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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

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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

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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

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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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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