates the ongoing CKD. Unfortunately, there are no effective treatment strategies available. It is well accepted that acute tubular necrosis is a key feature of AKI. Recent studies have found that programmed necrosis (necroptosis) contributes significantly to AKI. The necroptotic pathway has become a novel target for AKI treatment. Dragon is a membrane-associated protein. Our previous studies demonstrated that Dragon was highly expressed in tubular epithelial cells of the kidney, and tubular cell-specific deletion of Dragon increased necroptosis and AKI induced by ischemia/reperfusion (I/R) or oxalate crystals. We therefore hypothesize that exogenous Dragon protein also inhibits necroptosis in proximal tubular cells and prevents AKI. Our specific objectives included examination of the effects of Dragon.Flag and Dragon.Fc on kidney injury and functions in ischemia/reperfusion-induced AKI (IRI); and determination of the effects of Dragon.Flag on kidney injury and functions in cisplatin-induced AKI and renal lithiasis.

Methods: We induced acute kidney injury in mice by bilateral ischemic reperfusion (I/R), cisplatin and sodium oxalate. Mice were treated with and without Dragon.Flag.

Results: We found that Dragon.Flag protein inhibited necroptosis in proximal tubular cells in culture. Administration of Dragon.Flag protein into mice attenuated tubular epithelial cell necroptosis and ameliorated AKI induced by I/R, cisplatin or oxalate crystals.

Conclusion: Our results suggest that exogenous Dragon inhibits necroptosis and improves AKI in mice. Our previous study showed that Dragon induced apoptosis in renal tubular epithelial cells in the mouse model of unilateral ureteral obstruction. Therefore, the role of Dragon in kidney repair

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remains to be further investigated.

Project No.: 05161376

AMR-44-150

Endoscopic Submucosal Dissection (ESD) versus Transanal Minimally Invasive Surgery (TAMIS) for Early Rectal Neoplasms: A Prospective Randomized Controlled Trial

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Introduction and Project Objectives: Transanal minimally invasive surgery (TAMIS) is an effective surgical treatment for early rectal neoplasms not amenable to en bloc resection by conventional colonoscopic techniques. Endoscopic submucosal dissection (ESD) is a revolutionary endoscopic procedure that enables en bloc resection of large rectal neoplasms with low morbidity. This prospective, randomized, controlled superiority trial aimed to compare the short-term clinical outcomes, functional outcomes, quality of life, and costs between ESD and TAMIS for early rectal neoplasms.

Methods: Patients diagnosed with early rectal neoplasms (those without endoscopic signs of massive submucosal invasion or unfavorable histology on biopsy) ≥2 cm in size that were not amenable to en bloc resection by conventional colonoscopic techniques were randomly assigned (1:1) to receive either ESD or TAMIS performed by the same group of experienced colorectal surgeons. The primary outcome was 30-day morbidity/mortality. Secondary outcomes were en bloc resection rate, R0 resection rate, hospital stay, functional outcomes and quality of life, and costs. Planned enrollment was 114, but the trial was halted prematurely due to slow accrual as well as safety/efficacy data demonstrated by an unplanned interim analysis.

Results: From 6/2017 to 6/2019, 95 patients were screened for participation, and 53 eligible patients were randomly assigned to ESD (n=27) or TAMIS (n=26). The demographic data and tumor characteristics of the two groups were comparable. Two patients (7.4%) in the ESD group and 8 patients (30.8%) in the TAMIS group developed 30-day morbidity (P=0.039). One patient in the ESD group developed rectal bleeding on postoperative day 1 and required endoscopic clipping for hemostasis. No patients in the TAMIS group required reintervention for morbidity. All patients could achieve an en bloc resection, and R0 resection rate was similar between the ESD and TAMIS groups (88.9% vs. 92.3%; P=1.000). Length of hospital stay was significantly shorter in the ESD group (1.9±1.5 vs. 3.2±2.9 days; P=0.042). The total direct cost was also lower in the ESD group than in the TAMIS group (HK$80,133±15,569 vs. HK$99,782±31,416; P=0.005). Functional outcomes and quality of life did not differ between the two groups.

Conclusion: This trial was prematurely stopped because of slow accrual and a significantly lower 30-day morbidity rate demonstrated in the ESD group. The ESD group was also associated with shorter hospital stay and lower direct cost. However, given the premature termination of the trial, the results should be interpreted with caution.

Project No.: 04153006

AMR-45-152

Investigation into the Fungal Microbiome (Mycobiome) in the Cervices of Cervical Insufficiency Patients Receiving Cerclage Treatment and Resulting in Term or Preterm Birth

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Introduction and Project Objectives: Cervical insufficiency (CI), defined as premature cervical dilation/shortening, is a risk factor for spontaneous preterm birth <37 weeks (sPTB), a major contributor to neonatal mortality and morbidity. Surgical cerclage, which stitches up the weakened cervix, may prevent sPTB in CI patients, but about one-third of them still undergo sPTB after intervention. The latter group who do not benefit from cerclage could have been spared from surgical risks, but there is no good way to identify these patients. In this study, we investigated whether there were differentially abundant fungi between patients ending in sPTB and those ending in term birth (TB, birth on or >37 weeks) after cerclage intervention.

Methods: Before intervention, swab samples were collected from CI patients. Samples from women ending in sPTB and TB were sequenced for the fungal internal transcribed spacer 2 genomic region.

Results: Pre-cerclage cervical swab samples from 40 patients were sequenced. These patients ended in 14 sPTB and 26 TB after intervention. Phyla Basidiomycota and Ascomycota accounted for >90% of fungal taxa in these cervices. Fifty-three taxa including Candida parapsilosis were more abundant, and 14 taxa including Cladosporium cladosporioides were less abundant, in patients ending in sPTB after intervention than those ending in TB ($\log_2$ fold change, 1.1-8.4; adjusted p-value, 9.8E-20-0.05). A mycobiome score was calculated from the abundances of these differentially abundant taxa for each sample. Using the first quartile of the score of the sPTB group

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to define a positive test, 10 (true positive rate, 71%) of the 14 sPTB and 1 TB pregnancies (false positive rate, 4%) could be identified. Patients with a high score delivered sooner after sampling than their counterparts with a low score (Logrank test, p <1.0E-4). Notably, 95% high-score patients underwent sPTB, whereas 85% low-score patients underwent TB after intervention.

Conclusion: Patients with high loads of differentially abundant fungal taxa identified above in the cervix were more susceptible to sPTB after cerclage intervention. If further studies can ascertain that these fungi are useful for prediction of sPTB after cerclage, then certain patients can be spared from the surgery and counselled for other intervention for preventing sPTB.

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Project No.: 03141466

AMR-46-164
Investigation of Fibrosis Development in Marginal Graft after Liver Transplantation

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Introduction: Shortage of donor organs in liver transplantation results in expansion of donor pool to marginal (small-for-size and/or fatty) grafts. However, using expanded donor criteria poses increased risk for late phase complications such as fibrosis that may lead to graft dysfunction.

Project Objective: To explore the association between atypical biliary proliferation and fibrosis in marginal liver grafts and investigate the underlying regulatory mechanisms.

Methods: Using an orthotopic rat liver transplantation model and human post-transplant liver biopsy tissues, the dynamics of oval cells in marginal liver grafts was evaluated by the platform integrating immuno-labeling techniques and ultrastructure examination. Underlying mechanisms were further explored in oval cells and an Aldose reductase (AR) knockout mouse model simulating marginal graft injury.

Results: We demonstrated that activation of aldose reductase initiated oval cell proliferation in small-for-size fatty grafts during ductular reaction at the early phase after transplantation. These proliferative oval cells subsequently showed prevailing biliary differentiation and exhibited features of mesenchymal transition including dynamically co-expressing epithelial and mesenchymal markers, developing microstructures for extracellular matrix degradation (podosomes) or cell migration (filopodia and blebs), and acquiring the capacity in collagen production. Mechanistic studies further indicated that transition of oval cell-derived biliary cells toward mesenchymal phenotype by notch 2 signaling activation ensued fibrogenic development in marginal grafts after liver transplantation.

Conclusion: Oval cells contributed to fibrogenesis in small-for-size fatty liver grafts under dynamic regulation of aldose reductase and notch signaling. Aldose reductase-driven proliferation of hepatic oval cells dominated liver regeneration in marginal liver grafts. The subsequent biliary differentiation and mesenchymal transition of these oval cells contributed to chronic graft fibrosis under the regulation of notch signaling pathway. Intervention targeting oval cell dynamics may serve as potential strategies to refine current clinical management.

Publication: Oval Cells Contribute to Fibrogenesis of Marginal Liver Grafts under Stepwise Regulation of Aldose Reductase and Notch Signaling.
Liu XB, Lo CM, Cheng Q, Ng KT, Shao Y, Li CX, Chung SK, Ng IOL, Yu J, Man K*. Theranostics (impact factor: 11.556). 2017 Oct 24;7(19):4879-4893. doi: 10.7150/thno.20085. eCollection 2017.

Project No.: 02132366

AMR-47-187
Newly Developed Biodegradable Kirschner Wires in Upper-limb Fracture Fixations

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Introduction and Project Objectives: Upper-limb fractures are commonly seen among all types of bone fractures. Sports associated fractures have been mainly found in the paediatric and young adult population, while broken bones recorded in the elderly population are mainly caused by falls. Due to its ease of application, non-degradable Kirschner wires (K-wires) are commonly used by trauma and orthopaedic surgeons for fracture fixation either in open or percutaneous method (i.e. minimally invasive approach). The K-wire fixation technique is frequently used in hand and wrist fractures of adults, or most upper limb fractures in paediatric patients. However, some of the drawbacks for the usage of K-wires include (1) the requirement of additional surgery to remove the K-wires after bone healing; and (2) the risk of pin tract infection and skin impingement. Hence, we propose the use of a newly developed degradable K-wire, which is made of magnesium alloy as an alternative implant for fracture fixation.

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Methods: Degradable Mg K-wires will be tested on bone fracture models and non-degradable conventional K-wires serving the control. Eighty rats and sixteen goats will be used to study the biological responses and structural mechanical properties of newly formed bone. The surgical procedures and post-operation care were approved by the IRB of The University of Hong Kong.

Results: The binary fixation system made of degradable K-wire and conventional titanium wire effectively promoted the bone regeneration within the defect site as compared with the conventional group. This effect may attribute to the release of Mg2+ ions upon the degradation of the Mg K-wire. In the three-point-bending test, the bone tissue from the binary K-wire fixation group demonstrates significantly higher modulus than the conventional group after implantation for 36 weeks and indicates a better recovery. The osseointegration and bone mineral density (BMD) induced by Mg K-wire was significantly increased at 36-weeks post-implantation.

Conclusion: The degradable K-wire together with titanium wire can effectively fix fractured bone mechanically. Also, the modified system can stimulate local bone formation in which high quality of bone within a short period of time.

Project No.: 03142446

AMR-48-193

Lutein and Candesartan Co-Treatment Delays the Progression of Non-Proliferative Diabetic Retinopathy in the Diabetic Ins2Akita Mouse Model

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Introduction: there is an urgent need for novel interventions to delay the progression diabetic retinopathy, the most common microvascular complication of diabetes, in the early stage. Since long-term use is expected, an acceptable safety profile is of particular concern.

Project Objectives: to identify the therapeutic potential of long term co-treatment of lutein and candesartan in non-proliferative diabetic retinopathy

Study Design: male Ins2Akita/+ mice as an animal model of non-proliferative diabetic retinopathy received lutein and candesartan supplementation for up to 7.5 months.

Methods: lutein (4.2 mg/kg/day) and/or candesartan (0.01mg/kg/day or 0.1 mg/kg/day) was administered to mice in drinking water starting 6 weeks old daily until analysis at 6.5 or 9 months of age. Plain water served as non-treatment control.

Results: In animals treated with candesartan only or co-treated with lutein and candesartan, both co-treatment and single treatment resulted in a thicker nuclear layer. Best morphological improvement was observed with 0.1mg/kg/day candesartan single treatment, but with thicker inner plexiform layer and possibly retinal edema. Both co-treatment and single treatment reduced retinal cell loss in GCL. Co-treatment increased the immunoreactivity of PKCa and calbindin while single candesartan treatment increased that of calretinin. Glial reactivity in the retina was generally lowered in co-treated animals. Co-treatment resulted in better ERG a- and b-wave amplitudes up to 6.5 months.

Conclusion: long-term lutein administration is beneficial in preserving retinal function the Ins2Akita/+ mouse retina. Long term administration of lutein together with candesartan can provide better protection to the retinal cells and preservation of retinal function than single candesartan treatment. These results point to the potential of both lutein and lutein-candesartan as long-term therapeutic intervention for retinal degeneration in patients with early diabetic retinopathy.

Project No.: 04150746

AMR-49-200

Deep Expression and Functional Proteomics of Erythroid Cell Differentiation: A Molecular Resource for Understanding Red Cell Biology, Iron Metabolism and Related Diseases

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Introduction and Project Objectives: The remarkable transformation of red blood cell precursors into professional hemoglobin synthesizing cells and eventually mature erythrocytes is a fundamental model for understanding the complex molecular control of cell growth and differentiation, tissue specific gene regulation and red blood cell disorders. Understanding erythroid cell differentiation is also particularly important for elucidating the metabolism of heme and iron, which exhibit robust biosynthesis and utilization, respectively, during the red cell development. We are interested in mining the erythroid active proteome with an aim to understand the molecular mechanisms of erythroid differentiation as well as heme and iron handling. So far, proteomic studies in erythroid differentiation that provide comprehensive coverage, wide dynamic range, high accuracy in protein quantitation and functional information have yet to be established.

Methods: In the present study we have devised unprecedented strategies to obtain deep expression and functional proteomes of erythroid cell differentiation. Sub-proteomic analyses of isolated cytosolic and mitochondrial fractions and peptide pre-fractionation have been employed to obtain the proteomes of pro-erythroid cells and differentiating erythroid cells.

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Results: Our comprehensive proteomic analysis of an established model erythroid cell differentiation revealed a wide range of prototypical or previously unrecognized proteins related to hemoglobin synthesis, erythroid cytoskeleton, carbohydrate and lipid metabolism, redox regulation, vesicular transport and chaperon functions, establishing the basis for functional study of novel proteins involved in erythroid differentiation. We have also devised strategies to identify heme –associated proteins by integrative methodologies of two dimensional non-denaturing gel electrophoresis, heme staining and biological mass spectrometry to study the functional proteome of heme associated proteins.

Conclusion: Selected erythroid active proteins have been studied for their functional roles by CRISPR Cas9 knockout. In particular, functional studies making use of knockout of transferrin receptor 1 and erythroid aminolevulinc acid synthase showed not only their constitutive roles in hemoglobin production in red cells but also new iron or heme regulated proteins and mechanisms related to adaptive mechanisms toward iron or heme deficiency.

Project No.: 04151846

AMR-50-210

Investigating the Effect of Intracellular Sigma Protein in the Treatment of Amyotrophic Lateral Sclerosis and Multiple Sclerosis

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Introduction and Project Objectives: Following damage to the central nervous system, an inhibitory scar is formed around the lesion site to contain the spread of damaging factors. This scar persists over time and represents a formidable barrier to regeneration and recovery. CSPGs are a major component of this glial scar and inhibit axonal outgrowth and myelination of existing axons by binding to receptors such as PTPσ and LAR.

Methods: In the present study, we investigated the effects of a small peptide named Intracellular Sigma Peptide (ISP) that targets PTPσ on recovery in mouse models of two neurodegenerative diseases that have been associated with CSPG accumulation at lesion sites, Multiple Sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS). We modelled MS-like pathology using experimental autoimmune encephalomyelitis (EAE) and chemically induced demyelination via cuprizone feeding and administered daily doses of ISP while monitoring the animals for functional changes. Transgenic mice expressing the ALS-associated SOD1-G93A gene received ISP and were monitored for motor improvements over time. Histological analysis of the tissues via immunohistochemistry, immunoblotting and electron microscope was performed at the study endpoints. To explore the cell type specific effects of ISP on major cellular players in both MS and ALS pathology, we established primary cultures of oligodendrocytes, microglia, and astrocytes. We exposed these different cell types to CSPGs in cultured and used functional assays to explore responses to the addition to ISP.

Results: Results of the present study demonstrate that ISP treatment led to a significant improvement in MS models with regards to axonal sparing, remyelination, decreased neuroinflammation and ultimately translating to functional recovery. In both models of MS, ISP treatment led to significant improvements in the assessed behaviour. In the ALS mouse model, ISP treatment accelerated pathology and decreased survival. In a model of intracerebral haemorrhage, ISP increased myelination and functional recovery while preserving the ultrastructure of the lesioned corticospinal tracts. Cell culture experiments revealed an inhibitory effect of CSPGs on microglial phagocytosis oligodendrocyte and astrocyte outgrowth, however this effect was partially counteracted by ISP.

Conclusion: The present study is of potential clinical relevance for the use of ISP in demyelinating disorders and stroke but highlights concerns on the potential use in ALS.

Project No.: 05162936

AMR-51-211

Dysregulation of miR-223 and miR-431 Expression in Intestinal Tissues of Preterm Infants with Necrotising Enterocolitis: Roles in Altering Enterocyte Gene Expressions and Functions

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Introduction and Project Objectives: Necrotizing enterocolitis (NEC) is a severe inflammatory disease of the gastrointestinal tract that results in high morbidity and mortality in preterm infants. Gut dysbiosis and dysregulation of transcriptome have critical implications in the pathophysiology of the disease. Previously, we had demonstrated overexpression of tens of miRNAs in NEC tissues and provided evidence on the interactions with their target genes. Among all, miR-223 and miR-431 were in the top list of the highly expressed miRNAs. In this project, we aimed to identify the target genes of the two miRNAs and their roles in the pathophysiology of NEC.

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Methods: In silico prediction of target genes and luciferase reporter assays were employed to identify the direct miRNA/target genes. mRNA levels of downstream targets were measured by qRT-PCR in Caco-2 cells over-expressing miR-223 or miR-431 experiments and/or upon LPS or LTA challenge. Enterocyte functions were determined by cell proliferation and apoptosis assays using flow cytometry.

Results: Based on the collective evidences of bowel mRNA expressions in NEC patients and overexpression experiments in in-vitro cell models, we revealed that miR-223/NFIA and miR-431/FOXA1 could be involved in TLR4 downstream inflammatory and cellular functions, including apoptosis, cell proliferation, inflammation, muscle contraction and intestinal epithelium barrier integrity.

Conclusion: This study demonstrated dysregulation of miR-223 and miR-431 in NEC tissues, and identified the interaction between these two miRNAs and their target genes NFIA and FOXA1. The dysregulation of miR-223 and miR-431 in human intestinal tissue might play a role in NEC pathophysiology, including promoting apoptosis, suppressing proliferation, and increasing proinflammatory signals. Further, we have compared expression levels of miR-223 in enterocyte cells and purified cord blood neutrophils. Abundant expression of miR-223 have been observed in neutrophils, we speculated the increase of miR-223 bowel tissues would be contributed by the infiltrating neutrophils in the disease sites. In this regard, stool signifies a valuable sample medium for evaluation of bowel condition during the inflammatory process. Also, detection of miRNAs by quantitative assay is robust and ready to be developed into a point of care test. Thus, these miRNA targets represent potential diagnostic or prognostic biomarker for NEC and also other inflammatory bowel conditions.

Project No.: 02130566

Abstracts for Poster Presentation: Commissioned Research on COVID-19

COVID-1-32
Molecular Epidemiological Study of COVID-19 Cases in Hong Kong

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Introduction and Project Objectives: Hong Kong uses an elimination strategy with intermittent use of public health and social measures and stringent travel regulations to control SARS-CoV-2 transmission. So far, there were 4 waves of COVID-19 in this city. We conducted a near real-time molecular epidemiology study to understand the transmission dynamics of SARS-CoV-2 in our community in this period.

Methods: SARS-CoV-2 genomes in respiratory samples collected from local and imported COVID-19 cases were deduced using Illumina sequencing technology. About 20% of Hong Kong cases were studied. The deduced genomes were analysed by in-house analytical pipelines.

Results: We revealed the effects of fluctuating control measures on the evolution and epidemiology of SARS-CoV-2 lineages in Hong Kong. Our analyses on imported cases identified a vast number of SARS-CoV-2 variants, such as VOCs Alpha and Delta. Our results on these imported cases justify for the use of stringent follow-up control measures on inbound passengers and crew to prevent introduction of new SARS-CoV-2 variants from other regions in the studied period. Despite numerous importations, only three introductions were responsible for the majority of locally-acquired cases, two of which circulated cryptically for weeks while less stringent measures were in place. We also studied several major COVID-19 transmission events in different settings and identified the first reverse zoonotic transmission, reinfection case and in-flight transmission. In addition, our sequencing results also helped to reveal genetic relationships between COVID-19 cases, thereby providing evidences to epidemiologically link or delink cases in outbreak investigations.

Conclusion: Our molecular epidemiological investigations on COVID-19 cases can inform epidemiological investigations. Our study helps to understand the transmission dynamic of SARS-CoV-2 in a densely populated city and identifies risk factors that facilitate SARS-CoV-2 transmission. Such analyses also provide critical information to relevant stakeholders for developing evidence-based COVID-19 control policy and practice.

Project No.: COVID190205

COVID-2-37
Effectiveness of Remdesivir and in Combination with Dexamethasone among Hospitalized COVID-19 Patients in Hong Kong

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Introduction and Project Objectives: Evidence on the significant benefits of remdesivir and its combination with dexamethasone on mild-to-moderate COVID-19 patients is insufficient. Our research aims to investigate the disease progression, various clinical outcomes, changes in viral load, and duration of hospital stay associated with early remdesivir treatment as well as introducing remdesivir on top of dexamethasone among COVID-19 patients.

Methods: A territory-wide retrospective cohort of >10400 patients hospitalized with confirmed COVID-19 infection from 21st January 2020 to 31st January 2021 in Hong Kong SAR, China was analyzed. Early remdesivir treatment was evaluated using 352 patients who had initiated remdesivir within the first two days of admission, and 1,347 patients without early remdesivir treatment as controls at a 1:4 matching ratio. In addition, 466 patients with remdesivir use before or co-initiated with dexamethasone and 1078 patients who had received remdesivir after dexamethasone or only received dexamethasone treatment were selected to examine optimal timing of remdesivir initiation on top of dexamethasone use. Propensity-score matching or weighting were used to minimize residual confounding, and balance baseline covariates between exposure and non-exposure groups. Cox regression models estimated hazard ratios (HR) of event outcomes, while linear regression models examined the treatment effects on hospital length of stay (LOS).

Results: During a 14-day median follow-up, early remdesivir treatment was associated with significantly shorter time to clinical improvement (HR=1.14, 95%CI 1.01-1.29, p=0.038) and positive IgG antibody (HR=1.50, 95%CI 1.31- 1.70, p<0.001), lower risk of in-hospital death (HR=0.58, 95%CI 0.34-0.99, p=0.045), significant shorter hospital LOS among survivor (-2.56 days, 95%CI -4.86 to -0.26, p=0.029), in addition to achieving low viral load quicker (HR=1.51, 95%CI 1.24-1.83, p<0.001). Among hospitalized patients receiving dexamethasone within 13-day median follow-up, initiation of remdesivir prior to or co-initiated with dexamethasone had shorter time to clinical improvement (HR=1.23, 95%CI 1.02-1.49, p=0.032) and positive IgG antibody (HR=1.22, 95%CI 1.02-1.46, p=0.029), lower risk of

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in-hospital death (HR=0.59, 95%CI 0.36-0.98, p=0.042), as well as shorter hospital LOS by 2.65 days among survivors when compared with those receiving remdesivir after dexamethasone or non-remdesivir users.

Conclusion: For hospitalized COVID-19 patients with the moderate disease but not requiring oxygen therapy on admission, early remdesivir treatment could be a potentially effective choice. Among hospitalized patients receiving dexamethasone, early or co-initiation of remdesivir with dexamethasone demonstrated significant clinical benefits, and was associated with shorter time to clinical improvement and positive IgG antibody, lower risk of in-hospital death, in addition to significantly shorter length of hospital stay.

Project No.: COVID190210

COVID-3-39
Stability of SARS-CoV-2

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Introduction and Project Objectives: SARS-CoV-2 (formerly named as 2019-nCoV) is a novel human coronavirus and is the causative agent for COVID-19 pandemic. At the early stage of the virus emergence, little is known about the properties of this novel virus. Therefore, the objectives of this project are to understand the viral stability in different environmental conditions and on surfaces of different materials. In addition, we aim to determine the virus stability on several specially designed surfaces and to validate the methods to decontaminate the contaminated surfaces.

Methods: SARS-CoV-2 cultured from VeroE6 cells was used to determine the virus stability in buffer at different conditions and on surfaces of different materials. In addition, the effectiveness of different disinfectants against SARS-CoV-2 was tested. The infectivity of the virus was determined by TCID50 assay in BSL-3 laboratory.

Results: We demonstrated that the stability of SARS-CoV-2 decreases at higher temperature. A 30 min incubation at 56°C or a 5 min incubation at 70°C is sufficient to reduce the infectivity of the virus by at least 99.9%, while the virus remains extremely stable at 4°C up to 14 days. On the other hand, the virus remains stable in a wide range of pH. We also demonstrated that the virus are more stable on smooth surfaces, such as stainless steel, plastics and glass, than on rough surfaces, such as tissue paper and clothes. Strikingly, the infectious virus remains detectable on the surface of a surgical mask even after 7 days incubation at room temperature. With the findings above, we further demonstrated the feasibility of disinfecting the masks with heat treatment, enabling reuse of the masks in case of extreme shortage in supply. In addition, we demonstrated several metal alloys and surface coatings containing copper or copper compounds that are effective in reducing the infectivity of the virus on their surfaces. These materials could be applied on the common touch surfaces to reduce the risk of fomite transmission of the virus. Furthermore, we demonstrated that common disinfectants including household bleach, ethanol, chlorohexidine, benzalkonium chloride, etc at their working concentrations are effective in inactivating the virus within 5 min.

Conclusion: With the findings above, we gain more understandings on the properties of this novel respiratory virus and the effective ways in inactivating it. These could contribute to the determination of the control measures against the disease.

Project No.: COVID190116

COVID-4-63
A Novel Linker-Immunodominant Site (LIS) Vaccine Targeting the SARS-Cov-2 Spike Protein Protects against Severe COVID-19 In Syrian Hamsters

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Introduction: The Coronavirus Disease 2019 (COVID-19) pandemic is unlikely to abate until sufficient herd immunity is built up by either natural infection or vaccination. We previously identified ten linear immunodominant sites on the SARS-CoV-2 spike protein of which four are located within the RBD.

Methods: We designed two linker-immunodominant site (LIS) vaccine candidates which are composed of four immunodominant sites within the RBD (RBD-ID) or all the 10 immunodominant sites within the whole spike (S-ID). They were administered by subcutaneous injection and were tested for immunogenicity and in vivo protective efficacy in a hamster model for COVID-19.

Results: We showed that the S-ID vaccine induced significantly better neutralizing antibody response than RBD-ID and alum control. As expected, hamsters vaccinated by S-ID had significantly less body weight loss, lung viral load, and histopathological changes of pneumonia.

Conclusion: The S-ID has the potential to be an effective vaccine for protection against COVID-19.

Project No.: COVID190117

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COVID-5-66

One Health Investigation of Exposure to SARS-2-Related Coronaviruses in Trafficked Sunda Pangolins (Manis Javanica)

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Introduction and Project Objectives: Early in the COVID-19 pandemic, Sunda pangolins (Manis javanica) involved in illegal wildlife trade in mainland China were identified as hosts of SARS-2-related coronaviruses (SARS2r-CoVs).

Methods: Using a combination of virological and wildlife forensics tools, we investigated 89 Sunda pangolin carcasses seized by Hong Kong authorities during anti-smuggling operations in the territory conducted in 2013 (n=1) and 2018 (n=88). Swabs, organ tissues, and blood or other body fluids were collected from each animal during post-mortem examination. We aimed to examine the virome of these animals, to determine any previous exposure to SARS2r-CoVs, and to approximate the origin of these animals from wild populations throughout Southeast Asia.

Results: Several pangolin individuals were found to be seropositive or borderline seropositive using a double-antigen bridging assay to detect anti-SARS-CoV-2 spike antibodies. SARS-CoV-2 specific RT-qPCR and conventional RT-PCR with universal CoV primers was performed on >500 swab and tissue samples, though none of the samples tested positive. Putative seropositive individuals were determined to have originated from populations in Borneo, Java, and Sumatra, indicating that natural exposure to SARS2r-CoVs may be common due to the shared ecology of pangolins, bats, and potentially other host species, or this may indicate infection acquired during the illegal trafficking of these animals.

Conclusion: Our ongoing work aims to characterize the virome of these animals and to further investigate their origins. As wildlife trade has become a major focus of efforts to prevent the future emergence of novel pathogens, One Health approaches incorporating the expertise of multiple and diverse stakeholders are needed to investigate the origins and cross-species transmission of SARS2r-CoVs.

Project No.: COVID190223

COVID-6-67

Cytokine Profile in COVID-19 Patients

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Introduction and Project Objectives: The pathogenesis of coronavirus disease 2019 (COVID-19) is yet to be fully understood. Cytokine storm that played a critical role in other severe viral infections could be an important determining factor in SARS-CoV-2 infection as well. However, studies on longitudinal cytokine profiles in patients across the whole severity spectrum of COVID-19 are lacking.

Methods: We conducted a prospective observational study on adult COVID-19 patients admitted to two Hong Kong public hospitals. All cases were laboratory confirmed infection and were classified into mild (without pneumonia), moderate (pneumonia) or severe/critical (oxygen support) according to their clinical symptoms and severity. Profiling of 40 cytokines was performed on blood samples taken during early phase (within 7 days of symptom onset) and late phase (8 to 12 days of symptom onset). The difference in early and late cytokine profiles among patient groups with different disease severity were delineated, and associations between cytokines and clinical endpoints in critically ill patients were examined.

Results: A total of 40 adult patients (mild = 8, moderate = 15, severe/critical = 17) hospitalized with COVID-19 were included

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in this study. We found 23 cytokines correlated with disease severity, as proinflammatory Th1-related cytokines (IL-18, IP-10, MIG and IL-10) and ARDS-associated cytokines (IL-6, MCP-1, IL-1RA and IL-8) were progressively elevated with increasing disease severity. Furthermore, 11 cytokines were consistently different in both early and late phases, including 7 (GRO-α, IL-1RA, IL-6, IL-8, IL-10, IP-10 and MIG) that increased and 4 (FGF-2, IL-5, MDC and MIP-1α) that decreased from mild to severe/critical patients. IP-10, followed by IL-8 and IL-6, were the best performing early biomarkers to predict disease severity. Among critically ill patients, MCP-1 predicted the duration of mechanical ventilation, highest norepinephrine dose administered and length of intensive care.

Conclusion: Cytokine profile varied across different severity of COVID-19 over time. Th1 response and ARDS-associated cytokines were elevated in patients with increasing severity of COVID-19. IP-10 was the best performing early biomarker to predict severity. MCP-1 level at ICU admission was related to days on mechanical ventilation, highest dose of vasopressor and length of ICU stay.

Project No.: COVID190107

COVID-7-68
Hidden SARS-CoV-2 Infection in Hong Kong before Massive Vaccination

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Introduction and Project Objectives: Asymptomatic and mild SARS-CoV-2 infections are common. Delineating the prevalence of hidden (unrecognized) infection is essential to inform the extent of outbreak and provide a basis to evaluate mitigation strategies.

Methods: We conducted a prospective cross-sectional study from April 2020 to April 2021, following each major wave of COVID-19. Adults in the general population were recruited to estimate the prevalence of unidentified infection in Hong Kong. Evidence of SARS-CoV-2 infection was based on SARS-CoV-2 IgG detection by ELISA based on spike protein, and followed by confirmation with an electrochemiluminescence immunoassay based on the receptor binding domain (RBD) of spike protein.

Results: A total of 4,198 citizens aged ≥18 years who had not been diagnosed as having COVID-19 were recruited, including 903 (22%), 1,046 (25%) and 2,249 (53%) subjects following the three major waves, respectively. The proportion of participants aged 18-39, 40-59 and ≥60 years was 32%, 39% and 29%; with 60% female. 58% stayed in Hong Kong all along since November 2019; whilst 50% had received SARS-CoV-2 RNA tests with negative results. Only 4% reported ever contact with confirmed cases, and 5% had been isolated or quarantined. Up to 67% did not recall of any illnesses; whilst 18%, 5% and 9% had experienced respiratory symptoms, gastrointestinal symptoms, or both, respectively, prior to testing. As a result, six subjects were confirmed to be positive for anti-SARS-CoV-2 IgG. All except one subject had been tested one or more times for using deep-throat saliva, but were all negative.

Our findings estimated an adjusted prevalence of unidentified infection of 0.15% (95% C.I. 0.06% to 0.32%).

Extrapolating these findings to the whole Hong Kong, there were less than 1.9 unidentified infections for every recorded confirmed case. The overall prevalence of SARS-CoV-2 infection in Hong Kong before the massive rollout of vaccination was less than 0.45%.

Conclusion: The prevalence of unidentified SARS-CoV-2 infection was very low, implying the success of the pandemic mitigation by stringent isolation and quarantine policies even without complete city lockdown. More than 99.5% of the general population remain naïve to SARS-CoV-2, highlighting the urgent need to achieve a high vaccine coverage.

Most of the unidentified cases had received PCR test using deep-throat saliva, but were all negative. While they might not be tested at the right time, the possibility of false-negative should not be neglected; since deep-throat saliva has been shown to carry a false-positive rate of up to 31%.

Project No.: COVID190108

COVID-8-95
Effect of Cigarette Smoke on Airway Epithelium in the Pathogenesis of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection

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Introduction and Project Objectives: The coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a worldwide pandemic with over 219 million cases and over 4.5 million deaths1. It was reported that smoking-related chronic obstructive pulmonary disease (COPD) might be a crucial risk factor for COVID-19 patients to develop severe condition2,3. Cigarette smoking was also associated with the negative progression and adverse effect of COVID-194. Patients with smoking history showed more severe symptoms of COVID-19 in comparison to the non-smokers4. However, the role of CS-induced airway epithelial cell injury, which acts as the first barrier in the pathogenesis of SARS-CoV-2 infection, remains poorly understood.

Methods: Primary human airway epithelial cells were differentiated under air-liquid interface culture. Well-differentiated human airway epithelial cells were then exposed to cigarette smoke medium (CSM) before infection with SARS-CoV-2. The infection susceptibility, morphology, and the expression of proteins related to immune response, ciliated and goblet cell markers were evaluated.

Results: Despite no change in the replication of SARS-CoV-2 after medium (as control) or CSM exposure, an aggravated immune response was observed, with the upregulation of interleukin (IL)-6, IL-8, tumour necrosis factor (TNF)-α and interferon (IFN)-stimulated gene 15. In addition, CSM worsened SARS-CoV-2-induced airway epithelial cell injury, resulting in severe motile ciliary disorder and disruption of epithelial tight/adherens junctions.

Conclusion: The current findings suggest that smoking may lead to greater immune response and cell damage in SARS-CoV-2-infected airway epithelium. This study provides us better understanding of the pathogenesis of SARS-CoV-2 infection in smokers.

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Project No.: COVID190201

COVID-9-99

Assessing Novel Coronavirus Antibodies for Specificity and Function during Clinical Infection and Community Asymptomatic Cases

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Introduction and Project Objectives: Several serology tests for diagnoses of SARS-CoV-2 infection are currently in use which primarily assess Spike (S), and on occasion Nucleocapsid (N) antibodies. Most vaccines in use are Spike focused and inactivated whole virion vaccines are in limited use. Serology to detect infection is dependent on the retention of specific responses which have waning over time, contain antigenic changes, and specificity is dependent on low cross-reactivity with existing antibody responses.

Methods: We have defined the antibody landscape of the SARS-CoV-2 response after infection. We evaluated the anti-SARS-CoV-2 antibody profiles to 15 antigens by cloning and expressing open reading frames (ORFs) in mammalian cells and screened antibody responses from COVID-19 patients using the Luciferase Immunoprecipitation System (LIPS). We assessed responses in patient plasma and a large set of pre-pandemic samples to define cut-offs, and calculated assay sensitivity and specificity.

Results: The LIPS technique allowed us to detect antibody responses in COVID-19 patients to 11 of the 15 SARS-CoV-2 antigens, identifying novel immunogenic targets. We found that antigens ORF3b and ORF8 allow detection of antibody early in infection in a specific manner and revealed the immunodominance of the N antigen in COVID-19 patients. Antibodies that target non surface proteins can mediate Fc receptor functions, we therefore assessed ORF8-specific antibodies in patients for FcR binding to mediate cellular cytotoxicity and phagocytosis function.

Conclusion: These studies provide novel insights for SARS-CoV-2 replication, immunogenicity to identify key targets for specific diagnostics for breakthrough infections.

Project No.: COVID190115

COVID-10-110

Nowcasting COVID-19 Transmission Dynamics, Severity, and the Effectiveness of Control Measures

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Abstracts for Poster Presentation: Commissioned Research on COVID-19

Introduction and Project Objectives: The disease Coronavirus Disease (COVID-19), caused by the virus Serious Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was first recognised in December 2019 in a cluster of cases of atypical pneumonia linked to a wet market in Wuhan. Since then, infections have spread regionally across and outside China to the rest of the world, with over 146 million confirmed cases reported by 26 April 2021. The objectives of this study are: (1) To estimate the reproductive number in real-time throughout the epidemic, using a variety of data sources; (2) To estimate the "hospital fatality risk" and the "symptomatic case fatality risk" in real-time throughout the epidemic, using a variety of data sources, and (3) To estimate the impact of control measures on the COVID-19 epidemic such as isolation, quarantine, school closures, travel restrictions, and other social distancing measures and behavioural changes.

Methods: We use data from a variety of data sources, including: (1) Detailed reports on COVID-19 cases from Centre for Health Protection; (2) Detailed clinical information on COVID-19 patients from Hospital Authority; (3) Aggregate rates of hospitalisation rates for a variety of conditions to be obtained in December 2020, and (4) Community prevalence of illness over time from separately-funded surveys. Statistical and mathematical models will be used to estimate the incidence of infections, severity of infections, and the impact of control measures.

Results: Throughout the pandemic, we have been estimating the daily reproductive number in real time via our dashboard (https://covid19.sph.hku.hk), and found that the behaviour of the reproductive number was closely linked with the implementation of social distancing measures and border controls. Based on serological samples during March 2020, we estimated an infection rate of 0.76% (0.03%, 1.49%). Using the infection rate, we estimated the infection fatality risk up until the end of March 2020 to be 0.35% (0.17%, 2.14%). Finally, we found a substantial reduction in the reproductive number and number of cases of COVID-19 in Hong Kong related to the implementation of various social distancing measures, working from home and border closures.

Conclusion: As the COVID-19 pandemic continues in Hong Kong and the rest of the world this study provides important information on its epidemiology and control locally.

Project No.: COVID190118

COVID-11-112

Longitudinal Study of COVID-19 Seroprevalence in Health Care Workers in Comparison to the General Community

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Introduction and Project Objectives: Healthcare workers (HCWs) are at increased risk of emerging infectious diseases due to the potential for occupational exposures, particularly during the early phase of an outbreak or pandemic. As HCWs are essential to a fully functional healthcare system, the surveillance of emerging infectious diseases among HCWs is important to protect both HCWs and patients who are under their care.

Methods: We collected blood samples at 6-month intervals from healthcare workers in Hong Kong to estimate the seroprevalence of COVID-19 in healthcare workers (HCWs), a group that has elevated occupational exposure to COVID-19. When vaccines were made available in Hong Kong, we extended the study to collect post-vaccination blood samples from volunteer HCWs to assess the immunogenicity of COVID-19 vaccines. We tested the blood samples for antibodies to SARS-CoV-2 using an ELISA to detect antibodies that bind to the receptor binding domain of the spike protein, testing ELISA-positive samples for neutralising antibodies with a surrogate virus neutralisation (sVNT) assay, and then a plaque reduction neutralisation test (PRNT) with live SARS-CoV-2 virus.

Results: From June 18, 2020, to July 20, 2021, 1,729 HCWs were screened and 1,472 HCWs consented to participate in this study. Each of them provided at least one blood sample during the first 3 rounds of this study or after receiving the first or second dose of COVID-19 vaccine. Occupational exposure to COVID-19 patients in our cohort is high in general, but we only identified three seropositive samples and our estimate of the cumulative incidence of infection was 0.4% (95% CI = 0.1%, 1.1%). Antibody responses to BNT162b2 (BioNTech) were substantially greater than antibody responses to CoronaVac (Sinovac) at one month after the second dose.

Conclusion: By measuring levels of binding and neutralising antibodies against the SARS-CoV-2 virus, the seroprevalence of COVID-19 is estimated to be low in HCWs in Hong Kong despite high levels of occupational exposure. A simple comparison of mean neutralising levels of post-vaccination neutralising antibody titers in HCWs that were fully vaccinated in our cohort with published immunogenicity and efficacy data of available COVID-19 vaccines indicates that the vaccine efficacy of both the mRNA and inactivated vaccines in Hong Kong should be relatively high, particularly for the mRNA vaccine. Continuous follow-up of this cohort in the future will provide additional information on waning in antibody titers over time.

Project No.: COVID190119

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COVID-12-117

A Novel CRISPR-based Point-of-Care Test for Rapid Detection of SARS-CoV-2 Infection

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Introduction and Project Objectives: Rapid and reliable point-of-care (POC) testing for SARS-CoV-2 is an important component of the control strategy against the COVID-19 epidemic. Field application of conventional RT-PCR technology in rapid testing is often limited by the need of transporting samples to designated laboratories, installation of special analyzer and the laborious operations. Antibody-based POC testing is fast but detection is deferred because of the delay in host response following virus replication. Sensitivity is a concern for antigen testing and the low viral load setting in asymptomatic or mild cases. CRISPR-Cas system is a promising means for POC testing for viral infection, by virtues of its rapidity, affordability and reliability. The aim of this project is to study the feasibility of implementing a novel POC test for rapid detection of SARS-CoV-2, with the objectives of (a) developing a novel CRISPR-based lateral flow assay (LFA); (b) evaluating its performance in the detection of SARS-CoV-2; and (c) assessing the practicability of its use in healthcare setting.

Methods: Representative sequences of the coronavirus family were collected from literature and public databases. Short sequences of around 200bp emulating SARS-CoV-2 gene targets and the corresponding guide RNAs were designed. A LFA-CRISPR-based detection kit was designed and testing protocol was developed. The performance of the new system was evaluated by conducting mock virus testing in different institutions and environment.

Results: The synthesis of SARS-CoV-2 gene target and its guidance RNA has been successfully completed. A novel lateral flow dipstick based on fluorescence quantitative PCR by CRISPR-Cas technologies was established. A 2-step CRISPR-based POC test kit was fabricated and evaluated. Mock virus testing was performed in multiple facilities in Mainland China and Hong Kong. There were a total of 171 true positives, 5 false positives, 171 true negatives and 3 false negatives, giving a sensitivity of 98% and specificity of 97%.

Conclusion: The novel detection kit is potentially useful for enhancing the efficiency of SARS-CoV-2 diagnosis, complementing strategy for controlling the spread of the epidemic. The high specificity and sensitivity, the anticipated low cost for mass production, and the simple operation without requiring complex instruments are the advantages of the system. The practicability and impacts of LFA-CRISPR-based tests for SARS-CoV-2 infection in healthcare settings would be assessed in near future.

Project No.: COVID190102

COVID-13-123

Public Compliance with Disease Prevention and Public Health Measures to Control COVID-19

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Introduction and Project Objectives: Disease prevention measures (DPM) such as wearing face masks, social distancing, and vaccination are effective in controlling the spread of COVID-19. This study applied the Health Belief Model to identify facilitators of and barriers to DPM adoption.

Methods: A two-wave longitudinal telephone survey was conducted with 1225 and 1003 participants successfully interviewed in December 2020 and June 2021. Descriptive and logistic regression analyses were conducted to examine patterns of and factors associated with DPM adoption.

Results: Baseline adoption of DPM was high: 94.4% wore face masks in public areas; 88.4% avoided touching their eyes, nose, and mouth; 82.1% performed hand hygiene; 81.5% used alcohol-based hand rub; 74.6% practiced social distancing; and 39.7% tested for COVID-19 on a voluntary basis. Perceived benefits, perceived barriers, self-efficacy, encouragement from significant others, perceived acceptability, and COVID-19 related disruptions in daily life were associated with individuals' adoption of DPM at baseline. At 6-month follow-up, 48.8% demonstrated sustained or increased adoption of DPM. Sustained or increased adoption was associated with greater perceived benefits and obstacles of DPM. At baseline, 42% of the participants indicated intention to vaccinate, 31.5% showed vaccine hesitancy and 26.5% reported refusal. Intention to vaccinate at baseline was associated with male gender, older age, being employed, exposure to previous pandemic (such as SARS and swine flu), high perceived susceptibility, poor knowledge about COVID-19, lack of concerns about vaccine safety, acceptance of government prevention measures, encouragement from significant others, and high self-efficacy. At 6-month follow-up, 23.4% of the participants indicated that they received vaccination. Vaccination uptake at 6-month follow-up was not associated with intention to vaccinate at baseline. Major reasons cited for vaccination uptake were "required by work" (12.8%), "safeguard personal health (15.8%), "safeguard family's health" (15%), and "respond to government appeal" (9.9%). Older age, baseline exposure to COVID-19,

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baseline perceived susceptibility, baseline acceptance of government prevention measures, having family and friends who had been vaccinated were associated with actual vaccination up-take.

Conclusion: Based on these findings, we recommend promoting the benefits of DPM thereby encouraging citizens' continual DPM adoption. In order to encourage fellow citizens to get vaccinated, efforts should be made to promote the benefits of vaccination, especially in terms of safeguarding individuals' and their families' health. Amicable arrangements should be made to encourage individuals to accompany needed families and friends to vaccinate.

Project No.: COVID190216

COVID-14-132
SARS-CoV-2 Replication and Immune Response Induced in the Respiratory Epithelial Cells of Paediatric and Adult

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Introduction: SARS-CoV-2 infection ranges from asymptomatic infection to fatality. The majority of laboratory-confirmed cases are adults, while children cases comprise a small percentage with a milder clinical course. Thus, a direct comparison of the susceptibility and immune response between adults and children allows a better understanding of their clinical outcomes and their role in disease transmission.

Objectives: To compare the virus replication kinetics in the respiratory epithelial cells and the immune response in paediatric and adult subjects' nasal epithelial lining fluid hypothesized that there are intrinsic differences between the respiratory cells originated from children and adults, and therefore their susceptibility to SARS-CoV-2 infection. Moreover, the mucosal antibody response in the COVID-19 patients may have a role in the milder disease outcome in children compared with adults.

Method: Primary human nasopharyngeal epithelial cells (dHNPEC) were obtained from healthy children and adults for cell isolation and air-liquid interface differentiation. These in vitro cell cultures were subjected to SARS-CoV-2 virus infection. The viral replication kinetics between paediatric and adult cells were compared at 1, 24, 48, 72 and 96 hours post-infection. In addition, the mucosal antibody response specific to SARS-CoV-2 Spike protein in paediatric and adult COVID-19 patients was assessed by collecting their nasal epithelial lining fluid (NELF) longitudinally from disease onset every week until the 4th week. The SARS-CoV-2 specific IgA level and the neutralization potency were measured by ELISA and surrogate ACE2 - SARS-CoV-2 receptor binding domain assay, respectively.

Results: Effective replication of the SARS-CoV-2 was observed in the dHNPEC. Significant increase in viral titer in paediatric dHNPEC between 1-to-72 hpi (median log10TCID50/ml = 2.71 vs 6.96, p = 0.0394) and in adult's dHNPEC between 1-to-96 hpi (median log10TCID50/ml = 3.08 vs 6.39, p= 0.0253) were detected by Friedman test followed by Dunn's multiple comparisons test. No differences in the viral load between paediatric and adult dHNPEC were significant. A higher percentage of paediatric patients (n=33) possessed SARS-CoV-2 Spike protein 1 (S1) specific immunoglobulin A (IgA) than adult patients (n=18) in their NELF in the first nine days after diagnosis. S1-specific IgA was induced early in asymptomatic paediatric patients (n=14) than symptomatic patients (n=19). The IgA and IgG levels correlated positively with the surrogate neutralization readout. Within the first week of diagnosis, higher S1-specific antibodies in NELF and plasma and lower viral loads were detected in paediatric than adult patients with mild disease.

Project No.: COVID190112

COVID-15-135
How High is the Risk of Environmental Contamination and Airborne Infection of the SARS-CoV-2 Virus?

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Introduction and Project Objectives: This study aims to detect the presence of SARS-CoV-2 virus in the air and environment at frequently visited places of hospitals admitting COVID-19 patients, find out the risk factors affecting the presence of virus

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particles in the air and environment, and explore the potential of airborne transmission for SARS-CoV-2.

Methods: The study comprises of two parts. In part 1, bi-weekly surveillance was conducted in eight hospital areas through swabbing inanimate surfaces and collecting air samples for SARS-CoV-2. In part 2, a longitudinal study was conducted to follow COVID-19 patients for up to 10 days to detect presence of SARS-CoV-2 at surfaces and air inside the isolation room daily.

Results: In part 1, among the 2150 samples tested, only 2 air samples and 1 surface sample in outpatient areas were positive for SARS-CoV-2. All other samples including inpatient areas other than the COVID-19 isolation rooms and medical staff areas were negative. In part 2, 3291 samples were collected during 348 patient-days of follow-up. Around 5.0% of the samples were positive, including 6.6% of surface samples and 2.1% air samples, and 6.7% of samples in isolation room, 1.0% of samples in anteroom, and zero outside the anteroom. Environmental or air contamination was associated with pre-existing cardiovascular or respiratory conditions, cough or fever on day of sampling, CT value of the latest PCR test on respiratory tract samples, time since last disinfection of cubicle and lower environmental temperature.

Discussion: The findings showed at low to medium epidemic intensity under prevailing precautions for preventing COVID-19 transmissions, the risk of SARS-CoV-2 contaminating general hospital environment is low. This does not apply to the isolation room and anteroom where COVID patients are staying. Patients with pre-existing conditions, fever, cough and higher virus load would pose higher risk for environmental contamination. Six-hourly or more frequent environmental disinfection and higher room temperature could reduce the level of air contamination. Presence of coughing on day of sampling was associated with higher risk of finding virus in the air, but the virus was not consistently detected in the post-cough samples. Additional engineering measures in addition to negative pressure ventilation might be considered to further reduce contaminations in the vicinity of the patient.

Conclusion: Air and surface samples near the patient could contain virus. While prevailing measures seemed adequate for general hospital environment, additional engineering measures to further reduce chance of transmission in the isolation room might be considered.

Project No.: COVID190101

COVID-16-137
Utilization of CRISPR/cas9-Modified Lactobacillus Casei as an Oral Vaccine for Treating and Preventing COVID-19 Infection

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Introduction: COVID-19 is a highly infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Receptor binding domain (RBD) of the Spike (S) protein of SARS-CoV-2 is vital in binding to the angiotensin converting enzyme 2 (ACE2) receptor of human cells and facilitates viral entry. The mucosal delivery of vaccines for mass immunization is an explicit goal of the World Health Organization (WHO) to deal with global pandemic. In this project, we utilized CRISPR/cas9 gene-editing procedures (with bio-containment features) to manufacture recombinant Lactobacillus casei (an edible probiotic) which expressed sufficient quantities of individual antigenic epitopes of RBD of the S protein of SARS-CoV-2, and triggered immune responses, in vivo, after oral consumption.

Project Objectives:

1. To manufacture recombinant Lactobacillus casei using gene-editing CRISPR/cas9 procedures to express the antigenic epitopes of RBD of the S protein of SARS-CoV-2.
2. To evaluate the optimum dosing regiments of oral administration of recombinant L. casei and the generation of high-titre antibodies against the S protein in the serum of golden Syrian hamsters after oral consumption.

Methods: Antigenic epitopes (receptor binding motif (RBM), B-cell and T-cell epitopes) of the RBD of the S protein of SARS-CoV-2 were designed and constructed using DNA sequences predicted based on computational predictive algorithms, and inserted into the genome of L. casei using CRISPR/cas9 techniques (with bio-containment features). The growth rate (at 37oC) of individual type of recombinant L. casei was monitored and compared every hour by measuring the optical density of the bacterial culture medium (MRS) at 600 nm (OD600) using an automated spectrophotometer / incubator.

Results: All three antigenic epitopes of the RBD of the S protein of SARS-CoV-2 were successfully constructed and inserted into the genome of L. casei using CRISPR/cas9 procedures. The growth rate (37oC) of individual recombinant L. casei was "inversely correlated" with the size of the epitope expressed, i.e. RBM (~26.2 kDa, slowest growth) > B-cell epitope (~5.1 kDa) ≥ T-cell epitope (~3.5 kDa, fastest growth).

Conclusion: Our results illustrated that we have successfully constructed and inserted the antigenic epitopes of the RBD

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of the S-protein of SARS-CoV-2 into the genome of L. casei. It remains to be determined about the efficacy of these recombinant probiotics (administered alone or in combination) after oral consumption in triggering the immune responses against challenge of different variants of SARS-CoV-2 in golden Syrian hamster – a gold standard model for SARS-CoV-2 related research.

Project No.: COVID190219

COVID-17-140
Understanding Transmission Risk of SARS-CoV-2 in A&E and Patient Rooms

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Introduction and Project Objectives: To evaluate the exposure risk of SARS-CoV-2 virus in the hospital setting, an environmental surveillance was conducted at the Accident and Emergency (A&E) Department of a teaching hospital in Hong Kong from 7 April 2020 to 30 March 2021. This will be followed up by a multi-route modelling using patient care activity data in the second stage of the study. The used multi-route model has been evaluated using the two-bus outbreak of COVID-19 in Hunan in early 2020, in which some limited data of human behaviour at the time of infection became available. The airborne transmission was found to predominate while fomite transmission was negligible in the outbreak.

Methods: In response to the COVID-19 pandemic, in addition to the routine infection control guideline, the A&E Department has adopted enhanced measures according to Hospital Authority Communication Kit –Coronavirus disease 2019 (Hospital Authority, 2021). In addition, the A&E Department has designated areas for gown up and gown down respectively.

Results: From 39 sampling events, a total of 2216 surface samples and 339 air samples (paired with 339 negative control) were collected from 77 surfaces and 3 air sampling sites. Three surface samples were tested positive for the N-gene of SARS-CoV-2 RNA, resulting in a surface positive rate of 0.135% (3/2216). The sampled surfaces are classified into "patient area" (N=1189), "healthcare worker area" (N=531), and "patient-healthcare worker area" (N=496) based on the accessibility to patients and healthcare workers. None of the air samples was tested positive. The three positive surface samples were collected from the area accessible by both the health care worker and the patients (the wall next to the resuscitation room and the floor of triage area) and from the patient waiting area with limited access by health care workers (door handle of male washroom), suggesting a higher risk of contamination of patient accessible surfaces. The cycle threshold values of the three positive samples ranged from 36.7-38.4, indicating that the samples are likely non-infectious. During the study period, a total of 283 SARS-CoV-2 infected patients have visited or have been diagnosed at the A&E Department of this teaching hospital.

Conclusion: Overall, our results suggest that the risk of exposure to SARS-CoV-2 at the A&E Department has remained low, possibly due to the success of infection control measures.

Reference:
Hospital Authority: Hospital Authority Communication Kit – Coronavirus disease 2019: https://www.ha.org.hk/haho/ho/pad/Comkit.pdf. Last version 7.12 updated 23 September 2021.

Project No.: COVID190113

COVID-18-142
Identification of Lingnan Chinese Medicines against COVID-19 Infection

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Introduction and Project Objectives: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the causative agent of the acute respiratory disease (COVID-19), has resulted in millions of deaths worldwide since its outbreak in Dec 2019. Numerous efforts have been made globally to develop effective prevention and treatment therapeutics. In China, the use of traditional Chinese medicine (TCM) has been reported to have good efficacy in the clinical treatment of the viral infection. Intriguingly, TCMs derived from Lingnan region (Southern China) have long been used in clinical applications due to their efficacious antiviral activity.

Methods: Here, a screening platform of anti-SARS-CoV-2 infection has been established targeting an extensive library of Lingnan TCM herbs/single molecules. Those shown to have promising efficacy will be developed further, using well-established pharma drug trial procedures, for consideration as novel herbal prescriptions. During infection by SARS-CoV-2, the

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spike (S) protein of the virus recognizes angiotensin-converting enzyme 2 (ACE2) on the host cell surface, and this triggers viral entry via endocytosis. In addition, we propose that two-pore channels (TPCs; a family of pleiotropic cation channels) might mediate endocytosis of SARS-CoV-2 into host cells as they have been shown to do for Ebola and MERS-CoV viruses. Once inside the host cells, non-structural proteins, such as 3CL protease, enable viral replication and proliferation, leading to the widespread pathogenic damage that is characteristic of this disease. Thus, the S-protein, ACE2, 3CL protease and TPCs are the target proteins we are using for screening Lingnan TCMs both in vitro and in vivo.

Results: In total, over 300 TCM products (both water and ethanol extracts), and over 200 phytochemicals have been subjected for screening so far, from which over 40 hits have been identified. We have shown that the identified TCM extracts/phytochemicals can significantly inhibit the host cell entry of SARS-CoV-2 pseudovirus in a dose-dependent manner. In addition, these TCM herbs have an excellent safety record from their historical usage, which suggests they can be "fast-tracked" for clinical application.

Conclusion: Thus, over the last 12 months, we have established a multi-target screening platform and successfully identified several potent herbs/phytochemicals for subsequent drug development and/or clinical application.

Project No.: COVID190213

COVID-19-149
The Impact of COVID-19 on Physical Wellbeing of Survivors

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Introduction: The coronavirus disease 2019 (COVID-19) has infected > 219 millions of people worldwide. Although Hong Kong has a relatively low number of confirmed cases, it is not uncommon for COVID-19 survivors to experience various extents of cognitive, physical and psychosocial sequelae. Importantly, a few overseas studies also reported a high prevalence of fatigue in these survivors although factors related to such fatigue remain unclear.

Project Objective: (1) To assess the incidence of fatigue of COVID-19 survivors when discharge from hospitals; and (2) to determine factors predicting fatigue in these survivors.

Methods: Potential COVID-19 survivors were referred by their physicians from four local hospitals at discharge. These survivors were contacted and consented participants were invited to undergo assessments in the respective hospitals or on a university campus. All participants completed a battery of biopsychosocial tests including fatigue assessment scale, quadriceps strength and spirometry tests, functional evaluations using 6- minute walk and 30-second sit-to-stand tests, cognitive test using Chinese auditory verbal learning test. Descriptive analysis was used to summarize the findings. Factors affecting fatigues were analysed by a logistic regression model with age, gender, body-mass index post-COVID time, comorbidity, and education level being entered into first level.

Results: Ninety-four participants (age range: 24 to 88 years; 59.2% females; mean duration of COVID: 4.72±2.8 months) were assessed. Fatigue was reported in 45% of participants with 4% experience severe fatigue. Those reported fatigue had significantly lower forced vital capacity (FVC) (p=0.016) and a trend of reduced forced expiratory volume (FEV1) (p=0.051) and lowered normalized torque (left and right) of the quadriceps muscles (p=0.069). The regression model showed that COVID-19 survivors with lower FVC (odds ratio: 0.382, p=0.084), and quadriceps torque (odds ratio= 0.979, P=0.016) were more likely to have clinically significant fatigue.

Discussion: While up to 45% of COVID-19 survivors experience clinically significant fatigue, the mechanisms underlying post-COVID-19 fatigue remains unclear. Our findings suggest that self-perceived clinically significant fatigue at discharge from hospitals is characterized by poor forced vital capacity and poor lower limb strengths. Structured rehabilitation programs targeting the restoration of lung function and lower limb muscle strengths of COVID-19 survivors are warranted to reduce their fatigue, and enhance their ability in performing activities of daily living.

Project No.: COVID190222

COVID-20-151
Development of an Enzyme-Linked ImmunoSorbent Assay Detecting Antibodies against a Novel Secreted Antigen of SARS-CoV-2

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Introduction and Project Objectives: A novel human coronavirus, known as SARS-CoV-2, has infected millions of individuals globally since December 2019. Currently, early molecular diagnosis of human SARS-CoV infection mainly depends on the quantitative reverse-transcription-polymerase (RT-qPCR) and sequencing preformed in laboratory. There are also commercially available COVID-19 antigen rapid tests, and most of them are detecting spike or nucleoprotein in the format of lateral flow assay. In January 2020, we first reported that one of the main differences between SARS-CoV-2 and other human pathogenic coronaviruses is the presence of an uncharacterized orf8 viral protein (EMI, 2020). We further

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demonstrated that orf8 is a secreted viral protein as exemplified by the detection of secreted orf8 in COVID-19 patients' serum using Liquid Chromatography–Mass Spectrometry, and the detection of overexpressed orf8 in the supernatant of cultured lung epithelial cells (mBio, 2020). Therefore, we hypothesized that SARS-CoV-2 orf8 protein is an immunogenic secreted protein and the detection of its antibodies in patients may be an alternative for early diagnosis of COVID. In this project, we aimed to develop an accurate assay for the detection of orf8 antigen or anti-orf8 antibody in the serum samples of COVID-19 patients.

Methods: We optimized the recombinant orf8 protein production using human Expi293 expression system. Highly purified orf8 protein was used for the development of ELISA-based anti-orf8 antibody detection in serum samples of COVID-19 patients. In addition, we used the peptide library to identify the linear B cell epitopes of SARS-CoV-2 orf8 protein from COVID-19 patients.

Results: We characterized the SARS-CoV-2 orf8 as a novel immunogenic secreted protein and utilized it for the accurate diagnosis of COVID-19 (mBio, 2020). Extracellular orf8 protein was detected in cell culture supernatant and in sera of COVID-19 patients. In addition, using our optimized home-made ELISA, we demonstrated that orf8 was highly immunogenic in COVID-19 patients, who showed early seropositivity for anti-orf8 IgM, IgG, and IgA. Furthermore, we identified the most immunogenic linear epitope of orf8 protein from COVID-19 patients (EMI, 2021).

Conclusion: We hypothesized that orf8 secretion during SARS-CoV-2 infection facilitates early mounting of B cell response. It is evidenced by the early seropositivity for anti-orf8 antibodies in this study. Our optimized ELISA detecting anti-orf8 IgG antibody can be further developed for the serological test and diagnosis of COVID-19.

Project No.: COVID190120

COVID-21-153
Long Term Immunological Response and Longitudinal Seroepidemiology of SARS-CoV-2 in Hong Kong

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Introduction and Project Objectives: COVID-19 patients usually develop antibody response against SARS-CoV-2 within 2-3 weeks after symptom onset. For recovered COVID-19 patients, antibody status is useful for assessing the risk of reinfection, because seropositive patients have a much lower risk of reinfection. Furthermore, since SARS-CoV-2 antibodies can be detected in blood for several months, antibody test is useful for retrospective diagnosis for patients who were not diagnosed during the acute stage of infection. Serological surveillance is therefore an important tool in revealing the true burden of COVID-19. In this study, we monitored the long term kinetics of anti-SARS-CoV-2 antibodies among recovered COVID-19 patients, and we conducted serosurveillance to determine the burden of subclinical infection in Hong Kong.

Methods: The long term antibody response of COVID-19 patients was determined using binding antibody tests against the spike protein (including the receptor binding domain [RBD]) or nucleoprotein (N), surrogate virus neutralization test (sVNT), and conventional virus neutralization test (cVNT) and at 2, 6 and 12 months post symptom-onset (MPSO). For the serosurveillance study, sera from the general population were first screened using a binding antibody assay or sVNT, and seropositivity was confirmed using the cVNT.

Results: Long term antibody response among recovered laboratory-confirmed COVID-19 patients: The seropositive rates declined for all antibody assays at 6 or 12 MPSO. Among different antibody assays, anti-RBD IgG has the highest seropositive rate at all time points (>95%). The seropositive rates of sVNT or cVNT were lower than those of anti-RBD IgG at 6 (about 90%) and 12 MPSO (about 80%). Most patients were seronegative for IgM against spike or N proteins at 6 or 12 MPSO. Quantitative analysis showed that there was a gradual decline in the levels of antibodies in all assays between 2 and 12 MPSO. For sVNT and cVNT, the decline of antibody titers occurred mainly from 2 to 6 MPSO. General population serosurveillance study: Before April 2021, no serum specimen tested positive by both binding antibody assay/sVNT and cVNT. However, in April 2021, 2% of the serum specimens tested positive by both sVNT and cVNT.

Conclusion: The decline in antibody level among COVID-19 patients suggests that these patients should receive COVID-19 vaccine to prevent reinfection. Results from the serosurveillance study suggests that the rate of subclinical COVID-19 infection in Hong Kong remain low before April 2021. The seropositive individuals since April 2021 may be related to COVID-19 vaccines rather than subclinical infections.

Project No.: COVID190124

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COVID-22-155

Psychological Trauma and Unsafe Behaviour during the COVID-19 Pandemic: a Mixed-Method Study of People's Emotion, Knowledge, Attitude and Behavior

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Introduction: Everyone in Hong Kong has been affected by the COVID-19 pandemic in various ways, such as health, employment, education and social aspects. It is important to conduct a population-wide study to fully gauge the impact of this virus on citizens in Hong Kong.

Project Objectives: To examine Hong Kong residents' current level of psychological trauma, knowledge and attitudes about COVID-19, behaviours regarding infection prevention, reasons of not adopting appropriate preventative actions, such as receiving COVID-19 vaccination.

Methods: A mixed-method design was used. First, a telephone survey was carried out among 3011 adults in Hong Kong, one year since the beginning of the pandemic, to investigate their level of psychological trauma, compliance with preventative measures, effect of reading news reports on COVID-19, vaccine acceptance and willingness to participate in voluntary testing (phase 1). Logistic regression analyses were used to determine the association between demographic variables of interest, PTSD, the Prevention Score, vaccine acceptance and engagement in voluntary testing. Second, with a phenomenology approach, 31 older adults were interviewed for deeper understanding of their experiences, such as receiving vaccination (phase 2). A comprehensive analysis of qualitative data was conducted based on the framework of Critical Medical Anthropology.

Results: The prevalence of possible post-traumatic stress disorder was found to be 12.4%, lower than that reported by earlier studies. Socio-demographic correlates of psychological trauma and health-protective behavior were also found. Respondents were generally compliant with routine preventative measures, but less than half had accepted vaccination and voluntary testing. The qualitative findings further revealed struggles experienced among older adults at four social-levels according to the Critical Medical Anthropology framework: (1) individual (trust and confidence, social support networks), (2) micro-social (stigma of healthcare providers), (3) intermediate-social (government), and (4) macro-social levels (cultural stereotypes, civic and collective responsibility, economic) factors.

Conclusion: Socio-demographic factors, such as educational level, affected both psychological trauma and engagement in health-protective measures. Furthermore, deciding to receive COVID-19 vaccination is a complex decision and experience for older adults. These results have implications for the design of governmental policies to help manage the effects of the pandemic and to prevent future outbreaks.

Project No.: COVID190217

COVID-23-161

Investigation of Hong Kong's Early Detection, Assessment and Response (S-EDAR) System to the New Emerging Infectious Disease Outbreak COVID-19

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Introduction and Project Objectives: To investigate how Hong Kong's system of early detection, assessment and response (S-EDAR) to COVID-19 outbreak can be enhanced.

Methods: A formative evaluation is used with a two-stage design. In Stage 1, we assessed S-EDAR in Hong Kong and evaluated its effectiveness and implementation by literature reviews, comparative case study in 6 Western Pacific jurisdictions, key informant interviews, system dynamics modelling and expert workshops. In Stage 2, we develop an enhanced S-EDAR informed by international expert input and the feasibility and applicability in the local context from a Delphi survey. The study settings/participants include:

- Six regional case studies in Hong Kong, Japan, Malaysia, South Korea, Shanghai, and Singapore;
- Over 35 local key informants including policy makers, healthcare administrators and professionals, chairpersons of business organizations, and general public/patients;
- Over 17 local and international experts;
- SARS-CoV-2 infection surveillance and control data from the Centre of Health Protection and Hospital Authority

Results:

1. Scoping reviews

There was adequate empirical evidence for the effect of physical distancing at individual level and of partial/full lockdown in reducing transmission, but not for individual interventions including workplace/business closure. We analysed the implementation barriers and facilitators by the Consolidated Framework for Implementation Research.

2. Comparative case study

The key lessons highlight the need for an on-going surveillance

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system, broaden screening, comprehensive preparedness plans and regular drills, information technology, capacity for testing, contact tracing, isolation and quarantine. Measures should be proportionate to the stages of the outbreak to reduce socio-economic impacts. Relaxation of measures should be based on risk assessment, implemented in stages, and reversible when needed.

3. System dynamics modelling
The simulation suggests that both PCR-polymerase chain reaction(with a 7-day quarantine) and rapid antigen test screening to inbound travelers are unable to control the local outbreak if the travel volume returns to the level in 2019. Nevertheless, if the travel volume can be kept as a low level such as the level before the entry ban of all countries, screening can still work well.

4. Enhanced S-EDAR based on WHO guidelines, key informants and experts

We propose an enhanced S-EDAR with three components:1) Preparedness plan and resilience system for public health emergencies, 2)Readiness, and3)Response system with implementation strategies at government, healthcare and community levels.

Conclusion: The enhanced S-EDAR will equip the health system with instruments that have the capacity to capture the dynamic and complex context in preventing and controlling future pandemic threats.

Project No.: COVID190105

COVID-24-175
Role of Gastrointestinal Tract and Gut Microbiota in Pathogenesis of Coronavirus Disease 2019 (COVID-19): A Missing Site for Viral Replication & Transmission

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Introduction and Project Objectives: Although there is mounting evidence suggesting that the gastrointestinal tract is involved in COVID-19, role of GI tract and gut microbiota in pathogenesis of this disease remain unknown. We aim to quantify SARS-CoV-2 viral load in feces of COVID-19 patients, evaluate gut bacterial and viral microbiota in COVID-19 patients and its association with disease severity and outcomes, determine the effect of COVID-19 on gut inflammation and ACE2 expression, and explore gut microbes regulating ACE2 expression to decrease disease risk for severe COVID-19.

Method: 50 patients with COVID-19 hospitalized with laboratory-confirmed SARS-CoV-2 infection, 30 patients hospitalized with community-acquired pneumonia (pneumonia controls), and 30 healthy individuals (healthy controls) were recruited. The pneumonia patients with COVID-19 had stool and plasma sample collected in three sampled time until discharge. After discharge, 20 patients were followed, and one stool sample was collected at 1 week, 2 months and 6 months respectively. The pneumonia patients without COVID-19 and healthy controls have stool collected only once at recruitment. Specimen was subjected to laboratory tests including COVID-19 load, fecal bacterial and viral profiling, inflammatory markers profiling and ACE2 expression detection.

Result: 73.3% patients had SARS-CoV-2 nucleic acid detected in feces at hospitalization (median 3.86×103 copies per mL inoculum). 46.7% patients showed active SARS-CoV-2 infection with strikingly higher coverage the 3′ vs 5′ end of SARS-CoV-2 genome in their fecal viral metagenome profile, even after disease resolution. Patients with COVID-19 had disturbed bacterial and viral microbiota, compared with healthy controls ($P < 0.05$), which persisted up to 6 months after recovery. Several gut commensal bacteria with known immunomodulatory potential such as Faecalibacterium prausnitzii, Eubacterium rectale and bifidobacteria and two Pepper-derived RNA virus species (RNA virus) were underrepresented in patients. Depletion of these bacterial and viral taxa associated with more severe disease as well as elevated concentrations of inflammatory cytokines and blood markers ($P < 0.05$).

Conclusion: Our study showed prolonged and active SARS-CoV-2 virus in the gut of patients with COVID-19, even after recovery, which highlights the importance of long-term coronavirus and health surveillance and the threat of potential fecal-oral viral transmission. We for the first time identified several biomarkers of gut bacterial and viral microbiota specific to COVID-19 cases, and elucidate their associations with disease severity and host immune response. This will open up potential therapeutics to modulate the gut microbiota to reduce severity and complication of COVID-19 infections.

Project No.: COVID190111

COVID-25-189
Workplace Safety towards SARS-CoV-2 among Non-Healthcare Workers in Hong Kong, Nanjing and Wuhan: Prevention, Response and Sustainability

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Abstracts for Poster Presentation: Commissioned Research on COVID-19

Introduction and Project Objectives: There has been no validated tool to assess the performance of workplace prevention measures towards respiratory infectious diseases in non-healthcare work settings, especially for the COVID-19. This study aimed to develop a new tool to measure workplace safety towards infection control and prevention of COVID-19 in a variety of non-healthcare industries from cities of China with different socioeconomic development.

Methods: In this cross-sectional study during 07/2020 to 04/2021, 6684 non-healthcare workers were recruited from Hong Kong, Nanjing and Wuhan of China and responded a standard questionnaire containing information of prevention measures implemented by companies and individual workers towards infectious control, particularly SARS-Cov-2 and COVID-19. All participants were randomly stratified into two sub-samples of equal sample size as the training sample and validation sample. The workplace safety towards SARS-Cov-2 and COVID-19 index was developed and validated using exploratory factor analysis (EFA) and confirmatory factor analysis (CFA). The robustness of the index was further verified by the actual uptake of SARS-Cov-2 testing.

Results: We identified 14 variables in a newly developed "Workplace safety towards SARS-Cov-2 & COVID-19 index (WSSC index)", with three sub-indices named "Workplace's implementation of occupational safety and health prevention measures", "Company's management of occupational safety and health" and "Worker's exposure prevention behavior and awareness". The new WSSC index obtained a good internal consistency reliability (Cronbach's alpha coefficients ranged: 0.76-0.91), good composite reliability (composite reliability ranged: 0.70-0.95) and satisfactory fit of the model (GFI=0.95; SRMR=0.05; RMSEA=0.07). We further performed stratified analysis according to cities and the index remained stable. Workers with higher scores of the WSSC index were more likely to uptake virus testing. A higher score of this novel index indicates better awareness of workplace safety towards prevention and control of COVID-19.

Conclusion: "Workplace safety towards SARS-Cov-2 & COVID-19 index" is a novel and validated tool to horizontally measure the awareness of workplace safety towards SARS-Cov-2 & COVID-19 among non-healthcare workers across industries and cities of China with different layers of socioeconomic development. Whether the tool is valid for longitudinally monitoring is under testing.

Acknowledgment: this study is funded by Health and Medical Research Fund (Reference number: COVID190104). We appreciate the Hong Kong Federation of Trade Unions-Occupational Safety and Health Association for their support. Please contact shelly@cuhk.edu.hk

Project No.: COVID190104

COVID-26-203
Characterization of the Distribution of Aerosols Released from Drainage Ventilating Pipe of Public Housing Buildings

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Introduction and Project Objectives: Occurrence of COVID-19 cases in public house building suggested that aerosols released from drainage vent pipe at building rooftop can be a potential route for transmission of SARS-CoV-2. However, there is a lack of comprehensive studies on the spatial distribution of aerosols discharged from drainage vent.The project aims to characterise the spatial distribution of aerosols released from the drainage vent pipe at the rooftop and the top floor residential units, and to identify the key contributing factors influencing the distribution of aerosols. The ultimate goal is to develop of a risk assessment model for exposure to SARS-CoV-2.

Methods: The project employs computational fluid dynamic (CFD) simulation and mathematical modelling supported by onsite measurements to characterise distribution of aerosols discharged from the draining vent pipe. Four representative types of public housing blocks in Hong Kong will be studied. Tracer gas will be released by gas doser at the drainage vent discharge on the rooftop. Tracer gas will be tracked by wireless sensors placed at various sites on rooftop. Key contributing parameters, such as wind speed and height of vent pipe, that influencing the spatial distribution of aerosols in residential units on the first to third floors below the rooftop will be identified.

Results: So far, five public building blocks of cruciform type have been studied. The wind speed on the day of field measurement was 1.5 – 2.0 m/sec, which was regarded as low wind speed. When tracer gas was released at the vent discharge near the rooftop edge, tracer gas was detected at on the first and third floors (37/F and 35/F) below the rooftop, but not the second floor (36/F). This could be a result of turbulence effect. Similar result patterns were obtained when tracer gas was released at 1 m, 1.5 m or 2 m above ground level. However, when the tracer gas was released near the rooftop centre, tracer gas were detected at lower concentrations in the on 37/F and 35/F.

Conclusion: Aerosols discharged from the drainage vent pipe at the rooftop could reach the three floors below the rooftop. A turbulence effect was observed, and height of drainage vent pipe to as high as 2 metres did not have much influence on the distribution of aerosols. However, when source of aerosols was near the centre of the rooftop, lower aerosols concentration were detected at the three floors below the rooftop.

Project No.: COVID190203

Abstracts for Poster Presentation: Commissioned Research on COVID-19

COVID-27-208
Incident Mental Morbidity and Web-based Psychological treatment in COVID-19 (A WMH-COVID-19 study)

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Introduction and Project Objectives: The COVID-19 pandemic brought about unprecedented challenges in mental health care burden and care delivery in infection survivors, healthcare workers, quarantine camp confinees, and the general public. This study aims to (i) estimate the enduring mental health care burden and costs from COVID-19; (ii) test and implement web-based psychological treatment for depressive and anxiety disorders

Methods: PHASE 1 - 1-year web-based cohort study measuring mental morbidity (anxiety, depression, PTSD) and burden at baseline, 6 months and 12 months. Four samples include: (i) 500 COVID19 patients via hospital database (ii) 1000 Penny Bay quarantine camp confines (iii) 1500 representative public healthcare workers from major acute hospitals in Hong Kong (iv) 2500 persons via randomly selected household addresses through the Census and Statistics Department.

Progress and preliminary Results: Recruitment has been completed for health-care workers, and is ongoing for the other groups (71%, 90%, 51% registered for public, quarantined, and survivors groups).

To date (October 2021), of the 4283 survey baseline respondents, 50% were screened positive for at least one mental disorder (generalized anxiety: 39.7%, depression: 35.5%, suicidal thoughts or behaviours: 16.7% and PTSD: 13.7%). The figures were similar in healthcare workers, COVID 19 survivors, quarantine camp confinees and the general public. 38.3% of the COVID-19 survivors were screened positive for subjective cognitive impairment up to a year since index infection. The 6-month and 12-month waves of follow-up survey will track changes in mental health statistics and needs in these 4 groups.

PHASE 2 – web-based psychological treatment: The first 150 respondents with significant anxiety and depressive symptoms are randomized to receive either a web-based 2-month cognitive behavioral therapy-based psychological treatment or control (educational materials).

Progress: Recruitment is on-going, with 42 participants randomised (21 treatment, 21 control) to date. Ratings of depression, generalized anxiety, acute stress disorder and post-traumatic stress disorder symptoms and health-related quality of life will be obtained via self-report questionnaires.

Expected outcomes: It is hypothesized that web-based psychological treatment will result in a 50% reduction in PHQ-ADS score compared to control intervention at both 6 and 12 weeks from baseline.The proposed study estimates the incidence and associated burden of common mental disorders from COVID-19. It also provides web-based psychological treatment as an accessible and cost-effective solution to the escalating mental morbidity, which will serve as a model ready to serve the mental health needs of the population in the post-COVID-19 era.

Project No.: COVID190212

COVID-28-212
Discovery and Mechanistic Evaluation of Antiviral Treatment Options for Coronavirus Disease 2019 (COVID-19) Through Structure-based Drug Discovery and Drug Repurposing Approaches

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Introduction and Project Objectives: The Coronavirus Disease 2019 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel betacoronavirus first identified in patients with pneumonia in Wuhan, China, in late 2019 that quickly disseminated worldwide. Antiviral treatments for COVID-19 remain limited. This project aims to find rapidly available COVID-19 treatment options using our established high-throughput drug compound library screening and in-silico structure-based screening platforms, and to thoroughly assess the selected drug candidates' anti-coronaviral activities and mechanisms in-vitro, in ex-vivo organ tissue culture, and in-vivo models.

Methods: Drug discovery programmes were conducted by (i) high-throughput screening of drug compound libraries using automated robotic screening platform assisted by manual testing, and (ii) in-silico structure-based virtual screening of chemical libraries, followed by molecular docking and molecular dynamics simulations targeting the key viral enzymes and viral components of SARS-CoV-2. Top hit drug compounds with in-vitro anti-SARS-CoV-2 activity were further prioritized by their pharmacological properties and translational potentials for evaluation in our established COVID-19 ex-vivo organ tissue culture and/or Syrian hamster models. Mechanistic evaluation of selected drug compounds was performed to provide insights for drug analogue optimization.

Results: In a library of drugs encompassing approximately

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12,000 clinical-stage or clinically-approved small molecules, we identified 100 molecules that inhibit SARS-CoV-2 replication. Of these, 13 exhibit effective concentrations commensurate with achievable therapeutic doses in patients, including the antimycobacterial clofazimine, the PIKfyve kinase inhibitor apilimod, and numerous cysteine protease inhibitors. In particular, the orally available clofazimine possesses broad-spectrum anti-coronaviral activities against SARS-CoV-2 and other human-pathogenic coronaviruses. Mechanistically, clofazimine inhibits spike-mediated cell fusion and viral helicase activity. Prophylactic or therapeutic clofazimine resulted in reduced viral loads and inflammation in the respiratory tract of SARS-CoV-2-infected hamsters. Combination of clofazimine and remdesivir exhibited in-vitro and in-vivo antiviral synergy. Moreover, our in-silico screening and phenotypic antiviral evaluations identified numerous other anti-SARS-CoV-2 drug compounds, including recombinant interferons and lopinavir that are available for clinical evaluation.

Conclusion: Based on the novel findings in this project, clinical trials to evaluate the effect of clofazimine and other identified anti-SARS-CoV-2 drug compounds for treating COVID-19 patients have been started. The antiviral mechanisms of actions reported in this project provide novel insights for drug analogue optimization and development of anti-coronaviral drug compounds.

Project No.: COVID190121

COVID-29-219

Single-dose Intranasal Administration of an NSP16-deficient SARS-CoV-2 as a Candidate Live Attenuated Vaccine Provide Sterilizing Immunity in Hamsters and K18-hACE2 Mice

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Introduction and Project Objectives: Live attenuated vaccines can induce mucosal and sterilizing immunity against SARS-CoV-2 that the existing mRNA, adenoviral vectored and inactivated vaccines fail to elicit. The aim of our project is to harness the infectious molecular clone to construct a candidate stain for a live attenuated vaccine against SARS-CoV-2.

Methods: An NSP16-deficeint recombinant SARS-CoV-2 was constructed on the infectious molecular clone on a bacterial artificial chromosome (BAC).

Results: We designed and created a candidate live attenuated vaccine strain of SARS-CoV-2 in which the NSP16 gene encoding 2′-O-methyltransferase is catalytically disrupted by a substation at amino acid 130, in which aspartate (D) was replaced by alanine (A). This virus containing this D130A point mutation, designated d16, was severely attenuated in hamsters and K18-hACE2 transgenic mice, whereby it established an asymptomatic and non-pathogenic infection. A single dose of d16 vaccinated intranasally resulted in sterilizing immunity in both upper and lower respiratory tracts of hamsters, hence eliminating viral spread in a contact-based transmission model. It also robustly induced humoral and cell-mediated immune responses, therefore providing complete protection against lethal challenge with SARS-CoV-2 in the K18-hACE2 transgenic mouse model. The neutralizing antibodies elicited by d16 effectively cross-reacted with several SARS-CoV-2 variants including the δ variant. Importantly, secreted IgA was detected in the nasal wash of vaccinated mice.

Conclusion: Our work provides the proof-of-concept for harnessing NSP16-deficient SARS-CoV-2 to develop live attenuated vaccines and paves the way for further preclinical studies of d16 as a prototypic vaccine strain to which new features might be introduced to improve safety, transmissibility, immunogenicity and efficacy.

Project No.: COVID190114

COVID-30-224

The Blended Gaming COVID-19 Training System (BGCTS) with WHO guidelines for Staff in Residential Care Homes: Development and Pilot Testing

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Introduction and Project Objectives: Residents in residential care homes are at a high risk of being infected by COVID-19 due to their advanced age, associated co-morbidities, and state of dependence. The price paid for an outbreak in residential care homes is high. This is Phase 1 of a clustered randomized controlled trial. It aims to develop and test the Blended Gaming COVID-19 Training System (BGCTS) which provides infection control training to all staff in RCHs in Hong Kong.

Methods: This is a system development study with cognitive interviews with six RCH staff of different ranks. The cognitive interviews were video recorded and analyzed. The key

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recommendations and comments about the BGCTS system were collected.

Results: The contents of the BGCTS system were developed with reference to the World Health Organization (WHO) guideline 'the COVID-19 Risk Communication Package for Healthcare Facilities'. Animations and games were created by nurses, engineers and infection control specialists. One introductory animation and eight gamified topics were made and the topics include: preparing for COVID-19 at your facility, managing patients with suspected or confirmed COVID-19 at your facility, projecting yourself at work, personal protective equipment, symptoms and means of transmission, coping with stress, and 5 moments for hand hygiene. All the staff considered the BGCTS system as 'informative and motivational' for learning infection control practices. They appraised the animations as 'attractive' and the games as 'interesting and educational'. They have made more than 30 suggestions for refining the system in terms of graphical design, instructions to users, and presentation format and style. These are helpful to convey the key messages of infection control practices to the RCH staff.

Conclusion: The BGCTS system will be revised according to these recommendations and will be evaluated in a randomized controlled trial. The BGCTS is the first of this kind training, addressing the diverse health literacy levels of staff and helping RCH staff to comply with WHO infection control guidelines.

Acknowledgment: The project is funded by Health and Medical Research Fund - Commissioned Research on the Novel Coronavirus Disease (COVID-19), Food and Health Bureau, The Hong Kong SAR government (reference no.: COVID190218).

Project No.: COVID190218

COVID-31-228
Suppression of an Outbreak of COVID-19 Without Lockdown in Hong Kong: the Challenge of Inefficient Testing and Tracing

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Introduction and Project Objectives: Maintaining effective contact tracing to control COVID-19 is challenging. Rapid growth in the number of infected cases can overload tracing and testing capacity, resulting in failure to trace contacts and delays in confirming an infection until after symptom onset (confirmation delay), hence increasing transmissibility. A substantial outbreak in Hong Kong, which was suppressed with non-pharmaceutical interventions (NPIs), provided an opportunity to assess the impact of overloading contact tracing and of efforts to improve its efficiency.

Methods: Using epidemiological-link (epi-link) data, we calculated the probability and duration of confirmation delay for cases with and without an epi-link, among all 3,148 confirmed cases between 5 July and 15 August 2020. Logistic regression was performed to determine the relationship between the number of recently confirmed infections and the probability of confirmation delay for epi-linked (contact-traced) cases. We estimated the impact on this relationship of targeted testing of at-risk groups.

Results: The probability and duration of confirmation delay were associated with the rise in daily case number during growth of the outbreak. The proportion with confirmation delay among contact-traced cases increased from about 60% to nearly 85% as the number of cases grew from 1 to 50 per day (p-value = 0.003). The subsequent introduction of testing services for at-risk groups substantially reduced the proportion and it did not approach 85% again until the daily number of cases exceeded 125. This 2.5-fold improvement in capacity contributed crucially to suppression of the outbreak.

Conclusion: The number of recently confirmed infections is an indicator of the load on the contact-tracing system, the consequence of which can be assessed by the probability of confirmation delay. Measures to monitor and improve contact-tracing efficiency, alongside social distancing interventions, can enable outbreaks to be controlled without lockdown.

Project No.: COVID190215

COVID-32-229
The Safety of High Flow Nasal Cannula and Conventional Oxygen Therapy for Treatment of Patients with COVID-19 Complicated by Respiratory Failure

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Introduction and Project Objectives: Patients with COVID-19 may develop respiratory failure requiring supplemental oxygen or ventilatory support but there is concern about aerosol generating procedures causing nosocomial transmission.

Methods: This study performed air samplings and environmental swabs on 16 patients with COVID-19 on oxygen via nasal cannula or filtered Hudson mask or high flow nasal cannula (HFNC) to look for any contamination.

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Results: Among 177 air samples, only one positive sample with NiOSH size fraction > 4μm with CT value 37.1 was detected on an 87 yr old male on 2L of O2 via nasal cannula one day after admission while his respiratory specimen CT value was 17.79.

Among 110 environmental samples collected from bedrails, table, chair, bathroom door handle, bed trunk, window fill, floor, pillows and blankets) on 6 patients whose respiratory specimen CT values were 19.6(IQR 7.3) on the day of collection, positive PCR samples were noted on the floor (CT value 34.1) and right bedrail swabs (CT 36.4) in a 73 yr old lady receiving 2L/min O2 via conventional nasal cannula, 10 days after admission post air sampling while her respiratory specimen CT value was 18.54. In a 68 yr old male receiving 2 L/min of oxygen via conventional nasal cannula without coverage by a surgical mask, the pillow and the blanket swabs were positive (CT values 33.39 and 38.77 respectively) while only the pillow was positive (CT value 36.88) when a surgical mask was covering the nasal cannula.

All air and environmental samples were negative among those receiving oxygen via the Hudson mask with filters or HFNC. No patients with COVID-19 received non invasive ventilation at the hospital as this is regarded by the critical care physicians/ intensivists as risky.

Conclusion: This study has shown that oxygen delivery via conventional nasal cannula may cause air or environmental contamination while a Hudson mask with filters or HFNC appear safe for application in the hospital negative pressure isolation room (supported by HMRF#COVID190110).

Project No.: COVID190110

COVID-33-231

An Open-label Randomized Controlled Trial on Interferon β-1b and Remdesivir Combination versus Remdesivir as Treatment for COVID-19 Infection

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Introduction and Project Objectives: Previous studies suggested that early antiviral therapy was essential in the treatment of COVID-19 patients. We assessed the efficacy and safety of combined interferon beta-1b, and remdesivir for treating COVID-19.

Methods: We conducted a multicentre, prospective open-label, randomized, controlled trial involving adults hospitalized for COVID-19. Patients were randomly assigned to a 5-day combination of interferon beta-1b 16 million units daily and remdesivir 200mg loading on day 1 followed by 100mg daily on day 2 to 5 (double-group), or to remdesivir 200mg loading on day 1 followed by 100mg daily on day 2 to 5 (single-group) as control (1:1). The primary end-point was the time to complete alleviation of symptoms [National Early Warning Score 2 (NEWS) = 0]. The secondary end-points were the time to negative nasopharyngeal swab (NPS) and deep throat saliva (DTS) SARS-CoV-2 RT-PCR to negative and duration of hospitalization.

Results: Among the 212 treated patients (109 in double-group and 104 in single-group), the median days of treatment commencement from symptom onset was 3 days. The baseline demographics were similar. There was no mortality. Fourteen patients required intensive care treatment, 75 patients required oxygen therapy, 10 patients required high-flow oxygen therapy, 6 patients required ventilator support, 1 patient required extracorporeal membrane oxygenation support and 62 patients received subsequent concomitant stress doses of corticosteroid. The double-group had significantly shorter time to complete alleviation of symptoms (NEWS=0) (4 versus 6.5 days; hazard ratio [HR], 12.54; 95% confidence interval [CI], 0.76-1.04; P<0.0001), negative NPS VL (8.5 versus 12 days; hazard ratio [HR], 11.12; 95% confidence interval [CI], 1.05-1.51; p<0.0001), negative DTS VL (8.5 versus 13 days; hazard ratio [HR], 10.77; 95% CI, 0.91-1.31; p<0.0001), and shorter hospital stay (11 versus 13 days; HR, 9.93; 95% CI, 0.55-0.83; p=0.001) when compared to the single-group. The time to onset of IgG RBD seropositive was also significantly shorter in the double-group (8 versus 10 days; HR, 8.9; 95% CI, 0.61-0.96; p<0.0001) with significantly higher microneutralization antibody titre on day 9 (40 versus 5; HR, 12.3; 95% CI, 0.37-0.51; p<0.0001) in the double-group. Adverse events were self-limited with no difference between the two groups.

Conclusion: Early combination of interferon beta-1b and remdesivir was safe and better to remdesivir alone in alleviating symptoms, shorten viral shedding and hospitalization with earlier seropositivity in COVID-19 patients.

Project No.: COVID190125

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HHS-1-128
EGFR Mutation-Guided First-Line Target Therapies of Advanced Non-Small-Cell Lung Cancer (NSCLC) – A Health Economic Analysis

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Introduction and Project Objectives: Tyrosine kinase inhibitors (TKIs) therapy targets at epidermal growth factor receptor (EGFR) gene mutations in non-small-cell lung cancer (NSCLC). This project aimed to compare the EGFR mutation-guided target therapy versus empirical chemotherapy as first-line treatment of advanced NSCLC in the public healthcare setting of Hong Kong.

Methods: A 10-year Markov model (with monthly cycle) was designed to simulate health economic outcomes of a hypothetical cohort of advanced (stage IIIB/IV) NSCLC adult patients with un-tested EGFR-sensitizing mutation status from the perspective of public healthcare provider. Four treatment strategies were evaluated: Empirical first-line chemotherapy, and EGFR mutation-guided use of a TKI (afatinib, erlotinib, and gefitinib). Model outcome measures were direct medical cost, progression-free survival, overall survival, and quality-adjusted life-years (QALYs). Incremental cost per QALY gained (ICER) was estimated. Sensitivity analyses were performed to examine robustness of the model base-case results.

Results: Empirical chemotherapy and EGFR mutation-guided gefitinib gained lower QALYs at higher costs than the erlotinib group. Comparing with EGFR mutation-guided erlotinib, the afatinib strategy gained additional QALYs with ICER (540,601 USD/QALY) (USD1=HKD7.8). In 10,000 Monte Carlo simulations for probabilistic sensitivity analysis, EGFR mutation-guided afatinib, erlotinib, gefitinib and empirical chemotherapy were preferred strategy in 0.13%, 98.63%, 0.01% and 1.23% of time at willingness-to-pay (WTP) 47,812 USD/QALY (1x GPD per capita in Hong Kong), and in 30.54%, 67.54%, 1.79% and 0.13% of time at WTP 143,436,000 USD/QALY (3x GDP per capita), respectively.

Conclusion: EGFR mutation-guided erlotinib appears to be the cost-effective strategy in Hong Kong over a broad range of WTP. This study provides cost-effective findings and directions for future research on the affordability, budget impact and implementation feasibility of personalized oncology therapy in Hong Kong.

Project No.: 15160531

HHS-2-144
Incident Breast Cancer Burden Attributable to Modifiable Risk Factors: Evaluating Current Evidence and Projecting the Future Trends in Hong Kong

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Introduction and Project Objectives: Worldwide, female breast cancer is the most commonly diagnosed cancer. Hong Kong suffers heavy health and economic impact of breast cancer. This study aimed to evaluate the temporal trends in breast cancer incidence by estimating the relative effects of age at diagnosis, period of diagnosis, and birth cohort; forecast future trends in the short- to medium-term based on the earlier time trend extrapolation; and provide systematic assessment on the current disease burden attributable to known modifiable risk factors of interest for breast cancer in HK women population.

Methods: We examined age-specific cancer incidence for female breast cancers compiled from the HK Cancer Registry for the years 1976-2015. We fitted age-period-cohort model on the age, period and cohort effects, and used projections of these effects to predict future incidence to 2030. Additionally, we estimated the joint population attributable risk (PAR), a quantitative measure of contribution of a combination of risk factors/exposures to a disease, of the known modifiable risk factors for breast cancer including: excess weight (BMI >= 25), physical activity (at least 150-minute weekly moderate-intensity aerobic activity or 75-minute weekly vigorous aerobic activity, as per WHO recommendation), alcohol consumption and age at first live birth. We applied Bruzzi et al. methods for the joint PAR estimation where we took the relative risk ratios from the WCRF CUP report and Engmann et al. and the prevalence of risk factors from the population-based case control study HK Breast Cancer Study.

Results: We projected that age-standardised breast cancer incidence of women in HK would increase at a rate of 1.35% per annum from 70.2 per 100,000 women in 2016 - 2020 to 85.8 in 2026 - 2030, a cumulative of 22.3% increase in total. The rising incidence trends can be attributed to ageing and cohort effects, and the most recent period effect. Our PAR estimates also showed that 9.4% of new cases (i.e., a total of 411 out of the 4373 incident breast cancer cases in 2017 in HK) could be attributable to modifiable factors such as excess weight, physical activity, and alcohol consumption, and mostly through physical activity.

Conclusion: We predicted that age-standardised breast cancer incidence in HK would continue to increase. A possible mitigation to this rising trend could be through a promotion of healthier lifestyle. Our findings are important for health policy

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makers concerned with preventive measures and public health intervention establishment for cancer control.

Project No.: 15162611

HHS-3-22
Identifying Priority Research Questions for Addressing Unmet Cancer Palliative Care Needs Using Chinese Medicine with a Systematic Approach

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Introduction: Chinese medicine modalities, including acupuncture and Chinese herbal medicine (CHM), have been used as palliative interventions among cancer patients. More research should be conducted to confirm their effectiveness.

Objectives: The objective of this study was to prioritize Chinese medicine clinical research questions for cancer palliative care.

Methods: Twelve international experts, including physicians, Chinese medicine practitioners, nurses, and clinical research methodologists (n = 3 from each category), from Asia, North America, Australia, and Europe participated in a two-round Delphi survey for prioritizing 29 research questions identified from existing systematic reviews. The experts were asked to 1) rate clinical importance of answering the questions on a nine-point Likert scale; 2) provide qualitative comments on their ratings; and 3) suggest outcome measurement approaches.

Results: Eight research priorities reached positive consensus after the two-round Delphi survey. Six of the priorities focused on acupuncture and related therapies, of which median ratings on importance ranged from 7.0 to 8.0 (interquartile range: 1.00 to 2.50), and the percentage agreement ranged from 75.0% to 91.7%. The remaining two priorities related to CHM, with median ratings ranged from 7.0 to 8.0 (interquartile range: 1.00 to 1.50) and percentage agreement ranged from 75.0% to 83.3%. Neither positive nor negative consensus was established among the remaining 21 questions.

Conclusion: The findings will inform rational allocation of scarce research funding for evaluating the effectiveness of Chinese medicine for cancer palliative care, especially on acupuncture and related therapies. Further research on herb safety and herb-drug interaction should be performed before conducting international trials on CHM.

Project No.: 14153141

HHS-4-82
Retinal Microglia as a Therapeutic Target of the Traditional Chinese Medicine Lycium Barbarum in Alzheimer's Disease-Related Vision Loss

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Introduction and Project Objectives: Alzheimer's disease (AD) is the most common type of dementia and poses a significant challenge in health care options and expenditure for the rapid aging population. A low cost, accessible, non-invasive technique for early diagnosis of AD and monitor the effects of treatment would be invaluable. With the emerging evidence suggests that visual performance is impaired in the early stage of AD, using visual function detection might enhance the understanding of AD. Consumed as preventative and curative agent in visual health for thousands of years, Lycium barbarum extract (LBE) mediated neuroprotective effects occurring during retinal injury appear to be modulated through protection of the blood-retinal barrier/retinal vasculature, antioxidative functions, and glial cell activation. The objective of this study was to investigate whether the LBE could be used as a treatment option as well as a preventative agent to activate retinal microglial cells to a neuroprotective state, resulting in retinal ganglion cell protection during AD-related vision loss.

Methods: First, to determine the possible neuroprotective mechanism of LB-induced microglial cell activation prior to the onset of AD-related Aβ aggregation, microglia cell line (IMG) was pre-treated with LBE for an hour before oligomer Aβ challenge. LBE promoted M2 polarization, inhibited Aβ induced M1 polarization and inflammatory reaction. Second, to investigate the effect of LB treatment directly on cultured microglial cells during Aβ-mediated cellular stress, primary brain microglial cell was post-treated with LBE at an hour after oligomer Aβ challenge. LBE significantly reduced inflammatory cytokines. Finally, a triple transgenic mouse model of AD was chosen to characterize the effects of LB treatment on retinal microglial cell activation following the onset of AD in order to test its effectiveness as a treatment/curative drug.

Results: Although there was no detectable retinal microglia activation by LBE oral feeding to 3xTg AD mice, 2 months of LBE can preserve the retinal function at 2g/kg. Related mechanism might be through anti-oxidation, inhibition on the calpain-2 &-5 activation, stabilizing the synaptic protein of retinal intermediate neurons.

Conclusion: The current study indicated 150 mg/kg LBE might

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be proper dose for AD patient especially in those mild cases starting to have retinal function decline. Retinal function detected by ERG should be a good non-invasive measure for early diagnose and monitor method.

Project No.: 14151281

HHS-5-105

Suppression of Akt/mTOR-mediated HIF-1α/VEGF Activation in Retina Endothelial Cells by Berberine Improves Insulin-induced Diabetic Retinopathy

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Introduction & Project Objectives: Insulin is now the major therapy for patient with type I diabetes mellitus (DM). It is also used in patients with advanced type II DM patients who fail to respond to oral hypoglycaemic agents. However, the role of insulin therapy in controlling the incidence of diabetic retinopathy (DR), the major complication of DM, is controversial. The aim of this study is to investigate if whether insulin promotes DR in diabetic animals and whether berberine, a natural compound isolated from Chinese herbal Medicine can improve the therapeutic outcome of insulin by reducing the DR risk.

Methods: Both in vitro and in vivo studies would be used to understand the therapeutic potential of berberine in the presence of insulin. Cell lines of different retinal cells were screened, and the effect of berberine in improving DR were systemically investigated in vitro and in vivo.

Results: Among different retinal cell lines, insulin in particular activated the expression of HIF-1α and VEGF in retina endothelial cells, while co-treatment of berberine can suppressed the expression of HIF-1α and VEGF in dose- and time-dependent manner. Berberine inhibited Akt/mTOR activity, and restoration of this signaling pathway revoked the effect of berberine in retinal endothelial cellular. DR progression in both experimental type I and type II diabetic mice which received insulin therapy can be improved by berberine treatment.

Conclusion: Berberine improved DR in type I and type II diabetes by inhibiting insulin-induced activation of Akt/mTOR/HIF-1α/VEGF pathway in retinal endothelial cells. Berberine may be applied as complementary therapy for insulin treatment in DM patients.

Project No.: 15162961

HHS-6-125

Investigation of the Potential Herb-Drug Interactions Between Bone Protective Chinese Medicine and Selective Estrogen Receptor Modulators (Tamoxifen and Raloxifene) Using Established Preclinical Model

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Introduction and Project Objectives: The increasing use of "kidney" nourishing Traditional Chinese Medicine (TCM) as alternative approach for management of menopausal symptoms has aroused concerns about their safety and the potential interactions with clinically prescribed drugs such as selective estrogen receptor modulators (SERMs). Er Xian Decoction (EXD), Herba epimedii (HEP) and Rhizoma Drynaria (RD) are commonly prescribed TCM for improving bone health in China that have been demonstrated to act like estrogen via estrogen receptors. The present study aimed to investigate the tissue-selective estrogenic activities of these TCMs and their potential interactions with clinically prescribed SERMs (tamoxifen and raloxifene) on estrogen sensitive tissues.

Methods: Potential interactions between bone protective TCMs and SERMs, were investigated in four estrogen-sensitive tissues including uterus, breast, brain, and bone in both in vivo (mature ovariectomized (OVX) rats) and in vitro models (estrogen receptor (ER)-positive cell lines).

Results: EXD, HEP and RD alleviated estrogen deficiency-induced changes in bone and brain without inducing estrogenic effects in breast or uterus in OVX rats. Moreover, they did not alter the responses of estrogen-sensitive tissues to SERMs in OVX rats. Extract of EXD, HEP and RD-treated serum exerted direct estrogenic effects in ERs-positive cells. Two-way ANOVA indicated herb-drug interactions exist in regulating the circulating levels of follicle stimulating hormone and luteinizing hormone, dopamine transporter mRNA expression in striatum, serum osteocalcin and bone properties in OVX rats and estrogen sensitive parameters in four ER-positive cells. TCMs at their clinical equivalent doses did not alter the responses to SERMs in bone, brain, uterus tissues while TCMs-treated serum altered the effects of SERMs at certain concentrations in human neuroblastoma SH-SY5Y, endometrial Ishikawa and osteoblastic MG-63 cells. TCMs did not change the inhibitory effects of SERMs in mammary glands but reversed the inhibitory effects of tamoxifen in human breast cancer MCF-7 cells. No significant pharmacological toxicity was observed in major vital organs, including liver, kidney, lung and heart of rats from all treatment groups.

Conclusion: EXD, HEP and RD tissue-selectively exerted

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estrogenic effects in bone and brain but not uterus and breast tissues in OVX rats. Both in vivo and in vitro studies indicated the drug-herb interactions in bone. The combined treatments of TCMs at clinical equivalent dose and SERMs did not alter the estrogenic effects of SERMs in OVX rat model. Our study suggests that cotreatment of TCMs and SERMs can be explored for clinical management of bone loss and other menopausal symptoms.

Project No.: 13143771

HHS-7-148

Electroacupuncture Combined with Fast-track Perioperative Program for Reducing Duration of Postoperative Ileus and Hospital Stay after Laparoscopic Colorectal Surgery: A Randomized Controlled Trial

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Introduction and Project Objectives: Postoperative ileus (POI) remains a significant medical problem after colorectal surgery that adversely influences patients' recovery. Our previous study demonstrated that electroacupuncture (EA) reduces the duration of POI (defined by the time to first defecation) and hospital stay after laparoscopic colorectal surgery within a traditional perioperative care setting. Recent evidence also suggested that a 'fast-track' (FT) perioperative program may help accelerate recovery after colorectal surgery. It is uncertain whether the combination of EA and FT program will result in faster recovery after laparoscopic colorectal surgery when compared with FT program alone. This prospective, randomized, superiority trial aimed to compare the efficacy of EA combined with FT program vs. FT program alone in reducing the duration of POI and hospital stay after laparoscopic colorectal surgery.

Methods: Between 07/2018 and 10/2019, 72 consecutive patients undergoing elective laparoscopic resection of colonic and upper rectal cancer without conversion were randomized to receive either EA+FT program or FT program alone (36 per group). The primary outcome was time to defecation. Secondary outcomes were hospital stay, time to resume diet, pain scores, 30-day morbidity, quality of life, and medical costs. Data were analyzed by the intention-to-treat principle.

Results: The demographic data of the two groups were comparable. The mean time to defection was significantly shorter in the EA+FT group when compared with the FT group (44.5±14.9 vs. 63.9±30.1 hours; P=0.001). The time to first passing flatus was also significantly shorter in the EA+FT group (1.4±0.6 vs. 1.8±0.9 days; P=0.011). Multiple linear regression analysis revealed that the addition of EA to the FT program (P=0.001) and the absence of postoperative complications (P=0.002) were independent predictors of shorter duration of POI. Other clinical outcomes including pain scores, hospital stay, morbidity, and quality of life did not differ between the two groups. There was also no significant difference in the total direct cost between the two groups. No adverse event related to the use of EA was reported.

Conclusion: EA+FT program is more effective than FT program alone in reducing the duration of POI after laparoscopic colorectal surgery. The addition of EA to the FT program is an independent predictor of shorter duration of POI. The use of EA doesn't significantly increase the total direct cost of the perioperative strategy. The incorporation of EA into any clinical practice guidelines on FT perioperative program should be considered to benefit more patients by minimizing the development of POI.

Project No.: 15162641

HHS-8-176

Transcriptomic Profiling of the Gene Networks Reveals the Roles of BDNF and RragA in the Anti-Depressive and Analgesic Activities of Chinese Medicine Puerarin

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Introduction: Depression is recently recognized as a major healthcare issue, affecting 13-20% of the global population. Over 75% of depression patients may concomitantly suffer from pain due to a variety of pathological causes. Pain and depression mutually aggravate the sub-thresholds for painful and depressive symptoms, provoking suicide and violence.

Project Objectives: 1) To characterize the antidepressant and analgesic activities of puerarin in mouse models of depression and pain; 2) To discover the mechanisms underlying the antidepressant and analgesic effects of puerarin.

Methods: Puerarin was treated in spared nerve injury (SNI) model, lipopolysaccharide (LPS) model and ras related GTP binding A (RragA) transgenic mice model by oral gavage. Forced swim test and tail suspension test were used to assess the depressive behaviors. Von Frey monofilament assay was used to evaluate the pain responses. Western blotting, Immunostaining analyses, qPCR and next generation RNA sequencing were used to discover the molecular mechanisms underlying the antidepressant and analgesic effects of puerarin.

Results: Puerarin showed the antidepressant and analgesic activities in the animal models of depression and pain by activating BDNF. Puerarin exhibited antidepressive activities

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by regulating RragA. Puerarin did not attenuate the depressive behaviors in the RragA transgenic mice. Puerarin inhibited RragA/mTOR/p70S6K pathway in LPS-treated neuronal stem cells.

Conclusion: Puerarin exhibited antidepressive and analgesic activities by activating BDNF. Puerarin ameliorated depressive activities in LPS-treated mice by regulating RragA. Puerarin inhibited RragA/mTOR/p70S6K pathway in LPS-treated neuronal stem cells. Puerarin might be a potential dual antidepressant and analgesic drug candidate in the future.

Project No.: 15161731

HHS-9-180
Development of Topical Chinese Herbal Agent for Treating Osteoarthritis

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Introduction and Project Objectives: The potential adverse effects of conventional oral pharmacotherapy of osteoarthritis (OA) restrict their long-term use. Topical application of a Chinese herbal paste for relieving OA knee pain can be effective and safe. However, evidence-based scientific research is insufficient to support its application worldwide. The aim of this study was to investigate the in vivo efficacy of a topical Chinese herbal paste on relieving OA knee pain and its underlying mechanism.

Methods: An OA rat model was developed by anterior cruciate ligament transection (ACLT) followed by treadmill running. A herbal paste including Dipsaci Radix, Achyranthis Bidentatae Radix, Eucommiae Cortex and Psoraleae Fructus, named as DAEP, was applied topically on the knee joint of the rats (DAEP). The rats without DAEP treatment served as Control. Rats with surgery but without ACLT, treadmill running and DAEP treatment acted as Sham. The morphologic change of the knee joint was observed radiographically. Nociception from the knee of the rats was assessed using Incapacitent test and CatWalk gait system. The therapeutic mechanism was investigated by analyzing the gene and protein expression of inflammatory markers via qPCR and Western blot, respectively.

Results: Radiographic images showed less destruction at the posterior tibial plateau of the DAEP group compared with the Control after 2 weeks of treatment. The static weight ratio and the gait parameters of the Control were reduced significantly via Incapacitance test and CatWalk gait analysis, respectively. DAEP treatment increased the Print Area and Maximum Intensity significantly compared with the Control. DAEP significantly suppressed the upregulation of gene expression of interleukin (IL)-6, tumor necrosis factor (TNF)-alpha, and inducible nitric oxide synthase (iNOS).

Conclusion: DAEP exhibited its effect via the nuclear factor (NF)-κB pathway by suppressing the phosphorylation of IκB kinase αβ (p-IKKαβ) and cyclooxygenase-2 (COX-2) protein expression. This study provides scientific evidence to support the clinical application of the Chinese herbal paste on reliving OA pain.

Project No.: 14152591

HHS-10-188
Potential Repositioning of Antiepileptics Drug for the Treatment of Alzheimer's disease: Role of Qingyangshen, Gabapentin or Their Combination in Neurorgenesis and Disease Modification

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Introduction and Project Objectives: Alzheimer's disease (AD) is the most common neurodegenerative disease. Deposition of amyloid β plaques (Aβ) and neurofibrillary tangles (NFTs) is the key pathological hallmark of AD. Accumulating evidence suggest that impairment of autophagy-lysosomal pathway (ALP) plays key roles in AD pathology. Recent studies have revealed that the Transcription Factor EB positively regulate the autophagy-lysosomal pathway (ALP), a major cellular machinery responsible for the degradation of protein aggregates and damaged organelles. The present study aims to assess the neuroprotective effects of Qingyangshen (QYS), a Chinese herbal medicine, in AD cellular and animal models, to determine its underlying mechanisms involving ALP regulation.

Methods: QYS extract and its chemical components were characterized by LC/MS. The pharmacokinetics and acute toxicity of QYS extract were evaluated in Wildtype mice. The neuroprotective effects of QYS extract were determined in 3XTg-AD mice, by using a series of behavioral tests and biochemical assays, and the mechanisms were examined in vitro.

Results: Oral administration of QYS extract improved learning and spatial memory, reduced carboxy-terminal fragments (CTFs), amyloid precursor protein (APP), Aβ and Tau aggregates, and inhibited microgliosis and astrocytosis in the brains of 3XTg

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mice. Mechanistically, QYS extract increased the expression of PPARα and TFEB, and promoted ALP both in vivo and in vitro. QYS attenuates AD pathology, and improves cognitive function in 3XTg mice, which may be mediated by activation of PPARα-TFEB pathway and the subsequent ALP enhancement. In conclusion, QYS may be a promising herbal material for further anti-AD drug discovery.

Conclusion: Our results provide the first evidence that QYS mitigates Aβ and Tau pathology and thereby enhances memory function in 3XTg-AD mice. QYS activates PPARα and TFEB to promote ALP for degrading toxic protein aggregates in AD cell models. Since QYS is composed of several active molecules, exploring the bioactive phytochemicals and demonstrating the drug mechanism of action will be the subject of our future research work.

Project No.: 13144471

HHS-11-194
Elucidating the Involvement of IL-17-IL-6-STAT3 Axis in the Anti-Melanoma Effects of a Herbal Formula Comprising Flos Sophorae and Flos Lonicerae

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Introduction and Project Objectives: A formula (SL) comprising Flos Sophorae and Flos Lonicerae was used for treating melanoma in ancient China. Previously, we found that a standardized ethanolic extract of SL (SLE) possesses anti-melanoma effects and has the potential to inhibit IL-17-IL-6-STAT3 axis in melanoma. This work aimed to investigate whether inhibiting IL-17-IL-6-STAT3 axis is one of the anti-melanoma mechanisms of SLE.

Methods: Firstly, we investigated the dose-dependent effects of SLE in inhibiting melanoma growth, and the impact of SLE on IL-17-IL-6-STAT3 signaling in mice. SLE dose- and time-dependently inhibited melanoma growth and angiogenesis in an allograft mouse model. SLE prolonged survival time without observable toxicity in melanoma-bearing mice. SLE suppressed melanoma metastasis in a lung metastasis model. Secondly, we examined the involvement of the IL-17-IL-6-STAT3 pathway in the anti-melanoma effects of SLE in mice. In melanoma tissues, SLE downregulated protein levels of phospho-STAT3 (Tyr 705) and STAT3-regulated immunosuppressive cytokines, and lowered mRNA levels of STAT3-targeted genes, including IL-6 and IL-17. SLE increased Th, Tc and dendritic cells in mouse melanomas and spleens. Thirdly, we determined the contribution of IL-17-IL-6-STAT3 axis inhibition to SLE's anti-melanoma mechanisms in cultured melanoma cells.

Results: Our results showed that SLE inhibited viability, migration and invasion, induced apoptosis, and restrained STAT3 activation and nuclear localization in melanoma cells. In a co-culture system composed of B16F10 cells and mouse splenic lymphocytes, SLE inhibited STAT3 signaling, decreased the levels of immunosuppressive cytokines, including IL-17 and IL-6, increased the percentages of Th, Tc and dendritic cells. Furthermore, over-activation of STAT3 in melanoma cells diminishes SLE's effects. Recombinant IL-17 or IL-6 attenuated SLE's effects on STAT3 signaling and melanoma cell viability.

Conclusion: Our findings indicate that SLE exerts anti-melanoma effects, and inhibiting IL-17-IL-6-STAT3 axis contributes to the mechanisms of action of SLE. This study provides pharmacological groundwork for developing SLE as a modern agent for melanoma prevention/treatment, which should eventually benefit melanoma patients in Hong Kong.

Project No.: 14150571

HHS-12-195
Correcting Presenilin-1 Mutation-mediated Autophagy Deficit in Familial Alzheimer's Disease by Chinese Medicine Tetrandrine

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Introduction and Project Objectives: Tetrandrine is an alkaloid compound isolated from Stephania Tetrandra S. Moore. Animal study has indicated that tetrandrine ameliorates spatial memory impairment in a rat Alzheimer's disease (AD) model, however, the molecular mechanism is not fully understood. Recently, tetrandrine has been shown to inhibit lysosomal two-pore Ca2+ releasing channel (TPC2), that may affect lysosomal pH. Therefore, we hypothesize that dysregulation of TPC2 is involved in attenuated amyloid clearance in AD and potent TPC2 antagonist tetrandrine can correct dysregulated lysosomal Ca2+ and alkalization thus rescuing amyloid clearance. In this study, we aim to elucidate the molecular mechanism of autophagic-lysosomal deficits in AD and to evaluate if tetrandrine can correcting lysosomal deficits in AD.

Method and Results: Using neuroblastoma SH-SY5Y, we demonstrated that PS1 interacted with lysosomal TPC2 by co-immunoprecipitation. More importantly, mutant PS1 exerted stimulatory effect on TPC2 channel which reduces the storage of lysosomal Ca2+. Disrupted lysosomal Ca2+ homeostasis by mutant PS1 caused lysosomal alkalization as detected by LysoSensor and reduced cathepsin D enzyme activities. Furthermore, we detected an increase in LC3-II expression with associated p62 accumulation in human FAD fibroblast

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harboring PS1 mutation. Inhibiting TPC2 channel activity with NED-19 or tetrandrine restored lysosomal Ca2+ homeostasis and its acidic pH value. Intriguingly, intraperitoneal injection of tetrandrine not only significantly cleared amyloid plaques accumulation in cortices and hippocampi but also improved memory function of 5xFAD mice.

Conclusion: Our in vitro and in vivo data demonstrated that PS1 mutation reduces amyloid clearance by disrupting lysosomal Ca2+ homeostasis through the activation of the TPC2 channel. Targeting TPC2 by a Chinese medicinal compound, tetrandrine can restore lysosomal deficits, promote amyloid clearance, and restore memory dysfunctions in 5xFAD. In conclusion, our findings suggest using tetrandrine as a lead compound may open an avenue for novel anti-AD drug development.

Project No.: 15163421

HHS-13-204

A Pragmatic Randomised Controlled Trial Comparing an Integrated Electroacupuncture Protocol vs Sham-control in Chinese Adults with Generalized Anxiety Disorder and Diarrhea-predominant Irritable Bowel Syndrome

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Introduction and Project Objectives: Comorbid irritable bowel syndrome (IBS) and General anxiety disorder(GAD) is common and predicts increased functional impairment and health care costs. Previous studies suggested promising effect of electroacupuncture (EA) on patients with GAD or IBS, but its effect on patients with comorbid IBS and GAD has not been examined. In this study, we aim to examine the effectiveness of EA in improving bowel symptoms and anxiety symptoms of Chinese adults with GAD and comorbid IBS, and to assess the cost-effectiveness of electroacupuncture in reducing anxiety and improving quality of life of patients with comorbid GAD and IBS.

Methods: A randomized controlled trial was conducted with 74 Chinese patients with comorbid GAD and IBS. Patients were randomly assigned to treatment group or the sham control group. All patients were assessed at baseline, immediately after intervention and at 6-week follow-up. The treatment group received 10 weekly sessions of EA and sham control group received 10 weekly sessions of sham EA on the same acupoints. Outcome measures included self-reported anxiety symptoms (GAD-7) and bowel symptoms (bowel symptoms questionnaire), health related quality of life (EQ5D), other clinical symptoms (depressive symptoms- PHQ9, somatic symptoms - PHQ15)

Results: Thirty-seven participants were randomized to the intervention group and 37 to the control group, and were included in intention-to-treat analysis. All in the intervention group and 35 in the sham group completed the study treatment and endpoint assessments. 32.4% of the treatment group vs 21.6% in the sham group showed significant (50%) reduction of anxiety symptoms at week 10, but the difference did not reach significance. 25.7% of the treatment group vs 27% in the sham group showed significant reduction of anxiety symptoms at week 16, but the difference did not reach significance. Repeated-measures ANOVA and ANCOVA revealed significant main effect of time, but not treatment grouping, in anxiety symptoms reduction for both treatment ($F(1, 36) = 63.83$, $p<0.001$, $\eta p2 = .639$) and control group ($F(1, 36) = 24.66$, $p=.00$, $\eta p2 = .407$). No significant interaction effect was found in other outcome measures. Incremental cost effectiveness ratio was HKD98973.68 per QALY gained from EA over sham EA at 10 weeks.

Conclusion: Findings failed to support the effectiveness or cost-effectiveness of EA for patients with comorbid GAD and IBS. Further rigorous research is required to examine the clinical efficacy of different EA protocols for GAD and IBS, before it can be recommended in clinical practice.

Project No.: 12130671

HHS-14-35

Development of an Explanatory Model to Explore the Cervical Cancer Screening Behaviour of Ethnic Minority Women

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Introduction and Project Objectives: Cervical cancer, a common gynaecologic cancer worldwide, can be prevented or detected through timely cervical cancer screening. However, screening uptake remains low among ethnic minority women. We aimed to develop an explanatory model to explore the cervical cancer screening behaviour of ethnic minority women, specifically South Asian women, in Hong Kong.

Methods: This correlational and exploratory study was conducted from April to November 2017. An ecological model

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with five-level factors was adopted to guide the study design. A hypothetical path model with factors identified from a review was built to examine the relational effects of multilevel factors on cervical cancer screening behaviour (Papanicolaou [Pap] test uptake). South Asian women (Indian, Pakistani, and Nepalese) aged 21 years or above without a history of cervical cancer were recruited from the community to complete a survey comprising eight sections: socio-demographics, knowledge of cervical cancer and screening, acculturation, attitude towards and perceptions of screening, cultural barriers to screening and cancer fatalism. A path analysis of the hypothesised model was performed using Mplus Version 7.4. Goodness-of-fit indices, including the root mean square error of approximation (RMSEA), comparative fit index (CFI) and Tucker–Lewis index (TLI), and the chi-square to degree-of-freedom ratio ($\chi 2/df$) were used to assess the overall fit of the path model.

Results: In total, 909 South Asian women were approached, of whom 776 responded and completed the survey. The Pap test uptake rate was 40.3%. The final model demonstrated an acceptable model fit ($\chi 2/df = 2.52$, RMSEA = 0.044, CFI = 0.95 and TLI = 0.93). Fifteen multilevel factors remained in the final model and showed direct or indirect effects on women's screening behaviour: perceived barriers to and benefits of screening, cancer fatalism, knowledge, marital status and history of childbirth (intrapersonal level), friend's recommendation (interpersonal level), knowledge of available clinics, doctor's recommendation and having a primary care provider (organisational level), duration of residence, acculturation level, language use, modesty and crisis orientation (community level). Perceived barriers to screening served as an important mediator of other factors (modesty, knowledge about available clinics, language use, and cancer fatalism) influencing Pap test uptake.

Conclusion: Multilevel factors were found to affect South Asian women's cervical cancer screening behaviour directly and indirectly. Our findings provide valuable information for further development of a culturally relevant intervention to promote cervical cancer screening uptake among South Asian women in Hong Kong.

Project No.: 14151841

HHS-15-60
Effectiveness of a Brief, Self-Determination Intervention for Smoking Cessation (Immediate or Progressive) Among People Attending Emergency Departments: a Randomized Controlled Trial

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Introduction and Project Objectives: Clinicians have an opportunity to provide smoking cessation interventions to smokers who present to emergency departments (EDs). The effectiveness of a brief intervention based on self-determination theory for smoking cessation is uncertain. This study aimed to examine the effectiveness of a brief intervention based on self-determination theory for smoking cessation (immediate or progressive) among Chinese smokers presenting at EDs in Hong Kong.

Methods: This single-blind, multicenter intent-to-treat randomized clinical trial was conducted at the EDs of 4 major acute care hospitals in different districts of Hong Kong. In total, 1571 smokers 18 years or older who presented at 4 major EDs between July 4, 2015, and March 17, 2017, were randomized into an intervention group (n = 787) and a control group (n = 784). The intervention group received brief advice (about 1 minute) and could choose their own quit schedules (immediate or progressive). The control group received a smoking cessation leaflet. Follow-up visits were conducted at 1, 3, 6, and 12 months. The primary outcome measure, by intent to treat, was biochemically validated abstinence at 6 months.

Results: Participants (N = 1571) included 1381 men (87.9%); the mean (SD) age at baseline was 47.4 (16.4) years. Among participants who self-reported abstinence at 6 months, 50.3 (85 of 169) had biochemical validation by both an exhaled carbon monoxide test and a saliva cotinine test. Compared with the control group, the intervention group had statistically higher biochemically validated abstinence at 6 months: 6.7%(53 of 787) vs 2.8%(22 of 784) ($P < .001$), with an adjusted relative risk of 3.21 (95%CI, 1.74-5.93; $P < .001$). The intervention group also had higher self-reported quit rates at 6 months (12.2%[96 of 787] vs 9.3%[73 of 784], $P = .04$) and 12 months (13.0%[102 of 787] vs 8.5%[67 of 784], $P < .01$), as well as higher biochemically validated abstinence at 12 months (7.0%[55 of 787] vs 3.7%[29 of 784], $P < .001$). The additional cost for each intervention group participant was US $0.47, with an estimated gain of 0.0238 quality-adjusted life year. The incremental cost per quality-adjusted life-year (US $19.53) fell within acceptable thresholds.

Conclusion: This brief, low-cost self-determination theory–based intervention for smokers presenting at EDs effectively increased the biochemically validated quit rate at 6 months. If delivered routinely, such a simple intervention may offer a cost-effective and sustainable approach to help many smokers quit smoking.

Project No.: 12133111

Abstracts for Poster Presentation: Health and Health Services

HHS-16-71

A Randomized Controlled Trial Evaluating Efficacy of Promoting Human Papillomavirus (HPV) Vaccination among Chinese Men Who Have Sex with Men

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Introduction and Project Objectives: Men who have sex with men (MSM) are at high risk of contracting Human papillomavirus (HPV) and its related diseases. HPV vaccination is highly effective in preventing vaccine-type genital warts and cancers among MSM. The primary objective of this randomized controlled trial (RCT) is to evaluate the efficacies of 2 web- and theory–based interventions with and without brief motivational interviewing (MI) over the phone to increase the completion of HPV vaccination among unvaccinated participants within a 24-month follow-up period compared with the control group.

Methods: A three-arm parallel-group RCT was conducted between July 2017 and December 2019. Five telephone surveys were conducted at baseline and at 3, 6, 9, and 24 months. Participants were Hong Kong Chinese–speaking MSM aged between 18 and 45 years who were recruited from outreaching at venues, web-based recruitment, and peer referral. A total of 624 participants were randomized into either the online tutorial (OT) only group (n=208), the OT plus MI group (OT-MI; n=208), or the control group (n=208). In total, 459 (459/624, 73.6%) completed the follow-up evaluation at 24 months. Participants in the OT group received a fully automated OT developed based on the health belief model. On top of the same OT, the OT-MI group received brief MI over the phone. Participants in the control group received web-based health communication messages unrelated to HPV or HPV vaccination. Logistic regression models and multivariable linear regression models were used to test the between-group differences. Baron and Kenny's methods were used to test the mediation hypothesis.

Results: The participants in the OT-MI group reported a significantly higher validated completion of HPV vaccination at 24 months than the control group (36/208, 17.3% vs 15/208, 7.2%; P=.006). However, the difference in HPV vaccination completion between the OT and the control groups (24/208, 11.5% vs 15/208, 7.2%; P=.17), or between OT-MI and OT groups (P=.13), was not statistically significant. The association between randomization status (OT-MI group vs control group) and HPV vaccination completion became statistically nonsignificant after controlling for changes in the perceived susceptibility to HPV (24 months vs baseline), whereas perceived susceptibility remained strongly associated with HPV vaccination uptake in the model (P<.001). Changes in perceived susceptibility fully mediated the intervention effect.

Conclusion: Theory-based OT with brief MI over the phone was effective in increasing HPV vaccination completion among Chinese MSM. Local and international dissemination and implementation research are greatly warranted.

Project No.: 13141651

HHS-17-73

A Randomized Controlled Trial of a New Screening Strategy for Varices Based on Liver and Spleen Stiffness Measurement (LSSM) in Cirrhotic Patients

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Introduction and Project Objectives: Variceal bleeding is a common and life-threatening complication in patients with liver cirrhosis. Screening with upper endoscopy is recommended but is uncomfortable to patients. Non-invasive assessment with transient elastography for liver/spleen stiffness measurement (LSM and SSM) is accurate in detecting varices. We aimed to test the hypothesis that a new screening strategy for varices guided by LSM/SSM results (LSSM-guided) is non-inferior to universal endoscopic screening in detecting clinically significant varices in patients with cirrhosis.

Methods: This was a non-inferiority, open-label, randomized controlled trial. Adult patients with known chronic liver diseases, radiological evidence of liver cirrhosis and compensated liver function. The primary outcome was clinically significant varix diagnosed with upper endoscopy.

Results: Between October 2013 and June 2016, 548 patients were randomized to LSSM arm (n=274) and conventional arm (n=274) which formed the intention-to-test (ITT) population. Patients in both study arms were predominantly middle-aged men with viral hepatitis related-cirrhosis in 85% of the cases. In the ITT analysis, 11/274 participants in the LSSM arm (4.0%) and 16/274 in the conventional arm (5.8%) were found to have clinically significant varices. The difference between two groups was -1.8% (90% CI, -4.9%-1.2%, P<0.001). The absolute difference in the number of patients with clinically significant varices detected was 5/16 (31.3%) fewer in the LSSM arm.

Conclusion: Non-inferiority of the LSSM-guided screening strategy to the convention approach cannot be excluded by this RCT. This approach should be further evaluated in a cohort of larger sample size with more clinically significant varices.

Project No.: 12131201

Abstracts for Poster Presentation: Health and Health Services

HHS-18-106

Evaluation of an Interactive Computer-based Intervention to Safe Sex Practice for Female University Students: A Multicentred Randomized Controlled Trial

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Introduction and Project Objectives: Sexual health concerns among young adults worldwide help to motivate preventative practices against sexually transmitted infections. Our funded project developed an interactive computer-based intervention called "Smart Girlfriend" for female Chinese university students and systematically evaluated its effectiveness in promoting condom use.

Methods: A multicenter randomized controlled trial was conducted with 781 unmarried, female, Chinese university students aged ≥18 years old at 5 universities with dormitories in Hong Kong. Participants were randomly assigned to 2 groups: one group received an interactive computer-based intervention called "Smart Girlfriend" and the other group received a single webpage of online information about condom use. The intervention content was based on the Health Belief Model and the Continuum of Conflict and Control theory. The primary outcome was self-reported consistency of condom use with every partner at 3-month and 6-month follow-up assessments, analyzed using zero/one inflated beta (ZOIB) regression. The secondary outcome was an appraisal of the knowledge, attitudes, norms, and self-efficacy of condom use measured by Multidimensional Condom Attitudes Scale (MCAS). The intention to treat was applied in analyses.

Results: Of 1503 individuals that were screened, 781 (52%) were randomized into 2 groups. The retention rates at the 3-month and 6-month follow-ups were 92% and 91%, respectively. Most participants were born locally (536/746, 72%), and 18% (134/746) self-reported as a sexual minority. ZOIB results regarding the consistency of condom use were not significant [model 1: odds ratio (OR) 2.25 with a 95% credible interval (CrI) of 0.84-6.36; model 2: OR 8.03 (95% CrI 0.22-330.31); model 3: OR 1.21 (95% CrI 0.78-1.86)]. Consistency in the intervention group was 5% higher (95% CI −1.90 to 11.63) than the control group at the 3-month follow-up, and 1% higher (95% CI −5.81 to 8·02) at the 6-month follow-up. MCAS scores at the 3-month follow-up were significantly higher in the intervention group (mean 122.51, SD 15.97) than the control group (mean 119.86, SD 15.85; P=.02).

Conclusion: An interactive web-based sexual health literacy program did not significantly increase the consistency of condom use compared to a single webpage of condom use information; however, it did temporarily improve knowledge, attitudes, norms, and self-efficacy regarding condom use. The high response rate of participants enrolled in the study and high participation rates indicated the needs of youth's sexual health intervention in Hong Kong. Our findings provided insights that the future revision of the intervention should be personalised and delivered in a proactive approach.

Project No.: 14150971

HHS-19-124

How Can We Allocate the Screening Interval for Diabetic Retinopathy in Hong Kong: Towards a Personalized Approach

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Introduction and Project Objectives: Hong Kong started systematic screening for diabetic retinopathy (DR) as part of the multi-disciplinary risk assessment and management programme for diabetes (RAMP-DM) and adopted the Iceland model to tailor the screening interval. Screening for DR is cost-effective but the optimal screening interval remains controversial. The aim of this study is to develop a prediction model to predict the individual risk of sight threatening diabetic retinopathy (STDR) and support evidence for local risk-based screening intervals for DR.

Methods: Part 1 of this study developed a prediction model using parametric survival analysis with Weibull distribution. Discrimination and calibration performance were assessed

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by comparing the cumulative STDR events versus predicted risk in two years. The algorithm was used to estimate the time for an individual to reach a pre-set risk margin for STDR and converted to a 6-, 12-, or 24-month screening interval. We compared the observed time for new STDR being detected with the assigned intervals to determine the safety of the assigned interval. Part 2 was a cost-effectiveness analysis (CEA) using an individual Markov model to evaluate the long-term cost and consequences of risk-based screening by applying the risk algorithm developed in part 1, versus fixed annual screening.

Results: Duration of diabetes, HbA1c, systolic blood pressure, presence of chronic kidney disease, diabetes medication, and age were included in the prediction model. The validation showed that there was no significant difference between the 2-year predicted and observed risks of STDR for males (5.6% vs 5.1%, p=0.724) and for females (4.8% vs 4.6% , p=0.099). The discrimination power are moderate to good with an ROC of 0.797 for males and 0.810 for females. Using a 2.5% risk margin, 96.6% (1107/1146) subjects with STDR could have been assigned to a screening interval close to the time STDR being detected from screening. From provider perspective, it would prevent blindness and save sight years across lifetimes with incremental costs of HK$99,990 per case of blindness prevented and HK$20,752 per sight year saved comparing to annual screening.

Conclusion: We were able to derive a HK algorithm using local data. Using a risk-based interval is safe and reduces the need for more frequent screening of lower risk people. However, more research is needed to refine the risk for the higher risk people so that fewer of these cases need to be allocated to a 6-monthly screening interval.

Project No.: 14151971

HHS-20-143

An in vitro Microfluidic Device to Screen Silicone Oil Tamponades Based on Resistance Against Shear Emulsification in Eye

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Introduction and Project Objectives: Ophthalmic silicone oil (SilOil) is still an irreplaceable intraocular tamponade to treat complicated retinal detachment. However, its use in the eye can induce various complications including cataract, glaucoma, and inflammation. These complications are closely related to the emulsification of SilOil in-situ. Emulsification of SilOil is caused by shear stresses generated during eye movements and therefore is clinically inevitable. Material scientists have devised approaches to reduce emulsification of SiOil in-situ by modifying either the chemical structure or the physical properties of the conventional SilOil tamponade. However, without a proven platform for characterizing the resistance against emulsification, the existing and novel ophthalmic SilOil formulations cannot be easily benchmarked. Therefore, a widely accepted physical model for in vitro emulsification testing of SilOil is highly demanded.

The aims of this project were to establish a well-accepted in-vitro microfluidic platform that quantifies the emulsification resistance of ophthalmic SilOil against saccadic-like eye movements, and to apply this platform to benchmark novel ophthalmic SilOil formulations.

Methods: Using microfluidic technologies, we developed an eye-cavity-on-a-chip device to mimic the cross-section of the eye globe. The inner surface of the device was coated with mammalian cells to mimic the surface properties of retina. The device was then mounted on a stepper-motor system that could provide agitations of saccadic-like eye movements. This allows the mimicking of both the mechanical and physiological micro-environment of the posterior segment of the eye to study the emulsification of SiiOil tamponade. We validated our device using conventional SilOil with various viscosities.

Results: The results of the validation test showed that in general the higher the shear viscosity of the SilOil tested, the smaller the quantity of droplets formed under saccadic-like eye movements. This is consistent with the clinical findings, and therefore confirmed our platform's effectiveness for benchmarking SilOil. The resistance of SilOil against eye movement-induce emulsification could now be quantified by the total numbers of SilOil droplets formed within the microfluidic chip. To demonstrate the impact of this project, we then applied the microfluidic device to benchmark novel SilOil formulations, as well as test new concepts for developing emulsification-resistant SilOil.

Conclusion: All in all, we demonstrated our eye-cavity-on-a-chip platform's value in benchmarking various types of ophthalmic SilOil in an in vitro environment which is comparable to the environment inside the eye. The use of our platform in screening SilOil speeds up and therefore reduces the development costs of new ophthalmic SilOil formulations.

Project No.: 13144551

Abstracts for Poster Presentation: Health and Health Services

HHS-21-223

Factors Associated with Readiness to Screen for Colorectal Cancer: A Population-based Study Using Stages of Change Model

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Introduction and Project Objectives: Colorectal cancer (CRC) screening has been proven effective to reduce mortality, yet its success depends on persistent compliance with screening. Understanding the factors associated with its uptake is important to inform healthcare service providers. However, most previous evaluations only explored the factors associated with screening adherence as a binary outcome. The Stages of Change (SOC) model offers an alternative strategy to categorise screening participants into more specific groups. The objective of this study is to evaluate the socio-demographic factors that were associated with readiness to CRC screening based on components of the SOC model.

Methods: We performed a population-based telephone survey involving 2,400 individuals aged 61–70 years. Information on their socio-demographic factors, including age, sex, the highest educational level attained, marital status, occupation, income, smoking status and self-perceived health status. Their past experience; current status; and future intention to receive CRC screening were also recorded for each study participant. Using the SOC model, the participants were assigned into different groups, including pre-contemplation, contemplation, preparation, action, relapse, and maintenance. We evaluated the adjusted odds ratios (AORs) and their 95% confidence intervals (CIs) by constructing binary logistic regression models.

Results: We found that study participants at the pre-contemplation stage were significantly more likely to be older (AOR=1.07; 95% CI=1.04–1.11), females (AOR=1.54; 95% CI=1.15–2.07), and had lower monthly income (AOR=0.68; 95% CI=0.48–0.98) as compared to those at other stages (contemplation, preparation or action). Relapse screeners were more likely to be at more advanced age (AOR=1.08; 95% CI=1.03–1.13), at lower educational level (AOR=0.54; 95% CI=0.35–0.82), and cigarette smokers (AOR=1.92; 95% CI=1.09–3.38) when compared with maintenance screeners. Marital status, occupation and self-perceived health status were not associated factors.

Conclusion: The objective for promoting health programmes is to facilitate forward movement from the pre-contemplation stage to contemplation, preparation, action and finally maintenance. This study is among few evaluations that examined factors associated with readiness to undergo CRC screening based on SOC model. These findings inform future initiatives to develop interventions that could enhance long-term participation of CRC screening programmes.

Reference: This abstract was presented in the International Digestive Disease Forum in 2019 and published as an abstract in the journal GUT (https://gut.bmj.com/content/68/Suppl_1/A110.2?utm_content=americas&utm_campaign=usage&urm_medium=cpc&utm_source=trendmd).

Project No.: CCS-CUHK

HHS-22-49

Cost-Effectiveness of Anti-Epidermal Growth Factor Receptor Therapy Versus Bevacizumab in KRAS WildType (WT), Pan-RAS WT, and PanRAS WT Left-Sided Metastatic Colorectal Cancer

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Introduction and Project Objectives: Colorectal cancer (CRC) is a significant global health burden. Over the past decades, the introduction of molecular targeted therapy has dramatically improved the prognosis of metastatic colorectal cancer (mCRC) patients, with their median survival doubled from 14–16 months to over 30 months. Combination chemotherapy plus targeted therapy, either anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibody (mAb) or anti-vascular endothelial growth factor (anti-VEGF) mAb have become the current standard first-line treatment.Both anti-EGFR mAb and bevacizumab (Bev, an anti-VEGF mAb) have demonstrated efficacies as first-line therapies in KRAS wild-type (WT) patients. However, three randomized trials of head-to-head comparisons between the two agents showed conflicting results. The CALGB 80405 trial, which is the largest one, has demonstrated equivalence of anti-EGFR mAb and bevacizumab in terms progression-free survival (PFS) and overall survival (OS). However, both the FIRE3 and the PEAK studies have suggested the superiority of anti-EGFR therapy. Definitive evidence in supporting one agent remains lacking; therefore, authorities recommended both agents as the acceptable options. However, post-hoc analyses suggested that the benefit of anti-EGFR therapy is more pronounced in pan-RAS WT patients. Recently, the primary tumor location (PTL) has been validated as a response predictor of anti-EGFR mAb, whose benefit is mainly seen in patients of left-sided but not right-sided colonic tumors.We aimed to compare the economic value of chemotherapy plus anti-EGFR mAb against chemotherapy with bevacizumab as first-line treatment in KRAS WT, pan-RAS WT and pan-RAS WT left-sided mCRC patients from the Hong Kong societal perspective.

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Methods: We developed Markov models and 10-year horizon to estimate costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio (ICER) of chemotherapy plus anti-EGFR therapy against chemotherapy plus Bev in KRAS WT, pan-RAS WT, and pan-RAS WT left-sided mCRC. We considered two times of the local gross domestic product per capita (GDPpc) as the willingness-to-pay (WTP) threshold (2×GDPpc; US$97,832).

Results: Adding anti-EGFR mAb to chemotherapy provides additional 0.24 (95% confidence interval [CI] 0.19–0.29), 0.32 (95% CI 0.27–0.37), and 0.57 (95% CI 0.49– 0.63) QALY compared to adding Bev in KRAS WT, pan-RAS WT, and left-sided pan-RAS WT mCRC populations respectively. The corresponding ICER is US$106,847 (95%CI 87,806–134,523), US$88,565 (95%CI 75,678–105,871), US$76,537 (95%CI 67,794–87,917) per QALY gained, respectively.

Conclusion: Anti-EGFR therapy is more cost-effective than Bev as a first-line targeted therapy in left-sided pan-RAS WT and pan-RAS WT, with ICER < US$100,000/QALY, compared to KRAS WT mCRC population.

Project No.: 15161781

HHS-23-86

10-year Risk Prediction Models of Complications and Mortality of Diabetes Mellitus in Chinese Patients in Primary Care in Hong Kong

Prof Cindy LAM[1], Dr Daniel FONG[1], Prof Kathryn TAN[1], Dr Eric WAN[1], Dr Colman FUNG[1], Ms Ruby KWOK[2], Dr David CHAO[2], Dr Eric HUI[2], Dr Wendy TSUI[2], Dr King Hong CHAN[2]
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Introduction: Diabetes Mellitus (DM) is a leading global disease burden with rising prevalence in China. We need accurate models to predict the risk of long-term complications and mortality to facilitate cost-effective individualized interventions for Chinese DM patients.

Project Objectives: To develop and validate 10-year risk prediction models for total cardiovascular diseases (CVD), CHD, heart failure, stroke, ESRD and mortality in primary care Chinese DM patients. To develop simplified nomograms and charts for the prediction of 10-year risk of CVD and mortality.

Methods: 10-year retrospective cohort study. 141,516 patients who had a clinical diagnosis of T2DM without complication managed in public (HA) primary care clinics between January and December 2008 were included and followed up until December 2017. 2/3 subjects were randomly selected for development of sex-specific 10-year risk prediction models for each outcome by Cox regressions. The models were validated on the remaining 1/3 subjects by Harrell's C statistic and ROC. Up to seven most important predictors were used to construct the nomograms and charts.

Results: 10-year cumulative incidence of CVD, ESRD, and mortality was 22.9%, 6.0% and 19.8%, respectively. In addition to traditional risk factors, variabilities of SBP and HbA1c were significant predictors of CVD, ESRD and mortality. The use of transformation terms (e.g. SBP2) and interaction terms (e.g. age*WHR) significantly improved predictive power. The models performed well in the validation sample (Harrell's C for female/male CVD, ESRD and mortality was 0.748/0.709, 0.889/0.889, and 0.857/0.841, respectively). The CVD and mortality nomograms and charts differentiated different risk groups effectively.

Conclusion: 10-year risk of CVD, ESRD and mortality of primary care Chinese T2DM patients can be accurately predicted by routinely available parameters. The 10-year risk prediction models will enable accurate risk stratification of Chinese T2DM patients to guide clinical decision and patient activation.

Project No.: 14151181

HHS-24-101

Effect of Berberine on Cardiovascular Disease Risk Factors: A Mechanistic Randomized Controlled Trial

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Introduction and Project Objectives: Cardiovascular disease (CVD) is a major contributor to the global burden of disease. Berberine might exert its beneficial effects on CVD risk factors by lowering testosterone in men, which has not been examined previously. To assess the effect of berberine on CVD risk factors and the potential pathway via testosterone, we conducted a randomized, double-blind, placebo-controlled, parallel trial in Hong Kong.

Methods: 84 eligible Chinese men with hyperlipidemia were randomized to take berberine (500 mg orally, twice a day) or placebo for 12 weeks. CVD risk factors (lipids, thromboxane A2, blood pressure, body mass index, waist-hip ratio) and testosterone were assessed at baseline, and at 8 and 12 weeks after intervention. We compared changes in CVD risk factors and testosterone after 12 weeks of intervention using analysis

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of variance, and after 8 and 12 weeks using generalized estimating equations (GEE).

Results: Of the 84 men randomized, 80 men completed the trial. Men randomized to berberine had larger reductions in total cholesterol (-0.39 mmol/L, 95% confidence interval (CI) -0.70 to -0.08) and high-density lipoprotein cholesterol (-0.07 mmol/L, 95% CI -0.13 to -0.01) after 12 weeks. Considering changes after 8 and 12 weeks together, berberine lowered total cholesterol and possibly low-density lipoprotein-cholesterol (LDL-c), and possibly increased testosterone. Changes in triglycerides, thromboxane A2, blood pressure, body mass index and waist-hip ratio after the intervention did not differ between the berberine and placebo groups. No serious adverse event was reported.

Conclusion: Berberine is a promising treatment for lowering cholesterol. Berberine did not lower testosterone but instead may increase testosterone in men, suggesting sex-specific effects of berberine. Exploring other pathways and assessing sex differences would be worthwhile, with relevance to drug repositioning and healthcare.

Project No.: 15162621

HHS-25-102

Hot Weather and Suicide among Older Adults in Hong Kong: Time-series Analysis and Recommendations on Weather-driven Preventive Measures

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Introduction and Project Objectives: With global warming, adverse health outcomes related to hot weather were evidenced. Generally, literature suggested hot weather was associated with higher suicide rates. Yet, such association was inconsistently reported in Hong Kong. Furthermore, there was a lack of weather-driven intervention on suicide prevention. Hence, this study aimed to identify meteorological risk factors of suicide deaths among older adults in Hong Kong, so as to better inform weather-driven suicide prevention initiatives.

Methods: A retrospective study on suicide deaths among the older adults (aged≥65) in Hong Kong in 1976-2014 was conducted. The suicide deaths data were extracted from the Census and Statistics Department. Monthly suicide death rates, adjusted for the number of days in a month, was analysed. Suicides by violent methods (e.g. jumping, hanging, drowning, and cutting) and those by nonviolent methods (e.g. poisoning) were analysed separately. Daily meteorological variables were obtained from the Hong Kong Observatory and aggregated as monthly data. A time-series approach using transfer function models was adopted to identify meteorological risk factors of suicide among older adults.

Results: During the study period, 7,314 suicide deaths from violent methods and 630 from nonviolent methods among the older adults were analysed. Various meteorological variables including ambient temperature, ambient temperature change within a week, relative humidity, sunshine hours, total rainfall, ambient temperature above a threshold, and typhoons were associated with suicide deaths from both violent and non-violent methods. Among them, monthly average daily minimum ambient temperature was found to best predict the monthly rate of suicide deaths from violent methods. If a threshold was to be used, and a daily maximum ambient temperature of 30.3°C was considered the threshold. Regarding suicide deaths from nonviolent methods, the number of days in a month for which the daily maximum ambient temperature exceeded 32.7°C could best predict the monthly rate. Based on the results, it was recommended to implement suicide preventive measures (e.g. provision of more public air-conditioned areas) in May to September as most days are above 30.3°C. Apart from these months, whenever a maximum ambient temperature of 30.3°C is forecasted, the preventive measures shall also be triggered. Stakeholders involved the older adults and their caregivers, as well as service providers in both the public and private sectors.

Conclusion: This study found that not only suicide by violent methods were associated with hot weather, but also suicide by nonviolent methods. We recommended the stakeholders to implement the proposed weather-focused preventive measures.

Project No.: 14151741

HHS-26-120

Effects of Serious Illness Care Program to Promote Advance Care Planning in Hospital Care Setting

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Introduction and Project Objectives: Advance care planning (ACP) empowers patients to contemplate and communicate their end-of-life care preferences with family members and healthcare providers. However, many healthcare providers perceived themselves inadequately prepared for the difficult conversation or unavailable due to the heavy clinical workload. This study seeks to evaluate the effects of the Serious Illness Care Program (SICP), a program developed in the US for increasing fair access to ACP, in the local hospital setting.

Methods: We conducted a stepped-wedge randomized cluster trial in which the intervention sequentially rolled out across ten medical units of the medical department in an acute hospital. The SICP comprises three components: capacity building, a structured conversation guide and a template for documentation. An inclusive approach was adopted for ACP training to prepare all healthcare providers. ACP was delivered by 27 nurses who volunteered to be facilitators. Patients with advanced disease screened by using the Supportive and Palliative Care Indicators Tool were eligible to the study. Multivariate logistic regression analysis was performed to estimate the intervention effects.

Results: A total of 350 patients participated in the study, yielding a participation rate of 86.6%. Their mean age was 73.6 years (SD 10.7). The attrition rate at 3-month follow up was 34.8%, with a mortality rate of 15.7%. There was a significant increase in documentation regarding end-of-life care preferences in medical records (aOR = 29.2, 95% CI: 15.9 – 53.7, $p < .001$) and relevant family communication (aOR = 2.2, 95% CI: 1.1 – 4.4, $p = .022$) among participants recruited in the intervention period when compared with those in the control period at 1-week follow up, after adjusting for covariates and clustering. Among the deceased group (n=82) in 6 months, those recruited in the intervention period were less likely to receive cardiopulmonary resuscitation in the end-of-life care (aOR = 0.08, 95% CI: 0.02 – 0.24, $p < .001$]). Despite the positive results, qualitative findings revealed that more work is needed to overcome family resistance, collegial conflicts and limited organizational recognition for the sake of maintaining sustainability.

Conclusion: This study focused on the implementation science for respecting patients' right to express end-of-life care wishes. The findings suggest that patients were less likely to receive aggressive yet futile treatment in end-of-life care following ACP. This study demonstrated that a system-wide approach, including organizational support, capacity building and tool adoption, is a cornerstone to facilitate ACP implementation.

Project No.: 14152631

HHS-27-129

Role of Endothelial SIRT1 in the Prevention of Vascular Ageing - Focusing on Arterial Remodeling and Circadian Rhythmicity

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Introduction and Project Objectives: All tissues and organs have a biological clock to control the circadian rhythmicity. Abnormal circadian rhythm results in diseases, such as hypertension and heart failure. The present study aimed to evaluate the role of endothelial expression of SIRT1, a longevity regulator, in modulating the circadian rhythmicity of body temperature, heart rate, blood pressure, energy metabolism and physical activities.

Methods: Mice were maintained in C57BL/6J genetic background. At the age of 12 weeks, wild type controls (WT), mice with endothelial overexpression of human SIRT1 (EC-SIRT1) or a deletion in the Per-Arnt-Sim (PAS) domain of the murine Per2 gene (PER2-MUT), and the crossbreed litters of PER2-MUT-EC-SIRT1 were implanted with radiotelemetry transmitters. Core body temperature, systolic (SBP) and diastolic (DBP) blood pressure, heart rate and locomotor activity were recorded every four-weeks.

Results: Overexpression of human SIRT1 in endothelial cells enhanced the circadian rhythmic oscillation of body temperature in both EC-SIRT1 and PER2-MUT-EC-SIRT1, when compared to WT and PER2-MUT, respectively. Starting from the age of 16-weeks, the diurnal variation in diastolic, but not systolic blood pressure, was lost in PER2-MUT and restored by overexpression of human SIRT1 in endothelial cells. Similarly, a significant circadian variation in heart rate was present in WT, EC-SIRT1 PER2MUT-EC-SIRT1 but not PER2-MUT. Overexpression of endothelial SIRT1 prevented the elevation of both SBP and DBP caused by PER2 mutation.

Conclusion: SIRT1 in endothelia cells is actively involved in the regulation of circadian rhythmicity, which may at least partly contribute to its anti-hypertensive effects.

Project No.: 13142651

HHS-28-133

Long Term Effectiveness of Elderly Health Care Voucher Scheme Strategies: A System Dynamics Simulation Analysis

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Abstracts for Poster Presentation: Health and Health Services

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Introduction and Project Objectives: The elderly healthcare voucher (EHCV) scheme is expected to lead to an increase in the number of elderly people selecting private primary healthcare services and reduce reliance on the public sector in Hong Kong. However, studies thus far have reported that this scheme has not received satisfactory responses. In this study, we examined changes in the ratio of visits between public and private doctors in primary care (to measure reliance on the public sector) for different strategic scenarios in the EHCV scheme.

Methods: Based on comments from an expert panel, a system dynamics model was formulated to simulate the impact of various enhanced strategies in the scheme: increasing voucher amounts, lowering the age eligibility, and designating vouchers for chronic conditions follow-up. Data and statistics for the model calibration were collected from various sources.

Results: The simulation results show that the current EHCV scheme is unable to reduce the utilization of public healthcare services, as well as the ratio of visits between public and private primary care among the local aging population. When comparing three different tested scenarios, even if the increase in the annual voucher amount could be maintained at the current pace or the age eligibility can be lowered to include those aged 60 years, the impact on shifts from public-to-private utilization were insignificant. The public-to-private ratio could only be marginally reduced from 0.74 to 0.64 in the first several years. Nevertheless, introducing a chronic disease-oriented voucher could result in a significant drop of 0.50 in the public-to-private ratio during the early implementation phase. However, the effect could not be maintained for an extended period.

Conclusion: Our findings will assist officials in improving the design of the EHCV scheme, within the wider context of promoting primary care among the elderly. We suggest that an additional chronic disease-oriented voucher can serve as an alternative strategy. The scheme must be redesigned to address more specific objectives or provide a separate voucher that promotes under-utilized healthcare services (e.g., preventive care), instead of services designed for unspecified reasons, which may lead to concerns regarding exploitation.

Project No.: 14152711

HHS-29-146

In-depth Study of the Cost-effectiveness of the Risk Assessment and Management Programme for Hypertension (RAMP-HT) for Patients with Uncontrolled Hypertension in Primary Care in Hong Kong

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Introduction and Project Objectives: The Risk Assessment and Management Programme for Hypertension (RAMP-HT), a protocol-driven multi-disciplinary intervention launched by the Hospital Authority, improved blood pressure control of patients with uncontrolled hypertension over 1-year compared to those receiving usual public primary care. This project evaluated the long-term effectiveness on reducing cardiovascular complications and mortality, and the 5-year and estimated lifetime cost-effectiveness of RAMP-HT.

Methods: This is a prospective cohort study on adult patients with hypertension without complications or diabetes mellitus receiving public primary care in Hong Kong. A total of 79,161 RAMP-HT participants were matched with 79,161 patients receiving usual care in 2011-2013. Effects of RAMP-HT on the incidences of cardiovascular diseases (CVD) and all-cause mortality were evaluated using multivariable Cox regression. The number-needed-to-treat (NNT) to prevent one CVD/mortality event was determined. Programme cost of RAMP-HT was collected from the Hospital Authority using costing questionnaires. Public medical costs were estimated based on public health services utilization rates. A subset of 486 patients

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completed a survey on private medical costs. A Monte-Carlo simulation model was developed to evaluate the lifetime cost-effectiveness of the RAMP-HT, based on the transition probabilities for complications development and deaths for RAMP-HT and usual care patients; direct medical costs, and health preferences of hypertension patients of different complication statuses were calculated from empirical data.

Results: After a median follow-up of 5.3 years, RAMP-HT participants had significantly lower cumulative incidence of CVD (9.14%vs.14.95%, p<.001) and all-cause mortality (5.04%vs.10.99%, p<.001) compared to usual care patients. RAMP-HT was associated with a 38% and 46% relative risk reduction (p<.001) in CVD and all-cause mortality, respectively. The NNT was 17 to prevent one CVD event and 20 for all-cause death. The total programme cost over 5 years per RAMP-HT patient was HK$521. RAMP-HT participants had significantly lower direct public medical costs over 5 years than usual care patients (RAMP-HT: HK$61,904; Usual care: HK$91,561) but similar annual private medical costs (RAMP-HT: HK$3,347; Usual care: HK$3,588). The cost invested on RAMP-HT to prevent/gain 1 event-free-year was HK$9,058/HK$1,905 for CVD and HK$10,345/HK$3,490 for all-cause mortality. RAMP-HT was cost-saving and estimated to save HK$5,569 per RAMP-HT participant compared to patients receiving usual care over the lifetime.

Conclusion: The RAMP-HT was effective in preventing hypertension-related complications, mortality, and saving public healthcare costs. Integration of RAMP-HT to routine primary care for patients with hypertension could significantly reduce morbidity and mortality, alleviating the burden of chronic diseases on the public healthcare system.

Project No.: 13142471

HHS-30-168
Quality of Healthcare for the Ageing - Health System and Service Models to Better Cater for an Ageing Population

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Introduction and Project Objectives: The objectives are to: a. better integrate health care services for older people with chronic diseases, taking reference to international experiences and local initiatives; b. define pressure points in the current healthcare services and identify facilitators and barriers for integrating health services; c. recommend service models for integrated services; d. recommend service models for end of life (EOL) care and care of the terminally ill; e. recommend changes including legislation if required and measures to facilitate implementation in the community; and f. pilot the recommended service models.

Methods: Local and international evidence was used to identify service gaps and potential solutions. International practices were summarised using literature reviews and local evidence was derived from multiple sources, including, key informant interviews, focus groups, case studies and population surveys. A programme logic model was applied to develop the new service models to produce an inventory of service gap and evidence to inform what changes are needed, and why and how changes will happen.

Results and Conclusion: (1) A system integration via primary care-led hubs and community networks interlinked with the hospital system is recommended to join up the fragmented care system focusing on building connections around a strong primary care led hub and community networks. (2) Within this model, we identified 13 recommendations including governance, training and education, screening and assessment, and integrated service models to specific groups that are required across the system. In addition, a total of 33 recommendations in the aspects of policy, legal, cultural and organizational issues for end-of-life care is also identified. (3) A multi-disciplinary referral model, that integrates existing services horizontally between geriatric and emergency care, and vertically, the spectrum of health care (hospital, primary and community) and social care in the transition from hospital to the home, was piloted and showed to be effective in preventing hospitalization of frail elderly patients by diverting them to community and subacute care in in Prince of Wales Hospital (68.8%) and Ruttonjee Hospital (78.7%) if they are provided with adequate community support. Four major issues relating to required skills for training, workload, networking among departments and dissemination of information were identified as implementation barriers. (4) In scaling up the model, a meticulous implementation plan is needed to generate the knowledge for successful implementation from an involvement of at least 3 sites and other sites as control group with a consensus-building process to finalize the implementation strategies in Hong Kong.

Project No.: Elderly Care - CUHK

HHS-31-173
Adipocyte Fatty Acid Binding Protein as a Novel Marker of the Development of Sight-Threatening Diabetic Retinopathy

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Introduction: Sight threatening diabetic retinopathy (STDR) is a major cause of visual morbidity. It reduces quality of life of individuals and could substantially increase the healthcare burden of Hong Kong. There is a pressing need for well-validated biomarkers for early risk stratification. Adipocyte fatty acid-binding protein (AFABP) is a lipid chaperone protein involved in transport of lipids for storage and trafficking. Circulating AFABP level has been reported as a useful biomarker of various diabetic complications, including diabetic kidney disease. The association between circulating AFABP level and STDR, another major microvascular complication of diabetes, however, remains to be defined, especially among those with long duration of diabetes.

Project Objectives: We conducted this prospective cohort study to (i) investigate the association of baseline serum AFABP level with incident STDR in patients with type 2 diabetes, and (ii) examine whether an optimal serum AFABP cut-off can be derived to predict the development of STDR over and above established risk factors.

Methods: Serum AFABP levels were measured in 4558 Chinese participants without STDR as baseline, recruited from the Hong Kong West Diabetes Registry. Multivariable Cox regression analysis was performed to examine the association of their baseline serum AFABP levels with STDR development.

Results: Over a median follow-up of 5.6 years, 141 (3.1%) participants developed STDR, with a cumulative incidence of 0.6 per 100 person years. Baseline serum AFABP levels were significantly higher among those who developed incident STDR than those who did not ($p<0.001$). In multivariable Cox regression analysis, baseline serum AFABP level was independently associated with incident STDR (HR 1.34, 95%CI 1.03 – 1.74, $p=0.030$), together with duration of diabetes, systolic blood pressure, baseline HbA1c levels, severe albuminuria, use of insulin and statin, and the presence of background retinopathy at baseline. However, both the category-free net reclassification improvement and integrated discrimination improvement were not significant. This is probably driven by the relatively low number of events which could reflect an improved overall standards of diabetes care in Hong Kong.

Conclusion: Circulating AFABP level is an independent predictor of incident STDR. However, further studies are required to investigate the potential of serum AFABP as a clinically useful marker for early risk stratification in diabetic retinopathy.

Project No.: 14150781

HHS-32-178

A Cluster Randomized Controlled Trial to Test the Effectiveness of a Theory-Based and Setting-based Intervention in Promoting Strength Training among Older Adults in Hong Kong

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Introduction and Project Objectives: In Hong Kong, it was estimated that 12.3% of men and 7.6% of women aged 70 years above had sarcopenia. Decrease in muscle strength is associated with functional limitations as muscle is pivotal in activities of daily living (ADL). Although strength training (ST) is proven to increase muscle strength, muscle power and muscle endurance, very few interventions were conducted to promote ST among older adults in Hong Kong.

Methods: A two-arm clustered RCT was conducted. A total of 235 older adults were recruited from eight elderly centers and randomized to either intervention group or control group. Participants in the intervention group took part in a 6-month intervention that consisted of ST sessions, individual exercise prescription consultation, social gathering sessions and a buddy program; while participants in the control group took part in social gathering sessions. Participants were evaluated at baseline (Month 0), post-intervention (Month 6) and at 3 months follow up (Month 9). The primary outcome was prevalence of meeting the American College of Sports Medicine (ASCM) recommendations of ST.

Results: Participants in the intervention group reported significantly higher prevalence of meeting the ASCM recommendations of ST at post-intervention (I=78.2% versus C=4.2%; RR=81.69, 95% CI=27.0,247.19, chi-square=109.82, $p<.001$) and 3 months follow-up (I=57.9% versus 4.4%; RR=29.56; 95% CI=10.02, 87.23; chi-square=60.79, $p<.001$). Results from linear mixed model showed significant main effect of intervention in muscle strength, self-efficacy of ST, perceived susceptibility and perceived severity of sarcopenia, perceived barriers of ST, intention to perform ST, quality of life in physical health and psychosocial and physical well-being, adjusted for baseline score. Participants reported a high level of satisfaction towards to intervention.

Conclusion: The 6-month intervention was effective in increasing ST level, improving muscle strength, quality of life and psychosocial well-being, and improving cognitions associated with ST. It has the potential to be applied in other settings.

Project No.: 14153321

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HHS-33-190
Assessing the Influence of Deprivation on Chronic Diseases and the Access to Health Services among Persons with Chronic Diseases in Hong Kong

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Introduction and Project Objectives: This study aims to examine influence of socioeconomic factors and health behaviors on chronic disease and the influence of unaffordable health care on patient satisfaction. We hypothesize that: (1) Patients experienced unaffordable health care have lower patient satisfaction; (2) Impact magnitude of unaffordable health care varies across seven domains of patient satisfaction; and (3) Unaffordable health care is also a mediator of the association between the covariables and patient satisfaction.

Methods: We applied a quantitative survey to provide a more comprehensive view on whether socioeconomic factors and health behaviors had an influence on chronic diseases among the respondents. 878 individuals who attended a General Outpatient Clinic were invited to participate in the survey, and 756 were successfully recruited and completed the questionnaire face-to-face. Information on chronic disease, general physical and mental health status, depressive symptoms, loneliness, healthcare access and utilization pattern, patient satisfaction, lifestyle factors, and socio-demographic characteristics was collected in the survey. Multivariable logistic regression models were used to examine the statistical associations between diagnosed chronic disease and explanatory variables, while ordinary least squares regression was applied to explore the impact of unaffordable health care on patient satisfaction.

Results: At the individual level, older age, lower education, and unemployment were positively associated with greater risk of chronic disease. Moreover, participants who experienced unaffordable health care had significantly lower PSQ-18 score than those who did not (β=-0.22; 95%CI=-0.34 – -0.11). Unaffordable health care also had negative effect on general satisfaction (β=-0.32; 95%CI=-0.49 – -0.14), technical quality (β=-0.18; 95%CI=-0.30 – -0.05), financial aspects (β=-0.63; 95%CI=-0.78 – -0.47) and accessibility and convenience (β=-0.26; 95%CI=-0.42 – -0.10), and the negative effect of unaffordable health care on financial aspects remained significant at the 5% level after adjustments.

Conclusion: We confirmed the presence of health inequalities in terms of chronic diseases, which was found to be associated with older age, lower education level, and unemployment. Two policy implications are suggested. Firstly, both financial and non-financial socioeconomic indicators should be considered in identifying vulnerable individuals with chronic disease in Hong Kong; and secondly, the social determinants of health need to be taken into account for better chronic disease health care.

Project No.: 13141541

HHS-34-198
Impact of Pill-Splitting Training on Drug Physicochemical Properties and Clinical Outcomes in Elderly Population: A Parallel Study

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Introduction: Pill splitting by patients is common globally. One of the reasons for pill splitting is for cost saving since the institution may not need to stock too many drug items in their formulary. In addition, splitting drug may achieve dose flexibility particularly for patients requiring frequent dosing adjustment.8 Furthermore, some of the dosage may not be commercially available, especially those for off-label drug use. In these cases, splitting drugs may be essential. Nevertheless, it can also create other clinical issues including medication non-compliance, difficulties for patients to handle unscored pills or drugs that crumble after splitting, and inappropriate drug splitting for extended release formulations which may lead to treatment failure or toxicity.

Project Objectives: The project aimed to provide information on the clinical and physiochemical impacts of pill splitting training in elderly cardiac patients in Hong Kong.

Methods: A parallel study design was adopted. Patients taking lisinopril, amlodipine, simvastatin, metformin or perindopril who needed to split pills were recruited from the Cardiac or Hypertension clinics of the Prince of Wales Hospital. Patients were divided into three groups at their first visit. Group A patients would split drugs using their own technique, group B patients would use pill cutter after relevant training, and group C patients would take tablets that did not require splitting until follow-up. Primary outcome was the change of drug content before and after the pill splitting training. Assays were performed to determine the drug content. Secondary outcomes were the change of clinical outcomes, including blood pressure, haemoglobin A1c (HbA1c) and cholesterol levels, the change of attitude and acceptance towards pill splitting, the change of knowledge on pill splitting, and drug compliance at follow-up.

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Results: Two hundred and forty subjects were recruited and 106 returned for follow-up. The percentage of samples with both halved tablets within the assay limits increased in both group A and group B at follow-up, but did not reach statistical significance for both groups. Mean triglyceride level decreased while mean heart rate increased significantly in group B. Changes in other parameters were not significant.

Conclusion: This study highlighted the high variability of drug content after splitting. Pills with doses that does not require splitting would be preferable considering patients' preference. Patients should be educated to use pill cutter properly if pill splitting is inevitable.

Project No.: 14152111

HHS-35-85
A Randomized Controlled Trial of Psycho-Educational Interventions for Reducing Uncertainty and Anxiety, and Improving Sexual Functioning among Gynecological Cancer Patients in Hong Kong

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Introduction: The diagnosis of gynecological cancer (GC) and the effects of related treatments induce uncertainty in illness and have adverse effects to sexual functioning in the patients. The potential abilities of psycho-educational interventions to reduce uncertainty in illness and improve the emotional state and sexual functioning among patients with GC are poorly supported by existing evidence.

Project Objectives: To evaluate the effects of a theory-driven psycho-educational intervention program on uncertainty in illness, anxiety and sexual functioning in a cohort of Hong Kong Chinese patients with GC.

Methods: An assessor-blinded randomized controlled trial was conducted. Women with newly diagnosed GC planning for surgery as the first-line treatment were recruited from two regional hospitals. They were randomly assigned to receive either a 4-session, 12-week-long, culturally appropriate psycho-educational intervention program or attention from a nurse intervener. Patient-reported measures included Chinese version of Mishel's Uncertainty in Illness Scale (C-MUIS), Hospital Anxiety and Depression Scale (HADS) – Anxiety subscale and Sexual Function-Vaginal Changes Questionnaire (SVQ). Data on uncertainty in illness, anxiety and sexual functioning were collected at baseline and/or post-intervention. Qualitative data on opinions and feelings towards the program were collected by means of semi-structured interviews at post-intervention.

Results: We recruited 202 participants with an average age of 54 years. Stage I uterine cancer was the predominant diagnosis. Participants receiving the psycho-educational intervention (n = 102) reported significantly greater reductions in ambiguity, inconsistency and overall uncertainty in illness than those receiving attention only (n = 100), as measured by C-MUIS ($p < .01$). At post-intervention, participants in the intervention group were more likely to be sexually active ($p = .037$), to report greater sexual interest from their partners ($p = .008$) and to report a significantly higher level of intimacy ($p = .001$), compared to those in the control group. The qualitative findings suggested that the participants perceived the interventions as helpful and valued the psychological and informational support provided by the nurse intervener.

Conclusion: This was the first randomized controlled trial to demonstrate a significant effect of psycho-educational intervention on uncertainty in illness and sexual functioning, compared with traditional care, among Chinese patients with GC.

Implications: Our study findings support the inclusion of psycho-educational interventions in the routine clinical practices for patients with GC in Hong Kong. It can also be applied to other cancer groups to improve patient outcomes.

Project No.: 13141551

HHS-36-98
Effectiveness of Psychosocial Interventions for Dementia: A Network Meta-analysis

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Introduction: Psychosocial interventions may benefit people with dementia in cognitive and behavioral domains.

Project Objectives: To compare the cognitive and behavioral benefits of different psychosocial interventions in older adults with mild cognitive impairment (MCI) and dementia.

Study Design: Systematic review and network meta-analysis

Methods: Literature searches were performed in OVID databases. Randomized controlled trials (RCTs) that investigated the effectiveness of psychosocial interventions for MCI and dementia were included. Psychosocial interventions covering any types of non-pharmaceutical interventions were

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included, such as cognitive training, physical exercise, music intervention, social, and recreational activity. Usual care was used as the reference. Cognitive function was the primary outcome. Activities of daily living (ADL), agitated behavior, behavioral and psychiatric symptoms, depressive symptoms, and quality of life (QOL) were the secondary outcomes. All direct or indirect comparisons across the interventions were conducted by a network meta-analysis. Standardized mean difference (SMD) of different cognitive tests were compared before and after interventions. SMD with 95% confidence interval (CI), and rankings by effectiveness were compared across all interventions.

Results: A total of 20,806 participants from 262 RCTs were included. Twenty-one types of psychosocial interventions were categorized among studies for MCI and dementia. Cognitive training showed significant benefits in cognitive function to older adults with MCI and mild-to-moderate dementia (SMD, 95% CI = 0.49, 0.20-0.77 and 0.57, 0.39-0.75, respectively), but not to those with moderate-to-severe dementia. Physical exercise showed cognitive benefits to those with MCI or dementia. Music intervention only showed cognitive benefits to those with mild-to-moderate dementia (0.70, 0.09-1.32), but it could reduce agitated behavior (0.70, 0.23-1.17), psychiatric symptoms (1.55, 0.81-2.30) and depressive symptoms (0.79 (0.16-1.43) among patients with moderate-to-severe dementia.

Conclusion: Psychosocial interventions relief symptoms of dementia and improve functioning, but they work in diverse principles on different cognitive and non-cognitive domains. Personalized healthcare model for the population with different severity of dementia is highly recommended.

Implications: Psychosocial interventions showed different performance in older adults with MCI or dementia. Professional recommendations should be made by clinicians or health care professionals to assign appropriate psychosocial interventions with reference to the symptoms from traditional cognitive assessment.

Project No.: 15162451

HHS-37-145
In-depth Exploration of a Bidirectional Parent-child Health Relationship and its Mediating and Moderating Factors Among Low-income Families in Hong Kong

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Introduction and Project Objectives: Low-income families face increased exposure to stressors including material hardships, poorer social support, and violence, which can lead to physiological dysregulations and poor health outcomes of their members. Children from low-income families reported poorer health and more behavioural problems, potentially intensifying symptoms of stress in parents. This project examined the bidirectional relationship between parental stress and child health, and explored mediators/moderators for this relationship among low-income families in Hong Kong.

Methods: A prospective cohort study was conducted in 217 parent-child pairs recruited from two less affluent communities in Hong Kong (Tung Chung and Kwai Chung) between 2016 and 2017. Each parent-child pair was assessed at baseline, after 12- and 24-months by 1) parent-completed questionnaires on socio-demographics, medical history, parental stress and health-related quality-of-life (HRQOL), child's health and behaviour, family harmony, parenting style, and neighborhood cohesion; 2) physical examination; 3) buccal swab DNA sampling of the child and; 4) blood tests of the parent.

Results: At baseline, thirty-eight parents (17.5%) experienced significant stress, who were more likely to have a household income of <50% of the Hong Kong population median (50.0% vs 29.9%), be a single-parent (41.2% vs. 18.5%) or victim of intimate partner abuse (23.7% vs. 10.9%), and diagnosed with mental illnesses (23.7% vs. 5.1%). Children of stressed parents had poorer parent-perceived general health and HRQOL; and a higher degree of behavioural problems reported by parents (Total Difficulty Scores (SD) = 15.5 (6.5) vs. 9.3 (5.3), p<.001). Moreover, stressed parents reported lower family harmony scores (17.2 (4.9) vs. 19.9 (2.9), p<.001), lower neighbourhood cohesion scores (29.5 (7.7) vs. 33.3 (7.6), p=.007), and had a higher tendency for physical punishment, or neglecting their children, compared to parents who were not stressed. A bidirectional inverse relationship was observed between parental stress and child health at the respective timepoints, with cross-effects of baseline child health to later parental stress, and baseline parental stress to later child health. The relationship was mediated by parental depression, with parental stress positively predicting parental depression level but negatively with perceived child health.

Conclusion: Parental stress both precedes and is a consequence

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of child health and behavioural problems, impacting each other over the short- and long-term. Implementation of screening and intervention for parental depression is imperative to halt the adverse effects of stress on health of both parents and children. Further study to identify additional mediators can inform future development of targeted interventions for low-income families.

Project No.: 14151571

HHS-38-154
Adjunctive Light Treatment in Major Depressive Disorder among Evening Chronotype - A Randomized Controlled Trial

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Introduction and Project Objectives: Patients with unipolar non-seasonal depression and concomitant eveningness were associated with poor clinical outcomes and higher non-remission rate of depression. This study aims to examine the efficacy of adjunctive bright light therapy with gradual timing advance in a randomized controlled trial.

Materials and Methods: Participants were randomly allocated to receive 5 weeks of either bright white light therapy (BLT) or dim red light (DRL) with the same gradual advance protocol. Participants were followed up till 5 months after treatment, all outcomes were evaluated by blinded raters. Primary outcomes included (i) remission rate and (ii) the severity of depression. The analysis was conducted using Kaplan–Meier survival analysis, Cox proportional hazard analysis and linear mixed models.

Results: A total of 93 participants (46.4 ± 11.7 years old, 80% female) were randomized. The cumulative remission rate for the BLT and the DRL groups was 67.4% and 46.7%, respectively. Time to remission was shorter for the BLT group relative to the DRL group (log-rank test $p = 0.024$). Cox proportional hazard survival analysis showed that patients in the BLT group had a higher probability of achieving remission relative to patients in the DRL group [hazard ratio = 1.9 (95% CI = 1.1– 3.4), $p = 0.026$]. For those who were adherent to light therapy, sensitivity analysis demonstrated greater improvement in 17-Hamilton Depression Score (group × time interaction, $p = 0.04$) in the BLT group.

Conclusion: The use of bright light therapy with gradual advance protocol is an effective adjunctive treatment resulting in quicker and a higher rate of remission of depression in patients with non-seasonal unipolar depression and eveningness.

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2. Chan JW, Lam SP, Li SX, Chau SW, Chan SY, Chan NY, Zhang JH, Wing YK. Adjunctive bright light treatment with gradual advance in unipolar major depressive disorder with evening chronotype - A randomized controlled trial. Psychol Med. 2020 Sep 14:1-10. doi: 10.1017/S0033291720003232. PMID: 32924897.

Project No.: 12131131

HHS-39-207
Randomized Sham-controlled Trial of Augmentative Neuro-Navigated Right-Dorsolateral Prefrontal Cortex Low-frequency Repetitive Transcranial Magnetic Stimulation for Antidepressant Non-responding Bipolar Depression

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Introduction and Project Objectives: To examine the effect of augmentative low-frequency repetitive transcranial magnetic stimulation (rTMS) versus sham control on antidepressant-non-responding bipolar depression.

Methods: 60 subjects with antidepressant-non-responding bipolar depression were randomized to receive 15 sessions of sham or active rTMS under low-frequency (1Hz, 300 pulses per session, 4,500 in total) on right dorsolateral prefrontal cortex (DLPFC), as identified from structural MRI scans. Changes in depressive, anxiety, manic/hypomanic symptoms and overall clinical condition were gauged as ratings on the Montgomery-Åsberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS), Hamilton Anxiety Rating Scale (HAMA) and Clinical Global Impression Scale (CGI) respectively.

Results: 54 subjects (Active= 27, Sham=27) completed all treatment and study procedures. On intention-to- treat analysis, active treatment did not result in significantly increased rates of response (17% (active) vs 10% (sham), defined as 50% reduction in MADRS and CGI <=2) and remission (13%(active)

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vs 0%(sham), defined as MADRS <7 and CGI = 1) at treatment endpoint (week 3). Neither were significant between-group differences observed for response and remission rates at week 6 and 12, or anxiety and depressive symptom scores at any time point. Active treatment was not associated with increased risk of hypomanic/manic episodes, and was associated with significantly lowered YMRS scores at week 12 compared to sham.

Conclusion: 1-Hz right-DLPFC rTMS was not found to be an effective treatment for relieving anxiety or depression under current parameters. Whether it would result in reduced manic symptoms and enhanced stability would require further specific examination. Our findings highlighted the salience of sham comparison in randomised controlled trials, before asserting the effectiveness of any rTMS protocols. Further exploration of low frequency rTMS protocols would require a larger sample size, examination of different strength and frequency parameters, and exploration of potential pre-treatment predictors associated with clinical response to right-DLPFC low frequency rTMS treatment. Research from other groups showed promise for deep TMS, but costs and long-term effectiveness remain salient issues to tackle in further studies.

Project No.: 12130691

HHS-40-26
Electroacupuncture Plus On-Demand Gastrocaine for Refractory Functional Dyspepsia: Pragmatic Randomized Trial

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Introduction and Project Objectives: Treatment options for functional dyspepsia (FD) refractory to pharmacological treatments are limited but the effectiveness of electroacupuncture (EA) is uncertain. We assessed the effectiveness of EA combined with on-demand gastrocaine.

Methods: We conducted a single-center, assessor-blind, randomized parallel-group 2-arm trial on Helicobacter pylori negative FD patients of the postprandial distress syndrome subtype refractory to proton pump inhibitor, prokinetics, or H2 antagonists. Enrolled participants were block randomized in a 1:1 ratio, with concealed random sequence. The treatment and control groups both received on-demand gastrocaine for 12 weeks, but only those in treatment group were offered 20 sessions of EA over 10 weeks. The primary endpoint was the between-group difference in proportion of patients achieving adequate relief of symptoms at week 12.

Results: Of 132 participants randomly assigned to EA plus on-demand gastrocaine (n = 66) or on-demand gastrocaine alone (n = 66), 125 (94.7%) completed all follow-up at 12 weeks. The EA group had a compliance rate 97.7%. They had a significantly higher likelihood in achieving adequate symptom relief at 12 weeks, with a clinically relevant number needed to treat (NNT) value of 2.36 (95% CI: 1.74, 3.64). Among secondary outcomes, statistically and clinically significant improvements were observed among global symptom (NNT = 3.85 [95% CI: 2.63, 7.69]); postprandial fullness and early satiation (NNT = 5.00 [95% CI: 2.86, 25.00]); as well as epigastric pain, epigastric burning, and postprandial nausea (NNT = 4.17 [95% CI: 2.56, 11.11]). Adverse events were minimal and nonsignificant.

Conclusion: For refractory FD, EA provides significant, clinically relevant symptom relief when added to on-demand gastrocaine (ChiCTR-IPC-15007109).

Project No.: 12130211

HHS-41-33
Pocket-size Mobile Echocardiographic Screening of Thoracic Aortic Aneurysm in Hypertensive Patients

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Introduction and Project Objectives: Patients with hypertension may develop thoracic aortic aneurysm (TAA) that can be asymptomatic but potentially life-threatening. We sought to assess the prevalence of asymptomatic TAA among hypertensive patients with a point-of-care screening program using pocket-size mobile echocardiographic (PME) devices.

Methods: We prospectively performed transthoracic aortic ultrasound using a PME device on patients attended our hypertension clinics between June 2016 and July 2018. The echo examinations were performed by a research fellow to obtain aortic diameter measurements including the aortic sinus, sinotubular junction, ascending aorta, aortic arch and descending thoracic aorta through various standard echo views. Images were stored on the PME and transferred to a desktop computer for measurements and further statistical analysis.

Results: In the study period, a total of 1529 hypertensive patients (age, 62y [30y to 85y], 824 men) were recruited. The prevalence of TAA (defined as maximum aortic diameter of ≥4.5cm and/or >50% larger than the diameter of adjacent normal aorta) in our study population was 7.5% (115/1529),

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with aortic arch (43.4%) as the most frequent location of the aneurysm. Multiple logistic regression analysis identified male gender (odds ratio, 2.120; p<0.0001) and older age (odds ratio, 1.031; p<0.0001) as independent factors associated with TAA.

Conclusion: Silent TAA is common among hypertensive patients in Hong Kong. PME device is effective in detecting TAA in a clinic setting. Such approach may be useful for early detection of TAA among at-risk patients allowing aggressive blood pressure control and early surgical intervention to prevent catastrophic complications.

Project No.: 13140631

HHS-42-42
Impact of Breastfeeding on Postpartum Glucose Regulation in Women with Recent Gestational Diabetes

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Introduction: Rates of both Type II diabetes mellitus (DM) and gestational diabetes mellitus (GDM) are substantially higher among Asian populations. In non-Asian populations, breastfeeding has been shown to improve postpartum glucose tolerance among women with previous GDM and to lower overall rates of subsequent DM. No studies have investigated the impact of breastfeeding on postpartum glucose tolerance among Chinese women with previous GDM.

Project Objectives: To test the hypothesis that any and exclusive breastfeeding improve postpartum glucose tolerance in Chinese mothers who were diagnosed with GDM during pregnancy.

Methods: This study used a prospective cohort design. 830 women diagnosed with GDM in the index pregnancy were recruited after the diagnosis of GDM (normally from 24 to 34 weeks' gestation) from the obstetric outpatient setting of three public hospitals in Hong Kong between September 2015 and December 2016. Participants' baseline socio-demographic, maternal data, diet and exercise history, and planned method of infant feeding were collected at recruitment. Prevalence of Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IGF) by breastfeeding status (exclusive, non-exclusive, exclusive formula-feeding) among participants with GDM at 6 weeks postpartum.

Results: At 6 weeks postpartum, 20.6% (n=141) of participants had IGT (4.1%, n=28 had IFG only, 14.5%, n=99 had impaired 2-h glucose only and 2.1%, n=14 had both) and 2.9% (N=20) met the threshold for DM. Additionally, 36.0%, 43.2%, and 20.8% of participants were giving exclusive, non-exclusive, and no breast milk feedings (exclusive formula-feeding), respectively. When compared with participants exclusively formula feeding, the odds of IGT were lower in participants partially breastfeeding (OR=.53; 95% CI 0.32-0.88) and exclusively breastfeeding (OR=0.59; 95% CI 0.35-1.00). In overweight and obese participants, exclusive breastfeeding at 6 weeks postpartum reduced the odds of IGT by almost 70% (OR=.31; 95% CI 0.14-0.71) and 2 weeks of exclusive breastfeeding reduced the odds by over 50% (OR=.49; 95% CI 0.27-0.90). Similarly, there were graded inverse associations between breastfeeding exclusivity and IFG, with a greater effect in overweight and obese participants.

Conclusion: Exclusive breastfeeding improves glucose tolerance in mothers with GDM and especially overweight and obese women. Improving postpartum glucose tolerance in women with GDM could help to offset the later onset of DM. In women with GDM breastfeeding is a modifiable risk factor for later DM and should be encouraged and supported among this high-risk group.

Project No.: 12133361

HHS-43-43
A Randomised Controlled Trial of the Effectiveness of Adapted Taekwondo Training on Skeletal Development and Motor Proficiency in Pre-pubertal Children with Developmental Coordination Disorder

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Introduction and Project Objective: Motor performance, body balance and skeletal development in children with developmental coordination disorder (DCD) are compromised. Taekwondo (TKD, a Korean martial art and an Olympic sport) may be an effective intervention to improve motor proficiencies and bone health in these children. The objective of this project was to evaluate the effectiveness of a novel adapted TKD training program on skeletal development, motor performance, eye–hand coordination (EHC), sensory organization, and

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standing balance performance in prepubertal children with DCD.

Methods: It was a randomised controlled trial. One hundred forty-five children with DCD were randomly assigned to either a DCD-TKD group or a DCD-control group. Forty-seven children with typical development were allocated to a healthy-control group. The children in the DCD-TKD group participated in a weekly 1-hour adapted TKD training program and daily TKD home exercises for 12 consecutive weeks and those in the DCD-control group participated in a jogging program. The primary outcome (i.e., delay in skeletal development) and secondary outcomes (i.e., Movement Assessment Battery for Children [MABC] total impairment score [TIS]; EHC accuracy score, reaction time, and movement time; and modified Clinical Test of Sensory Integration of Balance [mCTSIB] sway indices) were measured at baseline, after the intervention, and 3 months after the intervention.

Results: Skeletal development showed similar improvement in all three groups over time ($p < 0.017$). Improvement in the MABC TIS was seen in both DCD groups over time ($p < 0.017$). Only the DCD-TKD group showed a significant improvement in the EHC movement time at 3 months ($p = 0.009$) and 6 months ($p = 0.016$). Both DCD groups revealed higher mCTSIB sway indices than the healthy-control group overall ($p < 0.017$), regardless of TKD training.

Conclusion: Adapted TKD intervention may be effective in improving the EHC movement time in children with DCD. For skeletal development, motor performance, and other EHC outcomes, the effects of maturation may be more profound. The adapted TKD intervention may not improve sensory organization and standing balance performance in children with DCD. Therefore, adapted TKD training may be incorporated into rehabilitation programs for children with DCD to improve specifically their EHC (movement time).

Project No.: 13142081

HHS-44-72
Dynamic Change of LSM-HCC Score and Enhanced Liver Fibrosis (ELF) Score to Predict Hepatocellular Carcinoma (HCC) in Chronic Hepatitis B Patients Receiving Antiviral Treatment

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Introduction and Project Objectives: Liver stiffness measurement hepatocellular carcinoma (LSM-HCC) score predicts HCC accurately in patients with chronic hepatitis B (CHB). We aimed to combine LSM-HCC with Enhanced Liver Fibrosis (ELF) score to predict HCC in CHB patients who received antiviral treatment.

Methods: CHB patients had transient elastography examinations in 2006-2013 with intermediate and high risk of HCC by LSM-HCC score (i.e. 11 or above) were included to repeat transient elastography at least 3 years later. ELF score was assessed by retrieved the stored serum samples 4 weeks within transient elastography examination. The primary endpoint is the cumulative incidence of HCC according to the dynamic changes in LSM-HCC and ELF scores.

Results: 453 CHB patients (mean age 51.7±10.3 years; male 74.4%) were recruited, 45 patients (9.9%) developed HCC during the mean follow-up of 56 months. For the change of LSM-HCC score, 71.4%, 24.3% and 4.3% of patients had LSM-HCC score improved, remained static and deteriorated respectively; whereas 36.9%, 57.8% and 5.3% of patients had ELF score improved, remained static and deteriorated respectively. The sensitivity (86.7%) and negative predictive value (NPV) (95.3%) of combined LSM-HCC and ELF score were higher than that of each score alone. Kaplan-Meier analysis showed that ELF score would help further differentiate the HCC risk in patients with intermediate risk by LSM-HCC score (P=0.026), but not in patients with high risk by LSM-HCC score (P=0.770).

Conclusion: The two-step algorithm combining LSM-HCC score and ELF score could improve the accuracy of predicting HCC of CHB patients received antiviral treatment.

Project No.: 13140651

HHS-45-78
A Randomized Controlled Trial of Upper Limb Training with Bilateral Cutaneous Electrical Stimulation to Improve Upper Limb Function in Patients with Chronic Stroke

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Introduction and Project Objectives: Recovery of voluntary upper limb function is among the most important goals of stroke rehabilitation. Transcutaneous electrical nerve stimulation (TENS) over the paretic limbs is an effective adjunct therapy that can improve paretic limb motor function in patients with stroke when applied with task-orientated training. Recent research has consistently demonstrated that interventions involving both the paretic and non-paretic limbs can yield greater improvements in motor control and function than interventions involving only the paretic limbs in people with stroke. The main objective of this study was to compare the efficacy of bilateral TENS combined with task-oriented upper limb training (TOT) versus unilateral TENS combined TOT in improving upper limb motor functions in patients with chronic stroke.

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Methods: A randomised, single-blinded, controlled clinical trial conducted in the Balance and Neural Control Laboratory. Total 110 subjects having stroke 1 to 10 years before the study who fulfilled the inclusion criteria were recruited.Subjects were randomly assigned to bilateral TENS+TOT or unilateral TENS + TOT and underwent 24 sessions of training over a 8-week period. The primary outcome measures was Fugl-Meyer Assessment of Upper Extremity (FMA-UE) and Wolf Motor Function Test (WMFT). The secondary outcome measures included maximal grip strength, the Chinese version of Motor Activity Log (MAL) and the Hong Kong version of the Short-Form Health Survey (SF-36). Questionnaires. Each participant was assessed at baseline, after 12 and 24 sessions of training, and 4 weeks after cessation of training.

Results: The subjects in the bilateral TENS+TOT group showed greater improvement in WMFT scores (mean difference, 6.31, P = 0.006), than those in the unilateral TENS+TOT group after 12 sessions of treatment. Only bilateral TENS+TOT group showed significant within-group improvement in WMFT scores, but not the Uni-TENS group. However, there were no significant between-group differences for other outcome measures. Both groups induced significant within-group improvements in FMA-UE scores and paretic grip strength. Generally, the training effects in both groups was maintained for 4 weeks after treatment ended.

Conclusion: The application of bilateral TENS over the median and radial nerves combined with TOT was superior to the application of unilateral TENS combined with TOT in improving WMFT after 12 sessions of training. Bilateral TENS could be a useful complement to TOT in improving upper limb functions of stroke survivors.

Project No.: 12131821

HHS-46-88
Obstructive Sleep Apnoea and CPAP Treatment Response In Patients with Non-alcoholic Fatty Liver Disease

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Introduction and Project Objectives: Obstructive sleep apnea (OSA) is associated with development of nonalcoholic fatty liver disease (NAFLD). The effects of continuous positive airway pressure (CPAP) on NAFLD in patients with concomitant OSA are unknown. We aimed to investigate the effects of autoCPAP versus subtherapeutic CPAP treatment over 6 months on NAFLD activities.

Methods: Patients with NAFLD and OSA, as defined by respiratory event index (REI) ≥ 5/hr diagnosed by a validated level 3 Embletta device, were randomized into group A) autoCPAP (4-20cmH2O) or group B) subtherapeutic CPAP (pressure fixed at 4cmH2O). Primary endpoint was the difference in changes in intrahepatic triglyceride (IHTG) as measured by proton-magnetic resonance spectroscopy (MRS) after 6 months of therapy. Key secondary endpoints included changes in controlled attenuation parameter (CAP) and liver stiffness measurement measured with transient elastography, and serum cytokeratin-18 fragment.

Results: A total of 120 patients were randomized equally into two groups. There were significant correlations between CAP and REI(r=0.203, p=0.026), percentage of total recording time with SaO2<90% (r=0.265, p=0.003), and oxygen desaturation index (r=0.214, p=0.019). Following 6 months of treatment, there were no significant differences of changes in primary and secondary endpoints between the 2 treatment groups. Regression analysis showed that weight change over 6 months correlated with both changes in IHTG and CAP (p<0.001).

Conclusion: Despite significant correlations between hepatic steatosis and markers of severity of OSA, CPAP alone did not improve hepatic steatosis and fibrosis. However, additional role of weight reduction through lifestyle modification deserves further investigation (Full article published in Am J Respir Crit Care Med. 2021 Feb 15;203(4):493-501).

Project No.: 13140801

HHS-47-89
Activation of Uncoupling Protein-1 as a Potential Therapeutic Strategy for Obesity-induced Endothelial Dysfunction and Atherosclerosis

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Introduction and Project Objectives: Perivascular adipose tissue (PVAT) surrounds most blood vessels and is abundant in uncoupling protein-1 (UCP1). UCP1 is regarded as the sole effector for adaptive thermogenesis. This study aims to investigate the role of UCP1 in PVAT in regulating vascular homeostasis independent of thermogenesis.

Methods: UCP1-deficient apoE-/- mice were employed to evaluate the role of UCP1 in the pathogenesis of vascular inflammation and atherosclerosis. The effects of UCP1 in PVAT on endothelium-dependent vasodilatation were evaluated by ex vivo co-culture and wire myograph. MMP and NLRP3-inflammasome/caspase-1/IL-1β axis were measured by fluorescence staining, Western blotting and biochemical assays.

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Results: UCP1 deficiency exacerbates dietary obesity-induced endothelial dysfunction, vascular inflammation and atherogenesis in mice, which was not rectified by reconstitution of UCP1 in interscapular brown adipose tissue (BAT). Mechanistically, lack of Ucp1 augments mitochondrial membrane potential (MMP) and mitochondrial superoxide (mtSuperoxide), leading to activation of the NLRP3-inflammasome followed by caspase-1-mediated maturation of interleukin 1β (IL-1β). UCP1-deficiency-evoked deterioration of vascular dysfunction and atherogenesis is reversed by IL-1 neutralzing antibody in vitro or the mitochondrial uncoupler BAM15 in vivo. Furthermore, reconstitution of UCP1 in swine model (which lack functional UCP1) protects against hypercholesterolemia/diabetes-induced vascular inflammation and coronary atherosclerosis.

Conclusion: UCP1 acts as a gatekeeper to prevent mtSuperoxide-evoked NLRP3-inflammasome activation and IL-1β production in PVAT, thereby conferring a beneficial effect against cardiovascular diseases. Strategies to enhance UCP1 action represent a new therapy for atherosclerosis.

Project No.: 13143731

HHS-48-94
Are Rigid Cervical Collars Necessary for Patients Undergoing Open-Door Laminoplasty and Titanium Arch Plates for Cervical Myelopathy? – A Randomized Pilot Clinical Trial

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Introduction and Project Objectives: Cervical collars are used after laminoplasty to protect the hinge opening, reduce risks of hinge fractures and avoid springback phenomena. However, its use may lead to reduced range of motion, axial neck pain and increased cost. We aim to investigate the clinical, radiological and functional outcomes of patients undergoing hinge laminoplasty with or without cervical collar immobilization by randomized controlled trial.

Methods: This was a prospective, parallel single-blinded randomized controlled trial. Patients undergoing laminoplasty for cervical myelopathy were randomly allocated into two groups based on the use of collar postoperatively for 3 weeks. Clinical assessments included cervical range of motion, axial pain (visual analogue scale/VAS), and objective scores (36-item short form/SF-36, Neck disability index/NDI, modified Japanese Orthopaedic Association/mJOA). Patients' group allocation was blinded to 3 assessors during radiographic measurements which included cervical alignment, spinal canal diameter and complications (implant loosening, springback). All assessments were performed preoperatively and at postoperative 1-week, 2-weeks, 3-weeks, 6-weeks, 3-months, 6-months and 12-months. Comparative analysis was performed via analysis of variance adjusted by the baseline scores, sex and age as covariates.

Results: A total of 35 patients with mean age of 64.9±11.4 years at surgery were consecutively recruited and randomized to collar use (n=16) and without collar immobilization (n=19). All patients completed all follow-up assessments without dropout, and had no complications. There were no differences between groups at baseline. Subjects had comparable mJOA scores, SF-36, NDI and range of motion at postoperative timepoints. Patients without collar use had higher VAS at postoperative 1-week (5.4 vs 3.5; p=0.038) and 2-weeks (3.5 vs 1.5; p=0.028) but subsequently follow-up revealed no differences between the two groups.

Conclusion: The use of a rigid collar after laminoplasty leads to less axial neck pain in the first two weeks after surgery. However, there is no additional benefit with regards to range of motion, quality of life, and complication risk. This difference in pain response only impacts in the initial postoperative period and does not impact the overall quality of life of patients.

Project No.: 13142371

HHS-49-111
A Pilot Study to Determine the Gut Microbiota of Hong Kong Infants Fed with Breast-Milk and Infant Formula

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Introduction and Project Objectives: Gut microbiota has been considered to have important impact for human health. Infants receive their initial gut microbes during giving birth which is highly dependent on the delivery mode. Maturation of infant gut microbiota is further affected by various factors including diet determined by feeding practice and play a critical role in shaping and maintaining the stability of infants' gut microbiota. Studies investigating the effect of feeding practice on the infant gut microbiota was rather lacking during the time of applying this project, hence this project aimed to set up a platform for determination of gut microbiota and study if early establishment of the gut microbiome is influenced by different feeding practice.

Methods/Implementation: Total 49 pairs of mother and infant aged 2-4 months without abnormality and complexity were

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recruited. Breastmilk and infant faecal samples were collected and subjected to 16S sequencing for determination of gut microbiota.

Results/Outcome: Among the mother-infant pairs, 28, 10 and 11 infants received exclusive breast-feeding (BF), exclusive formula-feeding (FF) and mixed feeding (MF) pattern of both, respectively. The biodiversity of breastmilk microbiota showed a great variation among subjects while all infant faecal microbiota had less variation. The average composition of breastmilk microbiota was more diverse than faecal microbiota regardless of the feeding pattern. The major bacteria phyla from the infant faeces differed slightly from US and European findings. Part of the BF faeces aligned quite well with the breastmilk samples and the relative abundance of Bifidobacterium spp. in the faeces of BF is higher than that of FF and MF, implying direct transferring of microorganisms including Bifidobacterium spp. from breastmilk to the gut of breastfed infants. Upon introduction of infant formula, the MF faeces started to deviate from the core microbiota and shifted toward to the FF group.

Conclusion: This project has successfully set up the platform to determine both the microbiota of breastmilk and infant gut in Hong Kong. Both exclusive and partial feeding with breastmilk supports the growth of Bifidobacterium spp., which has potential to help the maturation of immune system of infants. The findings from this project provide important information on the effect of feeding practice on infant gut microbiota, as well as the interrelationship between the breastmilk microbiota and gut microbiota of breastfed infants, paving the way to understand the effect of breastmilk and other maternal factors on the gut microbial community of infants in Hong Kong.

Project No.: 14150411

HHS-50-134
Regulation of Microrna Biogenesis by BRAF/MEK Targeted Therapy: Molecular Mechanisms and Role in Drug Resistance

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Introduction: Malignant melanoma is a highly aggressive skin cancer with increasing incidence and high mortality in the last decades. FDA-approval BRAF inhibitors are able to selectively kill advanced melanoma with the BRAF V600E mutation. However, its use is limited and hampered by its acquired resistance. Recent studies revealed that alteration of microRNA (miRNA) levels triggers drug resistance in melanoma cells. Nonetheless, the interrelation between miRNA expression and acquired BRAF-inhibitor resistance in melanoma cells is still unclear.

Objective: To investigate whether BRAF inhibitor-induced miRNA alterations are involved in acquired drug resistance.

Methods: In this research, human melanoma cell lines were treated with BRAF inhibitors. RT-qPCR, Western blotting and mouse studies were performed to explore the effects of vemurafenib on MITF-targeting miRNAs and drug resistance of cells.

Results: Our results showed that BRAF inhibitors down-regulated miRNA biogenesis machinery and therefore led to the decreased levels MITF-targeting miRNAs such as miR-155-5p and miR-340-5p, which are involved in BRAF inhibitor-induced drug resistance.

Conclusion: Our results demonstrated that modulation of MITF targeting miRNAs by BRAF inhibitors is involved in BRAF-inhibitor resistance. miRNAs mimics may serve as potential adjuvants of BRAF inhibitors in melanoma treatment.

Project No.: 15163441

HHS-51-160
Prevention of Vasovagal Reactions in Blood Donors: A Randomized Double-Blinded Controlled Comparison of Efficacy and Haemodynamic Effects of Oral Prehydration Fluids

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Introduction: Vasovagal reaction (VVR) results from haemodynamic disturbances from hypovolaemia after phlebotomy. Most symptoms are mild; however, adverse consequences as a result from these symptoms after donation have been reported. VVR contributes to the reduction in the willingness of both first-time and repeat blood donors. Despite the reduction in the incidence of VVR after oral prehydration, the underlying haemodynamic changes have not been evaluated previously.

Project Objective: To investigate the haemodynamic effects of different prehydration fluids in minimizing immediate and delayed VVRs among young and healthy blood donors.

Methods: This was a randomized, double-blinded controlled trial. A total of 2,101 young blood donors (16-22 years old) were recruited and equally allocated to: (1) Standard management (no prehydration) (Control); (2) 500 mL flavoured water (Water) or (3) 500 mL oral rehydration salt (ORS). Haemodynamic measurements were recorded in 426 donors at multiple time

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points using transcutaneous Doppler ultrasound. Predonation anxiety levels, post donation adverse effects and incidence of immediate and delayed VVRs were assessed and recorded.

Results: Both Water and ORS increased stroke volume (SV) by 10% and cardiac output (CO) by 5-8% compared to Control. The increase in SV and CO levels persisted throughout phlebotomy. Haemodynamic effects of water diminished at the end of recovery when donors were mobilized, while the effects of ORS were maintained when donors left the centre. Standing resulted in a 21% decline in SV before phlebotomy vs. 33-35% after phlebotomy. Compared to the Control, ORS was more effective in mitigating haemodynamic derangements after blood donation, with higher SV, CO and a lower systemic vascular resistance (SVR). The increase in SV and CO levels persisted throughout phlebotomy when donors were in the standing position. The incidence of delayed VVR were 11.9% for Control, 8.8% for Water and 7.7% for ORS. There was a reduction in odds ratios of VVR by 35%, comparable to a previous report of 38% in Morand's study (France 2016), even though it was not statistically significant.

Conclusion: Drinking fluids is recommended prior to phlebotomy. While both water and ORS mitigate the haemodynamic effects of blood donation equally, the effects of water were short and diminished when donors were mobilized. Circulatory expansion with ORS lasted longer, and restored CO to predonation levels after phlebotomy. Thus, ORS prehydration may have a role in mitigating the haemodynamic disturbance and prevention of VVR in blood donors.

Project No.: 12130731

HHS-52-177
Anaesthetic Depth and Delirium after Major Surgery: A Randomised Clinical Trial

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Introduction and Project Objectives: Postoperative delirium (POD) is a serious complication of surgery that is associated with prolonged hospitalization, long-term cognitive decline, and mortality. Identifying strategies to reduce the incidence of POD is critical to improving outcomes. The aim of this study was to determine whether targeting light anaesthesia using the bispectral index (BIS 50) was associated with a lower incidence of POD than targeting deep anaesthesia (BIS 35).

Methods: This study was a multicentre randomized clinical trial of 655 at-risk patients undergoing major surgery from 8 centres in 3 countries. Patients underwent delirium assessment for 5 days postoperatively using the 3 minute confusion assessment method (CAM) (3D-CAM) or intensive care unit (ICU)-CAM, and cognitive screening using the mini-mental state examination (MMSE) at baseline and discharge and the abbreviated mental test score (AMTS) at one year. Patients were assigned to light (BIS 50) or deep (BIS 35) anaesthesia during surgery. Mean arterial blood pressure was maintained within a prespecified target range. The primary outcome was the presence of POD on any of 10 assessments over the first 5 postoperative days. Secondary outcomes included mortality at 1 year, cognitive decline at hospital discharge and 1 year, unplanned ICU admission, length of hospital stay and time spent in electroencephalographic burst suppression.

Results: The incidence of POD in the BIS 50 group was 29% and in the BIS 35 group was 38% (OR 0·67 (95% CI 0·46 to 0·97), P=0·037). At 1 year those in the BIS 50 group demonstrated significantly better cognitive function than those in the BIS 35 group (6% impaired versus 19% impaired, p < 0·001).

Conclusion: Among patients undergoing major surgery, targeting light anaesthesia reduced the risk of POD and cognitive decline at 1 year.

Project No.: 13140851

HHS-53-206
Psychopathology, Executive Dysfunction and Role Impairment in Chinese Young Adults with a Previous Clinical Diagnosis of Childhood Attention-deficit/Hyperactivity Disorder in Hong Kong

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Introduction and Project Objectives: Attention-deficit Hyperactivity Disorder (ADHD) has been recognized as one of the most common developmental health problems with high persistence in adulthood and brings about substantial comorbidity and disability. In light of the lack of data on adult ADHD outcomes in Chinese communities, we set out to examine whether ADHD symptoms are similarly persistent and impairing in a sample of Hong Kong young adults. The primary objective was to evaluate the prevalence of early-adulthood (approximately 18-24 years old by 2014-15) persistence of ADHD amongst patients whom previously received a clinical diagnosis of ADHD (DSM-IV) or Hyperkinetic Disorder (ICD-10) at ages of 6-12 years. As secondary objectives, we also examined differences in executive functioning, psychiatric

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morbidity and early-adulthood role impairment between patients with remitted versus persistent ADHD.

Methods: We consecutively recruited 197 young adults who were under care from 2002 to 2005 at ages 6 to 12 and clinically diagnosed with DSM-IV ADHD or ICD-10 Hyperkinetic Disorder at one of the four tertiary child mental health clinic in Hong Kong for follow-up assessments. Outcome measures included 6-month prevalence of ADHD (subthreshold ADHD and those meeting ADHD full criteria, measured using ACDS v1.2), scores on a battery of neuropsychological assessments including ANT, WCST, Trail-making, Stroop Color and Word Test, Verbal Fluency and WMS, psychiatric comorbidity (SCID) and role impairment (WHO-DAS).

Results: 197 participants were recruited with a response rate of 33%. The 6-month prevalence of adult persistent ADHD, weighted for age and sex distribution of non-respondents, was 82% in the sample. Compared with the remitted group, the persistent ADHD group were more likely to suffer from a mental disorder (X2 (1, N = 184) = 5.57 , p =.018) , perform more poorly on neuropsychological assessments including Stroop Color and Word test (t(70.83)=-3.25, p=.002) and the WAIS digit symbol test (t(194)=3.15, p=.002), and suffered significantly greater impairments across the 6 domains of WHO-DAS, with a higher overall impairment score (U=983.50, P<.001).

Conclusion: We found that early-adulthood persistence of ADHD was highly prevalent, and significantly associated with psychiatric comorbidity, cognitive impairment and functional impairment. Our findings supported the cross-national validity of adulthood ADHD persistence in Hong Kong Chinese patients. It also suggested the need for development of monitoring, support and treatment service for the continued needs for adults with ADHD in Hong Kong and other Chinese communities.

Project No.: 12130681

HHS-54-227
Identification of Broad-Spectrum Antivirals against Respiratory Viruses and Novel Therapeutic Agents for Combating Antibiotic Resistant Bacteria

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Introduction and Project Objectives: Single stranded (ss) RNA viruses represent the most significant viral respiratory viruses leading to respiratory infections and viral pneumonia in mankind. Members of Coronaviridae (including SARS-CoV and MERS-CoV) and Picornaviridae (including human rhinovirus and enterovirus) are frequently linked to human respiratory infections in children and in adults, causing common upper respiratory discomforts to life-threatening systemic infections. Multidrug resistant "super bugs" such as methicillin-resistant Staphylococcus aureus (MRSA) has rendered many of the existing available drugs useless. Millions people dies every year due to drug-resistant emerging and re-emerging pathogens. The main objective of this project is to identify and characterize novel therapeutic agents that may be used to combat infections caused by clinically significant respiratory viruses and by antibiotics resistant bacteria.

Methods: Virology: Bioactive compounds isolated from previous screens were tested in influenza viruses, SARS-CoV, MERS-CoV, EV-71, RSV, adenovirus, and human rhinoviruses. Bacteriology: Bioactive compounds modulating virulence properties of MRSA were tested in mice infection model to evaluate the efficacies of the compounds to reduce bacterial loads in mice organs.

Results: 1. One compound with broad spectrum inhibitory activities against a panel of ssRNA RNA viruses has been identified and characterized. Mechanistic studies suggest that it is a pyrimidine synthesis inhibitor with involvement of the host antiviral response. 2. Two non-antibiotic compounds targeting MRSA have been identified and characterized. The two compounds inhibits staphyloxanthin production and suppress virulence genes expressions respectively and have shown in vivo efficacies in mice infection models.

Conclusion: Single-stranded RNA viruses have been implied in various respiratory infections and millions of people died due to ssRNA RNA infections. Conventional antivirals targeting viral components may elicit drug resistance easily and thus have made antiviral drug development very challenging. We have successfully identified and characterized a novel pyrimidine synthesis inhibitor with involvement of the host antiviral response. Modulating host targets and response to viral infection may offer new therapeutics with less likelihood to develop drug resistance from the viruses. Our identification and validation of non-antibiotic compounds targeting the virulence properties of bacteria has also offer new hope in combating multidrug resistance bacteria. The discovery of host-targeting broad-spectrum antiviral agents may ease the challenges of rapid development antiviral drug resistance. Likewise, the discovery of non-antibiotic compounds targeting the virulence properties of the bacteria may lead to novel therapeutics that are not subjected to selective pressure for antimicrobial resistance.

Project No.: HKM-15-M11

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HP-1-36
Exercise for Chronic Musculoskeletal Pain in Older People: A Randomized Clinical Trial

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Introduction and Project Objectives: Exercise therapy is commonly prescribed by primary care physicians (PCPs) in the management of chronic musculoskeletal (MSK) pain. We evaluated the clinical effectiveness of a supervised neuromuscular (NM) exercise program in older people with chronic MSK pain.

Methods: A 12-week, two-arm randomized controlled trial comparing 6 weeks supervised NM exercise versus waiting list control. We enrolled 72 participants with chronic MSK pain at seven public primary care clinics. Participants were randomly allocated (block size of 12) in 1:1 ratio to the NM (N=36) and control group (N=36). Data were collected at baseline, 6 and 12 weeks. The primary outcome was the Brief Pain Inventory (BPI) severity pain score at 6 weeks (post-intervention). Secondary outcomes included the BPI interference score, Pain Self-Efficacy Questionnaire (PSEQ), Short form of Health Survey (SF-12), General Anxiety Disorder-7 (GAD-7), and Patient Health Questionnaire-9 (PHQ-9) scores, and functional measurement using the Timed-Up-and-Go test and handgrip strength.

Results: Compared with the control group at 6 weeks, the NM group demonstrated a significantly greater improvement in the BPI-severity pain score (between-group difference -1.27, 95% CI = -2.08 to -0.45, P <0.01), PSEQ (between-group difference 6.50, 95% CI = 2.22 to 10.77, P <0.01) and SF12 physical scores (between-group difference 3.4, 95% CI = 0.05 to 6.75, P <0.05). Statistically significant overall trends of improvement were also observed for the BPI interference and PHQ-9 scores.

Conclusion: NM exercise has the potential of reducing pain, improving self-efficacy and physical function in older people with chronic MSK pain. It can be an option for PCPs in exercise prescriptions.

Trial registration: #ChiCTR1800014890

Project No.: 30160254

HP-2-44
Community-based Mental Wellness Project for Adolescents and Adults

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Introduction and Project Objectives: Based on the theory of positive psychology and the Joyful@HK themes (Sharing, Mind and Enjoyment, SME), we developed three community-based engagement projects for adolescents aged 12-17 years: A) SME App Pilot Project, B) Joyful Adventure Day Pilot Project, C) 'Fun · Feel · Share' – Lyrics-writing and Singing Show Pilot Project, and three for adults aged 18-59 years: D) Joyful Parenting Pilot Project, E) Healthy Community Pilot Project, F) SME Ambassador Pilot Project.

Methods: Projects A – E were cluster randomised controlled trials, while project F adopted a pre- and post-test design. The interventions were designed based on public health and family-focused approaches, delivered through a smartphone app (A), simple school physical activities (B), lyrics writing competition (C), appreciation and praise skills (D), simple family physical activities (E), and voluntary services (F). SME-related outcomes, subjective happiness, wellbeing, personal health and happiness, family health, happiness and harmony, awareness and understanding of mental health were measured at baseline, 1-month and 3-month. Focus group interviews of participants and individual in-depth interviews of service providers were conducted after the interventions.

Results: A total of 2641 adolescents and 527 adults were enrolled and provided valid baseline data. The average retention rate at 1-month and 3-month was 89.6% and 87.2%, respectively. A total of 26 focus groups and 22 in-depth interviews were conducted. For adolescent projects, small to moderate effect sizes (d: 0.19 to 0.52) were observed for increasing awareness of anxiety disorder symptoms, and small effect sizes (d: 0.14 to 0.21) were observed for improving the SME behaviours and other outcomes. For adult projects, small to large effect sizes (d: 0.46 to 1.06) were observed for increasing awareness of mixed anxiety and depressive disorder symptoms, and small to moderate effect sizes (d: 0.30 to 0.57) were observed for improving the SME behaviours and other outcomes. The qualitative findings supported the quantitative results in general. The adolescents liked the peer-based elements, such as the competition in fitness assessment, cooperation in the games, and the contest for prizes in the lyrics writing. Adult participants enjoyed the activities and welcomed more workshops and similar programmes in the future.

Conclusion: For the adolescents' projects, further improvements and trials with greater adherence are warranted. The

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interventions in the adult projects can be scaled up (with simple adjustments as appropriate), disseminated and evaluated, and further improvements and larger trials are warranted.

Project No.: CPP-HKU

HP-3-52
Resilience Enhancement in Mainland Immigrants to Hong Kong: A Randomized Controlled Trial

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Introduction and Project Objectives: Resilience resources facilitate positive adjustment of immigrants. By focusing on new immigrants from Mainland China to Hong Kong, this research project sought to fulfill two objectives: (1) to compare a resilience intervention with a resilience + information intervention in a randomized controlled trial and (2) to develop the training infrastructure to ensure that the evidence-based interventions can be sustained despite the completion of the research project.

Methods: Two hundred and sixty-nine Mainland immigrants who had arrived within 3 years of residence in Hong Kong were randomly allocated to the resilience intervention or the resilience + information intervention, and 168 participants completed evaluation at pre- and postintervention. Experienced social workers delivered these interventions in the group format. After the completion of this research project, we compiled training materials (e.g., intervention manuals and statistical analysis tools), organized a sharing symposium, and conducted a train-the-trainer workshop to transfer knowledge to social workers who had interest in conducting resilience-based intervention programs in the future.

Results: The interventions enhanced resilience by 11.91% as well as decreased depressive symptoms by 19.21% and adaptation difficulties by 9.76%. Although the Resilience + Information Intervention did not show higher increases in resilience or more decreases in depressive symptoms and adaptation difficulties compared with the Resilience Intervention, the compound intervention showed significantly greater increases in knowledge (Cohen's $d = 1.87$, $p < .001$), service utilization (Cohen's $d = 0.29$, $p = .01$), and service use capacity (Cohen's $d = 0.53$, $p < .001$). Fifty-seven social workers from 12 organizations attended the sharing symposium and train-the-trainer workshop, which substantially increased their understanding of the implementation of randomized controlled trials in social services.

Conclusion: This intervention program effectively empowered new arrivals from the Mainland to adapt to the new environment. Social workers acquired knowledge and skills related to delivering the resilience-based interventions and evaluating randomized controlled trials in the social service context. The knowledge transfer model strengthened the joint forces of academic and social service sectors to serve the community.

Project No.: 08150145

HP-4-58
Use of Nicotine Replacement Therapy (NRT) Sample and Brief Smoking Cessation Advice for Recruiting Smokers to Smoking Cessation Services and Motivating Quit Attempts

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Introduction and Project Objectives: Nicotine replacement therapy (NRT) sampling is effective to increase use of smoking cessation service use and tobacco abstinence in primary care settings. This study promoted the delivering of NRT sampling and brief smoking cessation advice to smokers and the effects of this strategy on smokers' recruitment and cessation outcomes when it was applied at outdoor smoking hotspots.

Methods: This is a pragmatic two-arm cluster-randomized trial which was conducted in 4 phases: (1) Training of smoking cessation (SC) ambassadors (SCAs) for the SC promotion; (2) SC promotion sessions to deliver the quitting advice and NRT sampling (experimental group), or the quitting advice only (control group); (3) Follow-up of the recruited smokers; (4) Evaluation of the effectiveness of promotion, quit outcomes, and use of NRT sampling.

Results: This project trained 59 SCAs, held 244 smoking cessation promotion sessions, approached 9224 smokers and offered SC counseling to 1427 (15.5% of all approached smokers) smokers onsite. This project helped 299 (21.0% of smokers received counseling) smokers to quit successfully. By intention to treat, the NRT sample significantly attracted more participants to receive nurses' onsite counseling (Adjusted incident rate ratio=1.35, 95%CI, 1.12-1.62, $p<0.01$). Group differences in other recruitment outcomes were not significant. The two trial groups showed similar quit attempts (RR (risk ratio) =1.02 and 0.90 at the 1-, and 3-month follow-up, respectively,

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all p-values > 0.05), but the experimental group reported lower use of cessation service (RR=0.72, and 0.85 at the 1-, and 3-month follow-up, respectively, respectively, all p-value < 0.05). Tobacco abstinence at 6-month was similar in both groups. At 1-month follow-up, in the experimental group who received NRT sample, 51.7% had ever used the NRT sample and 34.1% completed the full course of the NRT samples. At 1-month follow-up, no significant group difference in the use of any NRT in the past month was detected (39.8% and 34.4%, p>0.05).

Conclusion: Delivery of NRT sample at outdoor smoking hotspots increased uptake of onsite nurses' brief counseling. This strategy reduced enrolment of smoking cessation services, but it did not alter quit attempts and long-term tobacco abstinence.

Project No.: 01170418

HP-5-70
《穩步前行》社區長者防跌計劃

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Introduction and Project Objectives:
計劃以增強意識和主動識別作為預防跌倒的教育方針，讓長者認識跌倒危機的因素及學習預防跌倒之方法；培養長者健康運動的生活模式，提昇自我管理健康風險的能力。

Method:
透過不同健康推廣項目接觸了超過五千名長者，提倡防跌意識及進行防跌普查，篩選出 217 位有高危跌倒風險的長者作深入跟進，提供個人跌倒風險評估，讓他們清楚了解自己跌倒的成因，從而在生活作出調整，預防跌倒。

Results:
計劃亦安排「防跌大使」義工上門探訪，其中 24 位具特別需要的長者獲治療師進行家居環境改善建議及上門教授復康運動。此外，甄別了其中 82 位長者參加 8 期運動治療小組，治療師按評估結果教授相應運動，提高他們身體平衡力、增強四肢肌肉強度及改善步態，結果發現 87% 長者下肢肌力及平衡力有顯著進步或維持良好。

Conclusion:
計劃成功起動全面社區性預防跌倒服務，廣泛地提昇社區人士關注長者防跌的重要性，同時亦發現了長者潛在的跌倒風險因素，除了身體機能、家居環境、藥物及視力影響外，慢性痛症亦是主要因素，痛症治療是預防再次跌倒的重要因素。

Project No.: 30160484

HP-6-77
Sweet Home, Safe Home" Child Safety Project for Ethnic Minority Families Project

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Introduction and Project Objectives: In 2015, there were 62,000 children (aged 0-19) attended Accident and Emergency Departments due to injury, and home injuries being the most common. EM child injuries or even deaths were often reported in news. The project aimed that the child (aged 0-9) injury risks among participating EM families were reduced through

1) Facilitating EM families to provide a safe home environment for children in Home Safety Assessment and Enhancement Scheme
2) Equipping EM parents with the knowledge and skills of preventing and handling the child injury in the Home Safety and Maintenance Class
3) Enhance EM parents' awareness on home safety in Community Education

Method: The completed project consisted 1) Home Safety Assessment and Enhancement Scheme, 2) Home Safety and Maintenance Class, and 3) Community Education.

As the applications of the Home Safety and Enhancement Scheme and Home Safety and Maintenance Class were mainly through the referral from their community, this implied that the EM community had a strong network and it could be a way to promote health related message through their network.

Results: The Home Safety and Enhancement Scheme received 128 applications and eventually 100 applications was completed. During the first home visit, living room was found to be the major source of home accidents risk according to the assessment by the Home Safety Assessment tools issued by the Department of Health.

2-session Home Safety and Maintenance Class was conducted in 4 organizations. The class participation was active with interaction on discussing how to handle or prevent home accidents for child.

A total of 25 EM volunteers were recruited to facilitate the promotion of home safety among their community. They were responsible for translation and promotion through home visit, information booth and outreach.

Conclusion: To conclude, the knowledge and awareness of home safety were lacking among the EM communities. The completed project could both enhance the awareness of home safety and provide resources ($1000 subsidies) for low income EM families. The current project also followed up 3 months after the home safety items installment. There was no children

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injury reported. Moreover, all participating families received the assessment report during home visits. These demonstrated that the objective of enhancing awareness of home safety was achieved. Moreover, the active participation of Home Safety and Maintenance Scheme indicated that the need of EM parents on home safety knowledge. Overall, the project achieved the objectives in general.

Project No.: 29150124

HP-7-81

Improving Well-being of Children with Autistic Spectrum Disorder (ASD) and Their Families with Mindfulness Training in Hong Kong

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Introduction and Project Objective: Autism spectrum disorder (ASD) is a lifelong condition associated with significant neurodevelopmental hurdles and behavioural problems. Previous studies showed that mindfulness training for children with ASD combined with Mindful Parenting is a feasible and promising intervention to benefit adolescents with ASD and their parents. However, there is a lack of studies examining the effectiveness of mindfulness training on adolescents with ASD and their parents in the Chinese context. The current study was the first pilot randomized controlled trial to investigate the feasibility and effectiveness of mindfulness-based intervention (MYmind) on Chinese adolescents with ASD and their parents in Hong Kong.

Methods: This trial had two study arms: the MYmind group versus the waitlist control group. 37 eligible families were successfully recruited. 19 families were randomized to the MYmind group, and 18 families were randomized to the waitlist control group. In the MYmind group, both adolescents with ASD and their parents received an intervention including 9 weekly 90-min mindfulness training sessions. Outcomes were measured from parents in both groups before (pre) and after (post) the 9-week mindfulness intervention. The primary trial outcomes were the feasibility and acceptability of the MYmind program as measured by the recruitment, compliance, retention rates and program evaluation. The secondary outcomes included adolescent's social responsiveness and behaviour, parenting stress, mindful parenting, parenting style, and parent's rumination as measured by various scales.

Results: Current findings showed that the MYmind program had an 80% compliance rate, 0% dropout rate, and 89% response rate. No statistically significant differences were found in both within-group and between-group comparisons. Nevertheless, medium to large between-group effect sizes were found in the measures of parent's rumination (g= 1.16), mindful parenting (d=0.6), parenting style (d= 0.59) and parenting stress (d= 0.5). Results suggested that mindfulness might have beneficial effects on these aspects.

Conclusion: This study demonstrated the feasibility of the MYmind program with high attendance among Chinese adolescents with ASD. Further study with larger sample size and more extended follow-up period is suggested to better examine the effectiveness of mindfulness on adolescents with ASD and their parents.

Project No.: 29150654

HP-8-87

StickyRiceLove: Development, Evaluation and Dissemination of an Innovative Peer-Led Sexual Health Social Media Promotion

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Introduction and Project Objectives: Online dating apps are popular platforms among young adults. At the same time, they have been associated with risks such as unsafe sexual behavior and privacy concerns. An online intervention to promote safer dating app usage was designed and evaluated.

Intervention: A peer-led approach was adopted in key stages of the development process. Focus group discussions and a crowdsourcing contest were held to assess the experience and needs of dating app use. A one-day intensive workshop involving peer mentors was held for the production of creative interventional materials. The online intervention material included four short videos, an interactive scenario game, and a risk assessment tool.

Methods: A clustered randomized controlled trial was conducted among college students to evaluate the effectiveness of the intervention. Students aged 17 to 27 years were randomized into intervention and control groups. An existing website promoting physical activities and healthy living was used as a control. The general self-efficacy scale (GSE) was set as the primary outcome and the risk propensity scale (RPS) as the secondary outcome. Questionnaires were administered before, immediately after, and at 1 month after the intervention. Intention-to-treat analysis was

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adopted, and between-group differences were assessed using the Mann-Whitney U test. A post-hoc multiple linear regression model was used to examine the correlates of the GSE and RPS. Apart from this research, the intervention was disseminated online and promoted on social media.

Results: A total of 578 eligible participants (290 in the intervention group and 288 in the control group) participated in the study with 36 lost to follow-up. Overall, the participants in the intervention group reported favorable experiences when compared with the control group. There was significant improvement in the GSE score and reduction in the RPS score (P<.001) of the intervention group. Regarding public dissemination, the campaign website had 18,340 page view in 3 months. The total reach of promotional material on social media was 1,006,732.

Conclusion: It was feasible to develop an effective and popular online intervention with high peer participation. The online intervention was effective in improving general self-efficacy and reducing risk tendency among young students.

Project No.: 09160275

HP-9-90
School-based Physical Activity Intervention for Obesity among Adolescents with Intellectual Disability in Hong Kong

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Introduction and Project Objectives: To evaluate the effectiveness of a 9-month school-based adapted physical activity (APA) program in reducing weight among adolescent with ID who were overweight or obese.

Methods: A randomized controlled trial was implemented in six special schools in Hong Kong, China in the academic year of 2018/2019. Students who aged 12-18 years, had mild and moderate ID and were overweight or obese were recruited and randomly assigned into intervention and control groups. The APA intervention consisted of aerobic and resistance exercises with an overall moderate intensity and was delivered at two 45-min sessions per week for 9 months. Changes in body mass index (BMI, primary outcome) and those in BMIz, weight, percent body fat, waist circumference and waist-to-height ratio (secondary outcomes) were examined using general linear models.

Results: Totally 61 subjects (39 in intervention and 22 in control) completed the study and included in the analyses. After the intervention, the intervention group exhibited a reduced BMI of -0.66 kg/m2 (95% CI -1.06 to -0.25 kg/m2, p=0.002), while a significant increase in BMI was observed in control. After adjustment for age, sex and baseline BMI, a significant post-intervention between-group difference in change in BMI (-1.31 kg/m2 [95% CI -1.99 to -0.63], p < 0.01) was found in favor of the intervention group. Similar results were also observed in all secondary outcomes.

Conclusion: The study provides evidence that a 9-month APA intervention at a moderate intensity induced clinically meaningful effects on weight loss in adolescents with ID.
Trial Registration: Clinicaltrials.gov NCT04463069.

Funding: This study was financially supported by the Health Care and Promotion Scheme (HCPS) under the Health and Medical Research Fund (HMRF), administered by the Food and Health Bureau of Hong Kong (Ref. No. 01170068).

Project No.: 01170068

HP-10-108
Diabetes Prevention Program for South Asian Ethnic Minorities Families

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Introduction and Project Objectives: Hong Kong is a predominantly Chinese society but has a sizeable South Asian ethnic minority (EM) community. However, there is a dearth of health promotion programs that outreach to this group of people to promote healthy diet and physical activity for improving their healthy life.

Methods: This project was successfully implemented and well received by 59 South Asian EM adolescents aged between 12 -18 years and their parents/ grandparents (n = 116) recruited from a local designated school under the Education Bureau. The project was conducted in 3 phases. In Phase I, South Asian EM adolescents were trained as health ambassadors to learn the diabetes knowledge and to enhance their attitude and practice in healthy diet and physical activity. Two health ambassadors, recommended by school teachers, were invited to participate in the production of three 5-min Youtube video entitled "Candy Crush Health Crash" in different languages including English, Urdu, and Nepali. In Phase II, the trained health ambassadors delivered the 3-month behavioral change programme to their families that may involve parents and grandparents with the use of Youtube videos for information consistency. In Phase III, a Health Carnival was held in a community hall for disseminating the diabetes prevention messages to the EM communities.

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Results: There was no statistically significant improvement on the mean Brief Diabetes Knowledge Test (General) scores before and after the project. The physical activity levels on three areas: at work, transportation (walking and cycling) and leisure activities measured by the Global Physical Activity Questionnaire showed some improvement. For vigorous-intensity activities at work, 20.7% reported that they had increase in their involvement while 13.8% of them reported that they involved more for moderate-intensity at work. For walking or cycling, 29.3% of them started to develop such habit. For vigorous-intensity sports activities, there were 22.4% participants reported an increase in engagement while 19% participants reported doing more sports for moderate-intensity sports activities.

Conclusion: This project was not able to significantly enhance their diabetic knowledge but it enhanced physical activities among the participants. The results supported the necessity of cultural sensitivity and competence in health promotion for EM families. Appropriate strategies that target traditional beliefs on active lifestyle endorsed in the South Asian culture and the concerns on language and literacy in health promotion may warren more promising behavioral outcomes for future programs.

Project No.: 29150744

HP-11-127
The Treasure Of Gold : Using DementiAbility Methods: The Montessori Way™ To Re-discover The Abilities and Strengths In Persons With Dementia

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Introduction: There is a Chinese proverb "A family with an old person has a living treasure of gold "「家有一老，如有一寶。」. Every elderly has a unique personal story, a wealth of skills and experiences that define who they are. As dementia care providers and caregivers, we concern what is "lost" to the person and how to support their "limitations". How about what is "remain"? Are we able to re-discover and make meaning of the "treasures" within them? Dementia is a progressive condition and it does not steal the person's abilities and strengths completely right away, they remain for a long while and might be longer than we thought.

The Montessori Way™ (DMMW) is a non-pharmacological and person-centred care approach, developed by dementia specialist Gail Elliot. She was inspired by the work of Dr. Cameron Camp who successfully adapted Dr. Maria Montessori's educational philosophies and principles to dementia care. DMMW focuses on re-discovering the abilities in person with dementia; designing meaningful activities, roles and routines based on the person's needs and strengths; support the person in a prepared environment.

Objective: To explore the effect of Montessori-based activities on Behavourial and Psychological Symptoms of Dementia (BPSD) and the feasibility in implementing Montessori-based activities group in residential and day care setting

Methods: 30 participants with dementia and BPSD (mainly agitation and wandering) from nursing home and day care centres were invited to join the Montessori-based activities group. There were a total of 5 groups with 6 participants in each group. Each group consisted of 12 sessions (2 sessions per week, each session of 1 hour) with group-based warm up activities, followed by individualized Montessori-based activities. Frequency of agitation and wandering behaviours before and during the group were compared. Program evaluation was conducted through structured interviews with multidisciplinary stakeholders involving social workers, nurses and health care workers.

Results: Results showed a 53% reduction in overall frequency of agitation and wandering behaviours. All staff were positive towards the experiences in Montessori-based activities group i) activities are tailor-made and unlike a "set menu" ; ii) observed an increased engagement of all participants especially the ones who refused other usual group activities ; iii) opportunities to appreciate the "hidden treasures of participants .

Conclusion: Montessori-based activities group is a feasible non-pharmacological intervention for addressing wandering and agitation behaviours in persons with dementia.

Project No.: 08150095

HP-12-139
"No Alcohol for Cheers" - Reduce Alcohol Consumption Health Promotion Programme for Working Group

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Introduction: Alcohol plays an important social and cultural role in society. It is the world third largest risk factors among over 200 disease burdens and injury conditions, as well as the main contributing factor for non-communicable diseases. In Hong Kong, the working group is vulnerable population. Therefore workplace could be a health promotion setting on reducing alcohol consumption as well as induce behavioral change among the working group.

Project Objectives: By the end of this 12-month programme, the participated employees will have raised awareness and understanding towards alcohol-related health consequences and

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build up positive attitude to control over their drinking behaviour, as a result of promoting lowering alcohol consumption using workplace as platform and built up partnership with employers to take the initiative for health promotion.

Method: The programme included two levels of intervention initiated by programme outreach team including Registered Nurse and Registered Social Worker: Staff level and Employer's level. For staff level, talks and workshops were offered in workplace for alcohol harm educational purpose and skills enhancement to reduce risk factor for adopting drinking behavior . For employer's level, organizational healthy policy was suggested and implemented in a top-down approach to strengthen capabilities of individuals to take action in alcohol reduction by providing an encouraging and supportive environment.

Results: The programme successfully recruited 24 companies participated, with over half of them come from Property Management Industry. Throughout the 24 talks and 23 workshops provided, 516 employees are benefited from the service provision. Evaluation questionnaires have been given to the participated employees, in which positive change in knowledge, awareness towards harmful effect of alcohol drinking have been observed after attending the health talk; over 90% of workshop participants agreed they have learned positive ways from relaxation, social skills to refuse alcohol invitation, developed positive attitude to reduce drinking alcohol. Overall 97% of participants are satisfied on the service provision.

Conclusion: The result indicated health promotion on alcohol reduction has been successfully implemented using workplace setting. It fact, utilizing workplace as health promotion setting take the advantage of existing supportive environment created by colleagues and favorable internal health policy which act to empower drinkers for behavioral change and strive for a better health. It is foreseeable that there would be more corporates from different industries interested to the outreach based health promotion programme.

Project No.: 30160734

HP-13-167
「乳妳同盟」母乳餵哺社區支援計劃

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Introduction and Rationale:
本計劃旨在集結跨界別力量，如：護理專業人士、具母乳餵哺或具陪月經驗的婦女等，為準新手父母及母乳餵哺家庭提供支援服務，讓媽媽及其家庭成員在知識及照顧技巧層面獲得正確的資訊，同時承托媽媽在情緒層面上的需要，正面鼓勵及支持新生嬰兒媽媽以母乳餵哺孩子，增強她們對母乳餵哺的信心及延長母乳餵哺期。

Project Objectives:
(i) 提升新手父母的能力及信心；(ii) 集結跨界別力量，建立協作平台；(iii) 推動關愛精神，支援有需要的家庭；(iv) 提升家庭關係，以助延長母乳媽媽的餵哺期；(v) 加強公眾對母乳餵哺的認識。

Methods:
舉行「母乳好處及餵哺技巧」工作坊、「乳妳同盟」大使（指導員）訓練、「為母則強」社區互助小組、「乳妳同盟」大使支援服務及社區教育活動。

Results:
本計劃接觸到：(i) 126 位母乳餵哺的母親；(ii) 30 名母乳餵哺指導員；(iii) 84 名家庭成員；(iv) 8 個合作伙伴，包括：香港大學護理學院、香港助產士學院、廣華醫院產科門診部、瑪嘉烈醫院婦產科、葵青及荃灣區母嬰健康院、媽媽牌同盟、明愛綠色小腳板及社會福利署。及 (v) 420 位公眾人士。

Conclusion:
本計劃旨在集結跨界別力量，為準新手父母及母乳餵哺家庭提供支援服務，為媽媽及其他家庭成員在餵哺的知識及照顧嬰兒技巧層面提供正確的資訊，同時亦承托媽媽在情緒層面上的需要，正面鼓勵及支持母乳餵哺媽媽，增強她們的信心，並鼓勵延長母乳餵哺期。是次項目計劃共有 126 位新手父母及母乳餵哺家庭參加，計劃團隊同時招募了 30 名母乳餵哺指導員，透過不同的專業團體，為計劃參加者提供訓練及支援服務。當中有 90% 母親認同工作坊能增加對母乳餵哺的知識及技巧，並增強其餵哺母乳的信心，延長母乳餵哺期。此外，70% 母親滿意「母乳餵哺指導員」所提供支援服務。她們認同當遇上疑問及困難時，能夠有平台可以查詢，甚至有婦女義工進行家庭探訪，能協助改善母乳餵哺的實踐情況，有助她們舒緩身心壓力。另一方面，80% 指導員認同訓練內容實用，有助她們為計劃參與母親提供指導；而且她們所得的知識及技巧，能於日常生活中學以致用，甚至協助自己的親友，有助提升其自信心，同時加強人際關係。是次項目計劃邀請到不同的單位共同協作，如：廣華醫院產科門診部、瑪嘉烈醫院婦產科提供平台，讓計劃團隊招募新手父母、母乳餵哺家庭參與計劃；同時邀請到香港大學護理學院、香港助產士學院的專業團隊，為計劃參加者提供工作員及訓練活動等。80% 合作伙伴認同社區支援計劃能支援母乳餵哺的母親，願意繼續共同協作，於社區內推動母乳餵哺的工作。與坊間其他團體稍為不同的一點，是計劃團隊致力鼓勵及邀請家庭成員一同參與活動，包括新手爸爸及祖父母。工作員希望增強家庭成員們的能力和參與，能為母乳餵哺媽媽提供正面的支持甚至是正確的支援。90% 家庭成員認同透過講座能認識母乳餵哺的好處，表示願意支持母親以母乳餵哺嬰兒，並協助及鼓勵其延長母乳餵哺期。計劃團隊年度性地於社區內舉行社區教育活動，安排母乳餵哺大使於活動內協助向準新手父母推廣及宣傳母乳餵哺好處，同時向公眾人士推廣及宣傳母乳餵哺的資訊，以提升公眾人士對母乳餵哺的接受性。70% 回應的公眾人士認同增加對母乳餵哺的認識，表示支持及鼓勵身邊女性以母乳餵哺嬰兒。

Project No.: 30160474

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HP-14-169
The Effectiveness on Students' Knowledge and Absenteeism of a Comprehensive Health Education Programme for Communicable Diseases Prevention in Primary School Setting

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Introduction and Project Objectives: Young children (age 6-9) in the school setting are particularly at risk for transmission of communicable diseases (CDs). Although health education is a common approach for increasing people's knowledge, most educational materials are too complicated to this age group, making its effectiveness unknown. In addition, potential effectiveness in reducing student's absenteeism is still unclear. We developed and implemented a comprehensive health education programme (HEP) to promote knowledge against CD among young primary school students (grade 1-3), and examined its effectiveness on students' knowledge improvement and impact on reducing absenteeism during the influenza seasons.

Methods: A comprehensive HEP with four principle components, including mode of common CD transmission, cough etiquette, hand hygiene technique and face masks usage in a format comprehensible to student in primary 1-3 was conducted in local schools. Participated schools were randomised using a wait-list control design to receive the HEP either before (Semester 1) or after (Semester 2) the influenza season in 2018/19 academic year. The knowledge level was assessed at three timepoints using a simple test consisting of 27 questions on the four components. Mean total test scores were compared before (pre-test), 1 week after (post-test), and more than 3 months after the intervention (follow-up test). Feedback was gathered from teachers to evaluate the programme.

Results: The HEP was delivered in 90 local primary schools covering 29,396 students. Among whom 24,809, 21,673 and 8,503 children had completed the pre-tests, post-tests and follow-up tests respectively. There was a 11.92% ($P<0.05$) relative improvement in the overall mean scores in the pre- and post-test comparison. The absence of significant difference between the post- test score at 1 week and follow-up test score at 3 months suggested good long-term retention of the gained knowledge.

Comparing to schools receiving the intervention in Semester 2, schools receiving the HEP before the influenza season (in Semester 1) was having a significant 9% lower overall absence rate for the whole school (incidence rate ratio, IRR 0.91, 95% CI 0.86, 0.97), and a 23% lower specific absence rate for grade 1-3 students directly reached by the programme (IRR 0. 77, 95% CI 0.70, 0.85) during the influenza season.

Conclusion: Our result highlighted the effectiveness of the HEP to improve knowledge related to CD prevention and reduce student absence rate during the winter influenza season among primary school in Hong Kong.

Project No.: 01170588

HP-15-172
DASH A DAY - Community Nutrition Promotion Program

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Introduction and Project Objectives: Dietary Approaches to Stop Hypertension (DASH) diet is proven to prevent hypertension and improve patients with hypertension. This project aim to increase the awareness and capability to adapt DASH diet for the elderly and/or middle-aged adults, to provide train-the-trainer opportunities to community professionals (doctors and nurses) and to provide training and practicum with future community nutrition promoters.

Methods: Each Elderly Community Center (ECC) received one educational workshop and two focus groups (1.5 hour each). Workshop included education of relationship between diet and hypertension, low sodium and DASH diet. Participants who attended workshop were invited to join focus group one and two (about 1-2 months apart) to share practical experiences, successfulness and difficulties on adaption of DASH diet, in order to sustain long-term compliance.

Results: A total of 690 direct beneficiaries (80.9% attendance) joined the program. Average knowledge score on DASH diet components increased from 37.3% to 94.8%. Average attitude score towards willingness on adapting DASH diet increased from 91.3% to 95.2%. The average spreading of DASH diet information from participants joined focus group and not joined focus group was 85% and 61.2% with an average of one participant spread to 2.0 and 1.1 people, respectively. Also, 95.7% participants, who joined focus group (N=234), reported with adapting DASH diet in daily life 5.4 days per week, compared with 84.0% who without joined focus group (N=213), reported with adapting DASH diet in daily life 3.0 days per week. Participants were provided with practical experiences for knowledge attainment and DASH diet application and thus increase the frequency of applying DASH diet in their daily lives after this program.

Conclusion: This program enhanced participants' knowledge on DASH diet and further improved their attitudes towards DASH diet application. They were evaluated to increase their frequency of practicing DASH diet on their own after this

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program. Hence, it is necessary to educate the community on DASH diet, on top of a well-balanced approach, would be introduced earlier prior to middle-aged adults as preventive approach.

Project No.: 29150184

HP-16-199
Community Partnership Programme on Mental Health Promotion in Hong Kong (Elderly)

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Introduction and Project Objectives: The aging population is at risk of mental health problems, which are associated with cognitive impairment; maintenance of good mental well-being may help to delay onset of dementia. This project aimed to develop two interventions for community-dwelling older people to improve their mental well-being, cognitive functioning, and social engagement.

Methods: Two interventions were developed in this project. The Mindfulness Programme (MP) lasted for eight group sessions, one session per week for eight weeks, two hours per session. The Cognitive and Social Stimulation Programme (CSSP) consisted of 14 group sessions, two sessions per week for seven weeks, one hour per session. The effectiveness of the interventions was evaluated by a randomised controlled trial with waitlist design. 19 community centres (N=209 for MP, N=195 for CSSP) participated in the research. At each centre, participants were randomly assigned as intervention group or control group, with the control activities being usual activities at centres. The primary outcome of both interventions was mental well-being measured by the Chinese Short Warwick-Edinburgh Mental Well-being Scale (SWEMWBS). Other outcome measures included (1) Montreal Cognitive Assessment 5-minute version, (2) Verbal Fluency Test (VFT), (3) International Shopping List Test, (4) Peace of Mind Scale, (5) Geriatric Depression Scale (GDS), (6) Pittsburgh Sleep Quality Index, (7) Five Facet Mindfulness Questionnaire Short Form, (8) Self-Compassion Scale Short Form, and (9) Multidimensional Scale of Perceived Social Support (MSPSS) (7-8 for MP only, 9 for CSSP only). The outcome data were collected at baseline (T0), immediate post-group of intervention group (T1), and two months after intervention group completed the intervention (T2).

Results: For MP, the intervention group had better mental well-being (SWEMWBS score difference: 0.9 [95% CI: 0.1, 1.8], $p = 0.025$) and less depressive mood (GDS score difference: -1.0 [95% CI: -1.7, -0.3], $p = 0.002$) than the control group at T1. For CSSP, no between-group difference was observed, while significant improvement in verbal fluency (VFT: 29.6-32.3, $p < 0.001$) and self-perceived social support (MSPSS: 5.0-5.2, $p = 0.004$) were observed at T1 in the intervention group and the changes were sustained at T2 (ps < 0.001).

Conclusion: The Mindfulness Programme developed in this project benefited the mental well-being and self-perceived depressive mood of community-dwelling elderly while the Cognitive and Social Stimulation Programme might improve verbal fluency and self-perceived social support.

Project No.: CPP-CUHK

HP-17-213
Promotion of Dietary and Cognitive Health in Dementia Prevention to Elderly Community – a Pilot Project

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Introduction and Project Objectives: It is estimated that the Hong Kong population of over 65 years old will escalate to 24% in 2027, and exceed 30% by 2064. The rapid growth of ageing population implicates an expanding incidence of chronic diseases, including hypertension. Hypertension is a key risk factor for cognitive impairments, including dementia. Considering the close association of elderly with dementia and hypertension, health promotion intervention is therefore a timely and pivotal approach to enhance the primary care and well-being in the community of older people. This project focused on two main health issues, including hypertension and dementia, in elderly and aimed to improve the elderly participants' health status, quality of life and enhance their social engagement. The key objectives of this pilot project are: • To increase elderly's understanding of the diet-and-disease relationship of hypertension; • To enrich their knowledge of functional foods having desirable effects on cardiovascular diseases; • To maintain or even improve their cognitive activities through strategic games; and • To promote social connections among the elderly themselves and with the young volunteers.

Methods: Four health education workshops were arranged to the elderly participants. They were encouraged to join a recipe design campaign to propose healthy recipes to foster them to take initiative of their health. A recipe book was compiled. Hard copies of the recipe book were distributed to participants and the collaborating organizations. During the activities/ workshops elderly participants were engaged in various brain exercises. Lastly, a closing ceremony was arranged.

Target Group: 259 elderly were recruited from 7 elderly centres

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in Kwai Tsing district to participate in our activities. 39 young volunteers from the BSc (Hons.) in Health Care programme in Technological and Higher Education Institute of Hong Kong (THEi) were recruited.

Results: The health knowledge and concerns of the elderly participants were greatly enhanced through a series of health education workshops. Additionally, a recipe book was compiled. 39 student volunteers were trained with skills and knowledge to teach and communicate with the elderly participants. The total headcounts of elderly participating in all activities was 239. They could gain some knowledge on dietary and cognitive health through strategic games. This pilot project also promote social connections between the young volunteers and the elderly participants.

Conclusion: This pilot project could provide a good reference for various organizations to organize similar activities to the elderly in local community.

Project No.: 01171158

HP-18-225
A Pragmatic mHealth Program for People at High Risk of Diabetes: The Use of Diabetes Risk Score Mobile App (DRS App) and Telephone Counselling

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Project Objectives: This project aimed to promote diabetes risk self-assessment and lifestyle modification through a mHealth program.

Methods: This project adopted assess-advice-assess model to provide individualized health promotion through mobile app and telephone counseling. The inclusion criteria of participants were: 1) aged 40 or above; 2) Hong Kong Chinese Residents; 3) possess a smart phone; 4) able to communicate in Cantonese. A total of 18 health seminars, 36 sessions of health assessment and 54 sessions of telephone counselling were held. In the health seminars, the importance of regular physical activity and dietary advice was highlighted. Participants were assisted to download a Diabetes Risk Score mobile app (DRS app) developed by the Project Team. Diabetic risk score was shown in the app upon receiving the inputs from the participants. Those who were at high risk of diabetes were invited to join a health assessment in which HbA1c, physical fitness, dietary and exercise habits was recorded. Three phone calls were made by trained health ambassadors in 3 months. Post-intervention health assessment was carried out after 3 months.

Results: A total of 2,795 persons participated in various activities and 2,221 persons downloaded the app and used it to assess their risk. Majority (71%) of the participants were females and their mean age was 63.2 (SD 9.1). Participants' lower body strength (mean difference, m.d. = 2.24, $p<0.001$), aerobic exercise ability (mean difference, m.d. = 6.05, $p<0.001$), lower limb flexibility (m.d. = 2.07, $p<0.001$), upper limb strength (mean difference, m.d. = 2.14, $p<0.001$) and number of steps taken per day (mean difference, m.d. = 430, $p=0.016$) were significantly improved. Participants also had more vegetables daily (mean difference, m.d. = 0.178, $p=0.005$) than their usual practice after 3-month intervention. 37% participants increased their physical activity level after the intervention. Majority of the app users (64.7%) indicated their confidence to use the mobile app for recording after telephone counselling.

Conclusion: Participants used mobile app to assess diabetes risk, report lifestyle, learn the importance of physical activity and dietary modification in diabetes prevention. This DRS app and telephone counselling were evidenced as a useful and pragmatic diabetes prevention program to Hong Kong population.

Acknowledgment: The project is funded by Health Care and Promotion Fund, Health and Medical Research Fund, Food and Health Bureau, The Hong Kong SAR Government in 2016-2018 (reference no.: 29150794).

Project No.: 29150794

HP-19-226
Promoting Mental Health Literacy for Community-dwelling Older Adults: A Randomized Wait-listed Control Trial Using the Concept of Photovoice

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Project Objectives: This project aimed to promote community-dwelling older adults' mental well-being and develop their capacity to seek for mental health advices.

Methods: A randomized wait-listed control design was used to assess the efficacy of this mental health literacy program. Four weekly group meetings (the intervention) were arranged in community centers. Older adults took photos, expressed their feelings through photos, and discussed their feelings with community workers and peers. Community workers were

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trained to recognize the symptoms of depression/ negative emotions and encourage them to seek for supportive resources in the community. Eligible criteria of the participants were: aged 60 or above, cognitive intact (SPMSQ score > 7) and were able to communicate in Cantonese and ambulate independently. Geriatric Depression Scale (GDS), Patient Health Questionnaire (PHQ-9), Quality of life Short form (SF-12v2) and Lubben Social Network Scale-6 (LSNS-6) were measured before and after the intervention.

Results: A total of 540 older adults were recruited and screened for eligibility to join the programme. After screening, 458 older adults were eligible and agreed to participate in the programme. Among these, 240 were randomized into the intervention group (IG) and 224 were randomized in the waitlist control group (CG). The mean age of the IG participants was 74.87 (SD 6.68) and about 77% of them were female. After the 4-week intervention, participants in IG had significantly lower depressive level (GDS scores) than those of the CG, mean difference = -0.54, SD = 1.95, d = -0.278, p = 0.011. Help-seeking behaviors of IG was also significantly higher than the CG.

Conclusion: This program has reduced community-dwelling older adults' depressive level and encouraged them to seek help for mental health issues in the community. The community workers who received training possessed a new set of skills for promoting mental health literacy for community-dwelling older adults.

Acknowledgment: The project is funded by Health Care and Promotion Scheme, Health and Medical Research Fund, Food and Health Bureau, The Hong Kong SAR Government in 2017-2019 (reference no.: 09160175).

Project No.: 09160175

Abstracts for Poster Presentation: Infectious Diseases

ID-1-57

Preemptive Homology-Directed DNA Repair Fosters Complex Genomic Rearrangements in Hepatocellular Carcinoma

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Introduction and Project Objectives: Degree of genomic instability closely correlates with poor prognosis, drug resistance as well as poor survival across human cancer of different origins. We aim to identify the pathogenic molecular events in DNA damage response (DDR) and their functional significance towards genomic instability in hepatocarcinogensis.

Methods: This study assessed the relationship between DDR and chromosome instability in hepatocellular carcinoma (HCC). We investigated DDR signalling in HCC cells by analysing DNA damage-dependent redistribution of major DDR proteins to damaged chromatin using immunofluorescence microscopy and Western blotting experimentations. We also performed gene conversion and metaphase analyses to address whether dysregulated DDR may bear any biological significance during hepatocarcinogenesis.

Results: We demonstrated that HCC cell lines suffered from elevated spontaneous DNA double-strand breaks (DSBs). In addition, analyses of HCC metaphases revealed marked aneuploidy and more frequent sister chromatid exchanges when compared to immortalized hepatocytes, the latter of which were further induced following camptothecin-induced DSBs.

Conclusion: Our study showed that homology directed DNA repair is functional and augmented for DSB repair in HCC. The observed upregulated phosphorylation of ATM in HCC suggests that ATM activation and the downstream ATM-licensed molecular pathways might be essential in the initiation and/or progression of hepatocarcinogenesis. We propose that genomic instability in HCC may be caused by erroneous DNA repair in attempt to mend DSBs for cell survival. Such preemptive measures inadvertently foster chromosome instability and thus complex genomic rearrangements in HCC.

Project No.: 14131132

ID-2-30

Heterosubtypic Protection Induced by a Live Attenuated Influenza Virus Vaccine Expressing Galactose-α-1,3-Galactose Epitopes in Infected Cells

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Introduction and Project Objectives: Influenza A viruses have multiple HA subtypes that are antigenically diverse. Classical influenza virus vaccines are subtype specific, and they cannot induce satisfactory heterosubtypic immunity against multiple influenza virus subtypes. There is a need of novel strategies for developing broadly reactive influenza vaccines to induce heterosubtypic protection.

Methods: Anti-galactose-α-1,3-galactose (anti-α-Gal) antibody is naturally expressed at a high level in humans. It constitutes about 1% of immunoglobulins found in human blood. Here, we designed a live attenuated influenza virus vaccine that can generate α-Gal epitopes in infected cells in order to facilitate opsonization of infected cells, thereby enhancing vaccine-induced protection.

Results: We generated a live attenuated influenza virus vaccine that can generate α-Gal epitopes in infected cells. In the presence of normal human sera, cells infected with this mutant can enhance phagocytosis of human macrophages and cytotoxicity of NK cells in vitro. Using a knockout mouse strain that allows expression of anti-α-Gal antibody in vivo, we showed that this strategy can increase vaccine immunogenicity and the breadth of protection. This vaccine can induce 100% protection against a lethal heterosubtypic group 1 (H5) or group 2 (mouse-adapted H3) influenza virus challenge in the mouse model. In contrast, its heterosubtypic protective effect in wild-type or knockout mice that do not have anti-α-Gal antibody expression is only partial, demonstrating that the enhanced vaccine-induced protection requires anti-α-Gal antibody upon vaccination. Anti-α-Gal-expressing knockout mice immunized with this vaccine produce robust humoral and cell-mediated responses upon a lethal virus challenge. This vaccine can stimulate CD11blo/- pulmonary dendritic cells, which are known to be crucial for clearance of influenza virus.

Conclusion: Our approach provides a novel strategy for developing next-generation influenza virus vaccines.

Project No.: 14131092

ID-3-31

Detection and Characterization of Antibody-dependent Cell-mediated Cytotoxicity (ADCC) Responses against Human Influenza Virus in Humans and Mice

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Introduction and Project Objectives: Cross-reactive influenza virus-specific antibody-dependent cellular cytotoxicity (ADCC)-activating antibodies are readily detected in healthy adults. However, little is known about the kinetics of these ADCC

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responses. Here, we studied the role ADCC response against influenza virus infections.

Methods: We used human blood samples from health donors during 2009-2010 to study ADCC responses against hemagglutinin (HA) of human (pandemic H1N1/2009) or avian (H7N9) influenza virus. We used peptide libraries of influenza HA proteins to screen for ADCC-inducing epitopes in ELISA. Representative ADCC-inducing epitopes were tested in mice to determine its protective role against virus infection.

Results: All healthy donors had ADCC responses against 2009 pandemic H1 influenza virus and H7 avian influenza virus despite being seronegative for these viruses in standard hemagglutination inhibition and microneutralization serological assays. No correlation between ADCC responses to influenza virus-specific immunoglobulin G1 concentration or age. A(H1N1)pdm09 exposure did not boost ADCC responses specific for H7 HA antigens. Peptide-mapping for ADCC reactivity of H1-HA and H7-HA proteins from human serum samples identified high ADCC-inducing peptides in both the HA1 and HA2 regions. Vaccination of mice with single ADCC-peptides induced ADCC activity leading to partial protection from lethal influenza challenge, with increased survival, reduced viral loads, and reduced activation of NK cells in the lungs.

Conclusion: Cross-reactivity ADCC responses against different influenza viruses can be readily found in health human individuals. ADCC-epitopes are present in both the HA1 and HA2 regions, and single ADCC-activating peptides provided partial protection from lethal influenza challenge, therefore representing a possible target in future combination vaccination strategies.

Project No.: 15141052

ID-4-103

Comparative Analysis of Plasma Cytokine/Chemokine and In Vitro Transcriptomic/Lipidomic Profile Induced by Influenza B Virus and Human Rhinovirus Infection

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Introduction and Project Objectives: Influenza A virus (IAV), influenza B virus (IBV) and rhinovirus (RV) are common causes of respiratory tract infection. Few studies have directly compared these infections. Here, we used a multi-pronged approach to systemically compared IAV, IBV and RV infection.

Methods: Part I analyzed the clinical characteristics of critically-ill patients with RV. Part II compared the clinical characteristics of adult hospitalized RV patients with age-matched IAV/IBV patients. Parts III and IV used RNAseq and LC-MS to analyze the transcriptomic profile and lipidomic profile of RV/IAV/IBV infection in a bronchial epithelial cell line, respectively.

Results: Part I: Exacerbation of underlying pulmonary or non-pulmonary disease occurred in 54.5% of critically-ill RV patients. Among RV patients with pneumonia, the most common chest radiographic finding was consolidation (46.2%). The rate of seizure was higher among patients with RV (22.7%) than those with other respiratory virus infection. Part II: Severe disease was more common among RV patients than IAV/IBV patients (34% vs 11%). RV infection was characterized by a prominent TH2 response, including higher levels of eosinophil and interleukin-5 when compared with IAV/IBV infection, even among patients without asthma. CXCL-10 was found to be a potential biomarker differentiating IAV/IBV and RV infection (AUC, 0.918).
Part III: RV-infected cells exhibited a more blunted host response with fewer differentially expressed genes (DEGs) than IAV/IBV infection. DEGs that were highly expressed for all 3 viruses were mainly genes related to type I or type III interferons and chemokines. Notably, ICAM5, a known receptor for enterovirus D68, was highly expressed during RV infection only. Pathway analysis showed that pathways related to interferon response, innate immunity, or regulation of inflammatory response were most perturbed for all three viruses.
Part IV: Most lipid features were found to be downregulated for IAV, IBV or RV. Sphingomyelin metabolism was the most affected pathway. Bacterial sphingomyelinase suppressed the replication of IAV, IBV and SARS-CoV-2, but promoted the replication of RV.

Conclusion: RV is more likely to be associated with exacerbation of underlying lung disease and extrapulmonary complications. RV was associated with a TH2 type response. Transcriptomic study revealed a distinctive role of ICAM5 for RV infection. Lipidomic study showed that the sphingolipid pathway is downregulated for RV/IAV/IBV, although sphingomyelinase treatment has an opposite effect on the replication of RV and IAV/IBV/SARS-CoV-2. These studies have enhanced the understanding or RV/IAV/IBV infections, and have revealed potential therapeutic targets.

Project No.: HKM-15-M03

ID-5-162

A Randomized Controlled Trial on the Effect of Fever Suppression by Antipyretics on Influenza

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Introduction and Project Objectives: While fever is commonly

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regarded as an illness to be treated, preliminary evidence from animal and observational human studies are suggesting that antipyretic use for fever suppression in URTIs might prolong the duration of illness and increase the amount and duration of viral shedding, signifying that routine suppression of fever may potentially increase the risk of further transmission and propagation of epidemics, and carrying potential downstream public health implications. A robust examination of the effect of fever suppression by antipyretics on viral shedding and clinical symptomology in naturally-occurring influenza infections is currently lacking.

Methods: With a double-blind randomized placebo-controlled trial, a total of 1861 young adults aged 18-30 presenting with ≥2 URI symptoms within 48 hours of illness onset were screened in a university health clinic in Hong Kong from March 2016 to August 2018. Among whom 319 having a positive QuickVue Influenza A & B rapid testing result were randomized to receive either paracetamol 500mg or matching placebo four times daily for 5 days. Viral identification and subtyping by quantitative RT-PCR was performed on nasal and throat swabs on days 1 (baseline)/4/7/10. Self-recording of body temperature and common symptoms of influenza were monitored twice daily for ten days.

Results: A total of 206 patients with PCR-confirmed influenza infection were included in the analysis. No difference in clinical illness duration and symptoms severity was detected between the paracetamol (n=108) and placebo groups (n=98). Total symptom scores by AUC analysis were also comparable. In terms of transmissibility, no significant prolongation in viral shedding was observed in paracetamol group on the mean durations of viral shedding estimated, and the time to resolution of viral shedding. Total amount of virus shedding as reflected by the AUC for quantitative influenza viral load was also comparable.

Conclusion: Our findings suggested there is no observable evidence to substantiate that the use of paracetamol might significantly increase the amount of viral shedding, nor the clinical illness in naturally-occurring PCR-confirmed influenza infection in human. Current evidence is not sufficient for a conclusive argument on the impact of widespread usage of antipyretics on URI transmission and epidemic propagation in the community. Further study on the mechanisms between fever, viral shedding, infectivity, and disease transmission would be important for better informing the proper use of antipyretics in influenza virus infection.

Project No.: 15141162

ID-6-170

Using a Smartphone Application-Based School Absenteeism Monitoring to Improve the Surveillance Performance for Influenza Activity in Hong Kong

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Introduction and Project Objectives: Schools are high risk settings of influenza transmission and outbreaks, especially during influenza seasons. School absenteeism is becoming a major component of influenza surveillance systems in many parts of the world, and is reported to be useful for reflecting influenza activities in the community. Major drawbacks of school absenteeism data, however, included poor timeliness, heavy workload for manual collection, and suboptimal specificity. Currently, local surveillance of influenza-like-illness (ILI) is lacking a component for prospective, routine and continuous monitoring in local schools. We explored the feasibility of adopting a smartphone application (App)-based school absenteeism reporting platform for ILI surveillance in Hong Kong.

Methods: An App was developed for parents to submit applications for student absenteeism, with the simple reporting of also the nature (sickness/ non-sickness absence), cause, and symptom details if any. Product of the weekly proportion of ILI reported by the sentinel General Practitioner (GP) network and the weekly percentage of positive influenza isolates from the Public Health Laboratory Services Branch (PHLSB) were used as the gold-standard for assessing the performance of our App-based absenteeism data according to the US CDC evaluation framework. Each study weeks was classified as either having high or low influenza activity (epidemic/ non-epidemic) using specific thresholds. Surveys were completed by teachers and parents for assessing acceptability.

Results: Our App covered a total of 7,711 students in 13 participating schools, and captured 95,412 person-days of absence over the study period (11/2016-06/2018). The temporal pattern of ILI activity was much better delineated by the school absenteeism than the GP ILI data. Epidemic peaks shown by the student absenteeism data preceded those shown by GP ILI surveillance data by 2-3 weeks. Rescaling of all-cause absence rate by the percentage of sick leave due to upper respiratory tract infection (URTI/SL) improved the performance of the surveillance, in terms of sensitivity (from 68.4% to 73.7%), specificity (from 55.8% to 57.7%) and PPV (from 36.1% to 38.9%). Most teachers and parents found the App stable, simple, easy to use, and helpful to reduce their workload.

Conclusion: Smartphone App-based student absenteeism monitoring represents a feasible approach for prospective ILI

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surveillance. The system is stable and acceptable, and achieved an improvement of both data specificity and timeliness. The workload reduction may also help to avoid surveillance fatigue and contribute to better data accuracy and system sustainability.

Project No.: 15141522

ID-7-182

Harnessing the Potential of Blood Donation Archives for Influenza Surveillance and Control

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Introduction and Project Objectives: Many blood donation services around the globe maintain large archives of serum and/or plasma specimens of blood donations which could potentially be used for serologic surveillance and risk assessment of influenza. Harnessing this potential requires robust evidence that the outcomes of influenza serology in serum, which is the conventional choice of specimens, is consistent with that in plasma, which is rarely used for influenza serology.

Methods: We harvested EDTA-plasma specimens from the blood donation archive of Hong Kong Red Cross Blood Transfusion Services and compared their antibody titres and responses to that in serum. Influenza A/H1N1/California/7/2009 and A/H3N2/Victoria/208/2009 were the test strains.

Results: Our results showed that antibody titres in 609 matched serum/EDTA-plasma specimens (i.e. obtained from the same donor at the same time) had good agreement inferred by Intraclass Correlation Coefficient, the value of which was 0.82 (95% CI: 0.77–0.86) for hemagglutination inhibition assay and 0.95 (95% CI: 0.93–0.96) for microneutralization assay; seroconversion rates (based on hemagglutination inhibition titres) during the 2010 and 2011 influenza seasons in Hong Kong inferred from paired EDTA-plasma were similar to that inferred from paired sera.

Conclusion: Our study provides the proof-of-concept that blood donation archives around the globe could be leveraged as a valuable source of longitudinal blood specimens for the surveillance, control, and risk assessment of both pandemic and seasonal influenza.

Project No.: HKS-17-E14

ID-8-191

Interactions between Lung Microvascular Endothelial Cells and Alveolar Epithelial Cells in Severe Influenza Virus Infection Associated Acute Lung Injury

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Introduction and Project Objectives: Highly pathogenic avian influenza (HPAI) virus infections cause significant mortality in humans. In normal lungs, the integrity of the epithelial-capillary barrier is key to maintaining lung fluid clearance. However, the role of the respiratory epithelial-endothelial barrier in the pathogenesis of human influenza diseases remains unclear. The aim of this study is to establish an in vitro alveolocapillary lung injury model for investigating how influenza virus infection affects alveolar fluid clearance (AFC) and alveolar protein permeability (APP), which are important mechanisms involved in the exacerbation of lung injury. The regulation of sodium/chloride transporter proteins, cellular and tight junction integrity during infection will be examined along with the potential therapeutic effect of VEGF-A and ANG1 in resolving impaired lung function.

Methods: The HPAI viruses A/Shanghai/2/2013 (H7N9) and A/Hong Kong/483/97 (H5N1), a 2009 pandemic influenza virus A/Hong Kong/415742/2009 (H1N1pdm) and a seasonal influenza virus A/Hong Kong/54/1998 (H1N1) were used in this study. Alveolar epithelial cells (AEC) isolated from human non-tumour lung tissues and human lung microvascular endothelial cells (HMVEC) were used to develop the human alveolocapillary lung injury model. Virus infection of the lung injury model was carried out to observe the differential induction of AFC and APP, and to examine the therapeutic potential of VEGF-A and ANG1 upon HPAI or low pathogenic influenza virus infections.

Results: A highly physiologically relevant human alveolocapillary lung injury model was established with the co-culture of AEC and HMVEC. H5N1 significantly reduced AFC and increased APP compared to H7N9, H1N1pdm and H1N1 viruses. Significantly downregulated mRNA expressions of alpha1-Na+K+ATPase, alpha3-Na+K+ATPase and CFTR were observed in H5N1-infected AEC compared to H1N1-infected cells, with the effect being recapitulated in the virus-free conditioned medium-treated cells, which suggest that the soluble factors secreted by AEC upon H5N1 infection were responsible for the downregulation of ion channels. The mRNA expressions of major pro-inflammatory cytokines and chemokines were significantly greater in H5N1-infected AEC and HMVEC than in H1N1- or mock-infected cells. When administered simultaneously, VEGF-A and ANG1 restored the endothelial permeability and cellular integrity in both AEC and HMVEC cells upon H5N1 virus infection.

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Conclusion: The results offered an innovative insight into the mechanistic role of epithelial-endothelial cell interactions in the pathogenesis of influenza virus-induced lung injury. The ability of VEGF-A and ANG1 to enhance endothelial permeability and tight junction integrity indicate a novel potential therapeutic strategy for the treatment of severe human influenza virus-induced diseases.

Project No.: 15141022

ID-9-197

Limited Onward Transmission Potential of Reassortment Genotypes from Chickens Co-Infected with H9N2 and H7N9 Avian Influenza Viruses

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Introduction and Project Objectives: Live poultry markets where birds infected with genetically diverse avian influenza viruses congregate may have the potential to generate genetically diverse avian influenza viruses with increased zoonotic potential through genetic reassortment. We aimed to characterize the novel reassortant viruses after co-infection of A(H7N9) and A(H9N2) viruses in ovo and in chickens. We also investigated the sequential transmission potential of novel reassortant genotypes in chickens.

Methods: A Pearl River Delta lineage A(H7N9) viruses A/silkie Chicken/Hong Kong/1772/2014 (designated as HK1772) was selected to co-infect with four A(H9N2) viruses of different lineages, including A/chicken/Beijing/16/2013 (designated as BJ16) that belonged to the G57-lineage and co-circulated with the A(H7N9) viruses, A/chicken/Zhejiang/HJ/2007 (designated as HJ) that represents an early G57-lineage isolate, A/silkie chicken/Hong Kong/YU335/2007 (designated as YU335) that circulated prior to the G57 viruses, and A/quail/Hong Kong/G1/1997 that has been established in the Middle East countries. Novel reassortant genotypes generated in co-infected eggs or chickens were characterized by picking and testing individual plaques using high-resolution melting analysis. Sequential transmission experiments were performed by co-infecting donor chickens with A(H7N9) and A(H9N2) and exposing the 1st contact chickens with the donors (from day 1 to 3 post-inoculation) and followed by exposing the 2nd contact chickens with the 1st contacts (from day 3 to 5 post-inoculation).

Results: Co-infection with A(H7N9) and A(H9N2) viruses may lead to the emergence of novel reassortant viruses in ovo and in chickens, albeit with different reassortment patterns. We observed the dominance of A(H7N9) virus in ovo and the dominance of A(H9N2) viruses in co-infected chickens. Despite of detecting multiple novel reassortant viruses in donors after co-infection of A(H7N9) and A(H9N2) viruses, most of the novel reassortant viruses were not detected in contact chickens after exposure. Onward transmission of novel reassortant viruses from co-infected donors to the 1st and the 2nd contacts was only observed in the HK1772+YU335 group. Furthermore, among multiple novel reassortant viruses detected in donors co-infected with HK1772+BJ16, only the parental BJ16 virus was transmitted to the 1st and 2nd contacts. Taken together, these findings suggest limited onward transmission potential of novel reassortants generated in chickens co-infected with A(H7N9) and A(H9N2) viruses.

Conclusion: Our results demonstrated different patterns by which influenza viruses may acquire genetic diversity through co-infection in ovo, in vivo, and under sequential transmission conditions.

Project No.: 17160882

ID-10-209

Inference on Influenza Transmission in Swine Farms and During Transport in the Swine Supply Chain

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Introduction and Project Objectives: Newly emerging diseases, in particular those having a zoonotic origin, continue to be a threat to human health. Understanding the dynamics of viral transmission in animals is of importance in assessing feasibility of critical control points that may be amenable to disease control interventions. Swine have been considered as a possible intermediate host of influenza viruses and a source of pandemic emergence.

In Hong Kong, over 90% of the pigs are imported from mainland China, with an annual volume of about 1.5 million. Live pigs for consumption are transported in trucks from the source farm to a quarantine site at the Shenzhen-Hong Kong border. During this transport chain, there is opportunity for virus transmission between different consignments of pigs originating in different farms and stress association with transport may increase infection risk.

Methods: We utilized 6,675 paired serum samples and nasal swabs samples collected from a prospective longitudinal active influenza surveillance at the abattoir in Hong Kong, 2012-2016. We performed virological testing to identify influenza viruses in

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the swabs and serological testing on the serum samples against the A/Swine/Binh Duong/03_06/10-like H3N2 lineage. Antibody titers ≥1:40 were regarded as seropositive. Haemagglutination inhibition (HI) assays were used to identify and subtype virus isolates. Based on the test results from the paired samples, we identified recent primary infections of H3N2 and swine naïve to H3N2, which allows the estimation of the weekly force of infection in farms and during transportation.

Results: We detected low isolation rate (1%) of influenza H3N2 virus from swine originated from different places in mainland China. There was no strong seasonal pattern of H3N2 prevalence in the farms and also infections during transport. Based on different assumptions on the exposure durations in farms, the relative force of infection during transport versus in farms was about 40-119% and 17-50% in Guangdong and Hunan respectively, indicating a noticeable transmission risk during transportation for swine originated in Guangdong.

Conclusion: There is no evidence that longer distance of transportation increases the risk of transmission substantially. Transportation is an important component of biosecurity for the swine supply chain. The continued assessment of relative contribution of influenza transmission during transportation will inform the allocation of resources in improving disease control.

Project No.: HKS-15-E02

ID-11-215
PB1-F2 Protein of Influenza A (H7N9) Virus Specifically Suppresses MAVS Aggregation and Activation to Inhibit Type I Interferon Production and Inflammasome Activation

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Introduction and Project Objectives: Why human infection with avian influenza A (H7N9) virus results in high pathogenicity remains elusive. As a critical pathogenicity factor, PB1-F2 protein is known to suppress early type I interferon response and inflammasome activation, but its mechanism of action is incompletely understood.

Methods: Gain-of-function and loss-of-function experiments have been performed to characterize the MAVS suppressing activity of H7N9 PB1-F2 protein in transfected and infected cells including macrophages. Importantly, a recombinant influenza A virus which does not express H7N9 PB1-F2 has been constructed and analyzed in detail. The molecular mechanism by which H7N9 suppresses the function of MAVS has been investigated.

Results: In this study we demonstrate potent suppression of antiviral signaling by PB1-F2 protein of H7N9 virus. PB1-F2 forms protein aggregates on mitochondria and prevents MAVS from K63-linked polyubiquitination and aggregation. Unaggregated MAVS that accumulates on fragmented mitochondria is less stable and more susceptible to proteasomal and lysosomal degradation. This results in inhibition of TRIM31-MAVS and MAVS-NLRP3 interaction in infected cells including human monocyte-derived macrophages. These properties are subtype-specific and not seen in PB1-F2 of WSN virus. A recombinant virus deficient of PB1-F2 of H7N9 induces more interferon β and interleukin 1β in infected cells.

Conclusion: Our study documents an H7N9-specific mechanism for degradation of MAVS, suppression of interferon response and suppression of NLRP3 inflammasome activation by PB1-F2 of H7N9 virus. Our findings have implications in prevention and intervention of H7N9 infection.

Project No.: 15140662

ID-12-28
Unveiling the Characteristics of Emerging Staphylococcus Lugdunensis Sequence Type 3 Clone by Genomic Analysis

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Introduction: Antimicrobial resistance is emerging in Staphylococcus lugdunensis and linked to a clonal cluster (CC) 3 lineage.

Project Objectives: To resolve and characterize antimicrobial-resistant subclone(s) in S. lugdunensis by whole genome sequencing and to identify the mobile genetic elements profiles and repertoire of resistance and virulence determinants in the antimicrobial-resistant subclones.

Methods: Sixty CC3 and 65 non-CC3 isolates were sequenced. The isolates were sampled from previously published collections and clinical isolate archives, including isolates from six different hospitals, clinical and carriage isolate sources, community-associated and healthcare-associated sources and different time periods (1998-2002, 2008-2012, 2013-2017). The genomic data were analyzed by previously published bioinformatics methods and analyzed against available epidemiological data.

Results: In the 125 isolates, CRISPR (including 33 type II and 24 type IIIA) was detected in 57 isolates. CRISPR was deleted in 100% and 12% of the CC3 and non-CC3 isolates. Univariate analysis revealed that CRISPR deletion was positively associated with CC3 lineage, number of virulence factors and resistance genes (blaZ, mecA, tetK, aacA-aphD and ermC). However, only

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CC3 lineage was significantly associated with CRISPR deletion in the multivariate analysis. Mosaic plasmids, mainly in CC3 isolates were found to harbor multiple resistance genes. Novel SCCmec V subtypes with mosaic modules in J1 region were harbored by the methicillin-resistant strains which were mostly of CC3 lineage. In the non-CC3 isolates, novel putative anti-plasmid spacers were identified with BLAST hits to over 400 staphylococcal plasmids.

Conclusion: This study documented the genomic profiles of a multidrug-resistant CC3 lineage by whole genome sequencing.

Project No.: 15140862

ID-13-53

Augmented Surveillance and Infection Control Measures for Multiple Drug Resistant Bacteria in Hospitals and Elderly Homes

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Introduction and Project Objectives: Multiple drug resistant organisms (MDROs) pose an increasingly threat to our hospitals and elderly homes. We implemented active surveillance and promoted innovative infection control measure of directly-observed hand hygiene (DOHH) to tackle the emerging MDROs.

Methods: In Queen Mary Hospital, patients were prospectively screened for MDROs, including carbapenemase-producing Enterobacteriaceae (CPE), carbapenem-resistant or multiple-drug-resistant Acinetobacter baumannii (CRAB or MRAB), and vancomycin-resistant enterococci (VRE) in the active surveillance program (admission screening, opportunistic screening, safety net screening, and contact tracing screening during hospitalization). In the elderly homes, research nurses were recruited for collection of clinical and environmental samples. DOHH, delivery of alcohol-based hand rub to all conscious persons before meal and medication, was promoted in both hospitals and elderly homes.

Results: From 1 July 2011 to 30 June 2019, 199,192 fecal specimens from 77,194 patients were screened for CPE in Queen Mary Hospital. Although the incidence of CPE per 1000 patient admission significantly increased from 0.01 (2012) to 1.9 (2018) ($p<0.01$), the incidence of nosocomial CPE per 1000 CPE colonization day paradoxically decreased from 22.34 (2014) to 10.65 (2018) ($p=0.0094$) due to the implementation of DOHH-based infection control measure. With the practice of DOHH, the incidence of MRAB bacteremia reduced from its peak, 1.86 (14 cases) per 100,000 patient-days in 2013 to 0.77 (one case) in the first 6 months of 2014 ($p < 0.001$). Territory-wide implementation of DOHH reverted the rising VRE incidence of +16.5% per month ($p<0.001$) to a reduction of -9.8% per month ($p<0.001$), while the outbreak rate reverted from an increasing trend of +10.5% per month ($p<0.001$) to a decreasing trend of -13.3% per month ($p<0.001$) between January 2011 and October 2015. In the audit of DOHH, the compliance was 97.2% (428/440 episodes), which was significantly higher than patients' self-initiated hand hygiene (37.5%, 218/582 episodes, $p<0.001$).

Of 28 elderly homes, 1408 residents were screened between 1 July and 31 August 2015. CRAB, MRSA, CPE, VRE colonization was identified in 92 (6.5%), 454 (32.2%), 1 (0.07%), and 0 respectively. With the implementation of DOHH in elderly homes, environmental specimens revealed a significant reduction in MRSA (79/600, 13.2% vs 197/600, 32.8%, $p<0.001$) and CRAB (56/600, 9.3% vs 94/600, 15.7%, $p=0.001$) collected from July to August 2017.

Conclusion: An innovative DOHH-based infection control measure should be further promoted to tackle the emerging MDROs in both hospitals and elderly homes in Hong Kong.

Project No.: HKM-15-M12

ID-14-61

A Novel Anti-microbial Crystal for the Treatment of Helicobacter Pylori Infection

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Introduction and Project Objectives: Helicobacter pylori (H.pylori) is a gram-negative bacterium which colonizes the gastric mucosa of almost half of the world's population. Current treatments for H.pylori infection are based on a combination therapy consisting of a proton-pump inhibitor (PPI), H_2 antihistamine, bismuth, and several antibiotics. However, drug resistance poses a major threat to the continued efficacy of these antimicrobials, resulting in increasingly poor clinical outcomes. One avenue to overcome this challenge is the use of antimicrobial peptides (AMPs), which have shown to possess broad antimicrobial spectrum, including bacteria, fungi, parasite and enveloped viruses. However, one major obstacle in the application and delivery of AMPs is their sensitivity to proteolytic degradation, especially when targeting H.pylori due to the acidic and proteolytic environment in the stomach. Our laboratory has developed a novel delivery system that can potentially overcome this limitation. The delivery platform is based on sub-micrometer-sized Cry protein crystals that naturally form within the bacterium Bacillus thuringiensis (Bt). Previous studies have shown that Cry could be fused to different proteins and the resultant Cry-fusion proteins still

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formed crystals in the Bt cells without apparent loss of function. Notably, the Cry crystal framework appeared to protect the encapsulated protein cargo from proteases, thereby prolonging its lifetime in vitro and in vivo. We thus hypothesized that the Cry delivery platform could be utilized to enhance the anti-H.pylori activity of AMPs.

Methods: Different AMPs and three 7-mer peptides reported to specifically bind to H.pylori were screened. A metal ion-inducible autocleavage (MIIA) domain was mutated for controlled release of the AMP from the fusion crystal. The aforementioned elements were incorporated into the final expression construct for the production of Cry fusion crystals in Bt. The antimicrobial efficacy of the resultant fusion crystals was investigated both in vitro and in vivo.

Results: A synergistic combination of AMPs and a 7-mer peptide (P17) exhibiting the highest specific binding towards H.pylori were identified. The Cry-MIIA-AMP-P17 fusion crystals were successfully produced. In vitro antimicrobial assays indicated that these fusion crystals exhibited enhanced antimicrobial activity compared to the free AMP. H.pylori-infected mice orally treated with the fusion crystals have a significantly reduced H.pylori burden in their stomach compared to no treatment control.

Conclusion: Cry-MIIA-AMP-P17 fusion crystals were effective in inhibiting H.pylori growth in vivo. The Cry platform could potentially be used in the delivery of other AMPs for the treatment of other gastric diseases.

Project No.: 15140252

ID-15-113
Outcomes of Carbapenem-Resistant Enterobacteriaceae Infections in Hong Kong

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Introduction and Project Objectives: There is a paucity of data evaluating whether carbapenemase production is associated with worse clinical outcomes among patients with carbapenem-resistant Enterobacterales (CRE) infections. This study aimed to determine the outcomes of patients hospitalized with clinical infections caused by CRE

Methods: We performed a multi-centre retrospective observational study. Patients with carbapenemase producers were matched (by age, sex, pathogen and type of infection) for up to three controls with non-carbapenemase-producing CRE infections. We determined independent predictors of 30-days mortality in a multivariable logistic regression model.

Results: Forty-four patients with carbapenemase-producing CRE infections and 113 matched controls were included. Median age was 77 (IQR 63-86) years, 57% were male, 24% were nursing home residents, and most patients had urinary tract (48%) or respiratory tract infections (29%). Among carbapenemase producers, 26 (59%) were NDM, while 14 (35%) were KPC. Carbapenemase producers had a higher risk of being hospitalized outside Hong Kong
Thirty-day mortality did not differ between carbapenemase and non-carbapenemase producers (36% vs. 29%, p=0.385). On multivariable analysis, age, respiratory tract infection, primary bloodstream infection, and use of colistin as definitive treatment were independently associated with higher risk of 30-day mortality.

Conclusion: Carbapenemase and non-carbapenemase-producing CRE infections had similarly high 30-day mortality risk.

Project No.: CU-18-C23

ID-16-217
Investigation of the Transmission Risk of Methicillin-Resistant Staphylococcus Aureus (MRSA) in Residential Care Home for Elderly (RCHE) in Hong Kong

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Introduction and Project Objectives: Residential Care Homes for Elderly (RCHEs) are important reservoirs for Methicillin-Resistant Staphylococcus aureus (MRSA). Compared to hospitals, little is known about the MRSA epidemiology in RCHEs. Therefore, this project aims to identify the RCHE facility, characteristics of RCHE residents and infection control practice associated with MRSA infection/colonization and persistent colonization.

Methods: We applied a multi-level random-effects model, accounting for clustering of residents in RCHEs, to a previous

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dataset. It was about a longitudinal study of two rounds, which were 2.7-13.7 months apart, screening residents from study RCHEs in Hong Kong for MRSA in 2011-2012. Using the status of nasal colonization as the response variable, we consider variables of RCHE facility, residents' characteristics and infection control practice as possible covariates of the proposed statistical models. A statistical significance of 0.05 was specified.

Results: Data of 2278 residents from 32 RCHEs (Round 1) were analyzed. The study residents was on average 82.5 years, and the average length of stay in RCHEs was 3.6 years. Majority of residents had Charlson Index>1 (83%), and Barthel score ≤80 (68.4%). Most RCHEs (84.4%) had medium facility size or above (≥64 beds). Proportion of residents with urinary catheter (range: 0-13.9%) and that with nasogastric tube (range: 0-21.7%) varied by RCHEs. The rate of nasal colonization was 17.8%, and differed by RCHEs (range:4.0-31.1%). On the resident-level, MRSA colonization was associated with being male (adjusted OR[aOR]:1.38; 95% CI:1.09,1.74), Charlson Index (aOR:1.21-2.36; p<0.05), Barthel score (aOR:0.99; 95% CI: 0.98,0.99), use of medical device (aOR:1.79; 95% CI:1.33,2.41), and presence of skin conditions (aOR:2.44; 95% CI:1.39,4.26). On the RCHE-level, MRSA level appeared to be associated with the proportion of residents using medical device (p<0.05).There were 1832 residents who joined Round 2, and 6% (110/1832) of them were colonized in both rounds (denoted as persistent colonization). Except for gender, other variables associated with MRSA colonization in Round 1 remained significantly associated with persistent colonization.

Conclusion: The health status predominantly determined the MRSA colonization status. On the RCHE-level, the prevalence of MRSA colonization in a RCHE was associated with the use of medical device. While the individual health status is expensive and time-consuming to assess, the RCHE-level figures and data are handy to retrieve. Therefore, it will be useful to have RCHEs to routinely report RCHE-level health-related figures in order to grasp a macro-picture of the MRSA endemicity in community RCHEs.

Project No.: CU-17-C18

ID-17-51
Biological Crystal Subunit Vaccines for Mycobacterial Diseases

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Introduction and Project Objectives: This project focused on developing a TB vaccine by genetically fusing TB antigens and various inflammatory factors to crystal forming Cry proteins, producing these crystals in Bacillus thuringiensis, and delivering these Cry3Aa-TB antigen fusion crystals to mice. The objectives were to: (1) confirm the TB mouse protection studies of previous generation Cry3A-TB antigen constructs; (2) explore strategies to improve the protective immunity of Cry-TB antigen formulations against M. tuberculosis infection by altering the T-cell helper peptide used, and incorporating various TLR receptor binding ligands, and(3) test the optimized Cry-TB antigen formulation both alone and in prime boost with BCG to protect against M. tuberculosis infection.

Methods: Formulations consisting of crystals of Cry3A fused to the antigens ESAT6 and Ag85, an immune activating T-cell helper peptide, and a series of Toll like receptor sequences were prepared and their efficacy against TB was determined using mouse TB challenge experiments based on the level of infection in mice in the presence and absence of the vaccine formulation.

Results: Our results are summarized below.
1. We have confirmed that particles of Cry3AD1-Ag85-VSV-ESAT6-VSV provide modest protection against TB, albeit lower than BCG.
2. We show that replacing either VSV T-cell helper peptide in the original construct with a TT T-cell helper peptide does not provide increased protection against TB. Indeed, it appeared to primarily increase the toxicity of the vaccine.
3. We successfully fused 3 different TLR receptor-binding proteins to the C-terminus of Cry3AD1-Ag85-VSV-ESAT6-VSV. The results from these TB protection experiments for each construct were: a. Cry3AD1-Ag85-VSV-ESAT6-VSV-PorB showed no benefit. b. Cry3AD1-Ag85-VSV-ESAT6-VSV-FliC was ambiguous.c. Cry3AD1-Ag85-VSV-ESAT6-VSV-IC31, gave comparable to slightly better protection against TB than BCG in the lung and spleen.
4. Particles of both Cry3AD1-Ag85-VSV-ESAT6-VSV-FliC and Cry3AD1-Ag85-VSVESAT6-VSV-IC31 have also been used in prime-boost with BCG for TB protection. a. BCG + Cry3AD1-Ag85-VSV-ESAT6-VSV-FliC prime boost vaccination yielded improved TB protection over BCG alone in the spleen. b. BCG + Cry3AD1-Ag85-VSV-ESAT6-VSV-IC31 prime boost vaccination resulted in improved TB protection of the lung and spleen against TB infection when compared to BCG alone.

Conclusion: Cry3AD1-Ag85-VSV-ESAT6-VSV-IC31 was the most promising recombinantvsubunit TB vaccine construct identified in our study.

Project No.: 14130052

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ID-18-64

Broad and Effective Protection against Staphylococcus Aureus is Elicited by a Multi-Valent Vaccine Formulated with Novel Antigens

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Introduction and Project Objectives: With the emergence of various Methicillin-resistant Staphylococcus aureus (MRSA) isolates, Staphylococcus aureus infection is causing increased morbidity and mortality in hospitals. The demand for a prophylactic vaccine against MRSA has motivated numerous dedicated research groups to design and develop such a vaccine.

Methods: In this study, we have developed a multi-valent vaccine Sta-V5 composed of five conserved antigens involved in three important virulence mechanisms. In particular, PmtA and PmtC have made their debut as novel vaccine components.

Results and Conclusion: This prototype vaccine conferred exceptional protection against multiple epidemiologically relevant S. aureus isolates in five different mouse models. The vaccine not only elicits functional antibodies that mediate opsonophagocytic killing of S. aureus but also mounts robust antigen-specific T-cell responses.

Project No.: HKM-15-M09

ID-19-65

Virus-like particle (VLP)-based Mucosal Vaccine for Inducing Cross-serotype Immunity against Streptococcus Pneumoniae Infection

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Introduction and Project Objectives: Streptococcus pneumoniae (S. pneumonia) is a common pathogen in hospitals and in the community. In recent years, due to the emergence of multiple drug-resistant strains, the development of immunotherapy against S. pneumonia, whether active or passive, has resurgence.

Methods: Based on the conservative nature and surface localization of antigens in different serotypes, 67 unique potential epitopes were identified from 15 cell wall proteins from the S. pneumonia Genome Database (SPGDB). To enhance the immune response, VLP was choose as carrier for the vaccine candidates. We then chose the flexible and efficient SpyCatcher-SpyTag System to connect the VLP with antigen proteins.

Results: We successfully constructed fusion expression vectors of 9 proteins and SpyTag respectively. Soluble expression of 8 proteins were obtained for subsequent vaccine testing. Meanwhile, hepatitis B core (HBc) VLP with SpyCatcher fusion was successfully expressed and purified and confirmed by SDS-PAGE, Western blot, and transmission electron microscope (TEM). In the animal experiments, ELISA results showed that these 8 soluble proteins could induce significant specific antibody production. In lethal challenge experiment, immunization with Spr1875-R4 resulted in increased survival rate compared with control mice. Unfortunately, the mice immunized with LysM-R, LysM, SCP, Lys-O-I, Lys-OX, CWRP, CWAP did not shown any protection compared with the control mice. We also evaluated the efficacy of three potential antigens with VLP-Spy (VLP-Spr1875-R4, VLP-CWAP and VLP-LysO-X) in the pneumonia model. The survival rate of mice immunized with VLP-Spr1875-R4 (50%), VLP-Lys-O-X (40%) or VLP-Lys-CWAP (25%) was always significantly superior to that observed in mock.

Conclusion: From this result, we conclude that VLP can enhance the protection efficacy of these potential antigens.

Project No.: 16150422

ID-20-83

Economic Evaluation of the Introduction of Rotavirus Vaccine in Hong Kong

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Introduction and Project Objectives: Rotavirus is a common cause of severe gastroenteritis in young children in Hong Kong (HK) with a high economic burden. This study aimed to evaluate the cost-effectiveness of introducing rotavirus vaccination into the HK Government's Childhood Immunisation Programme (CIP) and to include the potential protective effect of the vaccine against seizures.

Methods: A decision-support model was customised to estimate the potential impact, cost-effectiveness and benefit-risk of rotavirus vaccination in children below 5 years over the period 2020–2029 in HK. Two doses of Rotarix® and three doses of RotaTeq® were each compared to no vaccination. Rotavirus treatment costs were calculated from a governmental health sector perspective (i.e., costs of public sector treatment) and an overall health sector perspective (both governmental and patient, i.e., costs of public sector treatment, private sector

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treatment, transport and diapers). We ran probabilistic and deterministic uncertainty analyses.

Results: Introduction of rotavirus vaccination in HK could prevent 49,000 (95% uncertainty interval: ~44,000–54,000) hospitalisations of rotavirus gastroenteritis and seizures and result in ~50 (95% uncertainty interval: ~25–85) intussusception hospitalisations, over the period 2020–2029 (a benefit-risk ratio of ~1000:1), compared to a scenario with no public or private sector vaccine use. The discounted vaccination cost would be US$51–57 million over the period 2020–2029 based on per-course prices of US$72 (Rotarix®) or US$78 (RotaTeq®), but this would be offset by discounted treatment cost savings of US$70 million (government) and US$127 million (governmental and patient health sector). There was a greater than 94% probability that the vaccine could be cost-saving irrespective of the vaccine product or perspective considered. All deterministic 'what-if' scenarios were cost-saving from an overall health sector perspective (governmental and patient).

Conclusion: Rotavirus vaccination is likely to be cost-saving and have a favourable benefit-risk profile in HK. Based on the assumptions made, our analysis supports its introduction into CIP.

Citation: Yeung KHT, Lin SL, Clark A, McGhee SM, Janusz CB, Atherly D, Chan KC, Nelson EAS. Economic evaluation of the introduction of rotavirus vaccine in Hong Kong. Vaccine 2021;39:45–58. https://doi.org/10.1016/j.vaccine.2020.10.052

Project No.: 16151032

ID-21-84
Increasing Influenza Vaccine Uptake in Children: A Randomised Controlled Trial

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Introduction and Project Objectives: Influenza vaccine is not included in the Hong Kong Government's universal Childhood Immunisation Programme but eligible children can receive subsidised vaccine through the private sector using the Vaccination Subsidy Scheme (VSS). This study examined whether a simple intervention package can increase influenza vaccine uptake in Hong Kong children.

Methods: Two study samples were enrolled: families of children who had participated in a previous knowledge, attitudes and practices study; and mother-infant pairs recruited from postnatal wards. Control groups received publicly available leaflets about VSS. Intervention groups additionally received: (1) a concise information sheet about influenza and its vaccine; (2) semi-completed forms to utilise the subsidy; (3) contacts of VSS clinics that did not charge above the subsidy; and (4) text message reminders for vaccination. Enrolled mothers were contacted when children were approximately 1 and 2 years old to determine influenza vaccination status of the families and their plan to vaccinate their children. Mothers' attitudes towards influenza vaccine were assessed at enrolment and at the end of the study.

Results: A total of 833 eligible mother-infant pairs were enrolled from the two samples. The intervention package improved influenza vaccine uptake by 22% at one year and 25% at two years of age. Maternal influenza vaccine uptake in intervention group was higher during this two-year period in those who had never been previously vaccinated. Mothers' self-efficacy regarding the use of influenza vaccine in her child, i.e., belief and confidence in her own ability to make a good decision, was also improved with the intervention.

Conclusion: A four-component intervention package could improve influenza vaccine uptake in Hong Kong children and their mothers during the first two years of life and depending on vaccine effectiveness could potentially reduce influenza-associated hospital admissions in children below 2 years old by 13–24%.

Citation: Yeung KHT, Tarrant M, Chan KCC, Tam WH, Nelson EAS. Increasing influenza vaccine uptake in children: A randomised controlled trial. Vaccine 2018;36(37):5524-5535. https://doi.org/10.1016/j.vaccine.2018.07.066

Project No.: 14131452

ID-22-109
Determinants of Seasonal Influenza Vaccination and Preferences for Future Vaccination Programmes among Hospital-based Healthcare Workers in Hong Kong

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Introduction and Project Objectives: Although annual seasonal influenza vaccination is recommended for healthcare personnel

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(HCPs), their vaccination uptake has been suboptimal. This study examined the psychosocial determinants of influenza vaccination among HCPs in Hong Kong using a longitudinal study design based on behavioral change theories.

Methods: Participants were invited to complete a baseline survey before the 2017/18 influenza vaccination campaign to measure their baseline perceptions and vaccination intention, and followed up for 9 months to measure actual vaccination uptake. The survey used a theoretical framework combining the Health Belief Model and Theory of Planned Behaviour with extended psychosocial factors for predicting HCPs' vaccination uptake. Structural equation modelling was used to test the theoretical model and estimate path coefficients (β) to infer associations of psychosocial factors with HCPs' influenza vaccination uptake.

Results: Of the 845 participants who completed follow-up, 43.0% indicated intending to take vaccination and 30.8% reported actual receipt of the vaccination. The structural equation modeling analysis showed that positive attitude towards influenza vaccination (β = 0.69), greater perceived susceptibility to influenza virus infection (β = 0.34), greater anticipated regret for not vaccinating (β = 0.31), and more cues to action (β = 0.29) were significantly associated with higher vaccination intention which directly predicted greater vaccination uptake (β = 0.82). Norms were found to have an indirect association with vaccination intention through the mediation of attitude towards influenza vaccination (β = 0.63). Self-efficacy was significantly associated with actual receipt of influenza vaccination (β = 0.13) but not vaccination intention. The structural equation model explained 84.7% and 69.6% of the variance, respectively, in HCPs' intention to receive and actual receipt of influenza vaccination.

Conclusion: Attitude towards influenza vaccination was the strongest predictor of HCPs' intention and actual receipt of influenza vaccination. Social norm approach may be an intervention strategy to shape HCPs' attitude towards influenza vaccination and their subsequent decision-making for influenza vaccination.

Project No.: 16150852

ID-23-116
Intra-season Waning of Influenza Vaccination Effectiveness in Children

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Introduction and Project Objectives: The protection conferred by influenza vaccination is generally thought to last less than a year, necessitating annual revaccination. However, the speed with which influenza vaccine effectiveness might decline during a year is unknown. We assessed how influenza vaccine effectiveness (VE) changes by time intervals between vaccination and admission to hospital in Hong Kong.

Methods: We analysed VE in children (aged 6 months to 17 years) who were admitted to hospital in Hong Kong in 2012-17. We included those who were admitted to general wards in four public hospitals in Hong Kong with a fever (≥38°C) and any respiratory symptom. We used direct immunofluorescence assay and reverse transcription PCR to detect influenza virus infection, and recorded children's influenza immunisation history. We compared characteristics of positive cases and negative controls and examined how VE changed by time.

Results: Between Sept 1, 2012, and Aug 31, 2017, we enrolled 15, 695 children hospitalised for respiratory infections, including 2500 (15.9%) who tested positive for influenza A or B and 13 195 (84.1%) who tested negative. 159 (6.4%) influenza-positive cases and 1445 (11.0%) influenza-negative cases had been vaccinated. Influenza-related admissions to hospital occurred year-round, with peaks in January through March in most years and a large summer peak in 2016; pooled VE for children of all ages was 79% (95% CI 42-92) for September to December, 67% (57-74) for January to April, and 43% (25-57) for May to August. VE against influenza A or B was estimated as 79% (95% CI 64-88) within 0·5-2 months of vaccination, 60% (46-71) within >2-4 months, 57% (39-70) within >4-6 months, and 45% (22-61) within >6-9 months. In separate analyses by type and subtype, we estimated that VE declined by 2-5 percentage points per month.

Conclusion: Influenza VE decreased during the 9 months after vaccination in children in Hong Kong. Our findings confirmed the importance of annual vaccination in children. Influenza vaccines that provide broader and longer-lasting protection are needed to provide year-round protection in regions with irregular influenza seasonality or lengthy periods of influenza activity.

Project No.: HKS-18-E18

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ID-24-118

Influenza Vaccine Effectiveness against Hospitalization among Partially and Fully Vaccinated Children in Hong Kong, 2012/13 - 2019/20

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Introduction and Project Objectives: Influenza virus infections can cause hospitalizations in children, and annual vaccination of children can provide protection against influenza.

Methods: We analyzed a test-negative design study with data spanning from 2010/11 through 2019/20 to evaluate influenza vaccine effectiveness (VE) against influenza hospitalization in children by age group, influenza type/subtype and time period within each season. We enrolled children admitted to hospital with acute febrile respiratory illnesses. Nasopharyngeal aspirates were tested by culture and/or RT-PCR to determine influenza status, and vaccination status was obtained by interviewing parents or legal guardians and was verified where possible. VE was estimated by conditional logistic regression model adjusting for sex, age and age-squared, matching on week.

Results: Influenza seasons in Hong Kong are prolonged with influenza-associated hospitalizations occurring in almost every month of the year during the study period. Influenza vaccination was effective in preventing influenza-associated hospitalizations in children of all ages. Influenza VE was higher in younger children than in older children, and higher against hospitalization due to influenza A(H1N1)pdm09 than A(H3N2) and B.

Conclusion: The childhood influenza vaccination program in Hong Kong has prevented influenza-associated hospitalizations particularly in younger children. Our findings support the use of influenza vaccines in children as an effective approach to influenza control and prevention.

Project No.: HKS-19-E20

ID-25-126

Effectiveness and Parental Acceptability of Using Social-networking Intervention to Promote Childhood Seasonal Influenza Vaccination: a Randomized Control Trial

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Introduction and Project Objectives: The seasonal influenza vaccination (SIV) uptake rate among young children remained suboptimal despite with active government promotion effort. This study was to test the effectiveness of sending a vaccination reminder through WhatsApp discussion groups (social-networking intervention) for promoting parents to take their young child for SIV and whether including a time reminder about the remaining time of optimal vaccination timing (time constraint) into the vaccination reminder could modify the effect of the vaccination reminders.

Methods: Mothers who had at least one child aged between six months and six years were randomly allocated to the Control who received no vaccination reminders, or the social-networking intervention groups who received either vaccination reminders with or without a time constraint component (SNI/+TC and SNI/-TC, respectively). All participants first completed a baseline assessment and then the intervention groups received the respective reminders, each per week over eight weeks in Oct-Dec 2017. The social-networking intervention groups also participated in the discussion about influenza and SIV with the facilitation of a moderator during the intervention period. A follow-up assessment was conducted in April-May 2018.

Results: A total of 205, 80, and 80 of mothers were randomly allocated into the Control, SNI/+TC and SNI/-TC, respectively, based on a ratio of 5:2:2. The SIV uptake rates among the target children at the follow-up were 37.9%, 38.3% and 33.3% in the Control, SNI/+TC and SNI/-TC, respectively. There was no significant effect of the vaccination reminders and time constraint component on children's SIV uptake. The social-networking intervention significantly promoted mothers' perceived self-efficacy in taking children for SIV (OR=2.56, 95%CI: 1.33-4.93) compared with the control. Content analysis of the WhatsApp discussion revealed that of 434 relevant participants' posts, 52.1% were about sharing experience/views, 27.4% were about seeking information/opinions and 24.4% were about sharing knowledge/information. Around 44.7% of the experience/views shared by participants were negative including their concerns over vaccine safety/side effects and vaccine effectiveness, negative values of vaccination, and negative vaccination experience. Although participants mainly shared their negative experience/views at

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the beginning of group discussion, with the involvement of moderator throughout the discussion, the group discussion shifted to more positive experience/view sharing and more knowledge/information sharing.

Conclusion: Participants remained having various concerns over SIV. The active involvement of health professional in the online discussion is likely to shape a positive discussion about vaccination, which can be useful for combating vaccine hesitancy in the Information Age.

Project No.: 16150752

ID-26-181
Cost Effectiveness Analysis of a Hypothetical Bivalent Vaccine against Hand, Foot and Mouth Disease in China

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Introduction and Project Objectives: New monoclonal antibodies (mAbs) and vaccines against RSV with promising efficacy and protection duration are expected to be available in the near future. We evaluated the cost-effectiveness of the administration of maternal immunisation (MI), infant mAb (IA) and paediatric immunisation (PI) as well as their combinations in eight Chinese cities.

Methods: We used a static model to estimate the impact of these preventive interventions on reducing the burden of RSV-ALRI in twelve monthly birth cohorts from a societal perspective. In addition to year-round administration, we also considered seasonal administration of MI and IA (i.e., administered only to children born in selected months). The primary outcome was threshold strategy cost (TSC), defined as the maximum costs per child for a strategy to be cost-effective.

Results: With a willingness-to-pay threshold of one national GDP per capita per QALY gained for all the cities, TSC of year-round strategies was: (i) US$2.4 (95% CI: 1.9-3.4) to US$14.7 (11.6-21.4) for MI; (ii) US$19.9 (16.9-25.9) to US$144.2 (124.6-184.7) for IA; (iii) US$28.7 (22.0-42.0) to US$201.0 (156.5-298.6) for PI; (iv) US$31.1 (24.0-45.5) to US$220.7 (172.0-327.3) for maternal plus paediatric immunisation (MPI); and (v) US$41.3 (32.6-58.9) to US$306.2 (244.1-441.3) for infant mAb plus paediatric immunisation (AP). In all cities, the top ten seasonal strategies (ranked by TSC) protected infants from 5 or fewer monthly birth cohorts.

Conclusion: Administration of these interventions could be cost-effective if they are suitably priced. Suitably-timed seasonal administration could be more cost-effective than their year-round counterpart. Our results can inform the optimal strategy once these preventive interventions are commercially available.

Project No.: HKS-18-E19

ID-27-186
Cost-benefit and Cost-effectiveness of Routine Female Adolescent Nonavalent HPV Vaccination for Reducing Cervical Cancer Burden in Hong Kong

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Introduction and Project Objectives: Although routine vaccination of females before sexual debut against human papillomavirus (HPV) has been found to be cost-effective around the world, its cost-benefit has rarely been examined. One major obstacle is the lack of data on assortativity of sexual mixing. In this study, we evaluate both the cost-effectiveness and cost-benefit of routine female adolescent nonavalent HPV vaccination in Hong Kong to guide its policy on HPV vaccination. We also infer the sexual mixing parameters from HPV epidemiologic data.

Methods: We use an age-structured transmission model coupled with stochastic individual-based simulations to estimate the health and economic impact of routine nonavalent HPV vaccination for girls at age 12 on cervical cancer burden and consider vaccine uptake at 25%, 50%, and 75% with at least 20 years of vaccine protection. Bayesian inference was employed to parameterise the model using local data on HPV prevalence and cervical cancer incidence. We use the human capital approach in the cost-benefit analysis (CBA) and GDP per capita as the indicative willingness-to-pay threshold in the cost-effectiveness analysis (CEA). Finally, we estimate the threshold vaccine cost (TVC), which is the maximum cost for fully vaccinating one girl at which routine female adolescent nonavalent HPV vaccination is cost-beneficial or cost-effective.

Results: As vaccine uptake increased, TVC decreased (i.e., economically more stringent) in the CBA but increased in the CEA. When vaccine uptake was 75% and the vaccine provided only 20 years of protection, the TVC was US$444 ($373–506) and $689 ($646–734) in the CBA and CEA, respectively, increasing by approximately 2–4% if vaccine protection was assumed lifelong. TVC is likely to be far higher when non-cervical diseases are included. The inferred sexual mixing parameters suggest that sexual mixing in Hong Kong is highly assortative by both age and sexual activity level.

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Conclusion: Routine HPV vaccination of 12-year-old females is highly likely to be cost-beneficial and cost-effective in Hong Kong. Inference of sexual mixing parameters from epidemiologic data of prevalent sexually transmitted diseases (i.e., HPV, chlamydia, etc.) is a potentially fruitful but largely untapped methodology for understanding sexual behaviours in the population.

Project No.: HKS-17-E12

ID-28-232

Immunogenicity of Intradermal Quadrivalent Influenza and 13-valent Pneumococcal Conjugated Vaccination with Topical Imiquimod in at Risk Individuals

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Introduction and Project Objectives: Both influenza and Streptococcus pneumoniae infection can cause life-threatening pneumonia and complications. Application of topical TLR7 pretreatment before intradermal (ID) influenza vaccination has demonstrated a better immunogenicity and clinical protection.

Method: We conducted three prospective double-blind randomised controlled trial among the elderly and health care workers (HCWs), between 1 January 2015 and 31 December 2019. In study 1, elderly subjects ≥ 65 years in the Queen Mary Hospital were enrolled. In study 2, HCWs <60 years working in the Queen Mary Hospital were enrolled. In both studies, subjects were randomized into 3 groups (1:1:1). Group 1 received ID quadrivalent influenza with topical imiquimod (ID QIV + IMQ). Group 2 received ID QIV with topical placebo aqueous cream (ID QIV + AQ) and Group 3 received IM QIV with topical AQ (IM QIV + IMQ). In study 3, elderly subjects were randomized into 3 groups (1:1:1). Group 1 received ID 13-valent pneumococcal conjugated vaccine with topical imiquimod (ID PCV + IMQ). Group 2 received ID PCV with topical AQ (ID PCV + AQ) and Group 3 received IM PCV with topical AQ (IM PCV + IMQ). The primary endpoints for study 1 and 2, were the seroconversion rate at the end of the third year. The primary endpoint for study 3 was the proportion of strong responders at 6 months, as defined by ≥4-fold increase of pre and post-vaccination mean pneumococcal IgG ELISA antibody.

Results: Between 1 January 2015 and 31 December 2019, 286 elderly subjects were recruited for study1 and 280 HCWs were recruited for study 2. In both studies, the primary end-point, the seroconversion rate at 36 months for all 4 antigens were significantly higher in the ID QIV + IMQ groups when compared to the ID QIV + AQ and the IM QIV + AQ control groups. For study 3, 300 elderly subjects were recruited. The primary end-point, the proportion of strong responders at 6 months were significantly higher for serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F and 23F in the ID PCV + IMQ groups when compared to the ID PCV + AQ and the IM PCV + AQ control groups. Adverse events were infrequent and self-limiting.

Conclusion: Topical pretreatment with TLR7 agonist imiquimod before ID QIV or ID PCV enhanced vaccine immunogenicity in the elderly subjects and also HCWs. Consecutive annual ID QIV with imiquimod pretreatment was not associated with hyporesponsiveness.

Project No.: HKM-15-M08

ID-29-29

Rapid Detection of cfiA metallo-β-lactamase-producing Bacteroides Fragilis by the Combination of MALDI-TOF MS and CarbaNP

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Introduction: Carbapenem resistance in Bacteroides fragilis is emerging and is mainly attributed to insertion sequence (IS)-mediated activation of the carbapenemase gene cfiA.

Project Objectives: To determine the prevalence of cfiA-positive B. fragilis among clinical isolates of B. fragilis group and to use MALDI-TOF-MS to distinguish cfiA-positive B. fragilis strains from cfiA-negative B. fragilis strains.

Methods: A collection of 424 B. fragilis isolates were included in this study. The isolates were recovered consecutively from clinical specimens submitted to two hospital-based, clinical microbiology laboratories (A and B) in Hong Kong during January-December 2015. ClinProTools software (V3.0 Bruker Daltonics) was used to develop a classification model by recognizing mass peaks that could differentiate B. fragilis cfiA-negative and cfiA-positive strains. The ability of the CarbaNP assay to detect IS-mediated activation of the cfiA gene was assessed and the results obtained by molecular analysis were used as reference methods.

Results: All 424 strains were confirmed as B. fragilis by species-specific PCR assays. Of the 424 B. fragilis strains, 81 (19.1%) were cfiA-positive. Prevalence of cfiA among isolates the two laboratories were similar, being 18.5% (49/265) for laboratory A and 20.1% (32/159) for laboratory B (P = 0.703). The support vector machine model generated by ClinProTools was found to be the most reliable algorithm for differentiation of cfiA-positive and cfiA-negative B. fragilis subgroups. Using the direct transfer method, all but one cfiA-negative isolates were correctly identified to the two subgroups by the model. The correct

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identification of the cfiA-negative isolate was obtained upon retesting by the extraction method. Of the 81 cfiA-positive isolates, PCR and sequencing showed that 30 had an IS element providing the promoter for activation of cfiA. CarbaNP test with reference to presence of IS element in cfiA upstream region had sensitivity, 100%; specificity, 80.4%; positive predictive value, 75.0% and negative predictive value, 100%.

Conclusion: The combination of MALDI-TOF MS and CarbaNP assay can be applied in diagnostic clinical laboratory for rapid identification of B. fragilis with IS-element activated cfiA gene.

Project No.: HKM-15-M10

ID-30-38
Persistence and Clearance of Oral Human Papillomavirus Infections: A Prospective Population-based Cohort Study

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Introduction and Project Objectives: This study aimed to evaluate the incidence of and factors associated with persistence and clearance of oral human papillomavirus (HPV) infections.

Method: A prospective cohort study invited 458 subjects (231 HPV-positive and 227 HPV-negative at baseline) to attend follow-ups at 12 months. Those 231 HPV-positive subjects and 10 new infections were invited to reassessment at 24 months. We used next-gen sequencing for detection and genotyping of HPV.

Results: α-HPV infections showed higher persistence rates than β/γ-HPV (22.7% vs 9.2% at 12 months [P < .05], 10.6% vs 6.8% at 24 months [P = .30]). Clearance rates of α-HPV were lower than β/γ-HPV at 12 months (31.8% vs 45.1%; P = .05) and higher at 24 months (7.6% vs 4.8%; P = .36). Persistence of β/γ-HPV was positively associated with males (crude odds ratio [COR] = 3.8, 95% confidence interval [CI] = 1.3-11.2), elderly (51-65 vs 16-50 years; COR = 5.1, 95% CI = 1.2-22.3), and smoking (COR = 4.3, 95% CI = 1.9-9.6). Drinking (COR = 0.5, 95% CI = 0.3-0.9), handwashing less than 90% of times before meals (COR = 0.6, 95% CI = 0.3-0.9), and using public bath more than once per month (COR = 0.5, 95% CI = 0.2-0.9) were risk factors hindering β/γ-HPV clearance.

Conclusion: This study identified factors associated with persistence and clearance of oral HPV infections among Chinese. Studies on other ethnogeographic groups may further inform prevention strategies of oral HPV infection and immunization programmes.

Project No.: CU-17-C20

ID-31-46
Factors Associated with TB Reactivation among HIV Patients on Antiretroviral Therapy

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Introduction and Project Objectives: TB reactivation rate among immunocompromised patients, including HIV-infected individuals, is higher than the general population. We aimed to determine the factors associated with TB reactivation among HIV patients in Hong Kong.

Methods: Baseline socio-demographics, longitudinal clinical and laboratory data of HIV patients attending a major HIV specialist clinic in Hong Kong were collected retrospectively. Patients who were diagnosed with HIV between 2002 and 2013, and were tuberculin skin test (TST) positive were included in the analysis. We defined TB reactivation as the diagnosis of TB at least one year after the first TST positive result. To examine the association of CD4 and CD4/CD8 ratio with TB reactivation, univariable and multivariable cox regression models adjusted by history of latent TB infection (LTBI) treatment were performed. Sub-analysis was performed after excluding TB reactivation before antiretroviral therapy (ART) initiation and ART naïve patients to examine the factors associated with TB reactivation in patients on ART.

Results: By 2017, 508 patients with 3203 person-years (PY) of follow-ups were selected for analysis. TB reactivation incidence from the last negative TST time-point was 4.68 cases per 1000 PY (95%C.I.=2.72-7.55) in general, and 2.93 cases per 1000 PY (95% C.I.= 1.43-5.38) after ART initiation. Low CD4 count and concurrent CD4≤200/μL and CD4/CD8 ratio≤0.5 were significantly associated with TB reactivation in both univariable and multivariable cox regression model. In the period between months 6-24 following ART initiation, CD4 ≤200/μL (aHR=5.01, p<0.05) and concurrent low CD4 and CD4/CD8 ratio (aHR=5.01, p<0.05) were significant factors. At the time of the first TST positive result, CD4 count (aHR=0.997, p<0.05), CD4/CD8 ratio (aHR=0.08, p<0.05) and ART status (aHR=0.18, p<0.05) were significant factors for TB reactivation. In sub-analysis, immunological markers remained significantly associated with TB reactivation in months 6-24 from ART and at the first positive TST.

Conclusion: TB reactivation incidence after ART initiation was lower than that for the overall HIV positive population. HIV patients with LTBI and who experienced very low CD4

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level were at higher risk of TB reactivation, and should receive screening for TB disease for timely diagnosis and treatment, and immediate ART initiation for immune recovery.

Project No.: CU-18-A17

ID-32-107

Cellular Mechanism of Reactivation of Lytic Cycle of Epstein – Barr Virus (EBV) by a Novel Compound, C7, in EBV-associated Epithelial Malignancies

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Introduction and Project Objectives: Pharmaceutical reactivation of Epstein–Barr virus (EBV) lytic cycle represents a potential therapeutic strategy against EBV-associated epithelial malignancies such as gastric carcinoma and nasopharyngeal carcinoma (NPC). A novel lytic-inducing compound, C7, which exhibits structural similarity to Dp44mT, a known intracellular iron chelator, was found to reactivate EBV lytic cycle in GC and NPC. This study aims to 1) delineate the mode of action of C7 and clinically available iron chelators in EBV lytic reactivation, and 2) to determine the cytopathic effect and synergism on EBV lytic reactivation by combining C7 with ganciclovir or other lytic inducers that possess distinct mechanism in EBV lytic reactivation such as histone deacetylase inhibitor (HDACi).

Methods and Results: Previous study showed the activation of the hypoxia signaling pathway upon C7/iron chelator treatment. We verified that the hypoxia signaling pathway was not the only pathway associated with EBV lytic reactivation induced by C7/iron chelators. Treatment with either the ERK1/2 or autophagy inhibitor significantly abolished C7-mediated EBV lytic reactivation but not in those induced by HDACi, suggesting the involvement of the ERK1/2-autophagy pathway in EBV lytic cycle reactivated only by C7/iron chelators. In addition, these two subclasses of lytic inducers imposed different cellular effects and led to distinct stages of cell cycle arrest in NPC cells. Furthermore, only the inhibition of autophagy initiation was required for EBV lytic reactivation. siRNA knockdown of various autophagic proteins of the early autophagy stages such as beclin-1, ATG3, ATG5, ATG7, LC3B, ATG10, AT12 and Rab9, revealed only the knockdown of ATG5 diminished EBV lytic reactivation, indicating a specific role of ATG5 in C7-reactivated EBV lytic cycle.

Conclusion: This study has introduced C7 and clinically available iron chelators as a new class of compounds for EBV lytic reactivation. They reactivate the viral lytic cycle through intracellular iron chelation and the activation of the ERK1/2-autophagy axis, which represent novel and distinct mechanism from that of the conventional lytic inducers. This supports the introduction of C7/iron chelators to the conventional drug reservoir to enhance the efficacy and explore possible drug combination in the lytic induction therapy against EBV-positive malignancies.

Project No.: 16150472

ID-33-114

Host Inflammatory Responses in Adults with Severe RSV Lower Respiratory Tract Infections

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Introduction and Project Objectives: Respiratory syncytial virus (RSV) is known to be an important cause of lower respiratory tract infection in infants and young children, leading to hospitalizations and death. Its impact in adults however, has only been appreciated in recent years. We aim to study the viral kinetics and host inflammatory response of RSV infection in older adults, and their correlation with disease severity.

Methods: We performed a prospective observational study in adults with RSV infection. We serially collected nasal-throat swabs for quantification of RSV-A and RSV-B viral load, and peripheral blood samples for measurement of cytokine/chemokine concentrations. The study endpoints were (i) requiring supplemental oxygen therapy, and (ii) non-invasive ventilation, intensive care, or died within 30 days of admission. We performed multivariable logistic regression models to identify independent variables for severe disease.

Results: We enrolled 71 hospitalized patients and 10 outpatients treated for RSV infection (median age 75 years, 51% male, and 74% with comorbidities). Among hospitalized patients, 61% required supplemental oxygen therapy, and 18% had severe disease requiring non-invasive ventilation or intensive care, or died within 30 days. Inflammatory cytokine/chemokines IL-6, CXCL8/IL-8, CXCL9/MIG and CXCL10/IP-10 increased significantly during the acute phase of illness. IL-6 concentration was independently associated with severe disease after adjusting for confounding factors. RSV viral load was not associated with disease severity throughout the course of illness.

Conclusion: Host inflammatory response is a major marker of severe disease in older adults with RSV infection.

Project No.: CU-16-A2

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ID-34-158
Novel Human Neutralizing Antibodies against HIV/AIDS

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Introduction and Project Objectives: Due to natural transmission of diverse HIV-1 subtypes in Hong Kong, we aim to discover novel broadly neutralizing antibodies (bnAbs) against HIV/AIDS in humans.

Methods: We have generated a panel of 40 Tier-2 HIV-1 pseudoviruses representing major subtypes throughout China to characterize human bnAbs. The potency and synergy of bnAbs were then tested against this panel of HIV-1 pseudotypes and some primary isolates in vitro and against live virus challenge in humanized mice.

Results: We have also established a diverse panel of 120 international HIV-1 pseudoviruses covering all major subtypes in the world. Using the pseudovirus assay, we screened 101 patient specimens out of 250 collected with focus on the identification of individuals with potent and broad anti-HIV-1 neutralizing antibodies. Meantime, we investigated the potency, synergy and breadth of an engineered bispecific broadly neutralizing antibody (bs-bnAb) as an innovative product for HIV-1 prophylactic and therapeutic interventions. We discovered that by preserving 2 single-chain variable fragment (scFv) binding domains of each parental bnAb, a single gene–encoded tandem bs-bnAb, BiIA-SG, displayed substantially improved breadth and potency. BiIA-SG neutralized the 40 and additional 84 collaborator's HIV-1– pseudotyped viruses tested, including global subtypes/recombinant forms, transmitted/founder viruses, variants not susceptible to parental bnAbs and to many other bnAbs with an average IC50 value of 0.073 μg/ml (range < 0.001–1.03 μg/ml). In humanized mice, an injection of BiIA-SG conferred sterile protection when administered prior to challenges with diverse live HIV-1 stains.

Conclusion: These results warrant the clinical development of BiIA-SG as a promising bs-bnAb–based biomedical intervention for the prevention and treatment of HIV-1 infection. Our outputs have served as one of the core technical platforms for one of the recent Innovation and Technology Commission funded HKU projects.

Project No.: 16150442

ID-35-159
Epidemiology of Human Papillomavirus (HPV) Infection among HPV-Vaccinated Young Adult Female in Hong Kong

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Introduction and Project Objectives: Human Papillomavirus (HPV) is a common viral infection with the extensive studies focused on exploring its prevalence and associated risk factors and health behaviour. HPV vaccine is one of the prevention strategies to prevent infection and reduce the risk of cervical cancer. However, study on the relationship between HPV prevalence, uptake rates of cervical cancer screening and other protective behaviour among HPV vaccinated women in Hong Kong is scanty. This study, therefore, not only to investigative the epidemiology of HPV infection among young adult women who have received HPV vaccination but also to explore the impact of introducing HPV DNA self-sampling on the uptake rate of cervical cancer screening in Hong Kong.

Methods: A mixed study design with a cross-sectional survey and laboratory HPV testing was adopted in which conducted in two phases accordingly. Young adult female aged ≥25 years who received HPV vaccine in the HPV Vaccination Campaign were recruited to have telephone interviews and collected their HPV self-sampling specimen if they agreed. Summary of participants' lifestyle behaviours and how past cervical cancer screening habit affected the current screening uptake using HPV self-sampling tool was reported. Prevalence and genotypes of HPV infection were also examined. Feedback on performing the HPV self-sampling test and future preference were recorded in the post-survey after the self-collected sampling procedure.

Results: A total of 651 respondents with a mean age of 30.4 (SD=1.8) were completed the telephone survey and 86 women who were successfully completed and returned the HPV self-sampling specimen for testing HPV infection in phase 2. The overall HPV infection was 1.2% (1/86) in which low-risk HPV (Lr-HPV 42) type was detected. Women who are elder, married and had sexual intercourse were more likely to have Pap smear screening before. The perception and acceptance of HPV self-sampling was very positive among the vaccinated young adult female and majority of them expressed that they would consider HPV self-sampling as a future preference of screening for cervical cancer prevention, especially to those who were under-screened.

Conclusion: This study provides a good insight to advance our knowledge on the evolution of HPV infection by evaluating the effectiveness of HPV vaccination in Hong Kong. The findings also provide a substantial information for policy formulation on cervical cancer prevention programme, especially the highly

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positive findings on acceptability and future preference of HPV self-sampling as an alternative cervical cancer screening in the health system in Hong Kong.

Project No.: CU-17-C19

ID-36-184

Comparative Benefit-cost Analyses of Health Interventions Using Human Papillomavirus Vaccination as a Case Study

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Introduction and Project Objectives: There is increasing interest in estimating the broader benefits of public health interventions beyond those captured in traditional cost-utility analyses. Cost-benefit analysis (CBA) in principle offers a way to capture such benefits, but a wide variety of methods have been used to monetise benefits in CBAs. This study aimed to understand the implications of different CBA approaches for capturing and monetising benefits and their potential impact on public health decision-making.

Methods: We conducted a CBA of human papillomavirus (HPV) vaccination in the United Kingdom using eight methods for monetising health and economic benefits, valuing productivity loss using either (1) the human capital or (2) the friction cost method, including the value of unpaid work in (3) human capital or (4) friction cost approaches, (5) adjusting for hard-to-fill vacancies in the labour market, (6) using the value of a statistical life, (7) monetising quality-adjusted life years and (8) including both productivity losses and monetised quality-adjusted life years. A previously described transmission dynamic model was used to project the impact of vaccination on cervical cancer outcomes. Probabilistic sensitivity analysis was conducted to capture uncertainty in epidemiologic and economic parameters.

Results: Total benefits of vaccination varied by more than 20-fold (£0.6–12.4 billion) across the approaches. The threshold vaccine cost (maximum vaccine cost at which HPV vaccination has a benefit-to-cost ratio above one) ranged from £69 (95% CI £56–£84) to £1417 (£1291–£1541).

Conclusion: Applying different approaches to monetise benefits in CBA can lead to widely varying outcomes on public health interventions such as vaccination. Use of CBA to inform priority setting in public health will require greater convergence around appropriate methodology to achieve consistency and comparability across different studies.

Project No.: HKS-17-E15

ID-37-205

The Clinical Severity Profile and Subclinical Infections of Enterovirus 71 in Children

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Introduction and Project Objectives: Hand-foot-and-mouth disease (HFMD) causes a substantial disease burden in Asian regions including Hong Kong, mainly in children below 5 years of age. Enterovirus 71 (EV-A71), coxsackievirus A16 (CV-A16) and the newly emerging coxsackievirus A6 (CV-A6) are the most common enterovirus serotypes causing HFMD in Hong Kong. However, EV-A71 is of particular interest as it is more likely to lead to severe outcomes including neurological complications. Only a small proportion of EV-A71 infections lead to severe disease. A larger proportion was mild or even subclinical cases. For EV-A71, the clinical severity pyramid has not been characterized. The proposed objective of this study is to characterize the risks of subclinical and clinical infections, and associated severe outcomes based on published evidence.

Methods: We obtained data on EV-A71 associated events and the prevalence of antibody titers against EV-A71 among healthy children aged 6-35 months from the published results of unvaccinated children reported by phase III clinical trials of EV71 vaccine candidates. Titer distribution and geometric mean titer (GMT) for unvaccinated children were also obtained from the trial reports. Case-severity risks of HFMD cases caused by EV-A71 were extracted from a large scale epidemiological study in China. Serological correlates of protection against EV-A71 associated disease were also extracted from the literature. We applied a hierarchical Bayesian model, which synthesized published evidence to reconstruct the severity profile of EV-A71 infections, including medically attended symptomatic disease, hospitalization, severe complications and death.

Results: We estimated that on average, 15.1% of children were infected by EV-A71 in a year. Most EV-A71 infections were mild, with about 10% symptomatic and seeking medical attention and 2.2% hospitalized. The model also suggested that 70% of children had ≥4-fold rises in antibody titers after infection.

Conclusion: The hierarchical Bayesian model provided a unified framework to synthesize evidence from multiple sources. Our model provided good estimates, consistent with other published studies and supported by simulation studies. Aggregated data on the serological correlates of protection against infection and the immune response were used, which are routinely reported by vaccine clinical trials. The approach can be applied to other diseases, allowing characterization of the severity profile which is important to the understanding of disease burden at the population level, transmission dynamics and guiding public health measures.

Project No.: HKS-18-E16

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ID-38-214

Comparative Analysis of Host Transcriptomic and Lipidomic Profile Induction by Human Enterovirus 71 and Human Coxsackievirus A16: Implications on Pathogenesis, Diagnosis, and Treatment

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Introduction and Project Objectives: Human enterovirus A71 (HEV-71) and coxsackievirus A16 (CV-A16) are major causes of hand, foot, and mouth disease (HFMD) which may be complicated by respiratory, neurological, cardiac, and systemic complications. This project aims to identify host factors which are biologically relevant in enterovirus infections through transcriptomics and lipidomics approaches, and exploit these host factors as novel antiviral strategies.

Methods: Transcriptomics and lipidomics analyses of enterovirus-infected human rhabdomyosarcoma cells were performed with RNA-Seq and ultra-high performance liquid chromatography-electrospray ionization-quadrupole-time of flight-mass spectrometry (UPLC-ESI-Q-TOF-MS), respectively. Integrative transcriptomic-lipidomic analysis and lipid modulator compound library screening were performed to identify host-targeting antivirals with broad-spectrum activities against enteroviruses and other human-pathogenic viruses.

Results: (i) Transcriptomics analysis identified growth arrest and DNA damage-inducible protein (GADD34) as a novel host dependency factor that facilitates HEV-71 replication. HEV-71 infection induces up-regulation of GADD34 expression, which reduces eIF-2α phosphorylation and promotes viral replication. The selective GADD34 inhibitor Sephin1 significantly inhibits HEV-71 and other picornaviruses in-vitro, in human small intestinal organoids, and/or induced pluripotent stem cells-derived human neural progenitor cells. (ii) UPLC-ESI-Q-TOF-MS-based lipidomics profiling reveals significant perturbations of intracellular lipid homeostasis in enterovirus-infected cells, with 47 lipids in 11 lipid classes being significantly perturbed after HEV-71 or CV-A16 infection. Four polyunsaturated fatty acids (PUFAs), namely, arachidonic acid (AA), docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), and eicosapentaenoic acid (EPA), were consistently upregulated upon HEV-71 and CV-A16 infection. Exogenously supplying AA, DHA, and EPA in cell cultures significantly reduced viral replication. (iii) Integrative transcriptomic-lipidomic analysis and lipid library screening identified AM580, a retinoid derivative and RAR-α agonist, to be highly potent in interrupting the life cycle of diverse viruses including HEV-71. Using click chemistry, the overexpressed sterol regulatory element binding protein (SREBP) was shown to interact with AM580, which accounted for its broad-spectrum antiviral activity. Mechanistic studies pinpointed multiple SREBP proteolytic processes and SREBP-regulated lipid biosynthesis pathways that are indispensable for virus replication.

Conclusion: Our project has identified novel host factors with important biological relevance in HEV-71, CV-A16, and other picornavirus infections, including GADD34, PUFAs, and SREBP, that may serve as druggable targets. The effects of Sephin1, PUFAs, and AM580 against HEV-71 and other picornavirus infections should be further evaluated in animal models and/or clinical trials.

Project No.: HKM-15-M04

ID-39-216

Roles of the Chromatin Architectural Protein CTCF in Hepatitis B Virus Transcription

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Introduction and Project Objectives: Hepatitis B virus (HBV) infection is highly endemic in Hong Kong. Over 25% of HBV carriers will ultimately develop life-threatening liver diseases such as hepatocellular carcinoma (HCC). Although anti-HBV therapy has improved remarkably in the past decade, it is still not curative mainly due to the pool of covalently closed circular DNA (cccDNA), which serves as the template for HBV transcription, a key step in HBV replication. Thus, a clear understanding of how HBV transcription is regulated by host cell factors may provide novel therapeutic targets for the design of anti-HBV drugs.

Methods: We first employed both gain-of-function and loss-of-function approaches to define the roles of CTCF in HBV transcription using both transfection and acute infection model systems. The binding of CTCF to cccDNA and the location of CTCF binding sites were then determined using a combination of chromatin immunoprecipitation (ChIP), in vitro binding assay, electrophoretic mobility shift assay (EMSA), and site-directed mutagenesis. We also explored whether CTCF may regulate HBV transcription by altering HBV promoter activity, spatial interaction between HBV promoters and enhancers, and histone modifications. Finally, we created several site-specific mutations that could disrupt different CTCF post-translational modifications to examine the effect of such modifications on the ability of CTCF to regulate HBV transcription.

Results: HBV infection enhanced the expression of endogenous CTCF, suggesting that CTCF is involved in HBV biology and pathogenesis. Overexpression of CTCF stimulated the production of HBV pgRNA and cccDNA while its knockdown resulted in the opposite, which showed that CTCF has a positive role in HBV transcription. CTCF was recruited to all HBV promoters and enhancers, and two CTCF binding sites in enhancer I were first predicted using bioinformatics and then

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verified by biological experiments. Also, three mechanisms of how CTCF can stimulate HBV transcription were shown. The first mechanism was the activation of S1 and S2 promoters. The second mechanism was the formation of spatial interaction between enhancer I and the S1/S2 promoters potentially via chromatin looping. The third mechanism was the establishment of the active histone mark H3K4me3 at the S1 and S2 promoters. Finally, we showed that poly(ADP)-ribosylation and SUMOylation of CTCF, but not its phosphorylation, inhibited the stimulatory effect of CTCF on HBV transcription.

Conclusion: CTCF binds to at least two sites on HBV cccDNA, and thereby functions as an activator of HBV transcription by direct binding for activation of promoter activity, chromatin looping, and histone modifications.

Project No.: 16150342

ID-40-24

Ifd6p is An Aryl Alcohol Dehydrogenase Which Modulates Biofilm Matrix Production and Susceptibility to Stressors in Candida Dubliniensis Biofilms

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Introduction: The regulatory mechanisms of biofilm matrix production in Candida dubliniensis are ill defined. By virtue of the pivotal role of alcohol dehydrogenases in biofilm development in C. albicans and the close phylogenetic relationship between C. albicans and C. dubliniensis, we set to investigate the molecular and cellular bases of C. dubliniensis biofilm matrix production with special attention to alcohol dehydrogenases.

Project Objectives: (1) To create IFD6, CSH1, and ADH5 null and overexpression strains in C. dubliniensis; (2) To examine and compare the phenotypic properties of the null and overexpression strains in biofilm development; and (3) To evaluate the pathobiological significance of alcohol dehydrogenase activity in C. dubliniensis.

Methods: C. dubliniensis alcohol dehydrogenases null, complemented, and overexpression strains were created using PCR-based gene targeting techniques, and their phenotypic determinants were investigated using biochemical, cell-based, and microscopic approaches. In vitro models of Candida infections were employed to evaluate the pathobiological significance of alcohol dehydrogenases.

Results: C. dubliniensis IFD6, CSH1, and ADH5 null, complemented, and overexpression strains were created and verified by PCR and Southern hybridization. Biochemical, cell-based, and microscopic analyses indicated that IFD6 played key roles in C. dubliniensis biofilm matrix production. Overexpression of IFD6 gene reduced biofilm and matrix biomass and increased susceptibility to certain antifungal agents and stressors. However, alteration in virulence was negligible.

Conclusion: The findings suggest that biofilm matrix production in C. dubliniensis is modulated by IFD6.

Implications: Unravelling the regulatory mechanisms governing biofilm development provides key data to the understanding of the role of alcohol dehydrogenase in C. dubliniensis, and cast light on the design of anti-Candidal strategy by modulating alcohol dehydrogenase activity.

Project No.: 14131202

ID-41-62

Dissecting the Molecular Mechanism of Anvm-Mediated Signal Transduction during Pseudomonas Aeruginosa Infection

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Introduction and Project Objectives: Pseudomonas aeruginosa is one of the most common pathogens in hospital-acquired infection, which is tightly controlled by a multi-layered regulatory network including quorum sensing system (QS), type VI secretion system (T6SS) and host immune resistance. In response to infection, phagocytic cells in the human immune system produce high concentrations of reactive oxygen species (ROS). However, P. aeruginosa needs to overcome the high concentration of ROS before successfully infecting host cells. In previous work, we found 80 cysteines that are highly sensitive to oxidative stress. The most sensitive cysteine is Cys44 (sensitivity ratio = 0.09) in the functional unknown protein P. aeruginosa 3880 (PA3880), which was named AnvM (anaerobic and virulence regulator) in our research. In the current study, we attempted to fully characterize this protein and found that it plays important roles in response to oxidative stress and virulence and to host response.

Methods: In the process of project research, we used MEGA7 software, which constructed phylogenetic tree of AnvM-like proteins. The characterization of AnvM is detected by reverse transcription-polymerase chain reaction (RT-PCR), cytoplasm and membrane protein purification, minimum inhibitory concentration (MIC) and real-time quantitative PCR. RNA-seq was carried out and Glutathione S-transferase (GST) pulldown assay was performed to screen potential proteins

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interacting with AnvM. C12-HSL activity, bioassay of C4-HSL and PQS production were measured to test the levels of QS molecules. Mouse experiment and histological analysis was used to determine the functional role of AnvM in influencing the host immune response. Bacterial burdens in the lungs after homogenization in PBS. Superoxide production in AMs was detected by NBT assay and H2DCF assay. Phagocytosis assay and lipid peroxidation assay were performed, and myeloperoxidase assay was tested for determining the oxidative burst in primary alveolar macrophages from infected or control mice. Immune pathway was confirmed by immunoblotting.

Results: In this study, we discovered anvM, acted as a regulator of anaerobic metabolism, response to oxidative stress and virulence in P. aeruginosa. At the same time, we found more than 30 anvM homologues in other bacterial genomes, indicating that anvM was widely distributed in the bacterial kingdom. In addition, the deletion of anvM gene changed the expression of more than 700 genes, including a set of virulence genes under both aerobic and anaerobic conditions. In order to further study the mechanism of anvM-mediated signal transduction in virulence, we used the bacterial two-hybrid test and found that the AnvM protein directly interacted with the QS regulator MvfR and the anaerobic regulator Anr. Subsequently, we found that the lack of AnvM protein can attenuate the pathogenicity of P. aeruginosa, resulting in increased the survival rate of mice, decreased the burden of bacteria, muffled inflammatory response and reduced lung damage in mice. In terms of mechanism, we identified that Cys44 was a key site for full function of anvM to affect the phagocytosis of alveolar macrophages and bacterial clearance. We also found that AnvM directly interacted with the host receptors TLR2 and TLR5, which might lead to the activation of the host immune response. Overall, the current characterization of AnvM will help to uncover new targets and strategies for the treatment of P. aeruginosa infection.

Conclusion: As a newly discovered member of regulatory proteins, AnvM is important in regulating the interaction between bacteria and the host immune system. AnvM has a multi-layered adjustment function, such as combining with MvfR, Anr, TLR2 and TLR5. It may be a key regulator of bacterial physiology and host response, and therefore represents a potential therapeutic target. This work provides novel details about the bacterial response to oxidative stress, virulence, host response to inflammation and may provide new insights into the regulation and function of the interaction between Pseudomonas aeruginosa and host cells.

Project No.: 17160022

ID-42-80

Comparisons of Exhaled Air Dispersion during High Flow Nasal Cannula Oxygen Therapy and CPAP

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Introduction and Project Objectives: High flow nasal cannula (HFNC) is an emerging therapy for respiratory failure but the extent of exhaled air dispersion during treatment is unknown. We examined exhaled air dispersion during HFNC therapy versus CPAP on a human patient simulator (HPS) in an isolation room with 16 air changes/hr.

Methods: HPS was programmed to represent different severity of lung injury. CPAP was delivered at 5-20 cmH2O via nasal pillows (Respironics Gel or ResMed Swift FX) or oronasal mask (Quattro, ResMed). HFNC, humidified to 37°C, was delivered at 10-60 L/min to the HPS. Exhaled airflow was marked with intrapulmonary smoke for visualization and revealed by laser light-sheet. Normalized exhaled air concentration was estimated from the light scattered by the smoke particles. Significant exposure was defined when there was ≥20% normalized smoke concentration.

Results: In normal lung condition, exhaled air dispersion, along the sagittal plane, increased from 186 (34) [mean(SD)] to 264 (27) mm and from 207(11) to 332 (34) mm when CPAP was increased from 5 to 20 cmH2O via Respironics and ResMed nasal pillows, respectively. Leakage from the oronasal mask was negligible. Exhaled air distances increased from 65 (15) to 172 (33) mm when HFNC was increased from 10 to 60 L/min. Air leakage to 620 mm occurred laterally when HFNC and the interface tube became loose.

Conclusion: Exhaled air dispersion during HFNC therapy and CPAP via different interfaces is limited provided there is good mask interface fitting (Full article published in Eur Respir J 2019 Apr 11;53(4):1802339).

Project No.: 15140282

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ID-43-92

Inhalable Dry Powder Formulation of Naked Sirna Using Spray-Drying Technology for the Treatment of Respiratory Diseases

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Introduction and Project Objectives: Small interfering RNA (siRNA) holds great promise for the treatment of various lung diseases including respiratory infections. It induces specific gene silencing through RNA interference (RNAi). RNA is a macromolecule notorious for its poor stability, rendering its delivery a big challenge. Inhaled dry powder formulation is attractive due to the ease of administration and good stability. High local concentration of siRNA can be achieved with reduced systemic exposure and side effects. Inspired by the ability of siRNA to be transfected in the airways without a delivery vector, we propose to formulate naked siRNA as dry powder. Spray-drying was examined for the preparation of inhalable siRNA dry powder. It involves the atomisation of siRNA solution into hot gas to allow the evaporation of solvent. However, RNA molecules are inevitably exposed to high shear stress and temperature, increasing the risk of degradation. This study aimed to develop an inhalable dry powder formulation of siRNA by identifying an optimal spray-drying condition and employing suitable excipients to ensure good aerosol properties while maintaining RNA integrity.

Methods: Mannitol was used as bulking excipient in the preparation of spray-dried siRNA powder. Two dispersion enhancers, L-leucine and human serum albumin (HSA) were investigated to improve the aerosol performance. The physicochemical properties and biological activities of the dry powder were also evaluated.

Results: Spray-drying produced particles of siRNA with wrinkled surface. Both L-leucine and HSA tend to accumulate at the liquid-air interface of the atomised droplets during solvent evaporation due to its hydrophobicity (L-leucine is a hydrophobic amino acid) or low mobility (HSA is a macromolecular larger than siRNA). They were enriched and formed a shell on the particle surfaces. When the solvent exhausted during evaporation, the shell collapsed, forming corrugated particles. Particles with dispersion enhancer displayed a better performance, as reflected by the high emitted fraction (the fraction that exited the inhaler) and fine particle fraction (the fraction with aerodynamic diameter suitable for lung deposition) in the cascade impactor study. The gel-retardation assay demonstrated that the short double-stranded siRNA is physically robust with no sign of degradation observed following spray-drying. The biological activity of spray-dried powder was also successfully retained.

Conclusion: Spray-drying is suitable for preparing siRNA formulations for inhalation. Both L-leucine and HSA can improve the aerosol performance of the powder. To enable its translation to the clinic, the evaluation of its therapeutic efficacy in animal models and long-term stability are paramount.

Project No.: 15140962

ID-44-115

Treatment and Outcomes of Community-acquired Pneuomonia (CAP) in Hong Kong - A Prospective Cohort Study

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Introduction and Project Objectives: Understanding local epidemiology and etiologies of community-acquired pneumonia in hospitalized patients is crucial for determining the appropriateness of treatment guidelines. We aim to determine the etiologies, severity, and outcomes in adults hospitalized for community-acquired pneumonia, and to study the impact of empirical antibiotic therapy on patient outcomes.

Methods: We performed a prospective observational cohort study involving adults hospitalized for community-acquired pneumonia in Hong Kong. Sputum, nasopharyngeal aspirate, blood and urine were collected for bacterial culture, molecular tests for detection of viruses and atypical pathogens, and antigen tests. Multivariable logistic regression model and Cox proportional hazard models were performed to determine independent factors associated with prolonged hospitalization and mortality.

Results: From February 2017 to July 2018, 258 patients were enrolled. The median age was 73 (interquartile range 61 – 80) years, 66% were male, 57% had underlying chronic illnesses, 13% had CURB-65 score ≥3, and 1-year mortality 10%. Pathogens were identified in 45% of patients; 20% had viral, 15% bacterial, and 9% polymicrobial pneumonia. Streptococcus pneumoniae (12%), influenza virus (12%) and Mycoplasma pneumoniae (1.2%) were the most common bacterial, viral and atypical pathogens respectively. Non-adherence to local empirical antibiotic treatment guideline (primarily recommending beta-lactam and doxycycline) was observed in 25%, and was independently associated with prolonged hospitalization (≥7 days) and higher mortality, after adjustment for age, underlying chronic illness, and disease severity.

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Conclusion: Adherence to treatment guidelines was associated with shorter hospitalization and improved survival. We provided evidence for the use of doxycycline for coverage of atypical pathogens in non-severe pneumonia.

Project No.: CU-17-A16

ID-45-119

Development and Evaluation of Novel Synthetic Bacterial Ribosomal RNA Transcription Inhibitors as Antimicrobials Against Methicillin-Resistant Staphylococcus Aureus (MRSA)

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Introduction: The emergence of bacterial pathogen methicillin-resistant Staphylococcus aureus (MRSA) is a global public health burden. Dwindling financial incentives for the development of antibiotics underlies a diminishing drug pipeline and ultimately a lack of approved novel antimicrobials. The transcription factors NusB and NusE forms a highly conserved heterodimer vital to bacterial transcription, thus their protein-protein interaction (PPI) interface presented a rational target for the development of transcription-inhibiting antimicrobials. Here we report the identification of "nusbiarylins" – a first-in-class inhibitor of bacterial transcription with novel mechanisms of action achieved through pharmacophore-based drug design and antimicrobial activity testing.

Project Objectives:

1. To make chemical derivatives of the bacterial rRNA synthesis inhibitor CUHK4.
2. To evaluate the antimicrobial activities and cytotoxicity of the bacterial rRNA synthesis inhibitor derivatives.
3. To confirm the mechanism of the optimized bacterial rRNA synthesis inhibitors at the molecular level.

Methods: The lead compound CUHK4 and its chemical derivatives were chemically synthesised and biologically characterised to assess their antimicrobial activity against clinically significant S. aureus strains including MRSA by broth microdilution, determine host cell cytotoxicity by MTT assay, probe for resistance generation by serially passaging at sub-inhibitory concentrations and to explore possible drug synergism with existing antimicrobials by checkerboard assay. The molecular mechanisms of nusbiarylins were assessed by quantitative polymerase chain reaction (qPCR) of 16S and 23S ribosomal RNA expression, while PPI target and potency were ascertained by our novel in vitro split-luciferase protein-fragment complementation assay (PCA). Binding affinity between nusbiarylins and NusB was evaluated by isothermal calorimetry (ITC).

Results: Our mini-library of nusbiarylin derivatives were found to strongly and specifically disrupt their intended molecular target, leading to impacted rRNA expression in treated cells which ultimately arrested bacterial growth. Biological investigations also suggested good antimicrobial activity for nusbiarylins – comparable to existing chemotherapeutic compounds – against both wild type and drug-resistant S. aureus strains, as well as low cytotoxicity in host cells, low rate of resistance emergence, and absence of antagonistic effects when used in combination with existing drugs. This presents a potential antimicrobial candidate with promising aspects for further investigation at early pre-clinical stages of drug development.

Conclusion: In this proposal we validated the druggability of a key bacterial PPI. Our findings encourage further development of more potent and optimised compounds within this novel family of transcription inhibitors to meet the urgent clinical needs of novel treatment options for multi-resistance bacterial infections.

Project No.: 17160152

ID-46-163

Efficacy and Mechanistic Evaluation of Banana Lectin (BanLec) as a Novel Pan-coronavirus Antiviral Agent: In-vitro and Ex-vivo Evidence

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Introduction and Project Objectives: Coronaviruses (CoVs) have repeatedly crossed species barriers from animals to human. In the past two decades, three coronaviruses, namely severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2, have emerged to cause epidemics or pandemics in humans. Effective anti-CoV treatment options remain scarce. The spike glycoprotein of CoVs is crucial for virus-cell membrane fusion and cell entry, and is a potential anti-CoV therapeutic target. Lectins are carbohydrate-binding proteins widely found in nature and some have potential antiviral activities. We have previously engineered a BanLec that has preserved broad-spectrum antiviral potency with significantly reduced mitogenicity by introducing a single amino acid substitution to replace histidine 84 with a threonine (H84T-BanLec). We hypothesized that H84T-BanLec may be a "pan-CoV" antiviral through binding with CoV spike glycoproteins. In this study, we aimed to study the anti-CoV activities of H84T-BanLec in in vitro, ex vivo, and in vivo models, and investigated the mechanism of H84T-BanLec's pan-CoV antiviral activity.

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Methods: The antiviral activity of H84T-BanLec against MERS-CoV, SARS-CoV-2, and other human-pathogenic CoVs was evaluated in in vitro, ex vivo, and/or in vivo models. In silico modelling, structural analyses, and mechanistic studies were performed to investigate H84T-BanLec's anti-CoV mechanism and virus-drug compound interactions.

Results: H84T-BanLec potently inhibited the highly virulent MERS-CoV, pandemic SARS-CoV-2 and its variants, and other human-pathogenic coronaviruses at nanomolar concentrations. MERS-CoV-infected human DPP4-transgenic mice treated by H84T-BanLec have significantly higher survival, lower viral burden, and reduced pulmonary damage. Time-of-drug-addition assay shows that H84T-BanLec targets virus entry. Structural analyses demonstrated binding of H84T-BanLec to multiple SARS-CoV-2 spike mannose sites with high affinity. Modelling experiments identify distinct high-mannose glycans in spike recognized by H84T-BanLec. The multiple H84T-BanLec binding sites on spike likely account for the activity against SARS-CoV-2 variants and the lack of resistant mutants.

Conclusion: The novel findings in this study provided the basis for further in vivo and clinical evaluation of H84T-BanLec as a pan-CoV antiviral compound for the ongoing MERS epidemic in the Middle East and the COVID-19 pandemic, as well as future emerging CoVs. The new mechanistic insights from the present study may facilitate the development of additional carbohydrate-binding agents as pan-CoV antiviral drug compounds.

Project No.: 15140762

ID-47-179
Sexual-related and Drug-related Risk on Depression and Suicidal Ideation among Young Women Engaging in Compensated Dating

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Introduction and Project Objectives: Women engaging in compensated dating were exposed to significant sexual and drug-related risk factors that could have adverse effect on their mental health. The present study examined the association between sexual-related risks (i.e. duration of engaging in compensated dating, number of clients per week, condomless sex, and history of sexually transmitted disease), drug-related risk (i.e. illicit drug use), depression, and suicidal ideation among young women taking part in compensated dating.

Methods: A total of 183 young women engaging in compensated dating were recruited from three sources (i.e. online outreach, organizations serving women engaging in compensated dating, and participant referral) and were invited to complete an online survey.

Results: A total of 75.5% of participants have scored above the cut-off for depression and 17.6% reported having had suicidal ideation in the past year. Results from structural equation modeling showed that sexual-related risks and illicit drug use were positively associated with depression which in turn, was associated with suicidal ideation.

Conclusion: Interventions that promote mental health and prevent suicidal risk for young women engaging in compensated dating are warranted and should minimize their sexual and drug-related risk.

Project No.: CU-16-C15

ID-48-183
Characterizing the Dynamics Underlying Global Spread of Emerging Infectious Diseases

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Introduction and Project Objectives: Over the past few decades, global metapopulation epidemic simulations built with worldwide air-transportation network (WAN) data have been the main tool for studying how epidemics spread from the origin to other parts of the world (e.g., for pandemic influenza, SARS, and Ebola). However, it remains unclear how disease epidemiology and the air-transportation network structure determine epidemic arrivals for different populations around the globe. This study aims to fill this knowledge gap by developing and validating an analytical framework that requires only basic analytics from stochastic processes.

Methods: We set up our framework by characterizing the probability distribution of epidemic arrival times (EATs) for all populations in three metapopulation networks with increasingly complex structure: (i) The two-population network which has the simplest metapopulation structure; (ii) the shortest-path-tree of the WAN (WAN-SPT) which is the dominant subnetwork driving global spread of epidemics; and (iii) the WAN. We build the global simulator using 2015 worldwide flight booking data from the Official Airline Guide (OAG) and the Gridded Population of the World Version 4 (GPWv4) data set from the NASA Socioeconomic Data and Applications Center (SEDAC) at Columbia University. The WAN in our global metapopulation epidemic model comprises 54,106 connections and 2309 populations and preserves more than 92% of the global air bookings. We apply the analytical framework retrospectively to the 2009 influenza pandemic and 2014 Ebola epidemic.

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Results: In the first case study of inferring the transmissibility of the 2009 pandemic influenza A/H1N1 virus, the reduction in computational complexity and requirement provided by our framework translates into substantial improvement for timeliness and efficiency in situational awareness. In the second case study of the 2014 West African Ebola epidemic, we estimate that the reporting proportion (and hence the total number of cases) would have been statistically identifiable and the results are robust against temporal variations in epidemic growth rate.

Conclusion: Our framework not only elucidates the dynamics underlying global spread of epidemics but also advances our capability in nowcasting and forecasting epidemics. The findings demonstrate that key epidemic parameters could be robustly estimated in real-time from public data on local and global spread at very low computational cost.

Project No.: HKS-17-E13

ID-49-185
Assessing the Impact of Respiratory Infections and Weather Conditions on Donor Attendance and Blood Inventory in Hong Kong

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Introduction and Project Objectives: Maintaining a stable, safe and sufficient blood supply is crucial to the healthcare system. Every year, seasonal influenza epidemics lead to substantial hospitalizations and pose intense pressure on blood transfusion service worldwide, especially in an ageing population of Hong Kong which often see bi-annual influenza outbreaks. However, limited quantitative studies have been performed to assess the impacts of influenza and other respiratory infections on blood supply.

Methods: We estimated the impacts of respiratory infections on donor attendance and blood inventory, considering the confounding effects of weather conditions. The method only required influenza-like illness data from the existing sentinel surveillance network, local weather data, donor attendance records from blood transfusion service and blood inventory levels from local healthcare system.

Results: We estimated the number of donor attendance dropped by 6–10% when the number of consultations with influenza-like illnesses (ILIs) reported by sentinel general outpatient clinics exceeded five per 1000 consultations, which is a moderate activity level and has been observed frequently in Hong Kong. Blood inventory decreased with increased ILI consultation rates reported by sentinel general outpatient clinics. Adverse weather conditions had negative impacts on both donor attendance and blood inventory.

Conclusion: Epidemics of influenza and other respiratory infections coupled with adverse weather conditions affected blood supply in Hong Kong. The pressure on blood transfusion service to maintain a stable and sufficient blood supply during influenza seasons should not be overlooked, especially in an ageing population of Hong Kong.

Project No.: HKS-18-E17

ID-50-218
Characterization of a Novel Transcript Isoform of STING that Negatively Regulates Innate Antiviral Response

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Introduction: STING plays a pivotal role in innate DNA sensing in human cells. It adapts the activation signal triggered by several different sensing pathways to cellular machinery of type I interferon (IFN) production. STING binds with and is activated by a novel second messenger termed 2'3'-cGAMP, which is a cyclic dinucleotide synthesized by the key DNA sensor cGAS and carries two mixed types of phosphodiester bonds.

Project Objectives: The overall goal of this project was to document fully a novel transcript isoform of STING termed STING-β and its function in cellular 2'3'-cGAMP signalling and DNA sensing.

Design: Subcellular localization was determined by confocal microscopy. Interaction of STING with 2'3'-cGAMP and partner proteins was analysed by affinity chromatography and co-immunoprecipitation. Activity of STING-β to perturb innate immune signalling was measured by reporter assays, RT-PCR and ELISA. Viral replication was monitored by plaque assays as well as viral RNA and protein detection.

Results: A novel transcript isoform of STING designated STING-β functioning as a dominant inhibitor of innate DNA and RNA sensing was identified and characterised. STING-β does not contain transmembrane domains and was found to express at low levels in many different types of human tissues and cells. Its mRNA was induced by viruses and an inverse correlation between its expression and IFN-β production was noted. In patients with systemic lupus erythematosus (SLE), which is an interferonopathy characterised by overproduction of type I interferons (IFNs), a decline in STING-β expression was observed. STING-β exerted a dominant suppressive effect

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on the activation of IFN production in response to all stimuli tested. On the contrary, when STING-β was specifically knocked down, the expression of IFNs, IFN-stimulated genes and other cytokines induced by cyclic dinucleotides, DNA, RNA and viruses was boosted. Mechanistically, STING-β antagonised STING-α through direct binding. STING-β was also capable of binding with TBK1 to impede the interaction of the latter with other protein partners including STING-α and TRIF. Finally, STING-β retained the complete 2'3'-cGAMP-binding domain of STING-α and was fully competent in binding with 2'3'-cGAMP, preventing it from binding with STING-α and thereby shutting down IFN-β transcription.

Conclusion: STING-β acts as a dominant inhibitor of innate DNA and RNA sensing by sequestering 2'3'-cGAMP cyclic dinucleotide and other transducer proteins.

Implications: Our study reveals another level of regulation for DNA and RNA sensing, with implications in rational design and developments of antivirals and immunomodulatory agents for combating viral and autoimmune diseases.

Project No.: 15140682

About Health and Medical Research Fund (HMRF)

Mission

The HMRF aims to build research capacity and to encourage, facilitate and support health and medical research to inform health policies, improve population health, strengthen the health system, enhance healthcare practices, advance standard and quality of care, and promote clinical excellence, through generation and application of evidence-based scientific knowledge derived from local research in health and medicine. It also provides funding support to evidence-based health promotion projects that help people adopt healthier lifestyles by enhancing awareness, changing adverse health behaviours or creating a conducive environment that supports good health practices.

Funding Opportunities

The HMRF provides funding support for the following types of projects –

(a) Investigator-initiated Projects – to support research studies and health promotion projects from individual applicants in response to "HMRF open call" invitations for grant applications guided by reference to the thematic priorities.

(b) Government-commissioned Programmes – to support specific programmes commissioned to, inter alia, build research capacity, fill knowledge gaps, support policy formulation, address specific issues, assess needs and threats, etc. Funding may cover research projects, facilities, infrastructure and other capacity building initiatives as appropriate.

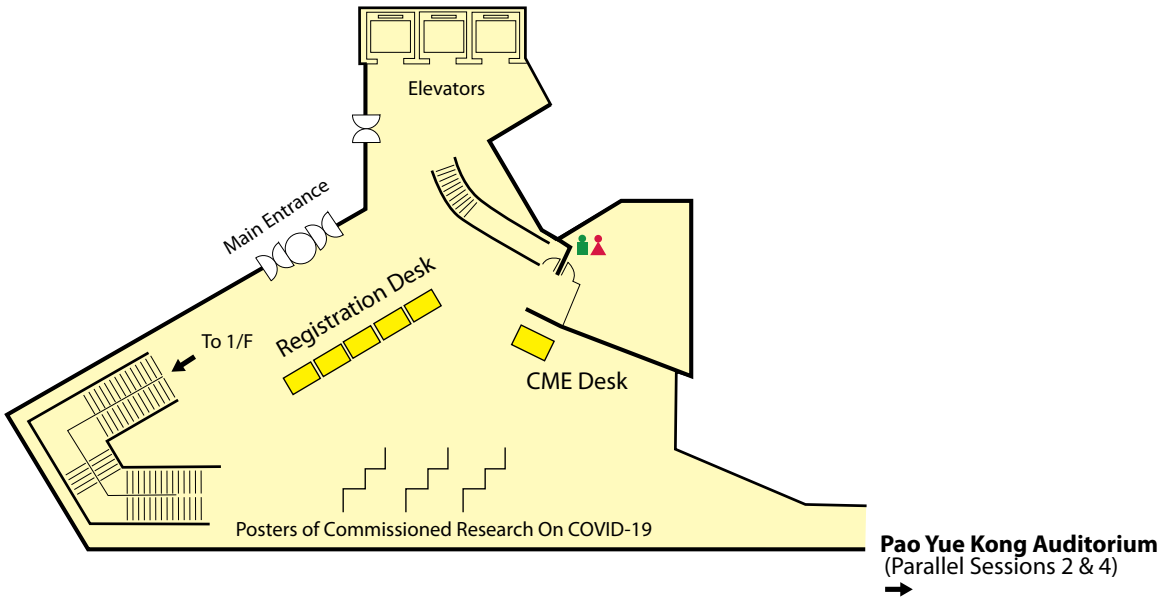
(c) Research Fellowship Scheme – to enhance research capability and build research capacity to facilitate the translation of knowledge into formulation of health policy and clinical practice. Research fellowships will be awarded to eligible candidates covering a range of research areas and specialties on the advice of the Research Council.

Applications are subject to peer review according to the established assessment criteria. Guidance notes and supplementary information, the abstracts and the budget of approved projects are available at Research Fund Secretariat's website at https://rfs.fhb.gov.hk.

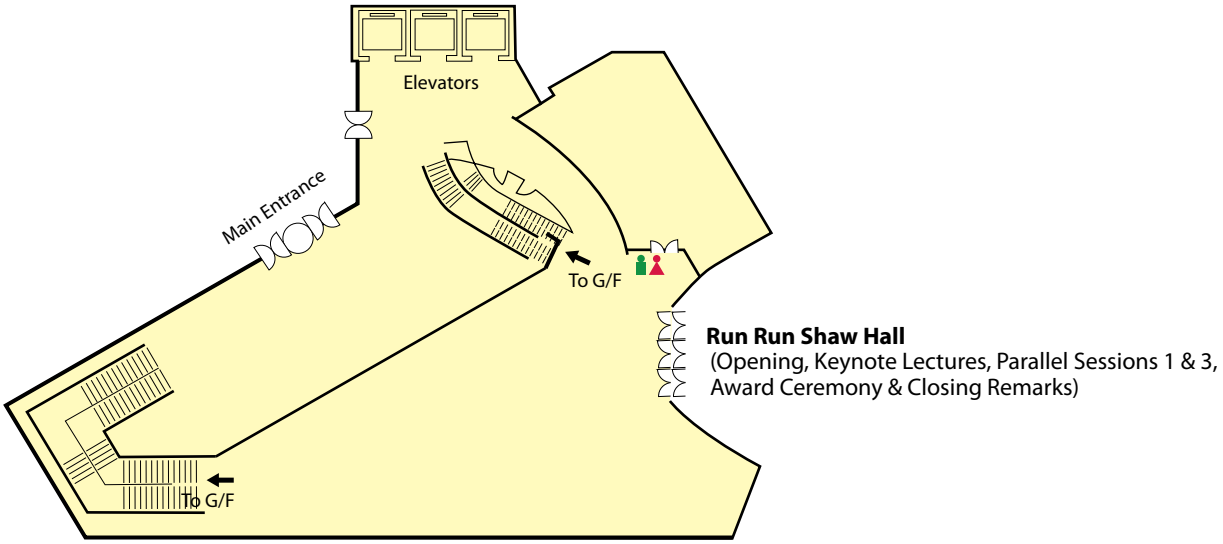
Venue Floor Plan

Venue: Hong Kong Academy of Medicine Jockey Club Building

Exhibition Hall (Ground Floor)



Foyer (First Floor)



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