SUPPLEMENT 1

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Mitochondrial dynamics in pathogenesis: a tale of two membranes

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Mitochondria are central players in cellular energetics, metabolism, and viability. Structurally, mitochondria are double membrane-bound organelles consisting of the outer membrane, inner membrane, intermembrane space, and the matrix. In the last two decades, researches have unveiled the dynamic nature of mitochondria: mitochondria constantly undergo fission and fusion under physiological conditions. Mitochondrial fission is mediated by Drp1, Fis1, and other proteins, whereas fusion is mediated by mitofusins, OPA1, and others. Our work has demonstrated that during cell stress, mitochondrial dynamics is shifted to fission leading to mitochondrial fragmentation. Inhibition of mitochondrial fragmentation protects cells and tissues in disease conditions, suggesting a critical role of mitochondrial fragmentation in disease pathogenesis. Mechanistically, we have identified the interaction of Bak (a proapoptotic Bcl2 family protein) with mitofusins. Notably, blockade of the Bak/mitofusin interaction prevents mitochondrial fragmentation and cell death, suggesting a role of Bak in mitochondrial fragmentation by interacting with mitofusins resulting in fusion arrest. In addition, Drp1 is dephosphorylated during cell stress and accumulates in mitochondria to promote mitochondrial fission. Most work has been focused on the outer membrane; less is known about the dynamic regulation of the inner membrane. Mitochondrial fragmentation should include the cleavage of both outer and inner membranes. Our latest work suggests that cleavage of the inner membrane is triggered by Bif-1 (Bax interacting factor -1), which translocates to mitochondria to interact with prohibitin-2, leading to the disruption of the 'prohibitin ring' to release the metalloprotease OMA1. OMA1 proteolyzes OPA1 to block inner membrane fusion, contributing to inner membrane cleavage. Investigation of mitochondrial dynamics under pathophysiological conditions may not only gain fundamental insights into mitochondrial biology but may also identify novel therapeutic strategies for related diseases.

Influenza: a remaining challenge

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Influenza virus belongs to the family of orthomyxoviridae. Three types of influenza viruses (A, B, C) affect humans. They are transmitted via droplets through the air from coughs or sneezes, mostly over relatively short distances. The virus can also be spread by touching contaminated surfaces. Its transmission factor R0 is rather low, varying from 1.5 to 3 (compare with 12 to 18 for measles). An infected person excretes the virus 1 to 2 days prior to having symptoms and remains contagious for over a week. Children spread the virus more and longer than adults.

The unique feature of the influenza virus is that it continually changes its genetic makeup, and accordingly, its structure, as it circulates the globe. Thus, the immunity to previous influenza viruses does not necessarily secure protection against the evolved new viruses. This is a constant challenge to influenza vaccine development.

The burden of influenza is difficult to measure as the clinical symptom varies from mild to extremely severe, and only a fraction of those infected get laboratory confirmation of the disease. It has been estimated that annually every one in ten adults contract influenza, and every one in three children. This results in a mean of 3 to 5 million cases of severe influenza cases and half a million deaths. The severity of influenza varies according to the type circulating. In the Southern and Northern hemispheres, outbreaks occur during wintertime. In the tropics, the infection is less seasonal; cases tend to occur throughout the year.

Antiviral drugs such as neuraminidase inhibitor oseltamivir and zanamivir are used to prevent and treat influenza A and B. Amantadine is used to prevent influenza A. Benefits of these antiviral drugs have been debated. Other forms of spread prevention are frequent hand washing and wearing a surgical mask. Vaccines remain the best form of prevention against influenza despite the unpredictability of their effectiveness.

Influenza vaccines have been developed in the 1960s, and used in large scale since early 1970s. They can be distinguished by their structure: live attenuated, killed whole cell, split whole cell, subunit, or adjuvanted. The global market of influenza vaccines is huge, presently estimated to be US$5 billion due to the width of the recommendations. In the US, practically all citizens are recommended to take the vaccine. Elsewhere, the recommendations are more targeted to risk groups such as those with severe underlying illness, small children, pregnant women, and health care workers (due to the indirect protection to their patients who are vulnerable and may not mount an adequate response to the vaccine).

Measuring the impact of influenza vaccine depends on the method used and the ability to control for the confounders such as access to vaccine and health care in general, health care–seeking behaviour, the physicians' choice of whom to test, and the test used for confirmation. The gold standard of measuring the effectiveness of influenza vaccine is considered to be the test-negative design. Countries that have large datasets have used population register–based cohort study approaches to enable near real-time vaccine effectiveness measurement. Depending on the age and risk groups as well as the match between the circulating virus to the vaccine virus, the influenza vaccine effectiveness has ranged from near zero to as high as 80%.

It is hoped that a more universal type of influenza vaccine will be available in future. So far attempts have not been very successful in identifying a virus structure that does not evolve over time and provide long-term protection to humans. Meanwhile, the public health community needs to rely on the presently available vaccines to combine direct and indirect protection to optimise the individual and public health benefits.

Gut microbiota evaluation and cirrhosis

Plenary 3

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Chronic liver disease with progression to decompensated cirrhosis and associated complications including hepatic encephalopathy, spontaneous bacterial peritonitis, and sepsis are a leading cause of mortality and morbidity. The pathophysiology of decompensated cirrhosis leads to gut microbiome changes and causes dysbiosis that is likely to be related to altered bile acid composition with a subsequent increase in relative abundance of potentially pathogenic bacteria that contributes to hepatic encephalopathy and leads to the translocation and development of spontaneous bacterial peritonitis and bacteraemia. Studies in germ-free animals have confirmed that specific microbiota are associated with ammonia and systemic inflammation that can result in neuro-inflammation, microglial and glial activation. In humans, the changes in neuronal integrity and astrocytes are likely to be associated with different groups of gut bacteria. Treatments for these conditions are based on the gut microbiome. Recent studies have evaluated the changes in gut microbiome using faecal microbial transplant in patients with cirrhosis. The study of microbiota is essential in further progression in the treatment of cirrhosis.

Irregularly irregular pulse: to impact clinical practice with research

Plenary 4

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Atrial fibrillation (AF) was first described in the oldest Chinese medical literature, Huangdi Neijing <黃帝內經> in 2600 BC. It is the most common type of cardiac arrhythmia in clinical practice. Although AF is known to confer a five-time higher risk of stroke, which can be effectively reduced with anticoagulation therapy, the utilisation of anticoagulation therapy has been low amongst Chinese. In contrast to the robust body of evidence for Caucasian population with AF, the scarcity of data in Chinese AF patients makes the management challenging. The challenge includes delicate balancing the benefit of stroke risk reduction with the risk of intracranial haemorrhage as there are perceptions that Chinese might have a lower risk of stroke attributable to AF, and a higher baseline rate of intracranial haemorrhage. Over the last 7 years, we have established a large cohort of Chinese AF patients and provided solid epidemiological data to facilitate everyday management of AF in Chinese. Inspired by the data and realising the huge unmet needs, we initiated a population-based AF screening programme at the primary care setting to screen 60 000 high-risk patients in a hope to reduce AF-related stroke in Hong Kong. We shall discuss the current understanding of stroke prevention in AF in Chinese and share our experience in research and clinical practice to healthcare policy related to AF.

1 Diabetic retinopathy status as a marker for more-severe reduction in circulating endothelial progenitor cells and systemic atherosclerosis in diabetics

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Objectives: Diabetes is associated with a reduction and dysfunction of circulating endothelial progenitor cells (EPC), which hastens the onset and progression of systemic atherosclerosis. We hypothesise that diabetic retinopathy status may serve as a marker for more-severe depletion of circulating EPCs and thus systemic atherosclerosis.

Methods: We examined 160 patients with type II diabetes (126 without retinopathy and 34 with retinopathy) for coronary calcification using multi-detector computed tomography, carotid intimal medial thickness, and arterial segment pulse-wave velocity (PWV), as well as their relationships with different subtypes of circulating EPC. Four subpopulations of EPC were determined by flow cytometry on the basis of surface expression of CD34, CD133, and KDR antigen: CD34+, CD34/KDR+, CD133+, and CD133/KDR+ EPC, respectively.

Results: The mean patient age was 67.6 years; the mean body mass index was 25.5 kg/m2; 45% of patients were male. Patients with diabetic retinopathy had a longer duration of diabetes than those without (15 vs 8 years). All had severely depleted levels of all circulating EPCs. Patients with diabetic retinopathy had significantly lower CD34/KDR+ count (1.42% vs 1.70%) and CD34+ EPC count (5.49% vs 6.55%) than those without, but the two groups did not differ significantly in CD133+ and CD133/KDR+ counts. Patients with diabetic retinopathy had a significantly higher Agatston score for coronary calcification (248.38 vs 143.57, P=0.02), carotid intimal medial thickness (0.91 vs 0.88 mm), heart-femoral PWV (976.68 vs 873.29), heart-ankle PWV (1084 vs 1080), and brachial-ankle PWV (1815 vs 1782) than those without.

Conclusion: The presence of diabetic retinopathy was associated with lower levels of circulating CD34+ and CD34/KDR+ EPCs, more severe carotid and coronary atherosclerosis, and increased central and peripheral arterial stiffness. Diabetic retinopathy status is a useful marker for severe depletion of circulating EPCs and systemic atherosclerosis.

2 Relative maximum apparent diffusion coefficient: a potential biomarker of disease activity in axial spondyloarthritis

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Introduction: Previous studies have suggested a role of diffusion-weighted imaging in axial spondyloarthritis assessment. This study evaluated the correlation between relative maximum apparent diffusion coefficient ($rADC_{max}$) of disco-vertebral lesions and clinical parameters in axial spondyloarthritis.

Method: We recruited 275 patients diagnosed with axial spondyloarthritis from three rheumatology centres. Clinical, biochemical, and radiological parameters were collected. All patients underwent magnetic resonance imaging of the whole spine and sacroiliac joints using the short-tau inversion recovery sequence and diffusion-weighted imaging. The mean apparent diffusion coefficient and $rADC_{max}$ of the disco-vertebral lesions were calculated and then compared with clinical parameters.

Results: Of the patients, 26 (9.5%) had disco-vertebral lesions at the thoracic (n=23) and lumbar (n=17) spine. Inter-observer agreement was excellent (kappa=0.895). $rADC_{max}$ correlated positively with intensity of back pain (r=0.46, P=0.02), morning stiffness (r=0.47, P=0.02), duration of stiffness (r=0.44, P=0.03), and stiffness score (r=0.49, P=0.01). There were no significant differences in the Bath Ankylosing Spondylitis Disease Activity Index score, C-reactive protein, and erythrocyte sedimentation rate in patients with or without disco-vertebral lesions.

Conclusion: In axial spondyloarthritis, $rADC_{max}$ of disco-vertebral lesions correlates significantly with intensity of back pain and morning stiffness. This parameter could be a potential imaging biomarker.

Evaluation of a new dermal cryotherapy system for the treatment of benign pigmented lesions in Asian patients

3

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Introduction: Photoageing in Chinese often presents with benign pigmentary lesions. Various light-based devices have been used for the management of benign pigmentary lesions, such as long-pulsed Nd:YAG laser, Q-switched laser, and picosecond laser. These light-based devices have a risk of post-inflammatory hyperpigmentation. This study aims to assess the efficacy of a dermal cooling system to reduce pigmentation in benign pigmentary lesions in Asian patients.

Method: Up to 100 Asian male and female subjects aged >18 years with good past health were recruited. They had at least one benign pigmentary lesion on their face. Standardised photography was taken at baseline, 1-month post-treatment, and 2, 6, 12 months after final treatment. Up to three treatments at a 1-month interval was given. The treatment area and parameter were determined by the physician after assessment. The end-point was patient real-time feedback in terms of a change in sensation. Any adverse event was recorded. Standardised photographs were assessed by two independent physicians. Subjective assessments were recorded at follow-up visits.

Results: The study was ongoing with 25 subjects: 36% had lentigines only, 36% had freckles only, and 28% had both. A total of 208 sites have been treated. Of 15 subjects who have reached 1-month follow-up, 57% had objective improvement in global assessment of the aesthetic improvement scale score, and 93% reported subjective improvement. No adverse event was recorded.

Conclusion: The new cryotherapy device is promising for the treatment of benign pigmentary lesions in Asians.

Acknowledgement
This study was supported by R2 Dermatology.

The use of a novel, localised, controlled skin cooling system for reduction of epidermal pigmentation

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Background: Lasers have been used for the treatment of epidermal pigmentation but can result in postinflammatory hyperpigmentation. Melanocytes are very susceptible to cryoinjury; such injury is typically reported after application for cryosurgery and results in long-lasting depigmentation and side-effects. The dosimetry and role of controlled skin cooling on epidermal pigmentation deserves further investigation. This study aims to evaluate the safety and effectiveness of this novel system for localised controlled cooling of the epidermal layer to reduce pigmentation in the absence of adverse events.

Methods: Two female Sinclair Yucatan pigs were treated at the left and right flank. The controlled cooling system with a flat cooling surface was used on 57 treatment sites and 8 positive control sites, whereas a cooling surface system with a microstructured cooling surface was used at 72 treatment sites and 8 positive control sites, leaving 6 to 7 untreated negative control sites per animal. The temperature and the exposure time of the cooling surface were varied. Digital photography was used to document the treatment sites for photographic review scoring. Biopsy samples for histopathology were taken from untreated sites before the treatment procedure and from treatment sites immediately following treatment, and then from untreated and treatment sites monthly thereafter. Clinical observations were performed at least once daily for 14 days, and then weekly thereafter.

Results: Microscopic evaluation revealed that localised epidermal cooling applied by device treatment was associated with favourable tissue responses, with decreases in melanocyte/pigmentation parameters. Compared with the continuous surface hand piece, treatment with the indented surface hand piece was associated with more consistent outcome. Specific exposure conditions were determined (cooling range of -3 to -9°C with exposure time of 15-60 seconds) that would consistently and safely elicited a response and that showed at least a mild reduction in pigmentation (score of ≤3) based on the photographic review. There was absence of any notable side-effects.

Conclusion: The novel controlled cooling system reduces epidermal pigmentation without any marked epidermal damage or side-effects in a pig model.

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Semi-individualised Chinese medicine treatment as an adjuvant management for diabetic nephropathy: interim analysis of an add-on, randomised, controlled, multicentre, open-label pragmatic trial

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Introduction: Big data studies from Taiwan showed that Chinese medicine (CM) might reduce the risk of end-stage kidney disease by 59% in a 6-year period. Nonetheless, clinical data to support the use of CM in diabetic kidney disease (DKD) management are limited, and the effect of combined Chinese and conventional medicine remains unclear.

Method: This assessor-blind, add-on, randomised, controlled, multicentre pilot pragmatic trial evaluated the effect of an adjuvant semi-individualised CM treatment protocol based on expert consensus. 148 patients diagnosed with DKD were to be recruited and equally randomised to either the 48-week additional semi-individualised CM treatment programme or standard medical care. Primary end-points were the changes in estimated glomerular filtration rate (eGFR) and spot urine albumin-to-creatinine ratio (UACR) between baseline and treatment endpoint. Outcomes were analysed as intention-to-treat by regression models. The trial registration number was NCT02488252.

Results: The first 40 patients have completed 24 weeks of treatment since July 2015. The two groups were similar in demographics. After adjusting for age, gender, baseline haemoglobin A1c, body mass index, blood pressures, eGFR, and UACR, the intervention group had higher mean (95% confidence interval [CI]) eGFR (53.4 [48.0-58.8] vs 50.1 [45.1-55.0] mL/min/1.73m^2) and adjusted mean (95% CI) UACR (186 [100-273] vs 173 [93-252] mg/mmol) than the control group. The regression model explained 86% variability and remained robust when the 24-week UACR was adjusted in the sensitivity analysis. Intervention contributed to an increase of 3.3 mL/min/1.73m^2 (P=0.18) in eGFR independent of UACR. The two groups were comparable in terms of fully adjusted 24-week mean UACR, glycated haemoglobin, blood pressures, aspartate transaminase and alanine transaminase levels, and severe adverse event rates.

Conclusion: Our interim analysis suggests add-on semi-individualised CM treatment may stabilise eGFR among DKD patients independent of albuminuria, glycaemic, and blood pressure control.

Acknowledgement
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Arsenic trioxide: an effective therapeutic for acute myeloid leukaemia with mutated nucleophosmin

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Introduction: Arsenic trioxide (As_2O_3) is a highly effective salvage therapy in acute promyelocytic leukaemia. The unique sensitivity of acute promyelocytic leukaemia cells to As_2O_3 is the consequence of the As_2O_3-mediated degradation of promyelocytic leukaemia–retinoic acid receptor-α. In leukaemia cells with mutated nucleophosmin (NPM1), the NPM1 cytoplasmic mutant (NPMc+) in contributing to leukaemogenesis has been described. Conspicuously, As_2O_3 is found to selectively and specifically degrade this mutated protein NPMc+ but not the wild-type NPM1. We aim to delineate the subsequent effects of As_2O_3 in vitro and to determine the efficacy of such As_2O_3-induced targeted NPMc+ degradation in vivo.

Methods: Arsenic-induced cytotoxicity and dysregulated NPMc+ expression were determined in an acute myeloid leukaemia (AML) cell line (OCI-AML3) model. The effects and mechanisms induced from As_2O_3-mediated NPMc+ degradation were explored in vitro and in vivo.

Results: Arsenic-induced NPMc+ degradation led to induction of myeloid cell differentiation as well as upregulation of biomarkers including p53, p21, and C/EBPα. In addition, proteasome inhibitor rescued the shortened half-life of NPMc+ due to As_2O_3 treatment. Knockdown of E3 ubiquitin ligase IBRDC2 prevented NPMc+ from degradation further suggested that As_2O_3 degraded NPMc+ through the ubiquitin-proteasome pathway by activating IBRDC2. Most importantly, As_2O_3 treatment effectively abolished/suppressed OCI-AML3-induced AML in vivo.

Conclusions: The specific NPMc+ degradation mediated by As_2O_3 further extends the potency of As_2O_3 towards AML with mutated NPM1. Together with the survival improvement on the AML-engrafted mice after As_2O_3 treatment, these results underscore the potential of As_2O_3 as a promising therapeutic for AML harbouring NPMc+.

Fatigability in old zebrafish (*Danio rerio*): from exercise tolerance to exhaustion recovery

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Introduction: Excessive fatigue is a symptom of frailty and can predict functional impairment, disability, and mortality in ageing population. Zebrafish (*Danio rerio*) is a prominent genetic behavioural model of ageing. We investigated the locomotor response to exhaustive exercise in naturally ageing zebrafish to identify the phenotypes of age-related fatigability.

Method: Wild-type zebrafish were divided into two age-groups: young (6 months; n=6) and old (24 months; n=6). Maximum sprint swimming speed (U_{max}) of zebrafish was determined in a sprint swimming test (exhaustive exercise) using the Loligo miniature swim tunnel. Locomotor activity of zebrafish was recorded by a camera for 5x60s pre- and post-exercise and quantified by Fiji software with tracking plugins. Relative travelled distance and swim speed to their body length were determined.

Results: The U_{max} of the old group was significantly lower than that of the young group ($P<0.001$). A linear increase of speed was observed in both young ($y=0.58x+1.51$, $r=0.54$, $P=0.02$) and old ($y=0.36x+1.66$, $r=0.64$, $P=0.04$) groups during 0-180s and then reach a plateau in spontaneous locomotor activity before exercise. A significantly higher swim speed was also found in the young than old group during 120-180s ($P=0.03$), but no significant difference was found in the total travelled distance. After exhaustive exercise, swim speed was significantly lower in the old group during 0-60s, 60-120s, 120-180s, 180-240s but not in the young group ($P<0.05$). A linear increase of speed was also found in the old ($y=0.28x+0.93$, $r=0.70$, $P=0.00$) but not the young group during 0-180s post-exercise. It took approximately 2 mins in the young group and 7 mins in the old group to recover the locomotor activity from exhaustion to the pre-exercise level.

Conclusion: Impaired acceleration, swim speed, and recovery time of locomotor activity before and/or after exhaustive exercise are the potential phenotypes of ageing-related fatigability. This zebrafish model of ageing may contribute to the development of anti-frailty intervention.

Peptidyl-prolyl isomerase PIN1 impairs the inhibitory activity of p27 on cyclin-dependent kinase 2

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Introduction: PIN1 interacts with and modulates functions of many phosphorylated proteins that promote cell cycle progression and oncogenesis. Moreover, PIN1 stabilises and increases the level of the cyclin-dependent kinase (CDK) inhibitor p27, which inhibits cell cycle progression by binding cyclin A- and cyclin E-CDK2. Notwithstanding the associated increase in p27 level, PIN1 expression promotes, rather than retards, cell proliferation. To explain the paradoxical effects of PIN1 on p27 levels and cell cycle progression, we hypothesised that PIN1 relieves CDK2 inhibition by suppressing the CDK inhibitory activity of p27.

Method: Cell proliferation, BrdU-positive cells and CDK2 kinase activity were determined by MTT cell proliferation assay, flow cytometry, and in-vitro fluorescence-based kinase assay, respectively. Co-immunoprecipitation assays were performed to determine the binding between p27 and cyclin A- or cyclin E-CDK2.

Results: PIN1-expressing cells exhibited higher p27 levels but had increased CDK2 activities and higher proliferation rates in the S phase, compared with Pin1-null fibroblasts or PIN1-depleted hepatoma cells. Using co-immunoprecipitation and CDK kinase activity assays, PIN1 bound to the phosphorylated Thr187-Pro motif in p27 and reduced p27's interaction with cyclin A- or cyclin E-CDK2, leading to increased CDK2 kinase activity. Suppression of PIN1 expression resulted in a more pronounced decrease in cell proliferation and proportion of BrdU-positive cells in the wild-type than the p27-depleted mouse embryonic fibroblasts.

Conclusion: Although PIN1 increased p27 levels, it also attenuated p27's inhibitory activity on CDK2 and thereby contributed to increased G1-S phase transitions and cell proliferation.

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

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Introduction: Acute myeloid leukaemia (AML) is a highly genetically heterogeneous disease. Each patient carries unique genetic mutational profile that may predict the clinical outcome. There are common patterns of co-occurring genetic mutations, indicating the potential cooperativity in driving leukaemia. This project presents a novel zebrafish platform that allows quick and easy evaluation of the impact of different genetic mutational combinations on leukaemogenesis and predict their drug response, paving the way for personalised medicine.

Methods: Zebrafish embryos at 1-cell stage were co-injected with a combination of mutations (FLT3 ITD with IDH1 R132H, IDH2 R140Q, or IDH2 R172K) in mRNA forms. The effect on haematopoiesis were determined by the expression pattern and intensity of myeloid lineage markers pu.1 (myeloid progenitor), mpo (macrophage), c-myb (haematopoietic stem cell) using whole mount in situ hybridisation, and Sudan Black B staining (neutrophils). As a drug-screening platform, zebrafish embryos co-injected with FLT3 ITD and IDH2 R140Q were treated with a panel of Food and Drug Administration–approved drugs such as quizartinib and enasidenib, and SSB staining was performed to assess the effect on mutations induced myeloid expansion. To demonstrate the efficacy of mRNA co-injection technique, EGFP and mCherry mRNA were co-injected and analysed.

Results: Compared with FLT3-ITD alone, overexpression of FLT3-ITD and IDH2 R140Q mutants in zebrafish embryos further promoted expansion of myeloid progenitors and granulocytes, whereas co-expression of FLT3-ITD and IDH2 R172K further promoted expansion of haematopoietic stem cell. FLT3 inhibitor quizartinib rescued FLT3-ITD induced myeloid expansion while having minimal effect on embryos with FLT3-TID and IDH2 R140Q mutant.

Conclusions: Zebrafish can be a unique platform for quick and easy study of the potential synergism between different mutations on myeloid expansion. We are establishing a high-throughput drug-screening platform with zebrafish for profiling drug responses of different mutational combinations.

Absence of inguinal lymph nodes impairs the browning of white adipose tissue

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Introduction: The browning of adipose tissue has been proposed as a therapeutic regimen to combat obesity. Anatomically, lymph nodes are located in the lymphatic system throughout the body to induce immune response. Most are surrounded by adipose tissue and overlapping with the regions of beige adipocytes formation. We aim to investigate the role of inguinal lymph nodes and how they regulate the browning of adipose tissue.

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

Results: The absence of iLNs in inguinal fat tissues in mice affected the browning process. Inguinal adipose tissue without iLNs showed lesser multilocular lipid droplets, lower expression of uncoupled protein 1 and other thermogenic-related genes. The loss of iLNs attenuated the recruitment of group 2 innate lymphoid cells, eosinophils, and alternatively activated macrophages. Similarly, the expression of type-2 cytokines such as interleukin 4 and interleukin 13 were also downregulated. In addition, the expression of tyrosine hydroxylase, the rate-limiting enzyme of catecholamine synthesis, was significantly upregulated in iLNs in the response to cold challenge.

Conclusion: iLNs may play a major role in promoting cold-induced white adipose tissue browning by interacting between neurological and immunological systems. Further studies are required to determine detail mechanism of iLN-dependent adaptive thermogenesis.

Blood lead level in Hong Kong in 2011 to 2016

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Introduction: Lead has no biological function and any amount in the body is harmful. Information on blood lead levels in the Hong Kong population is lacking. In a study of over 3000 Hong Kong children, the geometric mean blood lead level was 2.4 μg/dL.[1] We aim to estimate the blood lead level in Hong Kong using Hong Kong Hospital Authority records.

Method: We retrieved all blood lead levels in 2011 to 2016 in the Hong Kong Hospital Authority Clinical Data Analysis and Reporting System. Data were analysed by year, sex, and age group.

Results: In 2011 to 2016, 9510 persons (50% male; age range from newborn to 95 years) had their blood lead level measured. Blood lead levels in these persons showed a log-normal distribution and no sex difference (r=0.03). Age accounted for only <2% of the variance. The geometric mean (95% confidence interval) blood lead levels in years 2011 to 2016 were 2.73 (2.68-2.79), 2.48 (2.43-2.53), 2.21 (2.16-2.27), 2.05 (2.01-2.08), 2.64 (2.63-2.65), and 2.34 (2.27-2.40) μg/dL, respectively. Year 2015 was anomalous because a large number of tests were performed during the incident of lead in drinking water.

Conclusion: The geometric mean blood lead level in USA in 2013-4 was 0.84 μg/dL.[2] Blood lead level in Hong Kong is consistently more than double than that in USA. Lead in the solder in water pipes was the cause of elevated lead level in drinking water in housing estates. More attention should be paid to the quality of drinking water in Hong Kong.

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Phytosterol-fortified soya drink to lower blood cholesterol: a randomised controlled trial

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Introduction: Milk fortified with phytosterols reduces cholesterol absorption and serum low-density lipoprotein (LDL) cholesterol. Nonetheless, many Chinese adults have lactose intolerance. We conducted a randomised double-blind controlled trial to assess the efficacy and tolerability of a phytosterol-fortified soya drink in lowering serum LDL cholesterol.

Method: A total of 201 normocholesterolaemic healthy participants (100 men and 101 women) aged 19 to 79 years were randomised to receive either one pack per day of phytosterol-fortified soya drink that contained 2 g phytosterols (n=100) or a matched soya drink without phytosterols (n=101) for 3 weeks. The primary outcome variable was the serum LDL cholesterol. Adverse events, withdrawal, and compliance were documented. The study protocol was approved by the ethics committee, and all participants gave written informed consent.

Results: Only seven participants did not complete the study. The compliance rate was 99.6 ± 6.9% and 99.2 ± 6.3% in the treatment and control groups, respectively. Serum cholesterol decreased by 6.6% (from 2.91 ± 0.96 to 2.71 ± 0.83 mmol/L) in the treatment group and 1.6% (from 2.83 ± 0.81 to 2.75 ± 0.79 mmol/L) in the control group. Compared with the control group, the treatment group had reduced serum LDL cholesterol by 0.13 ± 0.06 mmol/L (P=0.02). Nonetheless, body weight, waist circumference, blood pressure, glucose, and lipids did not change significantly. 95% of those received fortified drink reported no adverse events. Five of the six adverse events were intestinal.

Conclusion: The phytosterol-fortified soya drink reduced LDL cholesterol and was well-tolerated. This non-pharmacological way of lowering LDL cholesterol is suitable for the general population who have not yet developed cardiovascular disease or cardiovascular risk factors.

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Implication of single nucleotide polymorphisms identified from recent genome-wide association studies of diabetic retinopathy in Chinese type 2 diabetes patients

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Introduction: Diabetic retinopathy (DR) is the most common microvascular complication of type-2 diabetes mellitus (T2DM). Novel DR-associated loci have been identified from recent genome-wide association studies. We aimed to examine the associations of these DR-associated single nucleotide polymorphisms (SNPs) with sight-threatening DR (STDR) in Chinese patients with T2DM.

Methods: In previous genome-wide association studies, 68 SNPs that showed top association signals with DR (r^2<0.9, P<5x10^{-4}) were genotyped in three groups of subjects: 1157 T2DM patients with STDR (STDR cases), 2080 T2DM patients without retinopathy (non-STDR controls), and 1021 non-diabetic subjects (healthy controls). Multiple logistic regression model with adjustment for confounding factors was used to determine the independent association between the SNPs and STDR.

Results: Comparing STDR cases with non-STDR controls, GSF21-KLHDC7A rs3007729 (odds ratio [OR]=0.87, P=0.026), C6orf170 rs7772697 (OR=0.83, P=0.034), LOC728275-LOC728316 rs227455 (OR=0.89, P=0.040), SLC25A32 rs3098241 (OR=0.88, P=0.030), COL5A1 rs7861012 (OR=0.83, P=0.016), and rs59126004 (OR=0.83, P=0.019) were significantly associated with STDR after adjusting for risk factors including age, sex, duration of diabetes, and the presence of hypertension. Comparing STDR cases with healthy controls, UBE2E2 rs11927173 (OR=0.79, P=0.039), BFSP2 rs1197310 (OR=1.23, P=0.022), and RASL11A rs1333347 (OR=1.36, P=0.022) were significantly associated with STDR after adjusting for age, sex, and the presence of hypertension. None of these SNPs showed significant association with T2DM.

Conclusion: We have successfully validated the significant and independent associations of several STDR-associated SNPs identified in previous genome-wide association studies in patients with T2DM.

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Low-dose aspirin and risk of gastric cancer development after *Helicobacter pylori* eradication: a territory-wide study with propensity score analysis

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Introduction: Individuals remain at risk of developing gastric cancer (GC) despite eradication of *Helicobacter pylori* (HP). Although aspirin was shown to be associated with a reduced GC risk in HP-infected subjects, it remains uncertain whether aspirin can reduce GC risk in HP-eradicated subjects. This study aimed to investigate the chemopreventive effect of aspirin in HP-eradicated subjects.

Method: Subjects who had received clarithromycin-based triple therapy between 2003 and 2012 in all public hospitals in Hong Kong were identified. Those who failed HP therapy and developed GC within 12 months were excluded. The observation period started from the commencement of HP therapy (index date), and patients were censored at the end of study (December 2015), death, or GC diagnosis. Aspirin use was defined as once or more weekly use. Cox proportional hazard model with propensity score adjustment for covariates (including age, sex, comorbidities, and concurrent medications) was used to derive the hazard ratio (HR) and 95% confidence interval (CI) of GC with aspirin use.

Results: Of the 63 605 eligible subjects (with a median follow-up of 7.6 years), 169 (0.27%) developed GC with an incidence rate of 3.5 per 10 000 person-years. Aspirin use was associated with a reduced GC risk (HR=0.30, 95% CI=0.15-0.61). Compared with the reference group (never use), more frequent aspirin use showed a significant decreasing trend of GC risk (P_{trend}<0.001), with lowest risk observed among daily users (HR=0.21, 95% CI=0.05-0.94). Compared with never use, a longer duration of aspirin use was also associated with a lower risk of GC (<2 years: HR=0.92, 95% CI=0.51-1.64; 2-5 years: HR=0.27, 95% CI=0.09-0.80; ≥5 years: HR=0.07, 95% CI=0.02-0.31; P_{trend}<0.001). Moreover, a lower risk was observed with a higher aspirin dose (<100 mg: HR=0.38, 95% CI=0.18-0.79; ≥100 mg: HR=0.15, 95% CI=0.03-0.65; P_{trend}<0.001).

Conclusion: Aspirin use was associated with a reduced GC risk in a dose-response manner in HP-eradicated subjects.

The University of Hong Kong Memory Clinic Registry: a retrospective cohort study

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Introduction: The University of Hong Kong Memory Clinic Registry aims to collect comprehensive clinical data on all patients who have attended the Memory Clinic of Queen Mary Hospital. Since its inception in 2003, the clinic has provided outpatient consultations for over 1000 Hong Kong Chinese patients with cognitive impairment, including Alzheimer's disease, vascular dementia, frontotemporal dementia, and Lewy body disease. Patients are assessed every 6 months by the specialist team under the Division of Geriatric Medicine.

Methods: The registry data was retrospectively collected from the Hospital Authority Clinical Management System. Clinical data recorded included patient demographics, clinical assessment scores (Montreal Cognitive Assessment, Abbreviated Mental Test, Geriatric Depression Scale, Neuropsychiatric Inventory, Barthel Index, Lawton's Instrumental Activities of Daily Living, and Functional Assessment Staging for Alzheimer's Disease), and patient-centred outcomes including institutionalisation, falls, stroke, acute coronary syndrome, hospital admissions, and death. A major focus was on the usage of various dementia drugs, including indications for drug initiation, dosages and changes, side effects, and compliance. Another focus was to identify the new incidences of delirium from each patient's hospitalisation since their initial clinic consultation, assessing for the predictors of delirium (eg surgery, general anaesthesia) and long-term prognosis (eg faster cognitive decline).

Results: So far, 250 patients have been included in this registry.

Conclusion: The strength of our registry is its comprehensive patient profiling with long-term longitudinal outcomes. Data from this registry provide essential Asian patient information on the clinical progression of dementia, dementia drug usage, and determinants and prognosis of delirium.

Efficacy of novel therapeutic agents for psoriatic arthritis: a network meta-analysis

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Introduction: Novel therapeutic agents are more efficacious in active psoriatic arthritis (PsA). Direct comparisons between different agents are lacking. We performed a network meta-analysis to compare the efficacy of different novel therapeutic agents for PsA.

Method: Relevant literature in ISI Web of Science, Scopus, Medline, Cochrane library, Clinicaltrials.gov, and EMBase was searched. Only randomised controlled trials that reported the proportion of PsA patients achieving an ACR20 response as one of the study outcomes were included. Studies were stratified into biologic naïve and inadequate response to tumour necrosis factor inhibitor (TNFi) populations. Results were analysed using R statistics version 3.3.2 with netmeta version 0.9-4. Summary odds ratios (OR) and 95% confidence interval (CI) were estimated using the random effects model.

Results: A total of 27 studies (19 for biologic naïve and 8 for inadequate response to TNFi) were included. In patients with an inadequate response to TNFi, apremilast had the highest probability to be the best therapeutic agent. With reference to apremilast, there was no significant difference in efficacy among other therapeutic agents: ixekizumab (OR=0.69, 95% CI=0.18-2.64), secukinumab (OR=0.47, 95% CI=0.12-1.90), tofacitinib (OR=0.49, 95% CI=0.13-1.84), and ustekinumab (OR=0.53, 95% CI=0.12-2.31). In biologic naïve patients, etanercept had the highest probability to be the best therapeutic agent. The efficacy of etanercept was better than adalimumab (OR=0.33, 95% CI=0.13-0.84), apremilast (OR=0.21, 95% CI=0.09-0.52), tofacitinib (OR=0.31, 95% CI=0.10-0.93), and ustekinumab (OR=0.29, 95% CI=0.10-0.79). There is no significant difference in efficacy between etanercept and certolizumab (OR=0.42, 95% CI=0.13-1.34), golimumab (OR=0.94, 95% CI=0.27-2.39), infliximab (OR=0.75, 95% CI=0.27-2.07), ixekizumab (OR=0.37, 95% CI=0.12-1.11), or secukinumab (OR=0.31, 95% CI=0.10-0.93).

Conclusions: In PsA patients with an inadequate response to TNFi, all novel therapeutic agents demonstrate similar efficacy. In biologic naïve patients, etanercept is more efficacious than adalimumab, apremilast, tofacitinib, and ustekinumab.

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Incidence and predictors of disease flare in Chinese patients with rheumatoid arthritis

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Introduction: Despite aggressive treatment with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), disease flare in patients with rheumatoid arthritis (RA) remains common. Definitive biomarkers for the prediction of disease flare have not been identified. We performed a prospective cohort study to evaluate the potential factors that may contribute to disease flare in Chinese patients with RA.

Method: RA patients in clinical remission or low disease activity were recruited in Queen Mary Hospital. Patient factors (age, sex, educational levels, disease duration, disability, drug compliance, and belief about medication), disease factors (rheumatoid factor, anti-citrullinated peptide antibody, disease activity score in 28 joints based on C-reactive protein (DAS28-CRP), and drug factors (number and types of csDMARD used) were evaluated at baseline. Disease flare is defined as a change in DAS28-CRP of >0.6 or a change from remission/low disease activity to moderate disease activity or above.

Results: Of 254 RA patients in remission or with low disease activity, 177 (69.7%) experienced disease flare during 1-year follow-up. Compared with those without disease flare, those with disease flare were more likely to be female (88% vs 68%, P=0.014), have higher baseline DAS28-CRP (2.41 vs 2.15, P=0.04), and have better belief about the necessity of medications (17.6 vs 69.3, P=0.012). In univariate analysis, female sex and belief about the necessity of medications were significant predictors of disease flare. In multivariate analysis, only belief about the necessity of medications remained the significant predictor.

Conclusions: RA patients with disease flare within 1 year are predominantly female and have higher baseline DAS28-CRP and better belief about the necessity of medications. Belief about the necessity of medications is a major predictor of disease flare in Chinese patients with stable RA.

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Rheumatology nursing consultation versus regular rheumatologist follow-up for rheumatoid arthritis patients with low disease activity: a randomised controlled trial

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Introduction: Conventionally, patients with rheumatoid arthritis are managed by rheumatologists every 3 to 6 months. Rheumatology nursing consultation has been established in Hong Kong for more than 10 years, but its efficacy in the management of rheumatoid arthritis patients with low disease activity has not been evaluated.

Method: This is a single-centre, randomised controlled, non-inferiority trial. Rheumatoid arthritis patients with low disease activity were recruited and randomised to receive rheumatology nursing consultation or regular rheumatologist follow-up. Patients were evaluated every 4 months from baseline. The primary outcome measure was the proportion of patients remaining at low disease activity at 12 months. Secondary outcomes measures include the proportion of patients with an increase in disease activity score in 28 joints based on C-reactive protein (DAS28-CRP) of ≥0.6 and the difference in drug compliance and physical disability measured by health assessment questionnaire.

Results: A total of 274 patients were recruited. In the rheumatology nursing consultation group, more patients remained at low disease activity (91.9% vs 81.2%, P=0.013) and fewer patients experienced disease flare during the 1-year follow-up (12.5% vs 55.1%, P<0.001), compared with the regular rheumatologist follow-up group. Using one-way repeated measure ANOVA, there was a significant difference in DAS28-CRP between different interventions over time. There was no significant difference in compliance and disability between groups.

Conclusion: Rheumatology nursing consultation is not inferior to regular rheumatologist follow-up for rheumatoid arthritis patients with low disease activity.

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Validity of Health Assessment Questionnaire and EuroQoL 5-dimension in Chinese patients with rheumatoid arthritis

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Introduction: The traditional Chinese translation of the Health Assessment Questionnaire–Disability Index (HAQ-DI) and EuroQoL 5-dimension 5-level (EQ-5D-5L) instruments has never been validated on Chinese patients with rheumatoid arthritis. This study aimed to assess the validity and sensitivity of the HAQ-DI and EQ-5D-5L in Chinese patients with rheumatoid arthritis.

Method: Patients attending a rheumatology specialist outpatient clinic were recruited to complete structured questionnaires that comprised HAQ-DI, EQ-5D-5L, and 36-item Short-Form Health Survey (SF-36). Construct validity was assessed using Spearman's correlation test against the SF-36 subscales measuring the similar constructs. Internal consistency was assessed using Cronbach's α coefficient. Sensitivity was determined by comparing with clinical known-groups using the independent t-test and effect size.

Results: A total of 704 Chinese patients with rheumatoid arthritis were recruited. Domain Scores of the EQ-5D-5L significantly correlated with those of SF-36 (r=0.45-0.64 for sensitivity). Domain scores of the HAQ-DI also significantly correlated with those of SF-36 version 2, except for the score of mental health (r= -0.46-0.77). The construct validity of HAQ-DI, EQ-5D-5L, and SF-36 was supported. In addition, HAQ-DI and EQ-5D-EL were sensitive in detecting differences between subjects with different disease activity, ie duration of disease and disease activity score in 28 joints based on C-reactive protein (DAS28-CRP).

Conclusion: The Chinese translation of HAQ-DI and EQ-5D-5L instruments is valid to assess the health-related quality of life of Chinese patients with rheumatoid arthritis.

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Antithrombotic therapy to prevent cognitive decline in people with small vessel disease on neuroimaging but without dementia: a Cochrane systematic review

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Introduction: Cerebral small vessel disease (SVD) can cause cognitive impairment and dementia. Antithrombotic therapy (ATT) is an established treatment for stroke prevention, but it is unclear whether ATT is also effective in preventing cognitive decline in people with SVD on neuroimaging but without dementia.

Method: We reviewed randomised controlled trials that compared ATT with none, or compared different ATT regimens including antiplatelet agents (as mono- or combination therapy), oral anticoagulants, or a combination of these two. We searched ALOIS, Cochrane Dementia and Cognitive Improvement Review Group's Specialized Register, and Cochrane Stroke Group's Specialized Register.

Results: We included one randomised controlled trial (with 280 patients aged 50 to 70 years) on the effects of 6-month treatment with DL-3-n-butylphthalide (an antiplatelet drug approved for ischaemic stroke treatment in China) on cognitive outcome in Chinese patients with vascular cognitive impairment caused by subcortical SVD but without dementia. The trial reported a small but significant difference in cognitive function (Alzheimer's Disease Assessment Scale–Cognitive Subscale) and global impression status (Clinician Interview–Based Impression of Change plus caregiver input). There was no difference for Mini-Mental State Examination, Clinical Dementia Rating, neuropsychiatric symptoms, or activities of daily living. DL-3-n-butylphthalide was a relatively safe drug.

Conclusion: Current evidence is positive but not strong enough to support the routine use of antithrombotic therapy to prevent cognitive decline in people with SVD on neuroimaging but without dementia. Results from three ongoing studies on aspirin and cilostazol are awaited.

Abnormal expression of inflammasome components in systemic lupus erythematosus patients

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Introduction: Systemic lupus erythematosus (SLE) is a highly complex autoimmune disease contributed by environmental, genetic, and hormonal factors. The inflammasome, expressed mainly in myeloid cells, is a multi-protein complex that oligomerises in cytosol following infections and/or endogenous stress to release the pro-inflammatory cytokines interleukin (IL)-18 and IL-1beta through the action of caspase 1 (CASP1). Inflammasomes usually comprise (1) a stimuli sensor such as members from the nucleotide-binding domain and leucine-rich-repeat-containing proteins (eg NLRP3) or the pyrin and HIN domain-containing family (eg absent in melanoma 2, AIM2), (2) an adaptor molecule apoptosis-associated speck-like protein (ASC), and (3) the pro-caspase-1 that will be self-cleaved to active CASP1. Inflammasomes are a protective innate response against infection, and are suggested to be dysregulated in various autoimmune conditions including SLE. This study aimed to evaluate and compare the expression levels of inflammasome components in monocytes in SLE patients and healthy volunteers. Monocytes were chosen because they are the main inflammasome responders in peripheral blood.

Methods: The expression levels of NLRP3, AIM2, CASP1, ASC, IL-18, and IL-1beta in monocytes were evaluated by quantitative real-time polymerase chain reaction.

Results: The mRNA levels of AIM2, CASP1, and ASC were elevated in SLE monocytes when compared with normal controls. Interestingly, SLE monocytes expressed lower NLRP3 mRNA transcripts. Expression levels of cytokines IL-18 and IL-1beta were not significantly different between the two groups.

Conclusion: Expressions of various inflammasome components are dysregulated in SLE monocytes. Correlation analyses of expression levels and different clinical parameters in SLE patients are warranted. The mechanisms for the dysregulated expressions should be further elucidated.

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Lactulose, lactose, and fructose ingestion induces specific patterns of gastrointestinal symptoms in Chinese subjects with functional dyspepsia and irritable bowel symptoms

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Introduction: The prevalence of functional dyspepsia (FD) in East Asia is three times higher than that of irritable bowel syndrome (IBS). Patients with IBS usually experience pain and discomfort in the upper abdomen and may be misdiagnosed with FD. Provocative hydrogen breath testing (HBT) with lactulose, lactose, and fructose may identify patterns of gastrointestinal symptom genesis in the Chinese population.

Methods: Subjects fulfilling the Rome III classification of FD and IBS, subjects with quiescent inflammatory bowel disease, and controls with no known gastrointestinal disorder/symptoms were recruited. All subjects underwent HBT with or without methane assessment with lactulose (10 mL), lactose (25 g) and fructose (25 g).

Results: A total of 399 subjects completed at least one breath test and 355 subjects completed all three breath tests. About 14.5%, 48.4%, 25.6%, and 11.5% were controls, FD, IBS, and inflammatory bowel disease subjects, respectively. All subjects were ethnic Chinese with a mean age of 53.2 (range, 18-76) years, and 30.6% (95% confidence interval [CI], 26-35%) were male. About 84.5% (95% CI=84-91%) of subjects were hydrogen producers and 100% were methane producers. Similar proportion of FD and IBS subjects experienced epigastric pain on consumption of lactulose, lactose, and fructose. More subjects with FD experienced belching than subjects with IBS after ingesting lactulose (58% vs 42%, P=0.011) or lactose (62% vs 46%, P=0.014).

Conclusion: Chinese subjects with FD or IBS commonly produce both hydrogen and methane after ingesting lactulose, lactose, or fructose. Furthermore, FD and IBS differ in their genesis of gastrointestinal symptoms in response to provocative HBT. Chinese IBS subjects commonly experience epigastric and abdominal pain.

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Pattern of habitual FODMAP consumption in Hong Kong Chinese patients with irritable bowel syndrome and functional dyspepsia

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Introduction: Dietary FODMAPs (fermentable, oligo-, di-, mono-saccharides and polyols) are well-established triggers of gastrointestinal symptoms in western patients with irritable bowel syndrome (IBS). There are no data on the FODMAP content of typical diets in Sino-sphere Asia. This study aimed to assess patterns of habitual FODMAP intake in a cohort of Hong Kong Chinese patients with IBS and/or functional dyspepsia (FD).

Methods: Subjects with IBS and/or FD (fulfilling the Rome III classification) and healthy controls were asked to complete food records over a 4-day period. Diaries were analysed quantitatively for total and individual FODMAP content using the FoodWorks nutrient analysis software and qualitatively for average servings of FODMAPs/d using the Monash University Low FODMAP app.

Results: Overall, 56 patients (17 with FD, 20 with IBS, and 19 with IBS-FD) and six healthy volunteers were recruited. The median patient age was 55 (range, 22-78) years; 39 were female. The median (interquartile range) FODMAP intake was 9.5 (6.5-26.1) g/d in IBS patients, 9.6 (2.9-12.9) g/d in FD patients, 11.6 (7.1-17.8) g/d in IBS-FD patients, and 15.5 (9.1-18.6) g/d in controls (P=0.36, Kruskal Wallis test). There was no significant difference in individual FODMAP intake across groups (P>0.05). In patients, the contribution of FODMAPs was derived predominantly from foods high or moderate in fructans (IBS: 4.8 serves/d, FD: 4.6 serves/d, IBS-FD: 4.4 serves/d) followed by excess fructose.

Conclusions: Typical FODMAP intake of Chinese Hong Kong patients with IBS and FD is lower than that in western countries, with fructans and excess fructose comprising major FODMAPs. These findings inform the adaptation of a low FODMAP diet therapy in this region.

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In-vitro T cell-based lung cancer suppression assay to identify biomarkers for anti-PD-1 immunotherapy

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Introduction: In cancer microenvironment, tumour escapes from T cell cytotoxicity by presenting specific ligands such as programmed death ligand-1 (PD-L1) that binds with the T-cell inhibitory receptor, programmed death-1 (PD-1). This binding suppresses T cell response via the immune-checkpoint pathway that plays an important role for tumour survival. To identify potential therapeutic biomarkers, this study focused on PD-1 and PD-L1 interaction between lung cancer cells and $CD8^+$ cytotoxic T lymphocytes.

Method: We performed direct co-culture of lung cancer cell lines with $CD8^+$ cytotoxic T lymphocytes isolated from peripheral blood of healthy donors or patients with non-small-cell lung cancer. $CD8^+$ cytotoxic T lymphocytes and the lung cancer cell lines were harvested at serial time points after co-culture, and flow cytometry was used to assess the expressions of PD-1 and PD-L1 on lymphocytes and cancer cells, respectively. MTT assays were performed to determine lung cancer cell viability after 24 and 48 hours of co-culture.

Results: In squamous lung carcinoma cell lines TS49, TS260, and CL100, their expressions of PD-L1 increased after direct co-culture, and the expressions of PD-1 on healthy donor $CD8^+$ T lymphocyte increased shortly after co-culture then decreased after 12 hours. Viability of these cancer cells decreased after co-culture.

Conclusion: There is no significant correlation between non-small-cell lung cancer cell lines PD-L1 expressions and their viability. Further study to investigate the potential biomarkers in this model is warranted.

Determining the optimal systolic blood pressure for hypertensive patients

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Introduction: Intensive blood pressure (BP) lowering to <120 mmHg has been shown to reduce mortality and cardiovascular events in non-diabetic hypertensive patients. This challenges existing guidelines. We therefore performed network meta-analysis to determine the relationship between achieved BP and outcomes.

Methods: We searched for randomised controlled trials targeting different BP levels and cardiovascular events. The mean achieved systolic BP (SBP) in different trials was classified into five groups (110-119, 120-129, 130-139, 140-149, and 150-159 mmHg). Data were analysed using frequentist approach and Bayesian framework in R.

Results: We included 13 randomised controlled trials with a total of 48 152 patients aged >50 years. Major adverse cardiovascular events and stroke were significantly reduced when SBP was controlled to 120-129 mmHg, compared to 130-139 mmHg (odds ratio [OR]=0.84, 95% confidence interval [CI]=0.73-0.96; OR=0.83, 95% CI=0.69-0.99, respectively), 140-149 mmHg (OR=0.75, 95% CI=0.63-0.90; OR=0.70, 95% CI=0.55-0.90, respectively), and 150-159 mmHg (OR=0.42, 95% CI=0.31-0.58; OR=0.39, 95% CI=0.23-0.67, respectively). Stroke was further reduced with more intensive control of SBP to <120 mmHg (OR=0.58, 95% CI=0.38-0.87; OR=0.49, 95% CI=0.31-0.77; OR=0.27, 95% CI=0.14-0.52, respectively). In contrast, cardiovascular mortality and myocardial infarction were increased with SBP ≥150 mmHg, compared to 120-129 mmHg (OR=2.05, 95% CI=1.27-3.30; OR=1.73, 95% CI=1.08-2.78, respectively) and 130-139 mmHg (OR=1.60, 95% CI=1.08-2.39; OR=1.53, 95% CI=1.03-2.29, respectively). No significant relationship between SBP and all-cause mortality was found.

Conclusion: BP lowering to <130 mmHg reduces major adverse cardiovascular events and stroke. Further controlling to <120 mmHg can be an option if the therapy is tolerated as it reduces stroke risk. The long-term SBP should not exceed 150 mmHg because of increased risk of cardiovascular mortality and myocardial infarction.

Effect of new antidiabetic drugs on cardiovascular outcomes: a network meta-analysis

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Introduction: The prevalence of cardiovascular disease is high in patients with type-2 diabetes mellitus (T2DM). New antidiabetic drugs are required to demonstrate cardiovascular safety in outcome trials. Direct comparisons among these drugs are limited. We performed a network meta-analysis to compare the effect of new antidiabetic drugs on cardiovascular outcomes.

Methods: We searched for cardiovascular outcome trials reporting major adverse cardiovascular events (MACE) and mortality in T2DM patients with established cardiovascular risks. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), sodium-glucose co-transporter 2 (SGLT-2) inhibitors, and dipeptidyl peptidase-4 (DPP-4) inhibitors were involved. Statistic analysis was performed using R.

Results: We included nine cardiovascular outcome trials with a total of 72 262 T2DM patients. Compared to placebo, both SGLT-2 inhibitors and GLP-1 RAs reduced MACE (odds ratio [OR]=0.86, 95% confidence interval [CI]=0.77-0.95; OR=0.89, 95% CI=0.82-0.97, respectively), cardiovascular mortality (OR=0.76, 95% CI=0.65-0.88; OR=0.85, 95% CI=0.73-0.99, respectively), and all-cause mortality (OR=0.78, 95% CI=0.69-0.88; OR=0.89, 95% CI=0.80-0.99, respectively). Moreover, SGLT-2 inhibitors reduced MACE (OR=0.87, 95% CI=0.77-0.98) and cardiovascular mortality (OR=0.75, 95% CI=0.62-0.90) when compared to DPP-4 inhibitors. In contrast, DPP-4 inhibitors had higher all-cause mortality than SGLT-2 inhibitors (OR=1.31, 95% CI=1.13-1.53) and GLP-1 RAs (OR=1.16, 95% CI=1.01-1.33).

Conclusion: SGLT-2 inhibitors and GLP-1 RAs reduce MACE and all-cause mortality. SGLT-2 inhibitors are the most beneficial in reducing MACE among the three drug classes. DPP-4 inhibitors are comparable to placebo but inferior to the other two drug classes regarding death. Our findings support SGLT-2 inhibitors and GLP-1 RAs as the preferred treatment for T2DM patients at high cardiovascular risks.

Efficacy and safety of prasugrel and ticagrelor versus clopidogrel in patients with acute coronary syndrome: a network meta-analysis

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Introduction: Newer $P2Y_{12}$ inhibitors (prasugrel and ticagrelor) are more potent than clopidogrel. Evidence of their efficacy and safety in patients with acute coronary syndrome (ACS) is limited. We performed network meta-analysis to assess the effect of newer $P2Y_{12}$ inhibitors on clinical outcomes.

Methods: We searched for randomised controlled trials that compared different $P2Y_{12}$ inhibitors (clopidogrel, prasugrel, and ticagrelor) or in combination with aspirin in ACS patients. The primary outcome was major adverse cardiovascular events (MACE) consisting of cardiovascular death, myocardial infarction, and stroke. Secondary outcomes were the components of MACE, all-cause mortality, stent thrombosis, and Thrombolysis in Myocardial Infarction (TIMI) major and minor bleeding. Statistical analysis was performed using R.

Results: We included 11 randomised controlled trials with a total of 31795 patients. Compared to clopidogrel, both prasugrel and ticagrelor significantly lowered the risk of MACE (odds ratio [OR]=0.88, 95% confidence interval [CI]=0.79-0.97; OR=0.85, 95% CI=0.76-0.95, respectively), myocardial infarction (OR=0.86, 95% CI=0.76-0.98; OR=0.81, 95% CI=0.70-0.94, respectively), and stent thrombosis (OR=0.52, 95% CI=0.32-0.86; OR=0.62, 95% CI=0.45-0.85, respectively). In addition, ticagrelor significantly reduced cardiovascular mortality (OR=0.83, 95% CI=0.70-0.99) and all-cause mortality (OR=0.82, 95% CI=0.69-0.96). Neither prasugrel nor ticagrelor increased TIMI major bleeding. Ticagrelor increased TIMI minor bleeding (OR=1.48, 95% CI=1.25-1.76).

Conclusion: Compared to clopidogrel, both prasugrel and ticagrelor reduce MACE, myocardial infarction, and stent thrombosis. Ticagrelor reduces mortality, although at the expense of an increased risk of minor bleeding. Our study supports the use of the newer $P2Y_{12}$ inhibitors in ACS patients.

The role of lactate in macrophage polarisation and adipose tissue inflammation

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Introduction: Obesity is characterised by adipose tissue hypoxia and lactate accumulation. Macrophage in obese adipose tissue mainly adopts pro-inflammatory M1 phenotype, which represents the major effector of obesity-associated adipose tissue inflammation. In addition, M1 polarisation is accompanied by lactate overproduction. This study aim to examine the role of lactate in macrophage polarisation and adipose inflammation upon obesity.

Method: Lactate and lactate dehydrogenase (LDH) activity were measured by biochemical-based assays. Peritoneal or bone marrow–derived macrophages were treated with lactate or inhibitor of LDH, the key enzyme for lactate production. Macrophage polarisation and inflammation were examined by western blotting and real-time polymerase chain reaction. Tissue-specific LDHA knockout mice were constructed by cre-LoxP system to study the physiological role of lactate in diet-induced obesity.

Results: Lactate and LDH activity were selectively upregulated in adipose tissues of obese mice. Although lactate alone could not stimulate M1 polarisation, depletion of lactate mitigated the induction of M1 and this effect was reversed by lactate replenishment. Lactate was essential for activation of hypoxia inducible factor and NF-kappa B pathways, both of which are regulated by PHD2. In addition, activity of PHD2 was found to be inhibited by lactate. The LDHA was effectively knocked out in adipose tissues and the mice were under high-fat-diet treatment.

Conclusion: Lactate upregulates the hypoxia inducible factor and NF-kappa B pathway in macrophage by inhibiting PDH2 activity and plays a crucial role in macrophage polarisation and inflammation.

SIRT1 in perivascular adipose tissues as a mediator of obesity-induced endothelial dysfunction by controlling brown-to-white transition

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Introduction: SIRT1 is a class III, NAD-dependent histone deacetylase that plays a key role in controlling adipose browning by dictating various gene expression. Perivascular adipose tissues (PVAT) are brown in healthy people and are turning to 'white-like' upon obesity. Meanwhile, dysfunction of PVAT has been implicated in atherogenesis. Using the adipocyte-specific SIRT1 KO mice, we aim to investigate whether SIRT1 modulates the function of PVAT in both lean and obese conditions.

Method: Wild-type and adipocyte-specific SIRT1 knockout mice were fed with either standard chow or high-cholesterol diet for 12 weeks. The aortic rings with or without PVAT were subjected to wire myography to assess the endothelial function. Expression of the brown adipocyte markers UCP-1 and PGC1α were evaluated by western blotting, immunohistochemistry and/or quantitative polymerase chain reaction. Mitosox and Mitotracker CMXRos were used to stain primary adipocytes from wild-type and adipocyte-specific SIRT1 knockout mice, followed by flowcytometry.

Results: In the presence of PVAT, the endothelial function in aorta was significantly impaired in obese mice, and the impairment was further exacerbated in obese adipocyte-specific SIRT1 knockout mice. In contrast to the brown phenotype of PVAT in lean mice, SIRT1 deficiency augmented obesity-induced 'whitening' transition. Fluorescence staining demonstrated that SIRT1-deficient PVAT exhibited more pronounced superoxide production and inflammatory cytokine production. In primary adipocytes, deletion of SIRT1 also led to more severe superoxide production and inflammation.

Conclusion: The brown phenotype of PVAT is associated with increased endothelial functions in blood vessels. SIRT1 plays a pivotal role in controlling PVAT browning via PGC1α, and deficiency of SIRT1 causes PVAT whitening, which in turn enhances superoxide production and vascular inflammation.

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Comparative analysis of high-fat diet and intermittent hypoxia impacts on C57BL/6N and C57BL/6J mouse strains

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Background: Obstructive sleep apnoea, featured with intermittent hypoxia (IH), is highly associated with obesity. Mouse inbred line C57BL/6N and C57BL/6J are both widely used for research. We performed a comparison of the two mouse strains to identify the different functional impacts of high-fat-diet-induced obesity and IH.

Methods: Male 4-week-old mice of C57BL/6N and C57BL/6J strains were used. Half were fed with standard diet and the other half were fed with high-fat diet (LabDiet; St Louis [MO], USA) to induce obesity. At the age of 13 weeks, mice of both strains were subjected to intermittent normoxia or IH (cycles of 10% O_2 for 60 seconds followed by 21% O_2 for another 60 seconds, 30 hypoxic events per hour; BioSpherix, USA) 8 hours per day. After 1 week of exposure, mice were sacrificed (n=4 in each group). Blood samples, subcutaneous and epididymal adipose tissues were collected. enzyme-linked immunosorbent assay was applied for the measurement of serum lipid and adipose tissue inflammatory markers.

Results: All mice fed with high-fat diet exhibited obesity. C57BL/6J mice showed slight decrease of body weight gain after IH exposure in the obese group. Serum lipid levels increased the obese group of both strains. IH led to significant reduction of low- and high-density lipoprotein and total cholesterol levels in lean C57BL/6J mice only. In subcutaneous and visceral adipose tissue, IH led to significant elevation of IL-6 level in C57BL/6J mice only.

Conclusion: The genetic difference between the C57BL/6N and C57BL/6J mice affects the interaction between metabolism and IH. The effect of high-fat diet may be more obvious in C57BL/6N mice, whereas the C57BL/6J mice may be more sensitive to IH. Therefore, the impact of background substrain should be considered before designing the experimental model.

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Long-term outcome of relapsed acute promyelocytic leukaemia in the oral arsenic trioxide era: a 16-year prospective follow-up study

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Introduction: For acute promyelocytic leukaemia (APL) in second complete-remission (CR2), optimal post-remission strategy remains undefined. Efficacy of arsenic trioxide (As_2O_3) in relapse with prior As_2O_3 exposure is unknown. Risk factors for central nervous system (CNS) relapse are unclear.

Objectives: We examined the long-term outcome and risk factors for repeated relapses and CNS involvement in APL.

Methods: Overall, 73 APL R1 cases were studied. Oral-As_2O_3-based re-induction resulted uniformly in CR2, irrespective of previous As_2O_3 exposure. All patients were given oral-As_2O_3-based CR2 maintenance.

Results: At a median follow-up of 94 (range, 9-205) months, 43 (58.9%) patients remained in CR2 with 49 (67.1%) patients having finished the planned 2-year CR2 AAA maintenance. Re-induction and maintenance treatment was well tolerated. Grade 1/2 headache occurred in 20 (27.4%) patients. Hepatotoxicity, all in the form of transaminitis, occurred in 35 (47.9%) patients (grade 1/2 in 26, grade 3/4 in 9). Three patients had self-limiting QTc prolongation. The 10-year leukaemia-free survival was 56.8%. Thirty patients developed R2. Oral-As_2O_3-based re-induction led to CR3 in 27 (90%) patients. Post-CR3 strategies included autologous and oral-As_2O_3 maintenance. At a median follow-up of 30 (range, 3-166) months post-CR3, 11 patients remained in CR3. The 5-year and 10-year overall survivals of the R1 cohort were 79.5% and 67.3%, respectively. Prior use of oral-As_2O_3 maintenance in CR1 was the only risk factor for inferior leukaemia-free survival. CNS involvement occurred in 15 patients, with five still surviving. Relapse during oral-As_2O_3 therapy was the only significant risk factor for CNS involvement.

Conclusion: As_2O_3 is well-tolerated and remained effective despite repeated As_2O_3 exposures. Oral-As_2O_3 maintenance was an effective post-remission strategy for CR2.

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Next-generation sequencing with a 54-gene panel identifies unique mutational profile and prognostic markers in Chinese patients with myelofibrosis

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Introduction: Myelofibrosis (MF) has the worst outcome amongst various myeloproliferative neoplasms. Its prognosis is determined by clinicopathologic features and mutations in key driver genes. An increasing number of gene mutations involving various biological pathways in myeloid malignancies has been discovered. The prognostic significance of these mutations has not been clearly defined. This study aimed to describe the genomic characteristic in a large cohort of MF patients and identify clinical and molecular predictors of outcome.

Methods: We evaluated the genetic profile of 101 patients with primary (n=70) or secondary (n=31) MF using next-generation sequencing with a 54-myeloid gene panel. Multivariate cox regression analysis was used to determine prognostic factors for overall survival (OS) and leukaemia-free survival (LFS).

Results: We identified mutations in 39 genes implicated in myeloid malignancies. 96 patients with MF had a mutation in ≥1 genes: 14 had one mutation, 38 had two, 18 had three, 15 had four, 7 had five, and 4 had ≥6. TET2/JAK2^{V617F} (n=16), ASXL1/JAK2^{V617F} (n=12), and ASXL1/CALR (n=10) were the most frequently co-mutated genes. Other frequently concomitant mutations included CUX1/JAK2^{V617F} (n=6), EZH2/JAK2^{V617F} (n=6), RUNX1/JAK2^{V617F} (n=5), SF3B1/JAK2^{V617F} (n=5), SETBP1/JAK2^{V617F} (n=4), and ZRSR2/JAK2^{V617F} (n=4). The median follow-up of the cohort was 49 (range, 1-256) months. The 5-year and 10-year OS were 66.3% and 35.4%, respectively. The 5-year and 10-year LFS were 84% and 63.3%, respectively. In multivariate analysis, significant negative prognostic indicators for OS were male gender (P=0.044), age >65 years (P=0.044), haemoglobin <10 g/dL (P=0.001), mutated CUX1 (P=0.003), and mutated TP53 (P=0.043), and for LFS were haemoglobin <10 g/dL (P=0.007), mutated TP53 (P=0.043), and mutated IDH2 (P=0.001). In primary MF, inferior prognostic indicators for OS were male gender (P=0.031), haemoglobin <10 g/dL (P=0.002), platelet count <100 x 10^9/L (P=0.021), mutated TET2 (P=0.011), and mutated CUX1 (P=0.011), and for LFS were haemoglobin <10 g/dL (P=0.027), mutated RUNX1 (P=0.019), and mutated DNMT3A (P=0.004). In JAK2^{V617F} positive MF, inferior prognostic indicators for OS were mutated ASXL1 (P=0.006) and mutated SRSF2 (P<0.001), and for LFS were mutated U2AF1 (P=0.037).

Conclusion: Our study demonstrated unique molecular profiles and prognostic predictors of outcome in Chinese patients with MF.

Risk of gastrointestinal bleeding in patients using ticagrelor or clopidogrel: a meta-analysis of randomised controlled trials

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Introduction: Ticagrelor is a novel oral reversible P2Y12 receptor inhibitor with rapid onset and more pronounced platelet inhibition than clopidogrel. Several large-scale randomised trials have confirmed the superiority of ticagrelor to clopidogrel on various cardiovascular or cerebrovascular disease outcomes. However, increase in bleeding has also been reported with ticagrelor. No study has compared the risk of gastrointestinal (GI) bleeding in patients taking ticagrelor or clopidogrel. This study aims to determine the risk of GI and all bleeding in patients using ticagrelor or clopidogrel.

Methods: We systematically searched PubMed, Cochrane library, and Web of Science to identify randomised controlled trials published until September 2017 that compared ticagrelor with clopidogrel in terms of efficacy and safety. The primary end-point was the rate of major or minor GI bleeding based on PLATO bleeding definition (other definitions were adjusted accordingly), expressed as risk ratio (RR) and 95% confidence interval (CI). The rates of all non–coronary artery bypass graft–related major bleeding and major plus minor bleeding were also analysed.

Results: We identified 23 randomised control trials involving 36 857 patients. Ticagrelor was associated with a higher rate of all major bleeding (RR=1.18, 95% CI=1.05-1.31), compared with clopidogrel. This trend was consistent for all major and minor bleeding (RR=1.12, 95% CI=1.05-1.20) in 14 studies involving 21 490 patients. Seven studies involving 2296 patients reported outcomes of GI bleeding. In fixed effects model, ticagrelor was not associated with increased risk of major or minor GI bleeding (RR=1.59, 95% CI=0.75-3.39), compared with clopidogrel. There was low heterogeneity among the included studies (I2 of 0%, 95% CI=0-52%). Result was consistent in sensitivity analysis. In subgroup analysis based on the duration of follow-up, the RR (95% CI) of GI bleeding in studies with follow-up >1 month and <1 month was 1.57 (0.64-3.84) and 1.66 (0.41-6.66), respectively. The Asian trials subgroup analysis of GI bleeding involving 1111 patients showed similar result (RR=1.55, 95% CI=0.58-4.17).

Conclusion: Ticagrelor was associated with a higher risk of all major bleeding but did not appear to increase the risk of GI bleeding, compared with clopidogrel. Nonetheless, as most relevant randomised controlled trials did not report GI bleeding outcomes separately, further analyses from the original data are needed.

The chemoresistant gene *LAPTM4B* is a novel therapeutic target for acute myeloid leukaemia

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Introduction: Acute myeloid leukaemia (AML) is a heterogeneous blood cancer with unsatisfactory treatment outcome by standard chemotherapy. Identification of novel therapeutic targets is urgent for this aggressive disease. Dysregulation of autophagy has been shown in different types of cancers, including leukaemia. Nonetheless, the clinical application of autophagy modulation in leukaemia treatment remains elusive.

Method: Differential expression of autophagy gene was analysed using the TCGA_AML database followed by real-time quantitative polymerase chain reaction validation of samples from normal peripheral blood stem cells, AML cell lines, and primary AML patients. Gene overexpression and knockdown was performed in MOLM-13 AML cell. Cell growth, apoptosis, and drug sensitivity were measured after gene modification.

Result: After analysing 458 autophagy genes, we identified 11 candidates (*LRBA*, *P4HB*, *CANX*, *RYR1*, *STX7*, *BLK*, *BAG3*, *GAPDH*, *LAPTM4B*, *AKT3*, *AP1S3*) that were differentially expressed in poor survival AML patients (TCGA_AML database). Particularly, the *LAPTM4B* (lysosome protein transmembrane 4 beta) was implicated in various cancers, but its role in leukaemia is unknown. Indeed, higher *LAPTM4B* expression was found in poor prognostic AML (monosomy 7) comparing to those of good prognosis [t(15;17)]. Importantly, MOLM-13 cell-overexpressed with *LAPTM4B* were less sensitive to chemodrug (etoposide, cytarabine, doxorubicin) treatment. Reversely, shRNA-mediated *LAPTM4B* gene knockdown induced significant apoptosis and inhibited MOLM-13 cell growth in vitro and in vivo.

Conclusion: The chemoresistant gene *LAPTM4B* is a novel therapeutic target in AML.

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Impact of provision of time in therapeutic range value on anticoagulation management in atrial fibrillation patients on warfarin

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Introduction: The importance of time in therapeutic range (TTR) in patients prescribed warfarin therapy for stroke prevention in atrial fibrillation (AF) cannot be overemphasised. This study aimed to evaluate the impact of provision of TTR results during clinic visits on anticoagulation management.

Method: This was a single-centred, randomised controlled study that involved 15 arrhythmia clinics, each randomised to either provision of TTR or control. The primary outcome was a documented discussion between doctors and patients about switching warfarin to a non-vitamin K oral anticoagulant (NOAC).

Results: Overall, 481 patients with AF prescribed warfarin were randomly assigned to the TTR provision group or control group. The mean patient age was 73.6 ± 12.0 years, and 60.7% of patients were male. The mean CHA_2DS_2-VASc score was 3.2 ± 1.6 and the mean HAS-BLED score was 1.7 ± 1.2. The mean TTR was 63.9 ± 29.9%. At the index clinic visit, 71 (14.8%) of 481 patients had a documented discussion about switching warfarin to a NOAC. Patients with provision of TTR results were more likely to discuss switching warfarin to a NOAC than controls (19.1% vs 10.6%, P=0.03), especially those with a TTR of <65% (35.2% vs 10.6%, P<0.001). A higher (not significantly) proportion of patients with provision of TTR results switched to a NOAC (5.9% vs 4.1%, P=0.49).

Conclusions: The provision of TTR amongst patients on warfarin was associated with a discussion about switching from warfarin to a NOAC in those with TTR of <65%, but did not result in actual switching to NOAC. This suggested additional barriers.

Secular trends and aetiologies of venous thromboembolism in Chinese from 2004 to 2016

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Introduction: Current epidemiological data for venous thromboembolism (VTE) are derived primarily from Caucasian populations. Little is known for other ethnic groups. This study aimed to describe the incidence, aetiologies, and the secular trends of VTE in a Chinese population.

Method: This was an observational study using a hospital VTE registry.

Results: Between 2004 and 2016, 2214 patients (mean age, 66.2 ± 17.4 years; 57.2% female) were hospitalised for a novel occurrence of VTE. Of these, 1444 (65.2%) had deep venous thrombosis and 770 (34.8%) had pulmonary embolism. Over the 13-year period, there was an increasing trend in the incidence of VTE from 28.1 per 100 000 population per year in 2004 to 48.3 per 100 000 population per year in 2016. There has been a disproportional increase in the incidence of VTE amongst those ≥aged 75 years. Aetiologically, the most common cause of VTE was active malignancy with an incidence that increased from 34.8% in 2005 to 60.9% in 2014.

Conclusions: The incidence of VTE in Hong Kong appears to be lower than that in previous Caucasian series. Nonetheless, there has been an increasing incidence of VTE over the past decade, primarily related to ageing and malignancy.

Epigenetic inactivation of the potential tumour suppressor gene *FAT4* in hepatocellular carcinoma

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Introduction: Hepatocellular carcinoma (HCC) remains a prevalent disease worldwide. Improvements in timely diagnosis and effective treatment are needed. Using targeted sequencing, we have identified frequent non-synonymous mutations of *FAT4* in hepatitis B virus–associated HCC. However, the role of *FAT4* in the development of HCC remains unclear. This study aimed to characterise and investigate the potential tumour suppressor role of *FAT4* in HCC.

Methods: The expression level of *FAT4* was determined by real-time polymerase chain reaction and western blot. The presence of *FAT4* promoter methylation was analysed by methylation-specific polymerase chain reaction followed by bisulfite sequencing. The percentage of methylation at specific CpG site within the target region was further quantitated by pyrosequencing. The role of *FAT4* on cell growth and proliferation was determined using siRNA-mediated *FAT4* knockdown.

Results: The mRNA and protein expression of *FAT4* were significantly downregulated on 28 pairs of HCC tumour samples, compared with their non-tumour counterparts ($P<0.001$ and $P<0.01$, respectively). Promoter methylation in HCC tumour tissues and cancer cell-lines was significantly higher than non-tumour tissues and normal liver cell-line, respectively (both $P<0.01$). Functional analysis using RNAi-mediated knockdown of *FAT4* revealed an increased cancer cell growth and proliferation, suggesting the putative tumour suppressor role of *FAT4* in HCC.

Conclusions: *FAT4* is a target of epigenetic inactivation. Suppression of *FAT4* expression in HCC tumours was associated with promoter methylation of *FAT4*. These findings indicate the putative tumour suppressor role of *FAT4* in HCC.

The FGF21-CCL11 axis mediates beiging of white adipose tissues by coupling sympathetic nervous system to type-2 immunity

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Introduction: Beige adipocytes are UCP1 positive adipocytes with thermogenic capacity and are scattered in white adipose depots and provide an important defence against hypothermia and excessive weight gain in response to cold or energy surplus. Although recent studies have identified the involvement of several types of immune cells and type-2 cytokines in the biogenesis of beige adipocytes, the physiological stimulators that trigger the type-2 immune responses are poorly understood.

Methods: Mice with adipose-selective ablation of FGF21 or its co-receptor beta-Klotho were used. Body temperature, UCP1 expression in adipose tissues, and adipose tissue morphology were examined to investigate thermogenic and beiging capacity in mice. Abundance of various types of immune cells were determined by flow cytometric analysis. The expression of type-2 cytokines and chemokines in adipose tissues was measured by real-time polymerase chain reaction analysis.

Results: Cold-induced type-2 immune responses and beiging in subcutaneous WAT (scWAT) were abrogated in mice with adipose selective ablation of FGF21 or its co-receptor, whereas such impairments were reversed by replenishment with chemokine CCL11. Mechanistically, FGF21 acts on adipocytes in an autocrine manner to promote the expression and secretion of CCL11 via activation of ERK1/2, which drives recruitment of eosinophils into scWAT, leading to increases in accumulation of M2 macrophages and proliferation and commitment of adipocyte precursors into beige adipocytes.

Conclusion: The adipose-derived FGF21-CCL11 axis coordinates beiging by coupling sympathetic nerve activation with type-2 immune response during cold exposure.

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Efficacy of clarithromycin-naproxen-oseltamivir combination in the treatment of patients hospitalised for influenza A (H3N2) infection: an open-label randomised, controlled, phase IIb/III trial

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Introduction: Influenza causes excessive hospitalisations and deaths. This study assessed the efficacy and safety of a clarithromycin-naproxen-oseltamivir combination for treatment of severe influenza.

Method: From February to April 2015, we conducted a prospective open-label, randomised, controlled trial. Adult patients hospitalised for influenza A (H3N2) were randomly assigned to either a 2-day combination of clarithromycin 500 mg, naproxen 200 mg, and oseltamivir 75 mg twice daily followed by 3 days of oseltamivir, or oseltamivir 75 mg twice daily without placebo for 5 days as controls. The primary end-point was 30-day mortality. The secondary end-points were 90-day mortality, serial nasopharyngeal aspirate virus titre, percentage of neuraminidase-inhibitor-resistant A(H3N2) virus (NIRV) quasispecies, pneumonia severity index, and duration of hospital stay.

Results: Among the 217 patients with influenza A (H3N2) enrolled, 107 were randomly assigned to the combination treatment. The median patient age was 80 years, and 53.5% were men. Adverse events were uncommon. Ten patients died during the 30-day follow-up. The combination treatment was associated with lower 30-day mortality (P=0.01), less frequent high-dependency unit admission (P=0.009), and shorter hospital stay (P<0.0001), as well as lower virus titre and pneumonia severity index at days 1-3 (P<0.01) and fewer nasopharyngeal aspirate specimens with NIRV quasispecies ≥5% at days 1-2 (P<0.01). Multivariate analysis showed that combination treatment was the only independent factor associated with lower 30-day mortality (odds ratio=0.06, 95% confidence interval=0.004-0.94, P=0.04).

Conclusions: Combination treatment reduced both 30- and 90-day mortality and length of hospital stay. Further study of the antiviral and immunomodulatory effects of this combination treatment for severe influenza is warranted.

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Long-term follow-up of combined influenza and 23-valent pneumococcal polysaccharide vaccine in the elderly subjects

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Background: Pneumococcal and influenza infections can cause severe morbidity and mortality in the elderly population. Dual vaccination with the 23-valent pneumococcal polysaccharide vaccine (PPV) and trivalent influenza vaccine (TIV) have been shown to reduce hospitalisation and death. Nevertheless, the long-term effect of dual vaccinations on these subjects remains unknown.

Methods: We followed up 36 636 elderly subjects aged ≥65 years previously recruited and reported in a prospective cohort study. Group 1 received both TIV and PPV; group 2 received TIV only; group 3 received PPV only; and group 4 received none. Demographics, subsequent hospitalisation, and outcome of the subjects were retrieved.

Results: Of 36 636 elderly subjects recruited in 2007 and followed up for 7 years, 7292 (19.9%) received both the PPV and TIV, 2076 (5.7%) received TIV alone, 1875 (5.1%) received PPV alone, and 25 393 (69.3%) were unvaccinated. By the end of the study, the median age of the recruited subjects was 75 (interquartile range, 70-80) years and 45.4% were male. Significantly fewer dual vaccinees died (hazard ratio [HR]=0.87, 95% confidence interval [CI]=0.83-0.92, P<0.001), developed cardiovascular events (HR=0.74, 95% CI=0.7-0.79, P<0.001), pneumonia (HR=0.74, 95% CI=0.69-0.79, P<0.05), or admitted to intensive care unit (HR=0.56, 95% CI=0.46-0.68, P<0.05), compared with the unvaccinated. Nevertheless, protection against mortality started to wane beyond 2 years of vaccination.

Conclusion: Dual PPV and TIV vaccination protected elderly subjects against complications, hospitalisation, and death. Both vaccines should be considered as part of the vaccination programme for the elderly by the health authority.

41 Unexpectedly higher morbidity and mortality of hospitalised elderly patients associated with rhinovirus compared with influenza virus respiratory tract infection

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Introduction: Rhinovirus is a common cause of upper and lower respiratory tract infections in adults, especially among the elderly and immunocompromised. Nevertheless, its clinical characteristics and mortality risks have not been well described.

Method: A retrospective analysis on a prospective cohort was conducted in a single teaching hospital over a 1-year period. We compared adult patients hospitalised for pneumonia caused by rhinovirus infection with those hospitalised for influenza virus infection during the same period. All recruited patients were followed up for 3 to 15 months. Independent risk factors associated with mortality for rhinovirus infection were identified.

Results: Between 1 March 2014 and 28 February 2015, 1946 patients were consecutively included for analysis. Of these, 728 patients were hospitalised for rhinovirus infection and 1218 patients were hospitalised for influenza virus infection. Significantly more rhinovirus patients were elderly home residents and had chronic lung diseases (P<0.001), whereas more influenza virus patients had previous stroke (P=0.02); otherwise, the two groups were comparable in terms of the Charlson comorbidity index. More patients in the rhinovirus group developed pneumonia complications (P=0.03), required oxygen therapy, and had a longer hospitalisation (P<0.001), whereas more patients in the influenza virus group presented with fever (P<0.001) and upper respiratory tract symptoms of cough and sore throat (P<0.001), and developed cardiovascular complications (P<0.001). The 30-day (P<0.05), 90-day (P<0.01), and 1-year (P<0.01) mortality was significantly higher in the rhinovirus group than the influenza virus group. Independent risk factors associated with 1-year mortality in patients hospitalised for rhinovirus infection were intensive care unit admission (odds ratio [OR]=9.56, 95% confidence interval [CI]=2.17-42.18), elderly home residents (OR=2.60, 95% CI=1.56-4.33), requirement of oxygen therapy during hospitalisation (OR=2.62, 95% CI=1.62-4.24), and haemoglobin level of <13.3 g/dL upon admission (OR=2.43, 95% CI=1.16-5.12).

Conclusion: Rhinovirus infection was associated with significantly higher mortality and longer hospitalisation when compared with influenza virus infection. Institutionalised older adults were particularly at risk. More stringent infection control among healthcare workers in elderly homes could lower the infection rate before an effective vaccine and antiviral become available.

42 Polyp burden in first-degree relatives of Chinese patients with familial colorectal cancer type X syndrome

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Background: Familial colorectal cancer type X (FCCTX) syndrome is a heterogeneous group of colorectal carcinomas (CRC) characterised by Amsterdam criteria but without mutations in the mismatch-repaired gene. Individual family member with FCCTX has an increased risk of CRC, but data on prevalence and characteristics of colonic polyps in this group of subjects are scarce.

Method: Eligible cases with their families were identified from the Hereditary Gastrointestinal Cancer Genetic Diagnosis Laboratory at The University of Hong Kong, which is a territory-wide registry for genetic diagnosis of suspected hereditary CRC. Those fulfilling the Amsterdam or Bethesda criteria but tested negative for mismatch-repaired gene were recruited. First-degree relatives were offered counselling and colonoscopy. Findings on their screening and surveillance colonoscopy were presented.

Results: We identified 71 first-degree relatives (31 were men) from 29 FCCTX families. Their mean age at screening was 52 ± 7.0 years. Nine (12.7%) subjects had metabolic diseases (diabetes mellitus, cardiovascular or cerebrovascular disease). At screening, 36 (50.7%) subjects were found to have colonic polyps, with a mean of 2.2 polyps and 1.4 adenomas per patient; 11 (15.5%) subjects had multiple polyps (≥3) and six (8.5%) had advanced adenoma. Of the 37 subjects who had surveillance colonoscopy after a mean interval of 3.6 ± 1.7 years, 19 (51.4%) were found to have polyps, with 14 (37.8%) having adenoma and 2 (5.4%) having advanced adenoma. Considering both colonoscopies together, 45 (63.3%) had polyps, 30 (42.3%) had adenoma, and 7 (9.9%) had advanced adenoma. Although no CRC was detected, there were four cases of extra-intestinal malignancy. Female gender was found to be associated with a lower risk of polyps (odds ratio [OR]=0.15, 95% confidence interval [CI]=0.04-0.52) and adenoma detected (OR=0.3, 95% CI=0.12-0.95). Polyp or adenoma detection was not associated with age, presence of metabolic diseases, or use of aspirin.

Conclusion: First-degree relatives of Chinese FCCTX family have a high prevalence of adenoma on both screening and surveillance colonoscopy. Strategies on screening and surveillance need to be tailored to these at-risk individuals.

Absolute impact of interventions to promote oral anticoagulation in patients with atrial fibrillation

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Background: Oral anticoagulants are commonly used in patients with atrial fibrillation (AF). The recently published IMPACT-AF trial suggests that multifaceted interventions can promote their appropriate use.[1] This prospective, international, cluster-randomised, controlled trial in AF patients compared the impact of on-going multifaceted educational interventions versus usual care for up to 1 year. Nonetheless, the value of such resource-intensive measures to achieve benefits must be gauged in absolute and relative terms.

Methods: From the published results of the IMPACT-AF trial that recruited 2281 patients, we calculated the 6-month and 1-year unadjusted, apparent odds ratio (OR), 95% confidence interval (CI), and absolute success rates (expressed as number needed to target to achieve one success) for promoting oral anticoagulant use in patients not using them at baseline. All calculations were based on previously developed algorithms to derive the relative risk and number needed to treat.[2]

Results: For the intervention group starting oral anticoagulants among those not taking them at baseline (380 intervention and 389 control patients), the OR (95% CI) and number (95% CI) needed to target were 2.4 (1.8-3.2) and 4.1 (3.2-5.5) after 6 months and 2.6 (2.0-3.5) and 3.4 (2.8-4.3) after 1 year, respectively.

Conclusions: The number needed to target after 1 year of ongoing educational intervention appear impressive, compared to the number needed to treat per year in many other drug intervention trials.[2] Decisions to deploy such resource-intensive measures must depend on local resource implications/priorities and locally expected hard end-point benefits from embolic event prevention and safety issues.

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The University of Hong Kong Neurocognitive Disorder Cohort: an ongoing observational study of Hong Kong Chinese with mild cognitive disorder

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Introduction: The University of Hong Kong Neurocognitive Disorder Cohort is a hospital-based, prospective, observational study of older Hong Kong Chinese adults with cognitive impairment, with a special focus on patients with subjective cognitive decline (SCD) and mild cognitive impairment (MCI). The cohort began in 2014 and is linked to the Dementias Platform UK (www.dementiasplatform.uk).

Methods: Comprehensive profiling of each subject was performed through a multi-domain assessment protocol including cognitive impairment status (SCD, MCI, dementia), Montreal Cognitive Assessment Hong Kong Version, Clinical Dementia Rating sum of squares, 15-item Geriatric Depression Scale, Neuropsychiatric Index, Barthel Index, Lawton Instrumental Activities of Daily Living Scale, Life-Space Assessment, Mini-Nutrition Assessment, Quality of Life for Alzheimer's Disease (patient and carer parts), frailty status, handgrip strength, walking speed, exercise status, sleep quality, and Charlson comorbidity index (age-adjusted). NACC UDS3 compatible: story recall, Benson's complex figure copy, colour trail test (black and white), verbal fluency, digit forward and backward span. Blood tests (serum, plasma, buffy coat (PBMC); also processed for microvesicles and exosome analysis). For selected patients: MRI (T1, T2, FLAIR, SWI, DTI, fMRI, ASL, MRS); and 128-channel EEG with ERP for Go/NoGo and Prospective Memory (PM) tasks. Annual follow-up for cognitive function and other patient-centred outcomes, and blood tests (stored for analyses). Our study's neuropsychological battery is also aligned with the US National Alzheimer's Coordinating Center UDS3 battery.

Results: So far, almost 300 patients have been recruited into this ongoing cohort.

Conclusion: This ongoing cohort will provide essential new data on SCD and MCI in Asia. It is the first-ever Asian dementia cohort to be formally linked with the Dementias Platform UK, achieving an international collaborative status with other UK-based cohorts (n>0.5 M).

Exosomal microRNA-486-3p mediates acquired resistance to anaplastic lymphoma kinase inhibitor in EML4-ALK translocated lung adenocarcinoma.

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Introduction: Cancer cells could release exosomes to modulate the activities of other cells in the tumour microenvironment or at distant metastatic sites. The microRNAs (miRNAs) in cancer-derived exosomes may modulate drug resistance in recipient cells. Anaplastic lymphoma kinase (ALK) gene rearrangement is one therapeutic target in lung adenocarcinoma that indicates response to treatment with ALK-tyrosine kinase inhibitors (ALK-TKI). The role of intratumoural heterogeneity in drug resistance remains elusive.

Method: We have established ALK-translocated lung adenocarcinoma cell lines and subclones. Expressions of miRNAs were detected by quantitative real-time polymerase chain reaction. Cell viability was determined by MTT assay.

Results: The exosomes from ALK-TKI-resistant subpopulation of lung cancer cells could reduce drug sensitivity in originally sensitive subpopulations. Circulating exosomal miR-486-3p was found to be correlated with disease progression of EML4-ALK-translocated lung adenocarcinoma patient on ALK-TKI treatment.

Conclusion: Exosomes released by drug-resistant subpopulation could induce resistance of other subpopulation of cells. Exosomal miRNA may serve as a novel therapeutic strategy and circulating prognostic marker for ALK-translocated lung cancer.

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Treatment modulation of transcriptional profiles in lupus nephritic patients

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Introduction: Systemic lupus erythematosus (SLE) is a complex autoimmune disease affecting multiple organ systems. The pathogenesis of SLE is heterogeneous with diverse clinical manifestations that often lead to poor prognosis and pose a major challenge in the treatment of SLE. Most SLE patients develop lupus nephritis (LN), which is a major cause of end-stage organ failure in lupus patients. Currently, overall SLE activity is assessed by routine testing of serum levels of complement C3 and C4, creatinine, and anti-dsDNA autoantibodies, whereas renal involvement is assessed by the urinary protein level, urinary sediment analysis, and creatinine clearance. These markers and tests aid diagnosis but lack the sensitivity and specificity for predicting LN flare and progression. Histological examination of renal biopsies is more reliable and remains as the standard test in LN diagnosis and classification. However, it is impractical to perform frequent invasive procedures. A reliable and less-invasive method for predicting and monitoring LN flare is needed. With the high-throughput sequencing technology, the study of blood transcriptomics can identify transcriptional signature of active LN patients, which may be translated into clinically useful molecular biomarkers. The aim of this pilot study is to determine the differential transcriptional profiles of LN patients pre-treatment versus post-treatment.

Methods: Whole blood was collected from nine SLE patients experiencing renal flare with biopsy-confirmed LN within 7 days before or after the scheduled biopsy. Blood samples were obtained again after 1-month treatment. Total RNA was extracted and sequenced using the Illumina HiSeq1500. Reads were mapped to the reference genome using STAR software and differential expression was determined using EBSeq software. Differential gene expression was further analysed by hierarchical clustering, Gene Ontogeny, and STRING analyses.

Results: A differential transcriptome expression pattern was observed in LN patients post-treatment compared to that of pre-treatment. A cluster of transcripts mainly involved in interferon signalling was downregulated after treatment while a panel of transcripts involved in antigen processing were upregulated.

Conclusion: The transcripts involved in interferon signalling and antigen presentation could be potential biomarkers for monitoring LN.

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Endogenous arginase 2 as a biomarker for PEGylated arginase 1 treatment in squamous cell lung carcinoma xenograft models

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Background: Arginine depletion induced by PEGylated arginase 1 (BCT-100) has shown encouraging anticancer effects among arginine auxotrophic cancers which lack argininosuccinate synthetase (ASS1) and ornithine transcarbamylase (OTC). High endogenous arginase 2 (ARG2) was previously reported in human lung cancers. Although high ARG2 level does not cause immunosuppression nor affect disease progression, it may affect the efficacy of PEGylated arginase 1 therapy. ARG2 was highly expressed in H520 lung squamous cell carcinoma (SCC) xenograft while undetectable in SK-MES-1 lung SCC xenograft. We proposed that high endogenous ARG2 expression might impede anti-tumour effect of PEGylated arginase 1 in lung SCC.

Methods: The in vivo effect of PEGylated arginase 1 was investigated using two lung SCC xenograft models (SK-MES-1 and H520). Protein expression, apoptosis, and arginine concentration were investigated by western blot, terminal deoxynucleotidyl transferase dUTP nick end labelling assay, and enzyme-linked immunosorbent assay, respectively.

Results: PEGylated arginase 1 (60 mg/kg) decreased rate of tumour growth in SK-MES-1 but not in H520 xenograft. ASS1 was highly expressed in SK-MES-1 xenograft while OTC expression remained low in both xenografts. Serum arginine level was declined significantly by PEGylated arginase 1 in both xenograft models. Intratumoural arginine level was decreased by PEGylated arginase 1 in SK-MES-1 xenograft only. In H520 xenograft, intratumoural arginine level in control group was already very low that could not be further reduced in PEGylated arginase 1 treatment arms. G1 arrest was indirectly demonstrated by suppression of cyclin A2, B1, D3, E1, and CDK4 with PEGylated arginase 1 in SK-MES-1 xenograft only. Moreover, downregulation of proliferation factor Ki67 and activation of apoptosis were observed in SK-MES-1 xenograft by PEGylated arginase 1 treatment only.

Conclusion: PEGylated arginase 1 treatment (BCT-100) was effective in lung SCC xenograft with low endogenous ARG2 level. High endogenous ARG2 expression may induce low intratumoural arginine level in lung SCC xenograft. ARG2 may serve as the third predictive biomarker, other than ASS1 and OTC, in PEGylated arginase 1 treatment in lung SCC.

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Clinical correlates, ethnic differences, and prognostic implications of perivascular spaces in transient ischaemic attack and ischaemic stroke

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Introduction: Perivascular space (PVS) is considered markers of small vessel disease. Their long-term prognostic implications in transient ischaemic attack (TIA)/ischaemic stroke patients are unknown. Ethnic differences in PVS prevalence are also unknown.

Methods: Two independent prospective studies were conducted: one comprising predominantly Caucasians with TIA/ischaemic stroke (Oxford Vascular Study) and another comprising predominantly Chinese with ischaemic stroke (University of Hong Kong study). Clinical and imaging correlates, prognostic implications for stroke and death, and ethnic differences in basal ganglia (BG) and centrum semi-ovale (CS) PVSs were studied with adjustment for age, sex, vascular risk factors, and scanner strength.

Results: Compared with Chinese (n=974), Caucasians with TIA/ischaemic stroke (n=1028) had a higher prevalence of both BG-PVS (>20: 22.4% vs 7.1%, P<0.0001) and CS-PVS (>20: 45.8% vs 10.4%, P<0.0001). Both >20 BG-PVS and >20 CS-PVS were associated with increasing age and white matter hyperintensity, although associations with BG-PVS were stronger (all P<0.0001). During 6924 patient-years follow-up, BG-PVS was independently associated with an increased risk of recurrent ischaemic stroke (<11 and 11-20: adjusted hazard ratio [HR]=1.15, 95% confidence interval [CI]=0.78-1.68, >20: adjusted HR=1.82, 95% CI=1.18-2.80; P_{trend}=0.011) but not intracerebral haemorrhage (P_{trend}=0.10) or all-cause mortality (P_{trend}=0.16). CS-PVS was not associated with recurrent stroke (P_{trend}=0.57) or mortality (P_{trend}=0.072). Prognostic associations were similar in both cohorts.

Conclusion: Over and above ethnic differences in frequency of PVSs in TIA/ischaemic stroke patients, BG-PVS and CS-PVS had similar risk factors, but whilst >20 BG-PVS was associated with an increased risk of recurrent ischaemic stroke, CS-PVS was not.

Long-term prognostic implications of cerebral microbleeds in Chinese with ischaemic stroke

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Introduction: To determine the clinical correlates and long-term prognostic implications of microbleed-burden and location in Chinese with ischaemic stroke.

Methods: We recruited 1003 predominantly Chinese patients with ischaemic stroke who underwent magnetic resonance imaging at The University of Hong Kong. We determined the clinical correlates of microbleeds and the long-term risks (3126 patient-years follow-up) of recurrent ischaemic stroke and intracerebral haemorrhage (ICH) by microbleed-burden (0 vs 1, 2-4, and ≥5) and location, adjusting for age, sex, and vascular risk factors and stratified by antithrombotic-use.

Results: Microbleeds were present in 450/1003 of the study population (119/450 had ≥5, 187/450 were of mixed-location). ≥5 microbleeds was independently associated with prior antiplatelet and anticoagulant-use, whereas microbleeds of mixed-location was independently associated with hypertension and prior anticoagulant-use (all P<0.05). Microbleed-burden was associated with an increased risk of ICH when compared with 0 microbleed (1 microbleed: hazard ratio [HR]=0.59, 95% confidence interval [CI]=0.07-5.05, 2-4 microbleeds: HR=2.14, 95% CI=0.50-9.12, ≥5 microbleeds: HR=9.51, 95% CI=3.25-27.81; P_{trend}<0.0001), but the relationships of microbleed-burden and risk of recurrent ischaemic stroke was not significant (P_{trend}=0.054). Similar findings were noted in the 862/1003 patients treated with antiplatelet agents only (ICH: P_{trend}<0.0001; ischaemic stroke: P_{trend}=0.096). Multivariate analysis revealed that independent of vascular risk factors, anti-thrombotic use, and other neuroimaging markers of small vessel disease, ≥5 microbleeds (HR=6.08, 95% CI=1.11-33.21, P=0.037) was an independent predictor of a subsequent ICH, but neither microbleed location nor burden were predictive of recurrent ischaemic stroke risk.

Conclusions: In Chinese with ischaemic stroke, a high-burden of cerebral microbleeds is significantly associated with an increased risk of ICH. However, neither microbleed location nor burden were associated with recurrent ischaemic stroke risk.

Total small vessel disease score and risk of recurrent stroke: validation in two large cohorts

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Introduction: In patients with transient ischaemic attack (TIA) and ischaemic stroke, we validated the total small vessel disease (SVD) score by determining its prognostic value for recurrent stroke.

Methods: Two independent prospective studies were conducted: one comprising predominantly Caucasians with TIA/ischaemic stroke (Oxford Vascular Study) and another comprising predominantly Chinese with ischaemic stroke (University of Hong Kong study). Cerebral magnetic resonance imaging was performed and assessed for lacunes, microbleeds, white matter hyperintensity, and perivascular spaces (PVSs). Predictive value of total SVD score for the risk of recurrent stroke was determined and potential refinements considered.

Results: In 2002 patients with TIA/ischaemic stroke (1028 in Oxford Vascular Study and 974 in University of Hong Kong study) with 6924 patient-years follow-up, a higher total SVD score was associated with an increased risk of recurrent ischaemic stroke (adjusted hazard ratio [HR] per unit increase=1.32, 95% confidence interval [CI]=1.16-1.51, P<0.0001; c-statistic=0.61, 95% CI=0.56-0.65, P<0.0001) and intracerebral haemorrhage (adjusted HR=1.54, 95% CI=1.11-2.13, P=0.009; c-statistic=0.65, 95% CI=0.54-0.76, P=0.006). A higher total SVD score predicted recurrent stroke in SVD (c-statistic=0.67, 95% CI=0.59-0.74, P<0.0001) and non-SVD TIA/ischaemic stroke (c-statistic=0.60, 95% CI=0.55-0.65, P<0.0001) subtypes. Including burden of microbleeds and white matter hyperintensity and adjusting the cut-off of basal ganglia PVSs potentially improved predictive power for intracerebral haemorrhage (c-statistic=0.71, 95% CI=0.60-0.81, P_{het}=0.45), but not for recurrent ischaemic stroke (c-statistic=0.60, 95% CI=0.56-0.65, P_{het}=0.76) on internal validation.

Conclusion: The total SVD score has predictive value for recurrent stroke after TIA/ischaemic stroke. Prediction of recurrence in patients with non-lacunar events highlights the potential role of SVD in wider stroke aetiology.

51 Non-invasive non-alcoholic fatty liver disease scores and cardiovascular diseases in the United States National Health and Nutrition Examination Survey 1999-2014

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Introduction: Non-alcoholic fatty liver disease (NAFLD) is highly prevalent in the general population. It is important to identify potential complications. We analysed the association of NAFLD with cardiovascular diseases in a large well-characterised population.

Method: 11 427 non-pregnant adult participants from the United States National Health and Nutrition Examination Survey 1999-2014 without viral hepatitis, prescription of anti-diabetic medications including insulin, and missing data in key variables were studied using the SPSS module for complex samples. Logistic regression was used to examine associations of four non-invasive NAFLD scores, fatty liver index, NAFLD liver fat score, hepatic steatosis index, and lipid accumulation product with cardiovascular disease outcome of coronary heart disease, myocardial infarction (MI), heart failure (HF), and stroke.

Results: The liver fat score was associated with increased risk of coronary heart disease (odds ratio [OR]=1.26 per standard deviation adjusted for age, gender, ethnicity, and high-density lipoprotein level, 95% confidence interval [CI]=1.14-1.39), MI (adjusted OR=1.20, 95% CI=1.11-1.31), and HF (adjusted OR=1.19, 95% CI=1.03-1.37), with the area under the curve (AUC) being 0.595, 0.592, and 0.590, respectively (P<0.0001). The fatty liver index was associated with increased risk of MI (adjusted OR=1.01, 95% CI=1.00-1.02) and HF (adjusted OR=1.01, 95% CI=1.01-1.02), with the AUC being 0.594 (P=0.013) and 0.616 (P<0.0001), respectively. The hepatic steatosis index was associated with increased risk of HF (adjusted OR=1.03, 95% CI=1.00-1.05). Lipid accumulation product was associated with increased risk of MI (adjusted OR=1.03, 95% CI=1.00-1.07). None of the NAFLD scores was associated with stroke.

Conclusion: There was a weak association of NAFLD with coronary heart disease, MI, and HF. Despite its high prevalence, NAFLD is generally benign with a slightly increased risk for cardiovascular diseases.

52 Clinicopathologic features, mutation spectrum, and clinical outcome of complex/monosomy karyotype acute myeloid leukaemia in young adult patients in Hong Kong

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Objectives: Acute myeloid leukaemia (AML) with complex/monosomal karyotype (CK/MK) is associated with poor clinical outcome. This study examined the clinicopathologic features, mutation spectrum, and clinical outcome of young adult patients with CK/MK AML treated with a uniform protocol in Hong Kong.

Methods: Young adult patients (18-60 years old) with CK/MK AML treated in seven regional hospitals in Hong Kong, from January 2003 to July 2016, were analysed retrospectively. CK AML was defined as those with ≥3 clonal abnormalities, whereas MK AML was defined as those with ≥2 autosomal monosomies or single autosomal monosomy and at least one structural abnormality. Treatment comprised induction (7+3 regimen or equivalent) and consolidation (high-dose cytarabine). Relapsed or refractory patients received salvage chemotherapy. All patients who achieved complete remission (CR) were referred to allogeneic haematopoietic stem cell transplantation (HSCT). Mutation spectra of their diagnostic bone marrow samples were analysed by MiSeq next-generation sequencing with the TruSight Myeloid sequencing panel targeting 54 genes covering full coding sequence of 15 genes and exonic hot spot for 39 genes. Leukaemia-free survival (LFS) and overall survival (OS) were evaluated by Kaplan-Meier curves and compared by log-rank test. Cox proportional hazard model was used in univariate and multivariate analyses.

Results: In 76 patients (41 men and 35 women) with CK/MK AML, 116 genetic mutations were found (median, 2; range, 1-7 mutations per patient). Five patients died before induction and two refused treatment. Of the 69 patients who received induction chemotherapy, CR was achieved in 48 (70%) after one (n=33) or two (n=15) courses. After 1, 2, and 5 years, the LFS was 41%, 26%, and 18% and the OS was 49%, 20%, and 12%, respectively. In univariate analysis, HSCT at CR1 was significantly associated with longer LFS (hazard ratio [HR]=6.1, 95% confidence interval [CI]=2.4-15.7, P<0.001). Longer OS was significantly associated with achievement of CR1 (HR=8.3, 95% CI=4.4-15.8, P<0.001), absence of -17/17p- (HR=3.2, 95% CI=1.7-3.2, P<0.001), and HSCT at CR1 (HR=5.7, 95% CI=2.4-13.5, P<0.001). TP53 mutations, number of karyotypic abnormalities and mutations were not predictive of CR, LFS, or OS. In multivariate analysis, superior OS was associated with achievement of CR1 (HR=4.3, 95% CI=2.2-8.2, P<0.001), absence of -17/17p- (HR=3.0, 95% CI=1.5-5.9, P=0.002) and HSCT at CR1 (HR=5.8, 95% CI=2.4-13.7, P<0.001).

Conclusion: Karyotypic abnormalities particularly the presence of -17/17p-, the achievement of initial remission upon induction, and timely HSCT are important factors associated with disease control and survival in CK/MK AML.

Combination of omacetaxine mepesuccinate (homoharringtonine) and sorafenib as an effective regimen for acute myeloid leukaemia carrying FLT3-ITD

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Objectives: Acute myeloid leukaemia (AML) with FMS-like tyrosine kinase-3 (FLT3) internal tandem duplication (FLT3-ITD) is associated with poor prognosis. In-vitro drug screening and laboratory mechanistic studies have identified omacetaxine mepesuccinate (OME) also known as homoharringtonine as an effective agent that demonstrated synergism with FLT3 inhibitors in this AML subtype. We report the clinical outcome of the first 40 FLT3-ITD AML patients treated with sorafenib and OME combination (SOME).

Methods: Patients with relapsed or refractory FLT3-ITD AML were recruited and treated with sorafenib (200-400 mg twice a day continuously) and OME (2 mg daily for 7 [first course] or 5 days [second course onwards] every 21 days) until disease progression or allogeneic haematopoietic stem cell transplantation (HSCT). Partial remission was defined as marrow or circulating blasts ≤50% of the pre-treatment state. Leukaemia-free survival (LFS) and overall survival (OS) were evaluated by Kaplan-Meier analysis and compared by log-rank test. Fisher's Exact test was used to compare nominal variables. Cox proportional hazard model was used in the univariate and multivariate analyses.

Results: Of 39 patients (16 men, 23 women) recruited between June 2013 and July 2017, 29 (74%) achieved complete remission (CR)/CRi (CR with incomplete blood count recovery), two patients showed partial remission and eight patients (of whom five have had exposure to FLT3 inhibitors) showed no response. The median LFS of the 29 patients who achieved CR/CRi was 5.5 months. Prior exposure to FLT3 inhibitors (P=0.007) and more than one induction chemotherapy before SOME (P<0.001) were associated with a lower rate of CR/CRi. Non-haematological toxicities were minimal and limited to hand-foot-skin reaction and rash associated with sorafenib. Univariate analysis showed that better LFS was associated with early treatment (≤10 months from diagnosis) with SOME (hazard ratio [HR]=4.3, 95% confidence interval [CI]=1.2-15.3, P=0.024) and HSCT after SOME-induced remission (HR=6.0, 95% CI=1.7-21.5, P=0.006). Superior OS was associated with achievement of CR/CRi after SOME (HR=4.2, 95% CI=1.4-12.1, P=0.009), <2 prior induction chemotherapy regimens (HR=3.7, 95% CI=1.3-10.2, P=0.013), early treatment with SOME (HR=3.0, 95% CI=1.2-7.8, P=0.024), and HSCT (HR=6.5, 95% CI=1.5-29.0, P=0.014). In multivariate analysis, HSCT was the only parameter associated with a better LFS (HR=5.2, 95% CI=1.4-19.4, P=0.015) and OS (HR=6.0, 95% CI=1.3-27.4, P=0.022).

Conclusion: SOME is an effective and safe regimen for relapsed or refractory FLT3-ITD AML. The molecular features predictive of treatment response as well as the emergence of tyrosine kinase domain mutations at relapse are being evaluated.

Predictors of vascular events and disease transformation in Chinese patients with myeloproliferative neoplasms during long-term follow-up

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Introduction: Myeloproliferative neoplasms (MPN) are a group of heterogeneous clonal haematopoietic disorders that comprise polycythaemia vera (PV), essential thrombocythaemia (ET), and primary myelofibrosis (MF). There is an increased risk of haemorrhage, thrombosis, cardiovascular event, and transformation to MF or acute leukaemia. This study aims to review the clinicopathological characteristics and outcome, and prognostic indicators in a large Chinese cohort of patients with MPN.

Methods: Patients with the diagnosis of PV, ET, primary MF, and MPN-unclassifiable were recruited from 2012 to 2016 in a tertiary referral centre in Hong Kong. Retrospective data from the date of diagnosis were retrieved from clinical records and reviewed by independent investigators. Progression-free survival (PFS) was defined as the duration from diagnosis to transformation to MF, acute leukaemia, or death. Overall survival (OS) was defined as the duration from diagnosis to death or last follow-up. PFS and OS were evaluated by Kaplan-Meier analysis and were compared by log-rank test. Univariate and multivariate analyses were performed with the Cox proportional hazard model.

Results: In 285 patients (142 men, 143 women) included, PV, ET, primary MF, and MPN-U accounted for 22%, 60%, 10%, and 8%, respectively. Cytogenetic information at diagnosis was available in 136 (47.7%) of patients, of which 113 (83%) had normal karyotypes. Among 230 molecularly annotated patients, 162 (70%) harboured JAK2 V617F mutation. In 28 JAK2 V617F negative patients, 14 (50%) and 1 (4%) had CALR and JAK2 exon 12 mutations, respectively. 13 patients were triple negative for JAK2, CALR, and MPL mutations. Of all patients, treatment included aspirin prophylaxis (92%, n=263), hydroxyurea (92%, n=261), pegylated interferon (10.5%, n=30), and ruxolitinib (6.3%, n=18). Cardiovascular events were observed in 45 (16%) of patients. Significant risk factors associated with cardiovascular events were age >50 years (P=0.002) and hypertension (P=0.038). Progression to MF was observed in 11 (17%) of PV patients and 21 (12%) of ET patients. Leukaemic transformation occurred in nine (3%) patients (ET, n=3; primary MF, n=1; secondary MF, n=5) at a median follow-up of 10.4 (range, 1.0-22.6) years. Age >60 years and presence of splenomegaly at diagnosis were associated with inferior PFS; and age >60 years was associated with inferior OS in PV/ET patients. Based on these clinical criteria, PV/ET patients were divided into three groups: age >60 years with splenomegaly (n=8), age ≤60 years without splenomegaly (n=83), and others (n=97). The corresponding median PFS were 12.9, 25.5, and 17.4 years; whereas the corresponding median OS were 15.5, 15.2, and 27.2 years. In univariate analysis, age >60 years and splenomegaly remained significant risk factors for inferior PFS. In multivariate analysis, splenomegaly was the only significant risk factor for inferior PFS.

Conclusion: Age >50 years and hypertension were associated with increased risk of cardiovascular events in MPN patients. Age >60 years and splenomegaly at presentation were risk factors for disease transformation in those with PV/ET.

25-Hydroxyvitamin D and the risk of incident diabetes in Hong Kong Chinese

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Introduction: We previously showed significant association between serum calcium and incident diabetes.[1] Nonetheless, the role of vitamin D in the association remains unclear. This study aimed to evaluate the relationship between serum 25-hydroxyvitamin D level and the risk of incident diabetes in Hong Kong Chinese.

Method: This retrospective cohort study included 4342 participants (1395 men and 2947 women) with a mean age of 54.3 ± 16.5 years from the Hong Kong Osteoporosis Study, who were free of diabetes at baseline. Incident diabetes was ascertained using electronic medical records. Serum 25-hydroxyvitamin D level was measured at baseline, and its association with incident diabetes was evaluated using multivariable Cox-proportional hazard regression.

Results: During 43 238.3 (median, 10.3) person-years of follow-up, 443 participants developed diabetes. The mean serum 25-hydroxyvitamin D level was 54.3 ± 16.5 nmol/L. In age, sex, and body mass index–adjusted Cox-proportional hazard regression, there was no significant difference in hazard ratios between the lower quintiles and the highest quintile of serum 25-hydroxyvitamin D level. Further adjustments with mineral variables, lifestyle factors, and other biomarkers for vitamin D did not alter the finding. In the analysis of the interaction effect between serum 25-hydroxyvitamin D level and serum calcium, the interaction term did not affect the risk of incident diabetes significantly (P=0.700).

Conclusion: Serum 25-hydroxyvitamin D level was not associated with the risk of incident diabetes in Hong Kong Chinese and this relationship was not modified by the serum calcium level.

Reference

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Adiponectin antagonises dietary-induced metabolic diseases via modulation of gut microbiota

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Introduction: The global prevalence of diabetes mellitus dramatically escalates in modern society. Altered gut microbiota has been identified in type-2 diabetic patients. Furthermore, animal studies have also demonstrated that gut microbial species can alleviate body weight and insulin resistance in obese mice. Whether the improvement of insulin sensitivity is due to the direct modulatory effect of gut microbiota or the secondary effect of body weight loss remains unknown. Adiponectin secreted by adipose tissue plays an essential role in regulating blood glucose level and insulin sensitivity. Adiponectin-deficient mice fed on high-fat diet (HFD) have been reported to develop severe insulin resistance without affecting body weight. Whether the anti-diabetic effect of adiponectin is partially mediated by gut microbiota needs to be investigated.

Methods: Both adiponectin-deficient mice and wild-type mice were fed on either normal chow diet or HFD for 12 weeks. Glucose tolerance test and insulin tolerance test were performed to evaluate insulin sensitivity. Faeces from the above four groups were transplanted into wild-type mice fed on HFD for 8 weeks.

Results: Adiponectin knockout mice fed on HFD displayed severe insulin resistance compared to wild-type mice fed on HFD, but there was no significant difference in body weight. Interestingly, recipients receiving faeces from adiponectin-deficient mice fed on HFD showed a decreased insulin sensitivity compared to mice receiving faeces from wild-type mice fed on HFD, suggesting gut microbiota itself is sufficient to regulate insulin sensitivity. Furthermore, microbiota from adiponectin-deficient mice fed on HFD led to decreased expression of intestinal tight junctions, leading to the impairment of gut barrier. The increased gut permeability enhanced the circulating endotoxin level, consequently increasing adipose tissue inflammation and insulin resistance.

Conclusion: Gut microbiota in adiponectin-deficient mice fed on HFD is sufficient to modulate insulin sensitivity. The anti-diabetic effect of adiponectin is partially mediated by modulating gut microbiota, suggesting the beneficial role of adiponectin may be achieved by mediating the crosstalk between adipose tissue and intestinal system.

Outcome associated with parainfluenza virus infection in hospitalised adults

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Background: Parainfluenza virus is a common cause of upper respiratory tract infections in adults. Nevertheless, its clinical characteristics and risk factors associated with mortality have not been well described.

Methods: A retrospective analysis on a prospective cohort was conducted in a single centre in Hong Kong. We compared adult patients hospitalised for parainfluenza virus infection with those hospitalised for influenza infection during the same period. All recruited patients were followed up for 1 year. Independent risk factors associated with mortality for parainfluenza virus infection were identified.

Results: Between 1 March 2014 and 28 February 2015, 1339 patients were recruited. Of these, 230 were hospitalised for parainfluenza virus infection and 1109 were hospitalised for influenza infection. Significantly more patients in the parainfluenza group were elderly home residents (P=0.003) and had a medical history of cardiovascular diseases (P<0.001) and stroke (P=0.04). Patients in the parainfluenza virus group had significantly longer period from symptom onset to hospital admission (P<0.001) and more symptoms of sputum production (P=0.03) and chest wheeziness (P<0.001) and required oxygen support upon admission (P<0.001). Significantly more patients in the parainfluenza group developed secondary pneumonia, cardiovascular complication, and sepsis (all P<0.001). Both the hospitalisation days and frequency of admission were higher in the parainfluenza group (P<0.001).The 1-year mortality rate was significantly higher in the parainfluenza than the influenza group (P<0.001). Cardiovascular complication (odds ratio [OR]=1.8, 95% confidence interval [CI]=1.01-3.20), invasive ventilation (OR=12.7, 95% CI=2.63-61.50), and abnormal lymphocyte count upon admission (OR=9.22, 95% CI=1.88-45.27) were independent risk factors associated with 1-year mortality in patients hospitalised for parainfluenza virus infection.

Conclusion: Parainfluenza virus infection in the adults was associated with significantly higher mortality and longer hospitalisation when compared with influenza virus infection. Patients with underlying cardiovascular diseases were particularly at risk. An effective vaccine and antiviral is needed.

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Assessment of sympathetic skin response for the diagnosis of post-stroke complex regional pain syndrome

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Introduction: To investigate whether absolute amplitude differences in sympathetic skin responses (SSR) and ratio of SSR amplitudes between hemiplegic and normal sides can help with the diagnosis of type-I complex regional pain syndrome (CRPS) after stroke.

Methods: We included 51 hemiplegic patients (13 with CRPS, 38 without CRPS) undergoing stroke rehabilitation, and 27 healthy age- and sex-matched controls. CRPS was diagnosed according to the Budapest Clinical Diagnostic Criteria proposed by the International Association for the Study of Pain. SSR were measured in both hands by a standardised method of stimulating the median nerve. We compared the ratio of SSR amplitudes between hemiplegic and normal sides for the hemiplegic patients, and the maximum ratio of SSR amplitudes between left and right hands for the healthy controls, using non-parametric tests.

Results: Baseline characteristics including age, sex, side of hemiplegia, and types of strokes were similar among groups. The mean SSR amplitudes of hemiplegic patients with CRPS, hemiplegic patients without CRPS, and healthy controls were not significantly different. However, the ratio of SSR amplitudes of hemiplegic to normal sides in hemiplegic patients with CRPS was significantly higher than that in hemiplegic patients without CRPS (P<0.001), and the maximum ratio of SSR amplitude in healthy controls (P<0.001). Receiver operating characteristic analysis revealed an optimal cutoff ratio of 1.8, with associated sensitivity of 92% and specificity of 74%.

Conclusion: The ratio of SSR amplitude between the hemiplegic and normal sides, rather than the absolute amplitude differences in SSR, may help with the diagnosis of post-stroke type-I CRPS.

Reduced expression of synaptic protein synaptogyrin 3 in striatum of LRRK2^{R1441G} knockin mice and its functional implication to dopamine uptake under Nurr1 regulation

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Introduction: Striatal presynaptic dysfunction perturbs dopamine (DA) turnover and causes nigrostriatal neurodegeneration in Parkinson's disease. Striatal synaptosomes from our LRRK2^{R1441G} knockin mice were more susceptible to DA depletion and locomotor deficits induced by reserpine and rotenone. We explored the functional role of a synaptic vesicle protein, synaptic protein synaptogyrin 3 (SYNGR3), and its expression under Nurr1 regulation.

Methods: The mRNA and protein expression level of SYNGR3 were measured by real-time polymerase chain reaction array and western blotting, respectively. Co-localisation and interaction between SYNGR3 and DA transporter in mouse striatum were determined by confocal microscopy, transmission electron microscopy, and immunoprecipitation. The functional role of SYNGR3 on DA uptake was determined by [^{3}H]-DA uptake assay in human SH-SY5Y neuroblastoma cells. SYNGR3 gene promoter activities were measured by luciferase reporter assays.

Results: Total SYNGR3 mRNA in FACS-sorted nigral DA neurons and its protein level in striatum were reduced in LRRK2^{R1441G} knockin mice. SYNGR3 co-localised with DA transporter in striatal synaptic terminal and bound to DA transporter as shown by immunoprecipitation. Overexpressing SYNGR3 in dopaminergic SH-SY5Y cells increased cellular DA uptake. Gene promoter studies of human SYNGR3 gene revealed a core promoter element specific to most TATA-less gene promoters, XCPE1, which is critical for SYNGR3 gene transcription. Moreover, three putative NBRE-binding sites were identified in 5′ flanking region of SYNGR3 gene, which specifically bound to Nurr1 as shown by gel-shift assays. Treatment of Nurr1 transactivator, C-DIM12, in SH-SY5Y cells significantly increased total cellular SYNGR3 level.

Conclusion: SYNGR3 facilitates cellular DA uptake via interaction with DA transporter. Reduced SYNGR3 expression may be a reason of higher susceptibility to synaptic dysfunction in LRRK2^{R1441G} knockin mice. Inducing SYNGR3 expression by Nurr1 transactivators may be a novel therapeutic strategy to attenuate synaptic dysfunction in Parkinson's disease.

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De-mything of vaccine allergies: data from two large allergy tertiary referral centres

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Introduction: Vaccinations are safe and allergic reactions are extremely rare. Only approximately one case of anaphylaxis or anaphylactoid reaction per vaccine doses have been reported (with no fatalities). Poor understanding of side-effects and common misconceptions lead to misdiagnosis of allergy.

Method: We reviewed the reasons for referral, vaccines, index reactions/symptoms, and outcomes of allergy testing of all patients referred to two large tertiary referral centres between 2007 and 2016.

Results: Overall, 95 patients, receiving 103 doses of vaccines, were reviewed. Twenty patients with suspected egg allergy were referred: seven (35%) were proven to be non-allergic after allergy testing, and four (20%) of these were incorrectly referred for mumps and rubella vaccinations. Nine patients were referred because of incorrect advice to avoid all immunisations after a reaction to one vaccine only. Four and two patients with suspected delayed hypersensitivity to gentamicin and latex were also inappropriately referred. No allergic reaction occurred during supervised vaccine administration and all 95 patients were vaccinated successfully.

Conclusion: Vaccinations are safe and allergic reactions are vanishingly rare. Our results should reassure physicians that most (if not all) patients with suspected vaccine allergy can be vaccinated successfully. Most immunisations could be performed in primary care, even for egg allergic patients. Physicians should encourage vaccinations. Allergists can facilitate vaccinations in the minority of patients with confirmed allergy to vaccine/vaccine components.

Importance of excipient testing in steroid allergy

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Introduction: Allergy to corticosteroid (CS) has been increasingly reported. Nonetheless, true allergy is rare and likely over-reported; many patients may be allergic to excipients instead. This leads to unnecessary avoidance or dangerous re-exposure.

Method: Patients with a confirmed diagnosis of allergy (positive skin prick test or drug provocation test [DPT]) or tolerance (negative DPT) to CS over the past 10 years at two large allergy tertiary referral centres were studied. Patient characteristics, route of administration, clinical indications, symptoms of index reaction, and outcomes of allergy testing were analysed. Use of carmellose eye drops was also investigated as a novel source of carboxymethyl cellulose for skin prick testing.

Results: A total of 64 patients underwent allergy testing for suspected type I CS hypersensitivity. True allergy to CS was confirmed in nine (14%) patients. Of whom, five (56%) with positive skin prick test or DPT were actually allergic to excipients (two to carboxymethyl cellulose and three to polyethylene glycol) rather than CS. Multivariate analysis showed respiratory manifestations were significantly associated with confirmed allergy (odds ratio=6.79, 95% confidence interval=1.36-34.03, P=0.02).

Conclusion: We report the largest cohort of patients with suspected type I allergy to CS undergoing allergy testing. Patients who experienced respiratory manifestations were significantly more likely to be truly allergic. True allergy to CS was rare and most confirmed cases were actually allergic to excipients. We highlight the importance of excipient testing and suggest carmellose eye drops as a novel source of carboxymethyl cellulose for testing.

Over-diagnosis of beta-lactam allergy and performance of skin testing in Hong Kong and United Kingdom

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Introduction: Beta-lactams (BL) are the most widely used class of antibiotics and also the most frequently reported drug allergy. Vast majority of BL allergy labels are incorrect after formal allergy evaluation. Despite severe entailing consequences, the limitations in capacity and costs (as well as availability of allergists) remain a significant barrier to comprehensive testing.

Method: We reviewed the clinical characteristics, skin test results, and drug provocation outcomes in a large cohort of patients who underwent BL allergy evaluations in tertiary allergy referral centres in Hong Kong and United Kingdom. Potential cost savings after optimising test reagents was also investigated.

Results: Out of 1122 patients, only 125 (11%) of patients were diagnosed with genuine BL allergy. Using benzylpenicillin polylysine (PPL) + minor determinant mixture (MDM) + benzylpenicillin (BP) + amoxicillin ± index BL for skin testing had a negative predictive value of 96.6%. Omission of PPL and MDM reduced this to 95.9%. In the United Kingdom, the cost of detecting one extra patient who tested positive to PPL and/or MDM was equivalent to 3.5 additional provocation tests. Clinically, absence in the history of anaphylaxis to BL, known index culprit drug, and a reaction of >1 year duration had a negative predictive value of 98.3% for immediate-type BL allergy. These findings were consistent in both Hong Kong and United Kingdom cohorts in subgroup analysis.

Conclusion: Ascertaining the history of anaphylaxis, index drug, and duration of immediate BL hypersensitivity may clinically help to predict genuine allergy. We recommend that BP + amoxicillin ± index BL for skin testing, prior to drug provocation test, is sufficient in areas with a low background prevalence of PPL and MDM sensitisation such as Hong Kong and the United Kingdom.

Performance of allergy investigations in adolescent and adult patients with peanut allergy

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Introduction: Peanut allergy is a major public health issue and its diagnosis involves skin prick tests (SPT), specific IgE (sIgE), component resolved diagnostics, and oral food challenges (OFC). Various SPT and sIgE cut-offs have been published, but almost all were exclusively based on paediatric studies. We reviewed the usefulness of clinical parameters, SPT, sIgE, and Ara h2 in predicting the outcome of OFC to determine optimal cut-offs for adolescent and adult patients.

Method: Records of patients referred for suspected peanut allergy who underwent OFC at two large allergy referral centres between 2007 and 2016 were reviewed.

Results: Of 64 patients who underwent peanut OFC, 16 (25%) had a positive OFC who had a larger mean SPT wheal diameter (7.9 ± 0.8 vs 2.6 ± 0.5 mm, P<0.01). Nonetheless, there were no significant differences in sIgE, Ara h2, or other clinical variables (P>0.05). SPT demonstrated excellent performance with the area under the curve (AUC) of 0.945 (P<0.01). In contrast, the AUC for whole peanut and Ara h2 sIgE were only 0.489 and 0.779, respectively. The optimal cut-off, maximising both sensitivity and specificity, for the SPT wheal diameter was ≥5 mm. All patients with a positive OFC had a SPT wheal diameter of ≥5 mm (sensitivity=100%), and 37 of 44 patients with a negative OFC had a SPT wheal diameter of <5 mm (specificity=84%).

Conclusion: SPT were superior in predicting allergy than sIgE or Ara h2 in this selected cohort of adolescent and adult patients. We caution against over-generalisation of specific cut-offs and recommend age-appropriate thresholds such as a SPT wheal diameter of ≥5 mm in this cohort of older patients.

Predictive value of skin prick testing and specific IgE in sesame allergy

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Introduction: Sesame (*Sesamum indicum*) allergy is the most common seed allergy and has been increasingly reported worldwide. Accurate diagnosis is crucial but the value of skin prick tests (SPT) and sesame-specific IgE (sIgE) have been questioned. We evaluated the utility of SPT, sIgE, and clinical variables in predicting sesame allergy confirmed by oral food challenges (OFC) in a large cohort.

Method: Records of patients who had undergone sesame OFC at two large allergy tertiary referral centres between 2010 and 2016 were reviewed. Results of SPT, sIgE, and various clinical parameters were analysed to evaluate their usefulness in predicting positive OFC.

Results: Ten (30%) of 33 patients were positive during OFC. Allergic and non-allergic patients were comparable in terms of age (P=0.41), gender (P=0.24), atopic history (rhinitis, P=0.06; asthma, P=0.06; eczema, P=0.12), and other food allergies (P=0.06), as well as the mean SPT wheal diameter (P=0.06) and sIgE value (P=0.25). SPT had a sensitivity of 10.0% and a specificity of 56.5%, whereas sIgE had a sensitivity of 10.0% and a specificity of 42.9%. There were two serious reactions during OFC, each requiring multiple doses of intramuscular adrenaline for refractory hypotension.

Conclusion: We present the largest cohort of adult sesame OFC ever reported. SPT and sIgE results are not predictive of sesame allergy in adults, and clinical parameters of allergic and non-allergic patients do not differ significantly. OFC remains essential for diagnosis, but it should be conducted cautiously due to the severity and unpredictability of OFC reactions.

Predictors and role of allergy testing in immediate-type hypersensitivity to opioids

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Introduction: Most reactions to opioids are due to direct mast cell degranulation, and IgE-mediated hypersensitivity reactions are rare. Drug provocation tests (DPT) remain the gold standard, but many patients are labelled without proper diagnostic evidence or testing. This may lead to unnecessary drug avoidance, and other culprits of hypersensitivity reactions can be missed. We evaluated the characteristics and predictors of DPT-confirmed opioid allergy.

Method: All available records of patients referred for suspected opioid allergy at two large allergy tertiary referral centres between 2008 and 2016 were reviewed. Patients underwent DPT with the same opioid implicated in the index reaction with individualised protocols.

Results: Of 98 patients included, 15 (15%) were diagnosed with opioid allergy and had significantly more frequent angioedema (odds ratio [OR]=5.66, 95% confidence interval [CI]=1.49-21.47, P=0.01) and hypotension (OR=5.00, 95% CI=1.15-21.70, P=0.03) and were more likely to be allergic when received opioids during anaesthesia (OR=6.74, 95% CI=2.05-22.13, P<0.01). In contrast, there was a negative association with patients who received opioids for analgesia (OR=0.27, 95% CI=0.08-0.86, P<0.01). All reactions were mild even with a history of anaphylaxis. Most codeine/morphine allergic patients tolerated synthetic opioids.

Conclusion: We present the largest published cohort of patients with suspected opioid allergy investigated with DPT. Opioid allergy can be erroneously over-diagnosed without proper allergy evaluation. Patients with angioedema or hypotension, and received opioids for anaesthesia (rather than analgesia) were more likely to be truly opioid allergic.

Review of the clinical characteristics and outcome of chronic granulomatous disease in Hong Kong

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Introduction: Primary immunodeficiencies such as chronic granulomatous disease (CGD) remain under-recognised in many parts of the world. CGD patients are classically susceptible to a wide variety of catalase-positive organisms, but autoimmune complications are increasingly recognised. The epidemiology of implicated pathogens and complications also varies per geographical location.

Method: We retrospectively reviewed all genetically confirmed CGD patients diagnosed at Queen Mary Hospital between 1999 and 2016, and reported region-specific characteristics and outcomes.

Results: There were 15 male (14 X-linked, 1 autosomal recessive) and four female (all autosomal recessive) patients with CGD. The median age of diagnosis and follow-up were 1.5 (range, 0-41) years and 14 (range, 1-50) years, respectively. Eleven patients had confirmed carriers in their relatives after screening. In contrast to western cohorts, *Mycobacterium*, *Klebsiella*, *Salmonella*, *Aeromonas* spp. were the most commonly isolated pathogen in our region. Nine patients had a history of microbiologically confirmed mycobacterial infection. Five patients experienced a variety of autoimmune complications. This cohort of patients had significantly lower rates of major infections in comparison to those without (mean: 0.2 ± 0.4 vs 2.2 ± 1.9 episodes/patient-year, P=0.036).

Conclusion: We reported on region-specific patterns of infections and identified significantly lower rates of major infections in those with autoimmune complications among patients with CGD. It is imperative for physicians to recognise these important geographic differences when tailoring specific diagnostic investigation and treatment.

The protective role of kallistatin in tubulointerstitial fibrosis

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Introduction: Kallistatin, a tissue kallikrein-binding protein, exerts renoprotective functions against renal fibrosis in various animal models of kidney disease. The underlying mechanisms remain poorly understood. Recent data suggest that kallistatin antagonises Wnt/beta-catenin signalling in cancer cells and that this signalling pathway plays a crucial role in the pathogenesis of renal fibrosis. We investigated the effect of kallistatin on Wnt/beta-catenin signalling and the pro-fibrotic process in renal proximal tubular epithelial cells.

Method: Cultured human proximal tubular epithelial cells (HK-2) were transfected with kallistatin plasmid (0.5-4 μg/mL) prior to transforming growth factor (TGF) beta stimulation (10 ng/mL) to activate Wnt/beta-catenin. The efficiency of kallistatin transfection was verified by enzyme-linked immunosorbent assay. The induction of TGF-beta–induced Wnt/beta-catenin signalling and the expression of fibrotic molecules was detected by real-time quantitative polymerase chain reaction and western blotting.

Results: TGF-beta–activated beta-catenin signalling in HK-2 cells as evidenced by increased phosphorylation of GSK3-beta and accumulation of beta-catenin in both the cytosol and nucleus. Additionally, TGF-beta significantly increased the expression of Wnt family members (Wnt5a, Wnt9a, and Wnt3) and the Wnt antagonist DKK1 in HK-2 cells. Overexpression of kallistatin in HK-2 cells not only inhibited TGF-beta, induced phospho-GSK3-beta and beta-catenin levels, but also decreased the expression of Wnt5a, Wnt 9a, and DKK1 as well as numerous fibrosis-related genes such as TGF-beta, Snail, PAI-1, and Collagen I in a dose-dependent manner.

Conclusion: Kallistatin attenuates the profibrotic effects of TGF-beta via inhibition of Wnt/beta-catenin and Akt signalling, thereby reducing the expression of fibrotic genes in tubular cells. These findings further support the renoprotective role of kallistatin and highlight its therapeutic potential in renal fibrosis.

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Effects of fine particulate matter collected in Hong Kong in human airway epithelial cells

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Introduction: Fine particulate matter (PM) of an aerodynamic diameter of <2.5 micrometre ($PM_{2.5}$) is considered a significant contributor in air pollution, and associated with an increased risk of lung cancer, cardiovascular and respiratory deaths and hospital admissions. Due to diversity in the origin and composition of $PM_{2.5}$, it is necessary to evaluate the complex mechanisms underlying local $PM_{2.5}$-induced adverse effects in human airway epithelial cells.

Methods: Atmospheric $PM_{2.5}$ samples were collected by two 47-mm Teflon filter on parallel using Desert Research Institute portable mid-volume samplers in one of the general air-monitoring stations in Hong Kong. $PM_{2.5}$ extracts were prepared by sonication with ultrapure 0.1 micrometre filtered water and vacuum-freeze drying. Particles were then suspended in certain amount of phosphate-buffered saline solution for further use. Human bronchial epithelial cell line (BEAS-2B) was cultured in the keratinocyte serum-free medium with essential supplements.

Results: Total $PM_{2.5}$ exposure caused cell morphology alterations in BEAS-2B cells, resulting in cell shrinkage and reduction in cell number after 24 or 48 hours' exposure. Exposure to total $PM_{2.5}$ (12.5-200 microgram/mL) caused elevations of pro-inflammatory cytokines interleukin-8 release in a dose-dependent manner.

Conclusion: Exposure to $PM_{2.5}$ collected in Hong Kong caused cellular toxicity and inflammatory response in human bronchial epithelial cell line BEAS-2B. Further study should be conducted to explore the underlying mechanisms of $PM_{2.5}$ on the regulation of inflammatory response in the airways.

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Elucidation of epidermal growth factor receptor pathway in cigarette smoke medium–mediated expression of mucin genes and release of IL-8 in human airway epithelial cells

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Introduction: Chronic obstructive pulmonary disease (COPD), an inflammatory disease characterised by chronic irreversible airflow limitation, is predicted to be the third leading cause of death worldwide by 2030. The most important risk factor of COPD is cigarette smoking. Chronic exposure of airways to cigarette smoke has been found to promote excessive mucus production and amplify inflammatory response leading to impaired mucociliary function and ultimately airway obstruction. We hypothesise that epidermal growth factor receptor (EGFR) pathway plays a crucial role in the regulation of airway goblet cell hyperplasia, mucus hypersecretion, and inflammation.

Methods: NCI-H292 cells were cultured in RPMI1640 (Gibco) supplemented with 10% foetal bovine serum. After starvation, cells were exposed to various concentrations of cigarette smoke medium (CSM) of 1 to 4% for 24 hours, or pretreated without or with AG1478 (0.1-10 μM) for 30 minutes before 4% CSM exposure for 24 hours. After treatment, cell lysates and cell culture supernatants were collected for gene expression studies, western blot analysis, and measurement of pre-inflammatory marker IL-8, respectively.

Results: CSM caused a concentration-dependent elevation of MUC5AC and MUC5B mRNA, and IL-8 release in NCI-H292 cells, but no significant induction of MUC2 mRNA was observed. AG1478 alone had no effect on mucins mRNA level and IL-8 release but inhibited CSM-induced elevation of MUC5AC and MUC5B mRNA and IL-8 release. Phosphorylation of EGFR was confirmed to be crucial in the cigarette smoke induction of mucins mRNA and IL-8 release.

Conclusion: EGFR activation by phosphorylation is crucial in CSM-induced mucus hypersecretion and airway inflammation. AG1478 may be a possible pharmacological intervention for the symptomatic treatment of mucus hypersecretion and the underlying chronic inflammation.

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Inhibition of A-FABP attenuates cerebral ischaemia injury via alleviating MMP-9 mediated blood brain barrier disruption

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Introduction: Ischaemic stroke is one of the biggest causes of death and permanent disability in the world. Adipocyte fatty acid binding protein (A-FABP) is a lipid chaperon adipokine mainly expressed in adipocytes and macrophages. Previous clinical studies reported that serum A-FABP is significantly increased in patients with ischaemic stroke and positively correlated with the severity of stroke outcomes. Nonetheless, the direct role of A-FABP in pathogenesis of ischaemic stroke remains unknown.

Method: Focal cerebral injury in adult male A-FABP knock-out mice and their wild-type littermates was induced by middle cerebral artery occlusion surgery. The infarct volume, neurological score, and blood brain barrier disruption were assessed after 23 hours of reperfusion. The serum and cerebral A-FABP were measured by enzyme-linked immunosorbent assay and immunohistochemical staining at different time points after surgery. Blood brain barrier tight junction–related protein (ZO-1 and occludin), matrix metalloprotease (MMP) and JNK/c-Jun activities were assessed by western blot and gelatine zymography. Adenovirus-mediated overexpression of A-FABP was performed to check the role of A-FABP supplementation in outcomes of ischaemia stroke.

Result: A-FABP deficiency protects mice from ischaemia-induced brain injury and neurological deficits. Serum levels of A-FABP and MMP-9 of ischaemic stroke patients are positively correlated. JNK/c-Jun activity in A-FABP KO mice were attenuated compared with wild-type mice.

Conclusion: A-FABP deficiency protects mice from middle cerebral artery occlusion–induced cerebral ischaemia injury by suppressing MMP-9 activity and blood brain barrier disruption. A-FABP enhances MMP-9 activity during ischaemic stroke possibly through JNK/c-Jun pathway.

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Correlation between right ventricular end-diastolic volume and age-related white matter hyperintensity in adults: an exploratory magnetic resonance imaging study

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Introduction: White matter hyperintensity (WMH) observed on magnetic resonance imaging (MRI) is associated with a higher risk of dementia. Nonetheless, the aetiology and pathological mechanism for WMH, especially the link between the heart and brain, remain unclear. We explored the correlation between cardiac parameters on cardiac MRI and age-related WMH on brain MRI.

Method: In this retrospective cross-sectional study, we recruited 25 adults who had both cardiac and brain MRI, within 2 years apart. WMH was measured using age-related white matter changes (ARWMC) rating scale. Cardiac parameters included ventricular volume, ejection fraction, ventricular mass, and strain. Subjects were divided into two groups based on the presence or absence of ARWMC; patient demographics and baseline clinical characteristics were extracted from medical records and were compared between the two groups.

Results: Patients with and without ARWMC were comparable for baseline characteristics including age, gender, history of cardiovascular diseases, smoking and drinking status. There was no significant correlation between the ARWMC group and the right atrial area, left atrial area, E/A ratio, left ventricular ejection fraction, left ventricular end-diastolic/systolic volume, stroke volume, left ventricular mass, or left ventricular end-systolic volume. However, the right ventricular end-systolic volume adjusted by body surface area was strongly associated with the ARWMC group (r=0.962, P=0.002).

Conclusion: The right ventricular end-systolic volume appeared to be associated with age-related WMH in adults. Larger prospective studies are required to determine the clinical impact of enlarged right ventricular end-systolic volume on neuronal damage and future cognitive decline.

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Can electroencephalography distinguish patients at the early stages of cognitive impairment? Results from an exploratory study

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Introduction: Non-invasive biomarkers of early cognitive impairment and dementia are needed for a prompt and accurate diagnosis. We aimed to determine whether distinctive features of electroencephalography (EEG) can be used to distinguish patients with subjective cognitive decline (SCD), mild cognitive impairment (MCI), and Alzheimer's dementia (AD).

Method: In this single-centred cross-sectional study, we recruited patients with SCD (n=26), MCI (n=22), and AD (n=26) from the Memory Clinic of Queen Mary Hospital. Patients with existing epilepsy or on antiepileptic drugs were excluded. Dementia diagnosis was made by dementia specialist according to the fifth edition of Diagnostic and Statistical Manual of Mental Disorders criteria after full physical and cognitive assessments. EEG phenotypes were based on the frequency of background activity and presence and degree of episodic abnormalities, when the patients were awake and alert.

Results: There are no significant between-group differences in terms of abnormal generalised slowing, epileptiform discharges, theta outbursts, K complexes, vertex waves, frontal intermittent rhythmic delta activity, mu rhythm, sharp waves, the frequency of dominant rhythm, and the presence of alpha, beta, and delta waves in any rhythm. However, the presence of theta waves in any rhythm (77%) was significantly more prevalent in AD (89%) and MCI (91%) as compared to SCD (54%) [p=0.003].

Conclusion: Presence of theta waves (4-7 Hz) may serve as a potential specific but not sensitive biomarker of the earliest stage of cognitive impairment.

73 Methylated septin 9 or carcinoembryonic antigen for diagnosis and postoperative monitoring of colorectal cancer

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Objective: Compare with other colorectal cancer (CRC) screening tests, blood test is simple and more acceptable to the public. This study evaluates the role of the second-generation methylated septin 9 (mSEPT9) on the diagnosis and postoperative monitoring of CRC as compared to carcinoembryonic antigen (CEA).

Method: Blood samples were prospectively collected from patients prior to colonoscopy for determination of mSEPT9 and CEA. Another cohort of CRC patients had serial blood tests taken after surgery at 3-monthly intervals. mSEPT9 was determined by commercially available assay in a blinded manner.

Results: The sensitivity of mSEPT9 was significantly higher than elevated CEA on diagnosing CRC (73.9% vs 48.2%, P<0.001). Both the sensitivity of mSEPT9 and CEA increased with higher tumour staging (P=0.003 and P=0.033). The overall specificity of the mSEPT9 assay and CEA in colonoscopy-negative subjects was 72.5% and 79.3% (P=0.412), respectively. An increase in the number of positive mSEPT9 polymerase chain reactions in the postoperative plasma samples was associated with a higher mortality rate (26.3% vs 4.2%, P<0.01), recurrence (47.4% vs 14.1%, P<0.01) and presence of metastasis (36.8% vs 8.5%, P<0.01). Overall, the proportion of patients with negative CEA was significantly higher than negative mSEPT9 at postoperative 6 months (71.8% vs 55.3%, P=0.035) and 12 months (68.1% vs 48.1%, P=0.028).

Conclusion: mSEPT9 was more sensitive than CEA in detecting CRC. After curative resection, mSEPT9 may be less specific than CEA for surveillance, but an increase in positive mSEPT9 reactions may indicate adverse outcome.

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74 Serum Mac-2-binding protein glycosylation isomer in assessing liver fibrosis in chronic hepatitis B infection

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Introduction: Mac-2-binding protein glycosylation isomer (M2BPGi) is a novel serum marker for diagnosis of liver fibrosis in various liver diseases. Data in chronic hepatitis B (CHB), especially longitudinal data, are limited. We aimed to evaluate the role of M2BPGi in diagnosing advanced fibrosis (F3) and cirrhosis (F4) in patients with hepatitis B e antigen negative (HBeAg-ve) CHB using liver stiffness measurement (LSM) as the reference.

Method: We performed LSM for HBeAg-ve CHB patients who were managed in Queen Mary Hospital. LSM was performed using Fibroscan, and presence of no/minimal fibrosis (F0/F1), grey area, and F3/F4 was defined using the alanine-aminotransferase-based EASL-ALEH criteria. Serum M2BPGi were measured using the HISCL-800 immunoanalyzer (Sysmex Corporation, Hyogo, Japan).

Results: Overall, 240 HBeAg-ve CHB patients (116 male and 124 female) with a median age of 47.5 years were recruited. Most (85.8%) were treatment-naive. The median alanine aminotransferase level was 26 (range, 10-180) U/L. The median liver stiffness was 6.9 (interquartile range, 4.9-11.7) kPa; 78 (32.5%) of patients had F3/F4 at baseline based on transient elastography. The corresponding M2BPGi for F0/1/2, F3, and F4 progressively increased in parallel with more advanced stages of liver fibrosis, with a cut-off index (COI) of 0.39, 0.46, and 0.82, respectively (P<0.01). The area under the receiver operating characteristic curve for diagnosing ≥F3 by M2BPGi was 0.754. Using a cut-off value of 0.605, the sensitivity, specificity, positive and negative predictive values for ≥F3 was 62.5%, 79.4%, 60.3%, and 80.9%. In a subgroup of 86 patients who had repeat LSM 10 years after the initial LSM, the proportion of patients with F3/4 reduced from 36.7% to 16.3% (P<0.001). The median M2BPGi COIs were significantly higher in patients with F3/4 than in those with F0/1/2 at baseline (0.67 vs 0.41, P<0.05) and at 10 years (0.62 vs 0.48, P=0.039). 21 (24.4%) showed significant fibrosis regression (ie F3 or F4 to F0 or F1). The median change in M2BPGi COI was -0.11 in those with significant fibrosis regression, compared with +0.03 in patients without significant fibrosis regression (P=0.011).

Conclusion: Serum M2BPGi is an accurate marker for liver fibrosis in HBeAg-ve CHB patients. Using a COI of 0.605, 80.9% patients without ≥F3 can be excluded. M2BPGi levels remained significantly higher for patients with ≥F3 compared to those with F0/1/2 even after 10 years. M2BPGi levels also decreased significantly in patients who had fibrosis regression after 10 years.

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Association of long-term glycaemic control on tear break up times and dry eye symptoms in Chinese patients with type-2 diabetes

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Purpose: To evaluate tear film stability and dry eye symptoms and their association with vascular risk factors in Chinese patients with type-2 diabetes mellitus (T2DM).

Methods: A cross-sectional study was conducted at the Lo Fong Siu Po Eye Centre (Grantham Hospital) from January to March 2017. Overall, 80 Chinese patients with T2DM were recruited from the diabetes clinic of Queen Mary Hospital. Non-invasive tear film assessment was performed using the Oculus Keratograph 5M (Oculus, Germany) to evaluate the non-invasive tear break-up time (NITBUT). Ocular symptoms were evaluated using the Ocular Surface Disease Index (OSDI). The association between OSDI, NITBUT, and metabolic parameters relating to diabetes were evaluated using multiple linear regression.

Results: Among the 80 patients (mean age, 64.95 ± 10.97 years, 44% women), 20% (95% confidence interval, 11-30%) had NIBUT ≤5 seconds. There were significant inverse Pearson correlations between glycated haemoglobin (HbA1c) and NITBUT (r= -0.314, P=0.007), and a positive but weak correlation between HbA1c and OSDI (r=0.249, P=0.022). Stepwise multiple linear regression analysis confirmed HbA1c to be the only significant independent variable for NITBUT (r^2=0.099, P=0.014), and OSDI (r^2=0.062, P=0.044) after controlling for potential confounders.

Conclusion: Symptomatic tear film instability was observed in one-fifth of patients with T2DM. Our findings highlight the importance of good glycaemic control as a modifiable risk factor for both dry eye symptoms and tear film instability in patients with T2DM.

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The incidence of vancomycin-induced nephrotoxicity in Hong Kong Chinese

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Introduction: Vancomycin-induced nephrotoxicity (VIN) has not been well studied in Hong Kong. This study aimed to explore the incidence of VIN and identify the characteristics of susceptible patients and the most likely risk factors.

Method: A retrospective study was conducted using the Hong Kong Hospital Authority Clinical Data Analysis and Reporting System. All data of patients with vancomycin prescription and measurement from 2012 to 2016 in Hong Kong were retrieved. Using the modified risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) criteria, patients with acute kidney injury were identified. Patients who had no baseline and follow-up concentration of creatinine, vancomycin treatment <3 days or trough concentration not at a steady state were excluded. Results were analysed using SPSS version 24. Logistic regression was used to identify the predictors for VIN.

Results: From 140 complete cases in Hong Kong from 2012 to 2016, 23 were identified as VIN. The cumulative incidence of VIN was 16%. From 2012 to 2016, the incidence was 9%, 23%, 26%, 11%, and 13%, respectively. There were no significant differences between VIN and non-VIN groups in terms of demographics. No significant association was found between vancomycin levels and the occurrence of nephrotoxicity. In logistic regression analysis, only length of hospital stay had a significant positive association with VIN (odds ratio=1.020, 95% confidence interval=1.004-1.035).

Conclusion: The incidence of VIN in Hong Kong is low but shows no decline. Longer hospital stay is a risk factor for VIN.

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Prevalence of hyperphagia in Alzheimer's disease: a meta-analysis

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Introduction: Unlike other behavioural and psychological symptoms of dementia, hyperphagia is less recognised among patients with Alzheimer's disease (AD). The prevalence of hyperphagia varies among studies. There has been no systematic review or meta-analysis.

Methods: A search on the literature up to 30 June 2017 on hyperphagia in AD was conducted. Data on the prevalence were retrieved. Meta-analysis with the random effect model was performed to determine the pooled estimate of prevalence. Meta-regression analysis was performed according to study characteristics, population demographics, or condition information.

Results: A total of 26 reported cases of hyperphagia could be identified. The mean age of onset was 70.7 ± 8.9 years with a male predominance (68.4%). Hyperphagia occurred in all stages of AD. Only eight studies reported the prevalence of hyperphagia. Meta-analysis showed a pooled prevalence of hyperphagia of 18.6%. Publication bias may be present. Meta-regression showed that ethnicity accounted for the variance among studies (coefficient= -1.247, 95% confidence interval= -1.978 to -0.516, r^2 analogue=0.77, P<0.001).

Conclusion: Hyperphagia occurs in all stages of AD. In this meta-analysis of eight studies, the prevalence of hyperphagia was 18.6%. In view of the possible publication bias, a large-scale study on hyperphagia is recommended.

The first case series of Chinese familial Alzheimer's disease patients with a comparison with biomarker-confirmed sporadic late-onset Alzheimer's disease patients

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Introduction: Familial Alzheimer's disease (FAD) patients are increasingly reported in Hong Kong. This study aimed to identify clinical features of FAD and compare FAD patients with biomarker-confirmed sporadic late-onset Alzheimer's disease (LOAD) patients.

Methods: All symptomatic Chinese FAD patients in the Memory Clinic of Queen Mary Hospital were included. Clinical features, baseline Mini-Mental State Examination (MMSE) scores, and presenting cognitive symptoms or atypical clinical features were collected. Clinical features of FAD patients were compared with those of 12 sporadic LOAD patients with cerebrospinal fluid biomarkers evidence of Alzheimer's disease and those of 14 LOAD patients with positive amyloid loading on Pittsburgh Compound B imaging.

Results: There were three FAD families affecting eight family members. The mean age of onset was 48.4 ± 7.7 years and the mean MMSE score was 7.9 ± 9.2. The local prevalence of FAD was 0.85 per 100 000 population. Comparing with the sporadic LOAD patients, FAD patients had an earlier age of onset and presentation (both P<0.001), were diagnosed later (10.1 ± 7.1 vs 2.8 ± 2.3 years, P=0.02), and attained lower MMSE score upon presentation (7.9 ± 9.2 vs 17.6 ± 7.2, P=0.01). FAD patients had less delusion (0% vs 41.7%, P=0.04), dysphoria (0% vs 50%, P=0.01), and irritability (0% vs 52.4%, 0.01). There was a trend of less frequent amnesia among FAD patients (75 vs 100%, P=0.05).

Conclusion: There are differences in clinical features between FAD and LOAD patients. Diagnosis is delayed in FAD patients. Promotion of public awareness of FAD is needed.

Non-invasive subcutaneous fat reduction using a small contoured cup cryolipolysis applicator in Asian subjects

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Introduction: Subjects with a smaller body frame and lower body mass index may be appropriate candidates for cryolipolysis given an applicator designed to cool their smaller proportions effectively. The new small contoured cup cryolipolysis applicator creates suction at the bottom of the hand piece leading to a better draw volume and less discomfort. This study explored this new applicator for non-invasive fat reduction in the abdomen and flanks of Asian subjects.

Method: Abdomens and flanks of eligible Asian subjects were treated with a small contoured cup cryolipolysis applicator. The number of treatments at each session was determined by the investigator. Each subject underwent two treatment sessions approximately 6 weeks apart and were followed up until 12 weeks after the final treatment. Any adverse effects related to the procedure were documented. Efficacy was assessed by comparing photos at baseline and 12-week post-final treatment by three blinded independent physicians, caliper and circumference measurements, as well as the subject satisfaction questionnaire.

Results: Overall, 24 women and men were enrolled and completed treatment and follow-up. Subjects mostly experienced mild-to-moderate erythema and oedema immediately after treatment, but all side-effects resolved by the 12-week post-final treatment visit. No device- or procedure-related adverse events were reported. Six subjects completed the subject satisfaction questionnaire, and all were satisfied with the treatment and results, and 83% would recommend the procedure to a friend. The mean fat layer decreased 0.95 mm and the mean circumference increased 0.98 cm at the 12-week post-final treatment visit.

Conclusion: The small contoured cup applicator is satisfactory in reducing subcutaneous fat in the abdomen and flank in this Asian population. This study demonstrated the safe use of this applicator for small pockets of fat, and provided a better fit for patient populations that may otherwise not have been candidates for the procedure due to the smaller size of the fat bulges.

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The efficacy of a dual-wavelength picosecond laser for facial treatment of melasma and skin rejuvenation

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Introduction: Photoageing in Chinese often presents with benign pigmentary lesions. In Asians, Q-switched laser has been reported to result in a 25% risk of post-inflammatory hyperpigmentation, whereas such a risk is lower after long-pulsed Nd:YAG. Picosecond lasers of various wavelengths have been introduced. This study aims to assess the efficacy of a picosecond laser for the treatment of melasma and skin rejuvenation.

Method: Ten subjects with melasma and 10 subjects with photoageing were recruited. Each subject received up to nine facial treatments. Each session involved four passes of picosecond laser at 1064 nm wavelength with an end-point of mild erythema. Standardised photographs were taken at baseline, each treatment visit, as well as 6 and 12 weeks after the final treatment. Photographs were assessed by two independent physicians. The physician who performed the treatment rated the Melasma Area and Severity Index (MASI) score for subjects with melasma and the global assessment score for subjects for skin rejuvenation. Any adverse event was recorded. At follow-up visits, subjects were assessed for improvement and satisfaction.

Results: The study was ongoing with five subjects for melasma treatment and seven subjects for skin rejuvenation. Overall, 59 treatment sessions have been carried out. For skin rejuvenation, 57% of subjects had slight improvement. There was reduction in the MASI score but not significantly. No adverse event was recorded.

Conclusion: The 1064nm picosecond laser demonstrated some improvement for skin rejuvenation and melasma.

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FABP4 mediates autoimmune diabetes by enhancing the crosstalk between innate and adaptive immunity

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Introduction: Type-1 diabetes (T1D) is an autoimmune disease resulted from self-destruction of insulin-producing pancreatic beta cells. The pathological pathways that trigger the autoimmune destruction remain poorly understood. Our previous 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 T1D. This study aimed to investigate the role and underlying mechanism whereby FABP4 participates in the pathogenesis of T1D.

Method: FABP4+/+ non-obese diabetic (NOD) and FABP4-/-NOD mice were used. Biochemical, immunological, and in vivo imaging analyses were performed to determine the dynamic change in the infiltration and activation of immune cells including macrophage and tissue resident memory T (Trm) cell in pancreas of FABP4+/+NOD and FABP4-/-NOD mice at different ages. Gain- and loss-of-function studies were performed to evaluate the effects of FABP4 in macrophage and Trm cell on insulitis and diabetes incidence. Flow cytometry analysis was performed to explore the effects of FABP4 in mediating the crosstalk of immune cells.

Results: A dynamic change in the expression of FABP4 was observed in macrophage and Trm cells in pancreatic islets of NOD mice at early or later stage. In 8-week FABP4+/+NOD mice, depletion of macrophage or Trm cell could only partially alleviated insulitis and reduced the development of T1D. However, depleting macrophages and Trm cells simultaneously delayed the onset of T1D. Flow cytometry analysis demonstrated that FABP4 deficiency significantly attenuated the polarisation and infiltration of pro-inflammatory macrophage and Trm cells into pancreas, reduced the production of inflammatory cytokines, alleviated islet inflammation and beta cell damage.

Conclusion: FABP4 potentiates innate immunity through enhancing the polarisation of macrophage to pro-inflammatory macrophage subtype in NOD mice at early stage. While at later stage FABP4 promotes the survival of Trm cell and exacerbates adaptive immunity. Furthermore, the inflammatory microenvironment created by FABP4 in macrophage and Trm cells enhances the release of cytotoxic molecules in pancreas and strengthens the autoimmune attack to beta cells.

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Stenotrophomonas maltophilia bacteraemia: impact of appropriate therapy and predictors of mortality

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Introduction: *Stenotrophomonas maltophilia* is an important nosocomial pathogen with considerable intrinsic resistance against multiple antimicrobials. Optimal treatment especially in severe infections remains undefined, and local data are lacking. This study aimed to evaluate the experience in managing *S maltophilia* bacteraemia in Hong Kong and to identify predictors of mortality.

Methods: A retrospective case-control study was conducted at a university teaching hospital between 2013 and 2016. Patients with *S maltophilia* bacteraemia were classified based on whether they had received appropriate antibiotics. Mortality and clearance of bacteraemia within 7 days were compared between the two groups. Potential predictors of mortality were identified using multivariate analysis.

Results: Overall, 153 blood cultures positive for *S maltophilia* were included and they belonged to 75 patient-episodes. Of them, 56 received appropriate antibiotics and 19 did not. Patients who received appropriate antibiotics had a higher 7-day survival than those who did not (91.1% vs 73.7%, P=0.048). Those who received appropriate antibiotics were more likely to have received combination antimicrobials (P=0.02) and infectious disease consultation (P=0.004). Nonetheless, neither of them resulted in higher survival on their own. Appropriate antibiotics tended to clear bacteraemia more successfully within 7 days (73.2% vs 42.1%, P=0.055). Clearance of bacteraemia resulted in a higher 7-day survival (95.9% vs 69.2%, P=0.001). Requirement of intensive care at onset of *S maltophilia* bacteraemia was independently associated with a higher 7-day mortality (hazard ratio=12.3, 95% confidence interval=2.52-60.1, P=0.002).

Conclusion: Appropriate antibiotics led to a higher 7-day survival and a tendency of more successful clearance of *S maltophilia* bacteraemia. Combination antimicrobial therapy and infectious disease consultation might have contributed to the use of appropriate antibiotics. Requirement of intensive care at the onset of *S maltophilia* bacteraemia was independently correlated with a higher 7-day mortality.

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Relationship between hepatitis B core-related antigen and chronic hepatitis B outcome in hepatitis B e antigen negative patients: a 10-year longitudinal study

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Introduction: Hepatitis B core-related antigen (HBcrAg) is a novel serological marker of hepatitis B virus (HBV). Long-term data regarding the predictive value of HBcrAg are limited. We aim to determine the relationship between HBcrAg levels after spontaneous hepatitis B e antigen (HBeAg) seroconversion and hepatocellular carcinoma (HCC).

Method: We recruited chronic HBV patients with a documented time of spontaneous HBeAg seroconversion. HBcrAg and HBsAg were checked at three time points: within 3 years (the baseline) and at 5 years and 10 years after HBeAg seroconversion. HBV DNA was measured at the baseline. Multivariate logistic regression was used to investigate the predictors for the development of HCC.

Results: We recruited 209 patients; 120 (57.4%) were male. The median patient age was 40 (interquartile range, 34-45) years. Cirrhosis was present at baseline in nine (4.3%) patients, and HCC developed in 16 (7.7%) patients during the follow-up period. Patients who developed HCC had a significantly older age of HBeAg seroconversion than those without HCC (median: 50.1 vs 39.3 years, P=0.002). More patients in the HCC group than in the non-HCC group had baseline cirrhosis (31.3% vs 2.1%, P<0.001). The median level of HBcrAg at baseline was significantly higher in HCC patients than patients without HCC (518.6 vs 59.6 kU/mL, P=0.003). Independent risk factors for development of HCC included age of HBeAg seroconversion >50 years (odds ratio [OR]=10.84, 95% confidence interval [CI]=3.04-38.66), presence of baseline cirrhosis (OR=6.29, 95% CI=1.06-37.50), and a higher baseline HBcrAg (OR=1.77, 95% CI=1.01-3.12). HBcrAg levels at 5 years and 10 years after HBeAg seroconversion were not associated with HCC, probably due to the limited number of patients with HCC after 5 years of HBeAg seroconversion (n=9).

Conclusion: High HBcrAg level within 3 years after HBeAg seroconversion was independently associated with the development of HCC in chronic hepatitis B patients, as were older age (>50 years) at HBeAg seroconversion and presence of baseline cirrhosis.

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Association between blood lead level and systolic blood pressure: United States National Health Nutrition and Examination Survey 1999-2014

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Introduction: Lead toxicity is an uncommon cause of hypertension. The blood lead level in the United States population has declined.[1] We examined if there is still an association between low blood lead level and systolic blood pressure (SBP).

Methods: We included participants who had blood lead level and blood pressure measurement in the United States National Health Nutrition and Examination Survey 1999-2014. Results were analysed using SPSS complex sample module version 22 with sample weight adjustment. We further analysed the association between blood lead level and SBP in people with blood lead level <5 μg/dL and in ethnic groups. We calculated regression coefficient and 95% confidence interval (CI) for every 2.72 times increase in blood lead level.

Results: Overall, 20 596 participants were included. Every 2.72 times increase in blood lead level was associated with an increase of 4.98 (95% CI=4.54-5.43) mmHg in SBP (P<0.0001). This remained significant after adjusting for age, gender, ethnicity, and waist circumference (0.75, 95% CI=0.30-1.20, P=0.001). This significant association was also found in participants with blood lead level <5 μg/dL (regression coefficient [95% CI] being 5.59 [5.12-6.07], P<0.0001) and in all ethnicities (Mexican Americans: 4.14 [3.45-4.83], P<0.0001; other Hispanics: 4.93 [3.56-6.30], P<0.0001; non-Hispanic Whites: 6.04 [5.40-6.67], P<0.0001; non-Hispanic Blacks: 5.82 [4.95-6.68], P<0.0001; other races: 3.28 [1.51-5.04], P<0.0001).

Conclusion: Blood lead level is associated with SBP in the general population; most of whom do not have elevated blood lead level. Reducing lead in the environment benefits both children and adults.

Reference

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Characteristics of Americans with stage-1 hypertension: United States National Health Nutrition and Examination Survey 2011-2016

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Introduction: The American Heart Association recently redefined hypertension to include people who have a systolic blood pressure of 130-139 mmHg or a diastolic blood pressure of 80-89 mmHg. We describe the characteristics of these people who are considered to have stage-1 hypertension.

Method: Participants of United States National Health Nutrition and Examination Survey 2011-2016 who had blood pressure measurements and were not on antihypertensive medication were included. Obesity and overweight were defined as a body mass index of ≥30 kg/m^2 and 25 to <30 kg/m^2, respectively. Central obesity was defined as a waist circumference of ≥94 cm in men and ≥80 cm in women. Results were analysed using R statistics version 3.3.3 with statistical package survey version 3.32-1.

Results: Among 16 913 participants analysed, 2497 or 17.1% (95% confidence interval [CI]=16.0-18.0%) had stage-1 hypertension. Among them, 44.8% (95% CI=41.5-48.0%) were aged <45 years. About 34.5% (95% CI=31.5-38.0%) and 40.5% (95% CI=37.7-43.0%) were overweight and obese, respectively. About 72.2% (95% CI=68.9-75.0%) of the men and 88.5% (95% CI=84.2-92.0%) of the women had central obesity. About 3.1% (95% CI=2.3-4.0%) and 9.13% (95% CI=7.46-11.0%) had a history of cardiovascular disease and albuminuria, respectively. The mean blood pressure was 131/79 mmHg.

Conclusions: Almost half of the people with stage-1 hypertension are young and most have central obesity. As a group, the mean blood pressure does not elevate much and very few have a history of cardiovascular disease. The utility of this new category of hypertension lies in identifying individuals for non-pharmacologic treatment.

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Decrease in urine arsenic level in the United States population: United States National Health Nutrition and Examination Survey 2003-2014

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Introduction: Arsenic is highly toxic and even at low levels can increase the risk of cancer. The blood lead level in the United States population has declined. We hypothesised that there might also be a decreasing trend in the arsenic level.

Method: As urinary arsenic level is commonly used as the index of exposure, we analysed data on participants who had urinary arsenic measurements in the National Health Nutrition and Examination Survey 2003-2014. Using SPSS complex sample modules version 22, we analysed the trend in urinary arsenic level in the whole population, as well as by gender and ethnicity. We calculated the geometric mean and 95% confidence intervals (CI) for each 2-year period.

Results: We included 16 474 participants in the analysis. Geometric mean (95% CI) urinary arsenic levels were 8.30 (7.26-9.47), 9.29 (8.13-10.61), 8.10 (7.48-8.79), 9.28 (8.52-10.11), 6.87 (5.92-7.98), and 5.60 (4.97-6.30) in 2003-2004, 2005-2006, 2007-2008, 2009-2010, 2011-2012, and 2013-2014, respectively. Overall, there was a decreasing trend (P=0.018). A decreasing trend was also found in males (P=0.008) and all ethnic subgroups (Mexican Americans: P<0.001; other Hispanics: P=0.001; non-Hispanic Whites: P=0.044; non-Hispanic Blacks: P=0.038; and other races: P=0.027).

Conclusion: There has been a significant decrease in urinary arsenic level in all segments of the United States population since 2009. This is encouraging and suggests that monitoring of the population for arsenic exposure should be continued.

Hyperlipidaemic effect of Janus kinase inhibitors: a meta-analysis

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

Methods: We conducted a literature search of the ISI Web of Science, Scopus, Medline, Cochrane library, Clinicaltrials.gov, and EMBase. Randomised controlled trials that reported the frequency of hypercholesterolemia or hyperlipidaemia were included. Results were analysed using RevMan 5.3.5. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using a random effects model.

Results: Eight trials were included for meta-analysis. JAK inhibitors were associated with hypercholesterolemia (OR=5.36, 95% CI=1.93-14.88). The association of JAK inhibitors with hyperlipidaemia did not reach significance (OR=2.89, 95% CI=0.90-9.28), but tofacitinib, per se, was associated with hyperlipidaemia (OR=4.12, 95% CI=1.02-16.63). There was no significant heterogeneity in both outcomes (I^2 statistics for both outcomes: 0%).

Conclusions: There was a significant association between JAK inhibitors and hypercholesterolemia. If the association was causal, there would be important clinical implications for rheumatoid arthritis patients. The association of tofacitinib with hyperlipidaemia requires further investigation.

Urine arsenic level and diabetes in the United States National Health Nutrition and Examination Survey 2009-2012

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Introduction: Arsenic is highly toxic. The association between low-level arsenic exposure and diabetes is controversial. We used data from the United States National Health Nutrition and Examination Survey (NHANES) to clarify this association.

Method: 1326 non-pregnant adults who had measurements of the urine arsenic level, fasting blood glucose level, and glycosylated haemoglobin level in NHANES 2009-2012 were included. Diabetes was defined as self-reported prescription of anti-diabetic medications, glycosylated haemoglobin of ≥6.5%, fasting serum glucose of ≥126 mg/dL, or self-reported previous physician diagnosis of diabetes. Participants were stratified by urine arsenic level into tertiles. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using SPSS complex sample modules version 22.

Results: Comparing the highest and lowest tertile of urine total arsenic level, there was no significant association between the urine arsenic level and diabetes in 2009-10 (OR=0.72, 95% CI=0.38-1.34) and 2011-12 (OR=1.43, 95% CI=0.84-2.42). This association was not strengthened after adjustment for age, gender, ethnicity, education, body mass index, serum cotinine, blood mercury urine creatinine, and prescription of anti-hypertensive medications.

Conclusion: Data of NHANES 2009-2012 do not support an association between arsenic exposure and diabetes. This is in contrast to our previous analysis of data prior to 2009 that showed a significant association. The declining levels of arsenic in the US might have diminished any harmful effect on glucose metabolism.

MDM2 inhibits very-low-density lipoprotein triglyceride secretion by suppressing ApoB expression in the liver

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Introduction: Very-low-density lipoprotein (VLDL) is a major vehicle for transporting lipids from liver to peripherals in plasma. VLDL-triglyceride (VLDL-TG) secretion is an important pathway for disposition of hepatic lipid, and its inhibition results in hepatic steatosis. VLDL assembly and secretion are controlled by lipid availability, microsomal triglyceride transfer protein and apolipoprotein B (ApoB) degradation. Most of the synthesised ApoB was degraded before secretion while the underlying mechanism was poorly understood. The E3 ligase MDM2 mediates the final step of ubiquitination. We previously found that MDM2 regulates glucose-stimulated insulin secretion via regulation of pyruvate carboxylase in pancreatic islet. As pyruvate carboxylase is a key metabolic enzyme that mediates gluconeogenesis in the liver, and MDM2 has been shown to control fatty acid oxidation in the liver, we investigated the role of MDM2 in in hepatic glucose and lipid metabolism using a hepatic-specific MDM2 knockout mouse model.

Methods: $MDM2^{floxed/floxed}$ mice were crossed with transgenic mice with Cre expression under the control of albumin promoter to generate hepatocyte-specific MDM2 knockout (HMDM2-KO) mice. Mice were fed with a high-fat-high-cholesterol diet for 16 weeks to induce obesity, insulin resistance, and hepatic steatosis. Basic metabolic parameters and VLDL secretion rate were monitored.

Results: Hepatocyte-specific deletion of MDM2 had no obvious effect on body weight, insulin sensitivity, glucose tolerance, and energy expenditure in mice fed with a high-fat-high-cholesterol diet. HMDM2-KO mice displayed attenuated hepatic steatosis and downregulated mRNA and protein level of inflammatory markers in liver when compared to their wild-type littermates. Hepatic protein level of ApoB and rate of VLDL-TG secretion were increased in HMDM2-KO mice. In the hepatoma cells HepG2, inhibition of MDM2 by Nutlin-3a increased protein level of ApoB, while overexpression of MDM2 exerted opposite effect. Further analysis revealed that MDM2 repressed ApoB expression by mediating its proteasomal degradation in HepG2 cells. In addition, co-immunoprecipitation assay indicated that MDM2 interacted with ApoB in HepG2 cells.

Conclusion: MDM2 regulates VLDL-TG secretion by suppressing ApoB expression.

Occult hepatitis B infection in hepatocellular carcinoma patients with undetectable hepatitis B surface antigen

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Introduction: Chronic hepatitis B and C infections are common causes of hepatocellular carcinoma (HCC) worldwide. It is not known whether patients with other causes of HCC, such as alcoholic liver disease (ALD), non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), autoimmune hepatitis, and primary biliary cholangitis have superimposed occult hepatitis B infection (OBI) as an additional risk factor causing HCC. We aimed to study the incidence of OBI in these HCC patients.

Methods: Liver DNA was extracted from tumour and adjacent non-tumour tissues from 90 patients with undetectable serum hepatitis B surface antigen and anti–hepatitis C virus. OBI was detected by four sets of nested polymerase chain reaction, using primers targeting the S, precore, polymerase, and X regions of the hepatitis B virus (HBV) genome. OBI was diagnosed when positive polymerase chain reaction detection was identified in ≥2 regions of the HBV genome.

Results: Of the 90 HCC patients, 18 (21%) had ALD, 14 (16%) had either NASH or NAFLD (denoted by mild histological fatty changes), two had primary biliary cholangitis, two had recurrent pyogenic cholangitis, one had autoimmune hepatitis, and the remaining 53 (60%) had cryptogenic HCC (ie no cause identified). OBI was detected in 50/90 (56%) of HCC patients. Specifically, OBI was detected in 7/18 (39%) patients with ALD, 8/14 (57%) patients with NAFLD/NASH, 1/2 (50%) patient with primary biliary cholangitis, and 34/53 (64%) patients with cryptogenic HCC.

Conclusion: Nearly 60% of patients with cryptogenic HCC had OBI. This suggests that the significance of HBV infection causing HCC may be underestimated. Around 40 to 50% of HCC patients with ALD or NAFLD/NASH had OBI, suggesting that OBI may be a common synergistic factor (with ALD or NAFLD/NASH) for hepatocarcinogenesis in these patients.

91 Predictive value of acute kidney injury for major adverse cardiovascular events following tricuspid annuloplasty: a comparison of three consensus criteria

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Background: Tricuspid annuloplasty is increasingly performed, but the clinical outcome is not always satisfactory. Acute kidney injury (AKI) is a common complication following cardiac surgery and can predict outcome. Nonetheless, the occurrence rate and prognostic value of AKI after tricuspid annuloplasty are unclear.

Methods: This study reviewed 339 consecutive patients (42% male) aged 65 ± 11 years who underwent tricuspid annuloplasty. The incidence of AKI was defined according to the risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) criteria, acute kidney injury network (AKIN), and kidney disease improving global outcomes (KDIGO) criteria. Major adverse cardiovascular event (MACE) was define as death, heart failure, stroke, and myocardial infarction (MI). The influence of AKI on MACE was evaluated as a short-term outcome and outcome beyond 30 days.

Results: The incidence of AKI, defined according to the RIFLE, AKIN, and KDIGO criteria, was 57%, 52%, and 53% respectively. MACE occurred in 94 cases (21 deaths, 63 heart failure requiring hospitalisation, 7 stroke, and 3 MI). For short-term outcome, AKI defined by all three scoring systems was independently associated with MACE and death ($P<0.01$ for both), but not heart failure, stroke, or MI. For outcome beyond 30 days, AKI by all three criteria was associated with MACE and heart failure. Only AKI defined by the AKIN and KDIGO criteria, but not the RIFLE criteria, was independently associated with death.

Conclusion: AKI affects over half of all patients who undergo tricuspid annuloplasty, and has a major and long-lasting impact on survival, MACE, and heart failure. The AKIN and KDIGO criteria are more useful than the RIFLE criteria when determining the prognostic value of AKI for mortality beyond 30 days.

92 The role of adipocyte fatty acid binding protein in the development of liver fibrosis

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Introduction: Liver fibrosis resulting from chronic liver injury contributes to the progression of hepatic cirrhosis. Under the stress of damage factors, hepatic stellate cells (HSCs) trans-differentiate into myofibroblast-like cells and take the main role of extracellular matrix secretion contributing to the development of liver fibrosis. Adipocyte fatty acid binding protein (A-FABP) is an adipokine that implicated in the pathogenesis of liver disease. We investigate the role of A-FABP in the bile duct ligation (BDL)-induced liver fibrosis.

Methods: A-FABP knockout (KO) mice and their wild-type littermates received common BDL or sham operation, and were assessed for liver injury for 2 weeks.

Results: Significant elevation of plasma and hepatic A-FABP were observed in BDL-induced wild-type mice. Comparing to the wild-type mice, BDL-induced A-FABP KO mice showed significantly reduced plasma bilirubin accumulation, hepatic necrosis area, and hepatic collagen formation, indicating a milder cholestatic liver fibrosis. A decreased expression of alpha-smooth muscle actin in BDL-induced A-FABP KO mice liver suggests the attenuation of HSC activation. Moreover, the BDL-induced expression of transforming growth factor beta 1 (TGF-beta1), a well-known multifunctional fibrogenic factor in liver, was also attenuated in A-FABP KO mice. Treatment of recombinant A-FABP significantly induced the expression of TGF-beta1 in primary HSCs. Mechanistic study showed that A-FABP stimulates the TGF-beta1 expression in HSCs through enhancing the binding activity of transcription factor AP-1 on its promoter region.

Conclusion: A-FABP facilitates the development of liver fibrosis by enhancing the expression of hepatic TGF-beta1 in HSCs.

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Deciphering the molecular mechanism of signal-transducing adaptor family member 1 in the regulation of hepatic cholesterol metabolism

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Introduction: Familial hypercholesterolemia is a common inherited disorder that causes elevation in the low-density lipoprotein (LDL) cholesterol level. Although the disease is inherited in an autosomal dominant manner, the disease exhibits a gene dosage effect. Mutations of three genes, namely LDL receptor (LDLR), specific domains of apolipoprotein B (APOB), and proprotein convertase subtilisin/kexin 9 (PCSK9), have been shown to cause familial hypercholesterolemia. Two independent studies identified that mutations in signal-transducing adaptor family member 1 (STAP1) is also associated with familial hypercholesterolemia. Although the phenotype for STAP1 carriers is milder than that for APOB or LDLR, STAP1 carriers showed significantly higher levels of plasma total cholesterol and LDL, and slightly but significantly higher triglyceride levels, compared with non-affected relatives. This study aims to validate these correlations and explore the mechanisms beneath.

Method and results: Our microarray data of comparison of the changes in hepatic gene expression in wild-type mice under standard chow or diet-induced obesity treatment found that the expression of hepatic STAP1 mRNA was dramatically upregulated by high-fat diet treatment. As shown in the amino acid sequence including the mutated regions, STAP1 are highly conserved between human and mouse (83% identity and 90% similarity). Therefore, diet-induced obese mice were used to decipher the molecular mechanism of STAP1 in hepatic glucose metabolism. Agreed with the microarray findings and expression databases (BioGPS and PaxDB), STAP1 mRNAs were mainly detected in the spleen of high-fat-diet mice and significantly increased in hepatic STAP1 mRNA, but not in other tissues. Additionally, we confirmed that STAP1 mainly expressed in the non-hepatocyte fraction by subcellular fractionation, and STAP1 mRNA was mainly detected at CD19+ B cells, which were enriched by B cell isolation kit (Miltenyi Biotec) and detected by flow cytometric analysis.

Conclusion: Our finding provides a novel and crucial role of STAP1 in a liver-specific way under diet-induced-obesity–induced lipid and glucose metabolisms.

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PRMT1 expression but not its methyltransferase activity contributes to high-fat-diet–induced hepatic insulin resistance via inhibition of Akt signalling pathway

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Introduction: Non-alcoholic fatty liver disease (NAFLD) is a medical condition characterised by high intrahepatic triglyceride accumulation due to various causes other than excessive alcohol consumption. Poor eating habits and malnutrition (including dietary deficient in methyl donors such as folate, B12, choline, etc) could lead to NAFLD. Protein arginine methyltransferase (PRMT) 1 is the predominant type of PRMTs responsible for at least 85% of all arginine methylation in cells, including hepatocytes. This study aims to investigate the mechanism underlying the roles of hepatic PRMT1 in the regulation of glucose and lipid metabolism of obese subjects.

Method and results: In diet-induced obese mice, hepatic mRNA and protein of PRMT1 were significantly upregulated but the level of hepatic arginine-methylated protein was paradoxically downregulated. To define the molecular mechanism underlying the elevation of the hepatic PRMT1 in diet-induced obese mice, mice fed with standard chow diet and treated with immunostimulant polyinosinic-polycytidylic acid showed significantly elevated expression of PRMT1 through the nuclear factor kappa B (NF-kappaB) pathway and overexpressing the NF-kappaB subunits, c-Rel and p65, induced significant expression of PRMT1. Besides, the cis-elements for NF-kappaB recruitment were identified at -1500 to -900 bp of PRMT1 promotor by promoter-reporter constructs. In addition, overexpression of PRMT1 in HepG2 cells inhibited insulin-stimulated Akt phosphorylation. Surprisingly, overexpression of catalytically inactive mutant PRMT1 (G98R) also suppressed the insulin-stimulated Akt phosphorylation.

Conclusion: Our finding provides the first evidence overexpression of PRMT1 in the liver of obese mice that may contribute, albeit partially, to hepatic insulin resistance.

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Effects of pegylated arginase on small cell lung cancer in vitro and in vivo

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Background: Small cell lung cancer (SCLC) is characterised by frequent relapse, and current treatments lack tumour specificity. Arginase is an important enzyme in human, but it is deficient in some tumours. Arginine deprivation has become a potential therapeutic option in selected tumours. BCT-100 is a pegylated arginase that has demonstrated anticancer activity in arginine auxotrophic tumours such as melanoma, hepatocellular carcinoma and acute myeloid leukaemia. One of resistance mechanisms to arginase is overexpression of argininosuccinate synthetase (ASS1) and ornithine transcarbamylase (OTC). This study aims to determine the effects of BCT-100 on SCLC in vitro and in vivo.

Methods: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay was used to detect cell viability of different SCLC cell lines after BCT-100 treatment. Western blotting was used to evaluate the protein expression. Knockdown of OTC was performed using specific siRNA. Xenograft models were established in nude mice for testing the anticancer effect of BCT-100.

Results: The half maximal inhibitory concentration (IC50) values of BCT-100 in H69, DMS79, H187, H209, H446, H510A, H526, H841, and SW1271 cells were 462.9 ± 112.2, >1000, 24.9 ± 6.4, 8.6 ± 0.8, 18.0 ± 0.7, 18.2 ± 4.0, 10.1 ± 0.7, >1000, and 49.2 ± 7.4 mU/mL respectively. Knockdown of OTC increased sensitivity to BCT-100 in H841 cells, partially mediated via apoptosis. Mitochondrial membrane depolarisation was observed in BCT-100 treatment and cytochrome c and SMAC were released from mitochondria to cytosol. Besides, cell cycle–specific proteins, cyclin A2, cyclin B1, and CDK4, were downregulated in a time-dependent manner. The tumour growth was inhibited and median survival of mice was prolonged in BCT-100 group in H446 and H510A xenograft models. Serum and intratumoural arginine level was sharply decreased, associated with G1 arrest and apoptosis in H446 and H510A xenografts.

Conclusion: The SCLC cell lines with low expression of ASS1 and OTC were susceptible to BCT-100 treatment. Reactive oxygen species was involved in BCT-100 induced-apoptosis. BCT-100 showed potential anticancer activity in SCLC xenograft models.

Antiphospholipid antibodies in lupus nephritis: impact on clinical manifestations and long-term outcomes

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Introduction: Antiphospholipid antibodies (APAs) are a heterogeneous family of autoantibodies that bind either phospholipid-binding proteins or phospholipid/phospholipid-binding protein complexes, and are associated with heightened risk of thrombotic and obstetric complications. The clinical significance of APAs in lupus nephritis (LN) remains controversial.

Methods: We retrospectively reviewed all LN patients from 2000 to 2017, and compared the clinical outcomes/complications between LN patients who were seropositive or seronegative for APAs.

Results: Overall, 149 LN patients (53 were seropositive and 96 were seronegative for APA) were followed up for 155.8 ± 61.0 months. Compared with APA-negative patients, APA-positive patients showed a more rapid decline in renal function (-1.44 mL/min/year vs -0.38 mL/min/year, P=0.027) and higher incidence of stage 3 or above chronic kidney disease after 5 years (9.4% vs 2.1%, P=0.043) but showed no difference in 15-year renal survival (P=0.537). APA-positive patients showed inferior long-term patient survival at 15 years (85% vs 95%, P=0.043), and had more thrombotic events (P=0.030) and miscarriages (P=0.006).

Conclusion: APAs contribute to renal function decline and thrombosis in LN patients.

B cell signatures in lupus nephritis: impact on disease stability

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Introduction: B lymphocytes and their signatures assume important roles in the pathogenesis of lupus nephritis (LN). Their impact on disease relapse in LN patients remains unclear.

Methods: We compared the B cell subsets and relevant signatures (BACH1, BACH2, and PAX5) in LN patients who were multiple relapsers (defined as ≥3 relapses unrelated to non-compliance) and non-relapers (defined as no relapse after the presenting episode).

Results: Overall, 33 patients (20 multiple relapsers and 13 non-relapers) were analysed. Multiple relapsers showed lower percentage of peripheral naïve cells (3.5% ± 4.5% vs 7.9% ± 8.9%, P=0.026) and memory B cells (1.3% ± 2.4% vs 2.2% ± 2.1%, P=0.012) and higher plasma cell-to-naïve B cell ratio (1.5 ± 2.2 vs 0.2 ± 0.3, P=0.011), compared with non-relapers. Multiple relapsers also showed higher miRNA148a in the serum (relative expression [RQ]: 4.3 ± 2.9 vs 0.7 ± 0.6, P=0.002) and plasma cells (RQ: 3.5 ± 1.6 vs 1.4 ± 1.2, P=0.128), and lower BACH2 expression in peripheral naïve B cells (RQ: 26.3 ± 13.8 vs 53.9 ± 12.3, P=0.018) and plasma cells (RQ: 12.9 ± 3.1 vs 28.1 ± 11.9, P=0.036) but showed non-significant difference in BACH1 and PAX5 (P>0.05 for both).

Conclusion: Increased miRNA148a in serum and B cell subsets might lead to BACH2 downregulation, and thus disturbed B cell subset profile and escalated risk of renal flares.

Cognitive impairments in chronic temporal lobe epilepsy patients: an event-related potential study of prospective memory

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Introduction: Cognitive impairments are common in patients with temporal lobe epilepsy (TLE), and impairment of prospective memory (PM) can seriously affect their daily independence. PM has several cognitive components related to working memory, inhibition, and other executive functions. This study aimed to delineate the PM impairment in patients with TLE.

Method: A total of 68 subjects were recruited including 23 refractory TLE patients, 19 well-controlled TLE patients, and 26 healthy controls. They were assessed with neuropsychological tests including the digit span test, verbal fluency test, and Symbol Digit Modalities Test. An event-related potential task was used to explore the neural correlates of the PM. A PM paradigm combined with sub-tasks, including an oddball task and a go/no go task, were performed to delineate which cognitive component was more impaired.

Results: TLE patients scored worse than healthy controls in the three neuropsychological tests. Reduction of the P300 amplitudes in the oddball task revealed impaired novel detection in the central-parietal sites in the well-controlled TLE patients. Decreased P3 amplitudes over the frontal-central sites in refractory TLE patients indicated impaired inhibition. Reductions in amplitudes of the prospective positivity component over the frontal, central, and parietal sites in refractory TLE patients suggested PM impairment.

Conclusion: Adverse effects of TLE on PM may be caused by complicated mechanisms involving frontal and central sites and are partly attributed to impairment of inhibition function.

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Effect of glucagon-like peptide-1 receptor agonist on hypertension-induced atrial remodelling

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Introduction: Atrial fibrillation (AF) is one of the most common causes of stroke. Hypertension-induced atrial remodelling is the most common risk factor for AF. Patients receiving GLP-1 receptor agonist have reduced AF. This study investigates the effect of glucagon-like peptide-1 receptor agonist (GLP1RA) on AF prevention.

Method: Hypertension was induced in 15 swines using angiotensin II infusion. At 8 weeks, GLP1RA was randomly given to the swines for 8 weeks in a ratio of 1:2. Effect of GLP1RA in atrial remodelling was assessed at 0, 8, and 18 weeks.

Results: At 0 and 8 weeks, the treatment (n=5) and control (n=10) group had no significant difference in body weight, blood pressure, interventricular septal thickness at diastole, left ventricular end-diastolic pressure, -dP/dt, or end-diastolic pressure volume relationship. At 18 weeks, the two groups had no significant difference in body weight (78.2 ± 2.26 vs 80.4 ± 2.67 kg, P=0.558), systolic blood pressure (144 ± 5.1 vs 169.2 ± 7.3 mmHg, P=0.229), or diastolic blood pressure (94 ± 5.1 vs 105.3 ± 5.6 mmHg, P=0.520). Nevertheless, the treatment group had significantly lower interventricular septal thickness at diastole (0.96 ± 0.09 vs 1.19 ± 0.03 mm, P<0.05), left ventricular end-diastolic pressure (8 ± 0.86 vs 10 ± 1.14 mmHg, P<0.05), -dP/dt (-943.6 ± 94.7 vs -1387.5 ± 58.4, P<0.05), and end-diastolic pressure volume relationship (0.224 ± 0.04 vs 0.434 ± 0.03, P<0.05). In biomarker study, the treatment group also had reduced TGF-β1 (178.9 ± 7.6 vs 348.5 ± 24.1 pg/mL, P<0.05), sICAM-1 (0.823 ± 0.56 vs 2.308 ± 0.378 ng/mL, P<0.05), serum TNF-α (36.92 ± 0.81 vs 56.03 ± 2.66 pg/mL, P<0.05), reactive oxygen species (13.86 ± 3.8 vs 30.27 ± 13.9 uM, P<0.05), and MMP-2 (19.08 ± 0.39 vs 28.16 ± 0.42 ng/mL, P<0.05) expression.

Conclusion: GLP1RA halted the progression of hypertension-induced left ventricular functional and structural remodelling independent of body weight or blood pressure but was associated with reduced profibrotic markers, inflammatory markers, and oxidative stress.

Myocardial dysfunction in diabetic patients with periodontitis

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Objective: To evaluate the relationship of periodontitis with myocardial function in type-2 diabetes mellitus (T2DM) patients.

Methods: Overall, 115 T2DM patients without documented cardiovascular disease history were recruited. Full-mouth periodontal examination and echocardiographic assessment were performed. Left ventricular (LV) systolic function was assessed using speckle tracking strain analysis to reveal subclinical dysfunction. Tissue Doppler was applied to evaluate diastolic function. Severity of periodontitis was evaluated by probing depth measurements. Blood samples were collected for detailed biochemical test.

Results: After periodontal examination, 83 patients with periodontitis were further divided to moderate (n=41) or severe (n=42) group based on the value of sites with probing depth of ≥4 mm (%), and the rest were controls. Patients in the moderate periodontitis group demonstrated significantly higher E/e ratio (10.5 ± 2.9 vs 8.4 ± 1.7, P<0.01) and global longitudinal strain (-17.5 ± 2.0% vs -19.2 ± 2.2%, P<0.01), compared with the control group. Multivariate analysis showed that periodontitis was independently associated with higher value of global longitudinal strain and E/e ratio (P<0.05), whereas tooth loss was associated with LV hypertrophy indicated by LV mass index. The number of endothelial progenitor cells defined by the expression of CD34, CD133, and KDR was lower in the periodontitis groups, compared with the control group (P=0.03). Moreover, the periodontitis groups showed significant higher level of high-sensitive C-reactive protein (P<0.01).

Conclusions: In patients with T2DM, periodontitis could be a risk factor in the development of myocardial dysfunction.

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