# Table of Contents

I. Welcome Message .................................................................................................................. i

II. Scientific Programme ........................................................................................................... ii

III. Abstracts ................................................................................................................................ P. 1

   A. In Shaw Auditorium

   **Cancer Research (1)**
   - The Comprehensive Cancer Trials Unit (CCTU) ............................................................... P. 2
   - Hepatocellular Carcinoma Research Group: Clinical Application of Functional Genomics ................................................................. P. 3
   - Hepatitis B and Its Complication ...................................................................................... P. 4
   - Liver Cancer (Hepatocellular Carcinoma): from the Bench Top to Operating Room ........... P. 6
   - Molecular Pathogenesis of Nasopharyngeal Carcinoma ................................................ P. 7
   - Methylation Profile in Cancer and the Potential Application as Molecular Markers Detected in Body Fluids .............................................. P. 8

   **Cancer Research (2)**
   - Molecular Signatures in Cervical Neoplasm ................................................................. P. 10
   - Stomach Cancer: from Carcinogenesis to Chemoprevention .......................................... P. 11
   - Effectiveness of Interventions for Reducing Breathlessness, Fatigue and Anxiety in Chinese Undergoing Lung Cancer Radiotherapy in Hong Kong ...................................................... P. 13

   **Bioinformatics, Genomics and Proteomics**
   - Bioinformatics and Application of Microarray Biotechnology in Medical Research .......... P. 14
   - Genomics and Heart Diseases ......................................................................................... P. 15
   - Application of State–of–the–art Proteomic Technology in Basic Medical Science Research ................................................................. P. 16

   **Biomedical Sciences (1)**
   - Linking the Basic Research of Pancreatic Functions to Pancreatic Diseases ..................... P. 17
   - Increased Susceptibility to Teratogens during Diabetic Pregnancy ..................................... P. 18
   - Alteration of Glucose Transporter Function in Central Nervous System (CNS) Symptoms ................................................................. P. 19
   - On the Origin of Anti–DNA Antibodies ........................................................................ P. 20
   - Circulating Fetal DNA and RNA in Maternal Plasma ...................................................... P. 21

   **Biomedical Sciences (2)**
   - Stem Cell Research Program: Ex Vivo Expansion, Plasticity and Embryonic Stem Cells .......... P. 22
   - Growth Hormone Secretagogue Receptors: Cell Signalling and Receptor Oligomerization ................................................................. P. 23
   - The Role of Nitric Oxide and Mitogen–activated Protein Kinase in Mediating the Inhibition by $\beta_3$–adrenoceptor Activation of Voltage–dependent L–type Calcium Channels of Guinea–pig Single Ventricular Myocytes ................................................................. P. 24
   - A Negative Feedback Pathway that Controls Cytosolic Ca$^{2+}$ and Nitric Oxide Levels in Endothelial Cells ................................................................................................................................. P. 25
B. In Kai Chong Tong

**Therapeutics and Treatment Research**
- Cost–effectiveness Analysis of High–dose Omeprazole Infusion as Adjuvant Therapy to Endoscopic Treatment of Bleeding Peptic Ulcer .................................................. P. 26
- Clinical Development of Connecting System for Prevention of Peritonitis in CAPD Patients .......................................................................................................................... P. 28
- Oxygen Therapy for Hypercapnic Patients with Chronic Obstructive Pulmonary Disease and Acute Respiratory Failure. A Randomized Controlled Pilot Study .......................................................................................................................... P. 30
- The Effects of High–inspired Oxygen Fraction during Elective Caesarean Section under Spinal Anaesthesia on Maternal and Fetal Oxygenation and Lipid–peroxidation ......................................................... P. 31

**Musculoskeletal and Related Research**
- Biophysical Research in Musculoskeletal Tissues ................................................................................................................................. P. 32
- Vertebroplasty Service and Research .................................................................................................................................................. P. 33
- Prevention and Treatment of Osteoporosis and Its Related Problems ................................................................................................................. P. 34
- Osteoporosis in Asia – The Results of a Decade of Multidisciplinary Research in the Faculty of Medicine, The Chinese University of Hong Kong ................................................. P. 36

**Psychological Health and Behavioral Sciences**
- Developing a Model to Predict Youth Risk Behaviours: Intentional Injury as an Example .............................................................................. P. 37
- Psychiatric Morbidity in First Time Stroke Patients in Hong Kong: A Pilot Study in a Rehabilitation Unit .................................................................................................................. P. 39
- A Psychiatric Epidemiological Study of Postpartum Chinese Women ..................................................................................................................... P. 40

**Public Health Research (1)**
- Phytoestrogens Intake and Women’s Health: Recent Studies ................................................................................................................................. P. 41
- Sexual Health Promotion amongst Hong Kong Adolescents: An Evaluation of Nurse–led Intervention .......................................................................................................................... P. 42
- Prevalence, Incidence and Risk Factors of Myopia in Primary School Children in Hong Kong .................................................................................. P. 43
- An Epidemiological Study of Obstructive Sleep Apnoea Syndrome in Hong Kong Children .................................................................................. P. 44

**Public Health Research (2)**
- Research on Air Pollution and Health in Hong Kong ................................................................................................................................. P. 45
- Ultrasound and MR Assessment of Obese Chinese Children ................................................................................................................................. P. 46
- Antimicrobial Resistance in the Community ................................................................................................................................................ P. 47
- Application of a Multiplex–PCR–Amplimers Conformation Analysis Technique (MPAC) for Rapid Detection of *Gyrase A* Mutations among Fluoroquinolone–resistant *Mycobacterium Tuberculosis* Clinical Isolates ................................................................................................................................. P. 48
Dear Colleagues,

On behalf of the Faculty of Medicine, we would like to welcome you to the Faculty Research Day. Modern biomedical research often requires the cooperation of experts from multiple disciplines. It is thus of strategic importance that researchers from different departments and units in the Faculty are aware of research that is being carried out by other members of the Faculty. The importance of such cross-disciplinary collaboration can clearly be seen from high profile projects that are funded by the various grant-giving bodies, both locally and abroad. One important goal of the Faculty Research Day is to provide a forum through which researchers from different departments and units can present their latest work, discuss new ideas and explore collaborative opportunities with other colleagues. We hope that by working together, novel research directions can be developed and new discoveries can be accelerated, ultimately bringing benefits to mankind.

Yours sincerely,

Sydney Chung
Dean
Faculty of Medicine
The Chinese University of Hong Kong

Dennis Lo
Associate Dean (Research)
Faculty of Medicine
The Chinese University of Hong Kong
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:30–9:00am</td>
<td>Registration</td>
</tr>
<tr>
<td>9:00–9:15am</td>
<td>Opening by Dean and Associate Dean (Research)</td>
</tr>
<tr>
<td>9:15–9:30am</td>
<td><strong>SHAW AUDITORIUM</strong></td>
</tr>
<tr>
<td></td>
<td>Cancer Research (1)</td>
</tr>
<tr>
<td></td>
<td>Chaired by Prof. Ho Keung NG, Dept. of Anatomical and Cellular Pathology</td>
</tr>
<tr>
<td>9:15–9:30am</td>
<td>The Comprehensive Cancer Trials Unit (CCTU)</td>
</tr>
<tr>
<td></td>
<td>Speaker: Prof. Anthony T.C. CHAN, Dept. of Clinical Oncology</td>
</tr>
<tr>
<td>9:30–9:45am</td>
<td><strong>KAI CHONG TONG</strong></td>
</tr>
<tr>
<td></td>
<td>Therapeutics and Treatment Research</td>
</tr>
<tr>
<td></td>
<td>Chaired by Prof. Francis K.L. CHAN, Dept. of Medicine and Therapeutics</td>
</tr>
<tr>
<td>9:30–9:45am</td>
<td>Hepatocellular Carcinoma Research</td>
</tr>
<tr>
<td></td>
<td>Group: Clinical Application of Functional Genomics</td>
</tr>
<tr>
<td></td>
<td>Speaker: Prof. Nathalie WONG, Dept. of Clinical Oncology</td>
</tr>
<tr>
<td>9:45–10:00am</td>
<td><strong>KAI CHONG TONG</strong></td>
</tr>
<tr>
<td></td>
<td>Cost–effectiveness Analysis of High–dose Omeprazole Infusion as Adjuvant</td>
</tr>
<tr>
<td></td>
<td>Therapy to Endoscopic Treatment of Bleeding Peptic Ulcer</td>
</tr>
<tr>
<td>10:00–10:15am</td>
<td>Speaker: Prof. Kenneth K.C. LEE, School of Pharmacy</td>
</tr>
<tr>
<td>10:15–10:30am</td>
<td>Hepatitis B and Its Complication</td>
</tr>
<tr>
<td></td>
<td>Speaker: Prof. Henry L.Y. CHAN, Dept. of Medicine and Therapeutics</td>
</tr>
<tr>
<td>10:30–10:45am</td>
<td>Liver Cancer (Hepatocellular Carcinoma): from the Bench Top to</td>
</tr>
<tr>
<td></td>
<td>Operating Room</td>
</tr>
<tr>
<td></td>
<td>Speaker: Prof. Paul B.S. LAI, Dept. of Surgery</td>
</tr>
<tr>
<td>10:15–10:30am</td>
<td>Molecular Pathogenesis of Nasopharyngeal Carcinoma</td>
</tr>
<tr>
<td></td>
<td>Speaker: Prof. Kwok Wai LO, Dept. of Anatomical and Cellular Pathology</td>
</tr>
<tr>
<td>10:30–10:45am</td>
<td>The Effects of High–inspired Oxygen Fraction during Elective Caesarean</td>
</tr>
<tr>
<td></td>
<td>Section under Spinal Anaesthesia on Maternal and Fetal Oxygenation and</td>
</tr>
<tr>
<td></td>
<td>Lipid–peroxidation</td>
</tr>
<tr>
<td>10:45–11:00am</td>
<td>Morning Coffee Break</td>
</tr>
<tr>
<td></td>
<td>Poster Viewing</td>
</tr>
<tr>
<td>Time</td>
<td>SHAW AUDITORIUM</td>
</tr>
<tr>
<td>-----------------</td>
<td>------------------------------------------------------</td>
</tr>
<tr>
<td>11:00–11:15am</td>
<td>Morning Coffee Break</td>
</tr>
<tr>
<td></td>
<td>Poster Viewing</td>
</tr>
<tr>
<td>11:15–11:30am</td>
<td>Molecular Signatures in Cervical Neoplasm</td>
</tr>
<tr>
<td></td>
<td>Speaker: Dr. T.H. CHEUNG, Dept. of Obstetrics and Gynaecology</td>
</tr>
<tr>
<td>11:30–11:45am</td>
<td>Stomach Cancer: from Carcinogenesis to Chemoprevention</td>
</tr>
<tr>
<td></td>
<td>Speaker: Dr. Enders K.W. NG, Dept. of Surgery</td>
</tr>
<tr>
<td>11:45–12:00pm</td>
<td>Effectiveness of Interventions for Reducing Breathlessness, Fatigue and Anxiety in Chinese Undergoing Lung Cancer Radiotherapy in Hong Kong</td>
</tr>
<tr>
<td></td>
<td>Speaker: Prof. Carmen CHAN, The Nethersole School of Nursing</td>
</tr>
<tr>
<td>12:00–12:15pm</td>
<td>Bioinformatics, Genomics and Proteomics</td>
</tr>
<tr>
<td></td>
<td>Chaired by Prof. Kwok Wai LO, Dept. of Anatomical and Cellular Pathology</td>
</tr>
<tr>
<td>12:15–12:30pm</td>
<td>Genomics and Heart Diseases</td>
</tr>
<tr>
<td></td>
<td>Speaker: Prof. Mary M.Y. WAYE, Dept. of Biochemistry</td>
</tr>
<tr>
<td>12:30–12:45pm</td>
<td>Application of State-of-the-art Proteomic Technology in Basic Medical Science Research</td>
</tr>
<tr>
<td></td>
<td>Speaker: Prof. Kenneth K.H. LEE, Dept. of Anatomy</td>
</tr>
<tr>
<td>12:45–2:15pm</td>
<td>Lunch Break</td>
</tr>
<tr>
<td></td>
<td>Poster Viewing</td>
</tr>
<tr>
<td>Time</td>
<td>SHAW AUDITORIUM</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| 2:15–2:30pm  | **Biomedical Sciences (1)**  
               Chair by Prof. Patricia P.H. CHOW, Dept. of Anatomy | **Public Health Research (1)**  
               Chair by Prof. Tai Fai FOK, Dept. of Paediatrics |
|              | **Linking the Basic Research of Pancreatic Functions to Pancreatic Diseases**  
               Speaker: Prof. Po Sing LEUNG, Dept. of Physiology | **Phytoestrogens Intake and Women’s Health: Recent Studies**  
               Speaker: Prof. Suzanne CHAN HO, School of Public Health |
| 2:30–2:45pm  | **Increased Susceptibility to Teratogens during Diabetic Pregnancy**  
               Speaker: Prof. Alisa S.W. SHUM, Dept. of Anatomy | **Sexual Health Promotion amongst Hong Kong Adolescents: An Evaluation of Nurse–led Intervention**  
               Speaker: Prof. Sheila TWINN, The Nethersole School of Nursing |
| 2:45–3:00pm  | **Alteration of Glucose Transporter Function in Central Nervous System (CNS) Symptoms**  
               Speaker: Prof. Yuan Yuan HO, Dept. of Biochemistry | **Prevalence, Incidence and Risk Factors of Myopia in Primary School Children in Hong Kong**  
               Speaker: Prof. Dorothy S.P. FAN, Dept. of Ophthalmology and Visual Sciences |
| 3:00–3:15pm  | **On the Origin of Anti–DNA Antibodies**  
               Speaker: Prof. Pak Leong LIM, Clinical Immunology Unit | **An Epidemiological Study of Obstructive Sleep Apnoea Syndrome in Hong Kong Children**  
               Speaker: Prof. Albert LI, Dept. of Paediatrics |
| 3:15–3:30pm  | **Circulating Fetal DNA and RNA in Maternal Plasma**  
               Speaker: Prof. Dennis Y.M. LO, Dept. of Chemical Pathology | **Afternoon Coffee Break Poster Viewing** |
| 3:30–3:45pm  | **Afternoon Coffee Break Poster Viewing** |                                                                 |
|              | **Biomedical Sciences (2)**  
               Chair by Prof. Mary M.Y. WAYE, Dept. of Biochemistry | **Public Health Research (2)**  
               Chair by Prof. Jean WOO, Dept. of Community and Family Medicine |
| 3:45–4:00pm  | **Afternoon Coffee Break Poster Viewing** | **Research on Air Pollution and Health in Hong Kong**  
               Speaker: Prof. Tze Wai WONG, Dept. of Community and Family Medicine |
| 4:00–4:15pm  | **Stem Cell Research Program: Ex Vivo Expansion, Plasticity and Embryonic Stem Cells**  
               Speaker: Prof. Karen LI, Dept. of Paediatrics | **Ultrasound and MR Assessment of Obese Chinese Children**  
               Speaker: Prof. Wyinnie W.M. LAM, Dept. of Diagnostic Radiology and Organ Imaging |
| 4:15–4:30pm  | **Growth Hormone Secretagogue Receptors: Cell Signalling and Receptor Oligomerization**  
               Speaker: Prof. Helen WISE, Dept. of Pharmacology | **Antimicrobial Resistance in the Community**  
               Speaker: Prof. Julia M. LING, Dept. of Microbiology |
<table>
<thead>
<tr>
<th>Time</th>
<th>SHAW AUDITORIUM</th>
<th>KAI CHONG TONG</th>
</tr>
</thead>
</table>
| 4:30–4:45pm | **The Role of Nitric Oxide and Mitogen–activated Protein Kinase in Mediating the Inhibition by β₃–adrenoceptor Activation of Voltage–dependent L–type Calcium Channels of Guinea–pig Single Ventricular Myocytes**  
Speaker: Prof. Yiu Wa KWAN, Dept. of Pharmacology                                                                 | **Application of a Multiplex–PCR–Amplimers Conformation Analysis Technique (MPAC) for Rapid Detection of Gyrase A Mutations among Fluoroquinolone–resistant Mycobacterium Tuberculosis Clinical Isolates**  
Speaker: Dr. Raphael C.Y. CHAN, Dept. of Microbiology                                                                 |
| 4:45–5:00pm | **A Negative Feedback Pathway that Controls Cytosolic Ca²⁺ and Nitric Oxide Levels in Endothelial Cells**  
Speaker: Prof. Xiaoqiang YAO, Dept. of Physiology                                                                 | End of Event                                                                                      |
Faculty Research Day 2004

Abstracts

Faculty of Medicine
The Chinese University of Hong Kong
The Comprehensive Cancer Trials Unit (CCTU)

Anthony TC Chan
Department of Clinical Oncology, The Chinese University of Hong Kong

The mission of the CCTU is to undertake research that contributes to the reduction of the incidence, morbidity and mortality from cancer. The unit is funded through research grants, donations and the pharmaceutical industry. Multi-disciplinary and inter-departmental collaborations focusing particularly on Asian Cancers including nasopharyngeal carcinoma, hepatocellular carcinoma and gastric cancer; as well as common cancers including lung cancer, breast cancer and colorectal cancer; have established the unit as a leading clinical and translational cancer research centre.

A good illustrative example of this success is in nasopharyngeal carcinoma, where collaborations from the Departments of Clinical Oncology, Anatomical and Cellular Pathology, Chemical Pathology, Surgery and Diagnostic Radiology have pioneered the use of combined chemoradiotherapeutic approaches in advanced disease; novel therapeutics tested on NPC cell lines and xenografts; as well as multicentre prospective studies hosted by the unit. The clinical applications of Epstein-Barr virus (EBV) DNA as a novel tumour marker has been established, within 3 years from discovery, through the joint effort of the departments. Studies aimed at reducing toxicities of treatment by using state-of-the-art intensity-modulated radiotherapy and Traditional Chinese Medicine are ongoing, as well as functional radiological imaging companion study in parallel with a prospective randomized trial. The leadership role of the multidisciplinary group is well presented in the recent 4th International UICC NPC Workshop held in conjunction with the 8th Annual Symposium of the Hong Kong Cancer Institute. Similar success has been achieved in hepatocellular carcinoma and further expansion of activities in gastric cancer is progressing.
Hepatocellular Carcinoma Research Group: Clinical Application of Functional Genomics

Nathalie Wong
Department of Clinical Oncology, The Chinese University of Hong Kong

Hepatocellular carcinoma (HCC) is a highly malignant tumor that is prevalent in China, including Hong Kong, and Southeast Asia. The current paucity on information related to the stepwise progression of HCC has prompted the organization of an investigative team within our faculty. This “Hepatocellular Carcinoma Research Group” comprises clinicians and basic scientists from inter-departments and two academic institutes. In collaboration with the Hong Kong University of Science & Technology (Dept. of Biochemistry), CUHK members from Departments of Clinical Oncology, Surgery, Anatomical and Cellular Pathology, and Chemical Pathology have assembled a collaborative effort to study an important health care issue that greatly affects our locality. The specific aims of our research group are to focus on understanding the molecular basis underlying the pathologic pathways that promote HCC development, and to translate research findings into clinical tests. The state-of-the-art technologies of expression array and proteomics are currently being employed in characterizing the molecular events during the malignant transformation of hepatocytes. The close collaboration between clinicians and scientists in this project is expected to foster a network whereby the usefulness of new biomarkers can be evaluated as non-invasive clinical tests. Furthermore, our research capabilities have been strengthened by the development of in-house HCC cell lines, which represent useful resources in the functional assessment of biological targets, and in the development of novel treatments. This “Hepatocellular Carcinoma Research Group” has recently received a Central Allocation Grant for the period 2003-2006 from the University Grants Council.
Hepatitis B and Its Complication

Henry Lik-Yuen Chan and Joseph Jao-Yiu Sung
Department of Medicine and Therapeutics, The Chinese University of Hong Kong

Chronic hepatitis B virus infection is the commonest cause of liver cirrhosis and hepatocellular carcinoma in Hong Kong. In the past few years, we have been collaborating with various departments to study the natural history, treatment and hepatocarcinogenesis related to chronic hepatitis B virus infection.

HBeAg seroconversion to negative HBeAg and positive anti-HBe antibody usually indicate successful immune clearance of the virus in chronic hepatitis B virus infection. However, some patients still have active liver disease in the HBeAg-negative state. Collaborating with Department of Microbiology and Department of Anatomical and Cellular Pathology, we have developed a model based on the liver biochemistry and HBV DNA level to stratify the risk of hepatitis relapse in HBeAg-negative patients.

Up to date, there is no effective treatment for chronic hepatitis B virus infection. We are collaborating with the Institute of Chinese Medicine to study the use of herbal medicine in the treatment of chronic hepatitis B. We have performed a dose-finding, double-blinded, placebo-controlled, randomized trial using *Phyllanthus urinaris*. Although this study shows negative results, we are planning to perform a pilot study on another *Phyllanthus* species from India. We are also currently working on another herbal medication formula (Rehassure) in the treatment of chronic hepatitis B.

We have recently received a grant from the Innovation and Technology Fund to study the genomic markers of hepatitis B virus in the prediction of hepatocarcinogenesis and treatment response to anti-viral agents. This project is a collaborative effort with the Department of Biochemistry, Department of Engineering, Department of Oncology as well as the Victorian Infectious Diseases Reference Laboratory in Australia. Currently we are in the process of complete genome sequencing of the hepatitis B virus. The database will then be transferred to our Engineering colleagues for data mining. We have also collaborated with Department of Surgery and Department of Anatomical and Cellular Pathology to study the relationship between COX-2, HBx protein and hepatocarcinogenesis. We found that HBx induces the expression of COX-2, which in turn increases proliferation and reduces apoptosis of hepatoma cell lines. We plan to further study the relationship between p53 and HBx in the process of hepatocarcinogenesis.

References
1. HLY Chan, SWC Tsang, CT Liew, CH Tse, ML Wong, JYL Ching, NWY Leung, JSL Tam, JJY Sung. Viral genotype and hepatitis B virus DNA levels are correlated with histologic liver damage in HBeAg-negative chronic hepatitis B virus infection. Am J Gastroenterol 2002;97:406-12.


Liver Cancer (Hepatocellular Carcinoma): from the Bench Top to Operating Room

Paul B. S. Lai
HBP Surgery, Department of Surgery, The Chinese University of Hong Kong

Liver cancer or hepatocellular carcinoma (HCC) is one of the top killers locally and worldwide. For the past 8 years, our team has established a collaboration with the Department of Clinical Oncology, Department of Chemical Pathology, and Department of Anatomical and Cellular Pathology in a number of research projects focusing on the molecular and cytogenetic aspects of HCC.

Cytogenetic aberrations are commonly found in malignant tumours. With the development of laboratory techniques and better handling of tumour samples, we have been able to establish a reliable and informative platform to study the aberrations in resected HCC samples by the method of comparative genomic hybridization (CGH).

While chromosomal aberrations are very useful in giving us directions of more in-depth studies, genetic events involved in liver carcinogenesis are also targets of our collaborative efforts. Using the cDNA microarray as a way to discover genetic targets, we have been able to identify a number of potentially important genes. The downstream studies on the functional significance of these genes are currently underway to decipher their roles in carcinogenesis, tumour progression as well as metastasis.

Detection of these targets in tumour samples as well as the blood stream has opened up an exciting area of early detection or screening of liver cancer. The usefulness of some of these potential biomarkers from the above-mentioned works is to be tested on in both retrospective and prospective manners.

More collaborative effort and cross-talks among researchers with different areas of expertise are important to the formation of a critical mass that would undertake and excel in the research of liver cancer.
Molecular Pathogenesis of Nasopharyngeal Carcinoma

K.W. Lo
Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong

Nasopharyngeal carcinoma (NPC) is prevalent among Southern Chinese. The high annual incidence of NPC poses a serious health problem in our locality. During the past decade, our group has been in the forefront of NPC research and identified several key genetic changes in this cancer. The major aim of our group is to unravel the molecular basis of NPC and thereby expand the prospects for the development of diagnostic/prognostic markers and novel therapeutic strategies. By closely collaborating with multiple research teams worldwide, we have intensively examined genetic and epigenetic alterations in this cancer. Furthermore, we have also investigated the role of EBV in NPC development. Our group was amongst the first to generate a comprehensive genome map of NPC by high resolution allelotyping and conventional comparative genomic hybridization (CGH) analysis. The identification of consistent 3p, 9p and 14q deletions in almost all NPC samples implies that inactivation of the tumor suppressor genes residing on these regions are critical events in NPC tumorigenesis. In particular, deletion of 3p/9p was further proven to be an early event and may occur prior to EBV infection in the epithelium. A NPC tumorigenesis model has hence been proposed. By positional mapping, we have delineated the NPC-associated tumor suppressor loci to multiple minimal deletion regions (e.g. 3p14-24.2, 9p21.3, and 11q21-23). Those findings lead to the discovery of critical tumor suppressor genes (e.g. p16, RASSF1A, and TSLC1) in this cancer. Molecular and functional characterization of these tumor suppressors has confirmed their important roles in NPC development. By CGH and array-based CGH analysis, we have targeted multiple amplification sites (e.g. TERC and PIK3CA at 3q26) in the NPC genome. With the advancement in the development of high-density array-based CGH analysis, we are systematically characterizing the recurrent amplicons and currently searching for the NPC associated oncogenes. In addition to genetic alterations, we are also the first group to report the significance of epigenetic changes in NPC tumorigenesis. Aberrant methylation of multiple cancer-associated genes (e.g. RARβ2, DAP-Kinase, H-cadherin, TIG1) was found in this EBV-associated cancer. Epigenetic inactivation of these genes may disrupt multiple pathways and play important roles in cancer development. To decipher the functional genome of NPC, we have also established the transcriptional profiles of an EBV-positive cell line (C666-1) and pooled normal epithelial outgrowths by serial analysis of gene expression (SAGE). A preliminary transcriptome map of NPC has thus been constructed. The integration of the genome and transcriptome data of these cell lines should provide important information for targeting critical cancer genes in NPC.
Methylation Profile in Cancer and the Potential Application as Molecular Markers Detected in Body Fluids

K.F. To
Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong

Gene promoter hypermethylation is a common mechanism leading to gene inactivation in human cancers. Each type of tumors may have a distinct profile of gene methylation. Such gene promoter methylation profile, on the one hand, is of biological interest and, on the other hand, may be useful molecular markers of cancer. With the collaborative efforts from different disciplines, we are investigating the gene promoter methylation profile in several human cancers and to assess the potential clinical application as molecular tumor markers. Together with the medical and surgical gastroenterological teams, we reported the methylation profile of gastric cancer and the detection of such epigenetic changes in patient’s serum. \(^{(1,2,3)}\) An extension of such analysis to colonic cancer is in progress and a more in-depth analysis is being supported by an ITF grant. A similar approach is applied to human liver cancer, with the collaboration with clinical oncology and surgical department, constituting part of the project supported by a Central Allocation grant. We also reported the methylation profile of urinary bladder cancer and being the first group to document the diagnostic potential of detecting methylation marker in voided urine. \(^{(4,5)}\) With the urology team, we will test the validity of such molecular diagnostic markers for detecting cancer in high risk groups. With the collaboration with surgical ENT and clinical oncology teams, we made use of nasopharyngeal brushing and reported that detection of methylation markers in such non-invasive procedure is feasible and may provide an alternative approach to collect samples directly from nasopharynx for analysis. \(^{(6,7,8)}\) We are in the process of designing a brushing instrument that is applicable to the nasopharynx and to assess the feasibility of detecting other molecular markers.

References


Molecular Signatures in Cervical Neoplasm

Y F Wong, T H Cheung, Tony Chung
Department of Obstetrics and Gynaecology, The Chinese University of Hong Kong

Worldwide, cervical cancer is a leading cause of cancer morbidity and mortality in women. Presently, cervical cancer is still the most common gynecologic malignancy in Hong Kong. Advances in early detection and management of cervical neoplasm must be made. We hypothesize that unique molecular alterations driving neoplastic transformation and progression in cervical epithelia may be developed into biomarkers for early diagnosis and molecular targets for effective prevention and treatment. We are studying the pathogenesis of cervical cancer with a view to identify molecular signatures related to this tumor. This involves studying (1) the HPV virus status, (2) genomic, and (3) proteomic changes in cervical neoplasm by using quantitative PCR and RT-PCR for assessing HPV viral load and HPV E6/E7 expression, using polymorphic microsatellite and SNP markers for high-density genotyping of selected chromosomes, using cDNA arrays for profiling of gene expression, and using SELDI protein chip for analyzing patterns of protein expression in cervical neoplasm from pre-invasive to invasive cervical cancer. We have assembled a large database and biorepository of specimens, including plasma, serum, cervical smear and frozen tissue from cancer patients and controls in the past 6 years. The project is a collaboration with multiple overseas medical centers. Eventually, our aim is to translate these research findings into early diagnosis and pharmacogenetic treatment of cervical neoplasm in women.
Stomach Cancer: from Carcinogenesis to Chemoprevention

Enders KW Ng and SC Sydney Chung
Department of Surgery, The Chinese University of Hong Kong
(In collaboration with: Department of Medicine and Therapeutics, Department of Microbiology and Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong)

Stomach cancer is the most common gastrointestinal tract malignancy in the world. It is also the most common cause of cancer-related mortality in China. For the past 10 years, our unit has been closely collaborating with the Department of Medicine and Therapeutics, Department of Microbiology, and Department of Anatomical and Cellular Pathology in a series of research projects focusing on the molecular biology of gastric carcinogenesis and chemoprevention of stomach cancer.

*Helicobacter pylori* is considered an important initiating agent in gastric carcinogenesis. In an earlier study we have identified a strong association between the null genotype of glutathione-S transferase µ (a human detoxifying gene) and gastric cancer related to the bacteria. Subsequently we found that N-nitrosation is a universal feature of all *H. pylori* strains, and significantly higher level of nitrosating activity has been found in strains collected from stomach cancer patients than those from non-cancer sources. Currently we are working on the cloning and characterization of the gene encoding this nitrosating capacity of the bacteria.

The effect of eradication of *H. pylori* on the precursor lesions (intestinal metaplasia and dysplasia) of gastric cancer has been investigated in a large-scale prospective randomized trial in a high cancer risk area in China (a collaborative project with the Beijing Medical University and Yantai city government). Preliminary results based on follow-up endoscopy reveal that clearance of *H. pylori* can result in regression of gastric inflammation but not intestinal metaplasia. Nevertheless, our group has discovered and reported a number of molecular events including promoter hypermethylation of tumor-related genes, increased expression of cyclo-oxygenase 2 (COX-2), recurrent genomic aberrations, missense p53 mutations, expression of trefoil peptides on samples harvested from stomach cancer patients. Among them, COX-2 over-expression is found in 80% of gastric cancer and is strongly associated with *H. pylori* induced chronic gastritis and intestinal metaplasia. Interestingly, though eradication of *H. pylori* is able to reduce the expression of cyclin D2 and p27, COX-2 expression remains unchanged. This is probably a reason for the persistence of intestinal metaplasia on gastric epithelium after *H. pylori* eradication.

Current ongoing clinical project includes screening of family members of stomach cancer patients for the presence of *H. pylori* infection and chronic gastritis. Thus far over 100 first-degree relatives have been studied. Despite the similar percentages of *H. pylori* infection, the prevalence of intestinal metaplasia is significantly higher among the family members than an age-and sex-matched control group of subjects. A prospective randomized trial on the use of selective COX-2 inhibitor as an attempt to reduce the severity or to halt the progression of intestinal metaplasia is now underway.

References


Effectiveness of Interventions for Reducing Breathlessness, Fatigue and Anxiety in Chinese Undergoing Lung Cancer Radiotherapy in Hong Kong

Carmen Chan¹, Sing-Fai Leung², Susanne Mak²
¹The Nethersole School of Nursing and ²Department of Clinical Oncology, The Chinese University of Hong Kong

Lung cancer is the leading site of cancer in Hong Kong males and the major cause of cancer death for both genders (Hong Kong Cancer Registry, 2000). Although advances in treatment can lengthen a patient’s life, patients undergoing lung cancer radiation experience many different types of symptoms with breathlessness, fatigue and anxiety having the higher prevalence.

Breathlessness, fatigue, and anxiety are distressing symptoms for patients with lung cancer and radiation, however, are often neglected areas in research and clinical practice. This randomized controlled trial is designed to compare three approaches to care: usual care, progressive muscle relaxation (PMR), and a combination of education and PMR, to alleviate the experience of breathlessness, fatigue, anxiety and promote the use of self care strategies.

The study is conducting in the Oncology unit of a public-funded acute hospital in Hong Kong. One hundred and eighty-four lung cancer patients undergoing radiotherapy will be recruited. The main outcome measures are: Visual Analogue Scale (VAS) of breathlessness and associated distress; Revised Piper Fatigue Scale (PFS) for determining the level of fatigue; and A-State Anxiety from the State-Trait Anxiety Inventory (STAI) for anxiety levels. The secondary outcome measures are: Functional sub-scale of the SF-36 Health Survey and patient satisfaction. ANOVA for repeated measures will be used to compare the outcomes among the 3 groups.

Findings of this study will provide information on the physical and psychosocial benefits of PMR, PMR combined with education, compared with usual care to lung cancer patients undergoing radiotherapy. Interventions found useful in reducing these symptoms will be able to be adopted by health professionals in promoting optimal functioning and enhancing patient satisfaction. This study commences in April 2002 and will be completed by March 2004.

Reference
Hong Kong Cancer Registry (2000) Cancer Incidence and Mortality in Hong Kong 1997. Hong Kong: Hospital Authority
Bioinformatics and Application of Microarray Biotechnology in Medical Research

Chi Chiu Wang
Department of Obstetrics and Gynaecology, The Chinese University of Hong Kong

Our department commenced microarray work in gynaecologic cancer research in 2000. Recently we have acquired advanced biochip technology from the Microarray Laboratory, Center for Information Biology and DNA Data Bank of Japan from the National Institute of Genetics, Japan. We have completed preparations of microarray chips cloned from a 15,000 mouse cDNA library from the National Institute of Aging, National Institutes of Health, USA. More than 15,000 fully annotated unique sequences from over 50,000 EST collections, together with around 1,000 control spots, have been successfully fabricated into glass slides.

Applying the technology, we performed preliminary genetic profiling of prenatal brain in mouse embryos. Several prominent gene expression patterns were established in the developing brain tissues using hierarchical and probabilistic clustering. A distinctive cell-cycle pathway for primitive dendritic cell function was also retrieved by Boolean gene regulatory network searches. The mediated transcriptional factors for particular parts of the developing brain compartments have been distinguished by simultaneous triple hybridisation and verified by whole mount in situ hybridisation.

We also studied the pathomechanism of melan-c albino melanocytes in the role of Waardenburg syndrome in mice (collaborated with Tohoku University, Japan). Impaired nuclear transcriptional progression, signal transduction pathways has been identified in associated with the STZ-induced diabetic embryopathy in mice (collaborated with Department of Anatomy, CUHK). We found abnormalities in dysregulation of the neuron-restrictive silencer factor and some of the neurological deficits in both transcription and translation level in neuronal stem cells and progenitor cells from a mouse embryonic stem cell line TT2F containing a single human chromosome 21 in vitro (collaborated with Tottori University, Japan). This technology may form a basis for stem cell therapy.

Lately, we have access to a strain of transgenic mouse with oestradiol-induced uterine leiomyomas (collaborated with Institut Cochin, Paris). This mouse model allows us to understand the molecular network of endometrium angiogenesis prone to uterine fibroid growth (collaborated with Department of Physiology, CUHK).

The mouse sequence tag of interest acquired from the animal experiments will be tested against the human ORF database to search for any homolog and will be mapped from human genome for clinical trial in the future as a potential essential regulator for the development and surveillance of diseases in mankind. We are now also developing our own cDNA libraries for gene expression study and future microarray usage from human embryonic tissues (collaborated with Department of Ophthalmology and Visual Sciences, CUHK).
Functional characterisation of putative disease genes and their protein products is an important step in the rational design of drugs. Over the course of our research in the past ten years, we have discovered over 100 genes that are differentially expressed in cardiomyopathy. The limited resources available allowed us to study in detail only 20 of these. Based on the resources established by the cardiovascular expressed sequence tags (ESTs) sequencing, we have isolated three LIM domain protein genes, which are preferentially or abundantly expressed and developmentally regulated in human heart. The LIM domain protein family is an important new family of proteins which carries a cysteine-rich zinc-binding domain called the LIM domain. This protein family is found in mammals, amphibians, flies, worms and plants, and they may be involved in cell identity, differentiation, growth control and developmental regulation. The intracellular localization of these LIM domain proteins has been studied and their interacting protein partners have been obtained. Moreover, previous results have shown that these protein genes can be differentially expressed in chemical hypoxia, dilated cardiomyopathy and hypertrophic cardiomyopathy, and in an embryonal-rhabdomyosarcoma cell line. We have also studied the cytoprotective role of a novel small heat shock protein HSPB3, and found an increased expression of this gene in some dilated cardiomyopathy patients and that it could be induced in vitro by hypoxia followed by re-oxygenation treatment. HSPB3 is also induced in rabbit collateral artery growth after artery occlusion. Thus studies of these genes might provide further insight to the treatment of heart disease and arterial occlusive disease. Learning the mechanism of action of regulation of these genes might help us in devising therapeutic protocols that would prevent the onset of the disease or reverse the course of its development.
Application of State-of-the-art Proteomic Technology in Basic Medical Science Research

Kenneth K.H. Lee
Department of Anatomy, The Chinese University of Hong Kong

Proteomics is the study of the protein profile of cells, tissues and sera. The technology is extremely powerful and has been used for: (1) identifying protein markers associated diseases and congenital abnormalities, (2) testing for the effects of drugs and (3) studying development and regeneration. In collaboration with the Department of Medicine and Therapeutics / Division of Cardiology, we have used proteomic techniques to discover proteins that are involved in the regulation of cardiac myocyte proliferation.

Background
Directly after birth, the cardiomyocytes in the mouse neonatal heart retain their ability to proliferate. However, this ability lasts only a few days and then the cardiomyocytes irreversibly lose their capacity to divide. To date, it is still not fully understood what factors are involved in the cessation of cardiomyocyte proliferation.

Methods and Results
Using Cell Nuclear Antigen (PCNA) antibodies, we established that cardiomyocytes could divide rapidly in 2-day- and 6-day-old mouse neonatal hearts and that they completely stop dividing at day 13. Subtractive 2-dimensional-gel electrophoresis was performed on proteins extracted from the 2-day- and 13-day-old hearts, in order to identify polypeptides that might be involved in the inhibition of cardiomyocyte proliferation. Using matrix-assisted laser desorption ionisation mass spectroscopy (MALDI-MS), we identified a protein, with pi 4.9 and 14.5 kDa, called Mammary-Derived Growth Inhibitor (MDGI) that was expressed in 13-day-old hearts but not 2-day-old hearts. We also identified another protein with the same molecular weight, but had a pi of 5.1, that was moderately expressed in 2-day-old hearts but it became strongly up-regulated in the 13-day-old hearts. The protein was identified as heart-type fatty acid binding protein (H-FABP). MDGI has now been identified as a H-FABP. We performed Western blot analysis to confirm that the 2 proteins we selected for analysis were pi 4.9 and 5.1 isoforms of H-FABP. We have also examined whether MDGI and PCNA were co-expressed in 2-, 6- and 13-day-old heart sections, immunohistochemically.

Conclusion
In conclusion, we have identified 2 important proteins that are activated in the cessation of cell growth during differentiation of neonatal cardiomyocytes of mice, which could be potentially important targets for the regeneration of the diseased heart.
Linking the Basic Research of Pancreatic Functions to Pancreatic Diseases

P.S. Leung
Department of Physiology, The Chinese University of Hong Kong

The pancreas is an important organ in the body that is best known for two major functions: the exocrine gland that secretes enzymes necessary for the digestion of food and the ductal epithelium that secretes bicarbonate for neutralization of acidic chyme, and the endocrine gland that secretes insulin and glucagon for glucose homeostasis. The most significant diseases of the exocrine pancreas are pancreatitis, cystic fibrosis and carcinoma while the most common diseases of the endocrine pancreas are diabetes mellitus and islet cell tumours. Novel regulatory systems for controlling the proper functioning of a normal pancreas have been intensively studied. Our main research direction is to deepen these investigations with a view of understanding more about the normal and diseased pancreatic functions using animal models of hypoxia, diabetes, pancreatitis and islet transplants. Aberrations from the normal regulatory systems could be potential targets for treating various endocrine and exocrine disorders of the pancreas. In this regard, our recent data shows that a pancreatic renin-angiotensin system (RAS) is important for regulating pancreatic islet hormone, acinar digestive enzyme, and ductal anion secretions. Future target for the pancreatic RAS by virtue of using specific RAS blockers might be a novel pathway for the potential treatment of endocrine and exocrine pancreatic diseases. From the standpoint of both morbidity and mortality, diabetes mellitus overshadows other pancreatic diseases. Inhibition of carbohydrate-digesting enzymes plays an important role in controlling postprandial hyperglycemia in patients with type-II diabetes. Enhanced secretion of insulin from the pancreas or increased sensitivity of the peripheral tissues towards insulin is also of therapeutic values in treating diabetes. Alternatively, targets for the development of potential therapeutic agents from synthetic and natural sources could be promising in manipulating some of the pancreatic diseases such as diabetes, pancreatitis and cancer. It is therefore our primary aims to link the basic studies of the pancreas to its clinical applications and to establish a leading role in basic and applied research on the pancreas, by consolidating collaborative research among Departments from Faculties of Medicine, Science, and School of Chinese Medicine.
Increased Susceptibility to Teratogens during Diabetic Pregnancy

Alisa SW Shum
Department of Anatomy, The Chinese University of Hong Kong

Maternal diabetes is known to be associated with an increased risk of congenital malformations in the offspring of affected pregnancies. Although it is clearly evident that diabetic embryopathy is the result of multifactorial interactions, few attempts have been made to investigate the association between diabetic embryopathy and other factors, such as food or drugs taken during pregnancy. By using a mouse model, we have recently demonstrated that embryos of diabetic mice were significantly much more susceptible to malformation than embryos of nondiabetic mice when maternally exposed to the vitamin A metabolite retinoic acid, a common drug with well known teratogenic properties (Diabetes 2002, 51: 2811-2815). Moreover, inducing transient hyperglycaemia in nondiabetic pregnant mice led to similar interaction with retinoic acid in increasing the incidence of malformation in the embryo, whereas reducing blood glucose level in diabetic pregnant mice could abolish the increased susceptibility of the embryo to retinoic acid.

To determine the cellular and molecular bases of interaction, two approaches were employed: (i) we have used in situ hybridization and RT-PCR to examine for any altered expression of known genes, and (ii) we have identified unknown genes by differential display. Our findings indicated that maternal diabetes/hyperglycemia enhanced the downregulation of some genes important in embryo development and also exacerbated cell death in the progenitor cells of affected tissues after retinoic acid treatment, thereby, increasing the incidence of malformation in the embryo.

In conclusion, we have demonstrated a positive interaction between maternal diabetic milieu and retinoic acid in increasing congenital malformations, which may have implications for humans in suggesting increased susceptibility to environmental teratogens during diabetic pregnancy. Moreover, our diabetic mouse model can serve as a tool to test for susceptibility to other environmental factors and pave the way to derive preventive measures against adverse pregnancy outcome associated with maternal diabetes.
Glucose movement across the blood-brain barrier is glucose transporter type 1 (Glut-1) dependent. We have studied glucose transport in patients with the Glut-1 deficiency syndrome (Glut-1DS) featured by infantile-onset seizures and developmental delays, as well as in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). Genetic and biochemical analysis revealed that the Glut-1DS patients harbor heterozygous loss of function mutations of the GLUT-1 gene. These defects contribute to the consistently low CSF glucose (<40 mg/dl) and low CSF lactate concentrations. Diabetes often accompanies MELAS. In patients carrying the A3243G point mutation in the mitochondria genome, an elevation of Glut-1 activity in pre-diabetic state and a reduction of Glut-1 activity in diabetic state were observed. Since patients with impaired Glut-1 function are likely to have reduced tolerance to further disturbances of glucose transport, dietary and therapeutic agents were evaluated for their effects on Glut-1 activity. α-lipoic acid (thioctic acid) and phenytoin stimulated Glut-1 activity whereas caffeine, arachidonic acid, barbiturates, and zonizamide were inhibitory. These results are consistent with the clinical observations that the Glut-1DS patients are unresponsive to phenobarbital treatment, and some reported modest improvement with α-lipoic acid supplement and some experienced sensitivity to coffee. In conclusion, impaired Glut-1 activity can impede energy supply to the brain and contribute to CNS symptoms. For the treatment of patients with disturbed CNS energy metabolism, the Glut-1 modulating effects of dietary and therapeutic agents should be considered.
On the Origin of Anti-DNA Antibodies

Pakleong Lim
Clinical Immunology Unit, The Chinese University of Hong Kong

Antibodies to double-stranded DNA are pathognomonic of systemic lupus erythematosus (SLE). It is not clear, however, how they originate since DNA is a self-antigen. We propose that these antibodies may be generated by accident following infection by some types of microorganisms, not because of stimulation of the immune system by microbial DNA or antigens, but rather, by the antibodies produced initially to the microorganism. We found that some types of antibodies encoded by certain types of genes (DFL16.1 in mice and DXP’1 in humans) carry an epitope that mimics DNA in structure. When these antibodies induce a second generation of antibodies as happens in a normal anti-idiotypic response, some of the antibodies produced will consequently be specific for DNA. From another study done in collaboration with the Department of Paediatrics regarding a young SLE patient who oddly had no anti-nuclear antibody but an abundance of anti-DNA antibodies, we suggest that some DNA-binding antibodies may actually be induced by guanosine triphosphate complexed to some protein carrier. These anti-guanylyl antibodies which are mistaken for anti-DNA antibodies but in fact recognize quite distinct cellular antigens, are presently not well understood.
In 1997, our group has discovered the presence of fetal DNA in the plasma of pregnant women. This finding has opened up new possibilities for non-invasive prenatal diagnosis. Through a close collaboration with the Department of Obstetrics and Gynaecology, our group has developed a robust methodology for the extraction and measurement of fetal DNA in maternal plasma. Using this methodology we have documented the temporal variation in circulating fetal DNA during pregnancy and have demonstrated its rapid clearance following delivery. We have also shown that quantitative aberration in circulating fetal DNA concentration can be seen in disorders such as preeclampsia, preterm labour and certain fetal chromosomal abnormalities. Diagnostically, we have shown that this technology can be used for the non-invasive prenatal diagnosis or exclusion of certain fetal genetic traits/diseases such as rhesus D status, beta-thalassaemia and congenital adrenal hyperplasia. Very recently, we have shown that in addition to DNA, fetal RNA is also detectable in maternal plasma. This latter observation is particularly surprising in view of the inherent instability of RNA. In this regard, we have produced evidence which shows that circulating RNA may be protected from degradation by being associated with particulate matter in plasma. The discovery of fetal RNA in maternal plasma has opened up new non-invasive prenatal diagnostic or monitoring assays, which may ultimately allow the performance of gene expression profiling of an unborn baby, just by analyzing a blood sample from the mother.
Stem Cell Research Program: Ex Vivo Expansion, Plasticity and Embryonic Stem Cells

Karen Li
Department of Paediatrics, The Chinese University of Hong Kong

Hematopoietic stem cell therapy has been applied for the treatment of malignancy and genetic diseases. A major limitation, especially for cord blood (CB) transplant, is the low cell dose in a collection, which is often associated with delayed engraftment and related morbidity and mortality. To address this issue, we have investigated alternative sources of stem cells, improved methods of CB collection, new agents and procedures of CB processing and cryopreservation. Using the NOD/SCID mouse model for assessing the engraftment capacity of human stem and progenitor cells, another objective of our stem cell program is to establish the ex vivo expansion of CB stem cells under optimized conditions of serum-free medium and cytokine combinations.

The new concept of stem cell plasticity has recently been suggested. If proven to be feasible, it might contribute significantly to the practice of regenerative medicine. In this area, we have initiated projects on the induction of bone marrow cells to cardiomyocytes, neurons and pancreatic islets. Another controversial model is the induction of human embryonic stem cells for the repair of damaged tissues. We have initiated a study on the induction of these cells to hematopoietic stem cells.

Our stem cell study is a joint program involving various Departments, including Paediatrics, Anatomical and Cellular Pathology, Chemical Pathology, Obstetrics and Gynaecology, Medicine and Therapeutics, Biology and the Laboratory Animal Services Centre. We have also established collaboration with the Center of Stem Cell, Second Hospital Affiliated to Sun-Yat-sen University, Guangzhou.
Growth Hormone Secretagogue Receptors: Cell Signalling and Receptor Oligomerization

Helen Wise¹ and Christopher H.K. Cheng²
¹Department of Pharmacology and ²Department of Biochemistry, The Chinese University of Hong Kong

Many therapeutic agents act on cell surface receptors belonging to a superfamily known as G-protein-coupled receptors (GPCRs). The interaction between activated receptors and their cognate G-proteins was thought to provide the important first step in a cell signalling pathway. Now it may be that GPCRs interacting with other GPCRs, by a process known as dimerization, may also be part of this essential step in cell signalling. Furthermore, a GPCR may dimerize with a GPCR from the same family or from a different GPCR family, or even with a completely different class of receptor.

The mechanisms underlying GPCR dimerization and the consequences for cell signalling may not be the same for all types of GPCRs. This project focuses on the growth hormone secretagogue receptor (GHSR) which regulates the pulsatile release of growth hormone from the pituitary gland. An interesting feature of the GHSR is that it exists in two forms: type 1a which is a classical GPCR with seven transmembrane domains, and type 1b which is a truncated version of type 1a, having only five transmembrane domains. The aim of this project is to explore the mechanisms of cell signalling of GHSR, and to determine the extent and importance of interactions between these two receptor subtypes. While much of this work features classical approaches to studying cell signalling, we are also introducing the newer methodology of bioluminescence resonance energy transfer (BRET) which allows us to examine protein-protein interactions in living cells.
The Role of Nitric Oxide and Mitogen-activated Protein Kinas in Mediating the Inhibition by β₃-adrenoceptor Activation of Voltage-dependent L-type Calcium Channels of Guinea-pig Single Ventricular Myocytes

YW Kwan¹, KW Tsui², WK Liu³
¹Department of Pharmacology, ²Department of Biochemistry and ³Department of Anatomy, The Chinese University of Hong Kong

Activity of mammalian heart is continuously under the influence of autonomic nervous system. Catecholamines released from sympathetic nerves through binding to the membranous receptor such as β-adrenoceptor (β-AR) leads to an increase in heart rate and force of contraction. It has been known that there are two β-AR subtypes (β₁-AR and β₂-AR) in heart and these receptors are responsible for the excitatory effect of endogenous catecholamines. Recent pharmacological and molecular biological studies, however, suggest the presence of another β-AR subtype (atypical or β₃-AR) in cardiac muscle. In stark contrast to β₁-AR and β₂-AR, activation of this atypical β-AR in human heart preparation resulted in a decrease in cardiac muscle contraction. Influx of Ca²⁺ through the Ca²⁺ channels (I_{CaL}) is important in the excitation-contraction coupling of the heart. However, the relationship of β₃-AR activation, I_{CaL} activity and heart muscle contraction has not been established in detail. In the preliminary study using single cells isolated from guinea-pig ventricular muscle, administration of synthetic β₃-AR compounds (isoprenaline and BRL 37344) and the endogenous catecholamine adrenaline slowly elicited an inhibition (~ 60-78 %) of basal I_{CaL} amplitude. However, the detailed cellular signaling pathway involved has not been elucidated. On the other hand, a decrease in I_{CaL} can be interpreted as one of the factors responsible for the reported reduction in muscle contraction. A decrease in contraction upon the activation of β₃-AR and the subsequent release of nitric oxide (NO) has been suggested importance in the development of heart failure. Despite the reported involvement of NO, the production of NO has not been monitored when β₃-AR is activated. Moreover, one of the manifestations of heart failure is cardiac hypertrophy and the mitogen-activated protein kinase (MAPK) and NO are said to be important. In this study, we will measure the release of NO fluorometrically and the activities of I_{CaL} electrophysiologically upon the activation of β₃-AR of ventricular cells. Furthermore, the expression of β₃-AR mRNA and involvement of MAPK will be determined using molecular biological technique. Results obtained in this study will provide important information for a better understanding of the physiological functions of this atypical β-AR and assist future drug development for an effective treatment of heart failure.
A Negative Feedback Pathway that Controls Cytosolic Ca\textsuperscript{2+} and Nitric Oxide Levels in Endothelial Cells

Xiaogiang Yao
Department of Physiology, The Chinese University of Hong Kong

Nitric oxide (NO) and Ca\textsuperscript{2+} are among the most important signaling molecules in the cardiovascular system. It is known that hemodynamic shear stress generated by blood flow as well as numerous blood-borne chemicals can elicit a rise in endothelial cytosolic Ca\textsuperscript{2+} level, which then acts to stimulate eNOS and PLA\textsubscript{2}, leading to the production and release of NO and other vasoactive substances such as PGI\textsubscript{2}, endothelium-derived hyperpolarizing factor (EDHF), etc. The effect of Ca\textsuperscript{2+} signaling is not limited to the regulation of vascular tone. In fact, Ca\textsuperscript{2+} signaling is involved in the control of such diverse processes as gene expression, exocytosis and cell proliferation. Some effects of Ca\textsuperscript{2+} signaling may be mediated through its stimulatory action on NO, which inhibits platelet aggregation and prevents atherosclerosis.

The great importance of NO/Ca\textsuperscript{2+} as cellular messengers calls for some elegant regulatory mechanisms to tightly control their cytosolic levels. In recent studies, we are able to identify a regulatory negative feedback pathway by which intracellular NO and Ca\textsuperscript{2+} levels can be finely regulated. Patch clamp studies record two Ca\textsuperscript{2+}-permeable channels, the activity of which can be inhibited by protein kinase G. The channels are likely to be the primary channel responsible for the blood flow-induced and store depletion-induced Ca\textsuperscript{2+} influx in vascular endothelial cells. Opening of the channels with PKG inhibitors causes vascular dilation in rat arteries. These studies suggest that the channels may play a crucial role in the regulation of vascular tension and blood pressure as well as in the vascular protection against oxidative stress. Recent study from our group indicates the possibility of this channel being one of the Transient Receptor Potential (TRP) channel gene families. An exciting aspect of this study is that it points out the possibility of targeting TRP channels as a therapeutic strategy for future development of new classes of antihypertensive drugs. Some results from the studies have been published in several prestigious journals such as FASEB Journal, Circulation Research, Journal of Biological Chemistry.
Cost-effectiveness Analysis of High-dose Omeprazole Infusion as Adjuvant Therapy to Endoscopic Treatment of Bleeding Peptic Ulcer

¹School of Pharmacy, ³Department of Economics, ⁴Department of Surgery, ⁵Department of Medicine and Therapeutics and ⁶School of Public Health, The Chinese University of Hong Kong; ²School of Pharmacy, University of London

Background
Intravenous administration of proton pump inhibitors after endoscopic treatment of bleeding peptic ulcers has been shown to decrease the rate of recurrent bleeding and the need for subsequent surgery. Yet extra cost due to the medication is required. The overall cost-effectiveness had never been formally assessed. The aim of this study was to examine the cost-effectiveness of this therapy by using standard pharmacoeconomic methods.

Methods
The present study was performed in conjunction with a randomised controlled clinical trial that included 232 patients who received either omeprazole (80 mg intravenous bolus followed by infusion at 8 mg/hour for 72 hours) or placebo after hemostasis was achieved endoscopically. A cost-effectiveness analysis was performed to evaluate the different outcomes of the trial. All related direct medical costs were identified from patient records. Cost values were obtained from either the HK Hospital Authority or the most recent Government Gazette. Cost-effectiveness ratios were calculated. The study was performed from a public hospital perspective.

Results
As reported for the clinical study, bleeding recurred in 7 of 115 patients (6%) in the omeprazole group and 26 of 117 (22%) in the placebo group. The therapy therefore led to a 72% reduction in bleeding frequency. Analysis by the Kolmogorov-Smirnov test showed that the direct medical cost in the omeprazole group was lower than that for the placebo group. Cost-effectiveness ratios for omeprazole and placebo groups were, respectively, HK$ 28,764 (US$ 3,688) and HK$ 36,992 (US$ 4,743) in averting one episode of recurrent bleeding in one patient after initial hemostasis was achieved endoscopically.

Conclusions
Intravenous administration of high-dose omeprazole appears to be a cost-effective therapy in reducing the recurrence of bleeding and need for surgery in patients with active bleeding ulcer after initial hemostasis is obtained endoscopically.
A Pharmacokinetic-genomic Approach for Prediction of Herb-drug Interaction: Experience with *Ginkgo Biloba*

Ophelia Q. P. Yin¹, Brian Tomlinson², Mary M. Y. Waye³, Albert H. L. Chow¹, Moses S. S. Chow¹
¹School of Pharmacy, ²Department of Medicine and Therapeutics, ³Department of Biochemistry, The Chinese University of Hong Kong

**Background**

Despite the increasing usage of herbal products worldwide, the present data on herb-drug interactions is insufficient and often lack good quality, due in part to the lack of a clinical method for detection of herb-drug interactions. We had previously used a “cocktail” approach for screening the effect of herbs on liver metabolizing enzymes, and found that *Ginkgo biloba* exerted a significant inductive effect on CYP2C19 activity. This study was thus designed to verify the potential interaction between *Ginkgo biloba* and omeprazole (CYP2C19 substrate), as well as to investigate if there are any differences in the magnitude of interaction among subjects with different CYP2C19 genotypes.

**Methods**

Eighteen healthy Chinese subjects received a single 40 mg omeprazole at baseline and then at the end of a 12-day treatment period with *Ginkgo biloba* (140 mg, bid). Multiple blood samples were collected over 12 h post omeprazole dosing. Plasma concentrations of omeprazole and its metabolites, 5-hydroxyomeprazole (mediated via CYP2C19) and omeprazole sulfone (mediated via CYP3A4), were determined by an HPLC method, and their pharmacokinetics calculated by non-compartmental methods. Genotyping procedures for identifying CYP2C19 wild-type (wt) and the two mutated alleles, CYP2C19m1 (m1) and CYP2C19m2 (m2), were performed by PCR-RFLP method.

**Results**

Plasma concentrations of omeprazole and omeprazole sulfone were significantly decreased, and 5-hydroxyomeprazole significantly increased following *Ginkgo biloba* administration in comparison to baseline. A significant decrease in the ratio of area under the plasma concentration-time curve (AUC) of omeprazole to 5-hydroxyomeprazole was observed, averaging 42.3% (p<0.01), 50.3% (p<0.05) and 70.6% (p<0.01) in the homozygous extensive metabolizers (wt/wt, n=6), heterozygous extensive metabolizers (wt/m1 and wt/m2, n=5), and poor metabolizers (m1/m1 and m1/m2, n=7), respectively. No significant changes in the AUC ratios of omeprazole to omeprazole sulfone were observed for all three groups (1.31 ± 0.51 vs. 1.52 ± 0.45; 1.21 ± 0.50 vs. 1.37 ± 0.48; 1.03 ± 0.39 vs. 0.86 ± 0.21 respectively, all p>0.05).

**Conclusion**

The results show that *Ginkgo biloba* can cause significant induction of omeprazole metabolism via the CYP2C19 pathway with the magnitude of interaction varying with individual genotype. The observed interaction substantiates our initial screening data and suggests that such a screening method may be potentially useful to predict herb-drug interactions involving CYP isozymes.
Clinical Development of Connecting System for Prevention of Peritonitis in CAPD Patients

CC Szeto, PKT Li  
Department of Medicine and Therapeutics, The Chinese University of Hong Kong

Continuous ambulatory peritoneal dialysis (CAPD) is now a well-proven effective treatment of patients with end-stage renal disease, a problem having significant impact on patients and on society in terms of health care resources (1). The success of CAPD as treatment modality has been made possible with reducing peritonitis rates. Early on the history of CAPD, peritonitis occurred approximately every other month. Notwithstanding the dramatic improvement thereafter, peritonitis remains a major cause of technique failure and morbidity. CAPD Peritonitis is one of the commonest reason for our renal failure patients requiring hospitalization and it can even lead to mortality.

Two-thirds of all episodes of CAPD peritonitis can be directly attributed to touch contamination of the connection between the transfer set and the dialysis bag containing fresh dialysis solution. It is in this context that disconnect system represented a cornerstone development to minimize touch contamination, which was borne out by our reporting a satisfactory peritonitis rate (17 patient-months per episode) and cost-effectiveness of Y-set disconnect system as compared to conventional spike system (2). The fundamental concept of disconnect system is “flush-before-fill”, which flushes with the dialysate any contaminating bacteria introduced during connection.

With the subsequent introduction of a novel double-bag system, a completely sterilized disposable integrated system connects an empty bag and a fresh dialysate-containing bag, again with flush-before-fill technique. The advantage of double-bag system, by virtue of fewer connecting procedures, is further tested in our population of incident CAPD patients using randomized prospective multicenter study design (3). The superiority in terms of patient acceptance rate was demonstrated as compared to Y-set disconnect system. Of note, a satisfactory peritonitis incidence rate of 33.5 patient-months per episode was reported.

Simplicity of double-bag exchange system was further made possible by means of a special switch disc device which controls and regulates all three phases of exchange: outflow, flush and inflow. This new system was shown to be easier to learn during the training period, as confirmed in our prospective randomized study involving 110 new CAPD patients (4). Peritonitis rate was 36.8 patient-months per episode.

The data of the several clinical trials from our center proved that improved connectology has increased the effectiveness of CAPD by reduced its complication rate. Clearly, achieving a remarkably low peritonitis rate sets the stage to further improve longevity of peritoneal membrane and the technique and patient survival in this group of high risk patients.

References


Oxygen Therapy for Hypercapnic Patients with Chronic Obstructive Pulmonary Disease and Acute Respiratory Failure. A Randomized Controlled Pilot Study

Charles D. Gomersall,¹ Gavin M. Joynt,¹ Ross C. Freebairn,¹ Christopher K.W. Lai,² Teik E. Oh¹
¹Department of Anaesthesia and Intensive Care and ²Department of Medicine and Therapeutics, The Chinese University of Hong Kong

Objective
To investigate the effect of oxygen therapy on outcome and on symptomatic hypercapnia.

Design
Randomized, controlled, single blind study.

Setting
Multidisciplinary intensive care unit of a university teaching hospital.

Patients
Patients admitted with a clinical diagnosis of an acute exacerbation of chronic obstructive pulmonary disease and a PaO₂ < 6.6 kPa (50 mmHg) and PaCO₂ > 6.6 kPa (50 mmHg) on air.

Interventions
Patients received oxygen therapy titrated to increase arterial oxygen tension to >6.6 kPa (50 mmHg) or >9 kPa (70 mmHg). Patients in the low oxygen tension group also received doxapram if they developed an acidosis with pH<7.2 while those in the high oxygen tension group received doxapram if they developed symptomatic acidosis. Bronchodilator, steroid and antibiotic therapy was standardized.

Measurements and main results
Two patients in the low oxygen tension group (n=17) required mechanical ventilation and another one died. No patients in the high oxygen group (n=17) had a poor outcome but this difference was not significant. No patient in either group became comatose or developed an acute cardiac arrhythmia.

Conclusions
Traditional teaching related to oxygen therapy for hypercapnic patients with an acute exacerbation of chronic obstructive pulmonary disease may be incorrect. A large randomized controlled study is required to confirm this impression.
The Effects of High-inspired Oxygen Fraction during Elective Caesarean Section under Spinal Anaesthesia on Maternal and Fetal Oxygenation and Lipid-peroxidation

Kim S. Khaw, a Chi C. Wang, b Warwick D. Ngan Kee, a Chi P. Pang, c Michael S. Rogersb
a Department of Anaesthesia and Intensive Care; b Department of Obstetrics and Gynaecology; c Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong

Background
Oxygen supplement is routinely given to parturients undergoing cesarean section under regional anaesthesia. While the aim is to improve fetal oxygenation, inspiring a high oxygen fraction (FiO2) can also increase free radical activity and lipid peroxidation in both the mother and baby. In this prospective randomised double-blinded study, we investigated the effect of high inspired oxygen fraction (FiO2) on maternal and fetal oxygenation and oxygen free radical activity in parturients having cesarean section under spinal anaesthesia.

Methods
Forty-four healthy parturients were randomized to breathe either 21% (air group) or 60% oxygen (oxygen group) via a ventimask intraoperatively. Maternal arterial blood was collected at 5 min intervals from baseline until delivery, and umbilical arterial and venous blood was collected at delivery. Measurements of blood gases and the products of lipid peroxidation, 8-isoprostane, malondialdehyde (MDA), hydroperoxide (OHP) and purine metabolites were performed.

Results
At delivery, the oxygen group had greater maternal arterial PO2 [mean 30.0 (SD 6.3) vs 14.2 (1.9) kPa; mean difference 15.8 kPa, 95% confidence interval 12.9-18.7 kPa, \(P<0.001\)] and greater umbilical venous PO2 [4.8 (1.0) vs 4.0 (1.4) kPa; mean difference 0.8 kPa, 95% confidence interval 0.0-1.5 kPa, \(P=0.04\)] compared with the air group. Maternal and umbilical plasma concentrations of lipid peroxides (8-isoprostane, MDA, OHP) were greater in the oxygen group compared with the air group (\(P<0.05\)).

Conclusions
We conclude that breathing high FiO2 modestly increased fetal oxygenation but caused a concomitant increase in oxygen free radical activity in both mother and fetus.

Postscripts
The findings from this study has been highlighted in discussion and editorial comments in journals specializing in Anaesthesia as well as Obstetrics and Gynaecology.1-3 A Competitive Earmarked Research Grant was subsequently awarded for an extension of this study, titled: “The effects of Maternal Oxygen Therapy during Emergency Caesarean Section”.

References
Biophysical Research in Musculoskeletal Tissues

KS Leung, KM Chan, WH Cheung, L Qin, JCY Cheng
Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong

Year 2001-2010 has been designated as the Bone Joint Decade (BJD). One of the most important goals set by the BJD is to promote cost-effective prevention and treatment for musculoskeletal disorders (http://www.boneandjointdecade.org).

Biological approaches (e.g. growth factors or gene therapy etc.) may have great potentials for treatment of many orthopaedic conditions but currently still remain experimental due to its high costs and difficulties in preparation and delivery. On the other hand, the study of biological responses of the skeletal tissues to external mechanical stimulation confirms its clinical applicability and cost-effectiveness, which has been our main focus in the past 10 years. These studies include distraction lengthening of bone, low-intensity pulsed ultrasound (LIPUS) stimulation, shockwave treatment, and low magnitude and high frequency vibrations intervention.

With local and international research funding supports (5 RGC-Earmarked grants and 3 AO/ASIF research grants) and the available state-of-the-art research facilities, we conduct comprehensive studies (in vitro, in vivo, and clinical) at micro (cellular, subcellular, molecular and biochemical approach) and macro-levels (tissue and organ) to investigate the interaction between different biophysical stimulations and biological tissues. For in vitro study, effect of LIPUS on human periosteal cells has been studied and results suggested that LIPUS enhanced proliferation of periosteal cells and therefore play a critical role in fracture healing enhancement.

For animal experiments, four projects are being conducted:
1) Combined effects of shockwave and LIPUS for treatment of osteoporosis using goat model;
2) The effect of LIPUS on acceleration of bone-tendon junction healing in rabbits;
3) Effect of LIPUS on distraction osteogenesis in rabbits, and
4) Effect of low magnitude, high-frequency vibration therapy on osteoporotic goats.

Findings obtained from above research are encouraging and some of have already been adopted in clinical applications, including the use of LIPUS for bone-tendon junction repair, fracture repair, treatment of delayed fracture union and non-union. Our clinical application may help relieve financial burden to both our patients and health care system in Hong Kong.

With distinguished research in biophysical intervention program for musculoskeletal tissues, we have also successfully organized a number of workshops and attracted industrial sectors to develop new and novel medical devices, such as an adjustable LIPUS. With efforts of years’ research, we enjoy reputation in this applied research for cost-effective treatment of musculoskeletal injuries.

Homepage with related information
Vertebroplasty Service and Research

G. Antonio  
Department of Diagnostic Radiology and Organ Imaging, The Chinese University of Hong Kong

Background
Acute vertebral body fractures are excruciatingly painful. It is a ubiquitous disorder and will probably become even more common in an aging population with a high prevalence of osteoporosis. Traditionally, these have largely been symptomatically treated with several weeks of bed-rest. The lack of mobility during this rest period results in significant morbidity (muscle atrophy, dependant ulcers, deep venous thrombosis) and mortality.

The Department of Diagnostic Radiology and Organ Imaging, in conjunction with the Department of Orthopaedics and Traumatology of The Chinese University of Hong Kong, has been offering a vertebroplasty service since the end of 2002. Vertebroplasty is a relatively recent development in intervention for pain relief in patients with vertebral body fractures. It involves injecting the fractured vertebral body with bone cement (similar to that used in orthopaedic surgery) under image guidance. The hardened cement will then immobilize the vertebral body fracture fragments and relieve the associated pain.

Method
Patients with an acute onset of back pain and a vertebral body fracture apparent on radiographs are first investigated with an early MRI, looking for an acutely fractured vertebral body that may explain the symptoms. The offending vertebral level is then accessed with a trans-pedicular approach using an 11 gauge needle under fluoroscopic guidance.

Since the procedure is performed: (1) under local anaesthesia; (2) with only a needle puncture wound; (3) produces instant fracture stabilization; the treated patients are usually discharged the following day pain-free.

As part of a research project on the behavior of the rest of the spine after vertebroplasty, these patients attend a follow-up MRI one month after the procedure.

Aside from patients with osteoporotic vertebral fractures, metastatic vertebral body fractures may be treated with the same approach for pain relieve.
Prevention and Treatment of Osteoporosis and Its Related Problems

KS Leung, PC Leung, JCY Cheng, KM Chan, WH Cheung, L Qin
Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong

Osteoporosis and its related problems such as fragility fractures is one of 5 musculoskeletal conditions that Bone Joint Decade (WHO designated for year 2001-2010) is focusing. The financial burden to family and society is high and the costs for its treatment and rehabilitation will reach $1,000 million towards 2010, which accounts for 20% of the total expenditure of the orthopaedic service in Hong Kong.

Osteoporosis and related research is a major interdisciplinary and inter-institutional (locally and internationally) research area within the Department. It involves medical personnel and research scientists. Our research also attracts industrial sectors for joint R&D of pharmaceutics, biomaterials, and related medical devices. Studies within our program include both preclinical experiments and clinical trials.

Preclinical studies include:
1) Systemic approach, such as joint R&D of Chinese herbal formulae;
2) Local approach, e.g. - biophysical intervention (therapeutic ultrasound, shock-ware, and vibrations); - osteoporotic fractural repair using cell and gene therapy (supplementation of mesenchymal stem cells and growth factors mediated by BMP-2 expressed recombinant Adenoviral); - enhancement of osteoporotic fractures using injectable biomaterials and specific fixation devices tested in a large osteoporotic goat model – the first kind of experimental model developed by our Department.

Meanwhile, we also provide research and clinical services for bone densitometry, static and dynamic 2-D and 3D histomorphometry, biochemical bone turnover markers, and biomechanical testing. Since we position our research as an application-oriented one, we apply our findings from laboratory to orthopaedic clinic and community.

Clinical studies and community service: In addition to transformation of our experimental findings obtained from the above preclinical research, we also contribute to:
1) Establishment of diagnosis criteria using the state-of-the-art diagnostic tools and population specific risk factors;
2) Modification of treatment protocols of using Western drugs for Chinese ethnics;
3) Health promotion of suitable exercises for elderly, such as Tai Chi exercise;
4) R&D of hip protectors and launching fall prevention program for our communities. It is emphasized that 90% of age-associated fractures result from fall. Therefore, fall prevention is essential in overall strategy. Our Department leads a comprehensive fall prevention program in Hong Kong (http://www.no-fall.org).
In addition, our research on secondary osteoporosis and bone metabolic diseases, such as bone distraction osteogenesis and adolescent idiopathic scoliosis has also contributed greatly to the related profession. We are also one of the key members of Hong Kong Jockey Club Center for Osteoporosis Care and Control (JOCOC). In the past 10 years, we have attracted a substantial amount of research and service grants, published numerous peer-reviewed publications, and organized a number of training courses. Meantime, we have become one of the world-recognized centers with such comprehensive program for prevention and treatment of osteoporosis. In addition, our staff is frequently invited to serve as journal editors, reviewers, co-organizers and keynote speakers by many international events.

Homepage
Information on our research program, research grants, publications (peer-reviewed journal papers, books and book chapters): http://www.ort.cuhk.edu.hk; www.no-fall.org; www.JOCOC.org
Osteoporosis in Asia –
The Results of a Decade of Multidisciplinary Research in the Faculty of Medicine, The Chinese University of Hong Kong

EMC Lau (on behalf of the Osteoporosis Research Programme and Jockey Club Center for Osteoporosis Care and Control)
School of Public Health, The Chinese University of Hong Kong

Research by the Osteoporosis Research Programme and Jockey Club Center for Osteoporosis Care and Control embraces epidemiology, genetics, clinical trials and biomechanics. This presentation will focus mainly on the results epidemiological studies.

In the Hong Kong vertebral osteoporosis study, 1,000 men and women were surveyed. Vertebral fracture was found to be a major health problem in Hong Kong, for as many as 30% of elderly women and 16% of elderly men suffered one or more vertebral fractures. The Asian Osteoporosis Study was the first large-scale multi-centered study conducted in Asia. It was found that the incidence of hip fracture in Hong Kong and Singapore was similar to those in US Caucasian white population, while the rates in Malaysia and Singapore were only 50% of these observed in American Caucasians. The major risk factors for both hip and vertebral fracture in Asians are a low dietary calcium intake and lack of physical activity. The Mr. Os Study is the only cohort study that has ever been conducted in Asian men. Two thousand men were studied, and the main risk factors for osteoporosis in men are being underweight, cigarette smoking, and low muscle strength. Diabetes mellitus predisposed to high bone mass in men. The results of these large-scale epidemiological studies are important in developing strategies for the prevention of osteoporosis in Asian.
Developing a Model to Predict Youth Risk Behaviours: Intentional Injury as an Example

Albert Lee
Department of Community and Family Medicine, and Centre for Health Education and Health Promotion, The Chinese University of Hong Kong

Background
The major causes of adolescent mortality and morbidity are not diseases, but preventable health risk behaviors such as intentional injuries, suicidal ideation or attempt. Recent researchers have shown that other health risk behaviours apart from depression and hopelessness also place the adolescents at risk of suicidal ideation and behaviour. It is therefore important to identify associating factors for prevention.

Study Design
A Youth Risk Behaviour Survey (YRBS) was conducted amongst a total of 7,192 Hong Kong students from 16 primary schools and 18 secondary schools from the school network of the Centre which composes schools of different academic levels in different geographical areas throughout the territory.

Measuring Instrument
Self administered questionnaire was utilized which was partly adapted from CDC-YRBS, Wessex Healthy Schools Award Scheme Students Evaluation Questionnaire. The questionnaire covered socio-demographic data, oral health, personal safety, food/nutrition, body weight, physical activity, violence-related behaviours, mental health, smoking, alcohol drinking, drugs and sexual behaviours. In the area of mental health, it also included the Depression Self-Rating Scale (DSRS).

Data Analysis
The data were tabulated and analyzed by the SPSS package. Multiple regression was used to identify which health risk behaviours and/or socio-demographic characteristics were independent associating factors with suicidal ideation and behaviour. Then an equation was formulated so one would calculate the probability of attempting suicide with presence of different risk factors.

Results
Amongst the health risk behaviours, smoking, alcohol, drug abuse, early sexual practice, and involvement in fighting had higher odds ratios having suicidal ideation and suicidal behaviours. The final multiple regression model shows that female, smoking, alcohol, drug abuse, early sexual practice, fighting, and depressive symptoms were all statistically significantly associated with suicidal ideation. The presence of suicidal ideation without other risk behaviours and depressive symptoms did not give a high probability of attempt suicide.
Conclusion
The implications of these findings suggest the need for a more supportive and positive environment especially at schools with the strong psychosocial correlation with health compromising behaviours. A key element in making a school a positive learning environment appears to be a personal environment that explicitly supports a students’ physical, emotional and social well-being in addition to their academic achievement. The concept of ‘Health Promoting Schools’ emphasizing holistic and school based approach would be beneficial for personal development of the students. The result would also help the family physicians as well as teachers, parents and also students to identify those adolescents at risk.
Psychiatric Morbidity in First Time Stroke Patients in Hong Kong: A Pilot Study in a Rehabilitation Unit

WK Tang¹, GS Ungvari¹, HF Chiu¹, KH Sze², J Woo², R Kay²
¹Department of Psychiatry and ²Department of Medicine and Therapeutics, The Chinese University of Hong Kong

Objective
To examine the prevalence and risk factors of post-stroke psychiatric morbidity in Chinese first-episode stroke patients, covering depressive and anxiety disorders, mania, and psychosis.

Method
157 subjects with first-episode stroke consecutively admitted to a rehabilitation unit participated in this prospective, cross-sectional study. Psychiatric diagnoses were made using the SCID-DSM-III-R.

Results
The prevalence of all depressive disorders was 17.2%. Major depressive episodes, adjustment disorder with depressed mood, dysthymia and generalized anxiety disorder were diagnosed in 7.6%, 8.2%, 1.3% and 0.6% of the subjects, respectively. No cases of mania, psychosis or other types of anxiety disorders were found. Only the Barthel Index score on admission predicted the development of depression while age, sex, family and past psychiatric history, and laterality of lesion were not significant predictors.

Conclusion
The finding of a surprisingly low morbidity of affective disorders in Chinese first-episode stroke patients requires further investigation.

Reference
A Psychiatric Epidemiological Study of Postpartum Chinese Women

Dominic TS Lee
Department of Psychiatry, The Chinese University of Hong Kong

Objective
Epidemiological studies in the 1980s suggest that depression is rare in the Chinese general population, and there is no postpartum depression (PPD) among Chinese women. However, subsequent small-scale studies of PPD in China yield contradictory and inconsistent findings. Furthermore, after two decades of profound socio-economic transformation, depression may no longer be rare in contemporary Chinese population. To clarify these issues, we conducted a psychiatric epidemiological study among contemporary postpartum Chinese women, using rigorous methodology and representative sample.

Method
Nine hundred and fifty-nine consecutive women were recruited at the antenatal booking clinic of a university-affiliated public hospital in Hong Kong. At 3-month postpartum, the prevalence and incidence rates were measured using a two-phase design. The participants were first stratified using the 12-item General Health Questionnaire. Subsequently, all high scorers and 10% of low scorers were assessed using the non-patient version of the Structured Clinical Interview for DSM-III-R. The 1-month and 3-month prevalence and incidence rates were estimated using reverse weighting.

Results
The 1-month prevalence rates for major and minor depression were 5.5% and 4.7% respectively. At three months, the corresponding prevalence rates were 6.1% and 5.1%. All together, 13.5% of the participants suffered from one or more forms of psychiatric disorders in the first three months of postpartum. Most of the PPD were incident cases.

Conclusions
PPD is common among contemporary Hong Kong Chinese women and a universal PPD screening program would be useful for early detection and treatment. Our data suggest that depression may no longer be a rare disorder in the Chinese.
Phytoestrogens Intake and Women’s Health: Recent Studies

Suzanne C Ho
School of Public Health, The Chinese University of Hong Kong

The phytoestrogenic compounds are isoflavones and lignans. The lignan type is found in almost all cereals and vegetables, with the highest concentration in the oilseeds, especially linseed. The isoflavone type is most commonly found in legumes and herbs, with concentrations particularly high in soybeans.

Epidemiological, animal and in vitro studies suggest that consumption of high levels of dietary soy protein or isoflavonoid phytoestrogens confers a lower risk for a number of symptoms/diseases, including hot flushes, breast cancer, hyperlipidemia and osteoporosis. The protective effect may partly be due to the weak estrogenic and anti-estrogenic effects of phytoestrogens. Soy protein or isoflavonoid phytoestrogens may also have other important non-hormonal properties contributing to the observed health effects.

The traditional diets of the Asian populations contain relatively high levels of phytoestrogens. Comparison of the urinary isoflavone levels in Asian and Western populations have revealed more than 100 fold differences. While many of the recent studies on soy-health relationship have been conducted in the West, published findings on the Asian populations are limited. Recent population-based cross-sectional study in Hong Kong found an inverse association between soy protein/isoflavones intake and cholesterol, and low-density lipoprotein. A 3-year longitudinal study has observed the beneficial effect of soy in the maintenance of bone mass in young Chinese women. Clinical trials have revealed the positive effect of soy isoflavones on bone mineral content, as well as the potential benefit of isoflavones on cognitive functions in early postmenopausal women.

The effects of soy isoflavones on calcium metabolism are presently being evaluated in both the early as well as later postmenopausal women.
Sexual Health Promotion amongst Hong Kong Adolescents:  
An Evaluation of Nurse-led Intervention

Sheila Twinn¹, Albert Lee², Eleanor Holroyd¹, Frances Cheng², Ann Shiu¹  
¹The Nethersole School of Nursing, ²Department of Community and Family Medicine, The Chinese University of Hong Kong

Despite limited available data on the incidence of teenage pregnancies amongst Hong Kong adolescents, evidence indicates increasing sexual activity amongst this age group as well as an increasing rate of termination of pregnancies. A consistent finding from local surveys undertaken with adolescents over more than a decade demonstrates their lack of knowledge of sexual health and healthy sexual behaviour, in particular negotiating personal relationships. International evidence indicates that the implementation of appropriately planned sexual health promotion projects delays the initiation and frequency of sexual activity, and reduces teenage pregnancy rates, thereby reducing the potential adverse social and personal costs of teenage pregnancy. The importance of a multidisciplinary approach has also been identified.

The aim of this two-year study was therefore to evaluate the effectiveness of a nurse-led health promotion project to increase knowledge about sexual health and reduce sexual risk-taking amongst Hong Kong adolescents. Two schools of similar educational banding, socio-economic characteristics and educational organization were selected for the intervention and a third similar school was selected as the control. Form 2 students were the target population. The intervention consisted of a needs assessment, and a sexual health promotion, including one-to-one counselling undertaken by a school-based nurse. A total of 613 students completed the needs assessment of which 201 and 210 were in the intervention schools and 202 in the control school. A different model of sexual health activities was implemented in each of intervention schools to assess any difference in outcomes.

The needs assessment demonstrated that making friends and self-understanding during adolescence were the two most frequently rated needs in each of the three schools. Dating was also identified amongst the top four needs in each school. The intervention for each school was designed to meet the identified needs of adolescents. The measurement of outcomes in terms of sexual knowledge and behaviour change is currently being completed. However a significant unintentional outcome of the study has been the value associated with a school-based nurse to the health of the school community.
Prevalence, Incidence and Risk Factors of Myopia in Primary School Children in Hong Kong

Dorothy SP Fan, Dennis SC Lam
Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong

Among the many types of myopia, school or “juvenile” or “physiologic” myopia, is the commonest. There has been a trend of an upsurge of this condition in many countries. It is possible that genetic and environmental factors are related to the development of school myopia. It has been shown that myopic parents tend to read more and that children in such upbringing may be influenced into performing a greater degree of near work than other children. We thus conducted a pilot study in two randomly chosen kindergartens to evaluate refractive error, ocular biometry and whether parental history of myopia is a predictor of eye size shape in Chinese preschool children. A total of 526 children were recruited and examined. This was the first study in the world in preschool children in which ocular dimension data were available. The results indicated that before the onset of myopia, eyes of children with one myopic parent had longer eyes compared to children with two myopic parents or no myopia parents. Parental history of myopia was thus not a predictor of refraction or eyeball size in preschool children. Few large-scale epidemiological studies evaluate the hypotheses that destined myopic eyes are initially normal in size but have faster growth rate. We undertake a large-scale epidemiology study on several thousand primary school children to evaluate these hypotheses. Our objectives include (1) to determine the prevalence and incidence of myopia in Hong Kong school children, (2) to correlate the above data with possible risk factors — including parental history of myopia, the amount of visual activities and presence of astigmatism, (3) to investigate whether destined myopic eyes are normal-sized to start with but have faster growth rate, and (4) to derive possible contributing factors to the development of myopia and progression, and to implicate possible effective preventive strategies.
An Epidemiological Study of Obstructive Sleep Apnoea Syndrome in Hong Kong Children

A. Li
Department of Paediatrics, The Chinese University of Hong Kong

Childhood obstructive sleep apnoea syndrome (OSAS) is a common and serious condition. If unrecognised and untreated, OSAS can result in significant morbidity and possibly mortality. Early reports documented such complications as failure to thrive, systemic hypertension, pulmonary hypertension with or without cor pulmonale and neurocognitive deficits, including poor learning, behavioural problems and attention deficit hyperactivity disorder. A link to the sudden infant death syndrome has also been proposed. Much controversy exists about the exact prevalence rate of OSAS in the paediatric population. Three studies (from Britain, Iceland and the United States) have shown similar prevalence rates of around 1-3% but these studies either used sub-optimal sampling methods, did not use conventional polysomnography (PSG) or used adult rather than paediatric polysomnographic criteria. Moreover, recent studies reported that ethnicity, especially African-Americans in United States and Indian descendents in the United Kingdom, was a risk factor for childhood OSAS and general sleep problems respectively. Thus, there is a timely need for a definitive epidemiological study across a different ethnic group. By using a two-phase sampling design with a validated screening questionnaire and followed by a second phase of confirmation with polysomnographic and clinical assessments, we aim to determine for the first time the prevalence rate and the risk factors of OSAS in Hong Kong Chinese children. Not only will the information to be obtained allow further cross-ethnic comparison, the study will also lay the foundation for establishing an epidemiological approach to paediatric sleep disorders in general. Theoretically, the finding should help to understand the aetiology and ethnic predisposition to childhood OSAS. At a practical level, the finding will help to determine the size of the problem and should assist in better health care planning so as to enable early detection and treatment of the childhood OSAS patients and to foster the development and planning of paediatric Sleep Medicine in Hong Kong.
Research on Air Pollution and Health in Hong Kong

Wong TW, Yu TS, Tam WS, Wun YT, Ho KP, Liu HJ, Gao Y
Department of Community and Family Medicine, The Chinese University of Hong Kong

Background
The association between air pollution and health outcomes has been intensively studied worldwide in the past decades. Short-term effects on health have been studied in the U.S., Europe, and some Australian and Asian cities (including Hong Kong) using a time series approach. Long-term effects of air pollution have been inferred from cross-sectional, comparative studies of the prevalence of respiratory diseases and lung functions between populations with contrasting differences in air pollution levels (including Hong Kong studies), and cohort studies in the United States.

Studies by this Research Team:
1. A comparative study of air pollution and health in two communities in Tsuen Wan
   In 1994, a cross-sectional study was conducted among pre-school children, adult females, and persons aged >65, that compared the prevalence of respiratory symptoms and diseases in two communities with different concentrations of air pollutants. The effects of ambient air pollutants and indoor air pollutants were sought. Respiratory diseases and symptoms were more prevalent in the more polluted community. Gas cooking and passive smoking were significant risk factors for respiratory ill-health.

2. A three-district comparative study on air pollution and respiratory health
   In 1995, a cross-sectional study was done among primary school children in 3 districts with contrasting air pollution profiles: Mong Kok, Kwun Tong and Shatin, to ascertain their prevalence of respiratory illnesses, lung function and cardiopulmonary fitness. Air pollution was associated with a higher prevalence of respiratory illnesses, poorer lung function and a lower predicted maximal oxygen uptake.

3. Air pollution and short-term effects on respiratory diseases
   (i) Air pollution and hospital admissions in Hong Kong (1997)
   (ii) Air pollution and daily mortalities in Hong Kong (1999)

   Three time series studies were conducted since 1997, on the relation between short-term variations in air pollution and hospital admissions, mortalities and GP consultations. All showed a significant, positive association between air pollutants (PM_{10} and the oxidant air pollutants – NO_{2} and O_{3}) and these health outcomes. These studies, with those in Korea, Beijing and Taipei, are the only Asian studies on the short-term health effects of air pollution. The GP study is one of two studies done so far on air pollution and respiratory diseases in primary care.

   The health impact of more than 100 toxic air pollutants (TAPs) monitored in Hong Kong on the health of the general population in Hong Kong were assessed using international environmental health standards. Diesel fumes accounted for about 80% of excess cancer risk among all TAPs. Other TAPs with significant health impact are: 1,3-butadiene, hexa-valent chromium, arsenic, cadmium, formaldehyde, benzene and carbon tetrachloride.
Ultrasound and MR Assessment of Obese Chinese Children

Winnie CW Chu¹, Albert M Li², Eric KH Liu¹, Dorothy FY Chan², YL Chan¹, Winnie WM Lam¹, EAS Nelson², Rita Sung², Constantine Metreweli¹
¹Department of Diagnostic Radiology and Organ Imaging and ²Department of Paediatrics, The Chinese University of Hong Kong

Background
Increasing rates of childhood obesity in Hong Kong, as elsewhere, are causing considerable concern. Unpublished data from School Health Service of the Department of Health shows that the rate of obesity in all children assessed increased from 12% to 14.1% between 1995 and April 2000. Risks of obesity in children include obstructive sleep apnoea syndrome and steatohepatitis. The latter can cause chronic liver dysfunction fibrosis and even cirrhosis. Visceral adipose tissue has been shown to be highly correlated with cardiovascular risk factors.

Objectives
1. To validate different obesity assessment measures (BMI, weight-for-height, percentage body fat) with MRI, DEXA and ultrasound and describe differential visceral and peripheral fat distribution in obese children.
2. To identify additional complications or predictors of obesity severity such as steatohepatitis and obstructive sleep apnoea syndrome.
3. To compare pre- and post-/treatment fatty liver scores and relate these to total body fat reduction in those subjects who have achieved successful weight reduction.

Materials and Method
Children with obesity attending the Paediatric Obesity and Lipid Clinic at the Prince of Wales Hospital were invited to participate in this study. These children were significantly overweight according to local and international standards. Enrolled children underwent a detailed assessment to identify the degree and pattern of obesity (visceral versus peripheral) and potential complications of obesity (abnormal blood lipids, obstructive sleep apnoea syndrome, steatohepatitis).

In the ultrasound examination of the abdomen, scoring was given to grade the presence of fatty liver (steatohepatitis). Measurement of different intra-abdominal fat layers (subcutaneous fat, preperitoneal fat and mesenteric fat) was performed.

For MR assessment, the volume of peripheral and visceral fat in the abdomen was measured. Furthermore, the level of single transverse scan of intra-abdominal fat with identifiable landmarks that best predicts intra-abdominal fat volumes was identified. The fat content of the liver was objectively assessed by the in-out phase techniques. In the region of the pharynx, the volume of fat deposits surrounding the oro- and laryngopharyngeal space was measured to look for correlation with the obstructive sleep apnoea syndrome.

All the imaging findings were correlated with clinical parameters and biochemical tests.
Antimicrobial Resistance in the Community

Julia M Ling
Department of Microbiology, The Chinese University of Hong Kong

Antibiotics are frequently prescribed before sensitivity results are available. Thus, doctors need recent local susceptibility data to guide their antibiotic choice. This is especially true for community doctors, as specimens are often not sent for culture. This study proposed to reduce the level of antibiotic resistance in the community by i) providing a laboratory service to community doctors; ii) producing a cumulative report on the antimicrobial susceptibilities of community-acquired bacterial pathogens to serve as a guide to community doctors in antibiotic prescription. Specimens from infected patients visiting general practitioners practicing in the whole of Hong Kong were cultured for bacterial pathogens and their antimicrobial susceptibilities determined. More than 4,700 specimens were collected from patients consulting 89 doctors, with 1.24 specimens from each patient. The most common specimens were throat swab, urine and sputum with an average culture-positive rate of 28%. More than 1,300 organisms were isolated, with *Escherichia coli* being the most common, followed by β-haemolytic streptococci and *Staphylococcus aureus*. Fluoroquinolone resistance was relatively high in organisms commonly causing urinary tract infection while more than 80% of pneumococci were resistant to 0.1 mg/l - 1 mg/l of penicillin. High prevalence of macrolide resistance in *Haemophilus influenzae* was noted. All *Neisseria gonorrhoeae* isolates were resistant to penicillin, more than 70% to the fluoroquinolones, but all were susceptible to ceftriaxone. Respiratory pathogens were relatively susceptible to the newer fluoroquinolones or third generation cephalosporins. The problem of antibiotic resistance in the community was therefore serious.

*Reference*
Application of a Multiplex-PCR-Amplimers Conformation Analysis Technique (MPAC) for Rapid Detection of Gyrase A Mutations among Fluoroquinolone-resistant *Mycobacterium Tuberculosis* Clinical Isolates

Augustine F. B. Cheng¹, Wing W. Yew², Edward W. C. Chan¹, Miu L. Chin¹, Mamie M. M. Hui¹ and Raphael C. Y. Chan¹

¹Department of Microbiology, The Chinese University of Hong Kong; ²Tuberculosis and Chest Unit, Grantham Hospital

A new strategy known as multiplex-PCR-amplimers conformation analysis (MPAC) was developed for detection of mutation in the *gyrA* gene of 138 clinical isolates of *Mycobacterium tuberculosis*. The method generated a single-stranded and heteroduplex DNA banding pattern of multiplex-PCR amplimers of the region of interest that was extremely sensitive to specific mutations, thus enabling much more sensitive and reliable mutation analysis when compared to the standard single-stranded conformation polymorphism (SSCP) technique. The genetic profiles of the *gyrA* gene of the 138 isolates as detected by MPAC were confirmed by nucleotide sequencing, and were found to correlate strongly with the *in vitro* susceptibilities of the mutant strains to six fluoroquinolones (ofloxacin, levofloxacin,sparfloxacin, moxifloxacin, gatifloxacin and sitafloxacin). All the 32 isolates that contained *gyrA* mutations exhibited cross-resistance to the six fluoroquinolones (ofloxacin MIC<sub>90</sub> > 16mg/l), although moxifloxacin, gatifloxacin and sitafloxacin (MIC<sub>90</sub> ≤ 4mg/l) were apparently more active than ofloxacin, levofloxacin and sparfloxacin (MIC<sub>90</sub> ≥ 16mg/l). All *gyrA* mutations were clustered in codons 90, 91 and 94, and aspartic acid 94 was most frequently mutated. Twenty-three isolates without *gyrA* mutations were also found to exhibit reduced susceptibility to ofloxacin (MIC<sub>90</sub> = 4mg/l), but largely remained susceptible to other drugs (MIC<sub>90</sub> ≤ 1mg/l). Another 83 isolates without mutations were fully susceptible to all the six fluoroquinolones (ofloxacin MIC<sub>90</sub> = 1mg/l). In conclusion, high-level phenotypic resistance to fluoroquinolones among *M. tuberculosis* clinical isolates, which appears to be predominantly due to *gyrA* mutations, may be readily detected by genotyping techniques such as MPAC.