HHS-1

Helping In-patients to Quit Smoking by Understanding their Risk Perception, Behavior, and Attitudes Related to Smoking

Li Ho Cheung William[1], Ho Ka Yan[1], Lam Ka wai[1], Lam Tai Hing[2], Chan Sophia[1]

[1]School of Nursing, The University of Hong Kong, [2]School of Public Health, The University of Hong Kong

Introduction and Project Objectives: Patients admitted to hospitals represent an excellent teachable moment for smoking cessation, as they are required to abstain from tobacco use during hospitalisation. Nevertheless, smoking behaviours of hospitalised patients, and factors that lead to smoking abstinence thereafter, remain relatively underexplored, particularly in a Hong Kong Chinese context. This study aimed at understanding the risk perceptions, behaviour, attitudes and experiences related to smoking hospitalized Chinese smokers, and exploring factors leading to their abstaining from cigarette use after being hospitalised.

Methods: In the first phase of the study, a phenomenological research design was used to develop understanding about the needs and concerns of 30 Chinese inpatients who were current smokers, including their behaviour, attitudes, risk perceptions and experiences related to smoking and smoking cessation. In the second phase, a retrospective cross-sectional study was conducted in three outpatient clinics in different regions in Hong Kong. A total of 382 Chinese patients were recruited. They were asked to complete a structured questionnaire which assessed their smoking behaviors before, during and after hospitalization.

Results: In the first phase of the study, four themes were generated: 1) associations between perception of illness and smoking; 2) perceived support from healthcare professionals to quit smoking; 3) impact of hospitalization on behaviour, attitudes, and experiences; and 4) perceived barriers to quitting smoking. For the second phase of the study, the results indicated 23.6% of smokers smoked secretly during their hospital stay, and about 76.1% of smokers resumed smoking after discharge. Multivariate logistic regression analysis found that number of days of hospitalisation admission in the preceding year (OR 1.02; 95% CI 1.01 to 1.27; p=0.036), patients' perceived correlation between smoking and their illness (OR 1.08; 95% CI 1.01 to 1.17; p=0.032), withdrawal symptoms experienced during hospitalisation (OR 0.75; 95% CI 0.58 to 0.97; p=0.027) and smoking cessation support from healthcare professionals (OR 1.18; 95% CI 1.07 to 1.36; p=0.014) were significant predictors of smoking abstinence after discharge.

Conclusion: To our knowledge, this is the first study to investigate the smoking behaviours of hospitalized patients in a Chinese context. The results indicated the importance of developing an intervention that helps to demystify misconceptions about smoking. Most importantly, an innovative and appropriate intervention is essential to help smoking patients achieve more successful smoking abstinence and less relapse.

Project No.: 13143141

HHS-2

A Randomized Controlled Trial Evaluating Efficacy of an Intervention which Enhances Social Support And Positive Affect through Online Social Networking in Smoking Cessations

Lau Joseph Tak Fai[1], Kahler Christopher[2], Abdullah Abu Robert Stempel[3], West Robert[4], Wong Martin Chi Sang[5], Ng Catalina Sau Man[6]

[1]School of Public Health and Primary Care, The Chinese University of Hong Kong, [2]Department of Behavioral and Social Sciences, Brown University, [3]School of Public Health, Florida International University, [4]Department of Epidemiology and Public Health, University College London, [5]Division of Family Medicine & Family Health Care, The Chinese University of Hong Kong, [6]Department of Early Childhood Education, Education University of Hong Kong

Introduction and Project Objectives: Online smoking cessation is effective. Peer support, positive affect, and immediate situational cue to action are new directions for smoking cessation; delivery of combinations of such interventions through online social networking has not been evaluated by randomized controlled trials (RCT). A 2-arm RCT was conducted evaluating the relative efficacy in smoking cessation. The control group (n=203) was sent weekly online messages based on the Health Belief Model to create cognitive changes. The multi-domain intervention group (n=205) included three additional novel and theory-based components: i) a peer support group, ii) positive psychology intervention (Three Good Things), and iii) immediate online interactions among peer group members to resist situational temptations.

Methods: The 2-arm non-blinded RCT design was used. The 2-month activities were conducted via WeChat. Participants included adult (>=18 years) current smokers who can communicate in Chinese. Exclusion criteria applied. Evaluation was conducted through phone interviews at baseline, 3 months and 6 months post-intervention. The primary outcome was self-reported 7-day point prevalence (pp) quit rate. At Month 6, self-reported quitting was validated by positive results of either exhale carbon monoxide test or saliva cotinine test. Secondary outcomes included reduction of cigarette consumption and other psychosocial variables.

Results: At Month 6, the self-reported quit rates were 29.0% and 27.3% in the intervention and active control groups, respectively (RR = 1.06; 95% CI: 0.74-1.53); the validated quit rates among all participants were 18.6% and 12.7% respectively. The average number of cigarettes consumed by the non-quitters decreased from 9.1 to 6.1, and 10.6 to 6.4 in the two groups (p.05). Conclusions: Both groups resulted in similarly large self-reported and validated quit rates. Non-significant between-group differences may be explained by the same active messaging component in the two groups, and that the intervention group showed very poor compliance to the three novel active components.

Conclusion: The effective active control group can be recruited and intervened at low cost and is sustainable, and may not require additional interactive social networking components; implementation of such components needs to consider compliance.

Project No.: 12130491

HHS-3

The effects of an activity-based lifestyle intervention on moderate sleep complaints among older adults: A sequential mixed method stu

Yu SF Doris[1], Low PL Lisa[2], Ng SM, Shamay[3], Siu MF Parco[4], Choi KC1, Lee TF Diana[1], Woo J[1]

[1]Faculty of Medicine, The Chinese University of Hong Kong, [2]Department of Health Sciences, Caritas Institute of Higher Education, [3]Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, [4]Division of Community Medicine and Public Health Practice, The University of Hong Kong

Introduction and Project Objectives: Sleep complaint is a highly prevalent problem affecting over 80% of the older population, and is strongly associated with imparied function, morbidity and even mortality. Research evidence identified a 'Expectation-Evidence paradox' on the sleep-promoting effect of exercise-based lifestyle intervention. This study was to investigate further on the effects and mediating process of a 16-week moderate-intensity endurance exercise on sleep quality and pattern among older adults with moderate sleep complaint, and to explore the users' overall perception on the exercise intervention.

Methods: This was a sequential quantitative-qualitative mixed method study. A RCT with waiting-list attention-controlled intervention randomized 227 older adutls (mean age = 74.6, SD =7.5) with moderate sleep complaint to receive either the 16-week moderate-intensity stepping exercise training or health education. Outcome evaluation included sleep quality as measured by the Pittsburg Sleep Quality Index (PSQI)and sleep pattern as measured by the waist actiwatch. Mood status and exercise capacity (estimated VO2max) were also measured by the Profile of Mood State and the Rockport Fitness Test respecitivty for examining the mediating mechanism. Thirty participants with different sleep-related responses to exercise were interviewed for perceived treatment effect and acceptability.

Results: Compared to the controls, generalized estimating equation indicated that the exercise training had significantly improved the sleep quality and VO2max at 16 weeks, with beta = -0.88 (95% CI = -1.72, -0.04, p = 0.04) and beta = 1.97 (95% CI = 1.22 - 2.72, p =<0.001), respectively. Even though there was significant improvement in the objective sleep parameters including total sleep time (p=0.002), sleep efficiency (p=0.001) and sleep latency (p=0.002) over time, no significant group*time intervention effect on objective sleep parameters was detected. Path analysis did not suggest the hypothesized mediating model. However, by using inductive thematic analysis for the qualitative findings, the participants did report the improvement in sleep latency, total sleeping time, wake after sleep onset and daytime sleepiness are relating to hypothesized mediators including reduced obsessive thoughts, improved temper, peaceful and relaxing mind, and increased daytime physical activity.

Conclusion: In view of the significant role of perceptual aspect of sleep pattern in predicting health and health service utilization outcomes among older adults, the moderate-intensity stepping exercise merits territory-wide application for managing moderate-sleep complaint. According to the narrative findings, the mood-enhancing and physical functioning mediating mechanisms deserve further investigation.

Project No.: 12131441

HHS-4

A case-control-family study of REM sleep behavior disorder: searching for familial aggregation and neurodegenerative biomarkers

Zhang Jihui, Liu Yaping, Lam Siu Ping, Li Shirley Xin, Mok Vincent Chung Tong, Wing Yun Kwok

Sleep Assessment Unit, Department of Psychiatry, The Chinese University of Hong Kong

Introduction and Project Objectives: Idiopathic rapid eye movement (REM) sleep behavior disorder (iRBD) is a precursor of alpha-synucleinopathy, such as Parkinson's disease and dementia with Lewy body. In this case-control-family study, we aimed to determine the familial aggregation of iRBD, and the presence of neurodegenerative diseases and related early biomarkers in the first-degree relatives of patients with iRBD.

Methods: A total of 404 and 387 first-degree relatives aged over 40 years were recruited from 102 iRBD and 89 non-RBD control families respectively for evaluation of RBD features, neurodegenerative biomarkers, and diagnoses of Parkinson's disease and dementia. Among them, 204 and 208 first-degree relatives of patients with iRBD and controls underwent face-to-face clinical assessment respectively, while 97 and 75 first-degree relatives of patients and controls underwent further video-polysomnographic assessment, respectively.

Results: Compared with the first-degree relatives of controls, first-degree relatives of patients had higher rates of probable RBD (14.9% vs. 4.9%, OR = 3.42, 95% CI = 2.00-5.85), video-polysomnography-confirmed RBD (8.4% vs. 1.4%, OR = 6.23, 95% CI = 1.81 – 21.74), and RBD features, including chin tonic electromyography activity level (1.5 ± 7.5% vs. 0.3 ± 1.0%, p = 0.01) and behavioral events during rapid eye movement sleep (11.3% vs. 1.9%, OR = 6.54, 95% CI = 2.21-19.23). First-degree relatives of patients had higher rates of clinician-diagnosed Parkinson's disease (3.1% vs. 0.5%, OR = 6.09, 95% CI = 1.38-26.95) and dementia (6.9% vs. 2.6%, OR = 3.16, 95% CI = 1.38-7.29). Moreover, first-degree relatives of patients had more constipation (8.3% vs. 2.4%, OR = 2.76, 95% CI = 1.01-9.00) and impaired motor function (mean Unified Parkinson's Disease Rating Scale part III score = 1.9 ± 3.2 vs. 0.9 ± 2.3, p = 0.001). Overall, unaffected first-degree relatives (without RBD) of patients demonstrated a higher likelihood ratio of prodromal Parkinson's disease (median [P25th-P75th]: 0.27 [0.10-1.29] vs. 0.22 [0.10-0.61], p = 0.02) than unaffected first-degree relatives of controls.

Conclusion: There is a familial aggregation of RBD from increased electromyographic activity, rapid eye movement sleep behavioral events, to full-blown disorder. First-degree relatives of patients with iRBD carry a higher risk of alpha-synucleinopathy in terms of neurodegenerative diseases and prodromal markers. The findings suggested the genetic contribution of iRBD and prodromal markers of alpha-synucleinopathy in iRBD families.

Project No.: 12131501

HHS-5
Serum 25-hydroxyvitamin D and the risk of stroke in Hong Kong Chinese

Cheung CL
Pharmacology and Pharmacy, The University of Hong Kong

Introduction and Project Objectives: Low vitamin D levels have been associated with various cardiovascular diseases; however, whether it is associated with stroke remains inconclusive. We aimed to evaluate the association between serum 25-hydroxyvitamin D and risk of stroke.

Methods: We conducted a cohort study consisting of 3,458 participants from the Hong Kong Osteoporosis Study aged ≥45 at baseline, examined between 1995 and 2010 and followed up using electronic medical records. Ischaemic and haemorrhagic stroke were defined using the ICD-9 code.

Results: In multivariable Cox-proportional hazard regression, quintiles 1 and 4 were significantly associated with increased risk of stroke when compared to the highest quintile (Quintile 1: HR, 1.78; 95 % CI, 1.16-2.74 and quintile 4: HR, 1.61; 95 % CI, 1.07-2.43). A similar association was observed in both men and women. In subgroup analysis, the association was specifically observed for ischaemic stroke, but not haemorrhagic stroke. Using a penalized regression spline, the association between vitamin D and risk of stroke was in a reverse J-shape, with the lowest risk of stroke being observed at 25(OH)D levels between 70 and 80 nmol/l.

Conclusion: In conclusion, a low vitamin D level is associated with increased risk of ischaemic stroke; however, whether high vitamin D level is also associated with increased risk of stroke requires further study.

Project No.: 12132451

HHS-6
Effectiveness of perceptual learning in reading rehabilitation for patients with diabetic macular oedema – Randomized controlled trial

Cheong AMY[1], Huang RYC[1], Tsang CLL[1], Wong IYH[2], Chong VNH[3], Cheung SH[4]
[1]School of Optometry, The Hong Kong Polytechnic University, [2]Department of Ophthalmology, University of Hong Kong, [3]Oxford Eye Hospital, University of Oxford, [4]Department of Psychology, University of Hong Kong

Introduction and Project Objectives: Our recent study showed that patients with diabetic macular oedema (DMO), after receiving laser photocoagulation, achieved good outcomes in distance acuity. However, some patients, particularly those developing parafoveal scotoma, still had difficulty in reading. The inability to read or reading very slowly can lead to the potential loss of a job, as well as the enjoyment of reading for leisure. This project is aimed at exploring the effectiveness of perceptual learning on reading performance of patients with DMO.

Methods: 55 Type II diabete patients who had complaint of reading difficulties after macular laser photocoagulation or micropulse laser for DMO were randomly assigned to one of the three groups: 1) placebo-control (control); 2) temporal processing speed training (TTT); and 3) combined temporal processing and spatial visual span training (combined). For the two intervention groups, participants received six weekly training session. Participants in the control group received six sessions of leisure reading activities. Temporal and spatial characteristics of visual span measures, reading performance, fixation stability and patient-reported outcome measures were assessed at baseline (Pre-test), immediately after training (Post-1), and 12 weeks after the cessation of training (Post-2).

Results: Results from the generalized estimating equation or mixed-model analysis showed significant improvement in temporal visual processing speed in both training groups (p 0.05).

Conclusion: Perceptual learning significantly improved participants' temporal processing speed and spatial characteristics of the visual span – two factors affecting the reading performance in visually-impaired patients. However, the training effect of the perceptual learning could not be transferred to the untrained reading tasks. The lack of transfer effect might limit our clinical application as patients might not find direct benefits on enhancing their compromised reading abilities due to vision loss. Further studies on improving the training paradigm will be needed to improve its clinical application.

Project No.: 12131601

HHS-7
Evaluating a technology-augmented self-monitoring model for glycemic and blood pressure control and medication adherence in type 2 diabetes and hypertension patients: a randomized controlled trial

Or Calvin Kalun[1], Liu Kaifeng[1], Lau Tracy[2], Yam Loretta[2], Chan Bernard[3], So Mike[4], Tiwari Agnes[5], Lau Emmy[2], Hui Grace[6], Cheng Hop-chun[6]
[1]University of Hong Kong, Hong Kong, [2]Pamela Youde Nethersole Eastern Hospital, [3]University of Hong Kong, Hong Kong, [4]The Hong Kong University of Science and Technology, [5]Hong Kong Sanatorium & Hospital, Hong Kong, [6]Tung Wah Eastern Hospital, Hong Kong

Introduction and Project Objectives: Patients with type 2 diabetes and hypertension are required to self-manage their conditions. Although digital health interventions are emerging as promising tools to improve patient self-care, their clinical effectiveness in managing diabetes and hypertension remains unclear. This study aimed to assess whether the use of a digital health intervention could improve glycemic and blood pressure control and other health-related outcomes compared with usual care.

Methods: A 24-week randomized controlled trial was conducted. Eligible participants were adult patients with comorbid type 2 diabetes and hypertension. Patients were randomly assigned to intervention or control groups. Patients allocated to the intervention group received a tablet-based self-monitoring system to support their self-care, while patients allocated to the control group performed self-monitoring using conventional devices. Primary outcomes included HbA1c, systolic blood pressure (SBP), and diastolic blood pressure (DBP). Secondary outcomes included

medication adherence, general adherence to treatment, adherence to disease-specific activities, diabetes knowledge, hypertension knowledge, and self-efficacy for coping with chronic disease. The outcomes were assessed at baseline, 8, 12, 16, and 24 weeks.

Results: A total of 299 participants were enrolled and randomized (Intervention = 151, Control = 148). Both groups yielded significant decreases in HbA1c after 12 (Intervention: 0.29%; Control: 0.34%) and 24 weeks (Intervention: 0.44%; Control: 0.35%). No significant differences in SBP and DBP were observed for both groups at most of the follow-ups. Significant improvements in adherence to disease-specific activities, diabetes knowledge, and hypertension knowledge were observed after 24 weeks for both groups. Medication adherence in the intervention group and self-efficacy for coping with chronic disease in the control group were significantly improved.

Conclusion: Both technology-augmented and conventional self-care yielded similar benefits. Strategies that can continuously motivate patients to adhere to self-care activities should be studied.

Project No.: 12133231

HHS-8
Development and Validation of a New Aphasia Screening Test for the Cantonese-speaking Population

Cho LS[1], Lee KYS[2], Lam JHS[2]
[1]Speech Therapy, Yan Chai Hospital, Hospital Authority Presenting, [2]Otorhinolaryngology, Head and Neck Surgery, The Chinese University of Hong Kong

Introduction and Project Objectives: A routine aphasia screening test which is short and easy to administer is not available in Cantonse speaking population. The aim of this study was to develop and validate a Cantonese Aphasia Screening Test (CAST).

Methods: The present study was conducted in three phases. Phase I was to determine the overall test structure through literature reviews, expert consultation and pilot study on translated FAST. Phase II was to construct test items under the four aspects of language. Phase III was the validation process in which items were tested on i)160 normal subjects, ii) 157 stroke patients with aphasia and iii) 50 stroke patients without aphasia. All subjects were also tested on the MMSE and MoCA. Obtained scores were compared with the score of CAST.

Results: Good internal consistency with alpha coefficient values larger than 0.90 was obtained in all tests. Inter- and intra-rater as well as test-retest reliability are highly satisfactory, value of coefficients 0.997, 0.999 and 0.890 respectively. Experts were satisfied with the general content of the test items to reflex the language ability of patients with potential aphasia. Close relationship between the CAST and MMSE and MoCA were found in the current study. The construct strength was found to be high, the correlation from 0.848 to 0.96.

Conclusion: An item bank for further development into a new language screening tool (CAST) which encompasses important language domains was developed and validated for patients with stroke. CAST will be simple, sensitive and predictive of aphasia in patients with stroke.

Project No.: 12133761

HHS-9
Age at Menarche and Cardiovascular Risk Factors – a Mendelian Randomization Analysis

Au Yeung SL[1], Jiang CQ[2], Cheng KK[3], Zhang WS[2], Lam TH[1], Schooling CM[1]
[1]School of Public Health, The University of Hong Kong, [2]Molecular Epidemiology Research Center, Guangzhou No.12 Hospital, [3]Institute of Applied Health Research, University of Birmingham

Introduction and Project Objectives: Observational studies show earlier age at menarche is associated with higher cardiovascular disease risk. However, childhood obesity or childhood socioeconomic position may confound the association. A Mendelian randomization design may help ascertain the causal role of age at menarche and cardiovascular disease. We hypothesized that earlier age at menarche is associated with higher blood pressure; poorer lipids and glycemic profile; and higher body mass index and waist hip ratio, which are risk factors of cardiovascular disease.

Methods: We conducted a Mendelian randomization study in a large Southern Chinese cohort, the Guangzhou Biobank Cohort Study (n=12,279). Stepwise regression with cross validation was used to generate a genetic allele score based on genetic predictors of age at menarche identified from genome wide association studies. We obtained the Mendelian randomization estimate using 2 stage least squares regression. To rule out the possibility of underpowered analyses, we included height as a positive control outcome.

Results: We derived a genetic allele score from 5 single nucleotide polymorphisms (rs17268785, rs1859345, rs2090409, rs4452860 and rs4946651). There was little evidence for weak instrument bias based on the allele score F statistics (19.9). Older age at menarche was associated with lower glucose (-0.39 mmol/L per year older menarche, 95% confidence interval (CI) -0.78 to -0.001) but not with other outcomes except height (control outcome).

Conclusion: Our study did not provide strong evidence for associations between age at menarche and cardiovascular risk factors except glucose, which needs to be verified in larger studies. Health care workers may need to monitor more intensively on the glycemic traits of adolescents with earlier age at menarche and provide relevant interventions to reduce their likelihood of developing diabetes in later life.

Project No.: 12132281

HHS-10
Tai Chi Exercise is More Effective than Brisk Walking in Reducing Cardiovascular Disease Risk Factors: A randomized Controlled Trial

Chan AWK, Chair SY
The Chinese University of Hong Kong

Introduction and Project Objectives: Physical inactivity is a major modifiable lifestyle risk factor associated with cardiovascular disease.

Tai Chi and walking are safe and popular forms of physical activity. The project objective is to evaluate the effects of Tai Chi versus brisk walking on reducing cardiovascular disease risk factors.

Methods: This was a three-arm parallel randomized controlled trial. 246 adults with hypertension and at least two but not more than three modifiable cardiovascular disease risk factors (diabetes, dyslipidemia, overweight, physical inactivity and smoking) were randomly assigned to either Tai Chi, brisk walking, or control groups (n = 82/group). The Tai Chi and brisk walking groups engaged in moderate-intensity physical activity 150 min/week for 3 months; daily home-based practice was encouraged for another 6 months. The primary outcome was blood pressure. Secondary outcomes were fasting blood sugar, glycated hemoglobin, total cholesterol, triglycerides, high- and low-density lipoprotein, body mass index, waist circumference, aerobic endurance, perceived stress, quality of life and exercise self-efficacy. Data were collected at baseline, post-intervention at 3 months and follow-up assessments at 6 and 9 months. Generalized estimating equation models were used to compare the changes in outcomes over time between groups.

Results: The mean age of participants was 64.4 (SD=9.8), age ranged from 30 to 91, with 45.5% men. At baseline, the participants had an average blood pressure = 141/81 and average body mass index = 26; 58% were were diabetics, 61% presented with dyslipidemia and 11% were smokers. No significant difference was noted between groups at baseline. The Tai Chi group significantly lowered blood pressure (systolic -13.33 mmHg; diastolic -6.45 mmHg), fasting blood sugar (-0.72 mmol/L), glycated hemoglobin (-0.39%) and perceived stress (-3.22 score) and improved perceived mental health (+4.05 score) and exercise self-efficacy (+12.79 score) at 9 months, compared to the control group. In the Tai Chi group, significantly greater reductions in blood pressure (systolic -12.46 mmHg; diastolic -3.20 mmHg), fasting blood sugar (-1.27 mmol/L), glycated hemoglobin (-0.56%), lower perceived stress (−2.32 score), and improved perceived mental health (+3.54 score) and exercise self-efficacy (+12.83 score) were observed, compared to the brisk walking group. No significant changes in the other cardiovascular disease risk indicators were observed over time between groups.

Conclusion: Tai Chi is more effective than brisk walking in reducing several cardiovascular disease risk factors and improving psychosocial well-being, and can be recommended as a viable exercise for building a healthy life free of cardiovascular disease.

Project No.: 12130041

HHS-11
Extended evaluation of stakeholder satisfaction of chronic disease management and family medicine training programmes of the Hospital Authority

Wong SYS[1], Wong MCS[1], Wong C[1], Wong ELY[1], LEE MK[2], Kung KL[1]
[1]The Jockey Club School of Public Health and Primary Care, Chinese University of Hong Kong, [2]New Territories East Cluster, Hospital Authority

Introduction and Project Objectives: To evaluate stakeholders' experience and satisfaction with specific areas of service provided by the Hospital Authority (HA) initiated Resources Allocation Exercise (RAE) Programmes since 2009, including 5 Chronic Disease Management (CDM) programmes: Multi-disciplinary Risk Assessment and Management Programme for Diabetes (RAMP-DM) and Hypertension (RAMP-HT), Nurse and Allied Health Clinics for Wound Care Programme (NAHC-WC) and Continence Care (NAHC-CC), and Patient Empowerment Programme (PEP), as well as the Family Medicine Training (FMT) Programme.

Methods: Patients aged 18 or above who joined the above programmes and their service providers, and FMT participants, were recruited from all 7 clusters of HA for two rounds of cross-sectional questionnaire survey conducted from 2012 to 2017. Modified Chinese version of Consumer Assessment of Healthcare Providers and Systems (CAHPS) Clinician and Group Survey Adult 12-Month Survey 2.0 was adopted as the patient satisfaction questionnaire. Chinese version of Patient Enablement Instrument (PEI) was chosen for measuring patient enablement in PEP. Modified version of Provider Satisfaction Survey developed by The Care Continuum Alliance was adopted as the provider satisfaction questionnaire. Modified version of Physician Worklife Survey (PWS) was used as FMT survey.

Results: 4,815 patients and 540 providers from 5 CDM programmes, and 636 participants from FMT programme were recruited. Results were similar in both rounds of survey. For CDM programmes, about 70-85% of the respondents gave a rating of the programme service, healthcare workers performance and clinic condition an 8 or above on a scale of 10. According to the PEI results, there was about 30% increase of patients who were clinically meaningfully enabled among those who attended more than 70% of the PEP programme, and a 4% decrease among those who defaulted their PEP follow up. There was a significant difference in the mean of PEI score change between completers (+2.72) and defaulters (+0.50). Patients with poorer self-rated overall health expressed lower satisfaction level in all CDM programmes. There was a high satisfaction level among service providers, ranged from 88-100%, in all CDM programmes. There were about 80% of the respondents who were satisfied with the training provided in the GOPC setting in the past 12 months in FMT.

Conclusion: Respondents in this study showed a high satisfaction level towards the CDM programmes. More patients were clinically enabled if they completed the PEP. Majority of the respondents in FMT were satisfied with the training provided. Promote person-centred care to patients with different health needs could improve satisfaction level. Recommend regular Patient Satisfaction Survey (PSS) to monitor the on-going changes.

Project No.: EPC-CUHK

HHS-12
A multi-center prospective study on the evaluation of maternal and obstetric factors leading to the hepatitis B immunization failure in Hong Kong

Cheung KW[1], Seto MTY[1], Kan ASY[1], Wong D[2], Kou KO[3], So PL[4], Lau WL[5], Jalal K[6], Chee YY[6], Wong RMS[6]
[1]Obstetrics and Gynaecology, Queen Mary Hospital, the University of Hong Kong, [2]Obstetrics and Gynaecology, Pamela Youde Nethersole Eastern Hospital, [3]Obstetrics and Gynaecology, Queen Elizabeth Hospital, [4]Obstetrics and Gynaecology, Tuen Mun Hospital, [5]Obstetrics and Gynaecology, Kwong Wah Hospital, [6]Paediatrics and Adolescent

Medicine, Queen Mary Hospital, the University of Hong Kong

Introduction and Project Objectives: To evaluate the maternal and obstetric factors leading to immunoprophylaxis failure (IF) and determine the optimal viral load threshold to predict IF

Methods: A prospective multicenter study was conducted from January 2014 to December 2016 at 5 hospitals in Hong Kong. Women with a positive hepatitis B surface antigen (HBsAg status) were recruited. Women receiving antiviral treatment during pregnancy were excluded. Maternal hepatitis B e antigen (HBeAg) was tested once on recruitment and the hepatitis B virus (HBV) DNA was quantified before and at 28–30 weeks. The duration of rupture of membranes, labour and mode of delivery were recorded. All newborns received standard HBV vaccination and immunoglobulin. HBsAg of infants was examined at 9–12 months. IF of infants (either infant in case of twin pregnancy) was defined as HBsAg positive status at 9–12 months of age.

Results: 641 women and 654 infants (13 pairs of twins) were included for final analysis. All infants completed the whole course of HBV vaccination on schedule. 352 women had HBV quantification 7.2log10IU/mL. The risks of IF with HBV DNA level of 8.2log10IU/mL were 0%, 8.6% and 3.1%, respectively. Positive HBeAg and HBV DNA >7.2log10IU/mL at 28–30 weeks were significant predictors of IF (4.5% [95% CI, 1.83%–9.08%] vs 0% [95% CI, 0%–0.76%], and 5.8% [95% CI, 2.36%–11.56%] vs 0% [95% CI, 0%–0.71%], respectively; P 0.05). Subgroup analysis in viral load > 7log10IU/mL and 8log10IU/mL also did not find a significant association between duration of rupture of membranes and labour with IF.

Conclusion: Viral load of 7.2log10IU/mL at 28–30 weeks of gestation could be the optimal HBV DNA cutoff to predict IF. Viral load quantification could be performed before 22 weeks of gestation to predict IF. Obstetric factors would not affect the risk of HBV vertical transmission following standard HBV vaccination.

Project No.: 11121661

HHS-13
Improving elderly healthcare voucher scheme to incentivise primary care in Hong Kong: How has health service utilisation changed?

Yeoh EK, Wong ELY, Yam CHK, Fung VLH
JC School of Public Health and Primary Care, The Chinese University of Hong Kong

Introduction and Project Objectives: To assess changes over time in awareness and attitudes towards Voucher Scheme amongst elderly persons and service providers, and its long term impact on the primary care system.

Methods: A mix of qualitative and quantitative analysis and data sources were used to permit triangulation in the synthesis of results to draw conclusions for the objectives of the study. It included (i) key informant interview with policymaker, (ii) repeated cross-sectional survey among elderly persons, (iii) longitudinal follow-up survey of elderly persons, (iv) linked administrative data analysis of Hospital Authority and Department of Health data, (v) focus group discussions among service providers, and (vi) public opinion survey of the general public.

Results: Overall, findings from surveys and focus group discussion showed that the current Voucher Scheme was more acceptable to elderly persons and services providers than at the time of initial launch as a pilot in 2009, reflected by the increased awareness and more positive attitudes towards the design of the voucher except for the subsidy amount. The usage has been increased to over 90% in 2016. Regarding its impact, 61.5% of elderly persons from cross-sectional survey thought that the voucher encouraged them to use primary care services in the private sector, in particular for one-off (episodic) curative services (90.3%) rather than for preventive services (40.3%) or for chronic disease management (12.2%). However, this has not been associated with a reduction in the service utilization in the public sector in the linked data analysis. The percentage of dual utilization of both public and private sector as their usual source of care increased to 61.9% in 2016 (up from 48.4% in 2010). The Voucher Scheme did not have a substitution effect of private services on public services utilization, and has led to more service utilization overall as well as an increase in price.

Conclusion: To ensure its financial sustainability and the long term development in view of the ageing population, there should be a re-design of the Voucher Scheme to meet the policy objectives of encouraging preventive services, enable chronic diseases management and facilitate continuity of care. Enhancements which should be considered are: (i) designated vouchers for preventive care especially for the soon-to-be-old group for early detection and treatment, and (ii) designated voucher for chronic diseases management. The effectiveness of vouchers will rely on engaging fully with providers as well as targeting specific populations and simple administrative processes for effective implementation.

Project No.: 12130651

HHS-14
Birth Ball for Pregnant Women in Labour - A Multi-Centre Randomised Controlled Trial

Yeung MPS[1], Tsang WKK[1], Ip WY[2], Tam WH[3], Yip BHK[1], Wong MKW[4], Hau FWL[5], Liu SH[6], Ng JWY[7], Fung BKY[8], Sing C[8], Chan CN[9], Chan SSW[1], Law CK[10], Wong SYS[1]
[1]*Jockey Club School of Public Health and Primary Care (JCSPHPC), The Chinese University of Hong Kong,* [2]*New Asia College, The Chinese University of Hong Kong,* [3]*Department of Obstetrics & Gynaecology, The Chinese University of Hong Kong,* [4]*Department of Obstetrics & Gynaecology, Prince of Wales Hospital,* [5]*School of Midwifery, Prince of Wales Hospital,* [6]*Department of Obstetrics & Gynaecology, Pamela Youde Nethersole Eastern Hospital,* [7]*Department of Obstetrics & Gynaecology, Princess Margaret Hospital,* [8]*Department of Obstetrics & Gynaecology, Kwong Wah Hospital,* [9]*Department of Obstetrics & Gynaecology, Queen Elizabeth Hospital,* [10] *Centre for Applied Health Economics (CAHE), School of Medicine, University of Griffith*

Introduction and Project Objectives: To examine the level of pain relief, satisfaction with pain control, sense of control in labour and satisfaction with childbirth experience, by comparing birth ball use with those without.

Methods: This is a prospective multi-centre randomised placebo-controlled trial. Participants were randomised based on parity (nulliparous and multiparous) and type of labour onset (spontaneous and induced). Women in the intervention group were actively offered and taught how to use a birth ball; those in the control group receive the usual midwifery care.

Results: We recruited 521 Chinese women with an uncomplicated singleton pregnancy at gestational age of 37 to 42 weeks. The majority(513, 98.5%) completed the study with 8 women withdrew. There were 250 participants in the intervention and 263 in the control group. There was no difference of subjective pain score comparing two groups on various occasions during the labour process. In subgroup analysis, there was pain reduction 15 to 30 min after analgesia in the nulliparous spontaneous intervention group when compared to control (Visual Analog Scale (VAS) 2.43 and 4.17, p=0.01), but not in other occasions during labour. The intervention group was more satisfied with using birth ball as pain control method (3.9/5 and 3.29/5, p=0.04). No difference was found between the intervention and control groups in the satisfaction of overall pain relief, sense of control in labour and satisfaction with childbirth experience.

A separate analysis was done comparing those using (n=182) and not using birth ball (n=331). It was noted a statistical significance in pain reduction when comparing the two groups in first assessment (VAS 3.87 and 5.21, p=0.000), 15 to 30 min after analgesia (VAS 4.01 and 5.95, p=0.000), 2 to 4 hours after first assessment (VAS 5.35 and 6.80, p=0.000) with and without uterine contraction and 4 to 8 hours after first assessment during uterine contraction (VAS 6.5 and 7.55, p=0.001). No difference in other primary outcomes, except the use birth ball group had a higher score in the Chinese version Postpartum Bonding Questionnaire S3 infant-focused anxiety about care (3.81 and 3.08, p=0.01).

Conclusion: Birth ball would be an alternative method for pain relieve during labour. However, the pain reduction effect was only significant comparing those using or not using birth ball, and no difference between intervention and control group. Birth ball had no effect on the sense of control in labour, reduction in assisted delivery and the satisfaction with childbirth experience

Project No.: 12131001

HHS-15
Validation of a New Definition of Lupus Low Disease Activity State (LLDAS): Clinical and Management Implications

Lau CS
Medicine, The University of Hong Kong

Introduction and Project Objectives: Systemic lupus erythematosus (SLE) is a chronic heterogeneous disease with considerable burden from disease activity and damage. This project is part of a multi-national, multi-ethnic study to evaluate the validity and application of a recently developed disease activity status clinical measurement too – the Lupus Low Disease Activity State (LLDAS).

Methods: A consensus definition of LLDAS was generated using Delphi and nominal group techniques. Preliminary studies using expert opinions, retrospective and prospective data analysis have shown LLDAS to be a valid tool to evaluate lupus disease activity status.

Results: Initial studies showed attainment of LLDAS was associated with a lower risk of lupus disease flare, probably lower accrual organ damage and poorer quality of life. Subsequent studies showed failure to attain LLDAS was associated with lower national social wealth status where the patient resided and was managed, but not her/his ethnicity. Short duration of disease and higher incidence of major organ involvement by lupus at the outset were also associated with a lower attainment of LLDAS. However, data accumulated so far does not allow a more definitive assessment of the relationship between LLDAS attainment and cumulative disease damage and mortality.

Conclusion: The establishment of the APLC has greatly enhanced the scope of lupus research in the Asia Pacific region. Studies on the clinical applications of LLDAS have so far been very encouraging and its evaluation has been extended to research groups in Europe and the North America. In the long term, it is hoped that the LLDAS will become a useful clinical measurement tool to evaluate quality of care, identify management gaps and as a target for the evaluation of drug treatments.

Project No.: 12132961

HHS-16
Meta-analysis of SLE GWAS followed by replication on X chromosome in cross-ethnic populations

Zhang Huoru, Zhang Yan, Yang Wanling
Paediatrics and Adolescent Medicine, University of Hong Kong

Introduction and Project Objectives: Systemic lupus erythematous (SLE) is a complex autoimmune disease with female predominance, particularly affecting those of childbearing age. We performed analysis of three genome-wide genotyping datasets of populations of both Chinese and European origin.To make the best use of existing GWAS data on X chromosome that would help us to a better understanding of the female preference of this disease without incurring new cost on the GWAS stage.

Methods: This study involved 5695 cases and 10,357 controls in the discovery stage. The lead signal on chromosome X was followed by replication in three additional Asian cohorts, with 2300 cases and 4244 controls in total. Conditional analysis of the known associated loci on chromosome X was also performed to further explore independent signals.

Results: Single-nucleotide polymorphism rs13440883 in GPR173 was found to be significantly associated with SLE (Pmeta=7.53×10-9, ORmeta= 1.16), whereas conditional analysis provided evidence of a potential independent signal in the L1CAM-IRAK1-MECP2 region in Asian populations (rs5987175 [LCA10]).

Conclusion: New X-linked susceptibility loci were identified and confirmed on SLE. Understanding the X-linked susceptibility genes of this complex disease would help elucidate the disease mechanisms. In the long run, the ever increasing awareness of genetic impact on different clinical manifestations of SLE, will move us closer to using

genetics to predict disease risks and disease outcomes, and guiding clinical treatment according to patient's genetic makeup.

Project No.: 12133701

HHS-17
Is It Safe to Use Estrogenic Chinese Herbal Medicines in Breast Cancer Patients? - a Preclinical Evaluation

Yue GGL[1], Wong LS[1], Gao S[1], Leung HW[1], Tsang JYS[2], Lin ZX[3], Tse GMK[2], Lau CBS[1]

[1]Institute of Chinese Medicine and State Key Laboratory of Research on Bioactivities and Clinical Applications of Medicinal Plants (CUHK), The Chinese University of Hong Kong, [2]Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong, [3]School of Chinese Medicine, The Chinese University of Hong Kong

Introduction and Project Objectives: Botanicals including Chinese herbal medicines (CHMs) contain estrogenic compounds, which are believed to have beneficial effects for women's health. Nonetheless, the stimulating activity of estrogenic CHMs in breast cancer patients or survivors has been regarded as a paradoxical perception over the decades. The present study aimed to systematically investigate the potential effects of estrogenic CHMs on breast cancer using both preclinical cell-based and tumor-bearing mouse models. Eleven CHMs, which have been previously reported to possess estrogenic effects, were selected in this study.

Methods: The selected estrogenic CHMs were evaluated in four homogeneous breast cancer cell lines with different molecular subtypes for their proliferative responses. The effects of Angelica sinensis (AS) and Cistanche deserticola (CD), both showed potent in vitro stimulatory activities, were also examined on the growth of human breast xenografts and mouse syngeneic tumors in mice. Further verification of the stimulatory activities of AS and CD were performed using primary breast cancer cells isolated from breast cancer patients.

Results: Our results showed that a few tested estrogenic CHMs (including AS and CD) stimulated the proliferation of breast cancer cells in different extents. The stimulatory activities of AS could be observed in short-term oral administration (e.g. 13-20 days) in syngeneic tumor-bearing mice, there was however no significant stimulatory activity of CD observed in human xenografts- or syngeneic tumor-bearing mice, suggesting the oral bioavailable AS or CD might not stimulate breast tumor growth in mice. Furthermore, treatments of AS or CD in cyclophosphamide-treated tumor-bearing mice did not significantly affect the tumor growth or tumor microenvironments. However, AS and CD were shown to enhance the proliferation of primary breast cancer cells, with potential correlation to the expressions of ER in the primary breast cancer cells.

Conclusion: Taking together, the estrogenic herbs AS and CD are not that stimulatory in breast cancer as demonstrated by both cell-based or tumor-bearing mouse models, though these herbs should still be used with caution particularly in ER-positive breast cancer patients. Findings from this study have certainly provided valuable information for breast cancer patients or survivors, Chinese medicine practitioners and clinicians on the safety use of tested estrogenic Chinese herbs in breast cancer, which may affect future clinical practice.

Project No.: 12130471

HHS-18
Lycium barbarum polysaccharides attenuate hepatic oxidative stress, inflammation, fibrosis and apoptosis through NFkappa-B and NLRP3/6 pathways in a non-alcoholic fatty liver disease mouse model

Xiao J[1], Wang F[2], Liong EC[3], Kwok KF[4], Tipoe GL[3]

[1]Department of Immunology, Jinan University, Guangzhou, China, [2]Digestive Institute, Tongji University School of Medicine, Shanghai, China, [3]School of Biomedical Sciences, LKS Faculty of Medicine, The University of Hong Kong, [4]Department of Ophthalmology, LKS Faculty of Medicine, The University of Hong Kong

Introduction and Project Objectives: We aimed to investigate whether LBP could alleviate the hepatic injury in a non-alcoholic steatohepatitis (NASH) methionine-choline deficient (MCD) mouse model.

Methods: NASH was induced in C57BL/6N mice by feeding with MCD diet for 6 weeks. During the experiments, 1 mg/kg LBP was intragastrically fed on a daily basis with or without MCD diet lasting from the 4th to 6th week. Control and vehicle-control (LBP + PBS) were fed with a regular animal chow.

Results: LBP significantly ameliorated NASH-induced injuries, including the increase of serum ALT and AST levels, hepatic oxidative stress, fibrosis, inflammation, and apoptosis. The hepatoprotective effects of LBP were accompanied by the attenuation of thioredoxin interacting protein, nod-like receptor protein 3/6 (NLRP3/6) and reduced NF-κB (nuclear factor-kappa B) activity. Vehicle LBP fed mice showed no adverse effect on the liver.

Conclusion: In conclusion, the suppression of the NLRP3/6 inflammasome pathway and NF-κB activation may partly contribute to the reduction of the hepatic injury during the progression of NASH by therapeutic LBP treatment.

Project No.: 12133881

HHS-19
A Study to Reduce the Toxicity of Xanthii Fructus

Kwan HY

School of Chinese Medicine, Hong Kong Baptist University

Introduction and Project Objectives: In traditional Chinese medicine (TCM), Xanthii Fructus (XF) is commonly prescribed to treat chronic bronchitis, nasal diseases, headache, urticarial, chronic rhinitis, allergic rhinitis, lumbago and other ailments. However, XF has acute toxicity. To reduce the toxicity, XF is usually processed by stir-baking.

Methods: We used both cell and animal models to compare the toxicities of non-stir-baked XF and stir-baked XF (SBXF) with different stir-baking protocols, and suggested the underlying mechanism of action of how stir-baking can reduce XF toxicity.

Results: Our study clearly showed that water-soluble glycoside carboxyatractyloside (CATR) was reduced progressively while glycoside atractyloside (ATR) was increased progressively as the stir-baking time increased. Since CATR is to known to be more toxic than ATR, we suggest that the non-stir-baked XF is more toxic than SBXF because the former has a higher level of CATR than the latter. However, we found that stir-baking XF for 40 min that resulted in a highly elevated level of ATR had severe toxicity in liver when compared to XF stir-baked for 20 min. Therefore, the stir-baking time is also a critical factor to reduce toxicity. ATR in SBFX can trigger Ca2+ release from mitochondria, causes deregulated Ca2+ matrix in the cells, which leads to matrix swelling and release of apoptotic proteins that cause cell death. Our data clearly showed that ATR triggered internal Ca2+ release and reduced cell viability.

Conclusion: Our study suggest stir-baking reduces XF toxicity because of the decarboxylation of CATR to ATR which is less toxic. Our study has a great implication. We demonstrate a proper stir-baking process that is critical to reduce XF toxicity, and identify CATR and ATR as toxicity markers for XF which will be useful for monitoring the stir-baking process for XF and assessing the toxicity of XF that are available in the market.

Project No.: 12133831

HHS-20
Cardiocrinum Seeds Contain Novel Antitussive Phytochemicals

Shou Jiawen[1], Wu Hoi-Yan[2], Jiang Renwang[3]
[1]School of Life Sciences, The Chinese University of Hong Kong, [2]LDS YYC R & D Centre for Chinese Medicine, The Chinese University of Hong Kong, [3]Guangdong Province Key Laboratory of Pharmacodynamic Constituents of TCM and New Drugs Research, College of Pharmacy, Jinan University

Introduction and Project Objectives: Cough is a world-wide concern and the discovery of new, safe and effective antitussive agents is important. Natural products from the traditional Chinese medicines are promising antitussive drugs for further development. Seeds of Cardiocrinum giganteum var. yunnanense (Leichtlin ex Elwes) Stearn (Liliaceae), also known as Doulingzi, have been used as a folk substitute for conventional antitussive herb "Madouling" (Aristolochia species) to treat chronic bronchitis and pertussis. The active antitussive phytochemicals in C. giganteum seeds are not known. The work aims at isolating the active phytochemicals in C. giganteum seeds and confirming their antitussive effects.

Methods: Petroleum ether, ethyl acetate, butanol and water were used to separate the methanol extract into different fractions. Active chemicals were isolated from and identified their structures. Antitussive effects were evaluated with the cough frequency of guinea pigs exposed to citric acid. Electrical stimulation of the superior laryngeal nerve in guinea pigs was performed to differentiate the acting site of potential antitussives.

Results: It was shown, among all the fractions, the n-butanol fraction had the strongest effect to inhibit coughs induced by inhalation of citric acid in guinea pigs. Two racemic biflavonoids (CGY-1 and CGY-2) were isolated from the n-butanol fraction. CGY-1 was identified as (S)-2"R,3"R- and (R)-2"S,3"S-dihydro-3"-hydroxyamentoflavone-7-methyl ether, which are new compounds and firstly isolated from C. giganteum seeds. Racemic CGY-2 was identified as (S)-2"R,3"R- and (R)-2"S,3"S-dihydro-3"-hydroxyamentoflavone. Both CGY-1 and CGY-2 could significantly inhibit coughs induced by inhalation of citric acid. Further, they acted on the peripheral reflex pathway to inhibit cough after electrical stimulation of the superior laryngeal nerve in guinea pigs.

Conclusion: These chemicals from C. giganteum seeds showed good antitussive effects. The data provide scientific evidence to support the traditional use of C. giganteum seeds as an antitussive herbal medicine.

Project No.: 12130851

HHS-21
A Novel Treatment of Intermittent Claudication in Patients with Peripheral Arterial Disease Using a Herbal Formula with Proven Efficacy

Yan BP[1], Xu DJL[1], Chan CKY[1], Chook P[2], Chan JYW[3], Koon JCM[3], Au WC[3], Tan GM[1], Fung KP[1], Leung PC[3]
[1]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, [2]Centre for Clinical Trials on Chinese Medicine, Institute of Chinese Medicine, The Chinese University of Hong Kong, [3]Institute of Chinese Medicine, The Chinese University of Hong Kong

Introduction and Project Objectives: Effective medical therapy for the treatment of intermittent claudication (IC) in patients with peripheral arterial disease (PAD) is limited. Danshen and Gegen (DG) are traditional Chinese medicines with vasodilatory and anti-inflammatory properties which may be a novel treatment in PAD. We conducted a prospective-randomized, double-blind, placebo-controlled trial (RCT) to evaluate the efficacy and safety of DG in symptomatic PAD patients and animal models to evaluate the vasodilatory and angiogenic response to DG.

Methods: We used isolated rat femoral artery to investigate in-vitro vasorelaxant activity and DG mechanisms-of-action. In-vivo functional recovery and in-vitro muscle perfusion and capillary density were assessed in a rat ischemic-limb model. 95 PAD patients with IC were randomly allocated to treatment group (n=48) with oral DG capsules (1.5 g bid) or placebo group (n=47) for 24 weeks. Primary outcome was change in maximal walking distances (MWD) on standardized graded-treadmill testing. Secondary outcomes included pain-free walking distances (PFWD) and functional status measured by Walking Impairment Questionnaire (WIQ) and Euro-QOL 5D.

Results: DG was associated with significant positive vasodilatory and angiogenic response in animal studies. The proportion of patients who achieved ≥50% improvement in walking distances was significantly higher in DG (43.2%) vs. control group (22.0%, P=0.044). Patients with moderate-to-severe IC (baseline MWD)

Conclusion: DG may be an effective treatment for PAD patients with severe claudication compared to placebo. However, long-term research in larger population is needed to better establish its safety and efficacy. (ClinicalTrials.org. ID NCT 02380784)

Project No.: 11120771

HHS-22

Investigation of the effects of Gastrodiae Rhizoma – containing herbal formula (DCXF) in traumatic brain injury rat model

Koon Chi-Man[1], Ko Chun-Kay[1], Wong Hing-Lok[1], Zhang Jin-Fang[2], Lam Ping-Kuen[3], Poon Wai-Sang[4], Leung Ping-Chung[5]

[1]Institute of Chinese Medicine, The Chinese University of Hong Kong, Shatin, [2]Department of Orthopaedic and Traumatology, Prince of Wales Hospital, Shatin, [3]Department of Surgery, Prince of Wales Hospital, Shatin, [4]Department of Surgery, Prince of Wales Hospital, Shatin, [5]State Key Laboratory of Phytochemistry and Plant Resources in West China, The Chinese University of Hong Kong, Shatin

Introduction and Project Objectives: The aim of this study was to investigate the effects of Gastrodiae Rhizoma – containing herbal formula (DCXF) in traumatic brain injury (TBI) rat model.

Methods: TBI was induced by the electromagnetic controlled cortical impact (CCI) device. DCXF were intragastrically administered daily for one week to the rats before CCI-TBI, and then DCXF treatments were continued post-TBI until the end of the experiments. After the TBI surgery, the animals were subjected to BBB integrity by Evans blue dye and brain water content assessments on day 3, Morris Water Maze test for cognitive assessment, spatial learning and memory were examined for 11 days, the motor coordination and maximal motor performance were tested using an acceleration rotarod motor test and the assessment of gait function was measured by CatWalk quantitative gait analysis test on day 3, 7 and 11, and histology and immunohistochemistry assessments of Nissl, GFAP, Iba-1, nestin in hippocampus nad cortex on day 11. The In vitro anti-inflammatory effects of DCXF were study by LPS-induced gene and protein expression of NO, PGE2, iNOS and COX-2. The NF-κB pathway was also measured by the expressions and phosphorylations of p65 and IκBα pathway.

Results: We demonstrated that herbal formula DCXF could protect the neuronal cell against oxidative insult and alleviate the injuries coming from TBI in rats. Treatment with DCXF significantly improved the learning ability and memory retention in Morris water maze test, and remarkably enhanced motor performances in acceleration rotarod motor test and catwalk quantitative gait analysis test after TBI. Moreover, DCXF treatment was able to reduce blood brain barrier permeability, brain edema, microglia and astrocyte activation, improve the proliferation of neural stem cells and decrease neurons loss in the brain with TBI. Besides, our in vitro studies also indicated that treatment with DCXF significantly suppressed the productions of NO and PGE2 through inhibitions of iNOS and COX-2 expressions in LPS-stimulated RAW 264.7 cells. DCXF significantly decreased IκBα phosphorylation, inhibited p65 expression and reduced p-p65 level. These results suggested the anti-inflammatory effect of DCXF was associated with the reduction of inflammatory mediators through inhibition of NF-κB pathway.

Conclusion: In conclusion, herbal formula DCXF is a potent neuroprotective agent and can impose healing effects in vivo.

Project No.: 12134111

HHS-23

Clinical Assessment of a Topical Application Containing Radix Rubiae for Plaque-Type Psoriasis - A Randomized, Double-blind, Vehicle-Controlled and Left-Right Comparison Pilot Study.

Lin Zhi-Xiu[1], Luk Nai-ming[2], Zee Benny Chung Ying[3], Leung Ping Chung[4], Zuo Zhong[5], Chan Yu Tat[1], Loo Steven[1]

[1]School of Chinese Medicine, Faculty of Medicine, The Chinese University of Hong Kong, [2]Dermatology Research Centre, Faculty of Medicine, The Chinese University of Hong Kong, [3]School of Public Health and Primary Care, Faculty of Medicine, The Chinese University of Hong Kong, [4]Institute of Chinese Medicine The Chinese University of Hong Kong, [5]School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong

Introduction: Psoriasis is a common chronic inflammatory skin disease for which currently there is no known cure. Our previous in vitro and in vivo studies have identified a Chinese herbal medicine named Radix Rubiae (茜草根) to have promising anti-psoriatic action.

Objectives: This study aimed to evaluate the clinical efficacy and safety of a topical preparation containing Radix Rubiae extract in patients with chronic plaque type psoriasis.

Methods:
Design: This is a 12-week, left-right intra-patient comparison, vehicle-controlled, randomized, assessor-blinded pilot clinical trial.
Setting: The study was conducted at The Chinese University of Hong Kong Chinese Medicine Specialty Clinic cum Clinical Teaching and Research Centre between February 2015 and April 2017.
Participants: Sixty patients with chronic plaque type psoriasis were enrolled.
Intervention: The patients were instructed to apply the Radix Rubiae-containing topical formulation to one side of the psoriatic lesion and the vehicle preparation to the opposite side of the lesion twice a day for a consecutive 12 weeks.
Outcome measures: The primary outcome assessment was performed using the scores of scaling, erythema, induration, and clearing percentage of target plaques by 2 blinded assessors after 6 and 12 weeks of intervention. Secondary outcomes included physician global assessment, quality of life (SF36) and impact of psoriasis questionnaire.

Results: The scores of induration and scaling showed statistically significant improvement in the active treatment side when compared with the vehicle controlled side after 12 weeks of intervention. The quality of life measure by SF36 remained no change after the treatment. The impact of psoriasis questionnaire showed much improvement after 12 weeks of treatment. Twenty-six (43.3%) participants dropped out during the study, of them 15 were due to some mild or severe adverse effects.

Conclusion: The study suggests the topical application of Radix Rubiae extract had some promising treatment effect for psoriasis; however, the active treatment involved certain degree of adverse effects. Further research is needed to reduce the possible adverse effects via optimizing the formulation making.

Acknowledgements: This study was supported by the Health and Medical Research Fund of the Food and Health Bureau, Hong Kong Special Administrative Region Government (Project no. 11121011; PI: Zhi-Xiu Lin, The Chinese University of Hong Kong). We are grateful to

Mr. Chun Kam Lee for his help in performing the outcome assessments.

Project No.: 11121011

HHS-24
Chinese Medicine Yuanhu Zhitong Prescription Alleviates Tau Pathogenesis and Ameliorates Memory in the Alzheimer's disease Models

Iyaswamy Ashok[1], Krishnamoorthi Senthil Kumar[1], Sreenivasmurthy Sravan G[1], Sandeep Malampati[1], Song Ju-Xian[2], Yang Chuan-Bin, Durairajan Siva Sundara Kumar[3], Li Min[3], Huang Chi-ying[4], Liu Yu-Wen[4]
[1]Hong Kong Baptist University, Hong Kong, [2]Medical College of Acupuncture-Moxibustion and Rehabilitation, Guangzhou University of Chinese Medicine, Guangzhou, China, [3]Department of Microbiology, Central University of Tamil Nadu, Thiruvarur, India, [4]Institute of Biopharmaceutical Sciences, National Yang Ming University, Taiwan

Introduction:
Background: Alzheimer's disease (AD) is a neurodegenerative disease characterized by the progressive memory dysfunction and the appearance of neurofibrillary tangles. We have identified a novel function of traditional Chinese medicine formula Yuanhu-Zhitong prescription (YZT) in treating AD mice models.

Objectives:
(1) To validate the neuroprotective effects of Yuanhu-Zhitong prescription (YZT, 元胡止痛散 in Chinese) in Alzheimer's disease (AD) mice models;
(2) To discover the molecular mechanisms of YZT and its multifunctional compounds using gene expression microarray and bioinformatics tools.

Methods: Liquid chromatography/quadrupole time-of-flight (LC-ESI-Q/TOF) was performed to quantify the chemical markers of YZT. Two-months old P301S Tau mice and six months old 3XTg-AD mice received two doses of YZT or vehicle in food admixture until 4- and 18- months old, respectively. Rotarod and Morris water maze test were used to assess motor function and memory, respectively. The differential extraction by ultracentrifugation followed by western blotting and immunohistochemistry were used to assess insoluble Tau deposition in the brain. The microarray experiments and Connectivity Maps (Clue) analysis was performed to reveal the up and down-regulated genes in the YZT, RC and RAD-treated SH-SY5Y cells expressing P301L Tau.

Results: From the LC-ESI-Q/TOF chromatograms of aqueous extracts of YZT, protopine, tetradydropalmatine and dehydrocorydaline are the most abundant compounds, followed by other isoquinoline alkaloids and imperatorin. Treatment with YZT significantly ameliorated the motor dysfunction and insoluble tau load learning deficits in P301S-Tau mice compared with vehicle control treatment. In 3XTg-AD mice, YZT treatment significantly ameliorated memory dysfunction and reduced insoluble phospho Tau species. According to microarray/CMaps, one of the mechanisms of action of YZT could be predicted as NF-kB inhibitor and participating in autophagy process. Finally, based on the differentially expressed genes from three hub genes, SQSTM1, TXNRD1, and HMOX1, YZT could be predicted to involve in NRF2-mediated Oxidative Stress Response. Similar analysis was performed and suggested that RC may be involved in Ubiquitination Proteasome pathway.

Conclusion: YZT decreases the phosphorylated, misfolded and total insoluble Tau as demonstrated in in vitro and in vivo studies, and YZT also enhances memory in 3XTg-AD mice. YZT could be a promising candidate for the treatment of AD in the future.

Project No.: 12132061

HHS-25
Impact of the Chinese herbal medicines on the combination therapy with clopidogrel and aspirin: pharmacokinetics and pharmacodynamics outcomes and related mechanisms in rats

Xiao Min[1], Qian Chenyu[1], Luo Xi[1], Yang Mengbi[1], Zhang Yufeng[1], Wu Cheyuen[2], Mok Chuntong[3], Lee Puiwai[3], Zuo Zhong[1]
[1]School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, [2]Institute of Integrative Medicine, Faculty of Medicine, The Chinese University of Hong Kong, [3]Department of Medicine and Therapeutics, Faculty of MedicineThe Chinese University of Hong Kong

Introduction and Project Objectives: Dual antiplatelet therapy (DAPT) with aspirin (ASA) and clopidogrel (CLP) has been consistently shown clinical effectiveness in patients with coronary artery disease. According to the literature, four traditional Chinese medicine (TCM) herbs effective for prevention cardiovascular diseases, namely Radix Salviae miltiorrhizae (Danshen), Radix Puerariae lobatae (Gegen), Radix Angelicae Sinensis (Danggui), and Rhizoma Chuanxiong (Chuanxiong), are of high potential to be co-administered during DAPT. The current study is proposed aiming to preliminarily evaluate the impact of these four commonly used Chinese medicinal herbs on the pharmacokinetics and pharmacodynamics of the combination therapy with clopidogrel and aspirin and its relevant outcomes and mechanisms.

Methods: In order to mimic the standard dosing regimen for DAPT in human, various Sprague-Dawley rats treatment groups were received a bolus oral dose of DAPT on day 1 followed by DAPT for consecutive 13 days in absence and presence of orally co-administered four TCM herbs (Danshen, Gegen, Danggui and Chuanxiong) at their low and high doses. On day 14, serial blood samples were collected after dosing to obtain the plasma concentrations of ASA, CLP and their corresponding metabolites by LC/MS/MS. At the end of last blood sampling point of each rat, about 4.5 ml of whole blood were collected to estimate the prothrombin time from each treatment groups. After all the blood sampling, the rats were sacrificed followed by collecting their livers for evaluations of enzyme activities and expressions in the related liver microsome preparations and stomach tissues for evaluations of their potential ulcer index.

Results: The results demonstrated that co-administration of Gegen and Danggui significantly altered the pharmacokinetics of ASA and CLP in DAPT with increased systemic exposure of ASA and CLP respectively. Although minimal impact on aspirin esterase activity for all co-administered herbs, significant inhibition on rCyp2c11 and carboxylesterase activities were observed for DAPT with Danshen, Gegen and Danggui co-treatment. In addition, a trend of decrease in PT of DAPT in presence of Gegen, Danggui and Chuanxiong was noticed. Nevertheless, all the treatments did not cause detectable

changes in COX and P2Y12 mRNA and protein expressions.

Conclusion: In conclusion, it was demonstrated that co-administration of Gegen and Danggui could lead to altered pharmacokinetics of DAPT with significant inhibition on rCyp2c11 and carboxylesterase activities. Although Gegen, Danggui and Chuanxiong might potentially offset the anticoagulant activity of DAPT, the overall pharmacodynamics outcome was not considered to be harmful due to lack of risk in bleeding, which warrant further verification for its clinical impact.

Project No.: 12131521

HHS-26
A Study of Efficacy on the Combination Use of Anti-osteoporosis Drug with Topical Chinese Herbal Paste on Facilitation of Fracture Healing

Siu WS[1], Hung LK[2], Ko CH[1], Leung PC[3]
[1]*Institute of Chinese Medicine, The Chinese University of Hong Kong,* [2]*Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong,* [3]*State Key Laboratory of Research on Bioactivities and Clinical Applications of Medicinal Plants, The Chinese University of Hong Kong*

Introduction: Patients with fracture occupy a lot of hospital beds and demand a lot of special services. Pharmaceutical agents advocated for fracture healing are controversial. Co-treatment using pharmacological medication and Traditional Chinese Medicine might be a beneficial intervention to enhance fracture healing.

Objectives: To study the efficacy of strontium ranelate (SrR) and a Chinese herbal formula containing Carthami Flos, Dipsaci Radix and Rhei Rhizoma (named CDR) on the facilitation of fracture healing, and find out if any synergistic effect exists.

Methods: This project was conducted in two parts: In vitro and in vivo. Part 1, bone-marrow mesenchymal stem cells (BMSC) isolated from rats, UMR106 and RAW264.7 cells were used. The BMSC and UMR106 were used to study the cytotoxic effect and find out the optimal concentrations of the CDR via MTT assays, as well as the bone formation properties of CDR and SrR via BrdU and alkaline phosphatase (ALP) assays. Raw264.7 was used to study the anti-osteoclastogenic and anti-inflammatory properties of CDR and SrR via TRAP and Griess assay, respectively. Part 2, Rats with artificially produced tibial fracture were treated with different regimens consisting of either oral SrR or topical CDR (supplemented with 2% borneol), or their combination. Micro-computed tomography and biomechanical tests were utilized to measure the differences in the physical and biomechanical properties of the calluses. Histomorphometry and measurement of serum biomarkers were checked to analyze the underlying mechanisms.

Results: The in vitro results showed that SrR and CDR were non-cytotoxic and increased the proliferation of BMSC at low concentrations. The combination of CDR and SrR also showed an additive effect on the promotion of ALP activities of BMSC. SrR and CDR alone reduced osteoclast formation and the effective concentration of SrR could be reduced in the presence of CDR. The in vivo results illustrated an additive effect of CDR on SrR on the load bearing strength, the size and the bone density of the callus of the fractured tibia.

Conclusion: This integrative approach by combining oral SrR and topical CDR was effective on promoting fracture healing probably through the additive effects on osteogenesis promotion as well as osteoclastogenesis suppression.

Project No.: 12130581

HHS-27
Tetramethylpyrazine as a Novel HIF Activator for Promoting Angiogenesis and Osteogenesis During Skeletal Regeneration

Wan C, Tsang WP, Zhang F
School of Biomedical Sciences, The Chinese University of Hong Kong

Introduction and Project Objectives: In clinic, impaired bone repair or regeneration including fracture non-union, large bone defects, and osteoporosis are difficult skeletal disorders that cause tremendous pain and cost to the patients and society. The pathology of osteoporosis and impaired bone repair is characterized by less capacity of bone formation associated with decreased vascularity. As current therapies remain to be unsatisfied, novel therapeutic agents for patients with impaired bone repair have significant clinical demand. Hypoxia inducible factor-1 alpha (HIF-1a) has been identified as a key transcription factor that involves in the coupling of angiogenesis and osteogenesis during skeletal development and regeneration. This study aims to discover novel small molecule targeting the HIF-1a pathway to enhance skeletal regeneration.

Methods: Small molecule screening and identification based on osteogenic and angiogenic phenotypes and functional assays were performed. Osteoblast and endothelial cell models, and ovariectomy (OVX)-induced osteoporosis and long bone fracture mouse models were employed to evaluate the pharmacological effects and the underling molecular mechanisms of the candidate molecule.

Results: We identify tetramethylpyrazine (TMP), an active ingredient from Ligusticum Wallichii, upregulates HIF-1a and induces its nuclear translocation in osteoblasts. TMP not only activates HIF-1a downstream targets but also enhances osteogenic marker genes expression. Intriguingly, TMP remarkably upregulates adenomedullin, a downstream target of HIF-1a and a potent stimulator of osteoblast function. Those enhancement effects are attenuated by Cre recombinase mediated deletion of HIF-1a in osteoblasts carrying HIF-1a loxP-flanked allele. TMP treatment rescues bone loss in OVX-induced osteoporosis mouse model. This phenotype is accompanied by enhanced angiogenic responses of TMP. In a mouse long bone fracture model, local delivery of TMP at the fracture site results in significantly increased bony callus volume with improved biomechanical properties of the newly formed bone at the consolidation phase of bone healing.

Conclusion: Our results suggest that TMP may serve as a potent anabolic agent to promote angiogenesis and osteogenesis for patients with osteoporosis or fracture repair.

Project No.: 12131041

HHS-28
Biomedical effects of green tea extracts on experimental age-related macular degeneration

Ng TK[1], Yang Y[1], Chu KO[1], Pang CP[1], Chan SO[2]
[1]Department of Ophthalmology & Visual Sciences, The Chinese University of Hong Kong, [2]School of Biomedical Sciences, The Chinese University of Hong Kong

Introduction and Project Objectives: Age-related macular degeneration (AMD) is a leading cause of irreversible visual impairment and blindness in most developed countries, affecting 50 million elderlies worldwide. It is a progressive neurodegenerative disease affecting the macula and resulting in a significant loss of central vision in advanced stages. Oxidative stress and inflammation are the pathological initiators in AMD pathogenesis. Since green tea extracts (GTE) exhibit anti-oxidative and anti-inflammatory actions, we hypothesized that GTE and its catechin constituents ameliorate sodium iodate-induced retinal degeneration in an experimental AMD model by counteracting oxidative stress.

Methods: Retinal degeneration was induced in adult Sprague-Dawley rats by intravenously injecting single dose of sodium iodate. GTE (Theaphenon-E) or combinations of its catechin constituents, including (-)-epigallocatechin gallate (EGCG), were administered intra-gastrically before injection. Photoreceptor degeneration was monitored by in vivo imaging and histological analyses. In addition, the oxidative status in the retina was also evaluated.

Results: Live imaging analysis using confocal scanning laser ophthalmoscopy and spectral-domain optical coherence tomography showed a progressive increase of degenerating profile across the retinal surface and decrease in thickness of outer nuclear layer (ONL) at Day-14 of post-injection. These lesions were significantly ameliorated by Theaphenon-E and catechin combinations with EGCG. Catechins with exclusion of EGCG did not show obvious protective effect. Histological analyses confirmed that Theaphenon-E and catechins containing EGCG protect the retina by reducing ONL disruption. Retinal protective effects were associated with reduced expression of superoxide dismutase, glutathione peroxidase and caspase-3, and suppression of 8-iso-Prostaglandin F2α generation in the retina.

Conclusion: In summary, GTE and its catechin constituents are potent anti-oxidants that offer neuroprotection to the outer retinal degeneration after sodium iodate insult, which EGCG is the most active constituent.

Project No.: 12130791

HHS-29
Therapeutic Treatment Against Ocular Inflammation by Green Tea Extract and Catechins in Experimental uveitis

Chu WK, Chu KO, Ng TK, Chan SO, Pang CP
The Chinese University of Hong Kong

Introduction and Project Objectives: To determine the treatment effects of green tea extract (GTE) and catechins against ocular inflammation in experimental uveitis models.

Methods: Endotoxin-induced uveitis (EIU) rat model and experimental autoimmune uveitis (EAU) mouse model. Ocular inflammation in EIU model was assessed by slit lamp photography, whereas that in EAU model was assessed by confocal scanning laser ophthalmoscopy, optical coherence tomography (OCT), fundus fluorescein angiography (FFA) and electroretinography (ERG). Tissue cells and molecules were investigated by confocal microscope, RTPCR, GCMS, and LCMSMS. After EIU induction, 275 and 550 mg/kg GTE were intragastrically fed into the rats 2, 8, 26, 32 hours after LPS injection. For the EAU model, 137.5 and 275 mg/kg GTE or 96.25 and 192.5 mg/kg EGCG catechins were fed once every two days starting from 5 days prior to EAU induction through day 21 post-immunization. The degree of ocular inflammation, amount of infiltrating cells and ocular histology were evaluated. Expression levels of targeted pro-inflammatory factors were determined in appropriate samples including plasma, humor, ciliary body, and retina tissues. Catechins in tissue cells were quantified for correlations with the molecular effects.

Results: Our results revealed the treatment effects of GTE and catechins on ocular inflammation in two established experimental models and provided new insights into the protective mechanisms of GTE and catechins on uveitis pathogenesis.

Conclusion: Our assessments showed that administration of GTE and catechins alleviated EIU and EAU in morphology and gene expressions, providing evidences for their therapeutic effects in ocular inflammations.

Project No.: 12130811

HHS-30
Comparative Effectiveness Analysis of Lung Cancer Data from Randomized Clinical Trials and Observational Studies

Pang H[1], Stinchcombe TE[2], Lee AW[3], Lee Victor[3], Lam Wendy[1], Vokes EE[4], Wang X[5]
[1]School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, [2]Duke Cancer Institute, Duke University Medical Center, [3]Department of Clinical Oncology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, [4]Department of Medicine, University of Chicago Medicine and Biological Sciences, [5]Department of Biostatistics and Bioinformatics, Duke University Medical Center

Introduction and Project Objectives: Elderly lung cancer patients are less likely than younger patients to participate in clinical trials. With sparse and conflicting findings, the optimal chemoradiotherapy and management of elderly patients is unclear. To conduct analyses for clinical trials and observational studies on the relative efficacy of chemoradiotherapy treatment paradigms in locally advanced NSCLC. To develop novel statistical methods for a unified analysis that yields efficient and valid estimation of treatment effect.

Methods: For the analysis of trials and observational data, the primary endpoint was overall survival. Statistical methods for selection bias control with propensity score inverse weighting was used to estimate treatment effects to compare the chemoradiotherapy treatment paradigms. We also used simulation to evaluate the finite sample properties of the new statistical estimators

under various conditions in terms of bias and efficiency. Along with the single-source analysis, the novel statistical method was used as a part of the unified approach to address the comparative effectiveness question of various different chemoradiotherapy treatment paradigms versus sequential chemoradiotherapy.

Results: Propensity score adjusted models for locally advanced NSCLC elderly patients showed significant pairwise comparison differences between consolidation chemoradiotherapy vs. sequential chemoradiotherapy, and induction chemoradiotherapy vs. sequential chemoradiotherapy (p

Conclusion: Adequate adjustments for patient characteristics can reduce bias. Combining trials and observational data can provide useful information on comparative treatment effectiveness.

Project No.: 12133251

HHS-31
The effects of the IKKß-specific inhibitor PS1145 on tumor formation and metastasis in nasopharyngeal carcinoma

Lung Hong Lok[1], Kan Rebecca[2], Chau Wai Yin[1], Li Lung Maria[2]
[1]Department of Biology, Hong Kong Baptist University, [2]Department of Clinical Oncology, University of Hong Kong

Introduction and Project Objectives: We and others have previously shown that the canonical nuclear factor kappa-B (NF-κB) pathway is essential to nasopharyngeal carcinoma (NPC) tumor development and angiogenesis, suggesting that the NF-κB pathway, including its upstream modulators and downstream effectors, are potential therapeutic targets for NPC. The inhibitor of upstream IKB kinase (IKK), PS1145, is a small molecule which can specifically inhibit the IκB phosphorylation and degradation and the subsequent nuclear translocation of NF-κB. The present study aims to determine the anti-tumor activity and drug resistance mechanism of PS1145 on NPC.

Methods: The anti-tumor and anti-metastasis effects of PS1145 were tested by using a panel of NPC cells lines and the nomal immortalized nasopharyngeal epithelial cell lines included as normal controls. Various in vitro and in vivo cell growth, migration/invasion, apoptosis and cell cycle, tumor formation, and metastasis assays were used to test the effects of PS1145.

Results: PS1145-alone could effectively inhibit both the in vitro and in vivo cell gowth of various NPC cell lines, it was likely due to cell apoptosis. Apparently no adverse effects were observed in the animal study. In addition, the cell mobility was also suppressed in the presence of PS1145. Drug resistance aganist PS1145 seems to be associated with the increased levels of active NF-κB p65 and change of expression levels of of kruppel-like factor 4.

Conclusion: As can be seen, PS1145 appears to be a safe agent for animal experiments and its effects are tumor-specific, and the proteins associated with the drug resistance of PS1145 are implied.

Project No.: 12133131

HHS-32
The use of curcumin to circumvent cisplatin resistance in nasopharyngeal carcinoma

Wong Thian-Sze, Gao Wei, Chan Yu-Wai
Surgery, The University of Hong Kong

Introduction and Project Objectives: Nasopharyngeal carcinoma (NPC), also commonly known as the "Canton tumour", is endemic in Southern China including Hong Kong. NPC can acquire resistance to cisplatin during treatment which affects the treatment outcome. At present, there is still no effective method to overcome cisplatin resistance in NPC. The current study aims to examine whether curcumin (diferuloylmethane), a natural polyphenol isolated from the rhizome of Curcuma longa, can be used to circumvent cisplatin resistance in NPC.

Methods: Cisplatin-resistant NPC cell line was developed by chronic treatment of cisplatin. In vitro toxicity assay was used to confirm the resistance level of cisplatin-resistant cell line. Liposomal curcumin was prepared by thin-film evaporation. NPC xenograft was generated in nude mice to examine the therapeutic effects of cisplatin and curcumin.

Results: In vitro toxicity assay indicated that cisplatin and liposomal curcumin could significantly inhibit proliferation of the cisplatin-resistant cells. Combination use of cisplatin and liposomal curcumin significantly enhanced the treatment efficacy. Further, combined treatment of NPC xenograft with liposomal curcumin and cisplatin blocked the progression of NPC xenograft in pre-clinicial model.

Conclusion: Chronic exposure of NPC cells to cisplatin can induce cisplatin resistance. Combination treatment using curcumin and cisplatin offers better efficacy in comparison to the single agent treatment on cisplatin-resistant NPC.

Project No.: 12133541

HHS-33
Association study of susceptibility genes in Wnt signaling pathway with attempted suicide

Waye MMY[1], Wing YK[2], Lam MHB[2], Tsui SKW[3], Rao S[1], Siu CO[4]
[1]The Nethersole School of Nursing, The Chinese University of Hong Kong, [2]Department of Psychiatry, The Chinese University of Hong Kong, [3]School of Biomedical Sciences, The Chinese University of Hong Kong, [4]COS and Associates Ltd, Central, Hong Kong

Introduction and Project Objectives: The suicide rate in the Chinese population is estimated to be around 12.7 per 100,000. Moreover, the number of suicide victims in China has been estimated to account for approximately 42% of suicide death all over the world. Although the pathogenesis of suicide attempts (SA) is still not explained clearly, it is generally believed that SA is affected by a combination of genetic variants, environmental factors, psychiatric disorders, clinical and psychological correlates. For genetic variants, most of the previous studies focused on the neurotransmitter system, mainly including the serotonergic, dopaminergic and glutamatergic systems. Our study focused on the Wnt signaling pathway which has

also been shown to be important in neuronal differentiation and development.

Methods: Our team performed a pilot genome-wide association study (GWAS) in Hong Kong Chinese samples constituted of 48 suicide attempters and 48 non-suicide attempters, both with major depressive disorder (MDD).

Results: Association analyses identified 8 candidate loci associated with SA passing the genome-wide suggestive threshold. WNT2B (Wnt family member 2B) is the most significantly associated signal with suicide attempts and withstands the multiple corrections out of the 26 candidate SNPs we tested. WNT2B was reported to function as the stem cell factor for neural or retinal progenitor cells during embryogenesis. Four single nucleotide polymorphisms (SNPs) located in a near physical position in Chr.11 that cover the ICEBERG gene in a linkage disequilibrium block (ICEBERG also is known as Caspase 1 inhibitor Iceberg) also associated with SA. The finding was also confirmed by gene-based analysis of the GWAS genomic data, which listed the ICEBERG gene as the top 1 signal associated with SA (p-value=1.70e-05). We have also performed replication studies for the top signals and tagging SNPs in the ICEBERG gene in an independent larger Hong Kong Sample set. Statistical analyses suggested that these SNPs were also significantly associated with SA. As the ICEBERG protein was involved in a negative feedback loop of inflammatory response system (IRS), the findings of this project suggested that the IRS is involved in the pathogenesis of suicidal behavior in Chinese and that the ICEBERG gene is an important biomarker.

Conclusion: An effective multifactorial risk model consisted of the interaction of the HOMER1 polymorphism and the NEO-C personality dimension was successfully identified and evaluated to have improved performance of explaining the variance of SA. We found 5 SNPs (of WNT2B and ICEBERG genes) that associated with SA in the patients with major depressive disorder we tested.

Project No.: 12131101

HHS-34

The effectiveness of group behavioural activation with mindfulness in the treatment of subthreshold depression in primary care in Hong Kong

Wong SYS[1], Tang WK[2], Leung MK[3], Li CC[4], Au AM[5], Yip BHK[1]

[1]Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, [2]Department of Psychiatry, The Chinese University of Hong Kong, [3]Department of Family Medicine, Hospital Authority, [4]Department of Psychology, The University of Hong Kong, [5]Department of Applied Social Sciences, The Hong Kong Polytechnic University

Introduction and Project Objectives: Sub-threshold depression is highly prevalent in primary care settings and is associated with significant reduction in quality of life, increased mortality and healthcare burden. To conduct a randomized controlled trial to assess the effectiveness of group behavioural activation with mindfulness (BAM) for reducing subthreshold depression in primary care in Hong Kong.

Methods: Adult patients aged 18 years or older with subthreshold depression were recruited from 16 public primary care clinics in Hong Kong and were randomly assigned to behavioural activation with mindfulness or care as usual (CAU) group. BAM group was provided with eight 2-hour weekly behavioural activation treatment with mindfulness by trained allied healthcare workers. Patients in the CAU received usual medical care with no additional mental interventions. The primary outcome was depressive symptoms measured by Beck Depression Inventory (BDI)-II at 12 month. The secondary outcomes included incidence of major depressive disorder at 12-month. Quality of life, Activity and Circumstantial Change, functional impairment, health service utilization, satisfaction, and anxiety were assessed at baseline, post-intervention, 5-month and 12-month.

Results: 115 participants were randomly allocated to BAM and 116 participants to CAU group (a total of 231). At 12-month, ANCOVA results demonstrated a statistically significant effect of BAM in reducing depressive symptoms when compared to CAU group (between-group mean difference=-3.85, 95%CI: -6.36 to -1.34; Cohen d=-0.46, 95%CI: -0.76 to -0.16). BAM group had lower incidence of major depressive disorder (10.8% in BAM group vs. 26.8% in CAU group) at 12-month. No significant differences were reported on other secondary outcomes at 12-month between the two groups.

Conclusion: Group behavioural activation with mindfulness appears to be beneficial in decreasing depressive symptoms and reducing the incidence of major depression among people with subthreshold depression in primary care. With proper training and supervision, this intervention can be learned by allied health professionals and can be implemented in local primary care settings.

Project No.: 11120501

HHS-35

The Role of Napping in Reducing Negative Attentional Bias in Depression

Lau KNT[1], Chan CS[2], Tseng CH[3], Lam YC[4], Cheng WY[4], Tse MSD[4], Chung KF[5], Wing YK[6], Lau EYY[4]

[1]Clinical Psychology Service, The Hong Kong Children and Youth Services, [2]Department of Psychology, The University of Hong Kong, [3]Research Institute of Electrical Communication, Tohoku University, Sendai, Japan, [4]Department of Psychology, The Education University of Hong Kong, [5]Department of Psychiatry, The University of Hong Kong, [6]Department of Psychiatry, The Chinese University of Hong Kong

Introduction and Project Objectives: Cognitive theories of depression hypothesized that affective-cognitive processing bias of emotional information, such as human faces, is related to the maintenance of depression. Sleep disturbances were found to maintain depression, and the possible role of sleep in the maintenance of depression through emotional processing bias still requires exploration. To further examine the specific sleep mechanism of the maintenance of depression, we focused on one of the affective-cognitive features in depression: attentional bias towards emotional faces. This study adopted a napping design to examine how sleep is associated with attentional bias towards emotional faces among patients with major depressive disorder (MDD).

Methods: Participants (n = 106, 18-60 years) were assessed by the research version of Structured Clinical Interview for DSM-IV-TR Disorders (SCID), clinician-rated Hamilton Depression Scale (HAM-D), self-reported Beck Depression Inventory-II (BDI-II) and Insomnia Severity Index (ISI). SCID identified 45 MDD patients (mean HAM-D score = 14.53, mean BDI-II score = 23.58, 87% female) and 61 non-depressed control (mean HAM-D score = 1.48, mean BDI-II score = 3.81, 69% female). All participants were randomly assigned to wake, 30-min nap and 90-min nap conditions. They completed the dot-probe task measuring attentional bias towards sad and happy faces before and after wake or nap.

Results: Repeated-measures MANCOVA controlling for sleep quality, diagnosis of insomnia, insomnia symptoms, positive and negative mood changes showed that participants with MDD showed higher attentional bias towards sad faces and lower attentional bias towards happy faces after wakefulness, but not after napping. On the other hand, the non-depressed controls had no significant changes in attentional bias after wakefulness and napping.

Conclusion: Our data provided the first evidence that napping is beneficial in ameliorating the escalating attention towards sad faces and declining attention towards happy faces among MDD patients throughout the day. Clinicians may consider the potential role of sleep on attentional bias in pharmacological and psychological interventions of depression.

Project No.: 12132951

HP-1
預防認知障礙 - 健體動腦齊實踐

CHAU YM, Cheong KM
Social Service Office, The Association of Evangelical Free Churches of Hong Kong

Introduction and Project Objectives: The Campaign was launched by AEFCHK-E.F.C.C.-Mei Foo Elderly Centre in 2015. The project aimed at raising the public awareness on cognitive health and the needs of dementia sufferers and their carers as well as offering trainings, preventive and support services to the people with Mild Cognitive Impairment (MCI) at 55 or above with reference to a proved significantly effective integrated model developed by a local researcher. Through the project, people at risk were identified and supported at community level before their cognitive problems getting further deteriorated.

Methods: A series of public education activities on dementia prevention were launched to promote public awareness on dementia prevention and caring to the patients and their families including roadshows, talks, caring card design competition and publication of project booklet. General screenings were conducted in community following with risk identifications and support services, so, the people at risk were handled. Various cognitive training groups such as board games, music intervention were held regularly to the targeted people for their development of long-term habit for cognitive health and social support network. An individual rewarding scheme (「健體動腦齊實踐」獎勵計劃) was used to encourage their involvements and sustainability.

Results: The project reached 6,089 man-time through public education programs and 852 questionnaires were collected in which more than 90% of them responded positively. Cognitive assessments were conducted to 351 community members while 33% of them had been classified as MCI and 154 of them have joined the rewarding scheme of project with over 80% participants met the rewarding scheme's targets.
Two assessment tools (MoCa and GDS-15) were used for outcome measurements. Comparing the pre- and post-test results, cognitive ability of around 73% of the MCI participants were enhanced and half of their emotional status has been improved. 90% of the participants who joined the cognitive training activities agreed that the campaign helped to widen their social network.

Conclusion: The public education was effective and the cognitive assessment services, cognitive stimulating activities, as well as cognitive training of the project were able to identify the MCI elderly in the community and to provide services at earlier stage. It showed that the project helped the targets to maintain their cognitive ability, and help them to establish social support for fighting against dementia.

Project No.: 28140174

HP-2
School Children: An Active Role in Disease Prevention

Or PL[1], Ching TY[2], Chung WY[1]
[1]Department of Health and Physical Education, The Education University of Hong Kong, [2]WHO Collaboration Centre for Infectious Disease Epidemiology and Control, School of Public Health, The University of Hong Kong

Introduction:
Background:
Influenza outbreaks occur every year. Pathogens, such as influenza viruses, can spread easily. Non-pharmaceutical interventions, such as hand hygiene, if implemented properly, can help stop the spread of pathogens in community settings (Pong, Holiday & Fernie, 2018).

Objective:
To evaluate whether hand hygiene compliance training of Hong Kong preschoolers improves their hand hygiene knowledge and performance, and reduces their absenteeism resulting from influenza symptoms.

Methods: This was a quasi-experimental study with pretest and posttest design. Preschoolers underwent a program on hand hygiene. Before and after the program, their hand hygiene knowledge were assessed by ten "true/false" questions and their handwashing skills by photos of their hands taken before and after handwashing. To determine whether a causal relationship existed between compliance and absenteeism, their absent data were collected over three months for analysis.

Results: A total of 114 K3 students had consented to participate in the program; however, 4 students had to drop out because of sickness. Of the remaining 110 preschoolers, 64.5% were boys and 35.5% were girls. The preschoolers had to answer 10 true or false questions on hand hygiene to enable the research team to compare

their knowledge before and after the training program. It was observed that the percentages in correct scores for 8 of the questions had increased with the exception of 2 questions (ie, questions 6 and 9), the percentages of which had remained the same without any change (Table 1).

After the program, the average percentages of colored (thoroughness of handrubbing) areas before handwashing were 87.7% on both hands and 83.4% on the backs of their hands. (Fig 1). After handwashing, the remaining colored (dirty) areas on the preschoolers' hands represented the part that had not been washed properly. A paired Student t test was performed to measure the differences in the percentages of the colored (dirty) areas after handwashing before and after the program, and significant differences were found on the colored (dirty) areas on the backs of fingers with P = .002, thumbs with P = .001, finger tips with P = .001. (Fig 2). The findings showed that preschooler absence owing to influenza symptoms had decreased in each of the 3 months, from 31%-30% and then to 25%, showing a decreasing trend in the 3 months in all participating kindergartens.

Conclusion: After the training program, the participants' hand hygiene knowledge and performance considerably improved. They washed their hands more thoroughly and there was a significant reduction in absences due to influenza.

Project No.: 29150014

HP-3
Empowering Senior Citizens to Advance Care Planning through Micro-movies

Chan HYL[1], Chan KS[2], Ng JSC[2], Ko PS[3], Ma TCM[2], Chan IKY[4], Chan CWH[1], Lee DTF[1]

[1]The Nethersole School of Nursing, Faculty of Medicine, The Chinese University of Hong Kong, [2]Pulmonary & Palliative Care Unit, Department of Medicine, Haven of Hope Hospital, [3]Palliative Care, Kowloon East Cluster, Hospital Authority, [4]Active Ageing Service, Hong Kong Christian Service

Introduction and Project Objectives: Empowerment is a process of supporting people to develop the abilities to exert control over their life situations. Evidence have shown that people generally lack insights of the possible health changes and care options in the last phase of life, given that the topic is deemed as cultural taboo. Their unpreparedness often resulted in family disputes, complicated grief, mistrust towards health professionals and high healthcare utilisation. The goal of this project was to develop a series of culturally-sensitive micro-movies for promoting advance care planning (ACP), thereby empowering people to think ahead for end-of-life care. The objectives were to enhance the public awareness towards ACP; promote their self-efficacy in ACP and equip health professionals in facilitating ACP.

Methods: This project entitled 吾可《預・計》was underpinned by the elements of empowerment, namely awareness, access to information, health literacy and self-efficacy in making decisions. It comprised three phases: (1) development and validation of project deliverables; (2) 3-hour ACP training workshops; and (3) 90-minute ACP educational talks for community-dwelling senior citizens aged 55 years and above.

Results: Three health professional training workshops and eight public talk were conducted in four District Elderly Community Centres (DECC) and Neighbourhood Elderly Centres (NEC). There were approximately 320 participants attended the talks and 69 health professionals joined the workshops. At baseline, most of the participants had never discussed with others their end-of-life care wishes. Following the talks, there was significantly less participants remained uncertain towards their end-of-life care preferences ($p < 0.001$) and their readiness towards communicating and documenting their care preferences were significantly increased ($p < 0.001$). The majority of them found the talk easy to understand and disagreed that the issues covered were sensitive. The health professionals generally appreciated the workshops because relevant training are lacking in the local community.

Conclusion: This is one of the first health promotion projects in Hong Kong developing specific resources to empower senior citizens and health professionals for ACP. It was successful with reference to the RE-AIM evaluation framework because the number of participants exceeded expectation; the project was effective in improving their self-efficacy in ACP; the team was invited by various non-government organizations and media to share the project deliverables and deliver training.

Project No.: 29150504

HP-4
An education programme: To prepare and empower staff for "Care of the imminent death in the residential home" for sustainability of "Dying in Nursing Home (DIN)" service in the community, outside the hospital.

Lam YT

Christine Haven of Hope Nursing Home, Haven of Hope Christian Service

Introduction and Project Objectives: The policy of dying in the hospital is a common practice in Hong Kong that people can hardly find dying in the community in Hong Kong. Haven of Hope Nursing Home has voluntarily pioneered the project of "Dying in Nursing Home" (DIN) since 2000. The experience accumulated by conducting 120 deaths (10% of the total deaths) in our home up to 2018 for 18 years has marked the landmark of success to make the dying in the community possible & sustainable. The sustainability of DIN service requires the transfer of appropriate attitude, knowledge and skill through education and clinical practice to staff. An education programme is designed for promotion of Dying in Nursing Home" service for HOHCS staff & the residential homes in community.

Methods:

The education programme is scheduled:

1. Part I – Training course in form of lecture and workshop for 3 days in form of lecture, worshops and sharing by the experienced frontline and professional staff
2. Part II – Clinical placement of "Care of imminent death" at Haven of Hope Nursing Home for 1 day

Method/implementation for:

1. Nurses, social workers, from HOHCS and partner nursing homes from the community.
2. Personal care workers from HOHCS.

Results:
1. Instead of 85%,the actual attendance rate is increased to 137% for Part I and 123.2% for part II of the participants from HOHCS and network partners .
2. A training manual named 「安享終老院舍中」服務培訓手冊 and a Press conference presentation on 9.6.2017 for promotion of the training manual to the government officials, health care institutions, NGOs & residential homes under SWD for knowledge transfer.

Conclusion: With the lecture, worshops, personal sharing, the educational programme has demonstrated the vivid experience that the participants have witnessed during the process of training. After the training, there were changes in mind set and increase in acceptance in the concept of "Dying in Nursing Home Service" more readily, via the pre and post training questionnaires. 1 Nursing Home has started the "Dying in Nursing Home" Service in the past 2 years after attending this training in 2017. A Press conference on 9.10.2018 onto the cost calculation of "Dying in Nursing Home Service" can have annual saving up to HK$300,000,000 to the Health Care Expenses in Hong Kong if the "DIN" service can be practiced at all the residential homes in Hong Kong.

Project No.: 07140065

AMR-1
Hypoxia-Induced Caveolin-1 Drives Tumorigenesis and Metastasis by Activation of NF-κB/S100P Pathway in Hepatocellular Carcinoma

Mao XW[1], Wong SYS[1], Tse EYT[1], Ko FCF[1], Tse SK[1], Yeung YS[1], Man K[2], Lo RCL[1], Ng IOL[1], Yam JWP[1]
[1]Department of Pathology, The University of Hong Kong, [2]Department of Surgery, The University of Hong Kong

Introduction and Project Objectives: In solid tumors, hypoxia triggers an aberrant vasculogenesis, enhances malignant character, and elevates metastatic potential. Clinically, intratumoral hypoxia is an indicator of poor prognosis and correlates with an increased risk to develop metastasis. The plasma membrane organizing protein caveolin-1 (Cav1) is increased in a variety of cancers, including hepatocellular carcinoma (HCC), where it contributes to metastatic capability. However, the reason for the elevation of Cav1 in tumor cells and the mechanistic basis for its contributions to metastatic risk are not fully understood.

Methods: The expression of Cav1 in normal liver and HCC cell lines under normoxia and hypoxia was analyzed by quantitative PCR and immunoblotting. In HCC xenografts, Cav1 expression and regions of hypoxia were revealed by immunohistochemistry. Stable clones of control and Cav1 knockdown cells were established and subjected to various in vitro and in vivo functional assays. Gene expression profiling of control and Cav1 knockdown cells was conducted to search for the downstream targets of Cav1. To study whether the functions of Cav1 was mediated by S100P calcium binding protein, the identified downstream target of Cav1, S100P expression was silenced in Cav1 knockdown cells. The S100P silenced cells were subjected to functional characterization. Western blot analysis was performed to examine the expression of potential molecular players that mediate the regulation of S100P by Cav1. The expression of S100P in HCC tissues was examined was to reveal the clinical relevance of S100P in HCC.

Results: In this study, we found that hypoxia elevated Cav1 expression in HCC cell lines. In addition, hypoxic region of HCC xenografts displayed elevated expression of Cav1. Hypoxia promoted HCC cell migration and invasion and distant metastasis to lungs in nude mice. However, such promoting effect was abolished in Cav1 knockdown cells. Gene expression profiling revealed that hypoxia-induced Cav1 functioned as a positive regulator of S100P by the activation of nuclear factor kappa B (NF-κB) pathway. The elevation of S100P under hypoxia was abrogated by silencing of Cav1 or NF-κB. Conversely, restoration of S100P in Cav1 knockdown cells rescued the migratory potential of HCC cells along with tumor formation and lung metastasis. In clinical specimens of HCC, S100P overexpression was significantly correlated with venous invasion, microsatellites, direct liver invasion and absence of tumor encapsulation.

Conclusion: Our findings demonstrated hypoxia-induced expression of Cav1 in HCC cells enhances their invasive and metastatic potential by the upregulation of NF-κB/S100P pathway.

Project No.: 02132846

AMR-2
RhoE/ROCK2 Regulates Chemoresistance Through NF-κB/IL-6/STAT3 Signaling in Hepatocellular Carcinoma

Ma W, Sze KMF, Chan LK, Lee JMF, Wei L, Wong CM, Lee TKW, Wong CCL, Ng IOL
Pathology, The University of Hong Kong

Introduction and Project Objectives: Liver cancer (hepatocellular carcinoma, HCC) is a major malignancy worldwide and the second commonest fatal cancer in Southeast Asia and China including Hong Kong, due to the high prevalence of hepatitis B viral infection. HCC is highly chemoresistant, limiting treatment options to patients. There is an urgent need to delineate the underlying molecular mechanism of HCC chemoresistance so as to identify novel therapeutic targets for this aggressive cancer. Small Rho GTPase (Rho) and its immediate effector Rho kinase (ROCK) are reported to regulate cell survival. Deregulation of Rho GTPase pathway is demonstrated to play important roles in HCC tumorigenesis, but the detailed molecular mechanism remains largely unknown. We had previously shown that Rho/ROCK signaling was highly activated in HCC. In addition, we had shown that RhoE is frequently downregulated in human HCCs and acts as a metastasis suppressor, whereas ROCK2 is upregulated in human HCCs. RhoE/Rnd3 belongs to the Rnd subfamily of the Rho GTPase which lacks the intrinsic GTPase activity.

Methods: Conventional chemodrugs cisplatin and doxorubicin and ROCK inhibitor were used to test chemoresistance. In vitro HCC cell models and in vivo nude mouse xenograft models were used. Quantitative PCR and western blot analyses were used to assess expression levels of gene targets.

Results: In this study, we demonstrated that downregulation of RhoE, a RhoA antagonist, and upregulation of ROCK enhanced resistance to chemotherapy in HCC in both in vitro cell and in vivo mouse xenograft models, whereas a ROCK inhibitor was able to profoundly

sensitize HCC tumors to cisplatin treatment. Specifically, the ROCK2 isoform but not ROCK1 maintained the chemoresistance in HCC cells. Mechanistically, we demonstrated that activation of ROCK2 enhanced the phosphorylation of JAK2 and STAT3 through increased expression of IL-6 and the IL-6 receptor complex. We also identified IKKβ as the direct downstream target of Rho/ROCK, and activation of ROCK2 significantly augmented NF-κB transcription activity and induced IL-6 expression.

Conclusion: These data indicate that Rho/ROCK signaling activates a positive feedback loop of IKKβ/NF-κB/IL-6/STAT3 which confers chemoresistance to HCC cells and is a potential molecular target for HCC therapy.

(This study was supported in part by the Hong Kong Health and Medical Research Fund [Project no.: 12133191])

Publication arising from this project: Ma W, Sze KM, Chan LK, Lee JM, Lai LW, Wong CM, Lee TK, Wong CC, Ng IO. RhoE/ROCK2 regulates chemoresistance through NF-κB/IL-6/STAT3 pathway in hepatocellular carcinoma. Oncotarget 2016; 7:41445-41459.

Project No.: 12133191

AMR-3

Targeting the metabolic machineries of HCC by understanding the roles of transketolase in hepatocellular carcinoma development

Wong CC, Xu MJ, Ng IO

Pathology, The University of Hong Kong

Introduction and Project Objectives: Metabolic reprogramming has emerged as a hallmark of cancer. Cancer cells preferentially utilize aerobic glycolysis instead of oxidative phosphorylation for energy production, a metabolic trait called the Warburg Effect. Glycolysis is connected with the pentose phosphate pathway (PPP) which is crucial for the production of antioxidant (NADPH) and nucleotide precursor (ribose-5-phosphate).

Methods: RT-qPCR, Western blotting, and IHC were used to quantitate TKT levels in human HCC samples. LC-MS was employed to evaluate the metabolites in HCC cells. Chromatin immunoprecipitation (ChIP) assay was performed to evaluate the binding of transcription factors NRF2/BACH1 in HCC cells. Orthotopic and subcutaneous implantations were performed to evaluate the effects of TKT inhibitor, xythiameine (OT), and Sorafenib o HCC growth in vivo.

Results: To understand the metabolic alterations in HCC, we globally examined all the metabolic genes in human hepatocellular carcinoma (HCC) by transcriptome sequencing. Interestingly, we found that all genes in the PPP are up-regulated in human HCC. Particularly, transketolase (TKT), the key enzyme that directly connects the PPP with glycolysis, was the most abundant and upregulated gene in HCC. Overexpression of TKT was significantly correlated with aggressive clinicopathological features, including venous invasion, larger tumor size, microsatellite formation and absence of tumor encapsulation. At the regulatory level, TKT was transcriptionally regulated by the NRF2/KEAP1/BACH1 pathway, a master regulator of redox homeostasis. By ChIP assay, we showed that NRF2 and BACH1 competitively bound to the antioxidant responsive element of TKT to regulate its transcription. Further expression study revealed that knockdown of NRF2 decreased TKT expression whereas knockdown of BACH1 and KEAP1 elevated TKT expression. Functionally, knockdown of TKT greatly suppressed HCC cell growth in vitro and in vivo. Knockdown of TKT decreased glucose uptake and NADPH production, leading to accumulation of ROS and ROS-associated cell cycle delay. To comprehensively investigate the metabolic functions of TKT, we performed metabolomics and carbon tracing studies in the TKT knockdown HCC cells. Knockdown of TKT caused the accumulation of intermediates in the PPP, which in turn obstructed the metabolic flux for NADPH production, leading to accumulation of ROS. Intriguingly, genetic knockdown and pharmacological inhibition of TKT sensitized HCC cells to Sorafenib, the only FDA-approved drug in HCC treatment, both in vitro and in vivo.

Conclusion: In sum, we demonstrate that HCC cells have increased reliance on the PPP and targeting the PPP via TKT represents a novel approach to synergize Sorafenib for HCC therapy.

Project No.: 03142936

AMR-4

Exploring the Mechanism for Cancer Associated Fibroblasts Recruitment and the Potential Therapeutic Value in Esophageal Squamous Cell Carcinoma

Guan XY, Wang Ying

The Department of Clinical Oncology, The University of Hong Hong

Introduction and Project Objectives: Cancer associated fibroblasts (CAFs) play critical roles in the establishment of suitable tumor microenvironment. As our previous study, FGFR2+ CAFs actively interacted with ESCC cells through secreting multiple factors to support ESCC tumorigenesis and promote tumor metastasis. a deeper understanding of FGFR2+ CAFs including their origins as well as the molecular mechanisms related to their recruitment and maturation might facilitate the discovery of new therapeutic target.

Methods: Xenograft models were constructed by tumor implantation and resection, and FGFR2+ cells were isolated and identified by flow cytometry and immunofluorescence. Flow cytometry was conducted to confirm the precursors of FGFR2+ cells, and fibrocyte distribution and tumor burden were detected by in vivo imaging system. The expression of FGF2 in ESCC cells and serum were detected by ELISA. RNA-Seq was conducted to reveals potential molecular mechanisms associated with the recruitment and differentiation of FGFR2+ fibrocytes.

Results: The results from xenograft model showed that tumor implantation could significantly increase FGFR2+ cells in BM, which was rapidly decreased to basal level after tumor resection. Flow cytometry results suggested that progenitors of FGFR2+ fibrocytes (FGFR2+CD34+CD45+) in BM were significantly increased in tumor-bearing mice, compared with non tumor-bearing mice. Furthermore, in vivo experiment demonstrated that FGFR2+ fibrocytes could be recruited into tumor tissue.

Conclusion: The results suggested FGF2 secreted by ESCC tumor cells could guide the maturation and recruitment of FGFR2+ fibrocytes. These findings give rise to new approaches that target CAFs before their incorporation into tumor stroma.

Project No.: 02131876

AMR-5
Functional Role of MicroRNAs in EGFR-Targeted Therapy Resistance in Non-Small Cell Lung Cancer

Chan WC, Cho CS, Meng F, Wang FF, Zhou R, Wong SC
Department of Health Technology and Informatics, Hong Kong Polytechnic University

Introduction and Project Objectives: Lung cancer is one of the most common deadly tumors with a high morbidity and mortality worldwide, of which 80% belong to non-small cell lung cancers (NSCLCs). The NSCLC patients with epidermal growth factor receptor (EGFR) mutant frequently respond to the EGFR tyrosine kinase inhibitors (EGFR-TKIs) treatment. However, the drug responses are not durable by reason of the acquired drug resistance. EGFR-TKI resistance has become a serious problem as no curative therapy is available for NSCLC patients with such resistance. MicroRNAs (miRNAs) are emerging was a new class of regulator, a kind of small noncoding and endogenous molecules, that can regulate the target gene expression. This study is aimed to overcome the resistance of EGFR-TKIs through (1) the inhibition of the shared downstream molecules (e.g. PI3K) of EGFR and IGF-1R, and (2) the miRNAs regulating these molecules.

Methods: In this study, we selected two key markers in the shared downstream signaling pathways PI3K and AKT to verify the effect of a candidate miRNA miR-30a-5p on the drug resistance in NSCLCs. MiR-30a-5p is predicted to regulate phosphoinositide-3-kinase regulatory subunit 2 (PIK3R2) by TargetScan and PicTar prediction databases. Furthermore, our previous study revealed that miR-30a-5p was negatively associated with the expression of PIK3R2 based on the multiple linear regression and support vector regression models. We hypothesize that inhibition of the shared downstream molecules (e.g. PI3K) of EGFR and IGF-1R can overcome the resistance of EGFR-TKIs, and miRNAs regulating the shared downstream molecules have the same effect to reverse the drug resistance. An in vitro study was performed using EGFR inhibitor, IGF-1R inhibitor, and miRNA mimics in two Gefitinib-resistant NSCLC cell lines, NCI-H1975 (with a secondary T790M mutation in EGFR) and NCI-H460.

Results: Knockdown of the shared downstream molecule PI3K could reduce the expression level of p-AKT, indicating PI3K may be a potential target for overcoming drug resistance or treating NSCLC directly. As the overexpression of miR-30a-5p significantly repressed PIK3R2 expression, the administration of miR-30a-5p mimic induced cell apoptosis, inhibited cell invasion and reduced cell migration.

Conclusion: This study identified new roles and mechanism of miRNA in overcoming the acquired resistance to EGFR-TKIs in NSCLCs. Hence, the combination of miR-30a-5p mimic and EGFR-TKIs may sensitize the cancer cells to targeted drug and provide a novel treatment approach for NSCLC.

Project No.: 02131026

AMR-6
Repurposing of Clinically Approved Drugs as Autophagy Modulators to Overcome Drug Resistance to Molecular Targeted Tyrosine Kinase Inhibitors (TKI) in Treating Lung Cancer

TO KK[1], LOONG HH[2], WU WK[3]
[1]School of Pharmacy, The Chinese University of Hong Kong, [2]Department of Clinical Oncology, The Chinese University of Hong Kong, [3]Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong

Introduction: The clinical efficacy of epidermal growth factor tyrosine kinase inhibitor (EGFR TKIs) in lung cancer patients carrying the sensitizing EGFR mutations is severely compromised by drug resistance. We aimed to develop novel drug combination by repurposing existing drugs not indicated for oncology to overcome drug resistance to EGFR TKIs.

Objectives:
(1) To investigate the role of autophagy in the therapeutic response of EGFR TKIs in a panel of NSCLCs with different sensitivities/drug resistance mechanisms
(2) To demonstrate and investigate the mechanism underlying the potentiation of anticancer activity of EGFR TKIs in NSCLC cells in vitro using the tested autophagy modulators
(3) To study the circumvention of EGFR TKI resistance in xenograft-bearing athymic nude mice by the most promising autophagy modulator identified

Methods: Drug combinations were evaluated by cell proliferation assay. Various standard techniques were employed to detect and evaluate the extent of autophagy and apoptosis, including fluorescence microscopy, flow cytometry, transmission electron microscopy, Western blot analysis and cell viability assays.

Results: Given the findings that autophagy induction contributed to the anticancer activity of EGFR TKIs in NSCLC, model autophagy inducers (Peroxisome proliferator-activated receptor gamma (PPARgamma agonists) were tested for resistance circumvention. PPARgamma also upregulates phosphatase and tensin homolog (PTEN) to inhibit cell signaling downstream of PI3K to mediate apoptosis. To this end, PTEN loss is a known mechanism contributing to resistance to EGFR TKIs. Using human NSCLC cell models with PTEN deficiency, the potentiation of EGFR TKI anticancer activity by PPARgamma agonists was evaluated. PPARgamma agonists were found to upregulate PTEN, subsequently inhibiting the PI3K-Akt signaling pathway, and thus enhancing the anticancer activity of gefitinib. Chemical and genetic inhibition of PPARgamma were shown to prevent this potentiation of anticancer activity by PPARgamma agonists, thus confirming the crucial role played by PPARgamma activation. Interestingly, the tested PPARgamma agonists were also found to induce autophagy, as evidenced by the increased expression of an autophagy marker LC3-II and the autophagic degradation of p62/SQSTM1. PPARgamma agonists-induced autophagic cell death was believed to contribute to the circumvention of resistance in PTEN-deficient cells because the genetic silencing of ATG5 (an autophagy mediator) was found to eliminate the drug potentiation effect. The drug combination was also shown to provide a slight but statistical significant potentiation of anticancer effect in tumor xenograft in mice.

Conclusion: PPARgamma agonist drugs were shown to sensitize resistant NSCLC cells to EGFR TKIs by (i) upregulating PTEN and thus inhibiting PI3K-Akt pathway; and (ii) inducing autophagy.

Project No.: 03140276

AMR-7

Delineating Pathogenic Mutations in Epstein-Barr Virus Genomes of Nasopharyngeal Carcinoma Using Next Generation Sequencing Technology

Chiang AK[1,2], Chan TF[1], Hui KF[1], Shen N[1], Sham PC[3], Kwong DL[4], Lung ML[2], Yang W[1]

[1]Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, [2]Centre for Nasopharyngeal Carcinoma Research, The University of Hong Kong, [3]Centre for Genomic Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, [4]Department of Clinical Oncology, Li Ka Shing Faculty of Medicine, The University of Hong Kong

Introduction and Project Objectives: Undifferentiated nasopharyngeal carcinoma (NPC) is highly prevalent in Southern Chinese populations and strongly associated with Epstein-Barr virus (EBV) infection. The main objective of this project is to determine whether certain variants of EBV are linked to the pathogenesis of NPC.

Methods: We performed a case-control study comparing genomic sequences of EBV isolated from saliva samples of 142 population carriers with those from primary tumour biopsies derived from 62 patients with NPC of Hong Kong.

Results: Cluster analysis discovered five EBV subgroups 1A-C and 2A-B amongst the population carriers in contrast to the predominance of 1A and -B in the majority of NPC. Genome-wide association study (GWAS) identified a panel of NPC-associated single nucleotide polymorphisms (SNPs) and indels in the EBER locus. The most significant polymorphism, which can be found in 96.8% NPC cases and 40.1% population carriers of Hong Kong, is a four-base-deletion polymorphism downstream of EBER2 (EBER-del) from coordinates 7188-7191 ($p = 1.91 \times 10\text{-}7$). In addition, the predicted secondary structure of EBER2 is altered with likely functional consequence in nearly all NPC cases. Using the SNPs and indels associated with NPC, genetic risk score is assigned for each EBV variant. EBV variants with high genetic risk score are found to be much more prevalent in Hong Kong Chinese than individuals of other geographic regions and in NPC than other EBV-associated cancers.

Conclusion: We conclude that high risk EBV variants with polymorphisms in the EBER locus, designated as NPC-EBERvar, are strongly associated with NPC.

Project No.: 02131706

AMR-8

Leukocyte Telomere Length Associates with Risk and Survival of Hong Kong Chinese Nasopharyngeal Carcinoma Patients

Ko Josephine Mun-Yee[1], Tsang Kay Hiu-Ki[1], Dai Wei[1], Ngan Roger Kai-Cheong[2], Kwong Dora Lai-Wan[1], Cheng Ashley[3], Lee Anne Wing-Mui[1], Ng Wai Tong[4], Tung Stewart[5], Lung Maria Li[1]

[1]Department of Clinical Oncology, University of Hong Kong, [2]Department of Clinical Oncology, Queen Elizabeth Hospital, [3]Department of Oncology, Princess Margaret Hospital, [4]Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, [5]Department of Clinical Oncology, Tuen Mun Hospital

Introduction and Project Objectives: Telomere attrition predicts age-related disease and occurs as an early event in tumorigenesis. The TERT-CLPTM1L locus associates with nasopharyngeal carcinoma (NPC) risk. Previous studies reported association of either shortest or longest leukocyte telomere length (LTL) with cancer survival. It remains unknown if LTL associates with NPC risk and survival.

Methods: The relative LTL (rLTL) was measured by quantitative-PCR in 2,996 individuals comprised of 1,284 NPC cases and 1712 matched controls. The odds ratio (OR) and 95% confidence intervals (CI) were calculated by logistic regression. The hazard ratio (HR) and 95% CI were calculated by Cox regression for survival analysis with rLTL and other clinical parameters in 1,243 NPC. NPC patients had significantly shorter telomere length than controls.

Results: Shorter rLTL significantly associated with increased NPC risk, when the individuals were dichotomized into long and short telomeres based on median-split rLTL in the control group (OR = 2.317; 95% CI = 1.989-2.700, $p = 4.10 \times 10\text{-}27$). We observed a significant dose-response association (ptrend $= 3.26 \times 10\text{-}34$) between rLTL and NPC risk with OR being 3.555 (95% CI = 2.853-4.429) for the individuals in the first quartile (shortest) compared with normal individuals in the fourth quartile (longest). A multivariate Cox regression analysis adjusted by age demonstrated an independent effect of rLTL on NPC survival for late-stage NPC patients, when the individuals were categorized into suboptimal rLTL versus the medium rLTL based on a threshold set from normal (HR = 1.471, 95% CI = 1.056-2.048, p = 0.022). Shorter blood telomeres may be markers for higher susceptibility for NPC risk. Suboptimal rLTL may be a poor prognostic factor for advanced NPC patients, as it associates independently with poor survival.

Conclusion: The current study provides evidence of an association of individuals with shorter blood telomere length and increased risk of NPC and prognostic role of suboptimal blood telomere length for late stage NPC is the first to strongly implicate the etiologic role of telomere biology in NPC development and disease progression.

Project No.: 02132016

AMR-9

Non-invasive Detection of Plasma mRNA Biomarkers for Colorectal Adenoma Using Targeted Sequencing

Wong Sze Chuen Cesar

Health Technology and Informatics, The Hong Kong Polytechnic University

Introduction and Project Objectives: Colorectal cancer is the commonest cancer in Hong Kong. Colorectal adenoma is the precancerous lesion of colorectal cancer. Thus, there has been great interest in developing population based screening for colorectal cancer to detect asymptomatic colorectal cancer, as well as its

precursor, colorectal adenoma. Many methods have been evaluated, such as fecal occult blood testing, flexible sigmoidoscopy, screening colonoscopy, virtual colonoscopy, and barium enema, but they have limited sensitivity, specificity, or are invasive procedures. Recently, our group has developed an optimized protocol for plasma targeted mRNA sequencing using a custom panel with 108 colorectal cancer related genes (Xue et al, 2018). Using this methodology, we performed plasma targeted mRNA sequencing for 40 colorectal adenoma patients and 39 normal controls in order to detect potential plasma mRNA biomarkers for colorectal adenoma.

Methods: Targeted sequencing using the Illumina MiSeq benchtop sequencer (Illumina, CA, USA) was used throughout the study.

Results: Results showed that GSK3A and RHOA had differential expression as identified by a cut-off of fold change > 2 and adjusted P value.

Conclusion: In summary, this study has shown that detection of differential expressed plasma mRNAs is feasible using targeted RNA sequencing and a larger scale study has been carrying out to validate these results.

Project No.: 02131226

AMR-10
A functional study of nuclear receptor LRH-1 and its targeting in prostate cancer

Xiao L[1,2], Wang Y[1], Xu K[2], Hu H[2], Xu Z[1], Wu D[1], You W[1], Ng CF[3], Yu S[1], Chan FL[1]

[1]School of Biomedical Sciences, The Chinese University of Hong Kong, [2]Department of Urology, Peking University People's Hospital, [3]Department of Surgery, The Chinese University of Hong Kong

Introduction and Project Objectives: Intratumoral androgen biosysnthesis is regarded as a key mechanism responsible for the castration-relapse growth of prostate cancer. Based on this fact, inhibition of steroidogenic enzymes (such as targeting the CYP17A by abiraterone acetate) has been used as a novel therapeutic strategy in the hormone therapy of metastatic castration-resistant prostate cancer (CRPC). However, resistance to steroidal inhibitors will develop shortly in patients, and the involved mechanism and also the regulation of the steroidogenic enzymes in prostate cancer tissues still remain largely unknown. This study aims to elucidate the role of the nuclear receptor, liver receptor homolog-1 (LRH-1, NR5A2), in the promotion of androgen biosynthesis in CRPC growth. We hypothesize that up-regulation of LRH-1 could facilitate CRPC growth by increased production of androgens and androgen receptor reactivation in prostate cancer cells via its transcriptional control of key steroidogenic enzyme genes involved in androgen synthesis.

Methods: Prostate cancer tissue microarrays were used to determine the LRH-1 expression pattern. LRH-1 expression and intratumoral androgen levels were determined in CRPC and abiraterone-treated CRPC xenograft models. The roles of LRH-1 in the promotion of castration-resistant growth and elevation of intratumoral androgen levels were elucidated by overexpression and knockdown studies. The effect of suppression of LRH-1 activity in the potentiation of sensitivity to androgen deprivation was determined by a LRH-1 inverse agonist.

Results: Our results demonstrated that high-grade prostate cancer tissues, many androgen receptor (AR) –positive prostate cancer cell lines and xenograft models of CRPC exhibited an increased expression of LRH-1, which was also accompanied with increased expressions of multiple key steroidogenic enzymes and elevated intratumoral and cellular androgen levels. Functional analyses revealed that LRH-1 could confer in vitro resistance to androgen deprivation in AR-positive but not AR-negative prostate cancer cells and also promote in vivo castration-resistant growth of prostate cancer xenografts, via its direct transactivation of key steroidogenic enzyme genes, including CYP17A and intratumoral androgen production. Importantly, our results also showed that pharmacological inhibition of LRH-1 activity could attenuate the LRH-1-mediated androgen deprivation-resistance of prostate cancer cells.

Conclusion: Our study shows for the first time that LRH-1 can play a key role in the castration-resistant growth of prostate cancer through its transactivation of key steroidogenic enzymes and promotion of intratumoral androgen biosynthesis, and also suggest that targeting LRH-1 is of potential therapeutic significance for the management of CRPC.

Publication: Xiao and Wang et al., Cancer Research 2018;78(9):2205-2218.

Project No.: 02130066

AMR-11
The role of BMI-1 in regulation of JAK-STAT signaling pathway in human leukemia

Ng RK[1], Lam YM[1], Lam SS[2], Leung AYH[2]

[1]School of Biomedical Sciences, The University of Hong Kong, [2]Department of Medicine, The University of Hong Kong

Introduction and Project Objectives: Aberrant activation of JAK-STAT pathway is crucial in leukemic transformation. SOCS family proteins are the negative regulators of the JAK-STAT pathway. The polycomb complex protein BMI1 regulates the self-renewal of hematopoietic and leukemic stem cells through repression of the INK4A-ARF locus. However, several studies revealed other cellular targets of BMI1 and demonstrated the tumor suppressive function of polycomb group proteins in hematological malignancies, indicating that the function of BMI1 in leukemia remains elusive. Interestingly, we noticed that JAK-STAT pathway is activated in many human leukemia cell lines, despite the fact that they showed lower BMI1 expression when compared to the primary leukemia samples. Therefore, we aim to investigate the epigenetic functions of BMI-1 in the modulation of JAK-STAT pathway in leukemia cells.

Methods: We established human leukemia cell line models overexpressing BMI1, followed by measuring the cellular properties and JAK-STAT pathway activity. ChIP-seq and RNA-seq analyses were performed to examine the alteration of epigenetic pattern by BMI1 in association with gene transcriptional program. Integration of the public available STAT5 ChIP-seq dataset with our in-house RNA-seq data for the identification of BMI1-associated STAT5-target genes in leukemia cells. Leukemia patient-derived cells were used to correlate JAK inhibitor responsiveness to the endogenous BMI1 and SOCS1 expression levels.

Results: Restoration of BMI1 in leukemia cell lines significantly reduced cell proliferation, which is associated with suppression of JAK-STAT pathway. The BMI1 overexpressing cells demonstrated global reduction of histone H2AK119 ubiquitination, which is associated with an increases protein stability of a component of polycomb repressive deubiquitinase complex BAP1. Importantly, loss of H2AK119 ubiquitination at promoters induces SOCS gene expression, which inhibits phosphorylation of STAT proteins. It suggests that BMI1 can epigenetically repress JAK-STAT signaling through H2AK119 modification. In addition, restoration of cellular BMI1 level urges leukemia cell apoptosis through deregulation of STAT5-targeted pro-apoptotic genes. We further demonstrated that a significant portion of primary patient-derived leukemia cells with high endogenous SOCS1 expression have higher BMI1 expression and are more sensitive to JAK1/2 inhibitor ruxolitnib treatment.

Conclusion: BMI1 mediates epigenetic repression of JAK-STAT signaling pathway in leukemia cells through derepression of SOCS genes, and subsequently prompts leukemia cell to undergo apoptosis. We propose that therapeutic stratification of acute leukemia patients for ruxolitinib treatment should consider their BMI1 levels. Taken together, our work provides mechanistic insights into the epigenetic function of BMI1, and underscore its potential in the treatment of hematological malignancies.

Project No.: 02132436

AMR-12
The use of a novel synthetic flavonoid to improve bioavailability of paclitaxel: a pharmacokinetic, mechanistic and in vivo efficacy study

Yan CSW, Kan JWY, Wong ILK, Chong TC, Hu XS, Chan TH, Chow LMC
Applied Biology and Chemical Technology, The Hong Kong Polytechnic University

Introduction and Project Objectives: This project aims to develop a new orally-available paclitaxel formulation for treating cancer. Paclitaxel is not orally absorbed due to the efflux action of intestinal P-gp.
We have designed a new P-gp inhibitor FM04 based on flavonoid monomer and administered it together with oral paclitaxel. We measured the pharmacokinetics of paclitaxel and FM04 in blood and determined the efficacy of co-administration of FM04 and paclitaxel in xenograft model of breast cancer using immunocompromised mice. We have also measured the effect of FM04 on the pharmacokinetics and metabolism of paclitaxel. The mechanism of how FM04 inhibits paclitaxel efflux was studied in CaCo2 epithelial model.

Methods: FM04 and paclitaxel are measured by UPLC-MSMS. For pharmacokinetics experiments, mice were orally fed with different concentrations of paclitaxel with or without FM04. Plasma concentration of FM04 and paclitaxel were measured by UPLC-MSMS.

Results: We have found that FM04 can inhibit the basal to apical trans-epithelial efflux of paclitaxel by P-gp using CaCo2 epithelial cells. Pharmacokinetics demonstrated that the Area Under Curve (dose adjusted) of oral paclitaxel (70 mg/kg) can be increased by 57- and 30-fold when FM04 was co-administered orally (45 mg/kg and 22 mg/kg). Xenograft studies indicated that the co-administration of paclitaxel FM04 (45 mg/kg) and paclitaxel (40 - 80 mg/kg) resulted in significant tumor shrinkage with tumor reduction of 73% (paclitaxel used at40 mg/kg), 86% (50 mg/kg), 82% (60 mg/kg), 95% (70 mg/kg) and 96% (80 mg/kg), respectively.

Conclusion: FM04 can increase the oral bioavailability of paclitaxel and the plasma concentration of paclitaxel is high enough for therapeutic purposes in in vivo xenograft model.

Project No.: 02131036

AMR-13
Mechanistic study of EBNA1-mediated latent DNA replication of Epstein-Barr virus

ZHU Guang, LEE Tunglun, XU Naining, LIU ChangDong
Division of Life Science, The Hong Kong University of Science and Technology

Introduction and Project Objectives: Epstein-Barr virus(EBV) persistently infects B lymphocytes in latent and lytic modes and is believed to associate nasopharyngeal carcinoma(NPC), a predominant cancer found in Hong Kong. Epstein-Barr nuclear antigen 1(EBNA1) is the only protein encoded by EBV required for the stable propagation of EBV episomes in latency and expressed in all NPC tumor cells. However, the detailed molecular mechanism for the EBNA1 related NPC DNA replication and cell proliferation remains elusive. This captioned study aimed to gain insight into the molecular mechanism of EBNA1-mediated latent DNA replication of Epstein-Barr virus through searching human cellular proteins and nucleic acids that forms complexes with EBNA1 followed by the detailed structure-functional study of these complexes. These results from our interdisciplinary approaches to study the fundamental biology of EBNA1-mediated latent DNA replication may facilitate the development of a new treatment strategy for the relevant diseases.

Methods:
Binding study: pull down assay, ITC and NMR spectroscopic methods.
Structural study: NMR spectroscopy, computer docking and modelling.
Functional assays: Study EBNA1 mediated latent DNA replication and transcriptional activity by transfecting 293T, Hela and HONE-1(EBV) cell lines with specific inactive or dysfunctional mutants of RNF216 and EBNA1 based on the above structural and binding study.

Results: RNF216 interacts with EBNA1 resulting in increased EBNA1 mediated DNA replication and transcriptional activity and elevated NF-κB activity through inhibition of RNF216 mediated TRAF3 proteasomal degradation. In the study of EBNA1/DNA/Cdc6 complex, we found a new structural fold of human telomeric DNA and determined G4-Cdc6 structure.

Conclusion: The new roles of EBNA1-RNF216 complex in latent EBV DNA replication and in NF-κB signalling pathway shed light on our understanding on EBV pathogenicity. Further study based on our results on DNA/Cdc6 complex will yield new information on EBNA1 mediated DNA replication.

Project No.: 02133056

AMR-14

Pharmacogenomics Assessment of Serious Cutaneous Adverse drug reactions (PASCA): A retrospective study

Cheung CL, Sing CW, Wong ICK
The University of Hong Kong

Introduction and Project Objectives: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are serious cutaneous disorders frequently caused by drug reaction. It is well acknowledged that genetic variant is a predisposing factor of SJS/TEN. However, whether there is a genetic variant underlying non-drug specific SJS/TEN is unknown. We aimed to identify non-drug specific variants of SJS/TEN in Southern Chinese population, using genome-wide association approach and re-sequencing in the HLA region.

Methods: Genome-wide association analysis was conducted in 48 SJS/TEN cases and 774 healthy controls. Relationship between the genetic markers and SJS/TEN was evaluated using the frequentist test and under the additive model. Logistic regression was used to perform the HLA association analysis.

Results: The association analysis showed that no SNP reached genome-wide significance level. However, in the HLA association analysis, a novel association of HLA-A*03:01 in SJS/TEN was identified. The odd ratio of the association of HLA-A*03:01 and SJS/TEN, regardless of the drug aetiology, was 14.14 (95%CI 4.07-44.99, P = 9.87 x 10-6).

Conclusion: This study identified a novel association of HLA-A*03:01 in SJS/TEN, regardless of drug aetiology. A replication study of the finding in other populations is warranted.

Project No.: 02132726

AMR-15

Development and Target-Specificity Profiling of Highly Fluorescent DNA-Mimetic Polymers as Therapeutics Agents for Gene Silencing

Lo Pik Kwan Peggy, Liu Ling Sum
Department of Chemistry - City University of Hong Kong

Introduction and Project Objectives: Gene silencing is an exciting field for functional genomics. Currently, RNA interference (RNAi) holds a great promise in the field of small interfering RNA (siRNA)-based therapeutics. These doubled-stranded siRNA molecules typically play an important role in RISC cleaving of complementary mRNA. However, they suffer from major drawbacks as a class of therapeutic agents due to their poor stability in biological media and poor uptake efficiency to the targeted cells. These factors highly restrict to their widely uses in clinic. To improve the physicochemical and biological properties of antisense oligonucleotides, researchers have started to modify oligonucleotides and generate their analogues with improved hybridization ability and a better selectivity toward nucleic acid targets. Peptide nucleic acid, locked nucleic acids and phosphorodiamidate morpholino oligomers have shown great promise as potential antisense agents. However, a progress in their biomedical applications has been limited by low water solubility, tendency to self-aggregation, poor cell penetration, rapid clearance and relative high toxicity. Thus, development of a new class of therapeutic agent is still of great research and clinical interest for gene silencing. We herein design and synthesize a new series of synthetic polymers (e.g. BADPs, PDPs and PTPs) and examine their binding specificity with DNA/RNA in solution and biocompatibility in cellular environment. Eventually, we explore their gene silencing applications in cell culture system and living animal models by two antisense mechanisms either inhibition of translation of undesirable protein or inducing degradation of targeted mRNA by enzymes.

Methods:
Circular dichroism
Thermal denaturation
Fetal bovine serum stability assay
Confocal fluorescence imaging
MTT assay
Live/dead staining assay
Flow Cytometry
In vitro GFP Protein and mRNA Expression

Results: BADPs and PTPs mimic the molecular recognition properties and monodisperse nature of DNA, but not for PDPs. Particularly, PTPs are highly non-biodegradable and cell-permeable with low cytotoxicity and a comparable binding selectivity towards other antisense oligonucleotides. We firstly show that PTPs exhibit their ability to inhibit GFP protein expression in cellular system via steric hindrance mechanism and show their potential applications in gene silencing.

Conclusion: The knowledge generated in this work will not only provide an insight of designing DNA-mimetic polymers, but also introduce a new generation of therapeutic agents for gene silencing applications. These synthetic polymers which mimic the specificity of DNA would also allow the use of the same programmable principles in the design of a number of nanostructured materials with anticipated applications in nanoelectronics, nanophotonics, solar energy conversion, high density data storage.

Project No.: 02131376

AMR-16

R4 RGS subfamily proteins suppress engraftment of human hematopoietic stem/progenitor cells and modulate SDF-1/CXCR4 downstream signals

Leung Lam Tong, Chan Yune Yee Kathy, Li Karen
Paediatrics - The Chinese University of Hong Kong

Introduction and Project Objectives: This study aimed to investigate (i) the expression profile of R4 Regulators of G-protein signaling (RGS) members in CD34+ hematopoietic stem/progenitor cells (HSPC) and their regulation upon stimulation with the chemokine stromal cell-derived factor-1 (SDF-1); (ii) the roles of 4 specific RGS members in SDF-1-mediated functions and signaling in vitro; (iii) the effects of RGS overexpression on engraftment of CD34+ cells in vivo; and (iv) the underlying mechanisms of RGS-regulated functions.

Methods: CD34+ cells were isolated from umbilical cord blood (CB) of term infants. Expression of R4 RGS mRNA at baseline and after

SDF-1 exposure was quantified by qPCR. Homing-related functions of lentiviral transduced CD34+ cells were assessed by transwell migration, calcium mobilization and Phosflow assays. Long-term multilineage engraftment of RGS-overexpressing cells was evaluated in the non-obese diabetic/severe combined immunodeficient (NOD/SCID) mouse xenotransplantation model. Mechanisms of RGS were investigated by genome-wide expression microarray.

Results: CB CD34+ cells expressed specific RGS mRNA, of which RGS1, RGS2, RGS13 and RGS16 were significantly upregulated by SDF-1. Overexpression of RGS1, RGS13 or RGS16, but not RGS2, inhibited SDF-1-directed chemotaxis, trans-matrigel invasion, calcium flux and phosphorylation of AKT, ERK and STAT3. In addition, bone marrow engraftment of CD34+ cells, including the B-lymphoid, myeloid and erythroid lineages, were substantially inhibited upon RGS1, RGS13 and RGS16 overexpression. Transcriptome profiling of RGS1, RGS13 or RGS16 overexpressing CD34+ cells revealed modulation of multiple functional effectors. Network mapping delineated the potential mechanisms of RGS1, RGS13 and RGS16 downstream of SDF1/CXCR4 and Gαi protein, leading to compromised AKT, ERK and STAT3 phosphorylation and negative regulation of stem cell functions (CCNA1, SPP1, LPAR5, IL 1RL1, HPSE), complement activation (C3AR1, C5AR2, C5AR1), proteolysis (TIMP3, MMP14) and cell migration (THBS1, F2RL2, PROS1, CCL1).

Conclusion: Our study provided a comprehensive expression profile of R4 RGS proteins and their regulation in CD34+ cells, and identified the unprecedented role of RGS1, RGS13 and RGS16 in homing-associated functions and hematopoietic engraftment. The findings could potentially be harnessed to derive strategies for improving clinical HSPC transplantation, especially when CB is utilized as the stem cell source.

Project No.: 01120706

AMR-17

The Roles of Platelet Derived Growth Factor Receptor Alpha (PDGFRA) in Urethra Tubularization and in Hypospadias

Lui V.C.H
The University of Hong Kong

Introduction and Project Objectives: Defective urorectal development results in anorectal malformations, which are common congenital developmental defects of the anus and the urethra in newborns. The etiology and embryology of the defects are still largely unknown. Platelet-derived growth factor receptor alpha (Pdgfra) is a cell surface receptor tyrosine kinase, upon binding to its ligands (Pdgfa-d), mediates intracellular signaling and regulates embryonic development. The expression of Pdgfra is tightly regulated in the developing urorectal mesenchyme, and its dysregulation is associated with urorectal defects in animals with urorectal defects. However, the underlying pahto-mechanisms are unknown.

Methods: To address the temporal requirement of Pdgfra in urorectal development, we conditionally deleted Pdgfra in Pdgfra-expressing tissues using a tamoxifen inducible Cre-loxP approach in mice, examined the urorectal development in Pdgfra conditional knockout (Pdgfra-cKO) embryos.

Results: Conditional deletion of Pdgfra in Pdgfra-expressing tissues at E10-E11 caused cloaca septation defect, anteriorly displaced anus, defective urogenital folds development and abnormal urethra tubularization in both male and female mice. Furthermore, our finding showed that Pdgfra was required for the survival of urorectal mesenchyme, deletion of Pdgfra caused apoptosis in the peri-cloacal, the peri-urethra and the urorectal septum mesenchyme of Pdgfra-cKO mutants, associated with an induction of p53, Ndrg1 and activation of caspase-3 in Pdgfra-cKO embryos.

Conclusion: Pdgfra is required for the development and survival of the urorectal mesenchyme in embryo, dysregulated Pdgfra signaling induced urorectal defects in mice resembling human congenital diseases of anorectal malformations and hypospadias. Perturbation of PDGFRA signaling may contribute to anorectal malformations and hypospadias in human.

Project No.: 02132306

AMR-18

Peak Oxygen Uptake in Healthy Chinese Children and Adolescents by Age, Sex and Maturation

Yu CCW[1,2], McManus AM[3], Au CT[1], So HK[1,4], Chan A[1], Sung RYT[1], Li AM[1]
[1]The Chinese University of Hong Kong, Hong Kong, [2]The Education University of Hong Kong, Hong Kong, [3]The University of British Columbia, Kelowna, Canada, [4]Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong

Introduction and Project Objectives: To investigate scaling approaches for evaluating the development of peak VO2 and improving the identification of low cardiopulmonary fitness in Southern Chinese children and adolescents.

Methods: We carried out a territory-wide cross-sectional study, recruiting subjects proportionally from all four geographical areas of Hong Kong, based on the size of the population living in these areas. Nine hundred and twenty Chinese children and adolescents (8 to 16 years) underwent assessment on anthropometric measurements and pubertal status. They also underwent graded cardiopulmonary exercise test on a treadmill until volitional exhaustion, with respiratory gas analysis. Peak VO2 expressed in absolute values, as a ratio standard to body mass and as adjusted for body mass using an allometric model, was compared by sex, age and maturation. Sex specific centile curves for absolute peak VO2 were generated using the LMS (lambda-mu-sigma) method. Z score equations for predicting peak VO2 were developed. Correlations between scaled peak VO2, z scores, body size and age were tested to examine the effectiveness of the approach.

Results: Eight hundred and fifty-two participants (48% male) were included in the analyses. Absolute and body mass-adjusted peak VO2 values were significantly higher in males than females for all age groups ($P<0.0005$). Absolute peak VO2 significantly increased with age in both sexes (both $P<0.05$), while ratio-scaled peak VO2 increased only in males ($P<0.05$). Allometrically scaled peak VO2 increased from 11 years in both sexes, plateauing by 12 years in girls and continuing to rise until 15 years in boys. Allometically scaled peak VO2 was not correlated with body mass, but remained correlated with height and age in all but the older girls. Peak VO2 z score was not

correlated with body mass, height or age.

Conclusion: Absolute and allometric scaled peak VO2 values are provided for Hong Kong Chinese children and adolescents by age and sex. Peak VO2 z scores improve the evaluation of cardiopulmonary fitness, allowing comparisons across ages and sex and will likely provide a better metric for tracking change over time in children and adolescents, regardless of body size and age.

Project No.: 02130486

AMR-19
Role of persistent organic pollutants on obesity in Hong Kong school children

Chung ACK[1], Cai Z[1], Kong APS[2]
[1]*State Key Laboratory of Environmental and Biological Analysis, Department of Chemistry, Hong Kong Baptist University,* [2]*Department of Medicine and Therapeutics, The Chinese University of Hong Kong*

Introduction and Project Objectives:
1. To examine the relationship between POP concentrations and obesity marker genes
Blood and urine samples of a total of 983 Chinese school children have been previously collected in 2014. We will measure POP concentrations in blood and urine by mass spectrometry and evaluate gene expression levels of obesity marker genes, the adipokines, leptin (LEP), adiponectin (ADIPOQ), and tumor necrosis factor α (TNFα) in blood by enzyme-linked immunosorbent assays.
2. To elucidate the metabolic alterations underlying the effects of POPs through metabolomics analyses. We will perform a metabolomics analysis by mass spectrometry to explore the metabolic alterations in blood and urine samples of a total of 983 Chinese school children underlying the effects of POPs during childhood obesity.

Methods: Stored aliquots of 983 Hong Kong Chinese school children being called back in 2014 for prospective follow-up study of a cross-sectional cohort study conducted during 2003-2004 were examined for serum levels of 13 POPs. The relationships between POP concentrations in blood from the cohort were examined.

Results: A total of 983 school children were called back for prospective study. Mean follow-up duration was 8.7 years. Mean age of the participants was 22.7 (SD 4.9) years at follow-up study. Up to date, we analysed 628 out of 983 samples (64%) with measured POP concentrations in serum and available BMI of the young people at age 20-22 years. In cross-sectional analyses, we observed a pattern of positive associations between serum POPs and BMI z-score at age 20-22. Serum levels of HCB, DDE, PCB 138, PCB 180, BDE 47, PFOA, and PFOS were associated with increased BMI z-score. In addition, HCB, DDE, PCB 138, PCB 180, BDE 47, PFOA, and PFOS also demonstrated statistically significant correlations with body weight and body fat. However, there were no relationship between levels of POPs and height.

Conclusion: Findings of this study support a role of POP exposure may contribute to obesity of Hong Kong Chinese school children.

Project No.: 03144376

AMR-20
Predicting Curve Progression In Adolescent Idiopathic Scoliosis Using A Support Vector Machine Approach

Hu Yong, Zeng Dewei, Cheung Prudence Wing Hang, Luk Keith DK, Cheung Jason Pui Yin
Orthopaedics and Traumatology, The University of Hong Kong

Introduction and Project Objectives: Accurate prediction of curve progression in adolescent idiopathic scoliosis (AIS) is necessary to determine which patients require early intervention or close observation. However, the ability to predict those who progress is still limited. As AIS is a complex disorder with highly variable patterns of progression, using a machine learning approach may help to predict curve progression by organizing and analyzing complicated variables. The aim of this study is to construct a decision system to determine AIS curve progression.

Methods: Based on 113 AIS patients with major thoracic curves, data from 11 variables including chronological age, gender, body height (BH), arm span (AS), coronal curve magnitude, Risser sign, any bracing given, family history of AIS, distal radius and ulna grading, and previous curve magnitude was used to create the model. Using support vector machine (SVM), a decision system was constructed for predicting curve progression and severity of progression. Severity of progression was classified into three groups as mild (less than 20 degree), moderate (between 20 and 40 degree) and severe (larger than 40 degree).

Results: Of the 181 follow-up records obtained, 44 mild, 119 moderate and 18 severe cases of coronal Cobb angle progression was identified. The optimal parameters of the model (radial basis function-SVM) in this study were C = 20.7494 and GAMMA = 16.4563. The proposed decision system reached a 78.4% accuracy in the testing set. However, the prediction accuracy in severe group showed a high accuracy (97.3%) with a sensitivity of 75% and specificity of 100.0%.

Conclusion: In this work, the proposed decision system shows high predictability for the severity of the curve progression. The decision system can provide guidance for clinicians to determine which patients will likely experience curve progression and hence require close observation or early intervention.

Project No.: 03142306

AMR-21
Illuminating the Functional Abnormalities of Brain Networks Underlying Social Communication and Repetitive Behaviors in Autism Spectrum Disorder (ASD): Implication on a Neurobiological Treatment of Neurofeedback

Wang Yang[1], ZHAO Kun-Yang[1], Xiao Xue-Zhen[1], Mo Flora Yi-Man[2], Lee Marshall Ming-Chung[2], Shea Caroline Ka-Sin[2], Chan Grace Fong-Chun[3], Leung Patrick Wing-Leung[1], Lai Kelly Yee-Ching[4], Tse Chun-Yu[1]
[1]Department of Psychology, Chinese University of Hong Kong, [2]Department of Psychiatry, Tai Po Hospital, [3]Department of Psychiatry, Queen Mary Hospital, [4]Department of Psychiatry, Chinese University of Hong Kong