SUPPLEMENT 1

HONG KONG MEDICAL JOURNAL 香港醫學雜誌

Volume 25 Number 1 February 2019

The official publication of the Hong Kong Academy of Medicine and the Hong Kong Medical Association

24th MEDICAL RESEARCH CONFERENCE

HKU Med
LKS Faculty of Medicine
Department of Medicine
香港大學內科學系

瑪麗醫院
Queen Mary Hospital

19 January 2019

ISSN 1024-2708

香港醫學專科學院出版社
HONG KONG ACADEMY OF MEDICINE PRESS

25(S1) HONG KONG MEDICAL JOURNAL 香港醫學雜誌 Volume 25 Number 1 February 2019 Supplement 1

once-daily Lixiana® edoxaban

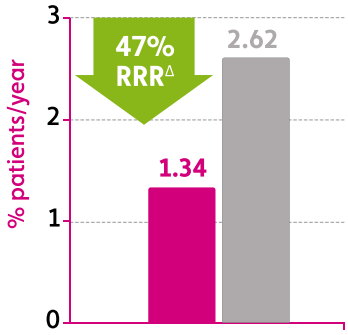
The Optimal NOAC for Asian Patients

Asian Data Matters Because we are Asian!

Engage AF TIMI 48

Largest and longest follow up NVAF# study with 1943 **East Asian** population[1]

Stroke / SEE (mITT, on-treatment period^)

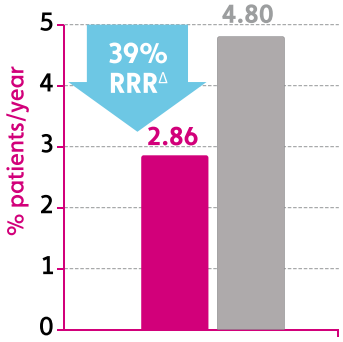


(HR 0.53; 95%CI 0.31 to 0.90; p=0.020)

PROVEN EFFICACY

Compared to well-managed∞ warfarin Asian patients

Major Bleeding (on-treatment period^)



(HR 0.61; 95%CI 0.41 to 0.89; p=0.011)

SUPERIOR SAFETY

Compared to well-managed∞ warfarin Asian patients

■ LIXIANA® (n=642) ■ Warfarin (n=641)

2017 APHRS AF Consensus*

ONCE daily LIXIANA® is the **ONLY** NOAC that has proven significant reduction in **All-cause death** in Asians[2]

Nonvalvular Atrial Fibrillation / ^ Time from first dose of study drug to last dose plus 3 days / △ Relative risk reduction / ∞ Median time in therapeutic range is 67.1% / * 2017 Consensus of the Asia Pacific Heart Rhythm Society on Stroke Prevention in Atrial Fibrillation

Ref. 1.Yamashita T et al.. Circ J 2016; 80: 860–869. 2. Chiang CE et al.. J. Arrhyth 33 (2017) 345–367.

LIXIANA® 60mg/30mg/15mg film-coated tablets: Each film coated tablet contains 60mg/30mg/15mg edoxaban (as tosilate). List of excipients: Mannitol (E421), Pregelatinised starch, Crospovidone, Hydroxypropylcellulose, Magnesium stearate (E470b), Hypromellose (E464), Macrogol 8000, Titanium dioxide (E171), Talc, Carnauba wax, Iron oxide yellow (E172), Iron oxide red (E172). Therapeutic Indications: Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA): 60mg LIXIANA® once daily. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults: 60mg LIXIANA® once daily following initial use of parenteral anticoagulant for at least 5 days. For NVAF and VTE 30 mg LIXIANA® once daily in patients with moderate or severe renal impairment (CrCL 15–50mL/min), body weight ≤60kg or concomitant use of P-glycoprotein (p-gp) inhibitors ciclosporin, dronedarone, erythromycin, or ketoconazole. Contraindications: Hypersensitivity to the active substance or any of the excipients; clinically significant active bleeding. Hepatic disease associated with coagulopathy and clinically relevant bleeding risk; Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities; Uncontrolled severe hypertension; Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, rivaroxaban, apixaban etc.) except under specific circumstances of switching oral anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter; Pregnancy and breast-feeding. Undesirable effects: Common: anaemia; epistaxis; lower GI haemorrhage; upper GI haemorrhage; oral/pharyngeal haemorrhage; nausea; blood bilirubin increased; gammaglutamyltransferase increased; cutaneous soft tissue haemorrhage; rash; pruritus; macroscopic haematuria/urethral haemorrhage; vaginal haemorrhage; puncture site haemorrhage; liver function test abnormal. Uncommon: hypersensitivity; intracranial haemorrhage (ICH); conjunctival/scleral haemorrhage; Intraocular haemorrhage; other haemorrhage; haemoptysis; blood alkaline phosphatase increased; transaminases increased; aspartate minotransferase increased; urticaria; surgical site haemorrhage. Rare: anaphylactic reaction; allergic oedema; subarachnoid haemorrhage; pericardial haemorrhage; retroperitoneal haemorrhage; Intramuscular haemorrhage (no compartment syndrome); Intra-articular haemorrhage; subdural haemorrhage; procedural haemorrhage.

Please see full Prescribing Information for LIXANA® before prescribing.

Daiichi-Sankyo

Daiichi Sankyo Hong Kong Limited.
Room 1801, 18/F., One Hysan Avenue, Causeway Bay, Hong Kong
Tel: (852) 2868 9079 Fax: (852) 2801 4341 www.daiichisankyo.com.hk

HK-DAI-LIX-1709011

HONG KONG MEDICAL JOURNAL 香港醫學雜誌
Volume 25 Number 1 **February 2019**
SUPPLEMENT 1

24th Medical Research Conference, 19 January 2019

Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Plenary 1

How alcohol-derived and endogenous aldehydes cause DNA damage and mutations in blood stem cells

KJ Patel
MRC Laboratory of Molecular Biology, Cambridge, United Kingdom

We have identified that endogenous and alcohol-derived aldehydes are a major source of endogenous DNA damage. A two-tier protection mechanism ensures that endogenous aldehydes do not cause permanent DNA damage and mutagenesis. New findings also reveal how a DNA crosslink caused by acetaldehyde is repaired, and they suggest the existence of a new DNA crosslink repair pathway that does not require DNA excision.

Plenary 2

Application of big data in the evaluation of real-life outcomes of pharmacological treatment in patients with attention deficit hyperactivity disorder

I Wong
Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong

Attention deficit hyperactivity disorder (ADHD) has a profound impact on many aspects of day-to-day life. People with ADHD have higher divorce rates, higher death and accident rates, and higher numbers of psychiatric hospitalisations, arrests, and incarcerations. Despite multiple clear indicators of negative outcomes, the majority of clinical trials continue to focus on reduction in core ADHD symptoms. This talk will demonstrate the application of big data in the evaluation of the effects of stimulant treatments on injury-related medical encounters, suicidal behaviour, psychotic behaviour, and criminality in people with ADHD. A particular emphasis will be on using healthcare big data from the Hong Kong Hospital Authority.

Diffusion-tensor cardiac magnetic resonance

D Pennell
National Heart and Lung Institute, Imperial College, London, United Kingdom

Only one tool exists to perform in vivo human non-invasive assessment of the myocardium at the microstructural level, namely diffusion-tensor cardiac magnetic resonance (DT-CMR). Diffusion-tensor cardiac magnetic resonance quantifies water diffusion in the myocardium, which is constrained by the myocardial micro-architecture. Diffusion aligned to the orientation of cardiomyocytes is greater than the diffusion in the perpendicular directions, and DT-CMR therefore yields information on cardiomyocyte organisation. The diffusion pattern can be visualised in three dimensions as an ellipsoid, which can be described by a mathematical tensor described by a set of mutually perpendicular eigenvectors E1, E2, and E3. We have published a robust histological validation[1] that shows E1 is aligned with cardiomyocyte orientation. Together with E2, this defines the sheetlet orientation (groups of cardiomyocytes about 6 thick separated by shear planes). Rotation and shear of the sheetlets during cardiac contraction is the predominant mechanism of left ventricular longitudinal shortening and radial thickening. We have shown in vivo impairment in sheetlet rotation with aberrant systolic and diastolic in hypertrophic and dilated cardiomyopathy, respectively.[1,2] Aberrant myocardial architecture is also evident in congenital heart disease[3] and myocardial infarction.[4] There is considerable potential in this new technology and its clinical utility remains to be elucidated.[5] However, it is already yielding considerable new insights into the functioning of the normal heart, bridging the gulf between the understanding of contraction of single cardiomyocytes at the microscopic level, and the contraction seen with clinical imaging techniques at the macroscopic level.

References

1. Nielles-Vallespin S, Khalique Z, Ferreira PF, et al. Assessment of myocardial microstructural dynamics by in vivo diffusion tensor cardiac magnetic resonance. J Am Coll Cardiol 2017;69:661-76.
2. Ferreira PF, Kilner PJ, McGill LA, et al. In vivo cardiovascular magnetic resonance diffusion tensor imaging shows evidence of abnormal myocardial laminar orientations and mobility in hypertrophic cardiomyopathy. J Cardiovasc Magn Reson 2014;16:87.
3. Khalique Z, Ferreira PF, Scott AD, et al. Deranged myocyte microstructure in situs inversus totalis demonstrated by diffusion tensor cardiac magnetic resonance. JACC Cardiovasc Imaging 2018;11:1360-2.
4. Kung GL, Vaseghi M, Gahm JK, et al. Microstructural infarct border zone remodeling in the post-infarct swine heart measured by diffusion tensor MRI. Front Physiol 2018;9:826.
5. Khalique Z, Ferreira PF, Scott AD, et al. Diffusion tensor cardiovascular magnetic resonance of microstructural recovery in dilated cardiomyopathy. JACC Cardiovasc Imaging 2018;11:1548-50.

1

Effects of *Dendrobium officinale* polysaccharides in cigarette smoke–induced inflammation in human airway epithelial NCI-H292 cells

YNE Au[1], YM Liang[1], MSM Ip[1], YB Zhang[2], JCW Mak[1,3]
[1]Department of Medicine, The University of Hong Kong, Hong Kong
[2]School of Chinese Medicine, The University of Hong Kong, Hong Kong
[3]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong

Background: Chronic obstructive pulmonary disease is one of the leading causes of death worldwide, and is incurable with currently available treatments. Cigarette smoking is one of the major risk factors. *Dendrobium officinale* polysaccharide (DOP) is the major ingredient extracted from the *D officinale* plant, which has been widely used as traditional Chinese medicine for years. This study aimed to explore the potential pharmacological effects of DOP on cigarette smoke–mediated airway inflammation.

Methods: NCI-H292 cells were cultured until 80% confluent. After cell arrest, cells were treated with cigarette smoke medium (CSM) in the absence and presence of DOP. The viability of cells at varying concentrations of CSM or DOP was assessed by MTT assay. Levels of pro-inflammatory marker interleukin (IL)-8 were measured by enzyme-linked immunosorbent assay in the supernatants of treated cells.

Results: NCI-H292 cells had poorer survival rate at CSM above 4%, whereas high dose of DOP did not exert any observable effect on cell viability. The CSM caused IL-8 release in a concentration-dependent manner. Low doses (<2.5 μg/mL) of DOP had no effect on IL-8 release, but high doses (5 and 10 μg/mL) of DOP caused significant elevation of IL-8 release that was effectively blocked by antioxidant N-acetylcysteine. Moreover, low dose of DOP (0.01 μg/mL) significantly inhibited CSM-induced IL-8 release, but high dose of DOP (10 μg/mL) showed potentiation on CSM-induced IL-8 release.

Conclusions: These findings suggest a narrow therapeutic range of DOP as an anti-inflammatory agent in airway cells.

Acknowledgement
This study was supported by the Seed Fund for Basic Research of the University of Hong Kong (Ref. 104004476) and by the Health and Medical Research Fund (Ref. 15161911).

2

Stroke incidence in Hong Kong after recall of contaminated generic valsartan

SLY Chan, MF Tsoi, TT Cheung, BMY Cheung
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: The Department of Health of Hong Kong notified doctors and issued a press release on 6 July 2018 about the recall of five products containing valsartan contaminated by N-Nitrosodimethylamine. Because sudden cessation of antihypertensive treatment can cause strokes, we studied the incidence of strokes to detect a possible increase following the recall.

Methods: Stroke episodes occurring from 7 July to 10 October 2018 were identified from the Clinical Data Analysis and Report System of the Hong Kong Hospital Authority. The number of strokes on each day was ascertained. As there is seasonal variation in the incidence of stroke, we used the corresponding period in 2017 for comparison. The mean number of strokes per day was analysed using unpaired *t* test.

Results: There were 5022 and 4717 stroke episodes in the respective time periods in 2017 and 2018. The daily incidence (mean ± standard deviation) was 52 ± 10 in 2017 and 52 ± 11 in 2018 (P>0.05). The mean difference (95% confidence interval) was 0.92 (-1.97 to 3.80).

Conclusions: Our results show no statistically significant increase in the number of strokes in Hong Kong following the drug recall. The fear was that hypertensive patients might have stopped taking their medications out of confusion. Our figures show that the withdrawal and replacement of the generic valsartan products were well managed, and there is no evidence of any increase in strokes during this period.

Evaluating cryolipolysis of submental fat in Asian patients

3

WMM Chan, SYN Shek, CK Yeung, HHL Chan
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Background: Submental fat can pose a significant aesthetic concern for some patients. Cryolipolysis is a non-invasive procedure that has been the United States Food and Drug Administration approved for the treatment of submental fat.

Objective: To assess the effect of cryolipolysis in the treatment of submental fat in Asian patients.

Methods: Six patients (all women) with mean age 46.5 (range, 30-63) years and of Asian descent were recruited into the study. All received one session of cryolipolysis, with treatment parameters of cooling temperature: -11°C and 45 minutes of treatment time. Assessments were done by comparing submental convexity in photographs taken at baseline, 6 weeks, and 12 weeks post-treatment. Submental convexity was scored by a physician on a 5-point scale: -1=worse, 0=no change, 1=slight improvement, 2=much improved, and 3=drastically improved.

Results: At 12 weeks after cryolipolysis treatment, one (16.7%) patient had much improvement, three (50%) patients had slight improvement, one (16.7%) patient had no change, and one (16.7%) patient had worsening of submental fat volume. Overall, four (66.7%) patients had some improvement in reduction of submental fat after treatment with cryolipolysis. There were no cases of reported numbness or adverse effects from treatment at 12-week follow-up.

Conclusion: Cryolipolysis appears to be safe and effective for the treatment of submental fat reduction.

Acknowledgement
This research was supported by Allergan Hong Kong Ltd.

Safety and efficacy of a 1060-nm diode laser for non-invasive body contouring

4

WMM Chan, SYN Shek, CK Yeung, HHL Chan
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Background: Non-invasive fat reduction and body contouring with cryolipolysis is gaining popularity, but pain and numbness can be an issue. The 1060-nm diode laser has been approved by the United States Food and Drug Administration for fat reduction treatments.

Objective: This study aimed to evaluate the safety and efficacy of 1060-nm diode laser machine for the treatment of subcutaneous abdominal fat reduction in Asian patients.

Methods: This was single-centre open-label retrospective cohort study, using a 1060-nm diode laser (parameters: fluence range 0.9-1.4 J/cm^2, 25 minutes for 1 cycle) for non-invasive body contouring. The treatment schedule was three treatments, 6 weeks apart. Patients were reviewed at baseline, 6 weeks, and 12 weeks. The efficacy of abdominal fat reduction using diode laser was assessed by ultrasound measurement of fat thickness at abdomen, right and left flank, at baseline, 6 weeks, and 12 weeks. The safety of the 1060-nm diode laser treatment was assessed by documentation of adverse events reported by patients.

Results: A total of nine patients (one man, and eight women) were recruited into the study. A total of 25 treatments were completed. Ultrasound of fat thickness at abdomen was 2.89 cm (0.89-3.36 cm) at baseline, 2.33 cm (1.08-3.31 cm) at 6 weeks, and 2.49 cm (2.05-3.21 cm) at 12 weeks. Five patients had reduction in abdominal thickness at 6 weeks (P=0.40). Six patients had reduction at 12 weeks although these changes were not statistically significant (P=0.67). Ultrasound of right and left flank at baseline, 6 weeks, and 12 weeks showed that changes in fat thickness were not statistically significant. One patient opted not to continue with treatment after the first session and the patient developed six lumps after initial treatment; this resolved after 5 months without intervention. Painless lumps with bruising was observed in a total of three (12.0%) treatments, and these resolved spontaneously from 2 weeks to 5 months. One patient developed a blister at the treatment site (4%); topical fusidic acid ointment was applied twice daily, and this resolved after 2 weeks.

Conclusion: The results show no significant reductions in reduction of fat thickness after diode laser treatment, based on ultrasound measurements. Long-term adverse effects of diode laser were not observed, but lumps and bruising developed in some patients. Larger scale studies are needed to observe the safety and adverse effects of diode laser for non-invasive fat reduction treatment.

Acknowledgement
This research was supported by Cynosure, Inc.

5

Effect of cigarette smoke on airway inflammation and mucus hypersecretion in submerged and well-differentiated airway epithelial cells

R Chen[1], MSM Ip[1], JCW Mak[1,2]
[1]Department of Medicine, The University of Hong Kong, Hong Kong
[2]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong

Introduction: Cigarette smoke (CS) is one of the major risk factors for the development of chronic obstructive pulmonary disease. To understand the pathogenesis and mechanism of CS-induced airway injury, submerged culture is widely implemented as a model for primary human airway epithelial cell research. However, a more effective and reliable model should be developed to replicate the characteristics of in vivo airway epithelia. We aimed to compare CS-induced inflammation and mucus hypersecretion in submerged and well-differentiated airway epithelial cells.

Methods: Primary normal human bronchial epithelial cells were cultured in either submerged condition in growth factor–supplemented medium to sub-confluence or differentiated at the air-liquid interface (ALI) for 28 days. The CS medium was directly applied to submerged culture or at the apical side of well-differentiated normal human bronchial epithelial cells for 24 hours (n=4). The expression of interleukin (IL)-6, IL-8, and *MUC5AC* were assessed by quantitative polymerase chain reaction and enzyme-linked immunosorbent assay.

Results: The basal secretions of both IL-6 and IL-8 were significantly greater in the supernatant of the basolateral side of the ALI culture than in the submerged culture (IL6: 812.5 ± 105.0 pg/mL vs 100.7 ± 7.5 pg/mL, P<0.001; IL-8: 28 955.0 ± 672.0 pg/mL vs 111.8 ± 10.2 pg/mL, P<0.001). Both IL-6 and IL-8 mRNA and protein were upregulated after CS medium exposure in both submerged and ALI culture. The CS medium also caused upregulation of *MUC5AC* mRNA in a dose-dependent manner with higher expression in ALI culture compared with submerged culture, in line with the observation of *MUC5AC* mucin elevation in ALI culture only.

Conclusion: Although CS induces airway inflammation and mucus hypersecretion in both submerged and ALI culture, ALI culture more closely resembles the in vivo environment with more serious inflammation and mucus secretion.

Acknowledgement
This work was supported by the YC Chan Scientist Award.

6

A novel functional screening platform using zebrafish model for the study of genetic mutations cooperation in acute myeloid leukaemia

YLB Cheng, BL He, DD Wong, AYH Leung
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Acute myeloid leukaemia is a highly genetically heterogeneous disease. Patients carry unique genetic mutational profile that affect their clinical outcome. Remarkably, there are common patterns of co-occurring mutations, indicating their potential cooperativity in driving leukaemia. This project presents a novel zebrafish platform that allows quick and traceable evaluation of the impact of different genetic mutation combinations on leukemogenesis and drug response, paving the way for personalised medicine.

Methods and Results: Zebrafish embryos were co-injected with combination of mutations (FMS-like tyrosine kinase 3 internal tandem duplications; *FLT3* ITD with *IDH2*^{R140Q}, *IDH2*^{R172K}, *IDH1*^{R132H} and *DNMT3A*^{R882H}), and their effect on the expression pattern and intensity of different myeloid lineage markers including PU.1 (myeloid progenitor), mpo (macrophage), c-myb (haematopoietic stem cell; HSC) and Sudan Black B staining (neutrophils or granulocytes) were evaluated. Consistent with TCGA database, which showed *FLT3* ITD mutation only co-occurred with *IDH2*^{R140Q} or *DNMT3A*^{R882H}, overexpression of *FLT3* ITD and *IDH2*^{R140Q} in zebrafish embryo promoted expansion of myeloid progenitors and granulocytes, while co-expression of *FLT3* ITD and *DNMT3A*^{R882H} promoted expansion of HSCs and granulocytes. No combinatory effects were observed between *FLT3* ITD and *IDH2*^{R172K} or *IDH1*^{R132H}. To establish a zebrafish-based platform for predicting differential drug responses for unique mutational profiles, zebrafish embryos were injected with *FLT3* ITD and *IDH2*^{R140Q} and a list of United States Food and Drug Administration–approved and preclinical drugs were examined for their efficacy on rescuing *FLT3* ITD/*IDH2*^{R140Q}-induced myeloid expansion. Although *FLT3* ITD inhibitor was able to rescue *FLT3* ITD–induced myeloid expansion, the effect was alleviated if *FLT3* ITD and *IDH2*^{R140Q} were co-expressed, indicating specific mutation patterns affected drug responses. To further validate our findings and study the long-term effect of mutation combinations, transgenic fish lines with *FLT3* ITD/*IDH2*^{R140Q} and *FLT3* ITD/*IDH2*^{R172K} under *Runx1* promoter (HSC lineage) were established.

Conclusion: Our results show that zebrafish can serve as an effective platform to study the cooperative effect of mutations in acute myeloid leukaemia and predict a better option for patients carrying unique genetic mutational profiles, paving the way for personalised medicine.

Acknowledgement
This research was supported by the Health and Medical Research Fund (Ref. 03144046).

7

Absence of inguinal lymph nodes impairs the browning of subcutaneous white adipose tissue in mice

LY Cheong[1,2], B Wang[1,2], L Shu[1,2], XP Wu[2,3], RLC Hoo[2,3], A Xu[1,2,3]
[1]Department of Medicine, The University of Hong Kong, Hong Kong
[2]State Key Laboratory of Pharmaceutical Biotechnology, The University of Hong Kong, Hong Kong
[3]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong

Introduction: The browning of white adipose tissue (WAT) has been proposed as a therapeutic strategy to combat obesity by enhancing energy expenditure. It is widely accepted that subcutaneous, but not visceral fat, can undergo extensive browning in response to cold exposure. However, the reason for this adipose depot specificity remains poorly understood. Interestingly, the anatomical location of lymph nodes (LNs) overlaps largely with the regions of adipose depots which are susceptible to browning (beiging). Thus, this study aimed to investigate the role of inguinal LNs (iLNs) in regulating the browning of WAT in mice.

Methods: Surgical removal of iLNs and pharmacologically induced LN-free mouse models using lymphotoxin beta receptor immunoglobulin fusion protein were performed. Mice were exposed to thermoneutral zone (30°C) and 2 days of cold challenge (6°C). Adipose tissues were then collected for the analysis of histologic structure, real-time polymerase chain reaction, immunoblotting, and flow cytometry.

Results: Mice without iLNs displayed impaired browning of inguinal WAT in response to chronic cold exposure, as evidenced by reduced multilocular lipid droplets, lower expression of uncoupled protein 1, and other thermogenic-related genes compared with control group in both mouse models. These impairments were reversed by replenishment with recombinant interleukin (IL)-33 protein. Mechanistically, IL-33 was released from iLNs into inguinal WAT to regulate the recruitment of group 2 innate lymphoid cells, oeosinophils, and alternatively activated macrophages. This led to the production of type 2 cytokines that are implicated in browning, such as IL-4 and IL-13. In addition, IL-33-induced type 2 immune responses and beiging were attenuated by sympathetic denervation of iLNs.

Conclusion: Inguinal LNs mediate cold-induced browning of WAT by facilitating the immunological and neurological crosstalk.

Acknowledgement
This research was supported by Hong Kong University Grants Committee RGC C7037-17W.

8

Epidemiology, characteristics, and survival of post-colonoscopy colorectal cancer in Hong Kong: a population-based study

KS Cheung, LJ Chen, WK Seto, WK Leung
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Population-based studies on post-colonoscopy colorectal cancer (CRC) from Asia are sparse. We aimed to determine the characteristics and risk factors of post-colonoscopy CRC in Hong Kong.

Methods: This is a retrospective cohort study recruiting patients aged ≥40 years undergoing colonoscopies between 2005 and 2013 based on a territory-wide electronic healthcare database in Hong Kong. Exclusion criteria included prior CRC, inflammatory bowel disease and prior colectomy. Post-colonoscopy CRC within 3 years (PCCRC-3y) was defined as CRC diagnosed between 6 and 36 months after index colonoscopy, while CRC diagnosed within 6 months of index colonoscopy was regarded as "detected CRC". Sites of CRC were categorised as proximal (proximal to splenic flexure) and distal cancer. We used multivariable logistic regression to derive adjusted odds ratio (aOR) of PCCRC-3y, and Cox model for adjusted hazard ratio (aHR) of all-cause mortality after CRC diagnosis.

Results: Of the 197 902 eligible patients, 10 005 (92.1%) were detected CRC and 854 (7.9%) PCCRC-3y (707 [82.8%] and 147 [17.2%] in the distal and proximal colon, respectively). The PCCRC-3y rate between 2005 and 2013 was 7.9%, with a significant increase in the PCCRC-3y rate from 4.1% to 9.7% (Poisson P<0.001) between 2005 and 2009, but a significant decrease from 9.7% to 7.7% (Poisson P=0.046) between 2009 and 2013. The median age at PCCRC-3y diagnosis was 75.9 (interquartile range [IQR], 65.5-83.8) years—a delay of 1.2 (IQR, 0.8-1.9) years from index colonoscopy—and 60.1% were men. Risk factors for PCCRC-3y included older age (aOR=1.07, 95% confidence interval [CI]=1.06-1.08), male sex (aOR=1.45, 95% CI=1.26-1.67), history of colonic polyps (aOR=1.31; 95% CI=1.13-1.51), polypectomy/biopsy at index colonoscopy (aOR=3.97; 95% CI=3.46-4.56), index colonoscopy by surgical specialty (aOR=1.53; 95% CI=1.31-1.78), and a higher annual colonoscopy volume of the centre. The median survival time was lower for patients with PCCRC-3y (1.9 years, 95% CI=1.7-2.6 years) when compared with those with detected CRC (5.2 years, 95% CI=4.8-5.6 years) [log-rank P<0.001]. Risk factors for all-cause mortality after CRC diagnosis included PCCRC-3y (aHR=1.31; 95% CI=1.19-1.43), proximal cancer location (aHR=1.42; 95% CI=1.31-1.54), and certain patient factors.

Conclusions: The PCCRC-3y rate is 7.9% in Hong Kong, with a high proportion (>80%) of distal cancers and a higher overall mortality compared with detected CRC. Measures to improve colonoscopy quality are needed to reduce the incidence of PCCRC in Hong Kong.

9

Statin use and gastric cancer risk in *Helicobacter pylori*–eradicated patients: a territory-wide study with propensity score matching

KS Cheung[1], EW Chan[2], AYS Wong[2], LJ Chen[1], WK Seto[1], ICK Wong[1,3], WK Leung[1]
[1]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong
[3]UCL School of Pharmacy, University College London, London, United Kingdom

Introduction: Despite successful *Helicobacter pylori* eradication, some individuals still progress to develop gastric cancer (GC). Although statins were shown to reduce GC risk, the results are largely confounded by *H pylori* status. The aim of this study was to investigate the effects of statins on GC development in *H pylori*–eradicated patients.

Methods: This was a cohort study using a territory-wide electronic healthcare database. All adult patients (≥18 years) who were prescribed clarithromycin-based triple therapy for *H pylori* infection between 2003 and 2012 were recruited. The observation period commenced from the date of *H pylori* therapy and follow-up was censored at GC diagnosis, death, or study end date (December 2015). Statin use was defined as >180-day use during the study period. Exclusion criteria included GC diagnosed within the first year of *H pylor*i therapy, a history of GC or gastrectomy, and failure of *H pylori* eradication. The subdistribution hazard ratio (SHR) of GC with statin use was estimated by competing risk regression with propensity score (PS) matching for other variables (age, sex, co-morbidities, and other medications).

Results: A total of 63 605 patients were recruited, with the mean (± standard deviation) age of receiving triple therapy being 55.6 ± 14.6 years. There were 29 640 (46.6%) men and 15 990 (25.1%) statin users. During a median follow-up of 7.6 years (interquartile range, 5.1-10.3 years), 169 (0.27%) of 63 605 patients developed GC (crude incidence rate: 3.5 per 10 000 person-years for the whole cohort; 2.4 vs 3.8 per 10 000 person-years for statin and non-statin users, respectively). A total of 22 870 patients were available for PS matching. A lower GC risk was observed in statin users (SHR=0.34; 95% confidence interval [CI]=0.19-0.61), with a PS-adjusted absolute risk difference between statin and non-statin use being 2.6 fewer GC (95% CI=1.56-3.12) per 10 000 person-years. A lower GC risk was observed with a longer duration of statin use (SHR=0.46; 95% CI= 0.25-0.86 for <5 years of use and SHR 0.43; 95% CI=0.29-0.66 for ≥5 years of use, P_{trend}<0.001). In addition, the SHR of GC with every 100 increases in cumulative defined daily doses of statins was 0.90 (95% CI=0.81-0.99).

Conclusions: Statin use is associated with a significantly lower GC risk among *H pylori*–eradicated patients, in a duration- and dose-response manner.

10

Mortality and causes of death in inflammatory arthritis patients in Hong Kong 1997-2016

TT Cheung, MF Tsoi, BMY Cheung, CS Lau
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Inflammatory arthritis patients have a higher mortality than the general population due to increased risks of cardiovascular diseases, infection, and cancer. Survival of these patients has improved significantly over the past decades due to improvement in treatment and complications. However, it is unknown if the survival of these patients in Hong Kong has also improved.

Methods: Patients with a diagnosis of rheumatoid arthritis (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS) from 1997 to 2016 were identified in the Clinical Data Analysis and Reporting System (CDARS). Patient demographics and causes of death were obtained from CDARS. Results were analysed using R version 3.4.3 with package "epitools" version 0.5-10. Mortality rate and standardised mortality ratio (SMR) were estimated every 5 years. Age and sex adjustment was conducted using census statistics from the Census and Statistics Department. A linear Poisson regression analysis was performed to evaluate the change in SMR over time.

Results: In all, 15 445, 2165 and 4488 patients with RA, PsA and AS were included in this analysis, respectively. The SMR of RA, PsA and AS dropped significantly over 20 years. There was a significant decrease in cardiovascular death in patients with RA and AS (P<0.001). However, infection remained the leading cause of death in the last 20 years.

Conclusion: Mortality in patients with inflammatory arthritis in Hong Kong has decreased significantly over the past 20 years.

11

Interferon-α induces AIM2 gene expression in systemic lupus erythematosus patients

JX Chow, IKY Lam, SYY Wong, CS Lau, VSF Chan
Division of Rheumatology and Clinical Immunology, Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Systemic lupus erythematosus (SLE) is a highly complex autoimmune disease. Excessive production of type I interferons (IFN-I), especially IFN-α and IFN-β, has been characterised in patients with SLE. The inflammasome, expressed primarily by myeloid cells, is a caspase-1 dependent multimeric protein complex that oligomerises in the cytosol following infections or endogenous stress to release pro-inflammatory cytokines interleukin (IL)-18 and IL-1β. The inflammasome generally comprises of (i) a sensor molecule, notably members of the nucleotide-binding domain and leucine-rich repeat–containing (NLR) protein family (eg, NLRP3) and the pyrin and HIN domain-containing family (eg, absent in melanoma 2 [AIM2]), (ii) an adaptor molecule apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and (iii) pro-caspase-1 which will be self-cleaved to active caspase-1. We have previously reported that SLE monocytes expressed abnormally elevated mRNA level of AIM2, which uniquely senses double-stranded DNA. The AIM2 expression also positively correlated with IFN-sensitive genes in SLE monocytes. This study therefore aimed to evaluate if serological factors in SLE serum, especially IFN-I, could dysregulate AIM2 inflammasome response in healthy monocytes.

Methods: Healthy monocytes were cultured overnight in pooled normal plasma, SLE plasma and purified IFN-α, respectively. The expression levels of AIM2, NLRP3, ASC, CASP1, MX1, LY6E, and IFIT1 were evaluated by quantitative real-time polymerase chain reaction.

Results: The SLE plasma and IFN-α treatment significantly induced the expression of AIM2 in healthy monocytes as compared with normal plasma and control treatments, respectively.

Conclusion: The SLE plasma dysregulates AIM2 gene expression in normal monocytes. The IFN-αinduction of AIM2 gene expression appears to be "dose" dependent. It remains to be verified if pathogenic IFN-I in the SLE plasma are solely responsible for driving the dysregulation of AIM2 inflammasome, and the mechanism for this dysregulation.

Acknowledgement
This project was supported by the Hong Kong RGC General Research Fund (Ref. 17123517).

12

Accuracy and reliability of detecting the intensity of spinal inflammation on short tau inversion recovery sequence according to the Spondyloarthritis Research Consortium of Canada Magnetic Resonance Imaging index in axial spondyloarthritis

HY Chung, TT Cheung, VWH Lau, KH Lee, FKP Chan, HHL Tsang, SCW Chan, CS Lau
Division of Rheumatology and Clinical Immunology, Department of Medicine, The University of Hong Kong, Hong Kong

Objective: To determine the accuracy of detecting the intensity of spinal inflammation on short tau inversion recovery (STIR) sequence according to the Spondyloarthritis Research Consortium of Canada (SPARCC) magnetic resonance imaging (MRI) index by comparing with the apparent diffusion coefficient (ADC) values of the active MRI lesions in axial spondyloarthritis.

Methods: Fifty active lesions in STIR sequence of spinal MRI were identified. With reference to sites of active lesions in STIR, the corresponding region of interest on ADC map was drawn to determine the maximum ADC (ADC_{max}), mean ADC (ADC_{mean}), normalised maximum ($nADC_{max}$) and mean ($nADC_{mean}$). Four independent readers, including a radiologist, two rheumatologists, and a medical trainee scored the identified active lesions as "intense" or "non-intense" according to the SPARCC MRI index. They were compared with ADC_{max}, ADC_{mean}, $nADC_{max}$, and $nADC_{mean}$ for assessment of accuracy. Regression analyses were used to adjust potential factors that could affect ADC. Cohen's kappa coefficient (K) was used to determine the inter-reader agreements.

Results: There were differences in ADC_{max} between "intense" and "non-intense" lesions scored by three of the four readers (1365.5 ± 288.0 vs 1196.4 ± 234.1, P=0.03; 1390.1 ± 248.9 vs 1229.6 ± 272.7, P=0.05; 1405.2 ± 290.2 vs 1232.6 ± 254.6, P=0.04). For ADC_{mean} of the lesions, differences were observed in "intense" and "non-intense" lesions scored by one reader only (868.1 ± 209.2 vs 720.2 ± 247.7, P=0.04). Inter-reader agreements were only slight to fair (K=0.08-0.34). Regression analyses showed the "intense" lesions were associated with higher ADC values after adjustment for confounders.

Conclusion: Humans are able to differentiate degree of spinal inflammation on MRI but reliability is only fair.

Apparent diffusion coefficient to assess spinal disease activity in axial spondyloarthritis

13

HY Chung, KH Lee, CS Lau
Division of Rheumatology and Clinical Immunology, Department of Medicine, The University of Hong Kong, Hong Kong

Purpose: To determine the associations between apparent diffusion coefficient (ADC) of discovertebral lesions and disease activities indices, and functional parameter in patients with axial spondyloarthritis (axSpA).

Methods: In this prospective study, 243 study participants with back pain diagnosed and fulfilled the Assessment of Spondyloarthritis International Society criteria for axSpA were recruited from four rheumatology centres between April 2014 and March 2018. Clinical, biochemical, and radiological parameters were collected. Bath indices (Bath Ankylosing Spondylitis Functional Index [BASFI], Bath Ankylosing Spondylitis Disease Activity Index [BASDAI], Bath Ankylosing Spondylitis Global Index [BASGI]) were determined. All participants underwent whole-spine magnetic resonance imaging using short tau inversion recovery sequence and diffusion-weighted imaging. Two independent readers identified the presence of discovertebral lesions. Regression analyses were used to determine the mean, maximum, and normalised mean/maximum ADCs ($nADC_{mean}$/$nADC_{max}$) of the discovertebral lesions with disease activity and functional parameter.

Results: There were 132 men (mean age, 41.4 ± 13.3 years) and 111 women (mean age, 45.3 ± 13.4 years) included in the study. Discovertebral lesions were found in 55 out of 243 (22.6%) participants. Ninety-one (5 cervical, 61 thoracic, 25 lumbar) lesions were identified. Upon adjusting for confounding factors, $nADC_{mean}$ and $nADC_{max}$ were positively associated with intensity of back pain ($nADC_{mean}$ B=0.14, P=0.04; $nADC_{max}$ B=0.27, P=0.01) and BASGI ($nADC_{mean}$ B=0.13, P=0.04; $nADC_{max}$ B=0.21, P=0.04). Maximum ADC was associated with intensity of back pain (B=0.05, P=0.05), stiffness score (BASDAI question 6; B=0.04, P=0.04), BASFI (B=0.05, P=0.02), and BASGI (B=0.04, P=0.05). Mean ADC was associated with BASFI (B=0.03, P=0.04). The Spondyloarthritis Research Consortium of Canada score was only associated with BASFI (B=0.60, P=0.01).

Conclusion: Apparent diffusion coefficients and nADCs of discovertebral lesions are positively associated with disease activity, functional impairment, and patient global assessment in axSpA.

Clinical predictors of disease relapse and mortality in immunoglobulin G4–related disease from a retrospective cohort in Hong Kong

14

SCT Wong, CS Lau, HY Chung
Division of Rheumatology and Clinical Immunology, Department of Medicine, The University of Hong Kong, Hong Kong

Objective: To describe and determine the clinical predictors of disease relapse and mortality retrospectively in a cohort of immunoglobulin G4–related disease (IgG4-RD).

Methods: Patients with an expert diagnosis of IgG4-RD were recruited from five rheumatology centres in Hong Kong. Clinical data, duration of follow-up, time to initial relapse, and time to mortality were recorded. Data were analysed using univariate and multivariate Cox regression models to determine clinical predictors of relapse and mortality. Kaplan-Meier log survival curves were plotted for variables stratified by use of immunosuppressant therapy.

Results: A total of 143 patients with IgG4-RD were recruited; 106 (74.1%) were men. Mean age of disease onset was 62.3 ± 12.7 years and mean disease duration was 3.8 ± 3.5 years. Multivariate Cox regression showed that combined surgery and steroid induction therapy (hazard ratio [HR]=2.46, 95% confidence interval [CI]=1.39-4.35, P<0.01) was positively associated with initial relapse and that immunosuppressant therapy (HR=0.45, 95% CI=0.23-0.86, P=0.02) was negatively associated with relapse. When the variable "immunosuppressant therapy" was replaced with "steroid-sparing immunosuppressant therapy" and "dosage of prednisolone" in multivariate Cox regression, the steroid-sparing therapy showed a tendency to be negatively associated with initial relapse (HR=0.36, 95% CI=0.11-1.19, P=0.09). In the models on mortality, multivariate Cox regression showed that "age at diagnosis" (HR=1.14, 95% CI=1.02-1.27, P=0.02), and "CRP level at diagnosis" (HR=1.03, 95% CI=1.00-1.06, P=0.03) were positive predictors of mortality.

Conclusion: We recommend steroid-sparing immunosuppressant maintenance therapy in selected group of patients and careful monitoring in elderly patients with IgG4-RD.

Clinical pathway to improve treatment compliance, coronary revascularisation rate, and patient outcome in non-ST elevation acute coronary syndrome

15

JX Fang, FCC Tam
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Background: Adherence to non-ST elevation acute coronary syndrome treatment guidelines is suboptimal especially in elderly patients. We examined the use of a checklist and a clinical pathway for better medical and interventional treatment.

Methods: Of 1510 consecutive patients, 294 patients with median age 79 years were managed with a checklist at Queen Mary Hospital, Hong Kong in 2014 to 2018. Mean follow-up was 463 days. Items on the checklist included medical therapy, risk assessment (Killip class/GRACE score), and revascularisation plan. Checklists were reviewed by cardiologists to plan further management. Data were collected retrospectively. Compliance to guideline-directed medical therapy, interventional strategy, major adverse cardiovascular event (MACE), and survival at 180 days, and length of hospital stay were compared. Multivariate Cox proportional hazard model adjusted for age, sex, diabetes, hyperlipidaemia, hypertension, heart failure, history of stroke, acute coronary syndrome, coronary revascularisation, chronic kidney disease stage (modification of diet in renal disease), Killip class, troponin elevation, malignancy, chronic lung disease, haemoglobin and bilirubin. Logistic regression, C-statistic, goodness-of-fit, followed by propensity score matching gave two groups each of 294 risk-adjusted patients. Kaplan-Meier function and log-rank test were done.

Results: Use of a clinical pathway decreased mortality and MACE in 180 days in the multivariate Cox model (hazard ratio=0.59, 95% confidence interval [CI]=0.42-0.81, P=0.001 for death; hazard ratio=0.69, 95% CI=0.53-0.88, P=0.003 for MACE). The model based on logistic regression had a C-statistic of 0.83 for 180-day mortality (Hosmer-Lemeshow goodness-of-fit P=0.18). After propensity score matching, 42 (14.3%) patients in pathway versus 72 (24.5%) patients not in pathway died in 180 days (log-rank P=0.0099). Major adverse cardiovascular event occurred in 61 (20.7%) patients in pathway versus 86 (29.3%) patients not in pathway (log-rank test P=0.0495). In-patient revascularisation approach was used in 51.0% of patients in the pathway group versus 21.4% not in pathway. Prescription of all major guideline-directed drugs improved (98.0% vs 88.1% for statin, P<0.001; 93.5% vs 75.9% for P2Y12 inhibitor, P<0.001). Median length of stay increased from 4 to 6 days.

Conclusion: Use of a clinical pathway for patients with non-ST elevation acute coronary syndrome improves treatment and patient outcomes but lengthens hospital stay.

Tricuspid regurgitation effects patient outcome in early and late heart failure

16

JX Fang, KH Yiu
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Background: Severe tricuspid regurgitation (TR) is associated with poor outcome, but TR remains poorly understood and undertreated. We examine the impact of TR at different stages of heart failure.

Methods: In total, 3275 patients with out-patient echocardiogram done at Queen Mary Hospital, Hong Kong between 2013 and 2015 with mean follow-up of 1092 days were analysed retrospectively. The TR was graded by a semi-quantitative approach using jet area on multiple views and inferior vena cava flow pattern. Multivariate Cox proportional hazard model assessed for mortality, time-to–first heart failure hospitalisation, and major adverse cardiovascular event in 3 years. Results were adjusted for age, sex, left ventricular ejection fraction, left atrial enlargement, pre-existing cardiovascular, peripheral vascular and cerebrovascular disease, moderate-to-severe aortic or mitral valve disease, pulmonary hypertension, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, malignancy, and heart failure stages (0=no heart failure, A=risk factor present, B=structural abnormality, C=symptomatic, D=advanced). Subgroup analysis stratified by heart failure stage 0, stage A-B, and stage C-D was done. Kaplan-Meier function, log-rank test, logistic regression, receiver operating characteristic curve, and goodness-of-fit test were done.

Results: In patients with stage A-B heart failure, severe TR had a hazard ratio of 2.93 for death in 3 years compared with no TR (95% confidence interval [CI]=1.11-7.73, P=0.03) and moderate TR had a hazard ratio of 2.35 (95% CI=1.28-4.31, P=0.006). In stage C-D, severe TR had a hazard ratio of 2.17 (95% CI=1.12-4.16, P=0.02) and moderate TR had no significant effect (hazard ratio=1.09, P=0.77). For heart failure hospitalisation, severe TR had no significant association in stage A-B but had a hazard ratio of 3.74 in stage C-D (95% CI=1.81-7.7, P<0.001). In this model, TR had no impact on major adverse cardiovascular events. No significant interaction was found between TR and heart failure stage, ejection fraction, or valvular heart disease. The model had C-statistics of 0.82 for 3-year mortality, 0.90 for heart failure hospitalisation, and 0.81 for major adverse cardiovascular events, with insignificant Hosmer-Lemeshow goodness-of-fit test P for each, indicating good fit.

Conclusion: The association between TR and increased mortality in heart failure is apparent early and attenuated later, whereas the association between TR and heart failure symptom decompensation appears later.

Cardiovascular outcomes in trials of new antidiabetic drug classes: a network meta-analysis

17

Y Fei, MF Tsoi, BMY Cheung
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: New antidiabetic drugs are required to demonstrate safety in cardiovascular outcome trials. However, they are rarely compared with each other. We therefore performed a network meta-analysis to compare new antidiabetic drug classes with respect to cardiovascular outcomes.

Methods: We searched for cardiovascular outcome trials involving glucagon-like peptide-1 receptor agonists (GLP-1 RAs), sodium-glucose co-transporter 2 (SGLT-2) inhibitors, and dipeptidyl peptidase-4 (DPP-4) inhibitors in patients with type 2 diabetes mellitus (T2DM) using major adverse cardiovascular events (MACEs) and mortality as endpoints. Network meta-analysis was performed using random-effects model in R.

Results: Ten trials with altogether 81 825 patients with T2DM were eligible to be included. Glucagon-like peptide-1 receptor agonists and SGLT-2 inhibitors significantly reduced MACEs (odds ratio [OR]=0.86, 95% confidence interval [CI]=0.78-0.94 and OR=0.86, 95% CI=0.76-0.96) when compared with placebo. Sodium-glucose co-transporter 2 inhibitors significantly reduced cardiovascular mortality and all-cause mortality when compared with DPP-4 inhibitors (OR=0.77, 95% CI=0.61-0.98 and OR=0.77, 95% CI=0.64-0.92) and placebo (OR=0.76, 0.63-0.92 and OR=0.79, 95% CI=0.68-0.91), respectively. Glucagon-like peptide-1 receptor agonists lowered the risk of MACEs (OR=0.87, 95% CI=0.77-0.99) compared with DPP-4 inhibitors, and showed a trend towards a lower risk of non-fatal myocardial infarction (OR=0.87, 95% CI=0.76-1.00) when compared with placebo. No significant differences were found in the risk of non-fatal stroke.

Conclusion: Glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter 2 inhibitors both reduce MACEs when compared with placebo. Sodium-glucose co-transporter 2 inhibitors are the most beneficial in reduce mortality while GLP-1 RAs reduce cardiovascular events the most. Dipeptidyl peptidase-4 inhibitors do not worsen cardiovascular outcomes, but are inferior to GLP-1 RAs and SGLT-2 inhibitors. Our findings support SGLT-2 inhibitors and GLP-1 RAs as the preferred treatment for patients with T2DM to reduce cardiovascular risk.

Efficacy and safety of newer P2Y12 inhibitors versus clopidogrel in patients with acute coronary syndrome

18

Y Fei, CK Lam, BMY Cheung
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Newer P2Y12 inhibitors are more potent than clopidogrel. Whether they are safer or more efficacious in patients with acute coronary syndrome (ACS) is uncertain. We used a network meta-analysis to compare different P2Y12 inhibitors with respect to clinical outcomes.

Methods: We searched for randomised controlled trials comparing clopidogrel, prasugrel, ticagrelor, or cangrelor, in combination with aspirin in patients with ACS. Those reporting major adverse cardiovascular events, bleeding events and deaths were eligible to be included. Network meta-analysis was performed using random-effects model in R.

Results: Fifteen trials with altogether 69 086 patients were included. Compared with clopidogrel, prasugrel significantly reduced major adverse cardiovascular events (odds ratio [OR]=0.80, 95% confidence interval [CI]=0.66-0.98) whereas ticagrelor significantly reduced all-cause mortality (OR=0.83, 95% CI=0.71-0.95). Prasugrel and ticagrelor both lowered the risk of myocardial infarction (OR=0.79, 95% CI=0.67-0.94 and OR=0.78, 95% CI=0.63-0.97), cardiovascular mortality (OR=0.87, 95% CI=0.76-0.99 and OR=0.84, 95% CI=0.73-0.98), and stent thrombosis (OR=0.48, 95% CI=0.35-0.64 and OR=0.62, 95% CI=0.45-0.86), respectively. However, there was a significant increase in thrombolysis in myocardial infarction major bleeds (OR=1.26, 95% CI=1.02-1.55) and minor bleeds (OR=1.44, 95% CI=1.16-1.77) with prasugrel. In addition, prasugrel had fewer stent thromboses than cangrelor (OR=0.60, 95% CI=0.39-0.93) but more thrombolysis in myocardial infarction minor bleeds than ticagrelor (OR=1.42, 95% CI=1.08-1.87). No significant increase in the risk of stroke was found.

Conclusion: Prasugrel and ticagrelor reduce the risk of cardiovascular events and deaths in patients with ACS when compared with clopidogrel. Cangrelor is comparable to clopidogrel. Prasugrel gives the most benefits among the newer P2Y12 inhibitors, but at the expense of an increase in bleeding. The choice of a newer P2Y12 inhibitor over clopidogrel should be made after considering the benefit-risk profile of each patient with ACS.

19

Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: a network meta-analysis

Y Fei, MF Tsoi, BMY Cheung
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Although the recommended duration of dual antiplatelet therapy (DAPT) after drug-eluting stent implantation has been shortened in the current guidelines, the optimal duration is as controversial as ever. We therefore performed a network meta-analysis incorporating the latest trials to assess the risks and benefits of different DAPT durations.

Methods: We searched for randomised controlled trials (RCTs) comparing different DAPT durations after drug-eluting stent implantation and reporting frequencies of cardiovascular and bleeding events. Data analysis was performed using R statistics.

Results: Fifteen RCTs with altogether 42 317 patients were finally included. Extended DAPT (>12 months) significantly reduced the frequencies of myocardial infarction (odds ratio [OR]=0.54, 95% confidence interval [CI]=0.44-0.65 and OR=0.54, 95% CI=0.41-0.70), and stent thrombosis (OR=0.43, 95% CI=0.29-0.63 and OR=0.51, 95% CI=0.33-0.78) when compared with 12-month and short-term DAPT (<12 months), respectively. However, the risk of major bleeding (OR=1.47, 95% CI=1.17-1.85 and OR=2.03, 95% CI=1.40-2.94) and all-cause mortality (OR=1.27, 95% CI=1.03-1.56 and OR=1.30, 95% CI=1.04-1.62) was substantially increased when compared with 12-month and short-term DAPT, respectively. No significant difference was found in cardiovascular mortality, stroke, and repeat revascularisation.

Conclusion: Extended DAPT has the lowest rate of myocardial infarction and stent thrombosis, but the highest risk of major bleeding and all-cause mortality. Clinical trial evidence favours short-term more than extended DAPT because of increased mortality. Duration of DAPT should be individualised according to the risk–benefit profile of each patient.

20

Role of lactate in obesity-induced adipose tissue inflammation

TS Feng[1,2], HXY Hui[1,3], AM Xu[1,2,3]
[1]State Key Laboratory of Pharmaceutical Biotechnology, The University of Hong Kong, Hong Kong
[2]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong
[3]Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Obesity is characterised by the increased inflammation level in adipose tissue, which contributes to the development of metabolic dysfunctions. Polarisation of macrophage serves as the major effector of adipose tissue inflammation. In addition, the expansion of the adipocytes in obesity increases the hypoxia level in adipose tissue, which induces the production of lactate. However, whether and how lactate plays a role in obesity-induced adipose tissue inflammation and macrophage polarisation remains poorly understood.

Methods: Lactate and lactate dehydrogenase activity were measured by biochemical assays. Adipose tissue–specific lactate dehydrogenase A knockout mice and wild-type mice were treated with high-fat diet to induce obesity. Body weight, fat mass and glucose tolerance test were monitored regularly. Macrophages were polarised to M1 with the treatment of lactate and different inhibitors. The inflammation levels of adipose tissue and macrophages were measured by western blotting, real-time polymerase chain reaction, and flow cytometry.

Results: Lactate level was found to be increased in obese adipose tissues compared with the lean control. The *Ldha* knockout mice had improved systemic glucose metabolism and alleviated M1 macrophage accumulation in the adipose tissue in obesity. In the in vitro study, lactate was found to be crucial for the M1 polarisation of macrophage by inhibiting the activity of prolyl hydroxylase 2 and activating hypoxia inducible factor and nuclear factor-αB pathways.

Conclusion: Obesity-induced lactate accumulation promotes the development of metabolic diseases by increasing the M1 polarisation of macrophage and aggravating the adipose tissue inflammation.

Acknowledgement
This research was supported by the Health and Medical Research Fund (Ref. 05163426).

21

Macrophage-specific knockout of Cpt1a leads to leaner phenotype and improved insulin sensitivity in mice under high-fat diet feeding

Y Gao, TS Feng, Q Liu, XY Hui, A Xu
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: M2 macrophages are known to have strengthened lipid uptake and β-oxidation. Cpt1a is a mitochondria membrane protein that limits long-chain fatty acid oxidation rate. However, the role and function of Cpt1a in macrophage polarisation has not been reported. Our objective is to investigate the possible role of Cpt1a in macrophage polarisation and its potential function in the development of obesity and insulin resistance.

Methods: We generated macrophage-specific Cpt1a knockout mice by using CPt1a-flox mice that we constructed previously, and LysM-cre mice from Jackson laboratory. The mice were fed with high-fat high-glucose diet (HFD) and the metabolic profiles such as body weight, body composition (fat/lean), respiration, glucose/insulin tolerance were tracked for further analysis. Bone marrow–derived macrophages from wild-type/Lys-Cpt1a mice were used for in vitro study.

Results: We found that Lys-Cpt1a mice have leaner bodyweight under HFD feeding, and the glucose and insulin tolerance of these mice also improved. In vitro, we found that the inflammation level of M1 macrophages were significantly decreased with CPT1a knockout.

Conclusion: Based on these preliminary results, we hypothesise that the absence of CPT1a in macrophages results in lower inflammation level of M1 macrophages, thus leading to a protective effect against obesity and insulin resistance. Further study is needed to verify these results.

22

Risk of gastrointestinal bleeding in low-dose aspirin users who had received *Helicobacter pylori* eradication therapy: a comparison of new users with chronic users

CG Guo[1], KS Cheung[1], EW Chan[2], L Chen[1], ICK Wong[2], WK Leung[1]
[1]Department of Medicine, The University of Hong Kong, Hong Kong
[2]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong

Introduction: The role of *Helicobacter pylori* infection in low-dose aspirin users remain controversial. We evaluated the risk of gastrointestinal bleeding (GIB) in a large cohort of *H pylori*–infected patients who had received eradication therapy and were newly started on aspirin as compared with chronic aspirin users.

Methods: We included *H pylori*–infected patients who had received a course of clarithromycin-based triple therapy from 2003 to 2012. Patients were divided into three cohorts according to aspirin use: new users (commenced after *H pylori* eradication), chronic users (commenced before and resumed after *H pylori* eradication), and non-users. The primary outcome was the risk of GIB in new aspirin users compared with chronic users. Cox regression model was used to compute the hazard ratios (HR) and 95% confidence intervals (CI) of risk of GIB. Propensity score matching was used to compare the GIB risk between new and chronic aspirin users.

Results: In total, 61 438 *H pylori*–eradicated patients were included in the analysis (6985 new users, 5545 chronic users and 48 908 non-users). The crude incidence rate of GIB in new, chronic and non-users was 15.4, 12.4 and 3.6 per 1000 person-years (log-rank test P<0.001), respectively. New aspirin users had a higher risk of GIB as compared with chronic users (HR with propensity score matching 1.89, 95% CI=1.29-2.70). The bleeding risk decreased over time (HR=0.91; 95% CI=0.84-0.99), which was only in upper but not in lower GIB. Gastro-protective agents were associated with a lower risk of GIB (HR=0.34, 95% CI=0.25-0.46).

Conclusion: After *H pylori* eradication, new aspirin users still have a significantly higher risk of GIB as compared with chronic users, but the risk decreases over time. Gastro-protective agents are associated with a lower risk of GIB in aspirin users after *H pylori* eradication.

Role of neuro-inflammation in cognitive impairment in epilepsy: a review of the current literature

23

CH Ho[1], RWH Ho[1], T Didik[1], WCY Leung[2], RSK Chang[2]
[1]Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[2]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Cognitive impairment is an integral component in the management of epilepsy. Found in 70% to 80% of patients with epilepsy, cognitive impairment leads to significant morbidity in terms of daily function and quality of life. It may be overlooked in daily clinical practice, poorly assessed, or poorly managed. We performed a qualitative review to explore the role of neuro-inflammation as a possible predisposing or contributing factor to cognitive impairment in epilepsy.

Methods: The PubMed database was searched, including relevant articles up to 1 October 2018, with combination of search terms including 'neuroinflammation', 'cognition', 'epilepsy', 'IL-1', 'TNF-alpha', 'COX', 'IL-6', and 'neuroimaging'.

Discussion: Microgliosis and the subsequent activation of neuro-inflammatory cascades are demonstrated in epileptogenesis. Through animal models, these cascades are shown to induce cognitive deficits by influencing neuronal apoptosis, excitotoxicity, hippocampal function, neuroplasticity, and neurogenesis. Clinically, elevated serum and cerebrospinal fluid inflammatory markers are well appreciated in epilepsy. Various neuroimaging modalities have demonstrated evidence of neuro-inflammation in areas of epileptogenic foci.

Conclusion: Neuro-inflammation may be an overlapping point in the neurobiological origin of epileptogenesis and cognitive deficits in epilepsy. This warrants further research on biochemical markers and neuroimaging as prognostic indicators of cognitive impairment, and the use of anti-inflammatory or immunomodulatory agents as part of management in epilepsy.

Clinical features and predictors of depression in people with epilepsy

24

PH Ho, CYW Leung, IYH Leung, RSK Chang
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: People with epilepsy are prone to depression. Studies on clinical features of this group have shown inconsistent results. This study aimed to further investigate this issue and to identify predictors of depression co-morbidity.

Methods: All adult patients at our epilepsy clinic were included; those with intellectual disability or other psychiatric disorders were excluded. Cases were divided into study and control groups depending on the presence of depression co-morbidity. Demographics, epilepsy details, clinical features, and use of anticonvulsants were compared. Relevant factors were analysed for their predictive value of depression development in people with epilepsy by binomial logistic regression. Patients with depression diagnosis before epilepsy onset were excluded from the regression model. Statistical significance was set at $P<0.05$.

Results: In total, 44 out of 558 people with epilepsy (7.9%) had depression co-morbidity. People with epilepsy with depression were more often female ($P=0.005$) and older age ($P<0.001$). Temporal lobe epilepsy ($P=0.012$) and higher number of anticonvulsant drug use ($P=0.003$) were more common in the depression group than in the control group. No difference was observed in other epilepsy-related factors including aetiology, seizure type, laterality of epileptic focus, and refractoriness. Binomial logistic regression showed that female sex ($P=0.01$; odds ratios [OR]=3.56), refractory epilepsy ($P<0.001$; OR=4.79) and clonazepam use ($P<0.001$; OR=14.41) were significant predictors of depression co-morbidity, whereas valproate use ($P=0.031$; OR=0.37) was a significant protective factor.

Conclusion: Our study demonstrates a bidirectional relationship between epilepsy control and depression co-morbidity. Antiepileptic drug use also plays a role in development of depression. Better understanding of clinical features may help future studies on the pathophysiology of depression in people with epilepsy, to formulate better treatment for these patients.

13-Valent pneumococcal conjugated vaccine in patients with chronic illness: a double-blind randomised controlled trial

25

IF Hung[1], KH Chan[1], A Tam[2]
[1]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]Department of Microbiology, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: *Streptococcus pneumoniae* infection can cause life-threatening pneumonia and extrapulmonary complications. Data on the direct comparison of the 23-valent pneumococcal polysaccharide vaccine (PPV) and the 13-valent pneumococcal conjugate vaccine (PCV) in adult patients with chronic illness are lacking.

Methods: We conducted a prospective double-blind randomised controlled trial among adult patients with chronic illness between 1 April 2015 and 30 March 2018, for virologically confirmed influenza A (H3N2) infection. Patients were randomly assigned to either a single dose of PPV or PCV in the ratio of 1:1. All enrolled patients were followed up for 18 months. The primary endpoint was the proportion of strong responders at 6 months, as defined by ≥4-fold increase of pre- and post-vaccination mean pneumococcal immunoglobulin G (IgG) enzyme-linked immunosorbent assay antibody. The secondary endpoints included the geometric mean concentration and the proportion of strong responders at 12 and 18 months; the hospitalisation rate for pneumococcal pneumonia, invasive pneumococcal disease, all-cause pneumonia, and underlying diseases; and mortality over 18 months.

Results: Between 1 April 2015 and 30 March 2018, 408 patients were screened, and 355 patients were recruited and randomised to receive a single dose of intramuscular PCV and PPV. The baseline demographics were similar between the two groups. There was no difference in both the proportion of strong responder and the overall IgG serotype-specific geometric mean concentration in the vaccine containing serotype 3 and 19F. The overall IgG response towards serotype 3 in both groups were poor. There was no difference in the clinical outcomes of all-cause mortality, mortality related to pneumonia and the overall hospitalisation rate between the two groups, despite a trend towards fewer hospitalisation and all-cause mortality in the PCV group. None of the patients in either group were diagnosed to have pneumococcal infection.

Conclusion: This study demonstrates that both PPV and PCV vaccination protect patients with chronic illness against pneumococcal infection. Overall immunogenicity of both vaccines against serotype 3 is poor. Long-term follow-up of these patients is be warranted.

Acknowledgement
This research was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (Ref. RRG-18).

Treatment of influenza A infection with celecoxib

26

IF Hung[1], KK To[2], KY Yuen[2], A Tam[2]
[1]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]Department of Microbiology, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Influenza A (H3N2) caused excessive hospitalisations and deaths. We assessed the efficacy and safety of celecoxib and oseltamivir combination for treatment of severe influenza requiring hospitalisation.

Methods: We conducted a prospective double-blind randomised controlled trial among adult patients hospitalised between December 2014 and March 2017, for virologically confirmed influenza A (H3N2) infection. Patients were randomly assigned to either a combination of oseltamivir 75 mg twice daily and celecoxib 200 mg daily for 5 days, or oseltamivir 75 mg twice daily and placebo capsule for 5 days as control (1:1). The primary endpoint was 28-day mortality. The secondary endpoint was serial changes in post-treatment nasopharyngeal aspirate viral load, National Early Warning Score (NEWS), cytokine interleukin (IL)-6 and IL-10 levels, and the length of hospitalisation.

Results: Between December 2014 and March 2017, we enrolled 120 influenza A (H3N2) patients. Of these, 60 (50%) were randomly assigned to the celecoxib-oseltamivir group. There was no difference in baseline findings between the two groups. Adverse events were uncommon. Twenty-three patients succumbed during the 28-day follow-up. The celecoxib-oseltamivir group had significantly lower 28-day mortality (P=0.037) than the control. Despite no difference in the serial viral titre, the serial IL-6 and IL-10 levels were significantly lower in the celecoxib-oseltamivir group than the control group from day 1 to 5 post-treatment (P<0.05) and the serial NEWS from day 1 to 3 (P<0.01) post-treatment.

Conclusion: The combination of celecoxib-oseltamivir reduces mortality, serial NEWS, and cytokine levels in hospitalised influenza A (H3N2) patients without increased adverse effects.

Acknowledgement
This research was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (Ref. RRG-18).

27

Adiponectin suppresses oligomeric amyloid-β–induced inflammatory response of microglia via AMPK–nuclear factor-κB signalling pathway

M Jian, JSC Kwan, M Bunting, RCL Ng, KH Chan
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Neuroinflammation mediated by microglia activation contributes to pathogenesis of Alzheimer's disease (AD). Adiponectin, an adipocyte-derived adipokine, has potent anti-inflammatory effects in both periphery and the brain. However, the role of adiponectin on microglia-mediated neuroinflammation in AD remains unknown. Here, we aimed to determine the role of adiponectin in oligomeric amyloid-β (AβO)-induced neuroinflammation in AD.

Methods: In vitro, the BV2 microglia cells were pretreated with adiponectin for 2 hours before being stimulated with AβO for 24 hours. To elucidate the underlying mechanism, adiponectin receptors (AdipoR1 or AdipoR2) siRNA and compound C, an AMPK inhibitor, were administered prior to adiponectin treatment. Levels of pro-inflammatory cytokines and protein expression were determined by enzyme-linked immunosorbent assay and western blot. To determine the neuroprotective role of adiponectin, conditioned medium from AβO-exposed BV2 cells was collected to treat HT22 hippocampal cells, and the cytotoxicity of HT22 cells were assessed by MTT reduction. We also studied the cytotoxicity of HT22 cells in a transwell system, in which BV2 cells were co-cultured with HT22 cells without cellular contact. In vivo, we generated adiponectin knockout mice by crossing 5xFAD mouse model of AD (adiponectin-/-5xFAD) to determine the effect of adiponectin deficiency on microglia-mediated neuroinflammation in AD.

Results: We found that AdipoR1 and AdipoR2 were expressed in BV2 cells and microglia cells in mice. Pretreatment with adiponectin reduced tumour necrosis factor (TNF)-α and interleukin (IL)-1β production and rescued the decrease of AMPK phosphorylation level and suppressed nuclear translocation of nuclear factor (NF)-κB induced by AβO in BV2 cells. Administration of compound C abolished the protective effects of adiponectin. Additionally, genetic knockdown of AdipoR1, but not AdipoR2, inhibited the ability of adiponectin to suppress pro-inflammatory cytokines production induced by AβO in BV2 cells. These results suggested that adiponectin suppressed microglia activation induced by AβO via AdipoR1/AMPK/NF-κB cascade. Moreover, adiponectin decreased cytotoxicity of HT22 neuronal cells exposed to culture medium of microglia cells stimulated with AβO. Lastly, we found that adiponectin deficiency increased microglia activation in adiponectin-/-5xFAD mice at age 9 months. Microglia activation was associated with upregulation of TNF-α and IL-1β in cortex and hippocampus in adiponectin-/-5xFAD mice.

Conclusion: Our data show that adiponectin can inhibit AβO-induced neuroinflammation in BV2 cells and adiponectin deficiency in AD increased microglia activation in 5xFAD, suggesting that adiponectin is a potential therapeutic agent to inhibit neuroinflammation in AD.

28

Glucose transporter 1 is crucial for cold-induced glucose uptake in brown adipose tissue

X Jiang, KKY Cheng, A Xu
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Brown adipose tissue (BAT) generates heat to maintain core body temperature and acts an active metabolic sink to metabolise up to 75% of blood glucose. Cold exposure activates BAT functions via the β3-adrenergic receptor, leading to upregulation of thermogenic program and glucose metabolism, which in turn prevents obesity and its related metabolic disorders. Although glucose transporter 1 (GLUT1) has been shown to be upregulated by cold exposure, whether it is necessary for the action of cold exposure on energy and glucose metabolism is currently unknown.

Methods: Male adipocyte GLUT1-specific knockout mice and their wild-type littermates were subjected to thermoneutral (30°C) or cold (4°C) environment, followed by assessment of adaptive thermogenesis using a metabolic cage and glucose uptake in BAT using positron emission tomography–magnetic resonance imaging.

Results: Cold exposure and the β3-adrenergic receptor agonist CL316243 upregulated protein expression of GLUT1 in BAT and brown adipocytes. Positron emission tomography–magnetic resonance imaging analysis revealed that glucose uptake is largely diminished in BAT of knockout mice when compared with their wild-type controls. Genetic deletion of adipocyte GLUT1 attenuated acute but not chronic cold-induced adaptive thermogenesis. Consistently, pharmacological inhibition of GLUT1 also abolished glucose uptake and thermogenic program in BAT.

Conclusion: Glucose transporter 1 is the key glucose transporter responsible for cold-induced glucose uptake in BAT. Cold-induced glucose uptake via GLUT1 is important for acute but not chronic cold-induced adaptive thermogenesis.

Acknowledgement
This research was supported by the National Natural Science Foundation of China (Ref. 81700746).

29

Long-term entecavir on hepatocellular carcinoma and hepatitis B surface antigen seroclearance: a large real-world cohort study

KL Ko, WP To, LY Mak, WK Seto, J Fung, CL Lai, MF Yuen
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Background: Real-world studies examining reduction of risk of hepatocellular carcinoma (HCC) in patients receiving antivirals are limited by the small size of the studies, or by data insufficiency and heterogeneity with short follow-up duration. We aimed to examine the real-world long-term outcome of patients receiving entecavir treatment on HCC incidence and hepatitis B surface antigen (HBsAg) seroclearance.

Methods: The incidence of HCC in 1225 entecavir-treated patients between 2002 and 2015 was compared with the HCC incidence estimated using the REACH-B (Risk Estimation for HCC in Chronic Hepatitis B), GAG-HCC (Guide with Age, Gender, HBV DNA, Core promoter mutations and Cirrhosis-HCC), and CU-HCC (Chinese University-HCC) scores. Standardised incidence ratios (SIR) were calculated. The impact of entecavir treatment on HBsAg seroclearance was also explored.

Results: The median follow-up duration of the cohort was 6.6 years, with 66 cases of HCC development. Using the REACH-B model, the reduction of HCC risk was significant from year 6 onwards with SIR of 0.68 (95% confidence interval [CI]=0.535-0.866) at year 10. In subgroup patients without cirrhosis, consistent risk reduction was observed from year 5 and SIR reached 0.51 (95% CI=0.271-0.704) by year 10. Benefit in cirrhotic patients was demonstrated when using the GAG-HCC and CU-HCC scores, with SIR at year 10 being 0.38 (95% CI=0.259-0.544) and 0.46 (95% CI=0.314-0.659), respectively. The cumulative rate of HBsAg seroclearance was 5.2%. Level of hepatitis B surface antigen at third year of treatment and baseline-to-3-year percentage reduction were predictive of subsequent HBsAg seroclearance.

Conclusions: Long-term entecavir therapy is associated with a significant reduction in HCC risk. However, HBsAg seroclearance rate remains low. Additional therapy may be considered in patients with adverse predictive factors for subsequent HBsAg seroclearance.

30

Natural history of patients with inflammatory bowel disease who are positive for hepatitis B core antibodies and require immunosuppressive therapy

KL Ko, LJ Chen, WK Seto, I Hung, WK Leung
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: The incidence of inflammatory bowel disease (IBD) is rapidly increasing in Asia, where hepatitis B virus (HBV) infection is endemic. We reported the outcomes of a cohort of Asian patients with IBD who are positive for antibody to hepatitis B core antigen or negative for hepatitis B surface antigen (anti-HBc+/HBsAg-) and receiving various immunosuppressive therapies without routine antiviral prophylaxis.

Methods: Newly diagnosed or referred patients were screened for HBV infection. Liver function, HBV serology, and HBV DNA were monitored. Patient demographics, follow-up duration, IBD phenotypes, and immunosuppressant use were retrieved from the hospital database.

Results: Of 518 patients with IBD, 114 (22.0%) had serologic evidence of past HBV infection (anti-HBc+), including 22 (4.2%) patients with confirmed chronic HBV infection (HBsAg+). The mean age at diagnosis was significantly higher in patients with anti-HBc+/HBsAg- than in patients with HBsAg+ (46.2 vs 39.3 years, P=0.004). The majority (88.0%) of patients with anti-HBc+/HBsAg- were positive for antibody against hepatitis B surface antigen (anti-HBs). The absence of anti-HBs was associated with a diagnosis of Crohn's disease (CD) [54.5% vs 22.2% in ulcerative colitis, P=0.03], prolonged use of steroid (63.6% vs 30.9%, P=0.045) and biologics use (36.4% vs 11.1%, P=0.017). None of the anti-HBc+/HBsAg- patients were given antiviral prophylaxis, whereas 12 (54.5%) HBsAg+ patients received antivirals. There was one (1.1%) case of HBsAg seroreversion in a patient with Crohn's disease who was given prolonged high-dose steroid and azathioprine.

Conclusions: Our findings show that reactivation of HBV is rarely observed among this group of anti-HBc+ and HBsAg- patients with IBD receiving immunosuppressants. However, a diagnosis of Crohn's disease and use of prolonged steroid or biologics use may be associated with the absence of anti-HBs. Close monitoring is needed, because HBsAg seroreversion is possible.

Lung cancer patient–derived organoid biobank for therapeutic screening

31

HH Kwok, NCM Lee, JY Deng, MSM Ip, DCL Lam
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Precision medicine for lung cancer requires accurate diagnostic tests for individual patients. An in vitro model that allows high-throughput therapeutic screening but can also fully replicate the histopathological and molecular characteristics of the original tumour is indispensable.

Methods: Resected tumour and the adjacent normal tissues from early-stage lung cancer patients were collected. Metastatic tumour cells from pleural effusion of advanced-stage lung cancer patients were also harvested and used for organoid culture establishment. Genomic analysis using whole-exome sequencing and histological examination were performed on those long-term cultured organoids. Drug sensitivity screening was performed on the tumour organoid cultures.

Results: We established a lung cancer organoid biobank that comprehends normal, cancer, and pleural effusion metastases from patients with diversity of histological and genomic backgrounds. The morphology and genomic profiles of the established organoids were closely comparable with the original tissues. High-throughput drug screening revealed the potential application of novel drugs.

Conclusion: This newly established and well-characterised lung cancer biobank is a viable tool for lung cancer research as well as development of precision therapy.

Acknowledgement
The work described in this manuscript was partly supported by the Lee and the Ho Families Respiratory Research Fund.

Efficacy of gefitinib at reduced dose in *EGFR* mutant non-small-cell lung carcinoma

32

WC Kwok, JCM Ho, DCL Lam, MMS Lui, MSM Ip, TCC Tam
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Background: Gefitinib is a first-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor that is approved by the United States Food and Drug Administration for treatment of advanced non-small-cell lung carcinoma (NSCLC) with sensitising *EGFR* mutations. However, gefitinib is known to have adverse effects, which may necessitate dose reduction or even change to an alternative preparation of EGFR tyrosine kinase inhibitor. The aim of the present study was to investigate whether dose reduction of gefitinib will affect the progression-free survival.

Methods: This was a retrospective single-centre cohort study conducted in Queen Mary Hospital in Hong Kong that included 159 Chinese patients with advanced adenocarcinoma of the lung that carried sensitising *EGFR* mutations and who had received gefitinib as first-line treatment. Patients who had their gefitinib dose reduced were compared with those who were maintained on the standard dose of gefitinib. The primary endpoint was progression-free survival.

Results: In all, 17 out of 159 (10.6%) patients were on reduced dose of gefitinib, 14 (82%) because of hepatotoxicity and three (18%) because of cutaneous side-effects. Patients on reduced dose and standard dose of gefitinib have comparable median progression-free survival. Hazard ratio was 1.121 (95% confidence interval [CI]=0.655-1.917, P=0.678) for the reduced dose group and 3.385 for the standard dose group (95% CI=2.181-5.255, P<0.001).

Conclusions: Dose reduction in gefitinib in response to adverse effects was not associated with inferior outcome for patients on first-line gefitinib for advanced NSCLC. Dose reduction is a feasible option for patients who have significant adverse effects with gefitinib.

33

Progression-free survival among progressed non-small-cell lung cancer with T790M mutation as guided by liquid versus tissue re-biopsy

WC Kwok, JCM Ho, DCL Lam, MMS Lui, MSM Ip, TCC Tam
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Background: Osimertinib has been approved by the United States Food and Drug Administration for non-small-cell lung carcinoma (NSCLC) harbouring acquired T790M mutation that have progressed while on other epidermal growth factor inhibitor (EGFR)–inhibiting therapy. We compared the progression-free survival (PFS) of patients whose T790M mutation was identified by liquid biopsy with those identified by tissue sampling.

Methods: This was a retrospective single-centre cohort study conducted in Queen Mary Hospital, Hong Kong. The study included 139 Chinese patients with advanced NSCLC who had disease progression after first-line EGFR tyrosine kinase inhibitor and received osimertinib upon detection of T790M mutation, either by liquid biopsy (by identification of circulating tumour DNA) or tissue re-biopsy. The primary endpoint was PFS.

Results: Patients with EGFR T790M mutation detected by tissue sampling (n=37) had significantly better PFS than those detected by peripheral blood liquid biopsy (n=102) [median 380 vs 213 days, hazard ratio=0.576, 95% confidence interval=0.359-0.925, P=0.021]. A small subgroup with positive liquid biopsy but concomitant negative tissue result (n=6) had the lowest PFS among the different cohorts (median PFS=57 days).

Conclusions: Tissue re-biopsy for T790M mutation is preferred for patients who have NSCLC that progressed after first-line tyrosine kinase inhibitor. For cases that only have confirmatory liquid biopsy results, clinicians should inform their patient that the expected PFS may be significantly shorter than those previously reported in literature.

34

Dysregulation of interleukin-18 receptor accessory protein in leukocytes of lupus nephritis patient

IKY Lam, VSF Chan, CS Lau
Division of Rheumatology and Clinical Immunology, Department of Medicine, The University of Hong Kong, Hong Kong.

Introduction: Systemic lupus erythematosus (SLE) is a complex autoimmune disease affecting multiple organ systems. Most SLE patients will develop lupus nephritis (LN), which is a major cause of mortality and morbidity. The aetiology of SLE is not completely understood but cytokine dysregulation is substantially involved in the immunopathology of SLE. Recent evidence suggests that interleukin (IL)-18 activity plays a role in the development of LN. Interleukin-18 is a pro-inflammatory cytokine that could activate a variety of leukocytes including T cells, natural killer (NK) cells and neutrophils, which express IL-18 receptors composed of an IL-18 binding alpha subunit and a signal transducing beta-subunit named IL-18 receptor accessory protein (IL18RAP). Aberrant response to IL-18 could lead to excessive inflammation and organ damage. The aim of this study was to investigate whether IL-18 receptors in leukocytes have a pathological role in LN.

Methods: Total blood leukocytes were collected from healthy controls and from SLE patients confirmed by biopsy as LN or non-LN. Total RNA was extracted and expression of IL18RAP was determined by real-time polymerase chain reaction. Correlation analyses with clinical parameters, type I interferon signature genes and genes associated with activation of neutrophils, T cells, and NK cells were performed.

Results: A significant increase in IL18RAP gene expression was observed in SLE patients when compared with healthy controls and its expression was higher in LN patients in comparison with non-LN patients. A significant correlation was observed between IL18RAP and serum C3 and albumin levels, which are reflective of LN activity. The IL18RAP expression was positively correlated with defensin alpha 1 and matrix metallopeptidase 9, which are associated with neutrophil activation. However, no significant correlation was observed with granzyme B, which is expressed by activated T cells and NK cells. The IL18RAP was also highly correlated with a number of interferon-inducible genes (IFIT5, IFITM1, IFI44 and IFI16).

Conclusion: The IL18RAP may have a pathological role in SLE neutrophils, particularly in LN. Also, interferon may have a regulatory role contributing to the abnormal expression of IL18RAP in SLE.

Targeting polyamines as potential adjuvant therapy in malignant pleural mesothelioma xenograft models

SK Lam, S Yan, S Xu, JCM Ho
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Inhaling asbestos fibres is a well-known common cause of malignant pleural mesothelioma (MPM). Although the import and use of asbestos have been restricted, the incidence of MPM is not expected to decline due to a long lag time in malignant transformation. In 2004, the United States Food and Drug Administration approved a combination of cisplatin with pemetrexed for treatment of unresectable MPM. Concurrently, development of novel adjuvant therapeutic agents for resected early-stage disease is also urgently desired. Ornithine decarboxylase (ODC) is highly expressed in 211H and H226 MPM xenografts and clinical tumour samples. Ornithine decarboxylase upregulation increases polyamine production and enhances tumour growth. Recent preclinical investigations have revealed the adjuvant effect of α-difluoromethylornithine (DFMO), a well-known specific ODC inhibitor, in colon cancers using xenograft model. Nevertheless, adjuvant effect of DFMO in MPM has not yet been disclosed. The aim of this study was to investigate the adjuvant effect of DFMO in MPM xenograft models.

Methods: Nude mice were fed with DFMO (in drinking water) 7 days before subcutaneous inoculation of 200 000 tumour cells (211H [biphasic] or H226 [epithelioid]). Mice with tumour size >600 mm^3 were considered reaching humane endpoint. Protein expression, spermidine levels, cytokine concentrations, and apoptosis were investigated by western blot, dot plot, enzyme-linked immunosorbent assay, and TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling) assay, respectively.

Results: Tumour growth was suppressed by DFMO in both xenografts. Median survival increased from 49.5 days in the control arm to 65 days in the DFMO treatment arm in mice with 211H xenograft (P=0.08), and from 44 days to 120 days in mice with H226 xenograft (P=0.0002). In the H226 xenograft model, 43% of treated mice did not reach humane endpoint, mimicking long-term survival. Upon DFMO treatment, decrease in spermidine level, increase in nitrotyrosine content (reactive nitrogen species; RNS), and activation of apoptosis were observed in both xenografts. In addition, increase in RNS, elevation of intratumoural interleukin-6, keratinocyte chemoattractant and tumour necrosis factor-α, upregulation of DNA lesion and inhibition of Akt/mTOR pathway were induced by DFMO in H226 xenograft, which may explain higher potency of DFMO in this xenograft.

Conclusion: There is a potential role for DFMO as adjuvant therapy in MPM; especially epithelioid mesothelioma, which is partially mediated by spermidine depletion, induction of RNS, and apoptosis. The findings from this study will provide scientific foundation for future design of clinical trials of DFMO for adjuvant therapy in early disease for advanced MPM.

Acknowledgement
This research was supported by the Hong Kong Pneumoconiosis Compensation Fund Board.

36

Disease modelling of laminopathy-related dilated cardiomyopathy—proarrhythmic effects and impaired electrical-contraction coupling due to altered mechanical coupling of lamin A

YK Lee, YM Lau, X Ran, Z Cai, WH Lai, CW Siu, HF Tse
Cardiology Division, Department of Medicine, The University of Hong Kong, Hong Kong

Background: Lamin A (LMNA) is an essential component in the nuclear matrix that serves to maintain chromosome and genome integrity. Laminopathy is highly associated with dilated cardiomyopathy (DCM). The mechanisms underlying the cellular electrophysiological responses to mechanical force could be adversely affected by *LMNA* mutations.

Purpose: We aimed to use human induced pluripotent stem cell–derived cardiomyocytes (hiPSC-CMs) bearing *LMNA* mutation to investigate the role of LMNA on the dilated cardiomyopathy phenotype in terms of (1) cytoskeletal organisation that affects force generation and ion channel behaviour; (2) proarrhythmic action potential changes; (3) and electrical-contraction (EC) coupling events.

Methods: The hiPSC-CMs of a patient bearing $LMNA^{R225X/WT}$, an isogenic corrected $LMNA^{WT/WT}$, and mutated lines $LMNA^{R225X/R225X}$ created by CRISPR-Cas9 were used in the current study. To investigate mechanical-related regulation, the hiPSC-CMs were treated with either F-actin depolymerisation small molecule, latrunculin B, or blebbistatin, a myofilament desensitiser. Action potential was recorded to study arrhythmic risk. To study the subsequent force–frequency relationship of the EC coupling, calcium transients and contractility were recorded in the hiPSC-CMs under electrical field stimulation.

Results: Disorganisation of F-actin in of $LMNA^{R225X/WT}$-hiPSC-CMs, interconnecting nuclear lamina to sarcomere and cell surface, reduced nuclear integrity and force generation. Action potential recording revealed that the $LMNA^{R225X/WT}$-hiPSC-CMs tends to be hyperpolarised with a significantly ~50% decrease in membrane diastolic potential ($n=14$, $P<0.05$). The more negative potential hampers the cardiac cells to reach threshold for action potential firing and account for the electrical instability. With respect to calcium homeostasis, the significant decline in diastolic calcium level (44.76%, $n=18$, $P<0.01$) of $LMNA^{R225X/R225X}$ could account for the hyperpolarised status. Furthermore, the compromised EC coupling in $LMNA^{R225X/WT}$ and $LMNA^{R225X/R225X}$ were obviously appeared in high rate pacing at 2 Hz showing significantly retarded upstroke and decay kinetics ($n=6$, $P<0.05$). Corresponding impaired contraction force generation was showed as reflected by the significant decline of cell shortening ($n=13$, $P<0.001$). Latrunculin B and blebbistatin that attenuate mechanical stress could relieve electrical instability and resume EC coupling.

Conclusion: Laminopathy-related dilated cardiomyopathy is probably due to the blunted coupling of lamin A with mechanical-related calcium-channels, which might contribute to the electrical instability and the impaired EC.

37

Mesenchymal stem cells derived from induced pluripotent stem cells and bone marrow are equally effective in ameliorating lipotoxicity-induced kidney injury

B Li, JCK Leung, LYY Chan, WH Yiu, KN Lai, SC Tang
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Human induced pluripotent stem cell–derived mesenchymal stem cells (iPS-MSCs) are promising as an alternative to bone marrow–derived mesenchymal stem cells (BM-MSCs) for cell-based therapy. Lipotoxicity is an important pathogenetic factor leading to chronic kidney injury. This study aimed to compare the therapeutic effects of iPS-MSCs and BM-MSCs in ameliorating lipotoxicity-induced kidney lesions.

Methods: Mice (C57BL/6J) fed normal diet (10 kcal%) or high-fat diet (HFD; 60 kcal%) for 12 weeks were randomly divided into vehicle control, iPS-MSC and BM-MSC subgroups (n=8 in each group), followed by infusion of saline or MSCs via tail vein and fed for further 8 weeks before sacrifice. Body weight, blood glucose, and urine albumin were monitored throughout the experiment. Renal histological changes were assessed by Periodic acid-Schiff staining. Renal endoplasmic reticulum stress, inflammation and apoptosis were evaluated by quantitative real-time polymerase chain reaction, western blot, and TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling) assay.

Results: Compared with the normal diet group, mice fed HFD had significantly increased (1) body weight, blood glucose, and urine albumin; (2) tubular injury score (tubular vacuolation and tubular glycogenated nuclei), glomerular size, and mesangial expansion; (3) expression of markers for endoplasmic reticulum stress (BiP, p-eIF2α, ATF4, p-IRE1α, CHOP) and related phosphorylated signalling molecules (p-NF-κB, p-ERK, p-JNK); (4) expression of pro-inflammation mediators (interleukin-6, CXCL1, CXCL2); and (5) apoptosis (Bax/Bcl-2 ratio and number of renal TUNEL-positive apoptotic cells). All these events were significantly attenuated by infusion with iPS-MSCs or BM-MSCs to the HFD-fed mice. Notably, iPS-MSCs and BM-MSCs infusion to HFD-fed mice had equivalent efficacy in ameliorating all the above-mentioned results in HFD-induced kidney injury.

Conclusion: Our study suggests comparable capability of iPS-MSCs and BM-MSCs in ameliorating lipotoxicity-induced kidney injury, supporting iPS-MSCs as a valuable alterative source to BM-MSCs for therapeutic application.

Acknowledgements
This research was supported by the Health and Medical Research Fund for Advance Medical Research (Ref. 03143726) and Mrs Rita T Liu SBS of the L&T Charitable Foundation Ltd.

38

Mitochondrial toxicity of fine particulate matter (PM2.5) collected in Hong Kong in human airway epithelial cells

YM Liang[1], LW Tian[2], KF Ho[3], MSM Ip[1], JCW Mak[1,4]
[1]Department of Medicine, The University of Hong Kong, Hong Kong
[2]School of Public Health, The University of Hong Kong, Hong Kong
[3]Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong
[4]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong

Background: Air pollution is considered as a serious problem worldwide, posing a harmful threat to public health. Fine particulate matter of diameter <2.5 μm (PM2.5) is associated with higher risk of respiratory diseases like asthma and chronic obstructive pulmonary disease. Mitochondria are highly sensitive to environmental toxicants and their roles on respiratory diseases have been well documented. However, studies on the relationship between PM2.5 and mitochondria in the respiratory tract are limited. Therefore, we aimed to study the effects of PM2.5 on mitochondrial function and dynamics in human bronchial epithelial cells.

Methods: Atmospheric PM2.5 samples were collected by 47-mm Teflon filters using Desert Research Institute portable mid-volume samplers in Hong Kong. Human bronchial epithelial cell line BEAS-2B cells were cultured until 80% confluent. After cell arrest, cells were treated with different concentrations of PM2.5 samples. The viability of cells was assessed by MTT and LDH assays. Mitochondrial function was measured by JC-1 probe. Protein expressions were examined by western blot analysis.

Results: The survival rate of BEAS-2B cells declined in a PM2.5 concentration-dependent manner. PM2.5 exposure also caused loss of mitochondrial membrane potential in a concentration-dependent manner. PM2.5 exposure reduced the expression of specific mitochondrial fusion proteins (OPA1 and Mfn1) and elevated the expression of mitochondrial fission protein (Fis1).

Conclusion: The results show that exposure to PM2.5 collected in Hong Kong caused mitochondrial toxicity by affecting mitochondrial function and dynamics in human bronchial epithelial cells. This provides further understanding on the detrimental effects of PM2.5 in airway injury.

Acknowledgement
This study was supported by the Hong Kong Lung Foundation Research Grant Award (Ref. 260008637).

Thyroid hormone activates adipose tissue thermogenesis independent of uncoupling protein 1

39

Q Liu, Y Gao, TS Feng, Y Cheng, XY Hui, AM Xu
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Brown adipose tissue is a main contributor to adaptive thermogenesis in small mammals. This is achieved by the mitochondrial inner membrane uncoupling protein 1 (UCP1) generating heat by uncoupling oxidative phosphorylation without ATP production. However, UCP1-deficient mice can also survive cold temperatures, suggesting that alternative thermogenesis pathways are induced to contribute to maintaining body temperature in UCP1-independent pathways. However, the intrinsic mechanism is still unclear.

Methods: The energy expenditure of mouse tissues and cells were examined by metabolic cage and seahorse bio-analyser, respectively. The thyroid hormone levels were quantified by enzyme-linked immunosorbent assay kits. The expression levels of Na+/K+-ATPases and cation leak channels were examined by quantitative polymerase chain reaction and western blotting.

Results: Energy expenditure was enhanced in inguinal white adipose tissue (WAT) of UCP1-deficient mice upon chronic cold adaptation. In particular, thyroid hormone T3 was selectively elevated in inguinal WAT of Ucp1 knockout mice after cold challenge. Loss of function study via iodine-deficient diet feeding in mice showed thyroid hormones were required for UCP1-independent thermogenesis, while gain of function study through T3 administration in mice indicated that T3 could enhance energy expenditure and evoke fat loss at thermoneutrality in an UCP1-independent manner. Through analysis of RNAseq data of T3-treated inguinal WAT and subsequent validation, the upregulation of Na+/K+-ATPases and cation leak channels might serve the UCP1-independent thermogenesis.

Conclusion: Na+/K+-ATPases are coupled with cation leak channels to establish the futile cycle to dissipate energy, which could partly explain the thyroid hormone induced thermogenesis in an UCP1-independent manner. The underlying mechanism warrants further investigation.

Bone quality in Chinese postmenopausal women with type 2 diabetes mellitus: a cross-sectional study

40

DTW Lui, VWK Chau, CHY Fong, KMY Yeung, KSL Lam, YC Woo
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Type 2 diabetes mellitus (T2DM) is associated with 1.34-fold increase in hip fracture risk despite higher bone mineral density (BMD). Trabecular bone score (TBS), an indirect index of bone microarchitecture based on lumbar spine image on dual-energy X-ray absorptiometry, captures a larger portion of T2DM-related fracture risk. Here we compared the bone quality in Chinese postmenopausal women with T2DM with those without diabetes mellitus (non-DM).

Methods: We conducted a cross-sectional study of postmenopausal women, with T2DM patients recruited from the Hong Kong West Diabetes Registry and non-DM patients from the Hong Kong Cardiovascular Risk Factor Prevalence Study, between November 2016 and October 2018. Type 2 diabetes was defined by fasting glucose ≥7.0 mmol/L, 2-hour oral glucose tolerance test (OGTT) ≥11.0 mmol/L, or glycated haemoglobin (HbA1c) ≥6.5%; pre-diabetes (pre-DM) by fasting glucose 5.6-6.9 mmol/L, 2-hour OGTT 7.8-11.0 mmol/L, or HbA1c 5.7% to 6.4%; and euglycaemia by normal fasting glucose, 2-hour OGTT, and HbA1c. Bone mineral density, vertebral fracture assessment, and TBS were measured by dual energy X-ray absorptiometry.

Results: A total of 322 patients (104 with T2DM, 218 non-DM) were included. Compared with non-DM patients, those with T2DM were older (63.7 vs 62.1 years, P=0.012) and heavier (25.6 vs 23.2 kg/m^2, P=0.002), and had higher lumbar spine BMD (0.93 vs 0.85 g/cm^2, P<0.001) but lower TBS (1.28 vs 1.26, P=0.031). Vertebral fractures were more prevalent in patients with T2DM and pre-DM compared with those with euglycaemia (P=0.03). Multivariable linear regression analysis revealed that TBS was significantly lower in patients with T2DM compared with non-DM patients, after adjustment for age, body mass index, and lumbar spine BMD (P<0.001). Trabecular bone score showed a significant decreasing trend with worsening glycaemic status after adjusting for covariates (1.30, 1.27 and 1.26 in patients with euglycaemia, pre-DM and T2DM, respectively, P=0.001). Subgroup analysis revealed that among patients aged ≥60 years, TBS was significantly lower in patients with pre-DM than in those with euglycaemia (P=0.020), but similar to that in patients with T2DM (P=0.206).

Conclusion: In Chinese postmenopausal women, T2DM is associated with higher BMD, but lower TBS compared with non-DM. Trabecular bone score decreases with worsening glycaemic status. Lower TBS with more vertebral fractures can be observed starting from pre-DM in older age-group, suggesting potential impact of early intervention of pre-DM from the perspective of bone health, which warrants further studies.

Characteristics of adrenal incidentalomas: a single-centre audit

41

DTW Lui[1], YC Woo[1], PCH Lee[1], KP Wong[2], JKY Lam[1], ACH Lee[1], EKH Leung[1], WS Chow[1], KCB Tan[1], KSL Lam[1]
[1]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Adrenal incidentalomas are commonly encountered due to increasing utility and sensitivity of imaging. We reviewed the characteristics and outcome of adrenal incidentalomas followed up in a single centre.

Methods: We retrospectively reviewed patients with adrenal incidentaloma referred to the endocrine clinic at Queen Mary Hospital, Hong Kong, between June 2012 and May 2015. We excluded cases where index imaging was done for suspected adrenal disorders, staging, or follow-up for malignancies, or where clinical features of endocrine disorders were missed due to superficial assessment. All patients were evaluated and followed up according to a standard protocol.

Results: Among 75 patients included (57.3% men, 42.7% women), 68 had unilateral lesions and seven had bilateral lesions. The majority of patients were aged 60 to 69 years. In all, 14.7% of patients had adrenal incidentalomas of initial size <1.0 cm, 60% had 1.0 to 2.0 cm, 22.7% had 2.1 to 3.9 cm, and 2.7% had ≥4 cm. Hormonal evaluations showed 50% of lesions were non-functional, 35% showed subclinical Cushing's syndrome, 12% showed primary aldosteronism, and 3% showed catecholamine oversecretion. Eleven patients underwent adrenalectomy: eight for adrenocortical adenoma with autonomous cortisol secretion, two for phaeochromocytoma, and one for adrenocortical carcinoma. In addition, 64 patients were managed non-operatively; 59 patients underwent reassessment imaging. Two showed complete resolution, 54 showed no interval growth over a median of 31.5 months (interquartile range 24-46.75 months). Three patients showed cumulative interval growth ≥5 mm from baseline: one remained under regular imaging surveillance, but the other two were lost to follow-up. Hormonal surveillance was performed in 11 initially non-functioning lesions; the majority were to reassess autonomous cortisol secretion, which did not alter management.

Conclusion: Hormonal evaluations should be performed for adrenal incidentalomas regardless of size. Subclinical Cushing's syndrome was the most common hormonal abnormality. Surgical intervention for subclinical Cushing's syndrome remains controversial among clinicians; co-morbidities associated with autonomous cortisol secretion should be monitored. Reassessment of dedicated adrenal imaging is necessary to ensure no interval change in size. Hormonal surveillance did not alter the management of initially benign non-functioning adrenal incidentalomas in our series.

Are blood lead levels in the United States still declining? The United States National Health Nutrition and Examination Survey 1999-2016

42

KWK Lui[1], MF Tsoi[1], TT Cheung[1], CL Cheung[2], BMY Cheung[1]
[1]Department of Medicine, The University of Hong Kong, Hong Kong
[2]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong

Introduction: Lead is a well-documented environmental toxin without a safe blood level. The current upper reference blood lead level (BLL), 5 μg/dL, came from the 97.5th percentile in children aged 1 to 5 years in the US National Health Nutrition and Examination Survey (NHANES) 2007-2010. We studied BLL, as reported in NHANES, to estimate the proportion of children with BLL ≥5 μg/dL.

Methods: We analysed 68 877 participants with BLL measurements in NHANES 1999-2016 using SPSS (Window version 25.0; IBM Corp, Armonk [NY], US).

Results: In NHANES 1999-2000, 2001-2002, 2003-2004, 2005-2006, 2007-2008, 2009-2010, 2011-2012, 2013-2014, and 2015-2016, the mean BLLs and 95% confidence intervals (CIs) were 1.66 (1.63-1.68), 1.46 (1.44-1.47), 1.43 (1.42-1.44), 1.29 (1.28-1.31), 1.27 (1.26-1.29), 1.12 (1.11-1.13), 0.97 (0.96-0.99), 0.86 (0.85-0.87), and 0.82 (0.81-0.83) μg/dL, respectively (P<0.001). The decline was significant (P<0.05) after stratification by age, sex, ethnicity, and pregnancy status. The estimated proportions (95% CIs) of children aged 1 to 5 years with elevated BLL in 1999-2000, 2001-2002, 2003-2004, 2005-2006, 2007-2008, 2009-2010, 2011-2012, 2013-2014, and 2015-2016 were 9.7% (7.2%-12.8%), 7.4% (6.1%-9.1%), 5.3% (4.3%-6.4%), 2.9% (2.4%-3.6%), 3.1% (2.6%-3.8%), 2.1% (1.7%-2.7%), 2.0% (1.3%-3.0%), 0.5% (0.4%-0.7%), and 1.3% (0.8%-2.3%), respectively (P<0.001). The estimated 97.5th percentile of BLL in children aged 1-5 years, was 3.71 μg/dL in NHANES 2015-2016.

Conclusion: In the overall US population BLLs continue to decline. However, in young children aged 1 to 5 years in 2015-2016, BLLs did not decline and appeared to increase. Data for 2017-2018 are needed to verify if this is a trend. Our data suggest that monitoring BLLs in the population is as necessary as ever and that efforts to reduce environmental exposure to lead must not be relaxed.

Superiority of the artificial intelligence image classifier for histological prediction of diminutive colorectal polyps based on non-magnifying endoscopic images

43

TKL Lui, WP To, KK Ko, LY Mak, WK Leung
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: "Resect and discard" of diminutive colorectal polyps without histological assessment has been advocated in the West to save costs, provided an accurate histological prediction can be made during colonoscopy. Artificial intelligence (AI) has been shown to be highly accurate in predicting histology of diminutive (<5 mm) colonic polyp based on magnifying endoscopic images. The performance of AI on non-optical magnifying images, which are more readily available in routine clinical practices, is unknown.

Methods: A total of 3804 endoscopic images of diminutive (<5 mm) colorectal polyps taken with non-magnifying narrow band imaging (NBI) techniques, including 1561 neoplastic and 2243 non-neoplastic lesions, were used to train the AI image classifier. The independent validation set consisted of 100 NBI images of diminutive polyps with histological confirmation. The accuracy, sensitivity, specificity, positive (PPV), and negative predictive value (NPV) in identifying neoplastic lesions were compared among the AI and three human endoscopists.

Results: The overall accuracy of AI was superior to that of all three endoscopists (96% vs 83%, 81%, and 83%, P<0.05). Other performance measures were also numerically better in AI than in human endoscopists (sensitivity: 98.1% vs 92.3%, 94.2%, and 82.7%; specificity: 93.8% vs 72.9%, 66.6%, and 83.3%; PPV: 94.4% vs 89.7%, 75.3%, and 84.3%; NPV: 97.8% vs 83.0%, 91.4%, and 81.6%). The AI also had a higher mean confidence level of endoscopic image prediction of histology than did the human endoscopists (95.3% vs 71.8%, 64.8%, and 84.3%, P<0.05).

Conclusion: Artificial intelligence is superior to human endoscopists in the histological prediction of diminutive colorectal polyps based on non-magnified endoscopic images.

Glomerulonephritis in myasthenia gravis: a case series and literature review

44

WCY Leung[1], BM Ma[1], RSK Chang[1], YZ Ng[2], HY Wong[2], JM Kwong[2]
[1]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

Background: Glomerulonephritis (GN) is associated with myasthenia gravis (MG). We reviewed cases in Queen Mary Hospital with MG who developed GN during the course of disease, with an interval between each diagnosis ranging from 2 to 17 years.

Methods and Results: Case records were retrieved from the Clinical Data Analysis and Reporting System of the Hong Kong Hospital Authority with ICD-9 diagnosis keywords of MG and GN from the year of 1995 to 2017. A total of six cases were identified. They were reviewed individually, and their clinical details were extracted.

Discussion: The association between MG and GN is not well understood compared with other immunological disorders. Described in multiple case reports, a pathogenetic link has been hypothesised. Among the reported cases, it is noted that GN usually develops 1 to 3 years after the diagnosis of MG. Renal biopsy results were diverse, including minimal change disease, membranous nephropathy, and mesangial proliferative GN. The clinical course also varied from spontaneous resolution to progression to end-stage renal failure. The six patients in our case series shared similarities with those described in literature. Serum auto-antibodies including anti-acetylcholine receptor antibody and anti-muscle specific kinase were common findings. The possibility of a causal relationship between MG and GN, or that both conditions are manifestations of a common primary immunological disorder, is yet to be explored.

Conclusion: Glomerulonephritis may be an important immunological manifestation associated with MG. Further studies are warranted to investigate the causal relationship, possible pathogenetic mechanisms, and the prognostic implications of various auto-antibodies associated with MG in the development of GN.

45

In vivo electroporation-mediated transfer of interleukin-35 gene decreases demyelination in animal model of multiple sclerosis

OKF Ma, RCL Ng, LW Yick, J Min, KH Chan
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Multiple sclerosis (MS) is an immune-mediated demyelinating disease, in which T cell tolerance is deteriorated to myelin antigens. Interleukin-35 (IL-35) is a novel anti-inflammatory cytokine, which belongs to the IL-12 family and includes p35 and Epstein-Barr virus (Ebi3). Evidence demonstrates that IL-35 has a potential to ameliorate autoimmune diseases by suppressing inflammatory lymphocytes and inducing regulatory lymphocytes. In this study, we aimed to clarify the IL-35 expression profile in response to experimental autoimmune encephalomyelitis (EAE), a model of MS in mice, and investigate the therapeutic potential of IL-35 by overexpressing it in EAE mice.

Methods: Experimental autoimmune encephalomyelitis was induced in C57BL/6 mice by immunisation with MOG_{35-55} peptide. Mice were sacrificed at 14 days (initiative phase), 21 days (progressive phase), and 28 days (recovery phase) after immunisation. For electrotransfer of IL-35, recombinant murine IL-35 was encoded in pIGneo DNA plasmid and transferred into bilateral tibialis anterior muscles of EAE mice by electroporation at 10 days and 17 days after immunisation. Mice were sacrificed at 21 days after immunisation.

Results: Expression of Ebi3 and p35 was downregulated during the progressive phase of EAE and upregulated during the recovery phase. Experimental autoimmune encephalomyelitis severity was attenuated in IL-35–transferred EAE mice. Correspondingly, the fluorescence intensity of myelin basic protein was elevated in IL-35–transferred EAE mice ($P<0.001$) accompanied with marked decrease of glial fibrillary acidic protein–positive (GFAP+) cells in the white matter of spinal cord from IL-35–transferred EAE mice compared with that from empty vector–transferred EAE mice ($P<0.001$). However, the fluorescence intensity of ionised calcium-binding adaptor molecule 1 did not show any significant difference.

Conclusion: Taken together, these results demonstrate that introducing IL-35 by electroporation effectively reduces EAE severity and prevents demyelination, which is probably through inhibiting the activation of GFAP+ astrocytes but not through microglia inactivation.

46

Cardiac and pulmonary inflammatory responses by intermittent hypoxia in C57BL/6N and C57BL/6J mouse strains

SM Wong[1†], W Lam[1†], MQ Ge[1], SC Yeung[1], YM Liang[1], MSM Ip[1], JCW Mak[1,2]
[1]Department of Medicine, The University of Hong Kong, Hong Kong
[2]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong
[†]These authors contributed equally to this work

Introduction: Mouse inbred lines C57BL/6N (6N) and C57BL/6J (6J) are both widely used as animal models of obstructive sleep apnoea, which is characterised by intermittent hypoxia (IH). In the current study, we investigated the degree of susceptibility to IH on cardiac and pulmonary inflammation between the two sub-strains.

Methods: Equal numbers of 13-week-old male mice of 6N (n=8; strain code: 027; Charles River, NCI Research Models and Services, Frederick [MD], US) and 6J (n=8; stock #000664; Jackson Laboratories, Bar Harbor [ME], US) sub-strains were randomly subjected to intermittent normoxia (IN) or IH (IH30; 30 hypoxic events per hour; BioSpherix Quick & Quiet O2 Profiler with A84XOV OxyCycler, Parish [NY], US) for 1 week. Between different groups, the pro-inflammatory mediators cytokine-induced neutrophil chemoattractant 1 (CINC-1), interleukin (IL)-6, and monocyte chemoattractant protein-1 (MCP-1) in heart and lung homogenates were measured by enzyme-linked immunosorbent assay.

Results: In both sub-strains, IH caused significant elevations of CINC-1 in heart and lung homogenates of both strains (6N heart: 113.1 ± 20.5 pg/mg protein and 60.5 ± 8.8 pg/mg protein for the IH and IN groups, respectively, $P<0.05$; 6J heart: 114.7 ± 10.3 pg/mg protein and 73.4 ± 8.7 pg/mg protein for the IH and IN groups, respectively, $P<0.01$; 6N lung: 81.7 ± 9.4 pg/mg protein and 57.8 ± 3.5 pg/mg protein for the IH and IN groups, respectively, $P<0.05$; 6J lung: 55.6 ± 2.7 pg/mg protein and 46.2 ± 2.7 pg/mg protein for the IH and IN groups, respectively, $P<0.05$). However, there was a differential IH-mediated elevation of IL-6 in lung homogenates of both strains but not in heart homogenates (6N lung: 8.0 ± 0.6 pg/mg protein and 5.5 ± 0.5 pg/mg protein for the IH and IN groups, respectively, $P<0.01$; 6J lung: 7.5 ± 0.7 pg/mg protein and 5.5 ± 0.4 pg/mg protein for the IH and IN groups, respectively, $P<0.05$). Intermittent hypoxia caused no difference in heart and lung MCP-1 levels of either strain.

Conclusion: Our data reveal that, despite the genetic differences between 6N and 6J mice, the effect on IH-induced cardiac and pulmonary inflammation is similar. Cytokine-induced neutrophil chemoattractant 1 is expected to be an excellent tool for investigating neutrophil-mediated inflammatory diseases due to cardiopulmonary sequelae of obstructive sleep apnoea.

Acknowledgement
This study was supported by a generous donation from Shun Tak District Min Yuen Tong of Hong Kong and a Stanley Ho Matching Grant.

47

Elevated faecal calprotectin in patients with spondyloarthritis without underlying inflammatory bowel disease

LY Mak[1], LJ Chen[2], HY Chung[2], WK Leung[2]
[1]Department of Medicine, Queen Mary Hospital, Hong Kong
[2]Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Inflammatory bowel disease (IBD) is an extra-articular manifestation in patients with spondyloarthritis (SpA). Asymptomatic disease is common, warranting screening for IBD in patients with SpA. Faecal calprotectin (FC) is a surrogate marker for colonic neutrophilic inflammation and is useful in patients with IBD. We aim to investigate the role of FC measurement in patients with SpA without known IBD.

Methods: Adults with SpA (ankylosing spondylitis [AS] or other types of SpA: non-radiographic axial SpA, peripheral SpA, and psoriatic arthritis) fulfilling the ASAS (Assessment of SpondyloArthritis international Society) criteria without known IBD were recruited from the Rheumatology Clinic at Queen Mary Hospital, Hong Kong. Stool samples were saved for FC quantification using the enzyme-linked immunosorbent assay by Quantum Blue Calprotectin Extended (Bühlmann Laboratories AG, Basel, Switzerland). Ileocolonoscopy was arranged in patients with persistent elevation of FC (arbitrarily defined as ≥150 μg/g for 2 times) or lower gastrointestinal symptoms.

Results: A total of 84 patients (70.2% men, mean age 48.4 ± 12.3 years, 17.8% smokers, 75% with AS, 92.6% seropositive for human leukocyte antigen–B27) were recruited. Lower gastrointestinal symptoms were reported in 15 (17.9%) patients. Elevated FC was seen in 29 (34.5%) and persistent elevated FC in nine (10.7%) patients. Ileocolonoscopy was performed in 17 patients and none of them had endoscopic features of IBD. Patients with elevated FC (≥150 μg/g) were older (age 52.4 vs 46.3 years, P=0.021) and had higher proportion of AS instead of other types of SpA (89.7% vs 67.3%, P=0.033), compared with patients with FC <150 μg/g. Patients with elevated FC showed a trend for elevated serum C-reactive protein >0.5 mg/dL (41.4% vs 25.5%, P=0.106). Binary logistic regression showed that age (odds ratio [OR]=1.043, 95% confidence interval [CI]=1.003-1.085, P=0.034) and diagnosis of AS (OR=4.216, 95% CI=1.125-15.801, P=0.033) were associated with elevated FC.

Conclusion: Elevated FC in one third of patients with SpA is associated with older age and diagnosis of AS. Longitudinal follow-up including repeat ileocolonoscopy might be needed to detect subsequent IBD.

48

Faecal calprotectin and faecal haemoglobin predict endoscopic disease activity in patients with inflammatory bowel disease

LY Mak[1], LJ Chen[2], SM Tong[2], KS Lau[2], WK Leung[2]
[1]Department of Medicine, Queen Mary Hospital, Hong Kong
[2]Department of Medicine, The University of Hong Kong, Hong Kong

Background: Accurate evaluation of disease activity is essential in patients with inflammatory bowel disease (IBD). Although endoscopic remission is an ideal therapeutic goal, serum and faecal biomarkers may be used as non-invasive surrogate parameters. We aimed to evaluate the accuracy of these markers in prediction of clinical and endoscopic IBD activity.

Methods: Patients diagnosed with ulcerative colitis or Crohn's disease were recruited. The clinical activity scores were recorded. Serum biomarkers included C-reactive protein (CRP), albumin, and haemoglobin. Faecal biomarkers included faecal calprotectin test (FCT) and faecal immunochemical test (FIT). These biomarkers were compared with endoscopic IBD activity in patients who had sigmoidoscopy or ileocolonoscopy within 1 year of recruitment.

Results: A total of 113 patients (mean age 44.7 ± 17.6 years, 63.7% men, 54.9% ulcerative colitis: 45.1% Crohn's disease) were recruited. Faecal calprotectin test correlated well with FIT (r=0.583), CRP (r=0.56), albumin (r= -0.543) and haemoglobin (r= -0.352); all P<0.001. The levels of these biomarkers were not significantly different between patients in clinical remission (72.2%) compared with those not in clinical remission (all P>0.05). Of 66 patients with recent endoscopy, 41 (62.1%) had endoscopically active IBD. These patients were younger (36.4 vs 47.2 years, P=0.025), had higher FCT (632 vs 49 μg/g, P<0.001), higher FIT (65 vs 16 μg/g, P<0.001), higher CRP (1.15 vs 0.37 mg/dL, P=0.005), lower albumin (41 vs 45 g/L, P=0.001), and lower haemoglobin (12.7 vs 13.7 g/dL, P=0.024). Among the five biomarkers, FCT demonstrated the best performance characteristics (area under the receiver operating characteristic curve, 0.958). Using a derived cut-off level of FCT for endoscopically active IBD of 168 μg/g, the sensitivity, specificity, positive predictive value, and negative predictive value were 82.9%, 100%, 100%, and 78.1%, respectively. Combining normal FCT (<168 μg/g) and FIT (derived cut-off, <16 μg/g) identifies 85.2% patients without endoscopically active IBD.

Conclusion: Elevated FCT accurately identified all patients with endoscopically active IBD. Combination of normal FCT and FIT may be used to exclude active IBD.

49

High-serum Mac-2-binding protein glycosylation isomer level is associated with incident hepatocellular carcinoma in entecavir-treated chronic hepatitis B patients

LY Mak[1], DKH Wong[1,2], WK Seto[1,2], KS Cheung[1], J Fung[1,2], CL Lai[1,2], MF Yuen[1,2]
[1]Department of Medicine, Queen Mary Hospital, Hong Kong
[2]State Key Laboratory of Liver Research, The University of Hong Kong, Hong Kong

Background: Hepatocellular carcinoma (HCC) development is not uncommon in antiviral-treated patients with chronic hepatitis B (CHB) who had low viraemia. Risk prediction is more difficult compared with untreated patients. Serum Mac-2-binding protein glycosylation isomer (M2BPGi) is a novel marker for significant liver disease. We investigated the role of serum M2BPGi in association with incident HCC in entecavir (ETV)-treated patients with CHB.

Methods: We identified CHB-related HCC cases diagnosed between year 2007 to 2016 in our unit. All patients were on ≥1 year of ETV treatment prior to HCC development. A group of patients with CHB without HCC (matched for age, sex, and baseline HBV DNA) were also identified during the same period in a 1:2 ratio (HCC:non-HCC) for comparison. Serum samples were retrieved at baseline (initiation of ETV) and after 3 years and 5 years of ETV treatment. Serum M2BPGi and HBV DNA levels were serially measured at the above time points. Cirrhosis was defined by ultrasound features of shrunken liver, nodular outline, splenomegaly, or presence of ascites. Excluding 11 non-HCC patients without retrievable serum samples, 95 HCC and 179 non-HCC patients were included.

Results: A total of 274 patients (mean age, 57.7 ± 9.5 years; 79.9% men) with a median duration of 7.2 (interquartile range [IQR], 5.6-8.8) years of ETV treatment were recruited. The median follow-up was 6.9 years for patients with HCC and 7.2 years for patients without HCC (P=0.486). All patients had undetectable HBV DNA (<20 IU/mL) after 3 years and 5 years of ETV treatment. Median time from ETV initiation to incident HCC was 4.0 (IQR, 2.5-5.7) years. Patients with HCC had lower baseline median albumin (41 vs 42 g/dL, P=0.001), higher baseline median bilirubin (13 vs 11 umol/L, P=0.01), and higher proportion of cirrhosis (38.9% vs 21.2%, P=0.002) than did patients without HCC. Serum M2BPGi were higher in patients with HCC than in controls at all three time points. Sex (P=0.558), alanine aminotransferase level (P=0.201), aspartate aminotransferase level (P=0.6), and platelet count (P=0.145) were not associated with incident HCC. Multivariate analysis showed that baseline M2BPGi was the only independent factor associated with incident HCC (odds ratio=1.227, 95% confidence interval=1.045-1.440, P=0.012).

Conclusion: High-serum M2BPGi levels at baseline and after 3 years of ETV treatment were significantly associated with subsequent HCC development in ETV-treated patients with CHB.

50

Interaction between genetic variants identified from genome-wide association studies and hypertension on the risk of sight-threatening diabetic retinopathy in Chinese patients with type 2 diabetes mellitus

KKK Ng[1], CH Lee[1], YC Woo[1], WS Chow[1], RLC Wong[1], CHY Fong[1], A Xu[1], PC Sham[2], KSL Lam[1], CYY Cheung[1]
[1]Department of Medicine, The University of Hong Kong, Hong Kong
[2]Centre for Genomic Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

Objectives: Susceptibility variants of diabetic retinopathy (DR) have been identified in previous genome-wide association studies (GWASs). Hypertension has long been considered as a strong risk factor of DR. Whether the GWAS-identified genetic variants interact with hypertension to confer an altered susceptibility to DR remains to be investigated. This study aimed to examine the interactions of the GWAS-identified single nucleotide polymorphisms (SNPs) with hypertension on the risk of sight-threatening DR (STDR) in Southern Chinese patients with type 2 diabetes mellitus (T2DM).

Methods: A total of 69 SNPs that showed top association signals (r^2<0.9, P<0.0005) in previous GWASs of DR were genotyped in 1161 patients with T2DM and STDR and in 2088 T2DM patients without retinopathy. The associations between the SNPs and STDR were examined by multiple logistic regression analyses with adjustment for traditional risk factors. Interaction with hypertension was examined by implementing an additional interaction term of SNP × hypertension in the logistic regression model.

Results: *FMN1* rs10519765 (P_{GxE}=0.002), *AKAP11-FABP3P2* rs117850847 (P_{GxE}=0.004), *AKT3-ZNF238* rs10927101 (P_{GxE}=0.014), and *SLC25A32* rs3098241 (P_{GxE}=0.016) showed significant interactions with hypertension for the risk of STDR. Of these SNPs, *SLC25A32* rs3098241 also showed a significant marginal association with STDR (odds ratio [OR]=0.88, 95% confidence interval [CI]=0.78-0.99, P=0.042). Stratified analysis showed that the minor allele of this SNP was associated with significantly lower risk of STDR in the non-hypertensive patients (OR=0.59, 95% CI=0.38-0.89, P=0.013), but no significant association in the hypertensive patients was observed.

Conclusions: We have demonstrated potential gene-environment interactions of several SNPs with hypertension for the susceptibility to STDR. Further studies to validate our findings are warranted.

Acknowledgement
This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (Ref. 03144016).

Targeting DNA damage and repair mechanism in *FLT3*-ITD acute myeloid leukaemia

51

NKL Ng[1,2], C Lynn[2], YL Kwong[1], ECW So[2], AYH Leung[1]
[1]Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[2]Department of Haematological Medicine, Division of Cancer Studies, King's College London, United Kingdom

Introduction: Internal tandem duplication (ITD) of fms-like tyrosine kinase 3 (*FLT3*) is one of the most common mutations in acute myeloid leukaemia (AML), occurring in nearly 30% of cases. The ITD of *FLT3* involves in-frame duplication of 300 to 400 base-pairs at the juxtamembrane, resulting in ligand-independent activation of FLT3 signalling. Induction of reactive oxygen species and DNA damage in *FLT3*-ITD AML has led to investigation of their mechanistic link and exploration of potential therapeutic targets.

Methods: Gene expression of key DNA damage response (DDR) gene were examined in primary AML patients by quantitative polymerase chain reaction. The Traffic Light Reporter assay was used to measure the fidelity of double-strand break repair, either via error-free homologous recombination or error-prone non-homologous end joining. The PARP inhibitor olaparib has been shown to suppress leukaemia growth in vitro in Ba/F3 *FLT3*-ITD cells and knockin *Flt3*$^{ITD/+}$ *Npm1*$^{c/+}$ murine leukaemic cells. To identify potential therapeutic targets that may be exploited in combination treatment with olaparib, an in vivo DDR shRNA library screening was performed.

Results: *BRCA2* expression was shown to be downregulated in *FLT3*-ITD AML when compared with AML with wild-type *FLT3* as well as normal hematopoietic cells. *BRCA2* is an important protein in mediating homologous recombination, providing a possible explanation for defective DDR in this AML subtype. The result of Traffic Light Reporter assay showed that homologous recombination was downregulated in murine Ba/F3 cells transduced with *FLT3*-ITD whereas non-homologous end joining remained active. The DDR shRNA library screening has identified potential candidate genes included those associated with checkpoint factors and DNA replication factors, for instance, Atr kinase and members of the family B DNA polymerase. Combination of chemotherapy and olaparib worked synergistically to eradicate leukemic cells in a MOLM-13 murine xenograft model.

Conclusion: The *FLT3*-ITD AML showed defective homologous recombination and higher levels of intracellular reactive oxygen species and double-strand breaks, and olaparib induced genomic instability and apoptosis. Targeting defective DNA repair in *FLT3*-ITD AML using PARP inhibitor might be considered as a novel therapeutic strategy.

Acknowledgement
This research was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (Ref. 04152326).

Adiponectin deficiency exacerbated neuropathogenesis and cognitive functions in Alzheimer's disease mice: potential application of AdipoRon as Alzheimer's disease treatment

52

RCL Ng[1], M Jian[1], M Bunting[1], OKF Ma[1], SK Chung[2], KH Chan[1]
[1]Department of Medicine, The University of Hong Kong, Hong Kong
[2]School of Biomedical Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

Introduction: Adiponectin (APN) reduces with age and has been implicated in Alzheimer's disease (AD). Adiponectin has insulin-sensitising and anti-inflammatory abilities. We aimed to study if (i) APN deficiency affects amyloid β (Aβ) deposition, neuroinflammation and cognitive functions in AD mice; (ii) AdipoRon alleviates AD pathologies and cognitive functions in AD mice.

Methods: Transgenic mice (5xFAD) carrying familial amyloid precursor protein and presenilin mutations were used in this study. We also generated an adiponectin-deficient AD mice (5xFAD;APN-/-) by crossing 5xFAD with APN-/- mice. These mice were fed with either vehicle or AdipoRon (50 mg/kg bodyweight per day) for 3 months. Cognitive functions of these mice were investigated. Neuropathological and molecular changes in the brains were examined.

Results: Adiponectin deficiency in 5xFAD mice exacerbated memory deficits, and AD pathologies. Immunostaining demonstrated that microglia was reactivated but its phagocytic activity to Aβ was reduced in 5xFAD;APN-/- mice. Pro-inflammatory cytokine levels were elevated in the brain. Liquid chromatography–tandem mass spectrometry analysis confirmed that AdipoRon can cross the blood-brain barrier. AdipoRon-treated 5xFAD and 5xFAD;APN-/- mice showed reduction of Aβ deposition in the cortex and hippocampus. AdipoRon also reduced generation of other cleavage products in amyloidosis. AdipoRon can suppress neuroinflammation, glial activation and resume the phagocytic activity of microglia. Mice treated with AdipoRon demonstrated increased activation of insulin signalling and insulin sensitisation. Lastly, AdipoRon reversed neuronal and dendritic spines reduction as well as cognitive functions in both 5xFAD and 5xFAD;APN-/- mice.

Conclusion: In summary, our results demonstrated that APN deficiency exacerbated AD pathologies and neurodegeneration. Oral administration of AdipoRon can reverse cognitive impairments and AD pathologies by insulin sensitisation, demonstrating its therapeutic potential to treat AD.

53

Amyloid-β positron emission tomography imaging effects patient management in the memory clinic: a systematic review and meta-analysis

YF Shea, PKC Chiu, FHW Chan
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Patients with cognitive impairment or dementias of uncertain aetiology are frequently referred to a memory disorders specialty clinic. The impact of and role for amyloid-β positron emission tomography (Aβ-PET) imaging may be most appropriate in this clinical setting. The primary objective of this study was to perform a systematic review and meta-analysis of the impact of Aβ-PET on aetiological diagnosis and clinical management in the memory clinic setting.

Methods: A search of the literature on the impact of Aβ-PET in the memory clinic setting between 1 January 2004 and 12 February 2018 was conducted. Meta-analysis using a random effects model was performed to determine the pooled estimate of the impact of Aβ-PET in the changes of diagnoses and changes in management plan.

Results: After rigorous review, results from 13 studies were extracted, involving 1489 patients. Meta-analysis revealed a pooled effect of change in diagnoses of 35.2% (95% confidence interval [CI]=24.6%-47.5%). Sub-analyses showed that the pooled effect in change in diagnoses if Aβ-PET was used under the appropriate use criteria (AUC) or non-AUC criteria were 47.8% (95% CI=25.9%-70.5%) and 29.6% (95% CI=21.5%-39.3%), respectively. The pooled effect of a change of diagnosis from Alzheimer's disease (AD) to non-AD and from non-AD to AD were 22.7% (95% CI=17.1%-29.5%) and 25.6% (95% CI=17.6%-35.8%), respectively. The pooled effect leading to a change of management was 59.6% (95% CI=39.4%-77.0%).

Conclusions: Amyloid-β positron emission tomography has a highly significant impact on both changes in diagnosis and management among patients being seen at a specialty memory clinic.

54

Clinical presentation and natural clinical course of biomarkers supported Alzheimer's disease and Lewy body dementia in Hong Kong

YF Shea, SC Lee, ACK Shum, PKC Chiu, LW Chu, FHW Chan
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Alzheimer's disease (AD) and Lewy body dementia (LBD) are two common forms of dementia. There are still controversies regarding whether LBD patients have a worse clinical course when compared with AD patients.

Methods: All patients with biomarker-supported AD or LBD who presented to the Memory Clinic of Queen Mary Hospital between 1 January 2008 and 30 December 2016 were retrospectively reviewed. The diagnoses of AD and LBD were supported by both clinical diagnostic criteria and biomarkers (including cerebrospinal fluid biomarkers or functional imaging ± pathological biomarkers). Patients with LBD included those with dementia with Lewy bodies (DLB) and those with Parkinson's disease dementia (PDD). Baseline demographics, presenting clinical features, degree of cognitive impairment, and specified clinical outcomes (including falls, dysphagia, pneumonia, pressure injuries, institutionalisation, and mortality) were compared.

Results: In total, 31 patients with AD and 25 patients with LBD (18 with DLB and 7 with PDD) were recruited. When measured from disease onset, patients with LBD had shorter overall survival (P=0.02) and shorter survival that was free of falls (P<0.001), dysphagia (P<0.001), pneumonia (P=0.01), pressure injuries (P=0.003) and institutionalisation (P=0.03) than patients with AD. Cox regression analyses showed that LBD group predicted fall (hazard ratio [HR]=5.86, 95% confidence interval [CI]=2.29-15.01, P<0.001), dysphagia (HR=10.06, 95% CI=2.5-40.44, P=0.001), pressure injuries (HR=17.39, 95% CI=1.51-200.1, P=0.02), institutionalisation (HR=2.72, 95% CI=1.12-6.60, P=0.03), and death (HR=2.96, 95% CI=1.18-7.42, P=0.02).

Conclusion: Lewy body dementia predicted these pre-specified long-term events.

Self-care peritoneal dialysis patients with cognitive impairment has a higher risk of peritonitis in the second year

55

YF Shea, MSC Lee, MYM Mok, MF Lam, LW Chu, FHW Chan, TM Chan
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Cognitive impairment is common among patients on peritoneal dialysis (PD). We hypothesise that cognitive impairment has a negative impact on the outcome of patients on PD, especially with regard to peritonitis.

Methods: This was a single-centre 2-year prospective cohort study involving 206 patients at one PD unit. Cognitive impairment was defined by the latest Hong Kong Montreal Cognitive Assessment (HK-MoCA) score multiple cut-offs as determined by age and years of education. Most patients (80%) returned for interval HK-MoCA score. The HK-MoCA was performed at baseline and after 1 year on PD. Potential risk factors for cognitive impairment and peritonitis were studied separately for the first and second year.

Results: For cognitive impairment at baseline, multivariate analyses showed that age (odds ratio [OR]=1.003, 95% confidence interval [CI]=1.003-1.065, P=0.03), female sex (OR=3.57, 95% CI=1.60-7.97, P=0.002), peripheral vascular disease (OR=3.46, 95% CI=1.33-9.01, P=0.01), and haemoglobin level (OR=0.60, 95% CI=0.43-0.84, P=0.003) were statistically significant factors. For cognitive impairment at 1 year, multivariate analyses showed that age (OR=1.07, 95% CI=1.02-1.012, P=0.007), female sex (OR=5.87, 95% CI=1.86-18.5, P=0.003), and peripheral vascular disease (OR=3.68, 95% CI=1.07-12.84, P=0.04) were statistically significant independent factors. For self-care PD patients at 2 years, patients with cognitive impairment had a higher rate of peritonitis (0.50 vs 0.27 episodes per year, P=0.048) and proportionately more patients had both peritonitis and exit site infection (25% vs 7.2%, P=0.049) than did patients without cognitive impairment. Logistic regression showed that only HK-MoCA-defined cognitive impairment (risk ratio [RR]=3.2, 95% CI=1.03-9.95, P=0.04) and HK-MoCA scores (RR=0.92, 95% CI=0.86-0.995, P=0.04) at 1 year were factors predicting peritonitis.

Conclusions: Increasing age, female sex, anaemia, and presence of peripheral vascular disease are risk factors for cognitive impairment in PD patients. Self-care PD with cognitive impairment at 1 year has a higher risk for PD-related peritonitis at 2 years. Interval HK-MoCA assessment is recommended to detect cognitive impairment in local PD patients.

Fatty acid-binding protein 4 mediates autoimmune diabetes by activation on macrophage and tissue resident memory T cell

56

LL Shu[1], XP Wu[2,3], LY Cheung[1], ZG Zhou[1], RLC Hoo[2,3], KSL Lam[1], A Xu[1]
[1]Department of Medicine, The University of Hong Kong, Hong Kong
[2]State Key Laboratory of Pharmaceutical Biotechnology, The University of Hong Kong, Hong Kong
[3]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong

Introduction: Type 1 diabetes mellitus (T1DM) is an autoimmune disease that results from the self-destruction of insulin-producing pancreatic beta cells. However, the pathological pathways that trigger the autoimmune destruction remain poorly understood. Our previous clinical studies demonstrated that increased circulating fatty acid binding protein 4 (FABP4), a pro-inflammatory adipokine that links obesity with its related metabolic diseases, is closely associated with beta cell autoimmunity in patients with T1DM. Here we investigate the role and underlying mechanism whereby FABP4 participates in the pathogenesis of autoimmune destruction of pancreatic beta cells in T1DM.

Methods: The FABP4+/+/NOD and FABP4-/-/NOD mice were generated by crossing FABP4-/- mice with NOD mice (a well-established model with spontaneous development of insulitis and autoimmune diabetes) for at least two generations. Biochemical, immunological, and in vivo imaging analysis were conducted to determine the dynamic change in the infiltration and activation of immune cells including macrophages and tissue resident memory T (Trm) cells in pancreas of FABP4+/+NOD and FABP4-/-NOD mice at different ages. Gain- and loss-of-function studies were employed to evaluate the effects of FABP4 in macrophages and Trm cells on insulitis and diabetes incidence.

Results: A dynamic change in the expression of FABP4 was observed in macrophages and Trm cells in pancreatic islets of NOD mice at different stages. Depletion of macrophages or Trm cells in 8-week FABP4+/+NOD mice partially alleviated insulitis and reduced the development of diabetes in NOD mice, whereas simultaneous depletion of macrophages and Trm cells prevented the onset of T1DM. Flow cytometry analysis demonstrated that FABP4 deficiency significantly attenuated the polarisation and infiltration of pro-inflammatory macrophages (M1) and Trm cells into the pancreas, reduced the production of inflammatory cytokines, and alleviated islet inflammation and beta cell destruction.

Conclusion: Fatty acid binding protein 4 activates both innate and adaptive immunity through enhancing the polarisation of macrophages to pro-inflammatory M1 subtype and promoting the survival of Trm cells, respectively, thus creating an inflammatory microenvironment leading to the autoimmune attack on beta cells. Pharmacological inhibitors of FABP4 are a promising drug candidate for prevention of autoimmune diabetes.

Acknowledgement
This research was supported by the National Natural Science Foundation of China and the Research Grants Council Joint Research Scheme (N_HKU726/14).

Serum beta-2 microglobulin predicts mortality after acute coronary syndrome

57

ASC So[1], MF Tsoi[1], CL Cheung[2], SW Lee[1], SH Tsui[3], EYT Chan[4], FCC Tam[1], BMY Cheung[1]
[1]Department of Medicine, The University of Hong Kong, Hong Kong
[2]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong
[3]Accident and Emergency Department, Queen Mary Hospital, Hong Kong
[4]Department of Pathology, Queen Mary Hospital, Hong Kong

Introduction: We have previously shown that serum beta-2 microglobulin (B2M) is significantly elevated in patients with acute coronary syndrome (ACS) in Hong Kong and is a predictor of all-cause mortality in the United States National Health and Nutritional Examination Survey. In this cohort study, we investigated the relationship between baseline B2M level and mortality in long-term follow-up.

Methods: In total, 88 patients with ACS and 79 controls matched for age and sex were recruited from Queen Mary Hospital between September 2015 and May 2016. Serum B2M was measured using a latex-enhanced B2M immunoassay (Siemens Diagnostics, Erlangen, Germany). Patient data up to 15 November 2018 were extracted from the Clinical Data Analysis and Reporting System of the Hong Kong Hospital Authority. Serum B2M levels were compared using analysis of variance with SPSS (Windows version 25.0; IBM Corp, Armonk [NY], United States).

Results: Seven patients died (6 in the ACS group) during the follow-up period. The geometric mean of serum B2M level was 3.13 μg/mL (95% confidence interval [CI]=2.14-4.58 μg/mL) in those who died and 1.97 μg/mL (95% CI=1.84-2.11 μg/mL) in those who survived (P=0.001). In the ACS group, the geometric mean serum B2M level was 3.50 μg/mL (95% CI= 2.73-4.49 μg/mL) in those who died and 1.99 μg/mL (95% CI=1.78-2.23 μg/mL) in those who survived (P=0.002).

Conclusion: Elevated serum B2M level is associated with higher mortality in patients with ACS. This test is readily available and may help to identify high-risk patients with ACS.

Acknowledgements
This study was supported by a Seed Funding for Basic Research Grant from the University of Hong Kong. ASC So received a Research Internship from the Li Ka Shing Faculty of Medicine, The University of Hong Kong.

Artificial intelligence–based identification of caecum by static colonoscopy images

58

NYH So, WK Leung, KL Lui
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Artificial intelligence (AI) has recently been shown to be accurate in colorectal polyp detection and characterisation. However, accurate recognition of anatomical landmarks is also important in the development of fully automated endoscopy. In particular, the caecum usually signifies the end of the colonoscopy and it is an important anatomical landmark.

Methods: An AI recogniser for the caecum was built on a convolutional neural network (with 5 convolutional layers and 3 fully connected layers) and was trained with a total of 2296 caecal images and 2300 normal non-caecal colonic images. An independent validation set of 49 static caecal images and 53 static non-caecal images from 49 colonoscopy reports was used to test the performance of the trained AI caecum recogniser.

Results: The AI caecum recogniser had a sensitivity 92.3% (95% confidence interval [CI]=81.4%-97.9%), specificity 92.0% (95% CI=80.8%-97.8%), positive predictive value 92.3% (95% CI=82.4%-96.9%), negative predictive value 92.0% (95% CI= 81.7%-96.7%), and accuracy 92.1% (95% CI=85.1%-96.5%). The area under the receiver operating characteristic curve was 0.92 (95% CI=0.86-0.98). The process speed was 3.4 images per second. The main reasons for missed recognition of caecum were the presence of a small diverticulum in the normal colonic image and the absence of ileocaecal valve in the caecal image.

Conclusion: The caecum can be accurately and rapidly recognised by the trained AI based on a single colonoscopic image.

Exploring the potential of non-coding RNAs as biomarkers of systemic lupus erythematosus and lupus nephritis

59

SY Sze, SYY Wong, CS Lau, VSF Chan
Division of Rheumatology and Clinical Immunology, Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Systemic lupus erythematosus (SLE) is an autoimmune disease with heterogeneous clinical manifestations. Lupus nephritis (LN) is one of the most common presentations in patients with SLE. Recently, long non-coding RNAs (lncRNAs) have emerged as important regulators of biological processes through regulating gene transcription and translation. Studies have identified a number of lncRNAs that are associated with disease activity of SLE and have suggested that these lncRNAs may play a role in pathogenesis of SLE. Therefore, this study investigated lncRNAs as biomarkers of SLE and LN that may help in diagnosis and monitoring.

Methods: Whole blood samples were collected from patients with SLE confirmed by biopsy as LN or non-LN. Total RNA was extracted, and cDNA libraries were prepared. The cDNA was sequenced using Illumina HiSeq 1500. Long non-coding RNAs that were differentially expressed were identified using EBSeq software. They were correlated with clinical parameters of patients and their potential interaction with other RNAs were investigated through the online database StarBase.

Results: Two lncRNAs, *LINC01268* and *LINC02207* were found to be significantly upregulated in patients with LN. The expression levels of these lncRNAs were positively correlated with SLE disease activity index. *LINC01268* was positively correlated with blood urea and creatinine. *LINC02207* was positively correlated with anti-dsDNA antibodies and negatively correlated with C3. Investigations on their possible interaction with other RNAs revealed that *LINC01268* may interact with the mRNA of human leukocyte antigen–DR.

Conclusion: *LINC01268* and *LINC02207* are potential biomarkers of SLE and LN. On-going studies include validating the RNA sequencing data with quantitative real-time polymerase chain reaction with an independent patient cohort of a larger sample size.

Association between blood lead level and gout: the United States National Health Nutrition and Examination Survey 2007-2014

60

MF Tsoi, BMY Cheung, CS Lau, TT Cheung
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Lead is a heavy metal without a biological role in humans. It is hypothesised to increase the risk of gout by increasing serum urate level and reducing renal function. High blood lead level (BLL) is associated with an increased risk of gout. Whether this association still holds at lower BLLs is uncertain. Therefore, we aimed to evaluate the association between BLL and gout in the US population.

Methods: Adult participants with blood lead measurements in the US National Health Nutrition and Examination Survey 2007-2014 were included in this analysis. Gout was defined as a self-reported diagnosis of gout. Results were analysed using SPSS (Windows version 22.0; IBM Corp, Armonk [NY], US). Logistic regression with sample weight adjustment was used to study the association between BLL and gout. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated using logistic regression with sample weight adjustment.

Results: A total of 18837 participants were included in this analysis. The prevalence of gout increased with BLL. Every doubling in the BLL was associated with gout (OR=1.66, 95% CI=1.50-1.84). This association remained significant after adjustment for estimated glomerular filtration rate, family poverty-to-income ratio, hypertension, diabetes, thiazide diuretics prescription, and body mass index (OR=1.43 [95% CI=1.24-1.66]). Using quintile 1, BLL <0.89 μg/dL, as reference, BLL ≥1.49 μg/dL was associated with increased gout risk (BLL 1.49-<2.21 μg/dL vs quintile 1: OR=2.48 [95% CI=1.55-3.97]; BLL ≥2.21 μg/dL vs quintile 1: OR=3.21 [95% CI=1.98-5.21]).

Conclusion: Blood lead level, even at low levels, is associated with gout. The risk of gout is increased when the blood lead level is ≥1.49 μg/dL. Therefore, measures should be taken to minimise the environmental exposure to lead.

61

Association between blood lead level and hypertension: the United States National Health Nutrition and Examination Survey 1999-2016

MF Tsoi, KKW Lui, TT Cheung, BMY Cheung
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Lead is a heavy metal without a biological role in human. High level exposure is known to be associated with hypertension. However, their association at low levels of exposure is uncertain.

Methods: Adult participants with blood lead measurements and blood pressure measurements, or self-reported hypertension diagnosis, whose data were included in the United States National Health Nutrition and Examination Survey were included in this analysis. If not already diagnosed, hypertension was defined according to the American Heart Association/American College of Cardiology 2017 hypertension guidelines. Results were analysed using R statistics version 3.5.1 with package 'survey' and sample weight adjustment. Logistic regression was used to study the association between blood lead level and hypertension. Odds ratio (OR) and 95% confidence interval (95% CI) were estimated.

Results: A total of 39 477 participants were included in this analysis. Every doubling in blood lead level was associated with hypertension (OR=1.45, 95% CI=1.40-1.50). This association remained significant after adjusting for age, sex, ethnicity, waist circumference, and smoking status. Using quartile 1, blood lead level <0.89 μg/dL, as reference, higher blood lead levels were associated with increased adjusted odds of hypertension (quartile 4 vs quartile 1: 1.22 [1.09-1.36]; quartile 3 vs quartile 1: 1.15 [1.04-1.28]; quartile 2 vs quartile 1: 1.14 [1.05-1.25]).

Conclusion: Blood lead level is associated with hypertension in the general population. Most of the population do not have elevated blood lead levels. Our findings suggest that reducing present levels of environmental lead exposure may benefit adults by reducing blood pressure and its attendant cardiovascular risk.

62

Hyperlipidaemic effect of Janus kinase inhibitors: a meta-analysis

MF Tsoi, TT Cheung, BMY Cheung
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Janus kinase (JAK) inhibitors are effective in treating rheumatoid arthritis. However, JAK is involved in lipid metabolism, so we investigated the association between JAK inhibitors and hyperlipidaemia.

Methods: We conducted a literature search using ISI Web of Science, Scopus, Medline, Cochrane library, Clinicaltrials.gov, and Embase. We included randomised controlled trials reporting the frequency of hypercholesterolaemia or hyperlipidaemia as a study outcome. Results were analysed using RevMan 5.3.5. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using a random effects model. The standardised mean differences (SMDs) and 95% CIs were estimated for the change in lipid profile.

Results: In all, 17 trials were included in the meta-analysis. Janus kinase inhibitors were associated with hypercholesterolaemia (OR=2.52, 95% CI=1.59-3.99; I^2 statistics: 0%) and hyperlipidaemia (OR=3.23, 95% CI=1.73-6.04; I^2 statistics: 0%). Both JAK inhibitors were associated with increase in serum high-density lipoprotein level (baricitinib: SMD=1.60, 95% CI=0.67-2.53 mg/dL; tofacitinib: SMD=2.80, 95% CI=0.61-4.98 mg/dL) and low-density lipoprotein level (baricitinib: SMD=2.47, 95% CI=0.40-4.53 mg/dL; tofacitinib: SMD=2.79, 95% CI=1.17-4.41 mg/dL).

Conclusions: Janus kinase inhibitors increased serum low-density lipoprotein and high-density lipoprotein levels. Significant associations between JAK inhibitors and hypercholesterolaemia as well as hyperlipidaemia were revealed. If causal, there would be important clinical implications for rheumatoid arthritis patients.

63 Incidence, prevalence, and utilisation of urate-lowering therapy in Hong Kong: a population-based study

MF Tsoi, BMY Cheung, CS Lau, TT Cheung
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: The prevalence of gout has increased significantly over the past decade in Western populations. We conducted this population study in Hong Kong to determine the incidence and prevalence of gout and the utilisation of urate-lowering therapy (ULT) among patients with gout.

Methods: A total of 2 741 862 patients who attended any out-patient clinics or accident and emergency department (with or without hospitalisation) in 2005 were identified from the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority. Patients who died before 2006 were excluded. All patients were followed up until the end of 2016 or death. Patient demographics, diagnosis of gout, serum urate levels, and ULT prescriptions were retrieved from CDARS. Gout was defined as the physician diagnosis coding in CDARS. The serum urate level achieved after prescribing ULT was taken as the mean of all serum urate levels 6 months after prescription. Results were analysed by R statistics version 3.3.3 with package 'prevalence' version 0.4.0.

Results: The crude incidence of gout increased from 113.05/100 000 person-years in 2006 to 211.62/100 000 person-years in 2016. The crude prevalence of gout increased from 1.28% in 2006 to 2.92% in 2016. Only 25.55% of patients with gout were prescribed ULT in 2016. Among them, 28.1% achieved a serum urate level <6 mg/dL.

Conclusion: Population ageing has led to increases in the incidence and prevalence of gout in Hong Kong. In 2016, the crude prevalence of gout in Hong Kong was 2.92%, which is similar to figures reported in Western countries. Only one in four patients with gout were prescribed ULT.

64 Hepatitis B virus DNA integration in hepatocellular carcinoma patients with occult hepatitis B infection

DKH Wong[1,2], S Cheng[1], LLY Mak[1], E To[1], TT Cheung[1], WK Seto[1,2], J Fung[1,2], K Man[2,3], CL Lai[1,2], MF Yuen[1,2]
[1]Department of Medicine, The University of Hong Kong, Hong Kong
[2]State Key Laboratory of Liver Research, The University of Hong Kong, Hong Kong
[3]Department of Surgery, The University of Hong Kong, Hong Kong

Background: Hepatitis B virus (HBV) DNA can cause hepatocellular carcinoma (HCC) by integrating into host chromosome and inducing chromosomal instability. Some hepatitis B surface antigen (HBsAg)–negative patients may have detectable HBV DNA and are defined to have occult hepatitis B infection (OBI). We aimed to study the prevalence of OBI and HBV integration in HBsAg-negative HCC patients.

Methods: We used nested polymerase chain reaction (PCR) to detect HBV DNA in liver tissues obtained from 90 HBsAg-negative HCC patients. Occult hepatitis B infection was diagnosed when ≥2 positive PCRs were detected in either tumour or non-tumour tissues. Hepatitis B virus integration was detected by Alu-PCR sequencing.

Results: Of the 90 HCC patients, 18 (21%) had alcoholic liver diseases, 14 (16%) had non-alcoholic fatty liver disease, two had primary biliary cholangitis, two had recurrent pyogenic cholangitis, one had autoimmune hepatitis, and the remaining 53 (60%) patients had unknown causes of (cryptogenic) HCC. Occult hepatitis B infection was detected in 62/90 (69%) HCC patients, including 9/18 (50%) with alcoholic liver diseases, 9/14 (64%) with non-alcoholic fatty liver disease, two (100%) with primary biliary cholangitis, two (100%) with recurrent pyogenic cholangitis, and 40/53 (75%) with cryptogenic HCC. The majority (53/62; 85%) of OBI patients did not have liver cirrhosis histologically confirmed. Hepatitis B virus DNA integration was detectable in 43/62 (69%) OBI patients. Chromosome 5 (5 cases) and chromosome 17 (4 cases) were two of the most frequent integration sites. Only 4/62 (6%) patients with HBV integration had cirrhosis. In some cases, HBV DNA integration was found in proximity to apoptosis/cell cycle-related genes (TERT or cyclin A2), tumour suppressor regulators (COP1), or genes involved in epigenetic regulation of cancer-related genes (KMT2B).

Conclusion: In all, 69% of HBsAg-negative HCC patients had OBI; 85% of HCC patients with OBI had no background of cirrhosis, and the oncogenic process might be explained by the high percentage (69%) of HBV integration detected. Hepatitis B virus integration, especially near cancer-related genes, can be a likely cause of HCC in OBI patients.

65

Impact of obesity on longitudinal changes to cardiac structure and function in patients with type 2 diabetes mellitus

MZ Wu, Y Chen, Z Zhen, YJ Yu, HF Tse, KH Yiu
Cardiology Division, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Aims: Few prospective studies have evaluated the natural progression of left ventricular (LV) remodelling in patients with type 2 diabetes mellitus (T2DM). The aim of this study was to evaluate the impact of obesity on longitudinal cardiac structural and functional changes in patients with T2DM.

Methods: This study comprised 274 patients with T2DM (mean age, 62.2 ± 11.4 years; 51.5% men). Echocardiographic parameters including LV geometry, and systolic and diastolic functions were measured at baseline and follow-up.

Results: The median follow-up was 24 months (range, 12-48 months). The entire cohort showed a significant increase in LV wall thickness, LV mass, and prevalence of concentric hypertrophy (19.6%-27.3%). Further, systolic function and diastolic function had deteriorated at follow-up assessment in all patients. Multivariable adjusted linear regression demonstrated that baseline body mass index (BMI) predicted longitudinal change to LV mass (β=0.29, P<0.01) and LV ejection fraction (β= -0.15, P<0.05). Patients were divided into three groups according to their BMI: normal weight (BMI <23 kg/m^2), overweight (BMI between 23 and 27.5 kg/m^2), or obese (BMI ≥27.5 kg/m^2). Importantly, obesity at baseline predicted a greater longitudinal increase in LV mass and decrease in LV ejection fraction compared with overweight and normal weight patients.

Conclusion: Being obese at baseline was associated with greater longitudinal increase in LV mass and greater deterioration in LV systolic function.

66

L-arginine and tetrahydrobiopterin reduce brain damage after ischaemic stroke in diabetic rats

Q Xu, RTF Cheung
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: This study aimed to determine whether administration of L-arginine and/or tetrahydrobiopterin (BH_4) would be neuroprotective against ischaemic stroke in rat models of diabetes mellitus.

Methods: Type 1 diabetes mellitus (T1DM) was induced in rats by a single intraperitoneal (i.p.) injection of streptozotocin at a high dose (60 mg/kg). Type 2 diabetes mellitus (T2DM) was induced using a combination of high-fat diet for 4 weeks and a single injection of streptozotocin at a low dose (35 mg/kg) after 2 weeks of high-fat diet. Middle cerebral artery occlusion (MCAO) was induced in T1DM, T2DM, and non-diabetic (non-DM) rats. The duration of ischaemia was 75 or 90 minutes in non-diabetic rats and 75 minutes in diabetic rats. Rats were either treated with BH_4 (10 mg/kg i.p.) or L-arginine (300 mg/kg i.p.) alone or in combination at 30 minutes before MCAO. After reperfusion for 24 hours, rats were subjected to a behavioural test of neurological deficit before they were sacrificed. The brains were collected for the assessment of infarct volume and oedema.

Results: In non-DM rats, the percentage of infarct volume over the total volume of right brain hemisphere was 48.1% after 90 minutes of ischaemia in the vehicle group. Compared with the vehicle group, injection of BH_4 or L-arginine alone prior to ischaemia reduced the percentage of infarct volume by 36.2% or 33.4%, respectively (P<0.01). The combination did not achieve any better outcome, with relative infarct volume reduced by 27.4% (P<0.01). All three treatments reduced oedema ratio and severity of neurological deficit. Mortality was 44.4% in T1DM rats and 11.1% in non-DM rats after 90 minutes of MCAO. Mortality was 12.5% in T1DM rats and 0 in non-DM rats after 75 minutes of MCAO. The percentage of infarct volume in vehicle groups after 75 minutes of ischaemia in non-DM, T1DM, and T2DM rats were 40.2%, 44.5%, and 37.6%, respectively. Treatment with tetrahydrobiopterin alone significantly reduced the relative infarct volume by 16.9% and 32.6% (P<0.05) in T1DM and T2DM rats when compared with the vehicle groups, respectively. Different treatments did not affect oedema ratio in diabetic rats. The behavioural performance improved after injection of BH_4 and L-arginine in T1DM rats.

Conclusion: Administration of L-arginine, BH_4, or the combination was neuroprotective against stroke in non-diabetic rat. Tetrahydrobiopterin but not L-arginine reduced the brain injury after stroke in diabetic rats.

The role of contactin 1 on acquired resistance in small-cell lung cancer

67

S Xu[1], S Yan[1], SK Lam[1], PN Cheng[2], JCM Ho[1]
[1]Division of Respiratory Medicine, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]Bio-cancer Treatment International, Bio-informatics Centre, Hong Kong Science Park, Tai Po, Hong Kong

Introduction: Small-cell lung cancer accounts for about 15% of all lung cancer cases. Small-cell lung cancer is characterised by ease of relapse, and current treatments lack tumour specificity. Arginine is an important amino acid in human, but some tumours lose the ability to synthesise it. Therefore, arginine deprivation has become a targeted therapy in certain tumours. BCT-100 is a pegylated arginase with anticancer activity in arginine auxotrophic tumours. Contactin 1 (CNTN1) is a cell adhesion molecule which plays an important role in drug resistance. The aim of this study was to determine the effects of CNTN1 on BCT-100 acquired resistance in small-cell lung cancer.

Methods: BCT-100-resistant (BR) cells, H446-BR and H526-BR, were developed by incubating respective parental cells with serially increasing concentrations of BCT-100. Gene chip assay was employed to extract potential targeted biomarkers in BR cell lines and MTT assay was used to detect cell viability. Western blotting was used to evaluate protein expression. Knockdown of CNTN1 was performed using specific shRNA. Wound healing assay was used to evaluate the cell migration ability in H446 and H446-BR adherent cell lines. Flow cytometry was used to detect the related biomarkers in BR cells.

Results: The protein expression of CNTN1 in H446-BR and H526-BR cells was 2.7-fold and 5.3-fold higher, respectively, than that in parental cells. Cell migration ability in BR cells was stronger than in parental cells: wound healing rate was greatly increased from 48.5% to 69.9% in H446-BR cells. Epithelial-mesenchymal transition (EMT) progression and AKT activation were observed in both BR cell lines. Knockdown of CNTN1 re-sensitised BR cells to BCT-100 treatment and reversed the EMT progression via inhibiting AKT pathway.

Conclusion: Contactin 1 modulates BCT-100 resistance through induction of EMT by activating AKT pathway in small-cell lung cancer.

Can polo-like kinase 4 inhibitors be used in treatment of tumour protein 53 mutant complex/ monosomal karyotype acute myeloid leukaemia?

68

N Yang, NKL Ng, AYH Leung
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Acute myeloid leukaemia (AML) is one of the most lethal cancers worldwide. Chemotherapy and allogeneic hematopoietic stem cell transplantation are the mainstays of treatment, but only 30% to 40% patients can be successfully treated. Acute myeloid leukaemia with complex or monosomal karyotype (CK/MK) responds poorly to conventional treatment and hence an unfavourable outcome. In particular, tumour protein 53 (TP53) mutant CK/MK AML showed an extremely unfavourable clinical outcome. Novel therapeutic targets and biomarkers are needed to improve disease monitoring and treatment outcome. Polo-like kinase 4 (PLK4), which is involved in centriole duplication and functions as a positive modulator of cell-cycle progression, has been shown its pathogenetic role in TP53 mutated cancers. This study investigated for the therapeutic potential of PLK4 targeting in CK/MK AML.

Methods: Human AML cell lines ML-2, MOLM-13, MV4-11, NOMO-1, and THP-1 were treated with PLK4 inhibitor CFI-400945 (PLK4i) to evaluate the effects of PLK4i. *TP53* knockout cell lines generated by CRISPR/Cas9 system were used to validate the affected targets in defective TP53 signalling by quantitative real-time PCR and western blot. Effects of chemotherapy on PLK4 in wild-type and mutant/knockout *TP53* AML models were examined as well.

Results: Dose-response curves of PLK4i shown cell lines ML-2, MOLM13 and MV4-11 were sensitive to PLK4i. Apoptosis were induced in these lines after 72 hours of treatment by PLK4i at 20 nM underscoring its potential therapeutic value in AML. *TP53* mutations/knockout led to defective TP53 signalling as evidence by failure to induce TP53 target genes *P21* and *MDM2* upon DNA damage agent etoposide. *PLK4* expression was significantly downregulated upon etoposide treatment in parental but not *TP53* mutations/knockout AML supporting the proposition that sustained *PLK4* expression may provide survival signals in *TP53* mutant AML upon chemotherapy treatment.

Conclusion: Activation of TP53 signalling via treatment of etoposide can suppress the expression of *PLK4* in TP53 wild-type lines but not in the *TP53* knockout lines, implicating an important role of PLK4 in the leukaemogenesis of *TP53* mutant CK/MK AML.

Bidirectional role of PM20D1 in the regulation of glucose metabolism

69

RY Yang, L Xu, XQ Yan, Z Huang, AM Xu
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Adaptive thermogenesis is important for the regulation of glucose metabolism. Recent studies suggest that N-acyl-amino acids act as uncoupling protein 1–independent uncouplers of respiration and thus enhance thermogenesis by dissipating chemical energy as heat. PM20D1 (peptidase M20 domain containing 1) is a bidirectional enzyme in vitro, catalysing both the condensation of fatty acids and amino acids to generate N-acyl amino acids and also the reverse hydrolytic reaction. Although we have demonstrated a significant increase of circulating PM20D1 concentration in diet-induced obese mice, the role of PM20D1 in the regulation of glucose metabolism in vivo is still unclear.

Methods: Adeno-associated virus serotype 8–mediated gene delivery system was developed to overexpress PM20D1 in C57BL6N mice. Glucose intolerance test and comprehensive laboratory animal monitoring system study were conducted on the mice, and serum levels of N-acyl-phe were detected in these mice housed at either thermoneutral or cold temperatures using liquid chromatography-mass spectrometry.

Results: Under thermoneutral conditions, mice with over-expression of PM20D1 exhibited exacerbated diet-induced glucose intolerance. In contrast, under cold conditions, over-expression of PM20D1 in mice significantly improved glucose tolerance in both lean and obese mice. Consistently, oxygen consumption was markedly increased in mice with over-expression of PM20D1 after cold exposure. Liquid chromatography-mass spectrometry analysis showed that serum levels of N-acyl-phe increased under thermoneutrality but decreased under cold exposure in mice with over-expression of PM20D1.

Conclusion: This study shows opposite roles of PM20D1 in the regulation of glucose metabolism between thermoneutral and cold temperatures. This may be achieved by the bidirectional enzymatic effects of PM20D1 on its metabolite N-acyl-phe in a temperature-dependent manner.

Antiphospholipid antibodies in lupus nephritis—long-term outcomes and clinical correlations

70

DY Yap, KM Thong, S Yung, CSO Tang, BMY Ma, TM Chan
Division of Nephrology, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Clinical significance of antiphospholipid antibodies (APA) in lupus nephritis (LN) remains controversial.

Methods: We retrospectively studied the long-term clinical outcomes of 149 patients with LN who were seropositive or seronegative for APA.

Results: In all, 53 (35.6%) APA-seropositive patients and 96 (64.4%) APA-seronegative patients (64.4%) were followed up for 150.3 ± 63.4 and 158.9 ± 5 9.8 months, respectively. The APA-seropositive patients showed poorer long-term patient survival at 10-year and 15-year follow-up (91% and 85%, respectively, compared with 99% and 95%, respectively, in APA-seronegative patients, P=0.043). Six APA-seropositive patients died; four because of thrombotic events and two because of bleeding complications related to anticoagulation. The APA-seropositive patients with LN also showed faster estimated glomerular filtration rate decline (-1.44 mL/min per year, compared with -0.38 mL/min per year in APA-seronegative patients, P=0.027) and less optimal long-term renal survival at 10-year and 15-year follow-up (82% and 74%, respectively, compared with 91% and 87%, respectively, in APA-seronegative patients, P=0.034). The APA-seropositive group also had higher incidence of thrombotic events and miscarriage (32.1% and 13.2%, respectively, compared with 16.7% and 2.1%, respectively, in the APA-seronegative group, P=0.030 and P=0.006).

Conclusion: In patients with LN, APA-seropositivity was associated with inferior long-term patient and renal survival, and escalated risk of thrombotic events and miscarriage.

71

Long-term outcomes of entecavir treatment in kidney transplant recipients with chronic hepatitis B virus infection

DY Yap[1], CSO Tang[1], J Fung[2], WK Seto[2], MKM Ma[1], BY Choy[1], TM Chan[1]
[1]Division of Nephrology, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]Division of Gastroenterology and Hepatology, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Background: Our group previously reported the short-term efficacy and safety of entecavir in hepatitis B surface antigen (HBsAg)–positive kidney transplant recipients (KTRs), but long-term outcomes data are lacking.

Methods: We retrospectively studied the clinical outcomes of 30 HBsAg-positive KTRs who received entecavir during 2007-2017.

Results: A total of 18 treatment-naïve (Group I) and 12 lamivudine-resistant (Group II) patients received entecavir for 48.4 ± 35.2 and 66.0 ± 26.0 months, respectively. Both groups showed substantial decrease in hepatitis B virus (HBV) DNA, but Group I achieved earlier undetectability after 11.9 ± 9.6 months (compared with 28.8 ± 24.2 months in Group II, P=0.033). Group I demonstrated higher rates of undetectable HBV DNA (31%, 89%, 94%, 94%, 100%, and 100% at 6, 12, 24, 36, 48, and 60 months, respectively, compared with 17%, 25%, 50%, 50%, 91%, and 91% in Group II, P=0.003). Normalisation of alanine aminotransferase occurred after 6.0 ± 1.9 and 6.8 ± 2.1 months in Group I and II, respectively. Four (33.3%) patients in Group II developed drug resistance (2 had sustained viraemia >5000 IU/mL and 2 showed virological breakthrough, at 40.3 ± 15.0 months). Group II showed higher liver stiffness after 5 years (7.7 ± 4.1 kPa, compared with 5.0 ± 1.6 kPa in Group I, P=0.046) and higher incidence of cirrhosis (4 [33.3%] patients, compared with 1 [5.6%] patient in Group I, P=0.049). Two patients (one in each group) developed hepatocellular carcinoma. Patient and graft survival did not differ between the two groups at 5 years (P=0.62 and 0.36, respectively).

Conclusion: Entecavir was associated with good long-term efficacy and safety in treatment-naïve KTRs. Non-response or virological breakthrough occurred in one third of lamivudine-resistant patients after entecavir treatment.

72

Differential effects of intermittent hypoxia on systemic and adipose tissue inflammation in lean and diet-induced obese mice

SC Yeung[1], MQ Ge[1], JCW Mak[1,2], MSM Ip[1]
[1]Department of Medicine, The University of Hong Kong, Hong Kong
[2]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong

Background: Obstructive sleep apnoea and obesity are increasingly associated with insulin resistance. The underlying pathophysiology remains unclear but inflammation of the adipose tissue has been proposed to play an important role. The main aim of this study was to investigate the effects of acute (7 days) or chronic (4 weeks) intermittent hypoxia (IH), a hallmark of obstructive sleep apnoea, on adipose tissue inflammation in lean and diet-induced obese mice.

Methods: Mice (C57BL/6J, age 4 weeks, n=6-8 in each group) were fed a regular or high-fat diet for 9 weeks and then exposed to IH (cycles of 10% O_2 for 60 seconds followed by another 60 seconds of 21% O_2, 30 hypoxic events per hour, 8 hours per day; BioSpherix Quick & Quiet O_2 Profiler with A84XOV OxyCycler, Parish [NY], US) or room air as controls for 1 or 4 weeks. At the end of the exposure, fasting blood samples, anterior subcutaneous adipose tissue (SAT) and epididymal visceral adipose tissue (VAT) were collected after sacrifice. Serum and adipose tissue inflammatory markers such as monocyte chemoattractant protein-1 (MCP-1/CCL2), interleukin (IL)-6, and tumour necrosis factor (TNF)-α were measured.

Results: Compared with lean mice, diet-induced obese mice had higher serum levels of free fatty acid and malondialdehyde, markers of oxidative stress, and MCP-1, a marker of inflammation. However, lean mice under IH caused significant elevation of serum free fatty acid and malondialdehyde levels after 1 week or 4 weeks of exposure, and serum MCP-1 only after 4 weeks of exposure compared with air-exposed group. Diet-induced obese mice showed no IH impact on those serum markers. High-fat diet induced a pro-inflammatory phenotype of SAT and VAT through upregulation of MCP-1, IL-6, and TNF-α. The IH caused elevation of MCP-1, IL-6 and TNF-α in SAT and VAT in lean mice but not in diet-induced obese mice after either 1 week or 4 weeks of exposure.

Conclusion: The current experimental setting of IH increases systemic and adipose tissue inflammation in lean mice but does not pose an additional factor to inflammation in diet-induced obesity.

Acknowledgement
This study was supported by a generous donation from Shun Tak District Min Yuen Tong of Hong Kong.

73

Memantine and pioglitazone ameliorate motor impairments and spinal cord pathologies in mice received aquaporin-4 autoantibodies from patients with neuromyelitis optica spectrum disorders

LW Yick, KH Chan
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Neuromyelitis optica spectrum disorders (NMOSD) are a group of central nervous system inflammatory demyelinating diseases characterised by recurrent optic neuritis and myelitis. Binding of the pathogenic aquaporin-4 autoantibodies (AQP4-IgG) to astrocytic AQP4 initiates neuroinflammation. Our previous findings suggest a role of glutamate excitotoxicity and microglial/macrophage activation in NMOSD pathophysiologies. Here we examined whether memantine and pioglitazone ameliorate motor impairments and pathologies in mice received AQP4-IgG.

Methods: Mice with breached blood–brain barrier received passive transfer of IgG purified from AQP4-IgG-seropositive NMOSD patients ($IgG_{[AQP4+]}$) or healthy individuals for 8 days. The $IgG_{(AQP4+)}$ mice received daily oral gavage of vehicle, 60 mg/kg memantine or 80 mg/kg pioglitazone. Motor functions were assessed by beam walking test. Spinal cords were collected for immunofluorescence analysis.

Results: Vehicle-treated $IgG_{(AQP4+)}$ mice required longer time with more paw slips to walk across narrow beams than did sham-treated mice. Both memantine- and pioglitazone-treated $IgG_{(AQP4+)}$ mice needed shorter time with fewer paw slips to walk across the beams than vehicle-treated $IgG_{(AQP4+)}$ mice, indicative of motor function improvement. In addition, vehicle-treated $IgG_{(AQP4+)}$ mice displayed marked AQP4 and glial fibrillary acidic protein (GFAP) loss, robust microglial/macrophage activation, and prominent demyelination and axonal loss in the spinal cord compared with sham-treated mice. Both memantine- and pioglitazone-treated $IgG_{(AQP4+)}$ mice had profoundly attenuated AQP4 and GFAP loss, microglial/macrophage activation, demyelination and axonal loss in the spinal cord compared with vehicle-treated $IgG_{(AQP4+)}$ mice, suggesting an improvement of $IgG_{(AQP4+)}$-induced pathologies.

Conclusion: Memantine and pioglitazone are potential drugs for repurposing in NMOSD.

74

Gut-derived lipopolysaccharide contributes to pathogenesis of lupus nephritis

J Yu, CCY Chan, CP Tai, Y Lo, M Chau, Q Zhang, S Yung, TM Chan
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Pathogenesis of lupus nephritis is complex and involves both genetic and environmental factors. Gut microbiota and their components have been implicated in the aetiology of autoimmune diseases. Bacterial products from the gut may enter the circulation and induce inflammatory responses. Lipopolysaccharide (LPS) is a component of the outer wall of Gram-negative bacteria. This study investigated serum LPS level in patients and mice with lupus nephritis, and its role in kidney inflammation and fibrosis.

Methods: Serum LPS level was determined in patients and mice with lupus nephritis using commercially available LPS assay. Intestinal mucosal permeability in NZB/W F1 mice was investigated with LPS-FITC administration and ZO-1 expression. Qualitative and quantitative changes to the gut microbiota were assessed by 16S rRNA sequencing. The effect of LPS on cytokine secretion and matrix protein expression was investigated in cultured HK-2 cells.

Results: Serum LPS level was significantly higher in patients and mice with lupus nephritis compared with healthy controls and BALB/c mice, respectively. 16S rRNA analysis showed a progressive decrease in Gram-positive bacteria phyla *Actinobacteria* and *Firmicutes* and a concomitant increase in Gram-negative bacteria *Bacteroides* and *Proteobacteria* as lupus nephritis progressed in severity. NZB/W F1 mice with active nephritis, but not BALB/c mice, showed increased gut permeability and a marked reduction in mucosal ZO-1 expression, and also the presence of LPS-FITC in renal proximal tubules. Lipopolysaccharide induced interleukin-6 and monocyte chemoattractant protein-1 secretion and fibronectin, laminin and collagen I expression in HK-2 cells, mediated in part through increased MAPK and PI3K signalling.

Conclusions: Our results demonstrate that there is increased gut-derived Gram-negative bacteria and translocation of LPS from the gut to the circulation and kidney in lupus nephritis, and this may contribute to inflammation and fibrosis in the renal tubulointerstitium.

Acknowledgement
This study was supported by the RGC General Research Fund (Ref. 17106015).

75

Right ventricular apical pacing versus non–right ventricular apical pacing–induced tricuspid regurgitation: implication of three-dimensional echocardiographic location of leads

YJ Yu, Y Chen, MZ Wu, CP Lau, HF Tse, KH Yiu
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Objectives: We sought to compare the degree of tricuspid regurgitation (TR) in patients with right ventricular apical (RVA) pacing versus non-RVA pacing, and the lead location in TR in patients with RVA vs non-RVA pacing, using three-dimensional echocardiography (3DE).

Methods: Conventional echocardiography and 3DE of the tricuspid valve were performed in 434 patients with prior pacemaker implantation. A subgroup of 249 patients with detailed pre-pacemaker implantation echocardiography were included to evaluate the development of significant TR prospectively.

Results: Patients with RVA pacing had a higher frequency of moderate (19.4% vs 15.3%, P<0.05) and severe TR (38.4% vs 24.1%, P<0.05) compared with those with non-RVA pacing. For RVA pacing, the lead was more likely to be located at the anterior, posterior, and septal positions that interfere with the normal leaflet mobility, compared with non-RVA pacing (73.8% vs 26.2%, P<0.01). Conversely, leads were more likely to be located at the central portion of the tricuspid valve, with no impingement of leaflet mobility, in patients with non-RVA pacing compared with those with RVA pacing (62.1% vs 37.9%, P<0.01). Among those with pre-implantation echocardiography showing none/mild TR, new-onset moderate to severe TR was more commonly seen in patients with RVA pacing compared with those with non-RVA pacing (69.8% vs 30.2%, P<0.05).

Conclusions: The present study demonstrates that patients with RVA pacing is more likely to develop significant TR compared with those with non-RVA pacing. By using 3DE, we demonstrate that lead impingement is a possible mechanism that could explain the higher frequency of TR in RVA pacing compared with non-RVA pacing.

76

Arsenic trioxide targets clathrin heavy chain–anaplastic lymphoma kinase fusion protein for degradation to induce growth inhibition and apoptosis in ALK-positive diffuse large B-cell lymphoma cells

LM Yue, DHW Chau, E Tse, YL Kwong
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Anaplastic lymphoma kinase-positive diffuse large B-cell lymphoma (ALK+DLBCL) is an extremely rare and aggressive type of DLBCL that responds poorly to conventional therapy. Clathrin heavy chain 1 (CLTC) is the most common genetic partner fuse to ALK in ALK+DLBCL, leading to the formation of fusion protein CLTC-ALK. Arsenic trioxide (As_2O_3) is a United States Food and Drug Administration–approved drug that has been used as a treatment for acute promyelocytic leukaemia (APL) patients. Arsenic trioxide was found to induce apoptotic cell death through targeting oncoprotein for degradation among different types of haematological malignancy, such as protein promyelocytic leukaemia–retinoic acid receptor α in APL. The current study focuses on elucidating whether CLTC-ALK is a target for As_2O_3 in ALK+DLBCL and the subsequent effects in vitro.

Methods: Arsenic-induced cytotoxicity and dysregulated CLTC-ALK expression were determined in CLTC-ALK+DLBCL cell line LM1. The effect of As_2O_3 on LM1 cell proliferation and apoptosis were analysed by cell proliferation assay and Annexin V 7-AAD staining. The mechanistic degradation of CLTC-ALK mediated by As_2O_3 was further explored in LM1 cells.

Results: Arsenic trioxide was found to induce growth inhibition and apoptotic cell death, analogous to the effect of ALK inhibitor on the LM1 cells. Arsenic trioxide downregulated the CLTC-ALK protein expression and its downstream targets in LM1 cells, including STAT3 and Akt. Proteasome inhibitor treatment rescued the As_2O_3–induced CLTC-ALK degradation indicated that As_2O_3 induces CLTC-ALK degradation through ubiquitin-proteasome pathway. Arsenic trioxide was also found to downregulate the ALK moiety of CLTC-ALK fusion protein in 293T cells indicated that the ALK moiety is a target of As_2O_3.

Conclusions: Arsenic trioxide is a potent therapeutic agent for treating ALK+DLBCL.

Risk of malignancy in patients who used thiopurines in Hong Kong: a territory-wide study

77

KYC Zheng[1], IOL Wong[2], LJ Chen[1], WK Leung[1]
[1]Department of Medicine, The University of Hong Kong, Hong Kong
[2]School of Public Health, The University of Hong Kong, Hong Kong

Introduction: Thiopurines are commonly used as an immunomodulators in autoimmune or rheumatological diseases, inflammatory bowel diseases, and after transplantation. It is suggested that patients who are exposed to thiopurines have higher risk of lymphoma and non-melanoma skin cancer in Western countries. We determined the cancer risk among thiopurine users in Hong Kong.

Methods: Adult patients who had received azathioprine or 6-mercaptopurine between 2005 and 2009 were retrieved from the Clinical Data Analysis and Reporting System of the Hong Kong Hospital Authority. We excluded those with baseline cancer. Patients were followed up from the start date of thiopurines until the development of cancer, death, or end of study in December 2017. Standardised incidence ratios (SIRs) of all cancers and cancer of specific sites were calculated with reference to data from the Hong Kong Cancer Registry.

Results: A total of 7454 patients who had used thiopurines (median age, 47 years, 36.4% men) were identified with total follow-up duration of 77592 person-years. Among them, 695 (9.3%) developed malignancy after thiopurine use with a SIR of 2.37 (95% confidence interval [CI]=2.20-2.55). Compared with the general population, the risks of non-Hodgkin lymphoma (SIR=11.67, 95% CI=9.56-14.12), thymus cancer (SIR=21.75, 95% CI=13.98-35.63), and non-melanoma skin cancer (SIR=4.60, 95% CI=3.33-6.20) were significantly higher than expected in the general population in Hong Kong. Patients with rheumatological diseases and inflammatory bowel diseases had higher overall risk of cancers with SIR of 2.11 (95% CI=1.84-2.42) and SIR of 2.35 (95% CI=1.70-3.17), respectively.

Conclusion: Thiopurine users are at a higher risk of developing cancer when compared with general population in Hong Kong. Close monitoring and surveillance are recommended for these high-risk patients.

AUTHOR INDEX

The Organising Committee of the Medical Research Conference would like to extend their gratitude to the following sponsors (in alphabetical order) for their support and generous contribution.

A. Menarini Hong Kong Limited

Amgen Hong Kong Limited

Bayer HealthCare Limited

Boehringer Ingelheim (Hong Kong) Limited

Daiichi Sankyo Hong Kong Limited

Novartis Pharmaceuticals (HK) Ltd

Pfizer Corporation Hong Kong Ltd

Eliquis 凝血通™
apixaban

No.1

OAC prescribed by US - Cardiologists[1]

THE SAFER CHOICE[2*]

with Dual Risk[‡] Reduction[2]

Superior Efficacy and Safety[2†]

Stroke/SE

21%

RRR

p=0.01

Major Bleeding

31%

RRR

p<0.001

† Compared to Warfarin

* ELIQUIS significantly lower the risk of major bleeding in NVAF compared to Warfarin

‡ Dual Risk is defined by the risk of stroke/SE and major bleeding

NVAF = Non-valvular atrial fibrillation; SE = Systemic embolism

References: 1. Based on Moving Annual Total (MAT) October 2016 - June 2018 in the US SHA Total Prescription Database (TRx). Oral anticoagulant prescriptions were written by cardiologists and filled by patients. Claim based on US cardiologist prescription data which is formally collected and analyzed by IQVIA, an independent data vendor – data on file at Pfizer and IQVIA. Claims valid as of 20th July 2018. 2. Granger et al. N Engl J Med 2011; 365: 981-992.

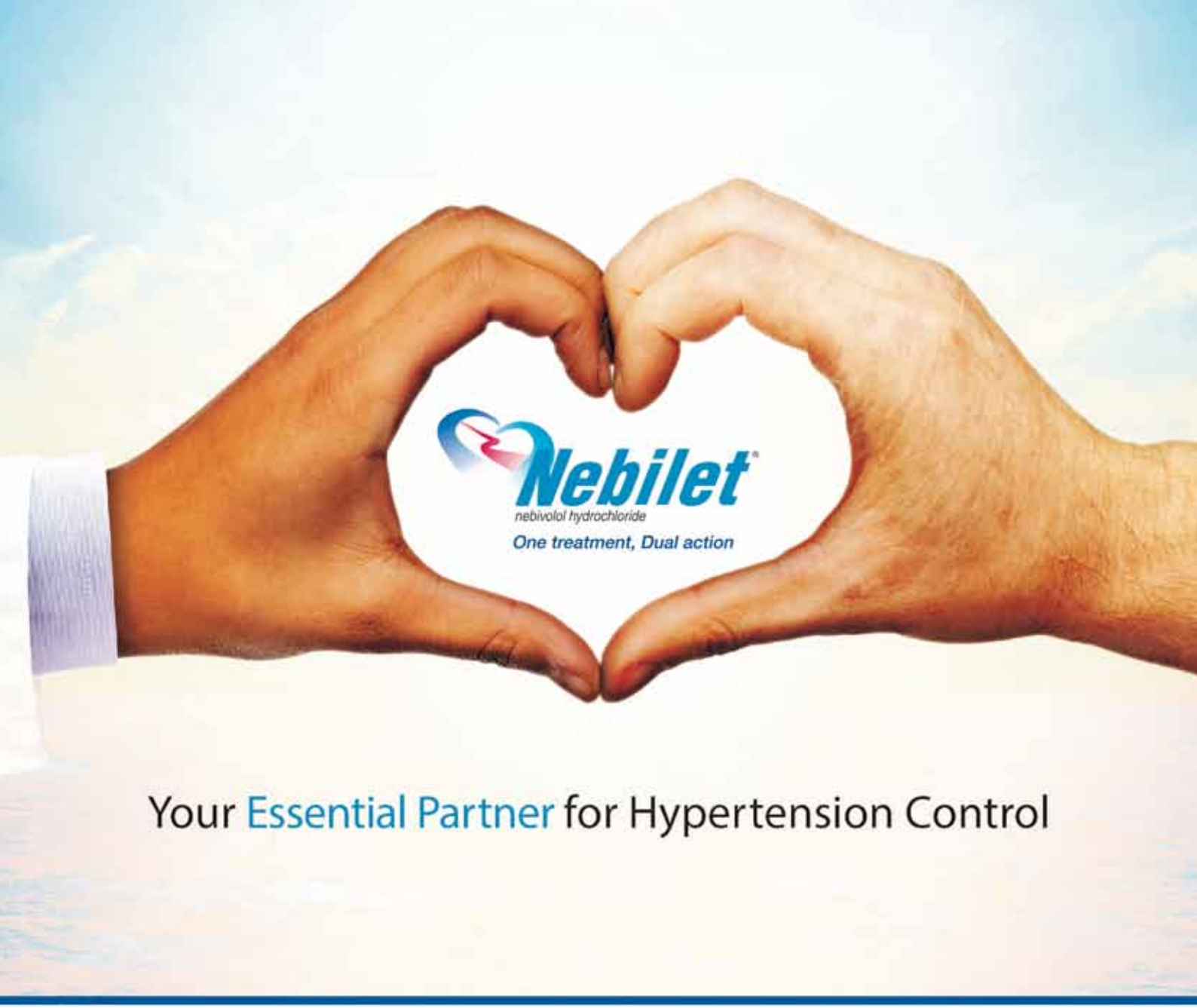
ELIQUIS ABBREVIATED PACKAGE INSERT **1. TRADE NAME:** ELIQUIS **2. PRESENTATION:** Eliquis 5 mg film-coated tablets **3. INDICATIONS:** Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II). Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. **4. DOSAGE:** Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF): 5 mg twice daily. 2.5 mg twice daily in patients with NVAF and at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 micromole/L). Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt): 10 mg twice daily for the first 7 days followed by 5 mg twice daily. When prevention of recurrent DVT and PE is indicated, the 2.5 mg twice daily dose should be initiated following completion of 6 months of treatment with Eliquis 5 mg twice daily or with another anticoagulant. **5. Method of Administration:** Eliquis should be swallowed with water, with or without food. For patients who are unable to swallow whole tablets, Eliquis tablets may be crushed and suspended in water or 5% dextrose in water (D5W) and immediately administered orally. Alternatively, Eliquis tablets may be crushed and suspended in 60mL of water or D5W and immediately delivered through a nasogastric tube. Crushed Eliquis tablets are stable in water and D5W for up to 4 hours. **6. CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. Active clinically significant bleeding. Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Lesion or condition if considered a significant risk factor for major bleeding. Concomitant treatment with any other anticoagulant agent. **7. WARNINGS & PRECAUTIONS:** Haemorrhage risk: carefully observed for signs of bleeding. Eliquis should be discontinued if severe haemorrhage occurs. Patients with prosthetic heart valves: Eliquis is not recommended. Surgery and invasive procedures: Eliquis should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding. Renal impairment: In patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore apixaban is not recommended. Hepatic impairment: Not recommended in patients with severe hepatic impairment. Laboratory parameters: Clotting tests (e.g., PT, INR, and aPTT) are affected as expected by the mechanism of action of apixaban. **8. INTERACTIONS:** Eliquis is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp. Concomitant use of Eliquis with strong CYP3A4 and P-gp inducers may lead to a ~50% reduction in apixaban exposure. **9. PREGNANCY AND LACTATION:** There are no data from the use of apixaban in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Apixaban is not recommended during pregnancy. It is unknown whether apixaban or its metabolites are excreted in human milk. A decision must be made to either discontinue breast-feeding or to discontinue/abstain from apixaban therapy. **10. SIDE EFFECTS:** Common: haemorrhage, contusion, epistaxis, and haematoma.

Reference: Eliquis 5mg HK Prescribing Information (Oct 2015)
Date of preparation: Dec 2017
Identifier number: ELIQ1217

FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.

Pfizer Corporation Hong Kong Limited
18/F., Kerry Centre, 683 King's Road, Quarry Bay, Hong Kong
Tel: (852) 2811 9711 Fax: (852) 2590 6364
Website: www.pfizer.com.hk

PP-ELI-HKG-0128



Your Essential Partner for Hypertension Control

- Hypertension remains a difficult disease to control.[1]
- Nebilet's unique nitric-oxide-mediated vasodilating properties *and* high cardioselectivity enables you to take back control by effectively lowering blood pressure.[2-7]
- Nebilet can also be easily added to an existing antihypertensive treatment regimen, or used as monotherapy in a broad range of hypertensive and chronic heart failure patients.[8-14]

REFERENCES: 1. Rahman AR *et al. Asia Pac Fam Med* 2015;14:2. **2.** Bleuse K *et al. Br J Pharmacol* 2001;133:1330-1338. **3.** Ignarro LJ *et al. Nitric Oxide* 2002;7:75-82. **4.** Menarini. *Nebilet® (nebivolol) prescribing information* 2013. **5.** Munjed T *et al. J Am Coll Cardiol* 2009;54:1491-1499. **6.** Versari D *et al. Diabetes Care* 2009;32 Suppl 2:S314-S321. **7.** Wojciechowski D *et al. Expert Rev Cardiovasc Ther* 2008;6:471-479. **8.** Dasgupta K *et al. Can J Cardiol* 2014;30:485-501. **9.** Edes I *et al. Eur J Heart Fail* 2005;7:631-639. **10.** Flather MD *et al. Eur Heart J* 2005;26:215-225. **11.** Jones PA *et al. JAMA* 2014;311:507-520. **12.** Mancia G *et al. J Hypertens* 2013;31:1281-1357. **13.** National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management. 2016. Available at: https://www.nice.org.uk/guidance/cg127/resources/hypertension-in-adults-diagnosis-and-management-35109454941637. (November 2016). **14.** Weber MA *et al. J Clin Hypertens (Greenwich)* 2014;16:14-26.

ABBREVIATED PRESCRIBING INFORMATION:

Nebilet® 5mg Tablets

Indications: Hypertension. Treatment of essential hypertension. **Chronic heart failure (CHF).** Treatment of stable mild and moderate chronic heart failure in patients aged 70 or over, in addition to other therapies. **Dosage and Administration: Hypertension.** The usual dose is 1 tablet per day. The dose should be taken preferably at the same time of the day. Elderly patients and patients with a kidney disorder will usually start with ½ (half) tablet daily. **Chronic heart failure (CHF).** The initial treatment starts with ¼ (quarter) tablet per day. This may be increased after 1-2 weeks to ½ (half) tablet per day, then to 1 tablet per day and then to 2 tablets per day until the correct dose is reached. The maximum recommended dose is 2 tablets (10mg) a day. **Side effects:** Most common side effects (1-10%): headache, dizziness, tiredness, an unusual tiring or tingling feeling, diarrhoea, constipation, nausea, shortness of breath, swollen hands or feet. **Precautions:** In common with other beta-blockers: anaesthesia, ischaemic heart disease, circulatory disorders, first degree heart block, diabetes, hyperthyroidism, chronic obstructive pulmonary disorders, psoriasis, allergen sensitivity. **Contraindications:** Hypersensitivity, liver impairment, pregnancy and lactation. In common with other beta-blockers: cardiogenic shock, uncontrolled heart failure, sick sinus syndrome, second and third degree heart block, history of bronchospasm, untreated phaeochromocytoma, metabolic acidosis, bradycardia, hypotension, severe peripheral circulatory disturbances.

Please refer to full prescribing information for further information.

Nebilet
nebivolol hydrochloride
One treatment, Dual action

MENARINI
A. Menarini Hong Kong Limited
Tel: (852) 3605 5811 Fax: (852) 2597 5231 www.menariniapac.com

HKNEB/122018/292