香港中文大學
The Chinese University of Hong Kong

Faculty of Medicine
The Chinese University of Hong Kong

生物醫學學院
School of Biomedical Sciences

School of Biomedical Sciences 生物醫學學院
Postgraduate Research Days 2011

27th, 28th October
The Chinese University of Hong Kong

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Welcoming Message from the Director of School of Biomedical Sciences

It is with great pleasure and pride I write this welcoming message for the *SBS Postgraduate Research Day 2011*. This is the second year of this flagship event of the School of Biomedical Sciences, which is organized by and for our students.

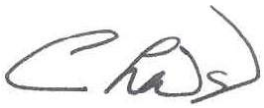
A student body with strong commitment and craving for pursuing research excellence is an integral part of any academic unit. The creativity, vigor and intellectual activeness of the student body, in terms of reflecting how thriving our School is, are certainly ***no less important than*** those demonstrated by academic staff and investigators. It is always my belief that the more the number of high-caliber graduate students we have, the better the academic and research performance of our academic staff, and vice versa.

We strive to provide a desirable and interactive environment for our graduate students. In this past year, I am most delighted to see the remarkable progress made in our graduate education, such as the restructuring of our graduate curriculum, the reorganization of the graduate seminar series, the formation of a new Graduate Student Association, the introduction of laboratory rotation system, etc. Our graduate students are also taking care of their welfare into their own hands. I am especially indebted to Ms Gu Shen and her team in pulling our students together in organizing the first ever student-organized Orientation Day for our incoming students. This is indeed a big achievement bearing in mind the fact that our School is scattered over five buildings. Indeed, I earnestly look forward to the upcoming relocation to the new Lo Kwee-Seong Integrated Biomedical Sciences Building where the cohesiveness, social and scholarly interaction, and scientific exchange between our students and academic staff can be further promoted.

Looking back to almost forty years ago, the time when I first started my life-long research career, the bittersweet journey was ***by no means different from yours*** which was also full of tears and laughter, joy and frustration, as well as self confidence and self doubt. These polar sentiments kept perplexing my mind along with the countless trials and errors, and so the many sleepless nights. While the local, regional and global landscape in research arenas has been increasingly competitive over the past decade, especially in terms of pursuing high-impact publications and securing research funding and peer recognition, being "curious, adventurous, humble and persistent" is still the ***very key*** to achieving scientific excellence, unveiling the unseen, unlocking the unexplored, and so to becoming a successful and well-respected investigator and scholar. As what the late Steve Jobs always remarked, "Stay hungry, Stay foolish" (求知若飢、虛心若愚) – this also serves as a motto for our graduate students who determine to excel in their career of choice.

Slightly different from last year, the *Postgraduate Research Day* this year is divided into two days, with the first day for poster presentations and the second day for oral presentations by the authors of the ten best posters to compete for different prizes. I would like to take this opportunity to congratulate all individuals involved in planning, organizing, and coordinating this event, in particular members of the Organizing Committee of the Graduate Student Association, for their dedication, effort, and time that make the event a reality. It is my hope that through organizing such activities, our students not only develop stronger sense of bondage and togetherness, but more importantly, their dexterity and versatility in team-work, collaboration, communication, mutual trust, and understanding, virtues needed for a successful career in any discipline. I would also like to extend my heartfelt gratitude to the Graduate Education office for it's unfailing effort in supporting our graduate students.

On behalf of all staff of the School of Biomedical Sciences, I wish you all a hugely successful *Postgraduate Research Day 2011*.



Wai-Yee Chan, Ph.D.
Professor of Biomedical Sciences &
Director, School of Biomedical Sciences
The Chinese University of Hong Kong
October 2011

School of Biomedical Sciences
Postgraduate Research Day 2011

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Special Acknowledgements

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Program of SBS Postgraduate Research Day

27th Oct, 2011 (Thursday)

Time	Event	Venue
09:00 – 09:15 am	Registration	G/F BMSB
09:15 – 09:25 am	Opening Ceremony (Speech given by Director)	G18 BMSB
09:25 – 09:30 am	Photo Session	G18 BMSB
09:30 – 10:45 am	Poster Presentation (Reproduction, Development and Endocrinology)	207 BMSB
10:45 – 12:00 nn	Poster Presentation (Stem Cell and Regeneration)	211 BMSB
-Break Time-		
01:00 – 02:15 pm	Poster Presentation (Cancer and Inflammation)	215 BMSB
02:15 – 03:30 pm	Poster Presentation (Neuro-degeneration, -development, and Repair)	211 BMSB
03:30 – 04:45 pm	Poster Presentation (Vascular and Metabolic Biology)	215 BMSB

*BMSB – Basic Medical Sciences Building

28th Oct, 2011 (Friday)

Time	Event	Venue
09:00 – 10:15 am	1st session of Oral Presentation	LG23 SC
10:15 – 10:30 am	Break	LG23 SC
10:30 – 11:45 am	2nd session of Oral Presentation	LG23 SC
11:45 – 12:00 nn	Closing Ceremony	LG23 SC
12:00 – 12:15 pm	Prize- giving Ceremony	LG23 SC

*SC – Science Centre

Cancer and Inflammation

Venue: Rm 215, BMSB

Title of Poster Presentation	Name	Abstract No.
The Human Host Defense Peptide LL-37 Induces Caspase-independent Apoptosis Via Apoptosis-Inducing Factor And Endonuclease G in Colon Cancer Cells	Ren Shunxiang Natalie	C1
Suppression of cancer cell senescence by orphan nuclear receptor TLX	Wu Dinglan	C2
Effects of Toll-like Receptor 2 Ligands on substance P-induced Activation from Human Mast Cells	Yu Yangyang	C3

Abstracts

Title(C1): The Human Host Defense Peptide LL-37 Induces Caspase-independent Apoptosis Via Apoptosis-Inducing Factor And Endonuclease G in Colon Cancer Cells

S.X. Ren and C.H. Cho

Program: PhD in Pharmacology; Supervisor: Cho C.H.

LL-37, a human host defense peptide, plays pivotal roles in diverse biological processes, including natural immunity, inflammation and tissue repair. However, the function of this peptide in tumorigenesis remains unclear. In this study, the effect of LL-37 on human colon cancer HCT116 cells was characterized. LL-37 induced extensive DNA fragmentation, chromatin condensation and phosphatidylserine externalization without causing caspase activation. Moreover, these effects were not blocked by caspase inhibitors. LL-37 induced apoptosis via downregulation of Bcl-2 and upregulation of Bak and Bax in a p53-dependent manner. In this connection, the pro-apoptotic effect of LL-37 was reversed by Bcl-2 overexpression, genetic ablation of Bax, or p53 siRNA. LL-37 also induced the upregulation and nuclear translocation of apoptosis-inducing factor (AIF) and endonuclease G (EndoG), whose targetings by siRNAs render the cells resistant to LL-37-induced apoptosis. Above all, the pro-apoptotic effect of LL-37 was found to be mediated through a pertussis toxin-sensitive Gi-coupled receptor. Taken together, we demonstrated that LL-37 induced caspase-independent apoptosis via the p53-Bcl-2/Bak/Bax and AIF/EndoG pathways. These findings may open up novel therapeutic avenue for the treatment of colon cancer using LL-37.

Title (C2): Suppression of cancer cell senescence by orphan nuclear receptor TLX

Dinglan Wu and Franky L. Chan

Program: PhD in Anatomy; Supervisor: Chan Franky L.

Cellular senescence represents an irreversible form of cell-cycle arrest that acts a key process of tumor suppression and targeting to pathways involved in this process can provide potential therapeutic strategies to cancer treatments. The *Tailless* TLX gene (NR2E1) is an orphan nuclear receptor and functions mainly as a constitutive transcriptional repressor in target cells. Functional studies reveal that TLX plays important roles in the maintenance and self-renewal of both embryonic and adult neural stem cells. In an expression profile study, we demonstrated that TLX exhibited an up-regulation expression pattern in many prostate cancer cell lines and high-grade clinical prostate cancer. Here we analyzed the functional role of TLX in prostate cancer cell growth regulation. Depletion of TLX by RNA interference dramatically suppressed *in vitro* cell proliferation caused by cellular senescence in two prostate cancer cell lines (LNCaP and DU145), as assessed by senescence-associated β-galactosidase (SA -βGal), and also their *in vivo* tumoroigenicity. Moreover, TLX overexpression enhanced many advanced malignant growth phenotypes in prostate cancer cells, via suppression of cellular senescence and also protected prostate cancer cells (LNCaP) against doxorubicin-induced senescence accompanied with a significant suppression of $p21^{WAF1/CIP1}$. Mechanistic dissection showed that TLX could suppress cellular senescence via its direct transcriptional regulation of $p21^{WAF1/CIP1}$ but independence of $p16^{INK4}$ and p53. Taken together, our results show for first time that TLX, which is overexpressed in prostate cancer, functions to suppress premature senescence and also targeting to TLX could be a potential therapeutic approach for prostate cancer treatment.

Title(C3): Effects of Toll-like Receptor 2 Ligands on Substance P-induced Activation from Human Mast Cells

Y.Y Yu and H.Y. Alaster Lau

Program: PhD in Pharmacology; Supervisor: Lau H.Y. Alaster

Human mast cells express Toll-like receptors and serve as key players in innate immunity against a wide variety of pathogens. The neuropeptide substance P is well known for its role in evoking neuroimmunology responses and in participating in disease conditions such as allergic asthma by activation of mast cells. In this study, we investigate the influence of Toll-like receptor 2 (TLR2) ligands peptidoglycan (PGN) and Pam3CSK4 on substance P-triggered degranulation and IL-8 release in the human mast cell line, LAD2 cells. PGN and Pam3CSK4 did not cause obvious degranulation on their own, but induced the release of IL-8. Pretreatment of PGN and Pam3CSK4 inhibited substance P-induced degranulation. Calcium mobilization is a key event for mast cell degranulaton. Pretreatment of Pam3CSK4, but not PGN blocked calcium mobilization-induced by substance P. In the case of IL-8 release, PGN acted in synergy with substance P, but Pam3CSK4 failed to demonstrate similar effect. Further study revealed that the release of IL-8-induced by PGN and Pam3CSK4 was blocked by PTX. Furthermore, the mitogen-activated protein kinase Erk played important role in PGN, Pam3CSK4 and substance P-induced IL-8 release. However, different from PGN, the release of IL-8-induced by Pam3CSK4 and substance P was blocked by Cyclosporin A (CsA), an inhibitor for Ca^{2+} /calcineurin-mediated nuclear factor of activated T cells (NFAT) activation. These findings suggest that human mast cells LAD2 can be differentially activated by different TLR2 ligands via distinct signaling pathways.

Neuro-degeneration, -development and Repair

Venue: Rm 211, BMSB

Title of Poster Presentation	Name	Abstract No.
Huperzine A attenuates amyloid pathology by regulating brain iron metabolism in Alzheimer transgenic mice	He Xuan	N1
Decreases of enteric neurons and GFAP positive glia in ileum of a mouse model of Alzheimer's disease	Hui Chinwai	N2
Alleviation of parkinsonian motor symptoms by deep brain stimulation: involvement of the antidromic response through the "hyperdirect" pathway	Li Qian	N3
Glucose-lowering and Emetic Action of the GLP-1 Receptor Agonist, Exendin-4, in the Ferret	Lu Zengbing	N4
Effects of Nicotine on Gastric Myoelectrical Activity in ICR Mice	Wang Eileen	N5
Ampakine rescues chronic intermittent hypoxia-induced impaired synaptic plasticity in mouse hippocampus and memory deficit	Xie Hui	N6
Suramin is a potent stimulator of retinal ganglion cell regeneration	Yu Sauwai	N7

Abstracts

Title(N1): Huperzine A attenuates amyloid pathology by regulating brain iron metabolism in Alzheimer transgenic mice

X. He, Q. Gong, T.Y. Tsim, Y. Ke and S.C. Michael Tam

Program: MPhil in Biomedical Sciences; Supervisor: Tam S.C. Michael, Ke Y.

The accumulation and deposition of amyloid-β (Aβ) peptides in the brain is a central pathological hallmark precipitating Alzheimer's disease (AD). Recent studies suggest a role of brain iron accumulation in the pathogenesis of AD. Huperzine A (HupA), a novel alkaloid isolated from the Chinese herb *Huperzia serrata*, is a potent inhibitor of acetylcholinesterase (AChE). It is found that HupA improves cognitive deficits and possesses multiple neuroprotective effects. However, no evidence exists to link the therapeutic effects of HupA to brain iron metabolism. In this study APPsw/PS1dE9 transgenic mice were fed with the control diet (containing 60 mg Fe/kg diet) or the high-iron diet supplied with 2.5% carbonyl iron (24310ppm Fe) from 2-month-old age. Meanwhile HupA (0.1mg/kg, po, once per day) or its vehicle (saline) was administered. The 9~10-month-old mice were detected for Aβ levels, oligomers formation and plaques aggregation as well as iron content and expression of iron transport proteins in the brain. Here, for the first time we report that HupA reduces insoluble but not soluble Aβ levels, markedly ameliorates amyloid plaques, but does not decrease the soluble Aβ oligomers in the brain of transgenic mice. In concert with these observations, we find that HupA decreases iron content in the brain. Moreover, alleviation of Aβ pathology by HupA can be reversed by feeding the transgenic mice with high-iron diet, which indicates that HupA could diminish Aβ pathology via regulating brain iron content. As a validation of these findings, we confirm that HupA decreases iron content through regulating expression of iron transport proteins including Transferrin Receptor (TfR), Ferroportin (Fpn), DMT1 with IRE in the brain. These results suggest that in addition to the cholinergic inhibition and neuroprotection, alteration of iron metabolism is a novel target of HupA and could also play important roles for the treatment of neurodegenerative diseases.

Title(N2): Decreases of enteric neurons and GFAP positive glia in ileum of a mouse model of Alzheimer's disease

C.W. Hui, C.K. Yeung, J.A. Rudd, H. Wise and L. Baum

Program: MPhil in Biomedical Sciences; **Supervisor:** Professor Rudd John A.

Alzheimer's disease (AD) is associated with a deposition of amyloid plaques and a loss of cholinergic neurons in the central nervous system. This can be modelled to a certain extent using transgenic mice (Tg2576), which express the human amyloid precursor protein (APP). Studying gastrointestinal (GI) tract functions using a valid AD model may provide new perspectives on the treatment of degenerative diseases. In the present study, we compare the structure of the antrum (in stomach) and ileum of Tg2576 mice and their wild type controls using immunohistochemistry.

Six-month old Tg2576 mice (n = 3) and their wild type controls (n = 6) were killed, and sections of antral and ileal tissues were dissected and fixed with 4% paraformaldehyde. Cells in the myenteric plexus were stained with primary antibodies against PGP to label enteric neurons, anti-CD117 to label interstitial cells of Cajal (ICC), and anti-S100 and anti-GFAP to label glia. Cells were visualised using confocal microscopy, and area was quantified using ImageJ software (National Institutes of Health). Statistical comparisons were made using Student's t-test (Prism, version 5, GraphPad Software Inc., U.S.A.).

The areas (mm^2) of neurons, glial cells (GFAP positive) and ICC in the antrum of wild type controls were 0.063 ± 0.005, 0.054 ± 0.005, and 0.093 ± 0.009, respectively; and the areas observed in Tg2576 tissue were not significantly different ($P > 0.05$). The areas of neurons, glial cells (GFAP positive) and ICC in the ileum of wild type controls were 0.068 ± 0.003, 0.036 ± 0.002, and 0.099 ± 0.008, respectively. Neuronal and glial (GFAP positive) areas in Tg2576 tissues were 58.9 ($P < 0.001$) and 67.6 % ($P < 0.001$) lower, respectively, but there were no differences for ICC ($P > 0.05$). There was no statistical difference between the ratio of GFAP positive glia and S100 positive glia (Tg2576: 0.58 ± 0.19, n = 3 and wild type controls: 0.45 ± 0.08, n = 6, $P > 0.05$).

In conclusion, neuronal and GFAP positive glial areas of Tg2576 mice were lower compared with their wild type controls. This provides a good model for the investigation of degenerative diseases by studying GI tract morphology.

Title(N3): Alleviation of parkinsonian motor symptoms by deep brain stimulation: involvement of the antidromic response through the "hyperdirect" pathway

Qian Li and Wing-Ho Yung

Program: PhD in Physiology; Supervisor: Yung Wing-Ho

Although deep brain stimulation of the subthalamic nucleus (STN-DBS) is now a recognized therapeutic option for Parkinson's disease (PD), the exact mechanism is still unsettled. Previous studies suggest that the action of STN-DBS is not confined to the local stimulation site, but more widespread throughout the connected network as a consequence of activation of axons. As the cortico-subthalamic projection (the "hyperdirect" pathway) provides a major input to STN, here we search for evidence of the antidromic activation of cortico-subthalamic projection during STN-DBS.

A conventional hemi-parkinsonian rat model was induced by unilateral injection of 6-hydroxydopamine into medial forebrain bundle (AP: -4.4, ML: -1.1, DV: 8.0mm). A bipolar stimulus electrode was inserted into ipsilateral STN (AP: -3.8, ML: -2.4, DV: 7.8mm). Neuronal activities were monitored by implanting two pairs of 16-channel micro-wire recording arrays into the primary motor cortex (MI, AP: +2.5, ML: ± 3.0, DV: 1.7mm) bilaterally. Improvement in motor functions during STN-DBS was assessed by open field test. Several stimulation frequencies and pulse widths were chosen to evaluate the dependency of the beneficial effect on stimulation parameters. Apomorphine-induced contralateral rotation test was also performed. It was found that only high frequency STN-DBS (>120Hz) could bring significant beneficial effects.

During behavioral tests, both spikes and local field potentials (LFPs) were recorded. Putative corticosubthalamic pyramidal neurons were identified by the antidromic activation effect. STN-DBS evoked a fixed short latency (1.13±0.07ms), presumed antidromic spike in these corticosubthalamic pyramidal neurons. Measuring the mean firing rate before, during and after the DBS, we found that the majority of corticosubthalamic pyramidal neurons (52.5%, 41/78) and cortical interneurons (58.5%, 38/65) increased their firing during stimulation. Furthermore, the abnormal burst firing pattern and pathological oscillatory rhythms in MI neurons were ameliorated, as shown by the Legendy surprise method, auto-correlation and spike-LFP coherence analyses.

Based on the results, we hypothesize that evoked antidromic activation of the "hyperdirect" pathways from the cortex to the subthalamic nucleus is a major contributor of the therapeutic effects of in STN-DBS by breaking the abnormal activities of motor cortex neurons known to underlie the parkinsonian motor deficits.

Title(N4): Glucose-lowering and Emetic Action of the GLP-1 Receptor Agonist, Exendin-4, in the Ferret

Z.B. Lu, N. Percie Du Sert, G Lin, D.T. Yew, P.L. Andrews and J.A. Rudd

Program: PhD in Pharmacology; Supervisor: Rudd John A.

Objectives: Glucagon-like peptide-1 (GLP-1) receptor agonists, such as exendin-4, are being developed for the treatment of type-2 diabetes and obesity. However, treatment with exendin-4 is associated with nausea and sometimes emesis. Previously, we demonstrated that exendin-4 could lower blood glucose levels, induce emesis and *c-fos* in *Sunus murinus*. In the present studies, we examine the glucose-lowering and emetic action of exendin-4 in the ferret.

Methods: *Glucose tolerance test:* male ferrets (1.2 – 2.0 kg) were anaesthetized using pentobarbitone (40 mg/kg, i.p.). They were then injected with exendin (9-39) (300 nmol/kg, s.c.) or saline (0.5 ml/kg, s.c.). 15 min later, exendin-4 (30 nmol/kg, s.c.) or saline (0.5 ml/kg, s.c.) were injected, followed by a glucose load (1.5g/kg, i.p.). Blood glucose levels were measured for up to 120 min.

I.C.V study: a guide cannula was implanted into the 3rd ventricle of male ferrets (1.2-2.0 kg) under general anaesthesia. 7 days later, they were injected with exendin-4 (0.3-30 nmol, i.c.v.) or saline (15 µl, i.c.v.) and behaviour was recorded for 1h.

Results: Prior to drug administration, the basal blood glucose level was 5.2 ± 0.4 mmol/l (n = 12). The administration of glucose caused a progressive elevation of blood glucose in the saline-treated animals, which peaked at 30 min before deceased gradually. Exendin-4 produced a 36.3% reduction in the $AUC_{0\text{-}120}$ values ($p<0.05$) (n = 3). Exendin (9-39) antagonized glucose lowering effect of exendin-4 ($P<0.05$) (n = 3), and exendin (9-39) alone increased $AUC_{0\text{-}120}$ values by 31.0% ($P<0.05$) (n = 3).

Exendin-4 at 30 nmol, i.c.v, induced 88.2 ± 48.7 retches and 11.6 ± 6.8 vomits in 14.8 ± 9.2 episodes, following a median latency of 14.9 min ($P<0.05$) (n = 3); lower doses did not induce emesis. Further, exendin-4 at 0.3-30 nmol, i.c.v, inhibited food intake ($p<0.05$) (n = 3-6), but not water intake.

Conclusion: GLP-1 receptors are involved in emesis and feeding, and in modulating blood glucose levels in the ferret.

Title(N5): Effects of Nicotine on Gastric Myoelectrical Activity in ICR Mice

E. Wang, N. Percie Du Sert, and J. A. Rudd

Program: PhD in Biomedical Sciences; Supervisor: Rudd John A.

Slow waves originate from the pacemaker network of the interstitial cells of Cajal (ICC). The enteric nervous system and smooth muscle cells are known to interface with ICCs through excitatory and inhibitory neurotransmitters. Electrogastrography reveals slow wave information. Nicotine was used to activate ganglia in an attempt to modulate excitatory and inhibitory neurons linked to ICC functioning. The aim of the study was to define the characteristics of GMA in mice, and to establish criteria for analysis. Male ICR mice were anaesthetized and surgically implanted with telemetry devices with recording wires sutured from the serosal surface of the stomach. 7 days later, baseline GMA recordings were obtained 2 h before injecting animals with nicotine (3 mg/kg, i.p.; n=8), or vehicle (saline 2ml/kg, i.p.; n=8). Recordings continued for a further 6 h. Raw data were analyzed using Spike2 (Cambridge Electronic Design, U.K.). The dominant frequency (DF) of the baseline recordings of the vehicle and nicotine treatment groups were 6.8 ± 0.4 and 6.6 ± 0.4 counts per min (cpm), respectively. For the baseline recording of the vehicle and nicotine groups, 40.9-41.8 % of the power was in the normogastric range (DF ± 2 cpm). 9.1-9.7 % and 26.6-26.6 % of the power was in the bradygastric (0 to DF-2 cpm) and tachygastric ranges (DF+2 to 15 cpm), respectively. Saline had no effect on slow waves during the experiment ($P>0.05$). Nicotine reduced the DF immediately to 5.9 ± 0.5 cpm ($P<0.001$). The effects of nicotine lasted for 2 h before the DF shifted back to pre-nicotine levels (6.8 ± 0.4 cpm). Nicotine caused bradygastria, suggesting an action to release inhibitory mediators to affect ICC. The studies demonstrate that radiotelemetry can be used to record GMA in conscious, freely moving mice, providing a convenient method to study GI functioning in a variety of circumstances.

Title(N6): **Ampakine rescues chronic intermittent hypoxia-induced impaired synaptic plasticity in mouse hippocampus and memory deficit**

Hui Xie and Wing-Ho Yung

Program: PhD in Physiology; Supervisor: Yung Wing-Ho

Obstructive sleep apnea (OSA) is a common sleep and breathing disorder resulting in intermittent hypoxia (IH), and can cause neurocognitive deficits including impairment in attention, planning and memory. It is well known that learning and memory involves long-term potentiation (LTP), a form of synaptic plasticity. Our recent work has shown that intermittent hypoxia (IH) impairs both early phase LTP (E-LTP) and late phase LTP in the hippocampus, and accompanied by a reduction in the level of brain-derived neurotrophic factor (BDNF). In this study, we examined the effects of administration of ampakine, a group of AMPA receptor modulator known to elevate endogenous BDNF level by short-term administration. Two groups of adult male mice were exposed to 7-day IH (90s cycles between 10% and 21% O_2 levels for 8 hrs) and received vehicle and ampakine injection respectively (from day 4 to day 7) while another group under normoxia served as control. We found that there was a significant increase in E-LTP in ampakine injection group (16 slices, 5 mice, 156.5±7.4%) compared with the vehicle-treated group (13 slices, 4 mice, 133.3 ± 7.9%; $P < 0.05$), and was similar to that of the normoxia group (6 slices, 4 mice, 159.1±7.6%; $P > 0.05$). Ampakine treatment also restored the decreased level of hippocampal BDNF in the IH-treated group, as revealed by Western blot. Furthermore, in radial arm maze test, ampakine administration improved the memory of the IH mice. Together, these data confirm the role of BDNF in chronic IH and that ampakine has therapeutic value for the neurocognitive symptoms of OSA subjects.

Title(N7): Suramin is a potent stimulator of retinal ganglion cell regeneration

S.W. Yu, W.K. Wong, W.S. Cheung and Y.P. Cho

Program: MPhil in Biomedical Sciences; Supervisor: Cho Eric

Background: Suramin is a polysulfonated naphthylurea that has been used as an anti-parasitic drug for many years. Interestingly, it has also been reported to be neuro-protective for some neurons and to reduce gliosis in the damaged brain. Since suramin can act as a non-specific P2 purinergic receptor antagonist, and purinergic signaling has been implicated in mediating neuronal injury and degeneration, we ask whether suramin would be beneficial in promoting regeneration of the central nervous system (CNS). Injury of the optic nerve is used as an experimental model to study the effects of suramin on the survival and regeneration of retinal ganglion cells (RGCs).

Methods: The ON of adult hamster was cut with micro-scissors to induce RGC degeneration. Suramin (dissolved in 0.9% saline) or its vehicle was injected intravitreally after injury. RGC survival was quantified by TuJ1 immunostaining. Expression of the growth-associated protein GAP-43 in surviving RGCs was studied. GAP-43 is highly expressed during neural development and its extent of expression in injured neurons correlates with the potential for regeneration. Peripheral nerve (PN) grafting to the cut ON was used to assess whether suramin could potentiate the regeneration of RGC axons into the graft. Intravitreal injection of ciliary neurotrophic factor (CNTF), a potent growth factor for RGC regeneration, was performed to compare its activity to suramin.

Results and Conclusion: Both Suramin and CNTF increased RGC survival above that of the vehicle control. Suramin, however, stimulated twice the number of RGCs to express GAP-43 compared to CNTF. Suramin also induced more RGCs to regenerate axons into the PN graft compared to CNTF. The results showed that suramin has a robust effect on RGC regeneration. However, whether its action is due to interaction with P2 receptors needs to be further examined.

Reproduction, Development and Endocrinology

Venue: Rm 207, BMSB

Title of Poster Presentation	Name	Abstract No.
Environmental factors involved in sacral neural crest cell migration in the hindgut of mouse embryos	Chen Jielin	R1
An investigation into the synergistic effects of sodium-glucose cotransporter-2 and dipeptidyl peptidase-IV inhibition on islet function and insulin sensitivity	Chen Lihua	R2
Embryonic Origin and Migratory Patterns of Mouse Microglia	Chow Wingho	R3
Comprehensively Functional Studies of miR-199a	Gu Shen	R4
Gene expression profiles of migrating sacral neural crest cells isolated from a mouse model for Hirschsprung's disease	Hou Yonghui	R5
GPER-1 mediates the inhibitory actions of estrogen on adipogenesis in 3T3-L1 cells through perturbation of mitotic clonal expansion	Yuen Manleuk	R6
Adaptor protein Dab2 is a novel regulator of skeletal muscle development and differentiation	Shang Na	R7
The biological functions of the novel prolactin(PRL2) in zebrafish retina during early embryonic development	Shi Yujian	R8
A study on the role of the cofactor β-klotho and its dependent fibroblast growth factors in pancreatic islet function	So Wingyan	R9
Ets1 regulates neural crest formation and migration in Xenopus	Wang Chengdong	R10
Regulation of hepcidin expression by BMP signaling in macrophages	Wu Xinggang	R11
Small molecule activators of microRNA-34a with anti-cancer activities identified through library screening	Xiao Zhangang	R12
Sodium-potassium pump mediates mitotic entry through upregulation of Aurora kinases activity	Xie Chuanming	R13
The role of IL-6 in regulation of GH receptor, SOCS3 and IGF-I expression in the liver	Zhao Yueshui	R14

Abstracts

Title(R1): Environmental factors involved in sacral neural crest cell migration in the hindgut of mouse embryos

Jie-Lin Chen, Xia Wang, Hideki Enomoto, Mai-Har Sham, Alan J Burns and Wood Yee Chan

Program: PhD in Anatomy; Supervisor: Chan Wood Yee

Hirschsprung's disease in humans is characterized by the absence or reduction of enteric ganglia in the distal part of the colon. It is known that all enteric ganglia in the distal colon originate from neural crest cells (NCCs) at both vagal and sacral levels during embryonic development.

Sacral NCCs in mouse embryos have been recently identified, and they were found to be able to migrate from the dorsal neural tube to the mesenchyme, aggregate as pelvic ganglia adjacent to the hindgut and then enter the distal hindgut. However, little is known about the factors that affect their migration. In the present study, we aimed to identify such factors in the microenvironment of the gut through which they migrated. We carried out a series of experiments using mouse embryos before sacral NCCs entered the hindgut at E12.5 and when sacral NCCs started to enter the hindgut at E13.5. The following results were obtained: (1) Nerve fibers extending from the pelvic ganglia were necessary for sacral NCCs to migrate into the gut tube; (2) Semaphorin-3A might be involved in regulating the entering of sacral NCCs to the hindgut; (3) Several proteins with differential expression in the distal hindgut between E12.5 and E13.5 were identified through 2D gel electrophoresis and mass spectrometry, and next we plan to investigate whether they are involved in modulating NCC migration; (4) Vagal NCCs were observed to interact with sacral NCCs and influence their migration when they met along the nerve fiber in the distal hindgut through gut recombination experiments. In summary, sacral NCC migration is a complex process with a lot of environmental factors involved.

Title(R2): An investigation into the synergistic effects of sodium-glucose cotransporter-2 and dipeptidyl peptidase-IV inhibition on islet function and insulin sensitivity

L. H. Chen and P. S. Leung

Program: PhD in Biomedical Sciences; Supervisor: Leung Po Sing

Dipeptidyl peptidase-IV (DPP-IV) inhibitors enhance incretin action and beta-cell function. Concurrently, sodium-glucose co-transporter (SGLT2) inhibitors are promising drugs to treat type 2 diabetes based on its potential for euglycemic control which is independent of insulin. In this study, we employed Linagliptin (a DPP-IV inhibitor) and BI-38335 (an SGLT2 inhibitor) to investigate their effects alone or in combination on glucose homeostasis, islet function and insulin sensitivity so as to elucidate the potential synergistic or additive effect whereby these drugs are involved.

Diabetic C57BL/KsJ db/db mice were gavaged with drugs (Linagliptin, 3mg/kg; BI-38335, 1mg/kg, alone or in combination) or vehicle once daily for 8 weeks. Serum triglycerides (TG) and non-esterified fatty acids (NEFA) levels were measured; glucose homeostasis and insulin sensitivity were assessed; islet function, β/α cells ratios and mRNA levels of genes of interest were studied.

Our results showed that 8-week combo treatment decreased blood glucose levels by 46%; increased islet glucose stimulated insulin secretion by 4 fold; improved glucose intolerance by 55%; and enhanced insulin sensitivity by 46%, all of which were significantly better than respective drug treatment alone. Combo treatments also significantly reduced serum TG by 62% and NEFA by 49% when compared with their mono-treatments. Meanwhile, combo treatment could markedly normalize islet beta/alpha cell ratio; decrease islet immune cell markers expression as well as suppressing inflammatory and other factors involved in toll-like receptor 2 (TLR2) pathway.

Taken together, these data indicate that combination treatment with BI-38335 and linagliptin appears to be synergistically or at least additively beneficial to islet cell function/architecture and insulin resistance thus improving glycemic control in db/db mice. Moreover, mechanism study has revealed that it is at least partially via the TLR2/MyD88 pathway that these two inhibitors alleviate inflammation and subsequently normalize islet morphology and thus enhance islet function.

Title(R3): Embryonic Origin and Migratory Patterns of Mouse Microglia

George W.H. Chow, T.C. Ng and W.Y. Chan

Program: MPhil in Biomedical Sciences; Supervisor: Chan Wood Yee

Microglia are resident phagocytic cells of the central nervous system sharing the same hematopoietic lineage with macrophages. Their precise embryonic origin is, however, still unknown, partly due to a lack of specific markers which can unambiguously identify pre-migratory and migratory microglial progenitors in developing embryos. In the present study, we attempted to locate the embryonic origin(s) of microglial progenitors and their migration pathways to the developing nervous system with a recently discovered early microglial lineage marker, Iba1. The spatiotemporal distribution of Iba1 immunoreactive cells and their topographical relationship with blood vessels were determined using double immunofluorescence staining for Iba1 and CD31, an endothelial cell marker. In addition, transplantation of eGFP-labelled cells from the yolk sac was also carried out. Our results support the notion that the yolk sac and the liver, the two successive hematopoietic sites at E9.5 and E10.5, are potential origins of microglial progenitors. Liver-derived microglial progenitors most probably migrate along blood vessels to the developing central nervous system. Finally, characterization of Iba1-EGFP$^{+/-}$ transgenic embryos using double immunofluorescence staining for Iba1 and eGFP showed that Iba1 expressing cells were invariably labeled with eGFP, making this transgenic mouse line an useful experimental tool for further studies.

Title(R4): Comprehensively Functional Studies of miR-199a

S. Gu, Y. K. Suen, H.H. Cheung and W.Y. Chan

Program: PhD in Biochemistry (Medicine); Supervisor: Chan Wai Yee

microRNAs (miRNAs) regulate gene expressions by pairing to the mRNAs of protein-coding genes to direct their posttranscriptional repression. Previous studies showed that hypermethylation silences the expression of miR-199a-2 in testicular germ cell tumors (TGCTs). It has been shown that miR-199a-2 is a tumor suppressor, normally modulating a spectrum of genes involved in TGCTs, and PODXL (podocalyxin-like protein) is one of such targets. We aim to find other downstream target(s) of miR-199a-2 besides PODXL and examine their roles in TGCTs. In addition, the relationship among these targets of miR-199a-2 and the overall regulation of tumorigenesis by miR-199a-2 will be studied. In contrast to the down-regulation of miR-199a-2 in TGCTs, we found that expression of miR-199a-2 was up-regulated in glioblastoma patient samples. The pathways under the regulation of miR-199a-2 to be established in TGCTs could be applied to the studies of its function in gliomas. By functional studies of the targets of miR-199a-2 in different models, a better understanding of the different functions of this microRNA in different tissues/diseases can be obtained.

Title(R5): Gene expression profiles of migrating sacral neural crest cells isolated from a mouse model for Hirschsprung's disease

Yonghui Hou, Jielin Chen, Na Shang, Taifung Wan, Hui Zhao and Wood Yee Chan

Program: PhD in Biomedical Sciences; Supervisor: Chan Wood Yee

Hirschsprung's disease (HSCR) is a congenital disease, which is found in approximately 1 in every 5000 live births. HSCR is characterized by the absence of neurons and glia in the whole or part of the gut. During embryonic development, vagal and sacral neural crest cells delaminate from the neural tube, migrate along distinct pathways, and colonize the gut to form a network of neurons and glia within the wall of the gut. Failure of neural crest cells to colonize the gut has been considered a possible cause of HSCR in humans. In this study, we analyzed with DNA microarray the gene expression profiles of migrating sacral neural crest cells isolated from the *Dominant megacolon (Dom)* mice, a HSCR animal model. We aimed to find out genes related to sacral neural crest cell migration that are specifically up- or down-regulated in the homozygous mutant when compared with their wild-type counterpart. When expression levels of various genes in normal and *Dom* homozygous sacral neural crest cells were compared, significant changes of the expression of genes including genes related to myelination, melanogenesis and adhesion molecules were found. Among all the adhesion molecules which showed changes in their expression levels, Cdh19, a type II cadherin, was significantly decreased in migrating sacral neural crest cells from $Sox10^{Dom/Dom}$ homozygous embryos as compared with those from normal wild-type embryos. The luciferase reporter assay demonstrated that Sox10 highly activated Cdh19 expression, which was seven times higher than the control level. Although it has been known that cell adhesion molecules are important for the initiation and cessation of neural crest cell migration, the role of Cdh19 in the migration of sacral neural crest cells is still not clear. In the future study, I plan to determine the expression of Cdh19 during mouse embryonic development and its role during sacral neural crest cell migration.

Title(R6): GPER-1 mediates the inhibitory actions of estrogen on adipogenesis in 3T3-L1 cells through perturbation of mitotic clonal expansion

Jacky M.L. Yuen, P. Zhu, Kathy W.Y. Sham and Christopher H.K. Cheng

Program: PhD in Biomedical Sciences; Supervisor: Cheng Christopher H.K.

Estrogen has been shown to inhibit adipogenesis. Estrogen replacement therapy therefore affects fat metabolism in post-menopausal women. A novel transmembrane estrogen receptor, GPER-1, is recently identified in various animals including mouse, rat, human and zebrafish. GPER-1 has been demonstrated to mediate various estrogenic actions in vertebrates, but the exact roles of GPER-1 in adipogenesis remain to be resolved.

GPER-1 could be found in mouse adipose tissues. We have observed an up-regulation in the expression of GPER-1 in the mouse preadipocytes cell line 3T3-L1 during induced adipogenesis. In addition, perturbation of cell differentiation was also observed in the presence of the specific GPER-1 agonist, G1, during mitotic clonal expansion (MCE) of the 3T3-L1 cells. By means of Oil-Red-O staining, the production of oil droplets in the G1-treated differentiated 3T3-L1 cells was shown to be reduced. FACS analysis and Western blotting analysis of cell cycle factors during MCE of the 3T3-L1 cells reveals an inhibition of cell cycle arrest at the G1 stage triggered by GPER-1 activation, while the viability of cells remained unaffected.

In conclusion, this study on the involvement of GPER-1 in mammalian adipogenesis reveals an elevated expression of GPER-1 during adipogenesis. In addition, an inhibition of adipogenesis by GPER-1 activation was also observed during MCE. It is therefore postulated that GPER-1 serves as a negative regulator of adipogenesis in adipose tissues. The results provide insights into the possible development of therapeutic agents for the treatment of obesity by targeting GPER-1.

Title(R7): Adaptor protein Dab2 is a novel regulator of skeletal muscle development and differentiation

Na Shang, Samuel C. Mok, Hui Zhao and Wood Yee Chan

Program: PhD in Anatomy; Supervisor: Chan Wood Yee

Dab2 is an intracellular adaptor protein and a potential tumor suppressor. In mouse embryos, our previous study indicated that Dab2 was expressed in the medial aspect of the dermomyotome at E9.5, and co-localized with the early muscle markers Pax3 and Myf5 at the ventrolateral lip of the dermomyotome at E10.5. It has also been found that Dab2 is involved in the MAPK, TGF-β and Wnt signaling, all of which play significant roles during muscle development and differentiation. These preliminary observations led to our hypothesis that Dab2 is an important regulator of the skeletal muscle myogenesis.

To further prove this hypothesis, *Xenopus laevis* embryos and C2C12 myoblasts were employed as *in vivo* and *in vitro* models in this study, respectively. *In situ* hybridization results showed that *XDab2* was expressed in somites of *Xenopus* embryos and co-localized with the muscle markers *XPax3*, *XMyoD*, *XMef2c and XMyos*. Knockdown of *XDab2* expression with antisense morpholinos down regulated the expression of several muscle markers in somites such as: *XPax3*, *XMyf5*, *XMef2c*, *XMyos and XAC100*. Down-regulation of MyHC (MF20) and 12/101 were also observed in whole mount preparations and transverse sections of *XDab2* morpholino injected embryos.

In vitro, when C2C12 myoblasts were induced to differentiate into myotubes, Dab2 expression was increased. Dab2 over-expression resulted in accelerated myoblast fusion and increased numbers of myotubes, while suppression of Dab2 expression with miRNAs led to reduction of myoblast fusion and decreased numbers of myotubes. Similarly, lentiviral shRNA mediated Dab2 stable knockdown reduced myotube formation and affected MAPK signaling. One stable clone, clone 5-2, showed sustained activation of p38 MAPK with simultaneous reduction of myotube formation when compared to the control. Inhibition of p38 MAPK activation on day2 or day3 with its inhibitor SB203580 could partially rescue the differentiation process in clone 5-2, indicating the role of Dab2 in p38 MAPK signaling and skeletal muscle differentiation.

These results demonstrated that Dab2 is an important regulator of the skeletal muscle development and differentiation.

Title(R8): The biological functions of the novel prolactin(PRL2) in zebrafish retina during early embryonic development

Yujian Shi, Xigui Huang, Kin Pong Lau and Christopher H.K. Cheng

Program: PhD in Biochemistry (Medicine); Supervisor: Cheng Christopher H.K.

The growth hormone/prolactin/somatolactin family plays important roles in many physiological functions. We have identified a novel prolactin (PRL2) that is mainly expressed in the eyes and brain of zebrafish, indicating its biological functions in the development of the central nervous systems (CNS). Using morpholino (MO) knockdown technique, at 48 and 72 hours post fertilization (hpf), there was a reduction in the expression of the marker gene Islet-1 located in the inner nuclear layer (INL) of retina. Another marker gene of bipolar cells, Lin7a, at 72 hpf also exhibited a similar trend as Islet-1 when compared to the control using whole mount in-situ hybridization (WISH). Electron microscopy (EM) further revealed that the cell morphology in the INL was altered after PRL2 MO knockdown at 48 hpf as compared to the control. By screening of a library of marker genes using real-time PCR, several transcription factors such as Pax6 and Rx that are important to eye development were found to be attenuated in the PRL2 MO group at 24 hpf. Our results were further verified and supported by WISH. In conclusion, PRL2 was demonstrated to be important in retinogenesis during embryonic development.

Title(R9): A study on the role of the cofactor β-klotho and its dependent fibroblast growth factors in pancreatic islet function

W. Y. So, L. H. Chen, Q. Cheng and P. S. Leung

Program: MPhil in Biomedical Sciences; Supervisor: Leung Po Sing

Fibroblast growth factors (FGFs) 19 and 21 are distinctive members of the FGF family whose actions require the cofactor β-klotho. FGF19 and FGF21 have been demonstrated to normalize glucose, lipid and energy homeostasis in disease models, e.g. diabetes. Restricted β-klotho expression in liver, pancreas and adipose tissue provides the mechanistic basis for tissue-specific actions of FGF19 and FGF21, implying important roles of β-klotho in these tissues. In this study, the physiological roles of β-klotho, FGF19 and FGF21 in islet function, especially their roles in the pathogenesis of type 2 diabetes, are investigated.

Pancreatic islets were isolated from db/db mice and their lean littermates. mRNA expression was evaluated by real-time RT-PCR. Protein expression and post-receptor signaling were analyzed by western blotting. Serum FGF21 levels were assessed by ELISA. Functional roles of β-klotho were investigated by gene knockdown where β-klotho or control siRNA was transiently transfected into islets.

mRNA and protein levels of β-klotho were reduced in db/db mice islets while the mRNA levels of FGF receptors remained unchanged and FGF21 levels were increased. Phosphorylation of FGFR substrate and expression of immediate-early-genes induced by FGF19 and FGF21 were reduced in db/db mice islets but FGF2, whose action is independent of β-klotho, could still trigger signaling in db/db islets. Preliminary data on gene knockdown showed about 80% reduction in β-klotho mRNA expression in normal islets.

Our findings demonstrate that diabetic mice islets are less responsive, or resistant, to β-klotho dependent FGFs (FGF19 & FGF21), the increased FGF21 levels in diabetic mice being a possible compensatory mechanism. These findings suggest that downregulation of β-klotho in islets under diabetic conditions may cause FGF19 & FGF21 resistance. The implications of these findings for β-klotho related signaling in normal and db/db islets will be further investigated by gene knockdown.

Title(R10): Ets1 regulates neural crest formation and migration in *Xenopus*

C.D. Wang and H. Zhao

Program: PhD in Biomedical Sciences; Supervisor: Zhao H.

The neural crest is a multipotent, migratory cell population that is transient in vertebrate embryos. It can differentiate into a large variety of tissues. Previous studies implicated a role of Ets1 in regulating neural crest development, but the mechanism remains unknown. Our results indicated that *ets1* was expressed in neural crest during neurula stages. Overexpression and knockdown of *ets1* caused neural crest defective phenotypes. Overexpression of *ets1* repressed the formation of both endogenous neural crest and neural crest induced by Pax3 and Zic1. Such effects were accompanied by increased neural fate. Ectopic *ets1* had little effects on mesoderm development, while it can attenuate BMP signaling. Knockdown of *ets1* impaired neural crest migration. The expression of *ets1* during neural crest formation was regulated by FGF signaling pathway.

Title(R11): Regulation of hepcidin expression by BMP signaling in macrophages

Xinggang Wu and Yin Xia

Program: PhD in Biomedical Sciences; Supervisor: Xia Yin

Hepcidin is a small peptide that is most highly expressed in the liver. Hepcidin is an important regulator of body iron stores. It decreases both intestinal iron absorption and macrophage iron release by binding to the iron exporter ferroportin and inducing its internalization and degradation. Recent studies suggest that BMP signaling plays a key role in regulation of hepcidin expression in liver cells. Interestingly, tissues other than the liver, can also synthesize hepcidin, including the kidney, the right heart atrium, and the spinal cord. Moreover, significant hepcidin expression has been found in spleen, alveolar, and bone marrow-derived macrophages. The paracrine/autocrine action of hepcidin may induce iron retention in macrophages. Although studies have shown that Lipopolysaccharide (LPS) can induce an increase of hepcidin in macrophages, whether hepcidin is also regulated by BMPs in macrophages is unknown. In the present study, we examined the effect of BMP signaling on hepcidin expression in RAW 264.7 and J774 macrophages. We found that BMP4 and BMP6 did not have any effect on hepcidin expression in RAW 264.7 and J774 cells although they dramatically stimulated Smad1/5/8 phosphorylation and Id-1 expression. In the presence of LPS, BMP4 was able to stimulate hepcidin expression in RAW264.7 cells. These results suggest that hepcidin expression in macrophages is regulated by BMP signaling in a different manner from that in hepatocytes.

Title(R12): Small molecule activators of microRNA-34a with anti-cancer activities identified through library screening

Z.G. Xiao, T. Xia, C.H. Li, C.H.K. Cheng and Y.C. Chen

Program: PhD in Biomedical Sciences; Supervisor: Chen YC, Co-supervisor: Cheng CHK

MicroRNAs play critical roles in various biological processes through regulating gene expression. Aberrant expression of microRNAs has been well documented in a variety of cancers. microRNAs function as oncogenes or tumor suppressors and represent promising therapeutic targets for cancer treatment. Small molecules modulating microRNA expression would thus constitute potential anti-cancer agents. microRNA-34a functions as a tumor suppressor and is downregulated or silenced in various cancers including hepatocellular carcinoma (HCC). In this study, we established the microRNA-34a luciferase report system and developed an assay for screening small molecule activators of microRNA-34a. The natural product library (Timtec) containing 640 pure compounds was screened to identify microRNA-34a activators. Two compounds were identified to be microRNA-34a activators. These two compounds dramatically activated microRNA-34a expression in HCC cells with microRNA-34a silencing. It was further demonstrated that these two compounds exhibited growth inhibiting activities on various HCC cell lines but not in non-tumorigenic human hepatocytes. These two compounds also downregulated the expression of microRNA-34a target proteins such as cyclin D1. The *in vivo* anti-cancer efficacy of these two compounds is under investigation.

Title(R13): Sodium-potassium pump mediates mitotic entry through upregulation of Aurora kinases activity

C.M. Xie and Christopher H. K. Cheng

Program: PhD in Biochemistry (Medicine); Supervisor: Cheng Christopher H. K.

The sodium-potassium pump (Na^+/K^+-ATPase or sodium pump) is an enzyme classically known for its involvement in regulating the cell volume and the membrane potential. Moreover, the sodium pump plays a critical role in cell growth, differentiation and cell death, but the mechanisms are not completely understood. In the current study, we have examined the effects of cardiac glycosides (e.g. bufalin, digoxin, and ouabain), the specific inhibitors of the sodium pump, on cell cycle progression. The effects of cardiac glycoside on cell cycle progression were determined by trafficking cell cycle progression in Hela cells stably expressing histone H2B-YFP by video-microscopy. The cells failed to pass through mitosis and enter into G1 phase with 2N DNA content after release from thymidine arrest followed by exposure to bufalin. This was characterized by the presence of sister chromatid cohesion, absence of chromosomes alignment on the metaphase plate, loss of mitotic spindle architecture, and a failure to exit mitosis. This result was confirmed by the increase in the percentage of 4N DNA in cells and accumulation of polyploid cells (>4N) in bufalin-treated HT-29 cells. These increased cells with 4N DNA were not in a tetraploid G1phase, as indicated by the cells reentering into the G1 phase with 2N DNA content after removal of bufalin. Moreover, the released nocodazoled-synchronized Hela cells passed through cytokinesis in the presence of bufalin under a video microscope. These results indicated that bufalin induced cell cycle arrest at prometaphase. Thereafter, we have also detected the Aurora kinases which are required for both centrosome separation and spindle assembly during mitosis. It was found that bufalin and other cardiac glycosides could significantly reduce the phosphorylation of Aurora kinases in HT-29 and Hela cells as well as by the Aurora kinases inhibitor VX680. The phosphorylation of histone H3, a downstream target of Aurora kinases, was completely blocked in HT-29 and Hela cells after exposure to cardiac glycosides. In addition, it was found that cardiac glycosides could reduce the protein levels of Aurora A but not Aurora B and Aurora C. Conclusions: Bufalin and other cardiac glycoside inhibitors of the sodium-potassium pump potently arrest cancer cells at prometaphase by downregulating the phosphorylation of Aurora kinases and the protein levels of Aurora A. It was demonstrated that the sodium-potassium pump regulates cell cycle progression through regulation of Aurora kinases activity.

Title(R14): The role of IL-6 in regulation of GH receptor, SOCS3 and IGF-I expression in the liver

Yueshui Zhao and Yin Xia

Program: PhD in Biomedical Sciences; Supervisor: Xia Yin

Acute and chronic inflammatory diseases induce protein hypercatabolism and muscle wasting. The underlying mechanisms have not been completely elucidated. Evidence suggests that during systemic inflammation, the liver becomes resistant to growth hormone (GH) actions, leading to downregulation of anabolic gene insulin-like growth factor-I (IGF-I) and activation of catabolic process. Increased production of proinflammatory cytokines IL-6, TNF-α and IL-1β have been implicated in the pathogenesis of hepatic GH resistance via potential mechanisms including downregulation of GH receptor (GHR), and upregulation of suppressor of cytokine signaling-3 (SOCS3). However, the relative importance of individual cytokines in regulating GH signaling is not fully understood. In our previous study, we identified Dragon knockout mice as a chronic inflammation mouse model, which showed increased expression of a number of inflammatory cytokines including IL-6, TNF-α, IL-1β and MCP-1. Consistent with other inflammatory models, these mice showed downregulation of GHR and IGF-1 and upregulation of SOCS3 in the liver compared to control mice. Neutralizing antibody to IL-6 did not alter GHR and IGF-I expression while it brought SOCS3 down to levels comparable to those in the livers of control mice. In Huh7 human hepatoma cells, IL-6 did not alter GHR expression while TNF-α and IL-1β inhibited GHR expression. Interestingly, IL-6 was much more potent in stimulating SOCS3 expression than TNF-α and IL-1β. These results suggest that IL-6 is a key inflammatory cytokine that regulates SOCS3 in liver cells, and that IL-6 and SOCS3 are not required for inhibition of IGF-I expression in response to inflammation.

Stem Cells and Regeneration

Venue: Rm 211, BMSB

Title of Poster Presentation	Name	Abstract No.
Hippo signaling interacts with Hedgehog signaling in the development of osteosarcoma	Chan Lokhei	S1
The Role of BRE in Human Umbilical Cord Perivascular Cells	Chen Elve	S2

Abstracts

Title(S1): Hippo signaling interacts with Hedgehog signaling in the development of osteosarcoma

L.H. Chan, W. Yeung and K.K. Mak

Program: MPhil in Biomedical Sciences; Supervisor: Mak K.K.

Osteosarcoma (OS) is one of the most common primary bone tumors and is frequently found in adolescence. However, little is known about the genetic cause and pathogenesis of OS and its prognosis remains poor. Hedgehog (Hh) signaling and Hippo signaling have been widely implicated in the development of many cancers and previous studies showed that these two pathways interact in medulloblastoma. Our previous data showed that cell autonomous upregulation of Hh signaling in mature osteoblasts leads to increased bone formation. Thus, we reasoned that deregulation of Hh signaling may be one of the risk factors in the development of OS. Here, we generated an osteosarcoma mouse model, *Ptch*$^{c/+}$*; p53*$^{+/-}$*; HOC-Cre*, in which Hh signaling is partially upregulated in mature osteoblasts in a *p53*$^{+/-}$ background to enhance the incident rate of OS. Ubiquitous upregulation of Hh signaling in osteoblasts (*Ptch*$^{c/c}$*; HOC-Cre*) is early lethal, which prohibits the development of osteosarcoma. Our results demonstrated that the *Ptch*$^{c/+}$*; p53*$^{+/-}$*; HOC-Cre* mutant developed OS at a relatively high frequency, starting from 7-8 months. Primary OS cancer cell lines derived from this mouse models showed upregulated *Gli1* and *Gli2* expression, the major effectors of Hh signaling. More interestingly, the main transactivator of the Hippo pathway, *Yap* (*yes-associated protein*) is also upregulated. Similar expression patterns were also found in the *Ptch*$^{c/c}$*; HOC-Cre* calvaria tissues, suggested that this interaction is p53-independent. Hh agonist, SAG, and antagonist, cyclopamine, activated and suppressed Hippo signaling in MC3T3-E1 osteoblastic cell lines, respectively, as revealed by dual luciferase assays. More importantly, the downstream target genes of Hippo pathway, *Ctgf* and *Cyr61*, were also upregulated in both OS cell lines and calvaria tissues of the *Ptch*$^{c/c}$*; HOC-Cre* mutant mice. These results strongly suggest that Hh signaling interacts with Hippo pathway in the development and pathogenesis of OS.

Title(S2): The Role of BRE in Human Umbilical Cord Perivascular Cells

E. Chen, M.K. Tang, Y. Yao and K.H. Lee

Program: PhD in Biomedical Sciences; Supervisor: Lee Kenneth K.H.

Stem cells therapy has gained considerable attention and following in recent years. However, the use of stem cells for tissue repair has been hindered due to its low survival rate after grafting into tissues, for approximately 80% of the stem cells died after implanting. Human umbilical cord perivascular (HUCPV) cells offer a rich resource of multipotent stem cells with the ability to differentiate into various mesenchymal cell lineages. HUCPV cells can be amplified more abundantly *in vitro* as compared with mesenchymal stem cells obtained from bone marrow or umbilical cord blood. We have isolated HUCPV cells from the perivascular regions of human umbilical cords. Flow-sorted CD105+ CD146+ HUCPV cells were used in our studies. We confirmed that the HUCPV cells were capable to differentiate into osteogenic lineage in monolayer culture and chondrogenic lineage using pellet culture. We also used silk fibroin as 3-dimenional scaffolds for the cells to grow on and differentiate into osteoblasts or chondrocytes in 3 to 4 weeks. We observed that the mRNA expression of BRE (brain and reproductive organ-expressed), derived from a putative pro-survival gene, were down-regulated when cells started to differentiate. Silencing BRE accelerates the osteogenic differentiation of HUCPV cells. We are investigating the role of BRE by microarray profiling of BRE-silenced HUCPV cells.

Vascular and Metabolic Biology

Venue: Rm 215, BMSB

Title of Poster Presentation	Name	Abstract No.
Cerebral vasodilator activities of major active constituents of a Danshen and Gegen formulation on rat basilar artery	Deng Yan	V1
Expression of TRP Channels in Aortic Baroreceptor Neuron	Lau On Chai	V2
Protective Mechanism(s) of N-Acetyl-L-Cysteine, *ex vivo*, in Pancreatic-islet β-cells against Glucose Toxicity and Oxidative Stress	Poon Chuiwa Christina	V3
Tanshinones-induced apoptosis in HCT116 and HT29 colon cancer cells	Wang Lin	V4
Miltirone induced-apoptosis involved reactive oxygen species-mediated activation of mitogen-activated protein kinases on doxorubicin-sensitive and -resistant HepG2 cells	Zhou Xuelin	V5

Abstracts

Title(V1): Cerebral vasodilator activities of major active constituents of a Danshen and Gegen formulation on rat basilar artery

Y. Deng, E.S.K. Ng, J.H.K .Yeung, Y.W. Kwan, C.B.S. Lau, J.C.M. Koon, L. Zhou, Z. Zuo, P.C. Leung, K.P. Fung and F.F.Y. Lam

Program: PhD in Pharmacology; Supervisor: Lam Francis

Danshen and Gegen are traditional Chinese medicines commonly used for the treatment of cardiovascular diseases. In this study, we have identified the major constituents of a Danshen and Gegen formulation (DG; ratio 7:3) and investigated their actions on rat-isolated cerebral basilar artery.
Rat basilar artery rings were precontracted with 100 nM U46619. Involvement of endothelium-dependent mechanisms was investigated by mechanical removal of the endothelium. Adenylyl cyclase, guanylyl cyclase, and potassium channel involvement were examined by pretreatment of the artery rings with their respective inhibitors. Calcium channel involvement was tested in artery rings incubated with Ca^{2+}-free buffer and primed with U46619 prior to adding $CaCl_2$ to elicit contraction. The constituents of a DG water extract were identified by HPLC.

Salvianolic acid B, danshensu, puerarin, daidzein and daidzin were identified in the DG water extract. All these agents produced concentration-dependent relaxation of the artery rings that were unaffected by adenylyl cyclase inhibitor, guanylyl cyclase inhibitor, or by endothelium removal, except the latter reduced the maximum response to puerarin by 28%. Moreover, puerarin had no influence on $CaCl_2$-induced vasoconstriction but all the other agents produced concentration-dependent inhibition. Pretreatment with a combination of K^+ channel inhibitors produced significant inhibition on the vasodilator actions to all these agents, but not on danshensu.

The vasorelaxant actions of salvianolic acid B, daidzein and daidzin involved opening of K^+ channels and inhibition of Ca^{2+} influx in the vascular smooth muscle cells. Danshensu produced vasorelaxation solely by inhibition of Ca^{2+} influx in the vascular smooth muscle cells. In contrast, puerarin produced vasodilatation via an endothelium-dependent mechanism and an endothelium-independent pathway mediated by the opening of K^+ channels. In spite of differences in their mechanisms of actions, the common cerebrovasodilator activities of these DG constituents suggest they could be beneficial in treatment of obstructive cerebrovascular diseases.

Title(V2): Expression of TRP Channels in Aortic Baroreceptor Neuron

O.C. Lau, C.O. Wong, Y. Huang and X. Yao

Program: PhD in Physiology; Supervisor: Yao Xiaoqiang

TRP channels are a superfamily of non-selective cation channels that can be divided into seven subfamilies: TRPA, TRPC, TRPM, TRPML, TRPN, TRPP, and TRPV. Many TRP isoforms have been reported to be sensors for diverse source of external and/or internal stimuli. Although still under debating, TRPC1, -C5, -C6 are suspected to be responsive to direct membrane stretch; TRPV1, -V4 are suggested be activated by stretch-induced cytoskeleton displacement and/or flow stimuli.

Arterial baroreceptors are the mechanosensor to detect blood pressure. Upon changes in arterial blood pressure, the baroreceptive nerve terminal on the blood vessel adventitia will be activated, resulting in action potentials which propagate to the cardiovascular control centre in the brain. However, the molecular identity of the baroreceptor mechanosensors is not well understood.

In the present study, immunohistochemistry and RT-PCR were employed to explore the expression of mechanosensitive TRP isoforms in the rat aortic baroreceptor. The results demonstrated that TRPC1, C5, C6, V4 are expressed in the aortic baroreceptor nerve terminal which is located on the aortic arch, along the nerve fiber (aortic depressor nerve) and in the ganglion region (nodose ganglion). Moreover, western blotting using isolated rat nodose ganglion also showed the expression of TRPC5 channels. In Ca^{2+} imaging studies of cultured aortic baroreceptor neurons, T5E3, a TRPC5 blocking antibodies, and daidzein, a TRPC5 potentiator, were able to block and potentiate the $[Ca^{2+}]_i$ response upon osmo-mechanical stimuli respectively. Electrophysiological studies showed that daidzein could potentiate the pressure-induced action potential firing in isolated aortic baroreceptor neurons and the action potential could also be blocked by 2-APB, which is a cation channel blocker.

In summary, this study suggests that TRPC5 is involved in the pressure sensing of aortic baroreceptor neurons. Other mechanosensitive TRP channels: TRPC1, -C6, -V4, might also be involved in blood pressure detection in the aortic baroreceptor.

Title(V3): Protective Mechanism(s) of N-Acetyl-L-Cysteine, *ex vivo*, in Pancreatic-islet β-cells against Glucose Toxicity and Oxidative Stress

C.C.W. Poon, A.H.P. Ho, S.K. Kong and Y.W. Kwan

Program: PhD in Biomedical Sciences; Supervisor: Kwan Y.W.

Type 2 diabetes mellitus (T2DM) is a complex and common disease (approximate 90-95% of all cases of DM diagnosed). In this study, isolated pancreatic islets β-cells of obese/diabetic (db^+/db^+) mice and its normal littermate (lean/non-diabetic (db^+/m^+) mice) were used to evaluate the underlying mechanisms involved in pancreatic islets dysfunction under diabetic conditions and the possible beneficial effects, *ex vivo*, provided by N-acetyl-L-cysteine (L-NAC, a common anti-oxidant).

Our results demonstrate that glucose (5 and 15 mM)-induced insulin release and insulin content of isolated pancreatic islets β-cells of obese/diabetic (db^+/db^+) mice were much lower compared to lean/non-diabetic (db^+/m^+) mice. In contrast, the basal and glucose (15 mM)-induced mitochondrial ROS levels were higher in single pancreatic islets β-cells of obese/diabetic (db^+/db^+) mice compared to lean /non-diabetic (db^+/m^+) mice. Moreover, a higher level of F-actin cytoskeleton polymerisation was detected in single pancreatic islets β-cells of obese/diabetic (db^+/db^+) mice, compared to that observed in lean/non-diabetic (db^+/m^+) mice. L-NAC (20 mM, 24 hr incubation) markedly suppressed mitochondrial ROS generation of single pancreatic islets β-cells of both strains of mice, in response to elevated glucose (15 mM) challenge. The attenuated mitochondrial ROS generation caused by L-NAC incubation was associated with the restoration of the blunted glucose-induced insulin release and an increase of insulin content of isolated pancreatic islets of obese/diabetic (db^+/db^+) mice. L-NAC incubation markedly attenuated the elevated F-actin cytoskeleton levels in single pancreatic islets β-cells of both strains of mice bathed in elevated glucose (15 mM) medium.

In conclusion, our results demonstrate, for the first time, that L-NAC incubation (24 hrs) provides protective effects (i.e. restoration of the blunted glucose-induced insulin release plus the reduced insulin content) against hyperglycemia-induced oxidative stress in pancreatic islets β-cells of obese/diabetic (db^+/db^+) mice via inhibition of mitochondrial ROS generation and promotion of F-actin cytoskeleton depolymerisation.

Title(V4): Tanshinones-induced apoptosis in HCT116 and HT29 colon cancer cells

L. Wang, X.L. Zhou, P.M.Y. Or and J.H.K. Yeung

Program: PhD in Pharmacology; Supervisor: Yeung John H.K.

Tanshinones have been reported to exhibit apoptotic and anti-tumor activity in a number of cancer cell lines and their tumor-bearing nude mice. A recent report showed that tanshinone I and tanshinone IIA showed cytotoxic effects on a Colo-205 human colon cancer cell line (Su et al., 2008). The aim of this study was to investigate the cytotoxicity of five major tanshinones (tanshinone I, tanshinone IIA, dihydrotanshinone, cryptotanshinone and miltirone) in HCT116 and HT29 colon cancer cell lines and its mechanisms.

Cytotoxic and apoptotic effects of tanshinones in HCT116 and HT29 cells were detected by MTT assay, LDH assay and Annexin V-PI double staining. Generation of total intracellular and mitochondrial reactive oxidative species (ROS) was detected with H_2DCF dye and Mitochecker-HTS dye, respectively. The role of NAD(P)H: quinine oxidoreductase 1 (NQO1) in tanshinones-induced cytotoxicity was studied using dicoumarol, a NQO1 specific inhibitor.

MTT assay showed that the cytotoxic effects of tanshinones to HCT116 and HT29 cells were concentration-dependent (0.39-100μM), with dihydrotanshinone being the most potent (IC50 = 0.98±1.1μM in HCT116 cells and IC50 =3.72±1.48 μM in HT29 cells). The cytotoxic effects of the tanshinones were significantly inhibited by dicoumarol in HCT116 cells. LDH assay indicated that tanshinones only induced necrosis at doses greater than 25 μM in both cell lines. Tanshinones significantly induced ROS production, with dihydrotanshinone and miltirone being the most potent among the tanshinones investigated. Pretreatment with N-acetyl-L-cysteine (NAC) significantly blocked the apoptotic effects of tanshinones. However, effects of dicoumarol on apoptosis induced by the tanshinones were much weaker.

In conclusion, tanshinones induced apoptosis in both HCT116 and HT29 colon cancer cell lines, which intensely related to ROS generation.

Title(V5): Miltirone induced-apoptosis involved reactive oxygen species-mediated activation of mitogen-activated protein kinases on doxorubicin-sensitive and -resistant HepG2 cells

X.L. Zhou, W.Y.W. Lee, L. Wang, P.M.Y. Or and J.H.K. Yeung

Program: PhD in Pharmacology; Supervisor: Yeung John H.K.

Background Chemotherapy is the main treatment options for patients with inoperable hepatocellular carcinoma (HCC). However, some HCC has low response to pharmacological treatment due to multidrug resistance with over-expression of P-glycoprotein (P-gp). Miltirone is an abietane type-diterpene quinone isolated from Danshen (*Salvia miltiorrhiza*). Previous studies have shown that miltirone exhibited concentration-dependent cytotoxic effects on a human hepatoma cell line (HepG2) and its doxorubicin-resistant counterpart (R-HepG2) with over-expressed P-gp and up-regulated glutathione-S-transferase (GST) activity, with EC_{50} 7.1 μM and 12.0 μM, respectively, as detected by MTT assay and LDH assay. Miltirone triggered caspase-dependent apoptosis on both HepG2 and R-HepG2 cells, with the cleavage of caspase-8, caspase-9, caspase-3 and poly-(ADP-ribose) polymerase, as well as bax translocation and cytochrome *c* release. Mitogen-activated protein kinases (MAPK) signaling pathway is one of well-investigated apoptotic pathways. This study aims to evaluate whether MAPK signaling pathway is involved in miltirone-induced apoptosis on HepG2 and R-HepG2 cells.

Methods Reduced and oxidized forms of glutathione were detected by an enzymatic kinetic method, and their ratio was monitored as the index of oxidative stress. The generation of intracellular reactive oxygen species (ROS) was measured by flow cytometry with H_2DCFH dye. Apoptotic mechanisms of miltirone were determined by Western blotting for the phosphorylated and total MAP kinases.

Results As shown by a decrease of reduced glutathione/oxidized glutathione ratio, miltirone significantly induced oxidative stress, which might be caused by intracellular glutathione depletion and ROS generation. Subsequently, miltirone concentration-dependently activated ROS-mediated MAP Kinases including p38 MAP Kinase and stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK), and inhibited extracellular regulated kinase 1/2 on HepG2 and R-HepG2.

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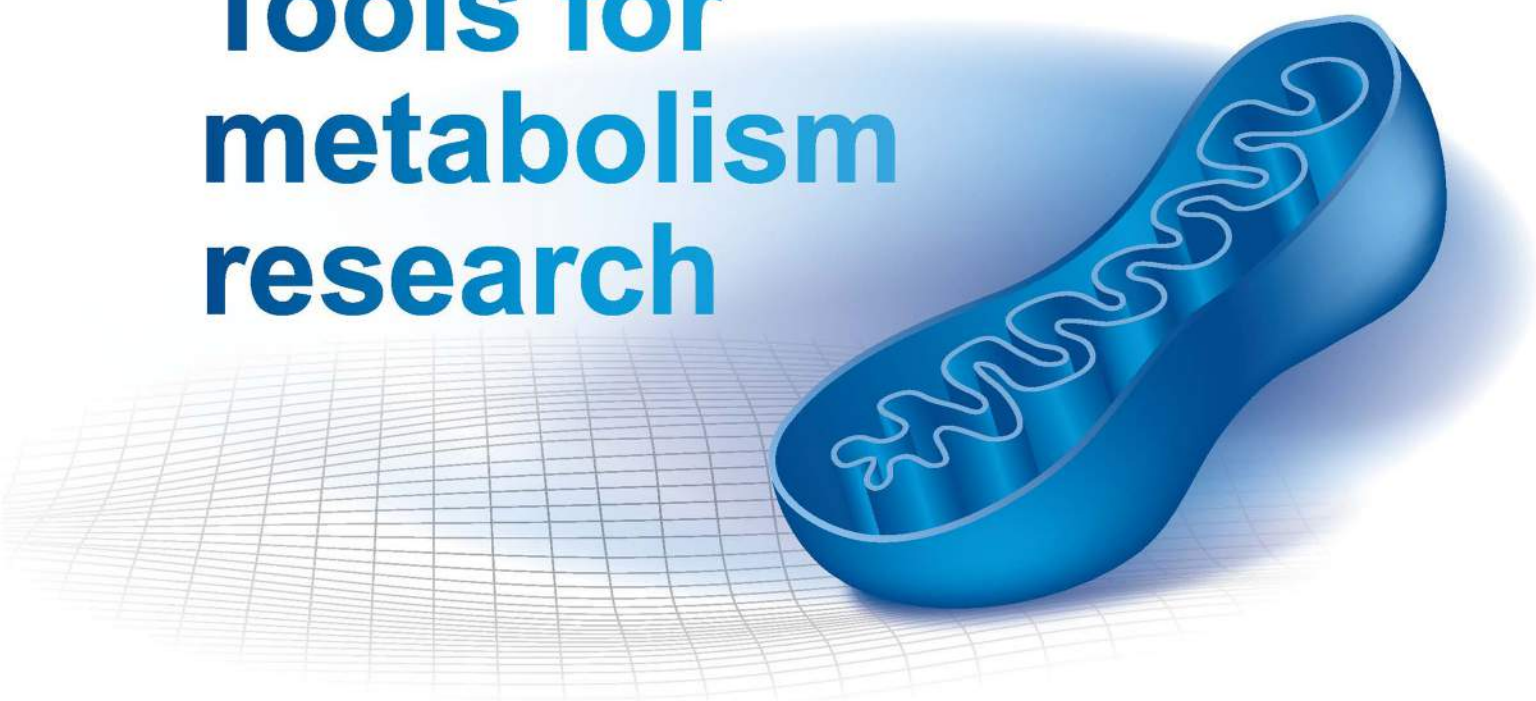

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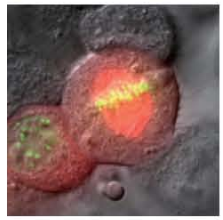

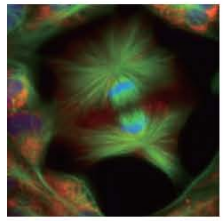

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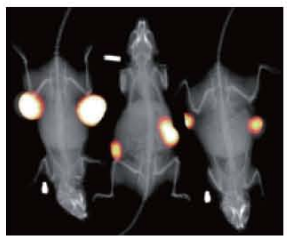

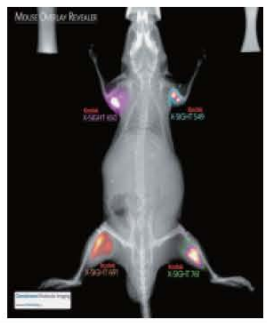

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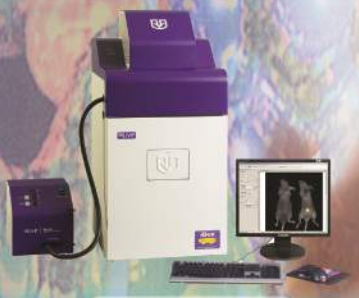

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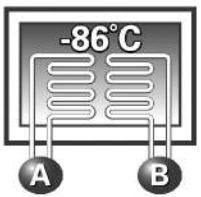

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