

## RESEARCH PROJECTS

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### A Randomized Controlled Trial of Auditory Evoked Potential Monitoring to Improve Recovery from General Anaesthesia

✉ CHAN Matthew Tak Vai • GIN Tony • IRWIN Micheal Garnet\*

☐ 1 October 2002

❖ Research Grants Council (Earmarked Grants)

Clinical assessment for "depth of anesthesia" is currently imprecise. Therefore, patients may be inadequately anesthetized or relatively overdosed despite the absence of clinical signs. This may contribute to the minor problems, like delayed emergence and postoperative vomiting, or it may result in dreadful complications due to unintentional intraoperative awareness. A reliable measure of anesthetic effect should optimize the use of anesthetic drugs. Recent studies have shown that auditory evoked potential (AEP) correlates with the level of consciousness and thus, may be used to indicate anesthetic depth. We hypothesize that anesthesia guided by AEP monitoring will facilitate recovery, decrease perioperative complications and may allow cost saving.

In this proposed randomized, double-blind, multicenter trial, 1,060 patients receiving either propofol or sevoflurane anesthesia will be randomly allocated to additional AEP monitoring or routine care. Intraoperative anesthetic usage, rate and quality of recovery and the total episode cost (from admission to hospital discharge) will be compared among groups.

Results from this trial will provide definitive evidence as to whether routine AEP monitoring is

justified for better quality of recovery from general anesthesia.

(CU02054)

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### PeriOperative Ischemic Evaluation Study

✉ CHAN Matthew Tak Vai • YIP Wai Kwok Gabriel\*

☐ 28 April 2003

❖ McMaster University (Canadian Institute for Health Research)

Heart disease is associated with significant problems after non-cardiac surgery. There exists strong biologic rationale for the use of  $\beta$  blocker to decrease the incidence of adverse cardiac events. Previous studies suggested that  $\beta$  blocker is promising but the apparent beneficial trends are untrustworthy because of the potential for publication biases, wide confidence intervals, and the fact that the majority of the data are derived from a single study.

This is a randomized controlled trial of metoprolol *versus* placebo in 10,000 moderate and high risk patients undergoing non-cardiac surgery. Participants, health care providers, data collectors, and judicial assessors of outcomes will be blind to whether patients receive metoprolol or placebo.

Patients will randomly allocated to receive metoprolol or placebo immediately before and continued for 30 days after surgery.

Indicators for possible adverse cardiac events (plasma troponin concentrations and ECG) will be measured for the first three postoperative days. Patients' outcome (death and cardiac morbidities) will be determined at 30 days and one year after surgery.

(MD02634)

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### Safety of Traditional Chinese Medicine in Patients Undergoing Anaesthesia

✉ GIN Tony • AUN Sui Tee Cindy • CHUI Po Tong • LEE Anna

□ 1 November 2002

❖ Research Grants Council (Earmarked Grants)

The use of Traditional Chinese Medicine (TCM) by patients before anaesthesia and surgery may be associated with morbidity and mortality. As there is no central mechanism for reporting adverse effects associated with TCM and no randomised controlled trials on the safety of TCM in patients undergoing surgery, much of the limited evidence is from case-reports, animal studies and predictions derived from known pharmacological results. The objectives of this project are: (1) to determine the proportion of patients taking common TCM before anaesthesia and surgery; (2) to examine the association between TCM and abnormal biochemical tests and intraoperative haemodynamic instability; (3) to assess whether TCM-related adverse effects are associated with changes in the anaesthetic management of these patients in the perioperative period. A random selection of 1525 elective surgical patients will be recruited into this study. Data collected will include: patient's demographics, use of any TCM before anaesthesia, preoperative tests (coagulation, electrolytes and random glucose level), intraoperative haemodynamic instability, changes in anaesthetic management in perioperative period (postponed operation, order extra tests, specific treatments to manage TCM side-effects), admission to intensive care unit and survival to hospital discharge. The results will be used to decide whether the routine preoperative history should include TCM use and whether special precautions are needed in the anaesthetic management of patients taking TCM before anaesthesia. (CU02056)

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### **Thoracic Paravertebral Block for Patients with Refractory Angina Pectoris**

✉ HO Ming Hei Anthony • KARMAKAR Manoj Kumar • WOO Kam Sang (Dept of Medicine & Therapeutics) • LAM Wai Man Wynn (Dept of Diagnostic Radiology & Organ Imaging) • ARIFI Ahmed A (Dept of Surgery)\* • LEE Anna • GIN Tony

□ 1 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

Angina pectoris ails millions of people around the world. Despite advances in therapy, some patients have angina that is refractory to aggressive medical therapy and yet are non-surgical candidates. Even if surgery is an option, it is sometimes not immediately available. In this study, we explore the use of unilateral thoracic paravertebral block (TPB) for these patients.

Unilateral TPB was used 50 years ago for angina sufferers but have been supplanted by medical and surgical therapies in recent decades. Thoracic epidural and stellate ganglion blocks have also been shown to relieve angina, improve exercise tolerance and myocardial performance. All these blocks reduce the sympathetic outflow to the heart and effect benefits well beyond what one would normally expect from the amount of local anaesthetics injected. TPB has the unique combined advantage of being not contraindicated by anticoagulation and being more amenable to infusion therapy via an indwelling catheter. Recently, we have demonstrated the dramatic reversal of ischemic ECG changes immediately after a right-sided TPB (Ho AMH et al. *Anesth Analg* 2002; 95:277-8). We also have

possibly the world's most extensive experience on TPB.

This ethics-approved study will consist of inserting a catheter into the left thoracic paravertebral space of a consenting patient with refractory angina who is waiting for surgery or who is not surgical candidate. Baseline angina pain score, ECG, and MRI scan of the heart are performed. The patient is then randomly assigned to receive saline or ropivacaine via the catheter, followed by a repeat of those measurements. Each patient in the saline group then receives a ropivacaine injection via the catheter and the same measurements will again be repeated. The person reviewing the ECGs and the MRI scans will be blinded to the types of paravertebral injections. In short, we have a double-blind randomized controlled trial, followed by a before-after trial so as not to deprive the patients in the saline group of the potential benefits of a TPB. We calculate that we will need 10 patients in each group to nullify the null hypothesis that a unilateral TPB does not result in any subjective or objective improvement in patients with refractory angina.

(MD02938)

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### **The Effects of Maternal Oxygen Therapy during Emergency Caesarean Section**

✉ KHAW Kim Sun • NGAN KEE Warwick Dean  
 • ROGERS Michael Scott (Dept of Obstetrics & Gynaecology) • TAM Wing Hung (Dept of Obstetrics & Gynaecology) • WANG Chi Chiu (Dept of Obstetrics & Gynaecology)

☐ 1 December 2002

❖ Research Grants Council (Earmarked Grants)

Prolonged or severe intrapartum fetal hypoxia results in harmful effects such as impaired myocardial function, periventricular haemorrhage and permanent

brain damage. Once fetal distress is confirmed, urgent delivery by emergency caesarean section may be required.

Maternal oxygen therapy has been used in attempts to lessen fetal hypoxia by increasing the oxygen supply to the fetus. However, there are no published data to support such practice, and as stated in The Cochrane review, '*no trials addressing maternal oxygen therapy for fetal distress could be located*'.<sup>1</sup>

Maternal oxygen therapy has also been recommended during cesarean section under regional anaesthesia<sup>2</sup> because of a deterioration in respiratory function.<sup>3</sup> Recently, we have demonstrated that breathing 60% oxygen during *elective* cesarean section, improved fetal oxygenation but also increased lipid peroxidation in the mother and fetus.<sup>4</sup> Thus maternal oxygen therapy confers benefit but also potential harm. Therefore, whether it should continue to be given while under regional anaesthesia needs scientific evaluation.

We aim to test the hypothesis in this prospective randomised double-blinded control study, that fetal oxygenation during emergency cesarean section performed for non fetal distress indications under regional anaesthesia, will be improved by maternal oxygen therapy. Secondary objectives will be a comparison of the degrees lipid peroxidation in the mother and fetus, and the fetal outcome. The conclusion will define the role of maternal oxygen therapy during emergency cesarean section, and provide guidelines that are not available in current literature.

(CU02060)

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### **A Comparative Traditional Dose-response Study of Ropivacaine and Bupivacaine for Epidural Analgesia in the First Stage of Labour**

✉ NGAN KEE Warwick Dean • KHAW Kim Sun  
• LEE Bee Beng\*

☐ 1 January 2003

❖ CUHK Research Committee Funding (Direct Grants)

Bupivacaine and ropivacaine are the local anaesthetics most commonly used for epidural analgesia in labour, but their dose-response curves have been incompletely defined. This is particularly important for comparative purposes because recent data have suggested that many of the advantages of epidural ropivacaine in obstetrics (greater differential sensory block, lesser toxicity) could be explained by lower potency compared with bupivacaine. Much of this evidence has come from simple comparisons or from the technique of up-down sequential analysis. The latter technique has been used to determine the median effective dose (ED<sub>50</sub>). However, other than a point estimate of ED<sub>50</sub>, these data do not provide information on the shape and slope of the dose-response curves, nor on the values for ED<sub>95</sub> which are closer to the doses used clinically.

In this prospective, randomized study, we will use traditional dose-response methodology to simultaneously determine the dose-response curves for ropivacaine and bupivacaine for epidural analgesia in labour. The methodology used will follow a model we have previously developed and used. Results will yield individual data for each drug as well as a clear measurement of relative potency. Clinically, this information may be used to facilitate both dosage and drug selection and for future research the data will provide important reference information for design of future studies.

(MD02786)

**Please refer to previous issues of this publication for more details of the following ongoing research at the department:**

<u>Edition</u>	<u>Title/Investigators</u>
2001-02	Postoperative Cognitive Function in Children (MD01002) ✉ AUN Sui Tee Cindy • MCBRIDE Catherine Alexandra (Dept of Psychology) • YEUNG Chung Kwong (Dept of Surgery) • LAI Yee Ching Kelly (Dept of Psychiatry) • GIN Tony
2001-02	Intravenous Magnesium Sulphate for Neuroprotection During Cerebral Aneurysm Surgery (MD01725) ✉ CHAN Matthew Tak Vai • GIN Tony • BOET Ronald (Dept of Surgery) • POON Wai Sang (Dept of Surgery)
2000-01	Evaluation of Two Traditional Chinese Medicine Formulations for the Treatment of the Metabolic Syndrome Regarding Cardiovascular Function and Insulin Sensitivity (CU00134) ✉ CRITCHLEY Lester Augustus Hall • CHAN Chung Ngor Juliana (Dept of Medicine & Therapeutics) • THOMAS Neil G (School of Pharmacy)# • TOMLINSON Brian (Dept of Medicine & Therapeutics)
2001-02	Evaluation of Ginseng on Indices of Chronic Stress in Patients with the Metabolic Syndrome (MD01618)

- ✎ CRITCHLEY Lester Augustus Hall 2001-02 Educating Patients about Anesthesia: A Systematic Review of Randomized Controlled Trials of Media-based Interventions (MD01937)  
 • THOMAS Neil G (School of Pharmacy)# • CRITCHLEY Julian A J H (Dept of Medicine & Therapeutics)#  
 ✎ LEE Anna • GIN Tony • CHUI Po Tong
- 2001-02 Establishing Patient and Health Professional Preferences for the Management of Postoperative Nausea and Vomiting: An Application of Conjoint Analysis (MD01912)  
 ✎ GIN Tony • LEE Anna
- 2001-02 Does the Enteral Administration of Lactobacillus Species to Critically Ill Patients Reduce the Severity of Multi-organ Dysfunction and Decrease Mortality? (MD01005)  
 ✎ GOMERSALL Charles David • CALCROFT Ross Michael\* • JOYNT Gavin Matthew
- 2001-02 A Randomized, Open Label, Comparative Multicenter Study of Voriconazole versus Conventional Amphotericin B Followed By Fluconazole in the Treatment of Candidemia in Non-neutropenic Subjects (MD01977)  
 ✎ GOMERSALL Charles David • JOYNT Gavin Matthew • RAMSAY Sarah Jane#
- 1998-99 Ropivacaine as an Intrathecal Agent: Part I – A Dose Response Study (MD98153)  
 ✎ KHAW Kim Sun • NGAN KEE Warwick Dean • CRITCHLEY Lester Augustus Hall
- 1999-00 Randomized Double-blind Comparison of Obstetric Outcome After Epidural Labour Analgesia Using Ropivacaine or Bupivacaine (MD99116)  
 ✎ NGAN KEE Warwick Dean • LEE Bee Beng • LAU Tze Kin (Dept of Obstetrics & Gynaecology) • KHAW Kim Sun
- 2000-01 Development of Effective Strategies to Reduce the Incidence of Hypotension During Spinal Anaesthesia for Caesarean Section (MD00860)  
 ✎ NGAN KEE Warwick Dean • KHAW Kim Sun • LAU Tze Kin (Dept of Obstetrics & Gynaecology)
- 2001-02 Vasopressor Therapy During Spinal Anaesthesia for Caesarean Section: Comparison of Administration by Intravenous Bolus or Infusion (MD01447)  
 ✎ NGAN KEE Warwick Dean • LEE Bee Beng • KHAW Kim Sun
- 2001-02 Randomized Controlled Trial of Remifentanyl at Induction of General Anaesthesia for Caesarean Section (MD01465)  
 ✎ NGAN KEE Warwick Dean • MA Kwok Chiu (Dept of Paediatrics) •

LEE Bee Beng\* • KHAW Kim Sun  
• WONG Sum Yee April • GIN  
Tony

Bupivacaine for Epidural Analgesia in  
the First Stage of Labour (MD01631)

✍ NGAN KEE Warwick Dean • LEE  
Bee Beng • KHAW Kim Sun

2001-02 A Comparative Traditional  
Dose-response Study of Ropivacaine and

## RESEARCH PROJECTS

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### Interleukin-10 Gene Polymorphisms in Malignancies Associated with Infectious Agents in Hong Kong

✉ CHAN Wing Yee • WHITNEY Bruce Montfort (Hong Kong Cancer Institute)# • LEI Ieng-Kit Kenny (Dept of Clinical Oncology)\*

☐ 1 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

As in the rest of the world, cancer is a leading cause of death in Hong Kong. Chronic infections with certain types of bacteria or virus have been suggested to contribute to development of some cancers. The Epstein-Barr virus (EBV) and *Helicobacter pylori* (HP) infect many people world-wide, about 90% and 57% respectively. Whilst in the majority of people this does not lead to cancer, some are found to develop cancers of specific types. These two organisms are classified as carcinogenic. Cancers associated with these two organisms including nasopharyngeal carcinoma and natural killer cell lymphomas (associated with EBV), gastric carcinomas and mucosa-associated lymphoid tissue lymphomas (HP associated) are common in Hong Kong. Are there any predisposing factors to account for the difference in susceptibility? It has long been postulated that there is a link between cancer and inflammation. It is known that some people launch a stronger inflammatory reaction to infections than others. In a few cases, this was shown to be due to a genetic variability in the ability to produce a key immune system protein, IL-10. IL-10 has the ability to weaken and stop immune

responses including inflammation. It has been shown that in Westerners that the ability to produce high or low levels of IL-10 is linked to specific changes in the IL-10 gene. These changes have been previously found in some Hong Kong patients with systemic lupus erythematosus, an uncommon autoimmune disease. However, the variability of the gene and its relationship to the amount of IL-10 produced has not been determined in the general population or patients with infectious disease in Hong Kong. We propose to study:

- (1) The frequency of various polymorphisms of the IL-10 gene, including some that have not been examined previously, in the general population in Hong Kong;
- (2) The relationship of these polymorphisms to IL-10 production and compare them with the Western data;
- (3) The frequency of different IL-10 polymorphisms in cancer patients and in non-cancerous individuals with EBV or HP infections.

As EBV and HP infect most of the population, it is not possible to watch over all infected individuals. By identifying polymorphisms associated with predisposition to the cancers, those at risk could be identified and watched closely. Early detection of cancer usually means more chance of cure.

(MD02338)

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### The Investigation of Multiple Mutations in Hepatocellular Carcinoma

✉ LIEW Choong Tsek • LAI Bo San Paul (Dept of Surgery) • LAU Wan Yee Joseph (Dept of Surgery) • LI Hiu Ming

☐ 15 October 2002

❖ Research Grants Council (Earmarked Grants)

Hepatocellular carcinoma (HCC), a common

malignancy worldwide; is the second most common cause of cancer death in Hong Kong and highly associated with chronic hepatitis B infection and cirrhosis of the liver. In 1998, this disease caused 1336 death in a population of 7 million in HK, contributing to about 12.5% of the total cancer death. Only 15 to 20% of the HCC are operable at the time of diagnosis and majority of the inoperable patients are dead within a few months.

The association of genetic change, methylation, chromosomal changes of tumor suppressor gene and oncogene are believed to be important mechanism in tumorigenesis. Multiple genes alterations are also believed to be part of the development of various human tumors.

Recently, hypermethylation of multiple tumor suppressor genes have been reported in lung and colorectal tumors. However, the status of hypermethylation of HCC is unknown.

Our preliminary investigations on 5 cases of HCC with the above mentioned genes indicated that high incidence of hypermethylation were found in p15, DAPK and E-cadherin, RB and GSTP1 genes while lower methylation rates are seen in p73 and hMLH1 as well as MCMT.

Therefore, we propose to investigate on the methylation status of multiple genes in 50 cases of HBV associated HCC and their corresponding non-tumor liver tissues with or without cirrhosis. Four normal human livers will be included. The panel of tumor related genes included will be MCMT, p73, DAP-kinase (DAPK), p15, Rb, GSTP1, E-cadherin and hMLH1.

The ultimate goal is to try to establish a reliable methylation status for HCC and hope that it will further help to improve the accuracy of HCC diagnosis.

(CU02066)

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### Molecular and Functional Characterization of a Novel Tumor Suppressor Gene, *TSLC1*, in Nasopharyngeal Carcinoma

✉ LO Kwok Wai • HUANG POON Wai Sin Dolly (Hong Kong Cancer Institute) • TEO Man Lung Peter (Dept of Clinical Oncology) • TO Ka Fai • TSUI Kwok Wing (Biochemistry)

□ 1 September 2002

❖ Research Grants Council (Earmarked Grants)

Our pilot study have shown that *TSLC1*, a tumor suppressor on 11q23, was frequently altered in the NPC. High incidence of aberrant methylation of the *TSLC1* promoter was found in NPC samples. The *TSLC1* gene expression was absent or reduced in the cell lines with promoter hypermethylation. In this proposal, we aim to characterize the role of *TSLC1* gene in NPC tumorigenesis. We will intensively search for the genetic alternations, including deletion, mutation and hypermethylation of this gene in the normal nasopharyngeal epithelia, nasopharyngeal carcinoma, and metastatic lesions. Expression of *TSLC1* will be examined by northern blotting, real-time RT-PCR and immunohistochemistry. The status of the *TSLC1* gene in these nasopharyneal samples will be correlated with their pathological features and clinical parameters including staging and survival rates. By examining the genetic and epigenetic changes of the *TSLC1* gene in plasma and nasopharyneal brush samples of NPC patients, the application of the aberrant *TSLC1* gene as molecular marker will be evaluated. The tumor suppressor function of the *TSLC1* gene will also be investigated *in vitro* by transfection and re-expression of the wild type and mutated clones in NPC cells. To better understand the biological function, the *TSLC1* regulated genes and associated pathway(s) will be identified by high-density cDNA array analysis on



the *TSLC1* transfected cells. Our proposed molecular and functional studies will help to reveal properties of this new suppressor and to define its role in the molecular pathogenesis of NPC.

(CU02067)

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**High-resolution Array-based Comparative Genomic Hybridization for Diagnosis for Distant Metastases in Nasopharyngeal Carcinoma**

✉ LO Kwok Wai • TO Ka Fai • HUI Bik Yu

□ 15 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

Nasopharyngeal carcinoma is an important health problem in Hong Kong since it has an unusually high incidence among southern Chinese who accounted for over 90% of our population. The annual incidence rate for Hong Kong male is up to 24.4 per 100,000. Although radiotherapy is an effective treatment for NPC patients with early diseases, 30% of NPC patients will develop metastases where treatment is much less effective. Therefore, identification of prognostic and metastasis markers for NPC patients will be of paramount importance. In this proposal, we aim to systematically search for genetic alterations involving in NPC progression by high-throughput array based comparative genomic hybridization analysis. By using the high-density genomic arrays containing about 1000 Bac clones, small chromosomal aberrations (~3 Mb) will also be detected in NPC genome. Copy number gains and losses in the genome of 20 primary tumors and their corresponding metastases tissue will be identified by this high-resolution analysis. Statistical analysis will identify genomic differences between primary tumors and their corresponding metastases. The recurrent genetic changes will be further confirmed

by FISH analysis. The results of this study will contribute to a much better understanding of the molecular events during NPC progression and provide useful prognostic and metastasis markers for this cancer. It will help to target the genes associated with the development of distant metastases in NPC patients.

(MD02640)

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**Molecular Genetics of Mucopolidosis II**

✉ LO Wing Ip Anthony • TANG Leung Sang Nelson (Dept of Chemical Pathology)

□ 30 June 2003

❖ CUHK Research Committee Funding (Direct Grants)

Mucopolidosis II (ML II, OMIM: 252500) is an autosomal recessive inborn error with defect in the enzyme, UDP-N-acetylglucosamine: lysosomal enzyme N-acetylglucosamine-1-phosphotransferase (GlcNAc-phosphotransferase). This enzyme catalyzes the phosphorylation of mannose to mannose 6-phosphate in the glycosylated side chain of newly-synthesized hydrolase and directed the protein to lysosomes. A defect of GlcNAc-phosphotransferase results in intracellular accumulations and exocytosis of the hydrolase. GlcNAc-phosphotransferase has 3 subunits:  $\alpha$ ,  $\beta$  and  $\gamma$ . Mutation of the  $\gamma$ -subunit has been shown to be responsible for a mild variant of ML II. It is generally believed that disruption of the function of the  $\alpha$  or  $\beta$  subunits might be responsible for the classical form of ML II. The molecular cloning and identification of the genes of these two subunits using conventional linkage analysis and somatic cell hybrids, however, prove to be problematic and controversial. We have initiated linkage analysis of two Hong Kong ML II families to identify and map

candidate gene loci. To complement this classical approach, we proposed to identify the  $\alpha$  and  $\beta$  subunits by a two-hybrid approach using the cloned  $\gamma$ -subunit as the bait. Identification of strong interacting proteins with the  $\gamma$ -subunit, supplement by data from linkage map analysis, will allow us to specifically perform mutation analysis for a limited number of candidate genes in affected family and in established ML II cell lines. Furthermore, other interacting proteins will provide clues to delineate this general lysosomal trafficking pathway.

(MD02358)

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**Study of the Multi-step Molecular Pathogenesis of Multiple Myeloma (MM) in Chinese: Identification of Early and Sequential Molecular Targets in MM Transformation and Progression and Mapping of MM-related Tumor Suppressor Loci on Chromosomes 4q and 13q**

✉ NG Heung Ling Margaret • CHAN Chee Wun Joyce (Dept of Medicine & Therapeutics)# • HOU Jian\* • LEI Ieng Kit Kenny (Dept of Clinical Oncology) • LO Kwok Wai • TSANG Kam Sze Kent

□ 31 December 2002

❖ Research Grants Council (Earmarked Grants)

Multiple myeloma (MM) is a clonal plasma cell malignancy with no effective treatment for cure. The disease progression is characterized with different clinical phases: an inactive phase, an active phase, and a fulminant phase. The critical genetic triggers associated with MM transformation and progression remains unidentified. In order to intensively search for genetic alterations in MM tumorigenesis, we aim to investigate the genome of MM and its precursors by two comprehensive approaches, comparative genomic hybridization

(CGH) and allelotyping on chromosome 4q and 13q. Our group has a long-standing committed interest in the study of molecular pathogenesis of MM in Chinese patients, where little genetic data are available. Recently, we have performed a preliminary study by CGH on anti-CD138 selected plasma cells isolated from 9 MM and 3 monoclonal gammopathy of undetermined significance (MGUS, a pre-MM condition) patients. Among other gains and losses, high incidences of -4q (3/3 MGUS, 6/9 MM) and -13q (2/3 MGUS, 6/9 MM) were identified in both MGUS and MM of our series, which suggests that they may be early critical events in MM etiology. To identify early and sequential molecular targets underlying MGUS-MM transition and MM progression, we propose to extend our study by CGH, to focus on the examination of particularly more MGUS and early MM patients recruited from three hematology centers in HKSAR and Shanghai, China. On the other hand, the high frequencies of -4q and -13q may suggest the presence of potential MM-related tumor suppressors on these chromosomal regions, which will be mapped for genetic deletions in the second part of the proposed study. Such a combined analysis will certainly contribute genetic information in MM etiology and biology.

(CU02068)

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**Studies on the Possible Association of ApoE and Receptor Genes with Vascular Dementia in Hong Kong Chinese**

✉ NG Ho Keung • BAUM Lawrence William (Dept of Medicine & Therapeutics) • CHAN Yu Leung (Dept of Diagnostic Radiology & Organ Imaging) • CHIU Fung Kum Helen (Dept of Psychiatry) • PANG Chi Pui Calvin (Dept of Ophthalmology and Visual Sciences) • WONG

Ka Sing Lawrence (Dept of Medicine & Therapeutics)

□ 30 October 2002

❖ Research Grants Council (Earmarked Grants)

Stroke often results in cognitive impairment and decline. Stroke is a common disease in Hong Kong and vascular dementia (VD) is the second commonest cause of dementia after Alzheimer's disease (AD). Although many risk factors have been proposed for VD, the role of genetic factors in the pathogenesis of VD is still poorly understood. The significant overlap in the pathology of VD and AD suggests that these two diseases may share similar aetiology, genetic predisposition and treatment strategies. In AD, the presence of the Apolipoprotein E (ApoE) ε4 allele is a consistent risk factor, both in western and Chinese populations. Polymorphisms of ApoE-related receptor genes, such as LDL-receptor related protein (LRP), VLDL-receptor there are recent studies showing a decreased risk of AD with anti-cholesterol therapy. These findings led to *hypothesize* a possible association of ApoE and its receptor and related genes in the pathogenesis of VD in Chinese, in whom there is a distinct stroke phenotype with predominance of small vessel disease. Some vessel disease is known to be associated with some forms of VD. Indeed, recent studies have suggested that the ApoE ε4 allele is also a risk factor for VD in certain ethnic groups. However, detailed stroke patterns are rarely documented in these studies.

(CU02069)

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**High-resolution Genomic Profiling of Medulloblastomas Using Array-based Comparative Genomic Hybridization Analysis**

✉ NG Ho Keung • HUI Bik Yu • LO Kwok Wai

□ 1 January 2003

❖ CUHK Research Committee Funding (Direct Grants)

Medulloblastomas are highly malignant paediatric tumor of the central nervous system. Pathogenesis of this cancer is still not well understood. Previously reported chromosomal aberrations include gain of 7, loss of 17p together with isochromosome 17q formation, LOH of chromosomes 8p, 10q, 11 and 16q, as well as amplification of N-myc, C-myc and EGFR genes. Genome-wide studies using CGH analysis had detected consistent losses of 8p, 10q, 11q, 16q and 17p, gains of 2p, 7, 8q and 17q, amplification of 17q, 7q, 8q24, 2p21, 5p15.3 and 11q22.3. Aberrant chromosomal regions detected in this approach are relatively large. To obtain a more detail genomic profiling, we propose to conduct a systematic screening of medulloblastomas using high-resolution array based CGH analysis. Microarray chips comprising 1403 BAC clones which span the genome at 2-4 Mb interval will be used. This high-throughput DNA array technology will define novel, and finely mapped minimal chromosomal regions of tumor suppressor loci and amplicons. The information will generate a comprehensive picture of the multiple genetic lesions involved in the tumorigenesis of this cancer and provide important clues for further identification of medulloblastomas-associated tumor suppressor genes and oncogenes.

(MD02423)

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**Identification of the Medulloblastoma-associated Tumor Suppressor Genes on Chromosome 8p22-23.1**

✉ PANG Chung Sean Jesse • NG Ho Keung

□ 1 November 2002

- ❖ CUHK Research Committee Funding (Direct Grants)

Medulloblastoma is the most common malignant brain tumor in children. The pathogenesis of medulloblastoma is largely unknown. To identify critical tumor suppressor loci that are associated with the carcinogenesis of medulloblastoma, we performed comprehensive genome-wide genetic studies to localize chromosomal regions with abnormalities. Recurrent genomic losses were identified on chromosomal arms 8p (67%), 16q (58%) and 17p (58%), indicating loss of these chromosomes plays an important role in the development of medulloblastoma. Finer deletion mapping of chromosomal arm 8p has localized a region of homozygous deletion (RHD) to a small interval of 1.8cM on 8p22-23.1. The RHD also overlaps with the minimal deletion region identified in breast cancer. These results strongly suggest the presence of a tumor suppressor gene (TSG) on 8p22-23.1. This project aims to identify the medulloblastoma-associated TSG on chromosome 8p. In this proposal, we intend to map out all the candidate genes that lie in 1.8cM RHD and screen for the presence of somatic mutations in these genes. The identification of the candidate TSG should facilitate functional characterization of the gene and its associated pathway in relation to tumor development. The outcome of this project will lead to improved understanding of the molecular pathogenesis of medulloblastoma and the potential discovery of novel targets for treatment of this malignant pediatric disease.

(MD02330)

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**Molecular Alterations in Normal Looking Nasopharyngeal Epithelia - Implication in the**

**Molecular Carcinogenesis of Nasopharyngeal Cancer (NPC)**

✉ TO Ka Fai • HUANG POON Wai Sin Dolly (Hong Kong Cancer Institute) • LO Kwok Wai

☐ 1 October 2002

- ❖ Research Grants Council (Earmarked Grants)

Nasopharyngeal cancer (NPC) is prevalence in Southern China, including Hong Kong and is rare in most of the other countries. NPC remains a significant health issue in our population. Our previous works have identified various critical genetic alterations in NPC. However, the sequence of molecular events in the carcinogenesis pathway of NPC remains unclear. Recently, we have reported that one of the frequent molecular alterations in NPC, namely, loss of heterozygosity (LOH) in 3p, can be detected in both nasopharyngeal (NP) precancerous lesions and normal looking nasopharyngeal epithelia in our local population. Interestingly, such genetic abnormality is rarely observed in normal NP epithelia from the populations with low risk of this cancer, e.g. northern Chinese and Caucasian individuals in western countries. Thus, our pilot study provides strong evidences for the prevalence of the clonal genetically abnormal cells in the NP epithelia in our population. It is suspected that some of such abnormal cell clones may develop into cancer while additional genetic damages accumulated and/or Epstein Barr virus (EBV) infection occurred. In the present study, we propose to perform detailed molecular analysis of the normal looking NP epithelia from both non-cancer and NPC subjects. By comparing the findings with NPC and NP precancerous lesions, we can have a better picture of the carcinogenesis pathway in NPC. Such findings not only enhance our understanding of molecular events that lead to cancer, but may also identify

potential markers of early detection, prevention or intervention for our local population.  
(CU02071)

**Please refer to previous issues of this publication for more details of the following ongoing research at the department:**

<u>Edition</u>	<u>Title/Investigators</u>
2000-01	Evaluation and Characterization of a New Composite Biocompatible Skin Graft Incorporated on the Noedermis of Integra in Experimental Burn Wounds (CU00153) ✍ LIEW Choong Tsek • CHAN Sun Yin Eric (Dept of Surgery)# • LAM Ping Kuen (Dept of Surgery)# • LI Hiu Ming
2001-02	The Correlation of Matrix Metalloproteinase and Recurrent Nasopharyngeal Carcinoma (MD01652) ✍ LIEW Choong Tsek • LAM PK* • TEO Peter*
2000-01	Comprehensive Study of Nasopharyngeal Carcinoma Genome (CU00154) ✍ LO Kwok Wai • HUANG POON Wai Sin Dolly (Hong Kong Cancer Institute) • PANG Chung Sean Jesse • TEO Man Lung Peter (Dept of Clinical Oncology) • TO Ka Fai

2001-02 Characterization of the RASSF1A Gene in Nasopharyngeal Carcinoma (MD01010)  
✍ LO Kwok Wai • HUANG POON Wai Sin Dolly (Hong Kong Cancer Institute) • TO Ka Fai • TSUI Kwok Wing (Biochemistry)

1999-00 Genomic Study of Selected Groups of CNS Tumours: A Combined Approach with Allelotyping, Molecular Cytogenetic and Microdissection Studies (CU99277)  
✍ NG Ho Keung • PANG Chung Sean Jesse • LO Kwok Wai • HUANG POON Wai Sin Dolly (Hong Kong Cancer Institute) • POON Wai Sang (Dept of Surgery)

2001-02 Genetic Characterization of Medulloblastomas (MD01906)  
✍ NG Ho Keung • POON Wai Sang (Dept of Surgery) • PANG Chung Sean Jesse

2000-01 Genetic Mechanism of Malignant Progression in Low-grade Astrocytomas (MD00421)  
✍ PANG Chung Sean Jesse • NG Ho Keung

## RESEARCH PROJECTS

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### **Gene Expression Analysis of an Orphan Nuclear Receptor, Estrogen Receptor-related Receptor (ERR), and Its Isoforms in Human Prostate Cancer**

✉ CHAN Leung Franky • CHEN Shiuan\*

□ 1 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

The estrogen receptor-related receptors (ERRs) belong to the orphan nuclear receptor subfamily and contain 3 closely related isotypes: ERR $\alpha$ , ERR $\beta$  and ERR $\gamma$ . ERRs are closely related to the estrogen receptors (ERs) in their protein structures and thus have their names. However, they do not bind to estrogens or any other known physiological ligands, and thus they are called “orphan nuclear receptors”. Similar to ERs, they can bind to the consensus estrogen responsive element and thus they can regulate the transcription of genes, which are regulated by the ERs. ERRs are constitutively transactivated without binding to any known physiological ligands in the eukaryotic cells and they can interact with a number of steroid hormone receptor coactivators and ERs. Expression studies demonstrate that ERRs are widely expressed in human adult and murine embryonic tissues, including the central nervous system, gonads, kidney, heart and musculoskeletal system, suggesting that ERRs are involved in many physiological processes. *In vitro* studies show that ERRs can transactivate a number of genes, such as lactoferrin, medium-chain acyl coenzyme A dehydrogenase, osteopontin, thyroid hormone receptor  $\alpha$ , breast cancer marker

gene pS2 and other orphan receptor. Based on the importance of ERRs in the homeostasis and development of many organs and their close relationship with ERs, we propose in this research project to study their expression and functional significance in the normal immortalized human prostatic cells and various cancer cell lines which represents different stages of the prostate cancer. The results of the proposed investigations would significantly contribute to our understanding on the potential roles of ERRs in the prostate carcinogenesis.

(MD02345)

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### **The Roles of Cell Adhesion Molecules on Patterning Axon Orders in the Retinofugal Pathway of Mouse Embryos**

✉ CHAN Sun On

□ 1 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

Retinal axons undergo several changes in fiber arrangements from the optic nerve to the optic tract. These changes in fiber organization are essential for the formation of normal patterns of neural connection in the visual pathways. The developmental mechanisms that control such changes in fiber arrangements are the focuses of this study. We will investigate functions of two cell adhesion molecules, L1 and NCAM, on patterning the fiber orders in the retinofugal pathway of mouse embryos. These two molecules are members of immunoglobulin super-family that are known to promote axon growth and fasciculation in the central and peripheral nervous systems. Their possible involvements in patterning the fiber orders will be investigated using immunohistochemistry. Functions of NCAM will

be further examined by investigating the axon routing patterns in the pathway after perturbing NCAM functions with blocking antibodies or with enzyme that removes polysialic acid from the NCAM molecule. The changes in partial decussation pattern, age-related order and segregation of retinal axons from dorsal and ventral retina in the chiasm and the tract will be determined. Results of these experiments will provide important insights into mechanisms that govern axon routing in decision regions of a neural pathway in the mammalian central nervous system.

(MD02573)

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### **The Roles of DOC-2/Dab2 in Cortical Development**

✉ CHAN Wood Yee • YEW Tai Wai David

☐ 3 March 2003

❖ CUHK Research Committee Funding (Direct Grants)

Disturbances that occur in the cortex of the brain during fetal development have been recognized as the causes of many congenital diseases including lissencephaly, holoprosencephaly, cortical heterotopia, double cortex, mental retardation, developmental delay and epilepsy in children and adults and also schizophrenia that may develop later in adults. However, cellular and molecular events even in normal cortical development have not yet been fully characterized, and studies on human development have particularly been slowed down by the limited availability of human specimens. Recently we have identified and characterized DOC-2/Dab2 as a mammalian ortholog of *Drosophila Disabled*, which has been known to be involved in neuronal development. Our studies also showed that disruption of *DOC-2/Dab2* gene

expression during early development of the mouse embryo resulted in malformation of the neural tube and disorganization of the neuroepithelial cells of the brain. Hence, in order to establish the roles of DOC-2/Dab2 during cortical development, we propose: (1) to fully characterize the temporal and spatial expression of the gene in human fetal brains which we have already collected; (2) to ascertain in parallel with the human studies the gene expression in mouse embryos; and (3) to genetically increase or decrease the gene expression in mouse embryos to determine the pathological sequences, and whether possible to correlate the expression with the functions of the gene. The results will give us information on the possible roles of DOC-2/Dab2 in normal cortical development and the pathological alterations following changes of gene expression.

(MD02775)

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### **Does Deletion of Male Accessory Sex Glands Produce Heritable Changes in Spermatozoa?**

✉ CHOW Pak Ham Patricia • O Wai Sum\* • FERGUSON-Smith A\*

☐ 1 January 2003

❖ CUHK Research Committee Funding (Direct Grants)

The production of healthy offspring is the ultimate goal of the living. Male mammals have evolved a complex system of reproductive structures made up of gametes, ducts and glands. Successful artificial intervention of reproductive process seems to suggest that procreation can be achieved by gametes alone. Thus it is commonly thought that apart from realizing such minor missions as transferring gametes, attracting the opposite sex or preventing double insemination, the accessory sex glands (e.g. the prostate and seminal vesicle) are largely dispensable.

However, our past studies give evidence that these glands are needed for proper development of embryos. Recently the revelation of genomic instability and its unfavourable consequence on embryo development has caught the attention of reproductive biologists. Even though modification can be inflicted without altering gene structure, the outcome is heritable. Genomic imprinting is the process that epigenetic marks are added to chromosomes in such a way that the parental alleles are expressed unequally in the offspring. Are accessory sex glands evolved in the male to help stabilizing the sperm genome so as to ensure healthy development of sired embryos? We propose to test this by studying the effects of deletion of these glands on methylation status and expression of some well-studied imprinted genes in the sperm and embryo of rodents.

(MD02605)

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**Offspring of Males without Accessory Sex Glands, Are They Different?**

✉ CHOW Pak Ham Patricia

□ 1 June 2003

❖ CUHK Departmental Funding

Accessory sex glands are integral components of the reproductive system in all male mammals, but their function(s) have not yet been clearly defined. In the golden hamster, removal of all the glands (TX) or the ventral prostate alone (VPX) considerably reduces fertility even though. The rate of successful fertilization *in vivo* and *in vitro* are not affected. Significant number of embryos so derived fail to develop to term although some survive to be born. In fact at the time of fertilization, oocyte activation and delayed entry into the first cell cycle and pronuclear development are delayed. Recently we

have reported that absence of these glands may result in oxidative damage to sperm and anomalies in genomic imprinting of sperm and embryo. The question we ask being “Are the F1 pups normal?” In this study, structure, physical growth and behavioural pattern of F1 from birth to the Day 56 will be examined. Physical development parameters such as body weight, femur length, muscle strength and relative organ weight will be measured. Behavioral patterns such as olfactory preferences, exploring a new environment (ambulation and rearing) and acoustic startle response (startle amplitude and startle habituation) will be studied.

(MD02930)

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**Cellular Mechanism of the Neurotoxicity of Type 1 and Type 2 Ribosome-inactivating Proteins**

✉ KWONG Wing Hang • NG Tzi Bun (Biochemistry) • LEE Ka Ho Kenneth

□ 1 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

Ribosome-inactivating proteins (RIPs) are classified into type 1 and type 2. Type 1 RIPs consist of a ribosome-inactivating chain. Type 2 RIPs consist of both a ribosome-inactivating chain and a cell-binding B chain. Type 2 RIPs are widely used in research and therapeutics. Type 1 RIPs are used only in some therapeutic studies. Whether type 1 RIPs possess neurotoxicity has not been reported. We hypothesize, based on our preliminary observations, that (1) type 1 RIPs alone, without the association of a lectin B-chain, can be taken up by neurons, transported in axons, and cause cell death; (2) the mechanism of intoxication, and the protection against it, involve glial cells; (3) some type 1 RIPs kill only specific types of cells. This project is therefore



aimed at: (1) determining the effects of type 1 RIPs on glial cells and neurons; (2) following the uptake and intracellular transport of type 1 RIPs, and the molecular processes associated with the destruction of the intoxicated cells; (3) testing the possibility that the specific toxicity of type 1 RIPs against certain cell types depends on both the structure of the RIPs and the presence of sugar groups / specific receptors on the cell. Type 1 RIPs including ricin A chain and trichoshanthin, type 2 RIP ricin, and lectin ricin B chain, will be administered to the spinal cord, sensory ganglia, and retina of the adult rat, and cells of these structures will be studied using immunohistochemical and electron-microscopic methods.

(MD02326)

**Please refer to previous issues of this publication for more details of the following ongoing research at the department:**

Edition      Title/Investigators

2000-01      An Expression and Functional Study of a Prostatic Secretory Protein of 94 Amino Acids in Normal and Neoplastic Rat Prostate Glands (CU00131)

✉ CHAN Leung Franky

2000-01      The Roles of Chondroitin Sulfate Proteoglycans on Axon Growth at the Mouse Chiasm (CU00132)

✉ CHAN Sun On

2000-01      Therapeutic Effects of Pien Tze Huang Without Natural Musk on Hepatitis (MD20021)

✉ CHAN Wood Yee • YEW Tai Wai David • KWONG Wing Hang • LEE Ka Ho Kenneth

2001-02      Migration of Neural Crest Cells to the Bowel in Normal and Congenitally Aganglionic Mutant Mice (MD01016)

✉ CHAN Wood Yee • COPP A J\*

2001-02      A Study on the Use of Sertoli Cells to Promote Retinal Ganglion Cell Regeneration (MD01017)

✉ CHO Yu Pang Eric

2001-02      Effect of Male Accessory Sex Gland Secretions on the Oxidative Stress, Functional Competence and Genomic Integrity of Hamster Spermatozoa (BS00621)

✉ CHOW Pak Ham Patricia • O Wai Sum\*

1999-00      Effects of Ribosome-inactivating Proteins on Motor and Ganglionic Neurons (BL97043)

✉ KWONG Wing Hang

2000-01      Role of *BRE*, a New Modulator of TNF- $\alpha$  Action, in Skeletal Muscle Proliferation and Differentiation (MD00801)

✉ LEE Ka Ho Kenneth

2000-01      Cloning, Sequencing and Biological Characterization of an Immunomodulatory Fungal Protein (CU00125)

✉ LIU Wing Keung Ken • NG Tzi Bun (Biochemistry)

- 2001-02 Anti-Proliferative Activity of Common Mushroom Lectins on Colon Cancer Cells (MD01430)  
✉ LIU Wing Keung Ken • NG Tzi Bun (Biochemistry)
- 1999-00 A Study of the Pathogenetic Mechanism of Renal Agenesis (CU99283)  
✉ SHUM Sau Wun Alisa • WOOLF Adrian S\*
- 2000-01 A Study to Determine Whether Hyperglycemia is Responsible for Increased Susceptibility to Vitamin A Embryopathy in Diabetic Pregnancy (MD00359)  
✉ SHUM Sau Wun Alisa
- 2001-02 A Study to Determine Whether Apoptosis and Reactive Oxygen Species (ROS) are Involved in Increased Susceptibility to Vitamin A Teratogenicity in Diabetic Pregnancy (MD01610)  
✉ SHUM Sau Wun Alisa
- 2000-01 Genes and Heroin Addiction in the Chinese Population: Association Studies on Receptor Gene (MD98904)  
✉ STADLIN Alfreda • LEE Tak Shing Dominic (Dept of Psychiatry) • TANG Leung Sang Nelson (Dept of Chemical Pathology) • LOH El-Wui\* • CHEN Chih Ken\* • CHAN Pui\* • CH'IEN James\*
- 2001-02 Glial Immune Response After METH ('Ice') or MDMA ('Ecstasy') Treatment (MD01546)  
✉ STADLIN Alfreda • CHANG Chuen Chung Ryamong\* • FENG Zhe Hui\*
- 2001-02 Cellular Mechanisms of Neuronal Loss During Aging (MD01023)  
✉ YEW Tai Wai David • CHAN Wood Yee

## RESEARCH PROJECTS

### Effect of Antisense Oligodeoxynucleotide of Glucose Transporter 5 on Human Breast Tumor

✉ FUNG Kwok Pui

☐ 1 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

Breast cancer is a leading fatal disease in female. Throughout the life span from age 50 of the female, the incidence is as high as 1:8 in Western countries and 1:24 in Hong Kong. Chemotherapy is commonly used to kill the remaining breast tumor cells locally after the tumor has been removed surgically and to treat patients at metastasis stage. Commonly used anti-tumor drugs exhibit adverse effect to the host, such as damaging the heart and liver. Furthermore, multidrug resistance will be developed in tumor after prolonged treatment. We plan to tackle these problems by using antisense oligodeoxynucleotide of glucose transporter 5 (GLUT5) to treat the tumor. Breast tumor cells specifically overexpress GLUT5 to compete glucose as a nutrient from the blood to promote rapid growth and to pump out the drug when the tumor cells have been developed into multidrug resistant. Our treatment protocol may suppress GLUT5 expression in the tumor cells resulting in glucose depletion which may kill the tumor cells and circumvent their multidrug resistance. Our results may shed light to the understanding of the mechanisms of the effect of antisense oligodeoxynucleotide of GLUT5 on breast tumor cells.

(MD02302)

### Identification and Characterization of Apolipoprotein Polymorphism-Induced Variation of Cell Function Involved in Atherosclerosis

✉ HO Yuanyuan • FUNG Kwok Pui • WAYE Mary Miu Yee

☐ 1 October 2002

❖ Research Grants Council (Earmarked Grants)

*Background:* Apolipoprotein E (ApoE), a surface component of plasma lipoproteins as well as a ligand for lipoprotein receptors, is expressed in many tissues. The three common allelic variations epsilon 2, epsilon 3, and epsilon 4, encoding isoforms apoE2, apoE3, and apoE4, respectively, have been associated with specific prediction for risks of atherosclerosis and Alzheimer's diseases. *Problem identified:* How different apoE genotypes modulate cellular function involved in atherosclerosis, such as lipid metabolism and cell growth is unclear. *Hypothesis:* ApoE modulates cell lipid metabolism and growth in an apoE genotype-specific manner. *Specific Aims:* Specific Aim 1 will compare lipid metabolism in cells carrying different apoE genotypes. Specific Aim 2 will compare proliferation and apoptotic responses of cells with different apoE genotypes. Specific Aim 3 will identify and characterize the signaling pathways and genes underlying the apoE polymorphism-induced functional changes observed in the first two aims. *Significance:* Specific Aims 1 and 2 will allow specific cell metabolic and growth properties to be associated with each apoE genotype. Specific Aim 3 will reveal the mechanisms responsible for the apoE genotype-specific functional changes. The knowledge obtained from the proposed studies will facilitate more accurate risk prediction and management of atherosclerosis and likely other human diseases.

(CU02274)

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**Characterization of the Glucose Transport-modulating Effects of Anti-epileptic Compounds**

✉ HO Yuanyuan • FUNG Kwok Pui • FOK Tai Fai (Dept of Paediatrics) • FUNG Lai Wah Eva (Dept of Paediatrics)

□ 1 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

The mammalian brains rely on sufficient glucose supply for normal function and glucose transport type 1 (Glut-1) is the principal carrier of glucose across the blood-brain barrier. Repression of Glut-1 activity due to metabolic diseases such as diabetes or genetic disorders such as the Glut-1 deficiency syndrome may reduce Glut-1 function and thus interfere with glucose transport to the brain causing neurological deficits. Restoration and preservation of glucose transport into the central nervous system is crucial to maintaining the brain function in patients with compromised Glut-1 activity. However, the effects of many compounds used for seizure control or chronic neurological conditions are not evaluated for their Glut-1-modulating properties.

*Hypothesis:* We hypothesize that Glut-1-mediated glucose transport can be altered by different anti-epileptic compounds.

*Aim:* The current proposal aims to characterize the glucose transport-modulating effects of anti-epileptic compounds and evaluate the relative risks of these compounds in compromising glucose supply to the brain using established cell models for glucose transport studies.

*Significance:* The knowledge obtained from the proposal studies will promote more comprehensive

understanding of how brain glucose metabolism may be influenced by the treatment of anti-epileptic compounds and facilitate better prescription decisions for patients with different metabolic needs/status.

(MD02769)

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**Induction of Anticancer Drug Resistance in Human Cancer Cells by Chronic Exposure to Growth Factors**

✉ KWOK Tim Tak

□ 1 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

Cancer is one of the major 'death-causing-diseases' in Hong Kong and in many other countries. Amplification and inappropriate activation of epidermal growth factor receptor (EGFR) are associated with development of many types of cancer. The signaling pathway for EGF shares its part with the pathway for anticancer agents and may therefore affect the response of cells to anticancer drugs. It is however not clear long term exposure to growth factor may alter the response of cells to common anticancer drugs, e.g. doxorubicin. By culturing cells continuously in EGF, drug resistance was found to be developed in human squamous carcinoma A431 and SiHa cells. The underlying mechanisms for the induced drug resistance will be investigated. The results from the proposal will provide an understanding of how anticancer drugs interact with growth factor signaling. Furthermore, the information obtained can be used in the design of new strategies for cancer therapy targeting specifically the critical molecules in signal transduction pathway. The design may benefit the cancer patients including those in Hong Kong.

(MD02989)

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### Effect of Baicalein on Hormone-responsive MCF-7 Tumor

✉ LEUNG Lai Kwok • CHEN Zhenyu (Biochemistry) • CHAN Leung Franky (Dept of Anatomy)

□ 1 January 2003

❖ CUHK Research Committee Funding (Direct Grants)

Flavonoids are polyphenolic compounds isolated from plants. Many flavonoids have been shown to be agonists of estrogen receptor (ER) with various potencies. Baicalein, a flavonoid extracted from the root of *Scutellaria* species is widely used as herbal medicine in some part of China. Because of the structural similarity to genistein, we examined the estrogenic and antiestrogenic properties of this phytochemical. Baicalein administration could inhibit ER positive breast cancer cells proliferation. It behaved as a weak agonist to ER  $\alpha$  and  $\beta$  in a cell expression and transfection system, whereas it acted as an antiestrogen to both ER  $\alpha$  and  $\beta$  when co-administered with 17 $\beta$ -estradiol. In this proposal we have divided our investigation into three sections. Regarding the mechanisms, estradiol hydroxylation assays and cell-free ER competition assays will be carried out to address the differences in antiestrogenic effect among baicalein and other flavonoids. Gene expression section addresses the pathway by which cell death may go through in a cell culture system. The designed experiments are to address the notion that some flavonoids could be natural alternatives for chemoprevention of estrogen-sensitive breast cancers.

(MD02487)

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### The Role of FHL Proteins in Cell Cycle Regulation

✉ TSUI Kwok Wing

□ 1 January 2003

❖ CUHK Research Committee Funding (Direct Grants)

Myocardial infarction is a leading cause of mortality because cardiomyocytes do not regenerate after injury. In human cardiomyocytes, the capability of mitosis and hyperplasia is lost three to six months postnatally. When they are terminally differentiated, they will undergo an irreversible commitment to the differentiated phenotype and permanent cell cycle arrest. Skeletal myocytes will also undergo similar cell cycle arrest after differentiation. Based on two former grants from the Research Grants Council, we have isolated many LIM domain protein genes, which are preferentially or abundantly expressed and developmentally regulated in human heart. Moreover, previous results have shown that one of the proteins are differentially expressed in failing human hearts, and one is a p53-responsive gene whose protein product induces apoptosis. Moreover, these LIM domain proteins can interact with many important cell cycle proteins. To uncover the functional significance of these three proteins, we shall investigate their arrangement in the corresponding protein complex and their role in cell cycle progression. We believe that the further characterization of these LIM domain proteins should be an important step towards the understanding of the terminal differentiation and regeneration of cardiomyocytes and enable new approaches for diagnosis and treatment of human heart diseases.

(MD02379)

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### Natural Inhibitors Against HIV-1 Integrase

✉ WAN Chi Cheong David • NG Tzi Bun

☐ 1 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

The human immunodeficiency virus type 1 (HIV-1) is known to be the causative agent of the acquired immunodeficiency syndrome (AIDS). Over the last two decades, there is great effort worldwide dedicated to both basic and clinical research, hoping to find a cure for this debilitating disease. This project is aimed at the characterization of a group of natural plant proteins, namely the ribosome-inactivating proteins, as inhibitors of HIV-1 integrase (HIV-1 IN). Recombinant luffins and saporin and their mutants will be used to probe the structural requirement for the inhibitory activity to HIV-1 IN. The results obtained will lay the way for the development of inhibitors to HIV-1 IN.

(MD02467)

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**Characterization of a RING-H2 Finger Protein, ANAPC11, the Human Homologue of Yeast Apc11p**

✉ WAYE Mary Miu Yee • ZIMMERMANN Rene\* • CHAN Hei (Biochemistry)

☐ 1 January 2003

❖ Germany/Hong Kong Joint Research Scheme

The human anaphase promoting complex subunit 11 (yeast Apc11p homologue), ANAPC11, was identified during a large-scale EST sequencing project. This 514 bp full-length cDNA has a predicted open reading frame (ORF) encoding 84 amino acids which possesses a RING-H2 finger motif and exhibits sequence similarity to subunits of E3 ubiquitin ligase complexes. The anaphase

promoting complex (APC) or cyclosome, an E3 ligase, regulates important events in mitosis: the initiation of anaphase and mitotic exit by targeting the degradation of inhibitors including securin and mitotic cyclins by the 26S proteasome through ubiquitination. We plan to analyze the expression of ANAPC11 by northern and western blot analyses as well as by immunohistochemistry in human and mouse heart tissues. The human tissue includes normal, hypertrophied as well as dilated myocardial tissue, whereas the mouse tissue comes from mouse of different developmental stages. We also plan to check the correlation of the expression of ANAPC11 gene with that of CARP gene and verify their co-expression in the same cell types since we have some preliminary data using yeast two hybrid assay that the two proteins interact with each other.

(BL02860)

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**Please refer to previous issues of this publication for more details of the following ongoing research at the department:**

Edition      Title/Investigators

1990-91      Comparative Endocrinology of Prolactin, Growth Hormone, and Their Receptors (BP88031)

✉ CHENG Hon Ki Christopher • NG Tzi Bun • WONG Chun Cheung (Dept of Physiology)

2001-02      Molecular and Functional Characterization of Ghrelin and Its Receptors in Seabream (BL01149)

✉ CHENG Hon Ki Christopher • WOO Norman Ying Shiu (Dept of Biology) • YU K L\*

- 2001-02 Functional Roles of Type II Angiotensin Receptor in Pancreatic Endocrine Cells (BL01792)  
 ✎ CHEUNG Wing Tai
- 2001-02 Mechanistic Studies of the Anti-tumour Effect of Arsenic Trioxide in Human Leukemia and Solid Tumour Cells (BL01516)  
 ✎ FUNG Kwok Pui
- 2001-02 Mechanistic Study of Anti-tumour Effect of Natural and Synthetic Saponins (MD01668)  
 ✎ FUNG Kwok Pui
- 2001-02 Signaling Mechanisms Underlying the Effects of Apolipoprotein E on Cell Proliferation and Apoptosis (BL01438)  
 ✎ HO Yuanyuan • FUNG Kwok Pui
- 2001-02 Functional Analysis of a Novel Gene Over-expressed in Doxorubicin Resistant Human Cancer Cells (MD01024)  
 ✎ KWOK Tim Tak • CHEUNG Wing Tai • KONG Siu Kai (Biochemistry)
- 2001-02 Isolation and Characterization of Novel Antifungal Proteins (MD01640)  
 ✎ NG Tzi Bun • WANG Hexiang\* • YE Xiu Yun\*
- 2000-01 Characterization of Differentially Expressed Genes during Terminal Differentiation of Cardiomyocytes (CU00116)  
 ✎ TSUI Kwok Wing • FUNG Kwok Pui • LEE Cheuk Yu# • WAYE Mary Miu Yee
- 2001-02 Characterization of Differentially Expressed Genes in HBV-induced Hepatocarcinogenesis (MD00829)  
 ✎ TSUI Kwok Wing
- 2001-02 Natural Inhibitors Against HIV-1 Integrase (MD01970)  
 ✎ WAN Chi Cheong David • NG Tzi Bun
- 2001-02 14-3-3 Epsilon and Calmodulin in Signal-transducing Complexes (MD01345)  
 ✎ WAYE Mary Miu Yee
- 2001-02 Study on the Expression of a G Patch Containing Protein (HSPC039) in Human and Animal Myocardial Tissues (BL01855)  
 ✎ WAYE Mary Miu Yee • ZIMMERMANN Rene\*

## RESEARCH PROJECTS

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### **Quantitative Analysis of Size Distribution of Plasma Epstein-Barr Virus DNA in Nasopharyngeal Carcinoma and Lymphoma Patients**

✍ CHAN Kwan Chee • LO Yuk Ming Dennis • CHAN Anthony Tak Cheung (Dept of Clinical Oncology) • LEI Ieng-Kit Kenny (Dept of Clinical Oncology)\*

☐ 1 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

The presence of cell-free nucleic acids in the plasma has opened up new possibilities for medical diagnosis. One of the most successful applications is the analysis of circulating Epstein-Barr virus (EBV) DNA in patients suffering from nasopharyngeal carcinoma (NPC).

NPC is one of the five commonest cancers in Hong Kong and is closely related to EBV infection. We have shown that high concentrations of EBV DNA can be detected in the plasma of NPC patients and the analysis of circulating EBV DNA is valuable in the detection, monitoring and prognostication of NPC.

However, the fundamental question concerning the origin and characteristics of these circulating EBV DNA molecules remains unanswered. Our group has looked into this matter from a number of directions. Firstly, we have subjected plasma of NPC patients to DNase I digestion and ultracentrifugation. The results indicate that circulating EBV DNA exists as DNA fragments instead of intact virions. To confirm this hypothesis, we used primer sets with different amplicon sizes to

amplify the circulating DNA extracted from NPC and lymphoma patients. Initial results of these experiments reveal that the sizes of circulating DNA molecules are around 200 to 400 base-pairs.

In this project, we plan to further quantify the different size fractions of the circulating EBV DNA in NPC and lymphoma patients. Results from different stages of the diseases will be compared. The resulting information will enhance our understanding of the biology of plasma EBV DNA in NPC and thus benefit the development of new molecular markers for cancer detection.

(MD02447)

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### **Quantitative Analysis of Circulating Mitochondrial DNA**

✍ CHIU Wai Kwun Rossa • LO Yuk Ming Dennis • RAINER Timothy Hudson (Accident and Emergency Medicine academic unit)

☐ 1 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

In view of the increasing number of clinical applications reported for the use of circulating nucleic acids and the increasing awareness of the relationship between mitochondria and disease, this project proposes to study the use of mitochondrial DNA quantification in plasma for disease assessment. There are two modules for this study. The aim of module 1 is to investigate the blood processing and handling protocol that one should adopt to ensure the reliability of mitochondrial DNA analysis. Module 2 concerns with the evaluation of the clinical usefulness of circulating mitochondrial DNA quantification as a tool for disease assessment by focusing on its use in acute trauma testing. In the present literature, there are no data describing the use



of mitochondrial DNA quantification in plasma. Hence, the information generated from this study would contribute to the advancement of science in addition to the exploration of a new tool for disease assessment and management.

(MD02310)

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**A Comprehensive Survey of Mutations in the Wilson Disease Gene (ATP7B) in Hong Kong Chinese : Frequencies, Haplotypes and Genotype-Phenotype Correlations**

✉ LAM Ching Wan

□ 1 August 2002

❖ Research Grants Council (Earmarked Grants)

Wilson disease is an autosomal recessive disorder of copper transport characterized by toxic accumulation of copper in the liver, brain, and kidney. Wilson disease is the most frequent inherited liver disease in Hong Kong. Wilson disease is treatable, but prevention of irreversible liver or brain damage is dependent on early detection of presymptomatic patients. No such method has been well established. In patients with liver disease of unknown origin, Wilson disease is often overlooked when established clinical and laboratory tests are used as diagnostic criteria. In these cases, only molecular analysis has proven decisive. To our knowledge, no studies have been undertaken to elucidate the molecular basis of Wilson disease in the Hong Kong Chinese. Therefore, we propose to do this and to establish a new protocol for diagnosis for Wilson disease in the Hong Kong Chinese population. Toward this end, we will delineate the spectrum of mutations in the Wilson disease gene in patients with Wilson disease in Hong Kong, and we will characterize the associated haplotypes. We will search for correlations between genotypes and several

phenotypic manifestations of the illness, including age of onset, neurological versus hepatic onset of the illness, the level of serum ceruloplasmin, and the presence of Kayser-Fleischer rings. In addition to providing the basis for molecular diagnosis, these findings will enrich our knowledge of the disease and its underlying biochemical and molecular causes. The results from this study will have immediate application in the clinical laboratory, and, if properly applied, will lead to a decrease in the mortality of Wilson disease in Hong Kong in the near term.

(CU02084)

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**Production of Nitric Oxide, Soluble Thrombomodulin, Soluble Adhesion Molecules, and Interleukin-18 in Systemic Lupus Erythematosus Patients with Renal Disease**

✉ LAM Wai Kei Christopher • LI Kwok Ming Edmund (Dept of Medicine & Therapeutics) • WONG Chun Kwok

□ 1 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

Recent studies have shown that excessive nitric oxide (NO) production may play a pivotal role in the pathogenesis of systemic lupus erythematosus (SLE). Increased production of NO has been documented in SLE. Thrombomodulin, a cell surface glycoprotein at the luminal surface of vascular endothelium, has been widely used as a marker of microvascular endothelial injury and thrombotic events in various diseases such as rheumatic diseases. Previous studies have reported that elevated sTM is associated with the disease activity, nephritis, and vasculitis of SLE. Adhesion molecules including vascular cell adhesion molecule-1 (VCAM-1), E-selectin and intercellular adhesion molecule-1 (ICAM-1), are

essential for cellular interactions, and play an important role in the activation and adhesion of cells. Plasma sVCAM-1 concentration is significantly elevated in patients with active lupus nephritis. Moreover, we have reported significantly elevated plasma pro-inflammatory cytokine interleukin (IL)-18 concentration in SLE patients compared to normal controls. Since the detailed pathological mechanisms of renal development in SLE patients are still not well understood, we wish to study the plasma concentrations of NO, sTM, sVCAM-1 and IL-18, and investigate their inter-correlation and their correlation with SLE disease activity index and renal function (in term of urea and creatinine) in SLE patients with and without renal disease and normal controls. Results should be useful for elucidation of the pathogenic role an interrelationship of these inflammatory factors in renal involvement of SLE, thereby providing a biochemical basis for these inflammatory factors to serve as the markers for SLE disease activity and efficacy of treatment.

(MD02791)

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**Study of Immunomodulatory and Anti-tumor Activities of HERBSnSENSESTM Cordyceps (Dong Chong Xia Cao)**

✉ LAM Wai Kei Christopher • WONG Chun Kwok • LEUNG Kwok Nam (Biochemistry) • KONG Siu Kai (Biochemistry)

☐ 1 March 2003

❖ GreaterChina Technology Group Limited

The human immune system plays an important role in immunosurveillance against many malignant cells and infections for keeping our body in good health. It is generally believed that the application of tonic Chinese medicinal herbs may enhance the body resistance. Many immunostimulating ingredients

isolated from Chinese herbal medicines including *Cordyceps militaris* (Dong Chong Xia Cao) have been found to modulate various immunological functions and exhibit anti-tumor activity. Therefore, elucidation of the immunomodulatory and anti-tumor mechanisms of *Cordyceps militaris* is an important and worthy pursuit in understanding Traditional Chinese Medicine (TCM). In our present study for the immunomodulatory activity of *Cordyceps militaris*, we shall investigate the *in vitro* cell-mediated immunity, *in vivo* immunomodulatory and anti-tumor activity using mice model. Moreover, a randomized, double-blind, placebo-controlled, cross-over study shall be undertaken to investigate if regular consumption of *Cordyceps militaris* can improve cellular and humoral immunity in healthy subjects. Results shall be useful for elucidating the mechanisms for promoting the cellular and humoral immune functions and quality of life by *Cordyceps militaris*.

(MD02709)

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**Molecular Characterization of Circulating Epstein-Barr Virus DNA in Nasopharyngeal Carcinoma Patients**

✉ LO Yuk Ming Dennis • CHAN Anthony Tak Cheung (Dept of Clinical Oncology) • TO Wai Hei Edward\*

☐ 30 December 2002

❖ Research Grants Council (Earmarked Grants)

Plasma Epstein-Barr virus DNA detection has been demonstrated to be a powerful tool for the diagnosis and monitoring of nasopharyngeal carcinoma. However, little is known regarding the molecular characteristics of such Epstein-Barr virus DNA. In this project, the origin of circulating Epstein-Barr virus DNA in the plasma of nasopharyngeal

carcinoma patients will be studied. Furthermore, the question regarding whether such DNA is from whole virions or represent fragments of DNA will be addressed.

(CU02086)

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**Development of a Maternal Plasma RNA Marker for Preeclampsia**

✉ LO Yuk Ming Dennis • NG Kai On • LEUNG Tse Ngong (Dept of Obstetrics & Gynaecology) • CHIU Wai Kwun Rossa • LAU Tze Kin (Dept of Obstetrics & Gynaecology)

☐ 1 June 2003

❖ CUHK Research Committee Funding (Direct Grants)

Previously, our group was the first to demonstrate the presence of fetal RNA in maternal plasma and this discovery opens up new possibilities for noninvasive prenatal diagnosis. In this project, we hypothesize that (1) the placenta is a significant source of such RNA and (2) that the concentrations of such RNA in maternal plasma may be elevated in preeclampsia. We propose to test hypothesis (1) by developing a real-time reverse transcriptase polymerase chain reaction assay to mRNA coding for corticotrophin releasing hormone (CRH). We aim to demonstrate the presence of CRH mRNA in the plasma of pregnant women and its clearance following delivery. If this first goal is achieved, then we plan to investigate if a quantitative abnormality involving maternal plasma CRH mRNA may be detectable in women with preeclampsia, when compared with control pregnant women matched for gestational age. When accomplished this project may provide us with a new marker for preeclampsia and will enhance our understanding of the origin of fetal nucleic acids in maternal plasma.

(MD02565)

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**Treatment and Diagnosis of Severe Acute Respiratory Syndrome**

✉ LO Yuk Ming Dennis

☐ 6 June 2003

❖ A Private Limited

This project aims to explore new treatment and diagnostic approaches for severe acute respiratory syndrome (SARS). State-of-the-art molecular approaches against the replication of the SARS-coronavirus will be tested. In addition, sensitive detection methods will be developed and tested.

(MD02397)

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**Establish a Diagnostic Laboratory for Inherited Metabolic Diseases in Hong Kong**

✉ TANG Leung Sang Nelson • FOK Tai Fai (Dept of Paediatrics) • LAM Wai Kei Christopher • CHEUNG Kam Lau (Dept of Paediatrics) • HUI Joannie (Dept of Paediatrics)

☐ 1 October 2002

❖ S K Yee Medical Foundation

This project will develop laboratory protocols and provide services for laboratory diagnosis of inherited metabolic diseases in Hong Kong.

Inherited metabolic disease is a collective term referring to hereditary diseases (more than hundred entities) which affect various biochemical pathways of metabolism. As these metabolic defects are inborn, patients are affected from birth and thus usually present in childhood. More widely recognized patients are those with storage diseases such as mucopolysaccharidosis. Patients of these

diseases share similar features characterized by gross facial appearance. However, many other patients do not have recognizable external features but are at risk of mental retardation, life-threatening episodes of acute metabolic crisis and even sudden infant death. And diagnosis of these patients relies on different laboratory assays.

Currently, limited laboratory diagnosis service is available in Hong Kong and many diseases could be under-diagnosed. This is partially due to the complexity of inherited metabolic diseases and also due to lack of local diagnostic service.

The laboratory protocols developed in this project will firstly provide service free of charge to patients in Hong Kong during the funding period and will then be further optimized for technical transfer for subsequent operation in routine hospital laboratory after the funding period. In this way, after the completion of the grant, the laboratory services will be continuously provided and maintained in hospital laboratory.

A list of laboratory tests to be developed is available from the principle investigator.

(MD02558)

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### **Genotypic Determinants of Circulating Levels of Proteins in the GH-IGF Axis in Chinese**

✉ TANG Leung Sang Nelson • TO Ka Fai (Dept of Anatomical & Cellular Pathology) • MAC-MOUNE LAI Fernand (Dept of Anatomical & Cellular Pathology) • CHAN Lung Wai\*

☐ 1 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

A good number of epidemiology studies showed that high level of circulating insulin like growth factors

and low level of insulin growth factor binding protein-3 (IGFBP-3) were strong risk factor for development of various cancers including prostate cancer and breast cancer. IGFs extent their action by binding to specific membrane receptor and this interaction is modulated by a group of binding protein. Production of IGFs are under regulation of growth hormone and growth hormone receptor. This series of proteins form a GH-IGF axis for control of cellular growth. The biochemical role of IGFs in control of proliferation, differentiation and apoptosis further reinforces the notion that this GH-IGF axis is a key player in oncogenesis in addition to its function in physiological growth. In addition to prostate cancer, previous studies reported that risk of liver cancer, breast cancer and colorectal cancer were also influenced by this axis.

Circulating level of these proteins are influenced by both genetic and environmental factors. The blood levels of baseline IGFs are also genetically programmed. Therefore, we propose to study the genotypic determinants of circulating level of these proteins in the local Chinese population in order to further understand the genetic mechanisms of their regulations.

#### *Objectives:*

- (1) Determine the association between microsatellites markers located around the candidate loci with circulating levels of IGFs and IGFBPs.
- (2) Detection of SNPs for those associated genes identified in part 1.
- (3) Determine if there is also a direct association between those SNPs found in part 2 with circulating levels of GH-IGF proteins

The project will provide information about the mechanism of genetic determination of circulation levels of proteins in the GH-IGF axis. Furthermore, the information will be crucial for subsequent

investigation on the relationship between these genes and risk of various cancers including liver cancer, breast cancer and other cancers having similar association with IGFs.

(MD02607)

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**Intracellular Signal Transduction for Tumor Necrosis Factor- $\alpha$  and Interleukin-18 Mediated Recruitment of Eosinophils in Allergic Inflammation**

✉ WONG Chun Kwok • LAM Wai Kei Christopher

□ 1 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

Allergic diseases such as asthma and allergic rhinitis are prevalent and have been increasing worldwide. Eosinophils are the major inflammatory effector cells accumulating at the site of allergic inflammation, e.g. airway submucosa. It has been shown that inflammatory cytokine tumor necrosis factor (TNF)- $\alpha$  is released in allergic responses from both mast cells and macrophages via IgE-dependent mechanisms. TNF- $\alpha$  can upregulate adhesion molecules and facilitate the immigration of eosinophils into the airway wall. Murine model of allergic asthma has indicated that another pro-inflammatory cytokine interleukin (IL)-18 can increase allergic sensitization, serum IgE, Th2 cytokines and airway eosinophilia. The primary objective of this research proposal is to elucidate TNF- $\alpha$  and IL-18 mediated intracellular signal transduction mechanisms in the control of eosinophil chemotaxis in allergic inflammation. This project will study the following: (1) *in vitro* effects of TNF- $\alpha$  and IL-18 on (i) the activation of NF- $\kappa$ B, (ii) p38 mitogen-activated protein kinase (MAPK) activity, (iii) chemotaxis, and (iv)

expression of adhesion molecules including intracellular adhesion molecule (ICAM)-1, ICAM-3 and very late antigen-4 (VLA-4) on eosinophils; (2) *in vitro* effects of TNF- $\alpha$  and IL-18 on the cDNA expression profile of NF- $\kappa$ B pathway related genes including NF- $\kappa$ B family, adhesion molecules, inflammatory cytokines and their receptors, and MAPK of eosinophils; and (3) relationship between the activation of NF- $\kappa$ B and p38 MAPK, and chemotaxis and the expression of adhesion molecules of eosinophils. This study will be useful for the development of new therapeutic strategies for treating allergic inflammation.

(MD02884)

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**Please refer to previous issues of this publication for more details of the following ongoing research at the department:**

<u>Edition</u>	<u>Title/Investigators</u>
1999-00	Mitochondrial Genome in Wolff-Parkinson-White Syndrome (MD99028) ✉ LAM Ching Wan • SANDERSON John Elsby (Dept of Medicine & Therapeutics) • WONG Lee Jun C* • FONG Win Hon*
2001-02	Elucidation of Intracellular Signal Transduction Mechanisms Controlling the Recruitment and Degranulation of Eosinophils in Allergic Inflammation (MD01351) ✉ LAM Wai Kei Christopher • WONG Chun Kwok

- 1999-00 Development of Plasma DNA-Based Diagnostic Technology (MD99015)  
✉ LO Yuk Ming Dennis • HJELM Nils Magnus# • JOHNSON Philip James (Dept of Clinical Oncology)
- 2001-02 Development of Genomic Strategies for the Non-invasive Detection of Down Syndrome (MD01862)  
✉ LO Yuk Ming Dennis • CHIU Wai Kwun Rossa • LAU Tze Kin (Dept of Obstetrics & Gynaecology)
- 2001-02 Molecular Characterization of Circulating Epstein-Barr Virus DNA in Nasopharyngeal Carcinoma Patients (MD00534)  
✉ LO Yuk Ming Dennis • CHAN Anthony Tak Cheung (Dept of Clinical Oncology)
- 2000-01 Enhanced Expression of a Novel Gene BRE That May Modulate Steroid Metabolism in Adrenal Gland and Testis (MD00669)
- ✉ PANESAR Nirmal Singh • CHAN John Y H\*
- 2001-02 Is Thyrotoxic Periodic Paralysis Resulted from a Calcium Ion Channelopathy? (MD01035)  
✉ TANG Leung Sang Nelson • CHOW Chun Chung Francis (Dept of Medicine & Therapeutics) • COCKRAM Clive Stewart (Dept of Medicine & Therapeutics) • YAO Xiaoqiang (Dept of Physiology)
- 2001-02 Elucidation of Nitric Oxide Mediated Mechanisms Controlling the Recruitment of Eosinophils in Allergic Inflammation (MD01925)  
✉ WONG Chun Kwok • LAM Wai Kei Christopher • LEUNG Ting Fan (Dept of Paediatrics)

## RESEARCH PROJECTS

### A Randomized Phase II Study of Concurrent Cisplatin-radiotherapy with or without Neoadjuvant Chemotherapy Using Taxotere and Cisplatin in Advanced Nasopharyngeal Carcinoma

✉ CHAN Anthony Tak Cheung • MOK Shu Kam Tony • LEUNG Sing Fai • TEO Peter\* • HUI Edwin P\* • LAM Kwok C\* • KAM K Michael\* • CHIU K W\* • KWAN Wing H\*

☐ 1 September 2002

❖ Aventis Pharma Limited (Aventis-HK)

This study has the following objectives:

*Primary objective:* To assess and compare the toxicities of patients with advanced NPC treated with concurrent cisplatin-RT with or without neoadjuvant and taxotere and cisplatin.

*Secondary objectives:*

- (1) To assess and compare the tumor control and survival.
- (2) To compare the quality of life of patients between two arms.

(MD02726)

### Studies on Markers of Tumor Hypoxia in Nasopharyngeal Carcinoma

✉ CHAN Anthony Tak Cheung • HARRIS Adrian L\* • HUANG POON Wai Sin Dolly (Hong Kong Cancer Institute) • HUI Pun • POON Chuen Wai • TO Ka Fai (Dept of Anatomical & Cellular Pathology)

☐ 1 November 2002

❖ Research Grants Council (Earmarked Grants)

Nasopharyngeal carcinoma (NPC) is a major public health problem in Hong Kong. Despite a high initial local control rate in locoregionally advanced disease, the rate of distant metastasis is high after radiotherapy. Patients with distant metastases have a median survival of around 12 months and new therapeutic strategies are therefore needed. Tumor hypoxia is known as a major cause of failure of radiotherapy. HIF-1 and CA9 are molecular markers of hypoxia that have recently been shown to be independent prognostic markers in a number of human cancers. Preliminary study by our team demonstrated expression of CA9 in 60% of the PNC biopsy tissues from our local Chinese population. This study aims to establish the expression pattern of several molecular markers of hypoxia including HIF-1 and CA9 and their clinical significance in NPC. By characterizing the hypoxia gene regulation pathways in NPC cell lines and xenografts and understanding their relationship with tumor behaviour, an experimental animal model suitable for future testing of hypoxia targeting therapy will be developed. Ultimately the overall treatment outcome of NPC patients may be improved by combing hypoxia targeting therapy with radiotherapy and/or chemotherapy.

(CU02093)

### A Phase I Dose Escalation Study to Evaluate the Safety of T138067-sodium Administrated Weekly in Patients with Advanced Refractory Cancer

✉ LEUNG Wai Tong Thomas • MOK Shu Kam Tony

☐ 1 August 2002

❖ Tularik Inc.

Hepatocellular carcinoma is a relatively chemotherapy resistant tumor. Research in new

drug discovery is important to change the dismal outlook of this common cancer. T-138067 is a novel anti-tuberlin which has been showed to have activity in hepatoma cell lines, as well as in early phase I clinical trial in hepatocellular carcinoma. However, the dose and schedule of this new compound in patients are still investigational. In this study, we will primarily entering patients with hepatocellular carcinoma and aim at finding the optimal dose of T-138067 for a weekly schedule. Secondary end point will be tumor response, tolerability and survival of patients.

(MD02346)

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**A Phase 2/3, Open Label, Multicenter, Randomized, Controlled, Study of Doxorubicin Hydrochloride Adsorbed to Magnetic Targeted Carriers (MTC-DOX) Administrated by Intrahepatic Delivery (via Hepatic Artery Catheterization) versus Intravenous Doxorubicin for Treatment of Patients with Unresectable Hepatocellular Carcinom**

✉ LEUNG Wai Tong Thomas • YU Simon\* • LEE Conrad\*

□ 1 August 2002

❖ FeRx Incorporated

Hepatocellular carcinoma (hepatoma) is a common disease. Most patients present at late stage and the tumor is not resectable. Currently, there is a lack of effective treatment for unresectable hepatoma. Doxorubicin is a moderately active agent in treatment of hepatoma. A new technology of delivering doxorubicin intra-arterially has been developed by FeRx incorporation of the USA which can enhance the activity of doxorubicin through a magnetic targeted carrier. This clinical trial will address the issue whether the new technology is effective and

better than conventional chemotherapy.

(MD02408)

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**A Randomized Placebo Controlled Study of OSI-774 (Tarceva) Plus Gemcitabine in Patients with Locally Advanced, Unresectable or Metastatic Pancreatic Cancer**

✉ LEUNG Wai Tong Thomas • MOK Shu Kam Tony • LAM K C\*

□ 1 August 2002

❖ OSI Pharmaceuticals, Inc.

Unresectable or metastatic pancreatic cancer is seldom curable and prognosis dismal. Gemcitabine chemotherapy is effective in palliation of symptoms but tumor response rate is still low. OSI-774 is a new epidermal growth factor inhibitor recently developed by OSI pharmaceutical for cancer therapy. This is a multi-national multi-center study looking at survival as end point whether the addition of OSI-774 to gemcitabine has additional benefit than gemcitabine alone. The trial will be conducted as a prospective randomized placebo control study. Likely outcome is improvement in treatment of unresectable or metastatic carcinoma of pancreas.

(MD02745)

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**A Phase II Study of the Efficacy and Safety of Irinotecan (Campto®) in Combination with Capecitabine (Xeloda®) as First-line Chemotherapy in Asian Subjects with Inoperable Hepatocellular Carcinoma**

✉ LEUNG Wai Tong Thomas • MOK Shu Kam Tony • CHAN Lam\*

□ 1 August 2002

❖ Aventis Pharma Limited (Aventis-HK)



Hepatocellular carcinoma (HCC) is a common disease in Asia. Most patients present at advanced stage and the disease beyond cure. Systemic chemotherapy for HCC has not been successful in the past because of primary resistance of the cancer. The drugs irinotecan and capecitabine are recently developed in the treatment of gastrointestinal cancers and they are promising agents. Irinotecan is a semisynthetic water-soluble anticancer agent derived from the plant alkaloid, camptothecin which inhibits are nuclear enzyme topoisomerase I, leading the lethal accumulation single-strand DNA breaks in the cell. Capecitabine is a fluoropyrimidine carbamate with antineoplastic activity and orally active in colorectal cancer. In the present study, combination of the 2 new agents are used the first time in HCC and aiming at documentation of response rate and side effects of treatment. The likely outcome of the study is an effective combination therapy for HCC and improve outlook of this aggressive illness.

(MD02970)

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#### **Determination of CYP3A4 Activity in Hepatocellular Carcinoma Tissues**

✍ LEUNG Wai Tong Thomas • LAU Wan Yee Joseph (Dept of Surgery) • WHITNEY Bruce Montfort (Hong Kong Cancer Institute)# • LAI Bo San Paul (Dept of Surgery) • LINEMEYER David L\* • BULLOUGH David\*

☐ 1 September 2002

❖ Metabasis Therapeutics, Inc.

Hepatocellular carcinoma (HCC) is a common disease. Systemic therapy is indicated for most advanced stage disease. However, there is a lack of effective drug for HCC. Recently, a new approach using prodrugs that are specifically activated by liver cells is developed and has the potential of a

completely new concept of drug treatment for HCC. This is a new strategy to deliver drugs specifically to tissues or cells that express the cytochrome P450 subtype CYP3A4. This has been called the “HepDirect” approach since CYP3A4 is most highly expressed in the liver. Consequently, HepDirect prodrugs are activated predominantly in the liver to provide high levels of active drug to this tissue, while minimizing delivery to other tissues or cells. The HepDirect approach can be applied to oncolytics for the treatment of HCC because HCC tissue has been reported to retain CYP3A4 activity in 40-70% of cases and at levels that are 25-40% of those in normal liver. This proposed study will evaluate whether a novel prodrug of a known oncolytic agent can deliver increased levels of the cytotoxic metabolite to the liver. The results of the proposed studies have the potential to identify a new class of drug candidate for the treatment of HCC.

(MD02593)

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#### **Identification of Changes in Protein Expression Patterns in Nasopharyngeal Carcinoma in Response to Anti-Epidermal Growth Factor Drug Cetuzimab (C225)**

✍ MA Buig Yue Brigitte • POON Chuen Wai • LO Kwok Wai (Dept of Anatomical & Cellular Pathology) • PANG Ting Kai Ronald • HUANG POON Wai Sin Dolly (Hong Kong Cancer Institute) • CHAN Anthony Tak Cheung

☐ 1 March 2003

❖ CUHK Research Committee Funding (Direct Grants)

Nasopharyngeal carcinoma (NPC) is a major public health problem in Hong Kong. Despite a high initial local control rate in locoregionally advanced disease, the rate of distant metastasis is high after

radiotherapy. Patients with distant metastases have a median survival of around 12 months and new therapeutic strategies are therefore needed. Studies on other tumour types expressing epidermal growth factor receptor (EGFR) indicate that monoclonal anti-EGFR antibody can inhibit cell proliferation, increase radiosensitivity, and enhance the anti-tumour effect of cytotoxic drugs. Recently C225, a human-mouse chimeric monoclonal anti-EGFR antibody, derived from mouse monoclonal anti-EGFR M225 has become available as an anti-tumour drug. Our pilot immunohistochemical study showed that EGFR was weakly, moderately, and strongly expressed in 9%, 36% and 49% of NPC cases respectively. Our recent *in vitro* experiments have demonstrated that anti-EGFR antibodies, M225 and C225 can inhibit the cell growth of NPC cell lines, which express EGFR. C225 is thus a potentially useful drug for NPC treatment. However, mechanism of how C225 kills the NPC cells is unknown. In this proposed study, using a proteomic analysis approach we plan to identify the changes in the protein expression patterns in three NPC cell lines before and after treatment of C225. The results of this proposed study should provide us invaluable information for understanding the functional mechanism of C225, and lay the foundation for future studies. Ultimately, elucidation of the functional mechanism of C225 can provide the basis for deciding the patient selection criteria for anti-EGFR antibody treatment in NPC.

(MD02776)

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**An Open-label, Multicentre, Randomised, Phase III Study Comparing Oral Topotecan/Cisplatin versus Etoposide/Cisplatin as Treatment for Chemotherapy-naïve Patients with Extensive Disease-small Cell Lung Cancer**

✍ MOK Shu Kam Tony • WONG Tze Ming

□ 3 November 2001

❖ GlaxoSmithKline

This study has the following objectives:

- (1) to evaluate the response rate in relapsed patients with small cell lung cancer treated with topotecan;
- (2) to evaluate the response duration, time to progression, time to response and survival in patients with small cell lung cancer
- (3) to evaluate the qualitative and quantitative toxicities of topotecan; and
- (4) to evaluate the effect on quality of life.

(MD01605)

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**A Cell Line Study on Cytotoxicity of Combination of Iressa (ZD 1839) and Chinese Herbal Extract**

✍ MOK Shu Kam Tony

□ 16 October 2002

❖ AstraZeneca UK Limited

This study has the following objectives:

Chinese herbal medicine (CHM) is currently, de facto, an integral part of the health care system in Hong Kong and China. Its popularity has spread to many Western countries including Europe and United States. With the deregulation by the Dietary Supplement Health and Education Act of 1994 United States has become one of the largest consumer markets for herbal medicine.

Iressa, an effective tyrosine kinase inhibitor for patients with advanced NSCLC, is expected to be approved in the near future. Being an oral agent associated with only mild toxicity, many patients who would have otherwise forfeit aggressive cytotoxic therapy may want to try the drug. And it is not

uncommon that the same group of patient will consume CHM concurrently.

Our center is conducting a double-blind placebo controlled randomized trail on the use of CHM in treatment of advanced NSCLC. All enrolled patients are to be assessed by a licensed CHM practitioner before an independent research assistant randomizes the patient to either an active treatment arm (CHM in granule, as per prescription by the CHM practitioner) or a placebo arm (nonspecific herb in granule). For such we have over 250 types of herbal granule in stock.

In this project, we plan to perform cell line study of Iressa plus a panel of commonly used herbs for NSCLC. The choice of the herbs will be obtained from the data-base of the clinical project. Comparison of the LTD on cell line will be made between Iressa and Iressa plus a herbal extract.

(MD02959)

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**Kinetic of Plasma HBV-DNA Following Transarterial Chemo-embolization: a Potential Tumor Marker for HCC**

✉ MOK Shu Kam Tony • ZHONG Sheng# • LEUNG Wai Tong Thomas • LEE Conrad\*

☐ 1 January 2003

❖ CUHK Research Committee Funding (Direct Grants)

*Objective:* To explore the kinetics of hepatitis B virus (HBV) DNA in the plasma following transarterial chemo-embolisation (TACE) of unresectable hepatocellular carcinoma (HCC). *Background:* 70% of HCC cases in Hong Kong are associated with chronic HBV infection. Almost all these tumours harbour the HBV genome, and the HBV DNA is localised specifically in liver and in tumour tissues. TACE has been shown to be an effective treatment

for HCC causing significant tumour necrosis.

*Hypothesis:* We hypothesize that following successful cytolytic treatment of the tumour, HBV DNA will be released into the blood stream as the cell are being killed, and that the absolute amount of the HBV DNA found in the plasma should be proportional to the number of cells killed.

*Methodology:* To study the kinetics the HBV-DNA in the plasma following TACE, we will analyse serial plasma samples taken from the subjects before, during and after the procedure. By using the quantitative real-time polymerase chain reaction (PCR) technique, we will quantify the amount of HBV DNA in each serial sample. We then plan to correlate the pattern of plasma HBV-DNA kinetics to objective radiological tumour response by CT scan and serological response by alpha-fetoprotein (AFP). Upon completion of this project we would be able to establish the feasibility of using HBV DNA as an indicator of tumour response.

(MD02993)

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**A Phase 2/3, Multicenter, Randomized, Controlled, Open Label Study of Intravenous T138067-sodium versus Intravenous Doxorubicin in Subjects with Chemotherapy-Naïve, Unresectable Hepatocellular Carcinoma**

✉ MOK Shu Kam Tony • MA Buig Yue Brigitte • ZEE Chung Ying Benny

☐ 15 May 2003

❖ Tularik Inc.

Hepatocellular carcinoma (HCC), or primary liver cancer, is a common cancer in Hong Kong as well as other Asian countries. Most patients presented in advanced stage and are not suitable for surgical resection. Systemic chemotherapy has not been successful because of resistance of HCC to most

cytotoxic agents. T138067 is a new drug that is able to bind irreversibly and specifically to beta-tubulin which is a key molecule in cellular structure and cell division. T138067 has finished phase I and II studies and were found to be well tolerated and gave objective tumor response in earlier studies. This is a clinical trial to test whether a new drug, T138067-sodium, is more effective than conventional chemotherapy. Patients with unresectable HCC are suitable to be enrolled into the study. It is a multicenter, randomized controlled study. Patients will be randomly assigned to either conventional single agent doxorubicin therapy as controlled or treatment with T138067. All the study subjects will be observed for the endpoints of tumor response and survival.

(MD02843)

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**Investigation of the Role of Mutants of Hepatitis B Virus X Protein on Pathogenesis of Hepatitis B Virus-associated Liver Cancer**

✉ POON Chuen Wai • WONG Nathalie • MOK Shu Kam Tony • JOHNSON Philip James

☐ 1 January 2003

❖ CUHK Research Committee Funding (Direct Grants)

Hepatocellular carcinoma, HCC, is a highly malignant tumour that is very prevalent in China, including Hong Kong. The main etiological factor is chronic infection with the HBV. Although it has been suggested that X protein of HBV (HBx) is involved in the pathogenesis of HCC, the molecular mechanism remains unknown. Studies have shown that mutations frequently occur in the HBx DNA in the chronic HBV carriers (> 40%) and HCC patients (> 90%). In our recent pilot study, similar hot spot mutations (1653 C to T, 1762 A to T, 1764 G to A)

have been found in our local chronic HBV carriers (90%) and HCC patients (70%), and such mutations resulted in amino acid substitutions in the HBx protein. Other studies have shown that naturally occurring HBx mutants found in HCC patients have functional properties that differ from wild-type HBx. Because proteins are the biomolecules performing biological processes, we propose, in this study, to investigate the effect of wide-type HBx and HBx mutants on changes in the protein expression profile in HepG2 cells, a hepatoma cell line. In this proposed study, we will construct expression vectors containing wild-type HBx and mutant HBx genes. The cell line will be permanently transfected with the control/various HBx vectors. Proteins will be extracted from each transfected cell lines, and separated by two-dimensional polyacrylamide gel electrophoresis. The gel images will be compared to identify the proteins that are up-regulated or down-regulated caused by expression of wild-type HBx or mutant HBx. The corresponding protein spots on the gel will be excised, and identified by the tryptic peptide fingerprinting method. The outcome of this proposed study will lead to the discovery of proteins that are potentially involved in the carcinogenesis of HBV-associated liver cancer.

(MD02544)

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**Characterizing Drug Resistance Pattern in Doxorubicin Insensitive Hepatocellular Carcinoma**

✉ WONG Nathalie • JOHNSON Philip James • LAI Bo San Paul (Dept of Surgery) • ZEE Chung Ying Benny

☐ 1 October 2002

❖ Research Grants Council (Earmarked Grants)

Hepatocellular Carcinoma (HCC) is a highly malignant tumor that is prevalent in China including Hong Kong. More than 80% of the patients present at an inoperable advanced stage and the majority has a dismal prognosis. Doxorubicin and analogues are widely used first-line chemotherapeutic agents for the inoperable HCC patients in Hong Kong. However the understanding of genetic events underlying tumor sensitivity and resistance to this chemotherapeutic agent is largely unclear. The aim of this work is to systematically investigate the HCC genome for target genes that may be associated with doxorubicin insensitivity. Cancer cell lines represent invaluable *in vitro* models in drug studies. Whilst there are limited numbers of HCC cell lines available commercially, we have successfully established 15 cell lines from the tumorous liver tissues of patients who underwent curative liver surgery for HCC at the Prince of Wales Hospital, Hong Kong. These cell lines, together with those accessible commercially, represent a repertoire of *in vitro* systems that would enable molecular profiling of genetic changes associated with drug resistance. We propose to narrow down the target regions, at the genomic level, by Spectral Karyotyping (SKY), conventional Comparative Genomic Hybridization (CGH) and array-based CGH. At the expression level, we propose to assess gene expression profiles by the high-density cDNA microarray technology. Our underlying hypotheses are that [1] insensitivity to doxorubicin chemotherapy in inoperable HCC is associated with intrinsic genetic alterations of the tumor, [2] identification of such molecular targets can predict patient response, and provide basis for future development of chemotherapeutic agents.

(CU02097)

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**Characterization of Common Chromosome 19 Aberrations in Hepatocellular Carcinoma**

- ✉ WONG Nathalie • CHAN Yuen Yee
- 1 October 2002
- ❖ CUHK Research Committee Funding (Direct Grants)

Hepatocellular carcinoma (HCC) is a highly malignant tumor that is prevalent in China, including Hong Kong, and Southeast Asia. It carries a high mortality rate and an overall dismal clinical outcome. Surgical resection of the tumor offers the only hope of long-term survival for patients. However by the time of clinical presentation, more than 80% of the patients are at a late stage of the disease. The frequent presence of intra-hepatic metastasis has rendered most tumors inoperable, and consequently only a minority of patients is often considered for curative surgery (10-15% of patients). Using Spectral Karyotyping (SKY) analysis, our group was the first to describe on rearrangement hotspots in HCC. As a continuation and extension to our published work, we have performed SKY analysis on HCC cases that were associated with multi-centricity and in solitary. We found a significantly higher incidence of chromosome 19 deletions in cases associated with multi-centricity than solitude tumors. Frequent loss of heterozygosity on chromosome 19 has recently been described in ovarian, pancreatic and breast cancers. Functional importance of genes residing on chromosome 19 in cell proliferation, motility and apoptosis was also further implicated. The role of chromosome 19 aberrations in the development of HCC has not been previously described. In this study, we therefore propose to define deletion hotspots of common chromosome 19 abnormalities found in multicentric HCC by microsatellite analysis. Our study will form the basis for future investigations for target genes that may be involved in the intra-hepatic metastasis

frequently presented in HCC.  
(MD02999)

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**Hepatocellular Carcinoma Research Group:  
Clinical Applications of Functional Genomics**

✉ WONG Nathalie • LAI Bo San Paul (Dept of Surgery) • POON Y C Randy\* • MOK Shu Kam Tony • LO Yuk Ming Dennis (Dept of Chemical Pathology) • TO Ka Fai (Dept of Anatomical & Cellular Pathology) • LIEW Choong Tsek (Dept of Anatomical & Cellular Pathology) • POON Chuen Wai • JOHNSON Philip J\*

□ 1 April 2003

❖ RGC Central Allocation • Supplementary Funding for RGC Central Allocation

Hepatocellular carcinoma (HCC) is a highly malignant tumor that is prevalent in China, including Hong Kong, and Southeast Asia. It carries a high mortality rate and an overall dismal clinical outcome. While prognosis of early HCC is favorable with surgical resection, most tumors are asymptomatic during the natural course of the disease. This has rendered most patients not being diagnosed in time for curative surgery, and consequently only a minority of patients is often considered operable (10-15% of patients). Most centers, including ours, have therefore adopted screening programs for the high-risk patients i.e. chronic hepatitis B carriers with underlying liver cirrhosis. However, the efficacy of current screening regime has not been able to reduce mortality from HCC. The current paucity on information related to the stepwise progression of HCC from its histological precursor, liver cirrhosis, has prompted the organization of our present investigative team. The proposed Hepatocellular Carcinoma Research Group will comprise researchers

with clinical and basic expertise from two academic institutes. The specific aims of our research will be to focus on understanding the molecular basis underlying the pathologic pathways that promoted HCC development from cirrhosis, and to develop diagnostic approaches for the early detection of HCC in high-risk patients. To achieve these goals, basic scientists will study the global expression patterns and proteome levels in the preneoplastic cirrhotic lesions and tumorous tissues of HCC provided by the clinicians. The state-of-the-art technologies of expression array and proteomics will be employed in these studies. Immunoassays on plasma & sera, and quantitative molecular techniques, will be applied to determine the efficacy of targeted biomarkers for prediction of HCC. HCC cell lines, established from within our team, will be used in functional studies to determine the oncogenic or tumor suppressive role of identified target genes. The close collaboration between the clinicians and scientists in this project is expected to foster a network where the usefulness of new biomarkers can be evaluated as clinical tests. Besides screening for patients with early HCC, specific intervention strategies can also be devised in future upon the biochemical changes recognized from this research.  
(MD02380)

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**A Randomised Three-arm Multi-centre Comparison of 1 Year and 2 Years of Herceptin® versus no Herceptin® in Women with HER2-positive Primary Breast Cancer Who Have Completed Adjuvant Chemotherapy**

✉ YEO Winnie

□ 1 October 2002

❖ Roche Hong Kong Limited

(1) To compare disease-free survival (DFS) in

patients with HER2 overexpressing breast cancer who have been randomised to Herceptin for one year versus no Herceptin;

- (2) To compare DFS in patients with HER2 overexpressing breast cancer who have been randomized to Herceptin for two years versus no Herceptin;
- (3) To compare overall survival (OS) in patients randomized to i) Herceptin for one year or no further therapy and to ii) Herceptin for two years or no further therapy;
- (4) To compare relapse-free survival (RFS);
- (5) To compare distant disease-free survival (DDFS);
- (6) To evaluate the safety and tolerability of Herceptin;
- (7) To compare the incidence of cardiac dysfunction in patients treated and not treated with Herceptin;
- (8) To compare outcomes (DFS, OS, RFS, DDFS, cardiac safety, overall safety) of patients treated with Herceptin for one years compared with Herceptin for two years.

(MD02457)

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**A Randomized, Double-blind, Parallel-Group Study Conducted Under In-house Blinding Conditions to Determine the Efficacy and Tolerability of Aprepitant for the Prevention of Chemotherapy-induced Nausea and Vomiting Associated with Moderately Emetogenic Chemotherapy**

✉ YEO Winnie • POON Annette\* • LAU S M June\*

☐ 23 November 2002

❖ Merck Sharp & Dohme (Asia) Ltd

A Randomized, double-blind, parallel-group study

conducted under blinding conditions to determine the efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy [doxorubicin-cyclophosphamide] in breast cancer patients.

(MD02388)

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**Genetic and Epigenetic Study of RASSF1A Gene in Hepatocellular Carcinoma**

✉ YEO Winnie • JOHNSON Philip James • ZHONG Sheng#

☐ 1 December 2002

❖ Research Grants Council (Earmarked Grants)

Hepatocellular carcinoma (HCC) is one the commonest cause of cancer morbidity and mortality in this geographical region. It is a highly aggressive tumour with only 10% of the patients being candidates for curative surgery. For the remaining 90%, the outlook is poor with a median survival of only 8 weeks. This is mainly due to advanced disease stage at presentation, with extensive local disease and/or systemic metastasis. Screening may permit early detection of HCC in high-risk populations, but proof that it decreases disease specific mortality is still lacking. More sensitive predictors of HCC development are needed. The RASSF1A gene is located in chromosome 3p21.3 and has been suggested to be a tumor suppressor gene. Inactivation of RASSF1A may involve gene mutation, inactivation of its promoter by hypermethylation and loss of allele of chromosome 3p21. Early results from recent studies in lung and breast cancers have demonstrated that promoter hypermethylation in RASSF1A and this is probably associated with the reported concomitant loss of the other allele at chromosome 3p21. The latter has not been reported

in HCC. However, our preliminary study on HCC cell lines and 10 HCC tissue samples have detected 2 or more copies of aberrant methylation in the promoter region of RASSF1A.  
(CU02098)

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**Please refer to previous issues of this publication for more details of the following ongoing research at the department:**

Edition      Title/Investigators

2000-01      Biweekly      Irinotecan (CPT-11), 5-Fluorouracil (5-FU) and Folinic Acid (FA) in Unresectable Liver Metastases from Colorectal Cancer: A Phase II Study (MD20018)

✉ CHAN Anthony Tak Cheung • MOK Shu Kam Tony • LEUNG Wai Tong Thomas • YEO Winnie • JOHNSON Philip James • LAI Bo San Paul (Dept of Surgery) • CHUI Ka Keung Albert (Dept of Surgery) • LAU Wan Yee Joseph (Dept of Surgery) • HUI Edwin P\*

2000-01      A Multi-national, Multi-Centre, Open-label Study to Evaluate the Efficacy of Cetuximab in Combination with Carboplatin in Patients with Recurrent or Metastatic Nasopharyngeal Carcinoma (NPC) (MD00719)

✉ CHAN Anthony Tak Cheung • MOK Shu Kam Tony • YEO Winnie • LEUNG Wai Tong Thomas • JOHNSON Philip James • LEE Chi Yan Conrad

2000-01      A Randomized, Open-label, Multicenter Phase III Study of 5-Fu/Leucovorin with or without Concomitant SU5416 in Patients with Metastatic Colorectal Cancer (MD20065)

✉ CHAN Anthony Tak Cheung • MOK Shu Kam Tony • YEO Winnie • LEUNG Wai Tong Thomas • JOHNSON Philip James • HO Wing Ming

2001-02      Studies on Anti-tumour Effect of M225, a Monoclonal Anti-epidermal Growth Factor Receptor Antibody, on Nasopharyngeal Carcinoma (MD01039)

✉ CHAN Anthony Tak Cheung • JOHNSON Philip James • POON Chuen Wai • TO Ka Fai (Dept of Anatomical & Cellular Pathology)

2000-01      A Phase III Randomized Trial Comparing Efficacy of Non-adherent Dressing Versus Gentian Violet for Treatment of Radiation-induced Moist Desquamation Wounds in Patients with Nasopharyngeal Carcinoma (BL20009)

✉ JOHNSON Philip James • MOLASIOTIS Alexandros (The Nethersole School of Nursing)# • ZEE Chung Ying Benny • MAK So Shan\* • CHAN Eunice\*

2001-02      Development and Application of a Novel Real Time PCR Assay for the Quantitation of HBV-DNA (MD01561)

✉ JOHNSON Philip James • ZHONG Sheng#



- 2000-01 Phase III Randomized Multicenter Comparatives Study of Peginterferon alpha2a vs. Roferon-A for the Treatment of Patients with Recently Diagnosed Chronic Phase Chronic Myelogenous Leukemia (CML) not Previously Treated with Interferon (MD20042)  
 ✍ LEI Ieng Kit Kenny • LEUNG Wai Tong Thomas • HUI Pun
- 2000-01 Randomized, Double-blind, Placebo-controlled Trial of Primary Prophylaxis with Recombinant Human Thrombopoietin (rhTPO) Administered to Patients Receiving DHAP Chemotherapy for Recurrent or Refractory Intermediate-grade or High-grade non-Burkitt's, non-Hodgkin's Lymphoma (NHL) (MD20067)  
 ✍ LEI Ieng Kit Kenny • LEUNG Wai Tong Thomas • HUI Pun
- 2001-02 Impact on Salivary Gland Function by Intensity-modulated Radiation Therapy in Treatment of Nasopharynx Cancer: A Prospective Randomised Trial (MD01041)  
 ✍ LEUNG Sing Fai • CHEUNG Kin Yin • KAM Koon Ming Michael • TEO Man Lung Peter
- 2000-01 A Phase I/II Open Label Study of T138067-sodium in Patients with Advanced Surgically Unresectable Hepatocellular Carcinoma (MD20061)  
 ✍ LEUNG Wai Tong Thomas • MOK Shu Kam Tony • JOHNSON Philip James
- 2001-02 Randomized, Double Blind, Controlled Trial Comparing Two Intravenous Doses of Recombinant Human Thrombopoietin (rhTPO) vs Placebo for the Reduction of the Need for Platelet Transfusions Following Myelosuppressive Chemotherapy in Adult Patients with Solid Tumor or Lymphoma (MD01656)  
 ✍ LEUNG Wai Tong Thomas • LEI Ieng Kit Kenny • HUI Pun
- 2000-01 A Double-blind Placebo-control Randomized Study of the Efficacy of Chinese Herbal Medicine in Reduction of Cytotoxic Chemotherapy-induced Toxicity (CU00109)  
 ✍ MOK Shu Kam Tony • JOHNSON Philip James • YEO Winnie • ZEE Chung Ying Benny
- 2000-01 Phase I/II Study of a Paented Labyrinthin Peptide Base Vaccine in Patients with Advance Stage Labyrinthin Expressing Cancer (MD20064)  
 ✍ MOK Shu Kam Tony
- 2001-02 A Double-blind Placebo Controlled Randomized Study on the Use of Chinese Herbal Medicine in Treatment of Advanced Non-small Cell Lung Cancer (MD01043)  
 ✍ MOK Shu Kam Tony • JOHNSON Philip James • ZEE Chung Ying Benny
- 2001-02 A Phase II Study of Sequential Administration of Irinotecan and Cisplatin Combination Followed by

- Docetaxel in Treatment of Advanced Non-small Cell Lung Cancer (MD01922)  
 ✉ MOK Shu Kam Tony
- 2001-02 A Randomized, Double-blinded, Placebo Controlled, Multicenter, Phase III Study of Tarceva Plus Chemotherapy (Cisplatin and Gemcitabine) Versus Chemotherapy Alone in Patients with Advanced (Stage IIIB or IV) Non-small Cell Lung Cancer (NSCLC) Who Have Not Received Prior Chemotherapy. (MD01660)  
 ✉ MOK Shu Kam Tony • HO Pui Ching# • WONG Tze Ming • LAM Kwok Chi
- 2001-02 Phase II Trial of Gemcitabine-carboplatin-paclitaxel as Neo-adjuvant Chemotherapy for Operable Non-small Cell Lung Cancer (MD01571)  
 ✉ MOK Shu Kam Tony • WONG Tze Ming • LAM Kwok Chi
- 2000-01 Adenocarcinoma of the Lung in Hong Kong Chinese Females: A Genome Investigation for Underlying Genetic Alterations (CU00112)  
 ✉ WONG Nathalie • TSAO Ming Sound\* • YIM Ping Chuen Anthony (Dept of Surgery)
- 2001-02 Chromosomal Aberrations in Hepatocellular Carcinoma: A Comprehensive Elucidation by Spectral Karyotyping and Comparative Genomic Hybridisation (MD01044)
- ✉ WONG Nathalie • LAI Bo San Paul (Dept of Surgery) • LEUNG Wai Tong Thomas
- 2001-02 Investigation for Candidate Genes Expression of 1q21-q25 in Hepatocellular Carcinoma (MD01498)  
 ✉ WONG Nathalie • LAI Bo San Paul (Dept of Surgery)
- 1997-98 High Dose Adjuvant Chemotherapy and Peripheral Stem Cell Transplant for High Risk Breast Cancer Patients (MD95266)  
 ✉ YEO Winnie • KWAN Wing Hong • TEO Man Lung Peter • LEUNG Wai Tong Thomas • SUEN Wang Ming Michael (Dept of Anatomical & Cellular Pathology) • KING Wing Keung Walter (Dept of Surgery)
- 1997-98 Randomized Trial of Tamoxifen versus Placebo for the Treatment of Inoperable Hepatocellular Carcinoma (MD97169)  
 ✉ YEO Winnie • JOHNSON Philip James • LEUNG Wai Tong Thomas
- 2000-01 Lamivudine for Prevention of HBV Reactivation in HBsAg Seropositive Patients Undergoing Cytotoxic Chemotherapy (MD20031)  
 ✉ YEO Winnie • JOHNSON Philip James • ZEE Chung Ying Benny • HO Wing Ming • HUI Pun • LEUNG Wai Tong Thomas • MOK Shu Kam Tony • LEI Ieng Kit Kenny • CHAN Anthony Tak Cheung • ZHONG Sheng# • CHAN

- Kay Sheung Paul (Dept of Microbiology)
- 2000-01 A Phase I/II Study of Weekly Paclitaxel, UFT and Leucovorin in Patients with Metastatic Breast Cancer (MD00480)  
 ✍ YEO Winnie • MOK Shu Kam Tony • CHAN Anthony Tak Cheung • LAM Kwok Chi
- 2000-01 Randomised Double-blind Trial in Postmenopausal Women with Primary Breast Cancer Who Have Received Adjuvant Tamoxifen for 2-3 Years, Comparing Subsequent Adjuvant Exemestane Treatment with Further Tamoxifen (MD00331)  
 ✍ YEO Winnie
- 2001-02 Detection of Mitochondrial DNA Mutation in Tumour and Peripheral Blood (Cell-free) of Patients with Hepatocellular Carcinoma (MD01045)  
 ✍ YEO Winnie • JOHNSON Philip James • ZHONG Sheng#
- 2001-02 A Multicenter Phase III Randomized Trial Comparing Docetaxel in Combination with Doxorubicin and Cyslophosphamide (TAC) versus Doxorubicin and Cyclophosphamide Followed by Docetaxel (AC → T) as Adjuvant Treatment of Operable Breast cancer HER2 neu Negative Patients with Positive Axillary Lymph Nodes (MD01478)  
 ✍ YEO Winnie
- 2001-02 Open-label, Multicenter, Randomized, Controlled Study of IM or Oral Exemestane (Aromasin<sup>R</sup>) in Postmenopausal Women with Advanced Breast Cancer (ABC) Having Progressed on Tamoxifen (MD01739)  
 ✍ YEO Winnie • HO Wing M\* • KWAN Wing H\*

## RESEARCH PROJECTS

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### **A Study of the Prevalence of Subclinical Atherosclerosis and the Associated Risk Factors in Early Postmenopausal Chinese Women in Hong Kong**

✉ HO CHAN Suzanne • WOO Kam Sang (Dept of Medicine & Therapeutics) • WOO Jean (Dept of Medicine & Therapeutics) • CHAN Sieu Gaen • HO Sin Yee Stella (Dept of Diagnostic Radiology & Organ Imaging) • LAM Wai Kei Christopher (Dept of Chemical Pathology) • AHUJA Anil Tejbhan (Dept of Diagnostic Radiology & Organ Imaging)

☐ 1 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

Cardiovascular disease is being viewed as an emerging epidemic in developing countries, including Asia. Though premenopausal women have lower risk of cardiovascular disease compared with men, the risk difference narrows with increasing age. The onset of menopause usually indicates a transition from a low to a higher risk for CVD with increases in levels of CVD risk factors.

Atherosclerosis is a disease of the intimal layer of large and medium-sized arteries, and develops silently over a period of time before manifestations of cardiovascular disease occur. Carotid intima-media thickness (IMT) serves as a marker of subclinical atherosclerosis, and can be assessed non-invasively with B-mode ultrasound.

This proposed study is designed to determine the prevalence of subclinical atherosclerosis (SA), as measured by carotid IMT, and the risk factors for SA

in early postmenopausal women. 220 women aged 50 to 64 and within the first 10 years of natural menopause will be randomly selected from the community-based population. Traditional risk factors (i.e. smoking, elevated cholesterol, blood pressure), other emerging risk factors (i.e. central obesity, fibrinogen status, lipoproteins, homocysteine, glucose intolerance, psychological stress) and potential protective factors that may be of special relevance in this population (e.g. dietary phytoestrogens intake) in terms of developing subclinical atherosclerosis will be evaluated.

(MD02374)

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### **A Study of Informal Caregivers and Association of Caregiving Status with Health and Quality of Life**

✉ HO CHAN Suzanne • WOO Jean (Dept of Medicine & Therapeutics) • LAU Tak Fai Joseph (Centre For Epidemiology & Biostatistics) • CHAN C M Alfred\*

☐ 2 January 2003

❖ Health Care & Promotion Fund, Hospital Authority

*Objectives:* The study aims to determine the proportion and describe the profile of informal caregivers in the adult population aged 35 years and above, to assess the type and the extent of care provided to the elderly care recipients and the caregiver strain experienced. A more in-depth interview of the primary informal caregivers will compare their health status and health-related quality of life with the noncaregivers.

*Design:* This is a cross-sectional study. Data collection on informal caregivers profile will be conducted through telephone interview of 1400 households with elderly persons, and 1,000

households without elderly persons contacted through random telephone dialing. A comparative study of health and quality of life of 240 primary informal caregivers and 480 age and sex matched-caregivers will also be conducted.

*Main outcome measures:* The outcome will be the proportion of informal caregivers among persons aged 35 years and above, frequency and intensity of assistance provided to the care recipients in activities of daily living and instrumental activities of daily living; and caregiver strain experienced. The association of primary caregiving and non-caregiving status with physical, mental health and quality of life will also be examined.

*Results:* This study will describe the proportion and profile of informal caregivers in the adult population aged 35 years and above, the type and extent of caregiving provided to the care recipients, and caregiver burden experienced. This study will also attempt to investigate the association of caregiving status with health and quality of life.

*Conclusions:* This will be the first population-based study of informal caregivers in Hong Kong. The results will provide basic information on the profile of informal caregivers as well as the possible impact of caregiving on their health and quality of life. The study result will form the basis of the Phase II Intervention study on the effects of caregiver support on health and health-related quality of life of informal caregivers.

(MD02923)

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**A Multicenter, Double-blind, Randomized, Placebocontrolled Study to Evaluate the Safety and Efficacy of Zoledronic Acid in the Treatment of Osteoporosis in Postmenopausal Women Taking Calcium and Vitamin D**

✉ LAU Edith Ming Chu • WOO Jean (Dept of Medicine & Therapeutics) • LEUNG Ping Chung (Dept of Orthopaedics & Traumatology) • CHOY Tak Kee Dicky (HK JCC for Osteoporosis Care and Control) • WONG Yeung Shan Samuel

□ 1 July 2002

❖ Novartis Pharmaceuticals (HK) Ltd

This is a prospective, randomized, double-blind study of a novel drug for treating osteoporosis. A total of 7400 patients will be recruited worldwide and 150 to 200 patients will be recruited locally in Hong Kong. The study duration is 4 years in total.

(MD02839)

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**The Prevalence of Vertebral Deformity in Asian Men and Women**

✉ LAU Edith Ming Chu • WONG Yeung Shan Samuel

□ 1 August 2002

❖ Pfizer Pharmaceuticals Inc

The objectives of the study was to conduct a multi-center study on the following aspects of vertebral fracture in Asian men and women:

- (1) Prevalence of subjects with one or more vertebral fracture.
- (2) Risk factors for severe vertebral fracture ( $\geq 3$  vertebral bodies or more), and mild vertebral fracture ( $\leq 2$  vertebral bodies or more).
- (3) Bone mineral density at the hip for subjects with severe vertebral fracture, and mild vertebral fracture, as compared with controls.

The study will be carried out in 3 or more ethnic groups in Asia (e.g. Thai, Malays, Philipinos, Chinese).

Random or cluster samples of community-dwelling men and women (6 years and older) will be recruited, the following measurements will be made:- Diagnosis of vertebral fracture – The radiology and digitization protocols developed by Black et al and Lau et al will be used. Measurements of risk factors – A standard, structured questionnaire will be administered by trained research nurses who will not know the fracture status of the subjects at the time of the interview. Statistical methods – The prevalence of men and women with 3 or more vertebral fractures, and 2 or 1, vertebral fracture will be calculated. The odds ratio and 95% CI for risk factors will be calculated (using subjects with 3 or more vertebral fracture, or 2 or less vertebral fracture, as cases respectively, and the rest as controls). The BMD and body composition between subjects with vertebral fracture and controls will be compared by the t-test.

(MD02449)

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**Improving the Services Standard of Rehabilitation Personnel**

✍ LEE Albert • TSANG Kwong Ka • CHENG YAM Fung Khing Frances

☐ 1 January 2003

❖ Social Welfare Department, HKSAR Government

The programme is aimed to improve the standard of services provided by rehabilitation personnel. It is also aimed to improve the quality of care for chronic illness patient and enhance the concept of care in the community.

(MD02556)

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**North District Health Promoting School Program (NDHPSP) Student Health Survey**

✍ LEE Albert • HO Man (Centre for Health Ed. & Health Promotion) • NG Pui Yue Phoebe (Centre for Health Ed. & Health Promotion) • CHENG YAM Fung Khing Frances

☐ 2 January 2003

❖ North District Hospital

To conduct a student health survey in 10 participating schools of North District Health Promoting School Program. The questionnaire covered the following areas: socio-demographic data, family relationship, perception of health and academic performance, oral health, personal safety, food/nutrition, body weight, physical activity, violence-related behaviours, mental health, smoking, alcohol drinking, drugs and sexual behaviours.

*Target group:* Primary Four students and Secondary One students (7 Primary schools and 3 Secondary schools).

(MD02997)

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**In-service Teacher Development Courses on Moral and Civic Education for Principals and Teachers of Primary and Secondary Schools for the 2002-2004 School Years (Category: Health/Drug Education)**

✍ LEE Albert • CHENG YAM Fung Khing Frances

☐ 1 March 2003

❖ Curriculum Development Institute, Education and Manpower Bureau

To provide a series of In-service Teacher Development Courses on Moral and Civic Education for Principals and Teachers of Primary and Secondary Schools for the school year 2002-2004.

The series of training courses, health/drug education with the aims to enhance principals' and teachers' understanding of the concepts and issues related to the promotion of health/drug education in schools and to enhance teachers' pedagogical skills in teaching related values and attitudes.

(ED02318)

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### Tai Po Safe and Healthy City

✍ LEE Albert • CHENG YAM Fung Khing Frances • FUNG Wing Yan (Centre for Health Ed. & Health Promotion) • SIU Chi Hong (Centre for Health Ed. & Health Promotion)

□ 1 March 2003

❖ Tai Po District Council

*Objective:* To explore community safety and health problems and recommend any feasible solution via data collection, data analysis and survey study.

*Study Design:* A cross-sectional study.

*Methods:* Residents living in Tai Po will be randomly sampled. Household survey will be conducted in order to understand residents' Quality of Life.

*Result:* The data collected in the study will provide a baseline data prior to develop relevant health promotion policies and campaign in the community. In addition, it will also serve as a programme evaluation tool for the Safe and Health project

(MD02304)

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### Tsuen Wan Youth Health-related Behaviors Survey

✍ LEE Albert • CHENG YAM Fung Khing Frances • SIU Chi Hong (Centre for Health Ed. & Health Promotion) • FUNG Wing Yan (Centre for Health Ed. & Health Promotion)

□ 4 March 2003

❖ Tsuen Wan Healthy Community Steering Committee

The aim of the study is to collect physical, social and psychological data in order to understand individual lifestyle among youth in Tsuen Wan. After the data analysis, it is expected to establish a youth health indexes in Tsuen Wan. It will also act as an outcome measurement tool for the coming local youth health promotion projects.

(MD02312)

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### Development of Health Promoting Schools: Intensive Course for School Teachers

✍ LEE Albert • CHENG YAM Fung Khing Frances • YUEN Suk Kwan (Centre for Health Ed. & Health Promotion) • HO Man (Centre for Health Ed. & Health Promotion) • AU Wing Yan Grace (Centre for Health Ed. & Health Promotion)#

□ 28 June 2003

❖ Education & Manpower Bureau, HKSAR Government

The Centre for Health Education and Health Promotion (CHEP) of the Chinese University of Hong Kong launched the 'Hong Kong Healthy Schools Award' in 2001. The Hong Kong Healthy Schools Award Scheme provides a structured framework for the development as well as a system of monitoring progress and recognition of achievement. CHEP has developed detailed indicators and rating system. CHEP has also developed a practical guide for Health Promoting Schools and published many papers in this area. Through the experience in launching Healthy Schools Award Scheme and academic programmes in Health

Education and Health Promotion, the Centre was commissioned to develop series of three days intensive course to enhance the pedagogical skills in teaching health related topics for teachers and principals. The course can also enable the school principals and teachers to acquire the concepts and practical knowledge about “Health Promoting Schools”.

The course will be under three main areas: school health policy and school environment, school health services, and personal health skills and hygiene. Training in these areas would enable the teachers in helping students to develop a strong commitment to personal hygiene, healthy lifestyles and civic responsibilities to sustain development of a health promoting society. Evaluation and follow up studies will be conducted to explore the how the schools implement the concept of Health Promoting Schools.

(MD02657)

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**Development and Analysis of Primary Care Prescribing Database**

✍ WONG Chi Wai • CHAN Cynthia Shiu Yee

□ 1 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

Prescribing is one of the most important activities by doctors, and one that is often criticised around the world but especially in Hong Kong. Yet we have little knowledge of how much they prescribe, and especially why they prescribe each drug. The primary care prescribing database is a collection of log book data from community doctors, which shows the diagnosis or diagnoses they make and the treatments given for each one. The participating doctors are candidates for the Diploma of Family

Medicine, and those sitting the examination of the HK College of Family Medicine. Collection has been occurring for three years, and each year logbooks from about 100 doctors are added to the database. There is now sufficient data to enable detailed analysis of the most common problems and drugs, and with further addition, there will be enough power to assess less common conditions.

This grant will enable collection, coding and cleaning for a further year of data, and analyses of common respiratory and gastrointestinal disorders. These results will be fed back to doctors in continuing education forums, to improve the pattern of prescribing for patients in Hong Kong.

(MD02322)

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**TROHI Project on Statutory Medical Examination in Occupational Health**

✍ WONG Tze Wai • YU Tak Sun Ignatius • LAM Tai Hing\* • LEUNG Lai Man Raymond\* • LO Wai Kee\*

□ 1 April 2002

❖ Occupational Safety and Health Council Research Grant (Col. w/ HKU)

In this project, we collate information on statutory medical examination from countries in the Asia-Pacific region through members of the TROHI (Towards Regional Occupation Health Initiative – a group headed by Prof. Wai-on Phoon, University of Sydney). The objective is to review and compare the legislative requirements for medical examination of workers in various occupations, the experience shared by these countries and the development of a “best practice” framework for statutory medical examination.

Questions will be used to collect information on statutory medical examination, and the current



legislations governing these examination will be sought and reviewed. Co-investigators in the CUHK are responsible for the development of questionnaires, the collection of information and the review of data.

(MD01678)

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**Air Pollution and Respiratory Diseases in Primary Health Care**

✉ WONG Tze Wai • WUN Yuk Tsan Kyran Patrick# • YU Tak Sun Ignatius • TAM Wai San Wilson

☐ 1 September 2002

❖ CUHK Research Committee Funding (Direct Grants)

We plan to study the relation between air pollutant levels and consultations to general practitioners (GPs) for respiratory diseases in Hong Kong. The research hypothesis is that an increase in the levels of air pollutants is associated with an increase in GP consultations. The study design is a prospective, time series approach. Ten GPs from different districts will be recruited to provide anonymous data on daily consultations including the diagnosis and other personal data (age, sex and district of residence and work). The data, collected over one year (2002), will be analyzed with the concentrations of 4 air pollutants: NO<sub>2</sub>, SO<sub>2</sub>, PM<sub>10</sub> and O<sub>3</sub> that are monitored on a daily basis in air pollutant monitoring stations located in these districts. Seasonal, weather and other cyclical patterns are related to air pollutant levels as well as the variations of GP consultations with time. When these factors are adjusted for, we would identify those respiratory diseases seen in general practice that are associated with air pollution. In addition, we would quantify the risk of air pollution, expressed in terms of a percentage increase

in doctor consultations per unit increase in the concentrations of each air pollutant. This risk estimate is important in the formulation of air quality standards and policies.

(MD01938)

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**Female Lung Cancer and Cooking Practice - A Case-control Study in Hong Kong**

✉ YU Tak Sun Ignatius • CHIU Yuk Lan • TANG Jinling • WONG Tze Wai

☐ 1 October 2002

❖ Research Grants Council (Earmarked Grants)

Hong Kong Chinese females have one of the highest lung cancer incidence rates in the world. Most of the cases could not be attributed to a history of smoking and the prevalence of smoking among females in Hong Kong is much lower than in many other countries where the lung cancer incidence rates are much lower. Various possible risk factors, including the type of fuel used in cooking, passive smoking, incense burning and diet, were studied in Hong Kong some years ago, but none has been conclusively found to be causally related to lung cancer. The reason(s) for high incidence rate for female lung cancer in Hong Kong still remains to be explored.

The present study will investigate whether exposure to fumes emitted from Chinese-style cooking will give rise to an increased risk of lung cancer among Hong Kong Chinese females after taking into full consideration the effects of various potential risk factors – smoking, diet, occupational exposures, radon exposure, etc. We shall study about 300 newly diagnosed female lung cancer cases and about 600 age-matched controls without lung cancer, selected from among hospital patients and the general population. They will receive an in-depth interview

using a standardised questionnaire asking for information on their cooking practices, smoking habits, passive smoking exposures, diet history, occupational history, previous diseases, etc. By comparing the differences in exposures between the cases and controls, we shall be able to show whether exposures to cooking fumes are related to the excess risk of lung cancer among Hong Kong Chinese females.  
(CU02103)

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**Please refer to previous issues of this publication for more details of the following ongoing research at the department:**

Edition      Title/Investigators

2001-02      Randomised Controlled Trial of Doctor Education to Increase Cervical Screening Rates (MD01952)  
 ✍ CHAN Cynthia Shiu Yee •  
 DICKINSON James Arthur# •  
 TANG Jinling • CHIN Robert\* •  
 FABRIZIO Cecilia\*

2000-01      Effects of Phytoestrogens on Calcium Metabolism in Chinese Postmenopausal Women (CU00162)  
 ✍ HO CHAN Suzanne • John J Anderson\* • LEE Simon K. M.\* • WOO Jean (Dept of Medicine & Therapeutics) • YU Jimmy C. (Dept of Chemistry)

2001-02      Development of Food Frequency Questionnaire and Database for Assessing Soy Isoflavones Intake in the Chinese Population (MD01047)

✍ HO CHAN Suzanne • CHEN Zhenyu (Biochemistry) • WOO Jean (Dept of Medicine & Therapeutics)

1998-99      Andec Supplementation Trial – A Randomized Controlled Trial of the Effect of Milk Supplementation on the Rate of Bone Accretion in Chinese Children (Aged 9-10 years) in Hong Kong (MD98087)

✍ LAU Edith Ming Chu • WOO Jean (Dept of Medicine & Therapeutics) • CHENG Chun Yiu Jack (Dept of Orthopaedics & Traumatology) • FOK Tai Fai (Dept of Paediatrics)

2001-02      A Randomized Controlled Trial of the Effect of Milk Supplementation on Bone Density in Women Aged 20-35 Years in Asia (MD01501)

✍ LAU Edith Ming Chu • WOO Jean (Dept of Medicine & Therapeutics) • LEUNG Ping Chung (Dept of Orthopaedics & Traumatology)

2001-02      Postmenopausal Evaluation And Risk Reduction with Lasofoxifene (PEARL) (MD01823)

✍ LAU Edith Ming Chu • WOO Jean (Dept of Medicine & Therapeutics) • LEUNG Ping Chung (Dept of Orthopaedics & Traumatology) • WONG Yeung Shan Samuel

1998-99      “Healthy Schools” and “Healthy Society”: Quality Education for Children and Teachers (MD98068)

✍ LEE Albert • LEE Shiu Hung • TO Cho Yee (Dept of Psychology)

- 2000-01 Comprehensive School Health Education Programme: Implementing the Concept of Health-promoting Schools to Enhance Quality Education (MD20016)  
 ✎ LEE Albert • LEE Shiu Hung • TSANG Kwong Ka • TO Cho Yee (Dept of Psychology)
- 2000-01 New Initiatives for School Based Management to Promote Healthy Educational Environments: The Hong Kong Healthy Schools Award Scheme (MD00896)  
 ✎ LEE Albert • LEE Shiu Hung • TO Cho Yee (Dept of Psychology)
- 2001-02 Testing the Effectiveness of an Intervention Programme in Reducing Non-urgent Utilization of Accident and Emergency Services: Pilot Study to Analyse the Feasibility and Develop the Framework of the Intervention (MD01314)  
 ✎ LEE Albert • CHENG YAM Fung Khing Frances
- 2001-02 Provision of Training Services to Frontline Rehabilitation Personnel for the Mentally Handicapped Persons (MD01916)  
 ✎ LEE Albert • TSANG Kwong Ka • CHENG YAM Fung Khing Frances
- 2001-02 A Study on the Prevalence, Brain Pain Centre Activity, Psychological Stress and Quality of Life of Subjects with the Irritable Bowel Syndrome (IBS) (MD01046)
- ✎ TANG Jinling • CHAN Ka Leung Francis (Dept of Medicine & Therapeutics) • LAU Edith Ming Chu • LEE Albert • LEUNG Chi Ming (Dept of Psychiatry) • SUNG Joseph Jao Yiu (Dept of Medicine & Therapeutics) • CHAN Cynthia Shiu Yee • WU Che Yuen Justin (Dept of Medicine & Therapeutics)
- 2001-02 Human Dioxin Levels in Hong Kong - A Pilot Study (MD01395)  
 ✎ WONG Tze Wai • NELSON Edmund Anthony Severn (Dept of Paediatrics) • HEDLEY Anthony J\* • LAM Tai Hing\* • FIELDING R\* • NGAI C\* • HO P C\*
- 2001-02 Assessment of Toxic Air Pollutant Measurements in Hong Kong (MD01308)  
 ✎ WONG Tze Wai • YU Tak Sun Ignatius
- 2001-02 A Comparative Study of the Effects of Air Pollution on General Practitioner Consultations in Hong Kong and London (MD01592)  
 ✎ WONG Tze Wai
- 1999-00 Lung Cancer Mortality in Relation to Silicosis: A Cohort Study of Hong Kong (CU99328)  
 ✎ YU Tak Sun Ignatius • WONG Tze Wai • CHAN Chi Kuen Alan\* • LEUNG Chi Chiu\* • TAM Cheuk Ming\*

## RESEARCH PROJECTS

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### **Glenoid Bone Loss in Recurrent Shoulder Dislocation: Quantification with Computer Tomography and Magnetic Resonance Arthrography**

✉ ANTONIO Gregory • GRIFFITH James Francis

☐ 1 March 2003

❖ CUHK Research Committee Funding (Direct Grants)

*Object:* Anterior glenoid bone loss is a recently recognized feature of recurrent shoulder dislocation. Presently, no accurate means of quantifying glenoid bone loss pre-operatively is available. The amount of bone loss has an important bearing on the type of surgery performed. If glenoid bone loss is significant, then open surgery with bone grafting, rather than arthroscopic soft-tissue repair, needs to be performed.

We aim to show that CT and MR Imaging could quantify glenoid bone loss pre-operatively, allowing the surgeon better pre-operative planning.

*Methodology:* Five scapular specimens will be imaged with CT and the glenoid bone surface area measured. These computer measurements are compared to the physical dimensions on the specimens to establish precision. Both shoulders of thirty patients with recurrent shoulder dislocation, and ten controls will be scanned with CT and corresponding measurements performed.

MR arthrography will be performed on the same thirty patients for comparable measurements.

*Results:* The results should confirm the finding of glenoid bone loss in recurrent shoulder dislocation already established in arthroscopic literature. The

comparison of both shoulders, and the use of controls, should demonstrate that relative bone loss is quantifiable with CT. Correlation with MR arthrography should show comparable changes.

*Significance of results:* This will be the first documented use of dedicated imaging for assessment of glenoid bone loss in recurrent shoulder dislocation, setting the standard of reference. This information from a non-/ minimally invasive test should: assist pre-operative planning; improve our knowledge on recurrent shoulder dislocation; increase the cost-effectiveness of imaging and surgery.

(MD02513)

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### **Combined Static-dynamic MR Urography for Congenital Urinary Tract Obstruction in Children before and after Corrective Surgery**

✉ CHU Chiu Wing Winnie • YEUNG Chung Kwong (Dept of Surgery)

☐ 1 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

In the children age group, urinary tract obstruction is primarily of congenital origin, that is a condition of impaired urinary drainage, if uncorrected, will limit the ultimate functional potential of the developing kidney.

Currently, magnetic resonance (MR) imaging has been explored as a new alternative method for imaging of urinary tract. The advantage of MR over conventional excretory urography or nuclear medicine diuretic renal scintigraphy is lack of radiation, and the contrast medium used in MR imaging has less toxic and adverse effect as compared with the radiographic contrast used in conventional excretory urography.

The aim of this study is to evaluate the diagnostic value of combined static-dynamic MRU technique in children presented with congenital urinary tract obstruction. Static MR image allows visualization of morphology of renal systems such as duplex kidney, which occasionally present in children presenting with urinary tract obstruction. This information is valuable to the surgeons for surgery planning.

For dynamic part of the study, MR contrast is injected into the patient so that the drainage function of the kidneys can be assessed and the anatomical site of obstruction is delineated by good anatomical resolution of MR images.

The new idea concerning MRU is that both morphological and functional information of the obstructed kidney can be obtained in a single examination. Furthermore, this study allows direct comparison of the renal function and degree of obstruction before and after surgery; therefore the effectiveness of the operation can be objectively evaluated. A decision of re-intervention can also be made earlier, if the post-operative results are not satisfactory.

We foresee that MRU is the art of imaging for future management of children urinary tract obstruction.  
(MD02950)

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**Proton Magnetic Resonance Spectroscopy (<sup>1</sup>H-MRS) for the Investigation of Extracranial Head and Neck Cancers**

✉ KING Ann Dorothy • LAM Sik Lok (Dept of Chemistry) • AHUJA Anil Tejbhan • VAN HASSELT Charles Andrew (Dept of Surgery) • CHAN Bik Wan (Dept of Anatomical & Cellular Pathology) • TSE M K Gary\* • YEUNG Ka Wai David\*

- 1 October 2002
- ❖ CUHK Research Committee Funding (Direct Grants)

Proton magnetic resonance spectroscopy (<sup>1</sup>H-MRS) produces information about cancer metabolism and it has become a widely accepted tool for evaluating brain cancer. However, there has been very little research into the role of <sup>1</sup>H-MRS for investigation of extracranial head and neck cancers. The study will document the MR spectra associated with cancers of the thyroid, salivary glands and lymph nodes (including lymphoma and metastatic lymphadenopathy). This information has the potential to identify metabolic markers that can be used for (1) the diagnosis of cancer (2) prediction of prognosis (3) monitoring response to treatment. Spectroscopic results obtained from three different techniques will be compared to assess the potential applicability of <sup>1</sup>H-MRS in clinical diagnosis and monitoring cancer. <sup>1</sup>H-MRS of the cancer within the patient (*in-vivo* <sup>1</sup>H-MRS) and <sup>1</sup>H-MRS on the cancer specimen after it has been excised at surgery (*S in-vitro* <sup>1</sup>H-MRS) are established techniques. <sup>1</sup>H-MRS of a cancer specimen obtained from the patient by image guided fine needle aspiration (FNA *in-vitro* <sup>1</sup>H-MRS), has not been previously reported. If FNA *in-vitro* <sup>1</sup>H-MRS produces comparative data to the other two <sup>1</sup>H-MRS techniques it would have several major practical advantages. Firstly it is a minor clinical procedure that can be performed without the need to surgically remove the tumour, and secondly it does not require the patient to be present during the long acquisition times it takes to perform *in-vivo* <sup>1</sup>H-MRS. FNA *in-vitro* <sup>1</sup>H-MRS has, therefore, the most potential for widespread clinical application in the diagnosis and monitoring of cancers of the extracranial head and neck.

(MD02539)

**Please refer to previous issues of this publication for more details of the following ongoing research at the department:**

Edition      Title/Investigators

2000-01      Turbo Spectroscopic Imaging Evaluation of Dose-response Relationship in Irradiated Normal Brain Tissue after Arteriovenous Malformation Radiosurgery (CU00104)  
✉ CHAN Yu Leung • CHIU Kwok Wing Samuel (Dept of Clinical Oncology) • LAM Ming Kuen Joseph (Dept of Surgery) • YEUNG Ka Wai David\*

2001-02      Clinical and MRI Evaluation of Skeletal Changes and Growth in Well Chelated

Thalassaemic Patients: Comparison of Oral Chelator with Desferrioxamine (MD01507)

✉ CHAN Yu Leung • CHIK Ki Wai (Dept of Paediatrics) • HA Shau Yin\* • OOI Gaik Cheng\*

2000-01      Are Western Skeletal Age Standards Applicable to Hong Kong Chinese? (MD20014)

✉ GRIFFITH James Francis • CHENG Chun Yiu Jack (Dept of Orthopaedics & Traumatology)

## RESEARCH PROJECTS

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### A Pilot Study of Curcumin for Treating Alzheimer's Disease

✉ BAUM Lawrence William • WOO Jean • KWOK Chi Yui Timothy • LAM Chiu Wa (Dept of Psychiatry) • CHIU Fung Kum Helen (Dept of Psychiatry) • ZEE Chung Ying Benny • CHOW Sing Sum Moses (School of Pharmacy)

☐ 1 June 2003

❖ CUHK Research Committee Funding (Direct Grants)

Alzheimer's disease (AD) is a common and increasing cause of death and disability. There is yet no effective treatment. Drugs to prevent or slow AD are urgently needed. Anti-oxidants, cholesterol-lowering drugs, and anti-inflammatory drugs show some evidence of slowing AD. Because curcumin, a widely used yellow food coloring extracted from the herb *geung wong* (*curcuma longa* root), has anti-oxidant, cholesterol-lowering, and anti-inflammatory effects, it was recently tested in AD animal models. Curcumin reduced amyloid plaque deposits, inflammation, and oxidative damage in brain, and also reduced memory loss. Possible mechanisms include: lowering cholesterol to inhibit amyloid production; reducing inflammation and oxidation to protect neurons; chelating metals to reduce amyloid aggregation; and inhibiting kinases which transduce amyloid toxicity.

The project aims to provide a preliminary assessment of the possible effectiveness of curcumin for treating AD. Pharmacokinetics will be tested first in a small number of normal volunteer subjects to determine optimal doses and methods of administration. A

short-term, dose-finding study then will be conducted with 60 AD patients to assess the uptake and metabolism of curcumin and its effect on biochemical markers of AD. AD patients will be randomized to receive placebo, 1 g/day, or 4 g/day curcumin for one month. Blood samples taken at the beginning and end of the month will be analyzed for levels of isoprostane and amyloid  $\beta$  protein. The dose producing the best effect may be used later in a larger, long-term, double-blind, placebo-controlled study, using rate of decline in cognitive function as the endpoint.

(MD02910)

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### Use of Software for Design of DNazymes

✉ BAUM Lawrence William

☐ 9 June 2003

❖ The University of Utah

Short strands of DNA designed to bind to a particular sequence of RNA (antisense oligonucleotides) can induce its cleavage by cellular enzymes, and thereby reduce expression of a gene or function of a virus. A particular short stretch of DNA can be added to the middle of an antisense oligo to make a DNzyme that directly cuts the target RNA. The project will involve using software to select the most accessible target sites within RNAs for design of DNazymes against viruses and genes for research or treating diseases.

(MD02506)

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### DNazymes against SARS Coronavirus

✉ BAUM Lawrence William

☐ 9 June 2003

- ❖ National Institute of Allergy and Infectious Diseases

The SARS coronavirus uses a single strand of RNA as its genetic material. Short strands of DNA designed to bind to the RNA (antisense oligonucleotides) can induce its cleavage by cellular enzymes. A particular short stretch of DNA can be added to the middle of an antisense oligo to make a DNAzyme that directly cuts the target RNA. The project will involve synthesizing several DNAzymes against SARS and other coronaviruses and testing their anti-viral activity *in vitro*. The synthesis and testing will be done by companies or collaborators, not by the PI.  
(MD02700)

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**Better Health for Better Hong Kong**

- ✉ CHAN Chung Ngor Juliana • KO T C Gary\* • WONG Patrick\* • CHAN Amy\* • CHAN Cecilia\*

□ 1 September 2002

- ❖ Hospital Authority

Chronic diseases such as cancer, diabetes, cardiovascular (heart disease and stroke), renal and respiratory diseases are now the 6 top killing diseases amongst patients under the care of the Hong Kong Hospital Authority. These diseases in turn are due to silent conditions such as high blood glucose, high blood pressure, high blood lipid level and obesity. These risk factors are closely related to unhealthy lifestyle characterized by smoking, excessive alcohol intake, increased psychosocial stress, high fat and low fibre intake and reduced physical activity. Since 2002, Hospital Authority Info-World and work unions have initiated a territory wide health risk screening program. More than 12000 subjects have

undergone this program using simple clinical assessments and measurement of capillary blood glucose and cholesterol levels. In the present project, a random sample of 400-600 subjects from the screening program will undergo detailed assessments on other health risks, lifestyle patterns, mental health as well as full assessments of cardiovascular risks using 75 gram oral glucose tolerance test and urine tests. These comprehensive assessments aim to validate the sensitivity and specificity of the screening program based on simple clinical measurements and capillary blood tests. In addition, 400 subjects will be invited to undergo a second phase study to assess the effect of a 1-month program of lifestyle modification or stress management or a combination of both interventions on these risk factors and lifestyles at baseline, 3 month and 12 months.

(MD02424)

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**Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA)**

- ✉ CHAN Chung Ngor Juliana • SO Wing Yee\* • OSAKI R\* • LAI Christopher\* • MA Ronald\*

□ 1 December 2002

- ❖ Sanofi-Synthelabo Hong Kong Limited

This is a phase III, randomised multicentre 5-year study to examine the effects of combination therapy of CLOPIDEGROL and ASPIRIN versus ASPIRIN alone on the development of cardiovascular mortality and morbidity in high risk subjects for thrombo-embolic diseases. In this study involving more than 15,000 people worldwide, 2000 patients will be recruited from Asia. Our Centre will be contributing 20-50 type 2 diabetic patients with multiple risk factors including nephropathy or clinical



evidence of atherosclerotic diseases (e.g. peripheral vascular disease, increased intima media thickness) to this trial. The results of this study will contribute to our understanding of optimal management for these high risk patients.

(MD02861)

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**A Multicentre, Randomised Study to Examine the Effects of Disease Management on Clinical Outcomes in Type 2 Diabetic Patients with Nephropathy**

✉ CHAN Chung Ngor Juliana • TONG Peter Chun Yip • COCKRAM Clive Stewart • ZHANG Xuejie (Dept of Community and Family Medicine) • LEUNG Y S Wilson\*

□ 1 January 2003

❖ Health Care & Promotion Fund, Hospital Authority

*Hypothesis:* Disease management using a multidisciplinary team to achieve and maintain optimal metabolic and cardiovascular risk factors control in Type 2 diabetic patients with nephropathy reduces the rate of decline of renal function and improves clinical outcomes compared to the usual clinic-based care.

*Study design:* A 2-year multi-centre, randomized study involving 6 public hospitals in Hong Kong

*Methods and subjects:* 240 Type 2 diabetic patients with plasma creatinine values between 150 and 350  $\mu\text{mol/l}$  will be followed by a diabetes team consisting of diabetologists, nurses and pharmacists according to a structured protocol with particular emphasis on periodic monitoring, treating to target and reinforcing patient compliance. The control group will consist of 240 patients receiving the usual clinic-based care

*Clinical endpoints:* The primary endpoint is the rate of decline in renal function expressed as the

regression coefficient of plasma creatinine reciprocal ( $\beta\text{-1/cr}$ ) over a 2-year period. Secondary, endpoints are death and cardiovascular and renal endpoints. Tertiary endpoints include number of hospital admissions, length of hospital stay and attendance at the Accident and Emergency Department. Cost-effectiveness analyses will be performed to examine the additional costs due to staff employment, laboratory tests and drugs required to preserve renal function and improve clinical outcomes in the disease management group compared to patients receiving usual clinic-based care.

(MD02610)

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**A Study on the Viral Kinetics of Different Regimes of Pegylated Interferon and Lamivudine Combination Therapy in HBeAg Positive Chronic Hepatitis B**

✉ CHAN Lik Yuen • SUNG Joseph Jao Yiu • CHAN Ka Leung Francis • LEUNG Wai Yee Nancy\* • HUI Y\*

□ 1 October 2002

❖ Schering-Plough Division of SOL Limited

Our preliminary results of a previous trial have suggested that combination of pegylated interferon and lamivudine is associated with good anti-viral response. The aim of this study is to investigate the best treatment regime of this treatment combination. Sixty chronic hepatitis B patients with positive HBeAg, elevated liver enzymes and detectable HBV DNA will be recruited. Patients will be randomized into 3 groups in 1:1:1 ratio receiving 3 different pegylated interferon- $\alpha\text{1b}$  (peg-intron) and lamivudine combination. Peg-intron will be either 8 weeks before, concomitantly, or 8 weeks after the commencement of lamivudine treatment. All patients will receive 32 weeks of peg-intron and 52

weeks of lamivudine. Liver biopsy will be performed before and after the treatment period, and blood will be checked for liver biochemistry, virology and other laboratory for safety surveillance. All adverse events will be reported to the local ethics committee and the sponsor. All patients will be followed up for 6 months after cessation of treatment. The primary endpoint is to the HBV DNA drop by different regimes as measured by real-time PCR assay.

(MD02499)

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### **Viral Factor of HBeAg Seroconversion in Chronic Hepatitis B**

✉ CHAN Lik Yuen • CHAN Ka Leung Francis • SUNG Joseph Jao Yiu • HUI Y\*

□ 1 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

HBeAg seroconversion to anti-HBe antibodies is often used as a marker of disease remission and response to anti-viral treatment in chronic hepatitis B virus (HBV) infection. Some patients however have disease reactivation after HBeAg seroconversion, either in the natural course of the disease or after cessation of anti-viral therapy. The level of virus and the presence of core promoter and precore HBV mutants that do not produce HBeAg might play a role in disease reactivation after HBeAg seroconversion.

The aim of this study is to investigate whether there is any viral factor(s) that can predict the disease progression after HBeAg seroconversion.

Consecutive HBeAg positive patients followed up in the Hepatitis Clinic with witnessed HBeAg seroconversion are studied. These patients are recruited since 1997 with serial serum samples available. Patients on anti-viral treatment in

ongoing therapeutic trials with documented HBeAg seroconversion are also studied. HBV DNA is measured by quantitative real-time PCR assay (sensitivity 100 viral copies/ml) in serum samples from the time of HBeAg seroconversion to the last follow-up visit. Core promoter and precore mutations are detected by polymerase chain reaction amplification and sequencing. The viral factors of patients who undergo disease remission after HBeAg seroconversion will be compared to those who develop disease reactivation.

The results of this study will have great impact on the understanding of HBeAg seroconversion in chronic HBV infection. This will aid the prediction of disease course after HBeAg seroconversion and the decision of treatment duration among patients who undergo HBeAg seroconversion on anti-viral treatment.

(MD02532)

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### **Salt Sensitivity of Blood Pressure in Chinese: the Role of Neurohormones and Genetic Factors**

✉ CHAN Yan Keung Thomas • CHAN Chung Ngor Juliana • THOMAS Neil G (School of Pharmacy)# • TOMLINSON Brian

□ 1 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

Hypertension and hypertension-related diseases (strokes and congestive heart failure) are increasingly common among Hong Kong Chinese, possibly because of increased salt and other factors. Genetic factors may impair the kidney's ability to excrete a salt load efficiently. This primary 'renal defect' could be related to alteration of the natriuretic systems, such as renal dopamine (DA) and renal kallikrein-kinin systems and/or the antinatriuretic

systems, such as the sympathetic nervous system (SNS). Consequently, these individuals show an increase in blood pressure when their salt intake is increased. Average dietary salt intake in the Hong Kong population increased from the 1980s to 1990s by about 28 mmol/day in men and women. Despite similar prevalence of hypertension (17%) in the local adult population, haemorrhagic strokes are seen 2-3 times more frequently here than in the West, suggesting ethnicity may modify the complications associated with hypertension. Studies of the gene-environmental (genetic factors-salt intake) interaction may lead to rational approaches to the prevention and treatment of hypertension. Salt loading studies in Chinese subjects will help us understand the pathophysiological and genetic basis for salt sensitivity and quantify the value of salt restriction, particularly in those with a genetic risk. Therefore, we shall compare the effects of dietary salt loading on blood pressure, the prevalence of salt sensitivity, renal DA and other neurohormonal activities between subjects with or without a family history of hypertension.

(MD02917)

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**Effects of COX-2 inhibitors on Leukemic Cells**

✉ CHENG Gregory

☐ 9 April 2003

❖ Pharmacia Corporation

*Materials and Methods:* ained from patients with aLeukemic cell line-HL60, K562, U937; bone marrow samples from patients without haematological malignancy; Bone marrow and peripheral blood samples obtcute leukemia., CML in chronic phase and accelerated phase, myelodysplastic syndromes in transformation; The *in vitro* effects of celecoxib on leukemic cells and normal hemopoietic

cells will be studied using the MTT assays and colonies assay

*MTT assay:* Mononuclear cells from normal bone marrow samples, leukemic patients and leukemic cell lines will be plated in 96-well flat – bottem plates at 30000 cells per well in a final volume of 200ul of supplemented RPMI growth medium and the following concentrations of celecoxib, 0ng/ml, 250ng/ml, 500ng/ml, 1000ng/ml, 2000ng/ml for 4, 8 16 and 24 hours. MTT solution will be added at the end of the incubation period. The cytotoxxic effects of celecoxib on adherent and non-adherent cells will be analysed by measuring absorbance at 570nm.

*Colony forming assay:* Mononuclear cells from the above samples will be plated in methycellulose/SCF-GCSF-IL3-RPMI growth medium at 1 million cells per ml and the above concentrations of celecoxib. The plates will be incubated at 37 degreeC, 5% CO2 for 7 days. Colonies (>40 cells) will be enumerated at the end of the incubation period with an inverted microscope.

(MD02613)

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**A Multinational, Randomized, Double-blind, Placebo-controlled, Forced-titration, 2 x 2 Factorial Design Study of the Efficacy and Safety of Long Term Administration of Nateglinide and Valsartan in the Prevention of Diabetes and Cardiovascular Outcomes in Subjects with Impaired Glucose Tolerance (IGT)**

✉ CHOW Chun Chung Francis • COCKRAM Clive Stewart • FUNG Wing Hong • CHAN W\* • CHAN Wing Bun • SO Wing Yee • CHAN N\* • MA R\*

☐ 15 November 2002

❖ Novartis Pharmaceuticals Corporation

In this placebo-controlled trial, the effect of

nateglinide and valsartan on progression to diabetes and prevention of cardiovascular morbidity and mortality events will be assessed in subjects with impaired glucose tolerance at increased risk of a cardiovascular event.

*Primary objectives:*

*Core phase:* To evaluate the effect of long-term administration of nateglinide and valsartan on the progression to diabetes in subjects with impaired glucose tolerance (IGT) at increased risk of a cardiovascular event.

*Extension phase:* To evaluate the effect of long-term administration of nateglinide and valsartan on cardiovascular morbidity and mortality, defined as a composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, revascularization procedure, and hospitalization for congestive heart failure or unstable angina. Data on the components of this composite endpoint will be collected for the entire duration (core and extension) of this trial.

(MD02454)

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**A Six-months, Multi-centre, Open, Randomised, Parallel Safety and Efficacy Comparison of Actrapid® Produced by the Current Process and Human Insulin with the Same Formulation as Actrapid®, Produced by the NN729 Process in Subjects with Type 1 Diabetes on a Basal/Bolus Regimen**

✍ CHOW Chun Chung Francis • OZAKI R\* •  
CHAN Wing Bun\*

☐ 1 May 2003

❖ Novo Nordisk Asia Pacific Pte Ltd

The purpose of this trial is to compare the safety of Actrapid (human soluble insulin) produced by a new method with the currently marketed Actrapid during a

6 months treatment period. Patients selected will be patients suffering from Type 1 diabetes on a basal-bolus treatment regimen. All patients participating will be given NPH insulin (Insulatard®) as basal insulin.

In the period between visit 1 and visit 2, patients' usual diabetes treatment will be given. The patients will be asked to perform 7 blood glucose tests in one single day (a 7 point profile) on a normal day in the week before their next visit to the clinic.

At visit 2 it will be decided by chance whether patients should take:

- (1) The marketed Actrapid *or*
- (2) Actrapid produced by the new method

The patient will continue with the mentioned treatment for 6 months. During this period the patients will be asked to come to the clinic twice; after 3 months and after 6 months.

The patient will be asked to perform 7-point blood glucose profiles on a normal weekday prior to these two visits.

In addition, the following safety checks will be performed: physical examination, examination of the heart function (electrocardiogram), blood pressure, pulse and blood samples will be examined. In addition, the patients will be asked to fill in a diabetes diary prior to each visit. During the trial the patients will be obliged to follow the physician's instructions and report any changes in their medication and health. This trial is planned to include 220 patients from several countries. Recruitment is planned to start in May 2003 and end in June 2003. The duration for each participant will be approximately 6 months from the first to the last visit.

(MD02572)

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**A Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of MK-0767 Added to Metformin in**

**Patients with Inadequately Controlled Type 2 Diabetes Mellitus**

✉ CHOW Chun Chung Francis • CHAN Wing Bun\* • OZAKI R\*

☐ 1 June 2003

❖ Merck & Co., Inc.

This will be a multicenter, double-blind, randomized, placebo-controlled trial of approximately 27 weeks in duration followed by a 2-week, post-study follow-up phone call.

*Screening Phase:* Patients with type 2 diabetes with inadequate glycemic control on maximally effective or tolerated metformin therapy (>1500 mg/day) will be screened at Visit 1/Week -7. If patients are NOT on maximally effective or tolerated doses of metformin at Visit 1/Week -7, then patients may have their dose of metformin up-titrated to protocol-specified doses (Appendix 12). A period of up to 6 weeks between Visit 1/Week -7 and Visit 2/Week -6 is allowed for up-titration. However, patients must be on a stable dose of metformin for at least 2 weeks prior to Visit 2/Week -6.

*Run-In phase:* Patients not on maximally effective or tolerated metformin at Visit 1/Week -7 will have FPG assessed at Visit 2/Week -6. These patients must have FPG  $\geq 140$  mg/dL (7.77 mmol/L) and  $\leq 240$  mg/dL (13.32 mmol/L) at Visit 2/Week -6 in order to continue in the study. Patients who meet inclusion/exclusion criteria may enter the 6-week run-in period at Visit 2/Week -t. At Visit 2/Week -6, patients will have the following performed: (1) receive counseling on diet and exercise; (2) be provided with a glucometer and be trained in performing self blood glucose monitoring (SBGM). Patients will return at Visit 3/Week -2 to have a FPG determination, and will be started on a 2-week, single-blind placebo regimen. Patients may be

randomized at Visit 4/Day 1 if their Visit 3/Week -2 FPG is  $\geq 140$  mg/dL (7.77 mmol/L) and  $\leq 240$  mg/dL (13.32 mmol/L) AND their Visit 3/Week -2 HbA<sub>1c</sub> is  $\geq 7.5\%$  and  $\leq 10.0\%$ .

*Double-Blind Phase:* At Visit 4/Day 1, patients must have a dosing compliance with single-blind placebo of  $\geq 75\%$  to be eligible for randomization. Patients will be randomized in a 1:1:1 ratio to receive either MK-0767 5 mg, MK-0767 3.5 mg, or placebo once daily. Throughout the double-blind treatment period, patients will be discontinued if there is persistent inadequate glycemic control, including significant hypoglycemia (as described above) or hyperglycemia, and at Visit 5/Week 4 and beyond, FPG is  $> 240$  mg/dL (13.32 mmol/L). After randomization, patients will return for clinic visits as follows: Visit 5/Week 4, Visit 6/Week 8, Visit 7/Week 12, Visit 8/Week 16 and Visit 9/Week 20.

(MD02446)

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**A Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of MK-0767 Added to Sulfonylurea in Patients with Inadequately Controlled Type 2 Diabetes Mellitus**

✉ CHOW Chun Chung Francis • CHAN Wing Bun\* • OZAKI R\*

☐ 1 June 2003

❖ Merck & Co., Inc.

This will be a multicenter, double-blind, randomized, placebo-controlled trial of approximately 27 weeks in duration followed by a 2-week post-study follow-up phone call. The study includes the following phases:

*Screening Phase:* Patients with type 2 diabetes with inadequate glycemic control on maximally effective sulfonylurea therapy (i.e.,  $\geq 50\%$  maximally effective

dose/day) will be screened at Visit 1/Week -7. If patients are NOT on maximally effective doses of sulfonylurea at Visit 1/Week -7, then patients may have their dose of sulfonylurea up-titrated to protocol-specified doses. A period of up to 6 weeks between Visit 1/Week -7 and Visit 2/Week -6 is allowed for up-titration. However, patients must be on a stable dose of sulfonylurea for at least 2 weeks prior to Visit 2/Week -6.

*Run-In Phase:* Patients not on maximally sulfonylurea at Visit 1/Week -7 will have FPG assessed at Visit 2/Week -6. These patients must have FPG  $\geq 140$  mg/dL (7.77 mmol/L) and  $\leq 240$  mg/dL (13.32 mmol/L) at Visit 2/Week -6 in order to continue in the study. Patients who meet inclusion/exclusion criteria may enter the 6-week run-in period at Visit 2/Week -6. At Visit 2/Week -6, patients will have the following performed: (1) receive counseling on diet and exercise; (2) be provided with a glucometer and be trained in performing self blood glucose monitoring (SBGM). Patients will return at Visit 3/Week -2 to have a FPG determination, and will be started on a 2-week, single-blind placebo regimen.

*Double-blind Phase:* At Visit 4/Day 1, patients must have a dosing compliance with single-blind placebo of  $\geq 75\%$  to be eligible for randomization. Patients will be randomized in a 1:1:1 ratio to receive either MK-0767 5 mg, MK-0767 3.5 mg, or placebo once daily. Throughout the double-blind treatment period, patients will be discontinued if there is persistent inadequate glycemic control, including significant hypoglycemia or hyperglycemia, and at Visit 5/Week 4 and beyond if FPG is  $>240$  mg/dL (13.32 mmol/L). After randomization, patients will return for clinic visits as follows: Visit 5/Week 4, Visit 6/Week 8, Visit 7/Week 12, Visit 8/Week 16, and Visit 9/Week 20.

(MD02540)

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### Psychosocial Stress and Neurohormonal Regulation in the Pathogenesis of Young Onset Type 2 Diabetes

✉ COCKRAM Clive Stewart • CHAN Chung Ngor Juliana • NG Chor Yin • TONG Peter Chun Yip

□ 1 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

It is now confirmed that visceral fat plays a central role in the development of type 2 diabetes and metabolic syndrome. It has been hypothesized that stress-induced increased cortisol can promote deposition of visceral fat. On the other hand, growth hormone (GH) has potent lipolytic effects so that reduced GH due to ageing or physical inactivity may increase this tendency of developing central adiposity. These visceral adipocytes are particularly responsive to the lipolytic effects of stress-related catecholamines and the consequent increase in free fatty acids can increase insulin resistance through fuel competition resulting in multiple cardiovascular risk factors. In subjects with compromised pancreatic  $\beta$  cell function, either due to genetic, immunological or in utero factors, diabetes may subsequently develop. As part of our ongoing project to examine the interactions between genetic and environmental/lifestyle factors in the pathogenesis of young onset type 2 diabetes in Chinese, we had recruited 200 families of young onset diabetes with 800 first degree relatives. All subjects had detailed documentation of clinical and biochemical characteristics including 75g OGTT with insulin secretory profiling. Of these 800 subjects, 400 were siblings, of whom, 50% had either impaired glucose tolerance or diabetes. The majority of these

young subjects with glucose intolerance had features of the metabolic syndrome characterized by central adiposity. To test our hypothesis regarding the role of pituitary adrenal axis on the development of diabetes and metabolic syndrome, we aim to examine the 9am cortisol, GH and insulin growth factor (IGF1) and IGF-binding protein in the saved serum of these 400 high risk siblings and 200 age and sex-matched control subjects who had normal glucose tolerance and no family history of diabetes. Both univariate and logistic regression analysis will be used to examine the relationships between these hormonal parameters and the phenotypes of these subjects with particular focus on the effect of hypercortisolaemia and reduced GH on central adiposity and associated cardiovascular risk factors.

(MD02517)

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**A Randomized, Placebo-controlled Study of the Effect of Nasal CPAP on 24 Hour Blood Pressure and the Sympathetic Nervous System in Obstructive Sleep Apnoea Syndrome**

- ✉ HUI Shu Cheong David • KO Wai San Fanny\* • FOK Pui Chu Joan\* • CHAN Chio Ho Michael\*
- ☐ 1 October 2002
- ❖ CUHK Research Committee Funding (Direct Grants)

Sleep-disordered breathing (SDB) briefly means cessation of breathing during sleep at least 5 times per hour. SDB affects 9 to 24% of the middle-aged and overall 4% of the middle-aged population suffers from the Obstructive sleep apnoea syndrome (OSA) i.e. SDB with associated daytime sleepiness. Several major epidemiological studies have shown that SDB is not only an independent risk factor for hypertension but it is also strongly associated with heart failure and stroke.

The mechanism for this linkage is not fully determined but surges in sympathetic nerve activity are seen at the end of each apnoeic episode accompanied by large rises in systemic arterial blood pressure (BP). The increased levels of muscle sympathetic nerve activity are diminished by nasal continuous positive airway pressure (CPAP) therapy. Despite robust evidence showing improvement of symptoms, cognitive function and quality of life in patients with OSA treated with nasal CPAP, there are conflicting data whether CPAP can reduce BP in patients with OSA. This randomized placebo controlled study aims to assess (1) the medium term effect of nasal CPAP on 24 hr BP over a period of 3 months and (2) whether the change in BP is related to activity of the sympathetic nervous system.

(MD02413)

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**A Randomized, Double-blind, Placebo-controlled, Parallel Group Trial Assessing the Rate of Decline of Lung Function with Tiotropium 18 mcg Inhalation Capsule Once Daily in Patients with Chronic Obstructive Pulmonary Disease (COPD)**

- ✉ HUI Shu Cheong David • KO Wai San Fanny\* • FOK Pui Chu Joan\* • TONG Mabel\* • CHAN Chio Ho Michael\* • CHAN Pui Shan • HO Wai Mun
- ☐ 1 January 2003
- ❖ Boehringer Ingelheim (Hong Kong) Limited

This is a randomized, double-blind, placebo-controlled, parallel group trial with primary objective to determine whether treatment with tiotropium (18 mcg) inhalation capsule via HandiHaler® reduces the rate of decline of lung function with tiotropium 18 mcg inhalation capsule once daily in patients with chronic obstructive pulmonary disease (COPD). Patients will be

enrolled from over 30 countries, approximately 600 centres to insure that a minimum of 6,000 randomized patients of either sex, 40 years of age or older, with a diagnosis of COPD participate in the study. Patients will be randomized to receive either tiotropium or placebo inhalation powder capsule (18 mcg) via the HandiHaler® device. Patients will be allowed to continue on their current medications with the exception of anticholinergic bronchodilators or combination drugs containing anticholinergic bronchodilators. In the case of life-threatening exacerbations, any and all therapies and interventions deemed medically necessary by the treating physician may be prescribed.

(MD02758)

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**A Comparison of the Effectiveness of Treatment with Symbicort® Turbuhaler® (budesonide/formoterol; 160/4.5 mcg) Single Inhaler Therapy and Seretide Diskus (salmeterol/fluticasone; 50/100, 50/250 or 50/500 mcg) plus Ventoline (salbutamol) as Needed in Steroid-treated Adult and Adolescent Asthmatic Subjects -- A Randomized, Open, Parallel-group, Phase IIIB, Multicentre, 12-month Study**

✉ HUI Shu Cheong David • HO Wai Mun • CHAN Pui Shan • KO Wai San Fanny\* • FOK Pui Chu Joan\* • TONG Mabel\* • CHAN Chio Ho Michael\*

☐ 15 January 2003

❖ AstraZeneca Hong Kong Limited

This is a multi-centre study to be conducted in 10-15 countries and approximately 2200 subjects will be enrolled in order to have approximately 2000 randomized subjects. The primary objective of the study is to compare the effectiveness of treatment with Symbicort Turbuhaler Single Inhaler Therapy

and Seretide Diskus plus Ventoline Diskus (or equivalent) as needed. The secondary objective is safety.

*Study design:* This is a randomized, open, parallel-group, phase IIIB, multicentre, 12-month study comparing the effectiveness of treatment with Symbicort® Turbuhaler® (budesonide/formoterol; 160/4.5 mg) Single Inhaler Therapy (i.e. Symbicort 160/4.5 mg as maintenance plus as needed) and Seretide™ Diskus™ (salmeterol/fluticasone; 50/100, 50/250 or 50/500 mg) as maintenance plus Ventoline™ Diskus (salbutamol) (or equivalent) as needed in steroid-treated adult and adolescent asthmatic subjects.

*Target subject population:* Male or female adults and adolescents with asthma, currently treated with inhaled glucocorticosteroids (GCSs), and with a documented use of medication for relief of asthma symptoms.

*Endpoints:*

*A - Efficacy:*

*Primary:* The primary efficacy endpoint is time to first severe asthma exacerbation.

*Secondary:* The secondary efficacy endpoints are:

- (1) total number of severe asthma exacerbations
- (2) forced expiratory volume in 1 second (FEV1) (pre- and post-bronchodilator)
- (3) Asthma Control Questionnaire (ACQ) score
- (4) use of study medication
- (5) use of other regular asthma treatment

*B - Safety: Health-related quality of life, Health Economics.*

(MD02588)

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**The Role of Methylcobalamin in Early Dementia Patients with Vitamine B12 Deficiency and Hyperhomocysteinaemia?**



✉ KWOK Chi Yui Timothy • LAM Chiu Wa  
(Dept of Psychiatry)

☐ 1 January 2003

❖ Eisai Company Limited

The clinical responses of dementia to vitamin B<sub>12</sub> supplementation in deficient subjects have been disappointing. However prospective studies of correction of vitamin B<sub>12</sub> deficiency did show some cognitive improvement in subjects with early dementia or mild cognitive impairment. The exact mechanism whereby vitamin B<sub>12</sub> deficiency influences brain function is unclear. One possible explanation is it causes hyperhomocysteinaemia which has recently emerged as an important independent risk factor of cerebrovascular disease and Alzheimer's disease. We therefore propose to perform a prospective study to examine the effect of correction of vitamin B<sub>12</sub> deficiency by methylcobalamin on the cognitive function of outpatients with early dementia and hyperhomocysteinaemia.

Consecutive early dementia patients aged 60 years or more, with serum vitamin B<sub>12</sub> level < 200 pmol/l are recruited from geriatric and psychogeriatric outpatient clinics in Prince of Wales Hospital, Shatin and Taipo Nethersole Hospital, Taipo. Fasting blood is taken for plasma homocysteine and Isoprostane level – a marker of lipid peroxidation. Those with plasma homocysteine level greater than 10 umol/l are recruited for therapeutics trial. All subjects are given intramuscular injection of methylcobalamin three times in the first week, then one methylcobalamin tablet three times a day for another 15 weeks. Neuropsychological testing including Mattis Dementia Rating Scale, Category fluency test, Delirium Rating Scale, Neuropsychiatric Inventory and MMSE will be performed at baseline

and at 16 weeks. Blood test will also be repeated at 16 weeks.

(MD02478)

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**A Randomized Controlled Trial of Resistance Exercise in Improving Insulin Sensitivity in Old Age Home Resistant**

✉ KWOK Chi Yui Timothy • CHAN Chung Ngor  
Juliana • WOO Jean • LAU Edith Ming Chu  
(Dept of Community and Family Medicine)

☐ 1 January 2003

❖ CUHK Research Committee Funding (Direct Grants)

*Background:* Insulin insensitivity and diabetes mellitus are common in old age. There is good evidence that aerobic exercise improves insulin insensitivity and can prevent non-insulin dependent diabetes mellitus. Similar data exists for resistance exercise. But there is lack of data in frailer older people who cannot perform high intensity resistance exercise. In these people, low to moderate intensity resistance is more practicable than aerobic exercise. But its impact on insulin sensitivity is uncertain.

*Objective:* To examine the effects of resistance exercise on insulin sensitivity of old age home residents

*Design:* Randomized controlled trial

*Subject:* Old age home residents

*Method:* Ninety residents of three old age homes are randomized into resistance exercise and control groups. The supervised individualized exercise programme comprises of gradually progressive moderate resistance training of major muscles in upper and lower limbs, lasting for one hour, two times a week. Control subjects are asked to continue with habitual physical activity but without resistance exercise. The primary outcome is Insulin

resistance index. The secondary outcomes are muscle strength, serum albumin, fat percentages as estimated by skinfold thicknesses, and corrected arm muscle area. 24 hour food record by direct observation and Baecke activity questionnaire will also be measured. All the measurements are repeated at four months follow-up.

*Data-analysis:* Intention to treat analyses will be used for the outcome variables. Repeated-measures analysis of variance will be used to determine the effects of exercise.

(MD02806)

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**Detection of Aberrantly Methylated DNA in Blood and Feces: A Novel Non-invasive Screening Method for Gastrointestinal Cancer**

✉ LEUNG Wai Keung • TO Ka Fai (Dept of Anatomical & Cellular Pathology) • CHAN Ka Leung Francis • SUNG Joseph Jao Yiu

□ 1 October 2002

❖ Funding from Industrial Sponsors • Innovation and Technology Support Programme, ITF, Innovation & Technology Commission

Colorectal and gastric cancers are among the top three leading cancers globally and yet a non-invasive screening test is unavailable. Both diseases if diagnose early is potentially curable. Recently, there has been an intense interest in the identification of a cost-effective and acceptable screening method for these cancers. Of particular interest is the development of a molecular diagnostic test that is based on the detection of altered DNA in stool and/or blood. In this project, we propose a novel non-invasive approach in the detection of altered DNA in the stool and blood of patients with gastrointestinal cancer. We sort to detect aberrant methylation, a common epigenetic phenomenon

found in many forms of human cancer, in stool and blood DNA. The ultimate goal is to identify a specific panel of aberrant methylation markers that can be used as a non-invasive diagnostic test in the population screening of gastrointestinal cancers.

(MD02474)

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**A Randomized Placebo Controlled Trial of Traditional Chinese Medicine in the Treatment of Irritable Bowel Syndrome**

✉ LEUNG Wai Keung • CHAN Ka Leung Francis • CHE Chun Tao (School of Chinese Medicine) • LIANG Songming (School of Chinese Medicine) • SUNG Joseph Jao Yiu

□ 1 December 2002

❖ Research Grants Council (Earmarked Grants)

Irritable bowel syndrome (IBS) is a common functional disorder of the digestive tract in which there is no reliable effective treatment. Based on our previous epidemiological study, the prevalence of this disease in Hong Kong is comparable to western countries. Despite the benign nature of the diseases, the impact on the patients and their quality of life is substantial. Additionally, the burden on the community, in terms of direct health related cost and indirect cost, is considerable. To date, the outcome of western medicine in treating this condition has been disappointing. Several potential new therapeutic agents had been withdrawn because of serious adverse events. Traditional Chinese medicine (TCM) has been used in the treatment of IBS for centuries but very few studies examined its usefulness scientifically. This study evaluates the efficacy and safety of TCM in the treatment of IBS in a double-blind randomized controlled manner. A standardized formulation packed in capsule form delivered by gastroenterologist will be used in order

to eliminate any potential placebo effect related to the practice of Chinese medicine. The outcome assessment consists of patients' global assessment, individual symptoms and quality of life measures. The ultimate aim is to develop a standardized preparation of Chinese herbal medicine that is effective for IBS.

(CU02116)

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**A Phase II, Randomized, Partially-blinded Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of 12 Weeks of Treatment with Clevudine (10mg, 30mg or 50mg QD) in Patients Infected with Hepatitis B Virus**

✉ LEUNG Wai Yee Nancy • CHAN Lik Yuen

□ 1 September 2002

❖ Triangle Pharmaceuticals, Inc

To evaluate different dosages of antiviral agent, Clevadine, in terms of safety, tolerability and pharmacokinetics and antiviral activity during 12 weeks of therapy and post therapy, follow-up in patients with active viral hepatitis B.

(MD02682)

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**A Phase IIB Extension Study of LdT (Telbivudine), Lamivudine, or LdT plus Lamivudine in Patients with Chronic Hepatitis B Who Have Completed NV-02B-003**

✉ LEUNG Wai Yee Nancy

□ 1 March 2003

❖ Idenix Pharmaceuticals, Inc

Patients who participated in protocol NV02B-003 have now completed / are completing one year therapy. Preliminary data showed good efficacy in

all 5 therapeutic aims. This extended protocol (NV-02B-010) intends to study the efficacy of the 3 therapeutic refiners with better results as shown in fewer analyses.

(MD02492)

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**A Randomized, Double Blind Trial of LdT (Telbivudine), versus Lamivudine in Adults with Compensated Chronic Hepatitis B**

✉ LEUNG Wai Yee Nancy • YIU C H Desmond\*

□ 27 June 2003

❖ Idenix Pharmaceuticals, Inc

Having participated in LdT Phase IIB study, the preliminary results are good (presented in AASID 2002). The Phase III study is a global multicentre study evaluating the efficacy of LdT as compared to lamivudine for 2 years.

(MD02314)

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**Endothelial Dysfunction as an Early Index of Atheromatous Disease in Systemic Lupus Erythematosus and its Association with Markers of Oxidative Stress and Inflammatory Mediators**

✉ LI Kwok Ming Edmund • THOMAS Neil G (School of Pharmacy)# • GRIFFITH James Francis (Dept of Diagnostic Radiology & Organ Imaging) • TOMLINSON Brian • TAM Lai Shan\*

□ 1 January 2003

❖ CUHK Research Committee Funding (Direct Grants)

Systemic lupus erythematosus (SLE) presents with a wide range of clinical manifestations and is a systemic disease involving multiple organs, characterised by autoantibody production. In

Chinese, SLE is 4-5 times more common relative to Caucasian populations. SLE patients with chronic disease have a high burden of cardiovascular disease and as such they are an interesting group in which to study atherogenesis. Although conventional risk factors play an important role in this process, little is known as to the impact of autoantibodies and other inflammatory mediators on endothelial function in lupus. Assessing longitudinal markers may allow detection of those at high risk, will also allow a clearer understanding of the development of accelerated atherogenesis in patients with SLE. Assessment of endothelial function, as a surrogate marker of atheroma, in SLE will enable a better understanding of the earlier stages in the process, rather than observing the end points in patients with vascular events, the survivors of which may not be representative of the group as a whole. Atherosclerosis is a chronic process therefore, longitudinal data, such as those which will be generated by the current study are required. These data from this study will help clarify the pathogenic mechanisms that promote the development of atherosclerosis in this patient group. Understanding such mechanisms is prerequisite to finding the means to reduce the excessive morbidity and mortality resulting from vascular disease in these patients.

This study was originally submitted for Research Grants Council Earmarked Grant Application 2002/2003 and was rated as “fundable but unfunded”. As such we are proposing an abbreviated version of the study, which we feel will answer a number of the study goals and give supporting data for future funding of the original proposal.

(MD02733)

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**A Randomized, Double-blind, Placebo Controlled, Parallel Group Study of the Safety and Efficacy of**

**SB 207266 in Patients with Symptomatic Persistent Atrial Fibrillation**

✉ SANDERSON John Elsby • KUM Chi Chiu Leo  
• MA Wing Yan • CHAN Kit Wan Skiva •  
FUNG Wing Hong\*

□ 1 July 2002

❖ Glaxo Smith Kline

Atrial fibrillation is the most common arrhythmia, and is responsible for substantial morbidity and mortality in the general population. Current therapies are unsatisfactory for a variety of reasons. SB 207266 has specific 5-HT<sub>4</sub> antagonist activity. The 5-HT<sub>4</sub> receptor is located predominantly in atrial tissue and serotonins/5-HT<sub>4</sub> are a potential therapeutic target for atrial fibrillation. The objective of this study is to determine the effect of SB 207266 on preventing recurrence of symptomatic AF in patients with persistent AF.

(MD02464)

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**A Study of Sympathetic Activity and Cardiac Hypertrophy and Dysfunction in Hypertensive Chronic Renal Failure Patients**

✉ SANDERSON John Elsby • WANG Yee Moon  
Angela • METREWELI Constantine (Dept of  
Diagnostic Radiology & Organ Imaging)#

□ 1 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

Increased sympathetic activity is a recognized feature in chronic renal failure and is important in the genesis of hypertension in renal failure patients. Sympathetic overactivity is associated with poor prognosis in heart failure patients. In a pilot study, we demonstrated that hypertensive renal failure

patients had more severe diastolic dysfunction than non-renal failure patients. Whether this is related to greater sympathetic overactivity in chronic renal failure is unknown. Increased sympathetic activity in chronic renal failure may originate from the failing kidneys as bilateral nephrectomies normalize muscles sympathetic nerve activity. Our recent study demonstrated an important cross-sectional relationship between residual kidney function and cardiac hypertrophy in renal failure patients on maintenance dialysis. This raises the possibility that the degree of sympathetic overactivity may be related to the degree of renal impairment and may be at its maximum among patients whose kidneys have completely lost excretory function. Moreover, the degree of sympathetic overactivity may be associated with the severity of cardiac hypertrophy and cardiac dysfunction.

This study therefore aims to test the hypothesis that the degree of sympathetic overactivity is directly proportional to the degree of renal dysfunction and is the highest among anuric patients. Moreover, we hypothesized that the degree of sympathetic overactivity is associated with the severity of cardiac hypertrophy, systolic and diastolic dysfunction in hypertensive chronic renal failure patients.

This study will increase our understanding of the pathogenesis of cardiac hypertrophy in renal failure patients and will have important implications for the management of hypertensive chronic renal failure patients.

(MD02348)

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**Left Ventricular Remodelling Post Myocardial Infarction – The Effect of Infarct Size, Transmural Extent and Treatment with Spironolactone Assessed by Contrast Enhanced MRI**

✉ SANDERSON John Elsby • LAM Wai Man Wynnie (Dept of Diagnostic Radiology & Organ Imaging) • PENNELL Dudley\*

□ 4 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

Left ventricular (LV) remodeling is integral to the development and progression of myocardial dysfunction after myocardial infarction. It is not known how much these changes are dependent of infarct size, its transmural extent and presence of previous infarction. Contrast enhanced cine MRI has the unique ability to accurately measure infarct size, quantify viable but non-functioning myocardium and to accurately measure volumes. We plan to study the impact of these variables on LV remodelling over 1 year post infarction. In addition, spironolactone – an aldosterone antagonist has been proven to have a beneficial effect on heart failure patients and it is known that aldosterone has an important effect on extracellular matrix even in patients on angiotensive converting enzyme inhibitors. It is not known if spironolactone given post MI will benefit or reduce LV remodelling. We propose therefore to conduct a pilot prospective longitudinal study of 30 survivors of an acute myocardial infarction randomised into two groups, one of which will receive a low dose spironolactone daily and the other half will receive standard treatment including ACE inhibitor and beta blocker. MRI will be performed at 1 week and 12 months using an inversion recovery sequence twenty minutes after an intravenous injection of the MRI contrast 0.2mmol/kg Gd-DTPA. This study has the potential for the first time to accurately assess the evolution of an area of myocardial infarction and the surrounding injured tissue, its impact on the global changes of ventricular size and function that determine the

prognosis, and the additional effect of spironolactone on the remodelling process. This information will provide the template for further therapeutic interventional studies.

(MD02960)

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**A Study of the Potential of a Semi-purified Extract from Chinese Medicine *Dagencao* in Stimulating Both Early Angiogenesis and Myogenesis in Infarcted Heart**

✉ SANDERSON John Elsby • LI Ming • LEE Ka Ho Kenneth (Dept of Anatomy)

□ 1 January 2003

❖ CUHK Research Committee Funding (Direct Grants)

Coronary heart disease remains a major cause of morbidity. Apart from prevention most available therapies only relieve symptoms and unfortunately, even with all the recent advances cure is rarely possible. At present blockages in the arteries can only be relieved by surgery or angioplasty. There is no effective medicine that can stimulate the growth of new vessels. Furthermore, after myocardial infarction the myocardium is incapable of regenerating itself to replace the lost muscle cells. A scar forms which causes further deterioration of cardiac function. Therefore, it is clear that alternative revascularization strategies should be sought to relieve ischaemia and stimulate replacement of damaged or lost heart muscle cells.

We identified new compounds purified from *Dagencao* that showed a potent effect on stimulating the early growth of new vessels in skeletal injury animal model. It is possible that these compounds could also stimulate angiogenesis in heart. Therefore, in this proposal, we propose to use the well-established heart infarction animal models in our

laboratory to study the angiogenic effect of these compounds systematically. The underlying scientific basis of the enhanced angiogenesis by these compounds in heart muscle will also be studied by a quantitative study of neo-vascularization, the histological study of infarcted heart muscle healing, the balance and the timing of some inhibitory and mitogenic factors, such as angiostatin, endostatin, VEGF, PDGF, aFGF, bFGF, angiogenin, interleukin-8 and proliferin. In addition we will assess whether the result of angiogenesis will lead to reduced myocyte loss and fibrosis.

(MD02852)

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**A Multicentre Phase III Study of Interferon-beta-1a for the Treatment of Chronic Hepatitis C in Asian Patients**

✉ SUNG Joseph Jao Yiu • CHAN Ka Leung Francis • LEUNG Wai Yee Nancy\* • HUI Y\* • CHAN Lik Yuen

□ 1 October 2002

❖ Serono International SA

Two hundred and fifty chronic hepatitis C patients of Asian origin will be randomized to receive either interferon-beta-1 or placebo. All patients have no exposure to interferon previously. At week 12, the treatments will be unblinded. Patients receiving interferon-beta-1 will receive another 12 week of treatment. HCV RNA will be performed for patients receiving placebo, and placebo nonresponders will be rolled over to receive 24 week of interferon-beta-1 and ribavirin combination treatment starting at week 16. All patients will be observed for 24 weeks after the cessation of treatment. The primary objective is the proportion of patients achieving sustained virological response, which is defined as the absence of HCV RIVA at the end of 24

week treatment and at the end of 24 week observation period.

(MD02926)

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**Acid Suppression by Proton Pump Inhibitor in Peptic Ulcer Bleeding**

✉ SUNG Joseph Jao Yiu • LEUNG Wai Keung • CHAN Ka Leung Francis • WU Che Yuen Justin • LAU Yun Wong James (Dept of Surgery) • CHUNG Sheung Chee Sydney (Dept of Surgery)

□ 1 January 2003

❖ CUHK Research Committee Funding (Direct Grants)

When acid-pepzin injury erodes arteries crossing the ulcer floor, it causes bleeding. Histology of the ulcer base shows blood clot in continuity with eroded vessel wall forming a “plug” on the leak. *In vitro* studies suggested that a non-acidic environment (pH>6) is crucial for platelet aggregation and coagulation. It has never been proven that intra-gastric pH levels correlate with recurrent bleeding in peptic ulcers. We have previously demonstrated that high-dose intravenous infusion of proton pump inhibitor (PPI), as an adjuvant to endoscopic therapy, reduces recurrent bleeding, and the need for second endoscopy and surgery. However, intravenous PPI therapy is expensive and not widely available. Question has been raised whether oral PPI would confer the same benefit. In this proposed double-blinded placebo-controlled study, informed consenting patients with active ulcer bleeding (Forrest I & II) will be randomized to receive oral or intravenous omeprazole after endoscopic therapy. Primary outcome parameters are clinical rebleeding, blood transfusion, surgery and mortality in the 2 treatment groups. Assessors of

recurrent bleeding are blinded to treatment given. Patients will also be monitored for intragastric pH after endoscopy. Clinical rebleeding will be correlated with median intragastric pH, percentage of time in various pH ranges and percentage of time with intragastric pH>6.

(MD02996)

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**Intravenous Pantoloc in Aspirin-induced Ulcer Bleeding**

✉ SUNG Joseph Jao Yiu • WU Che Yuen Justin • CHAN Ka Leung Francis • LEUNG Wai Keung • LEE Yuk Tong • HUNG Cheung Tsui • HUI Aric Josun

□ 10 February 2003

❖ Altana Pharma

Aspirin is an essential drug for the treatment of various medical conditions such as stroke and ischemic heart disease. Unfortunately, a significant proportion of patients taking may suffer from peptic ulcer bleeding, which is the commonest adverse effect of aspirin. Risk of recurrent bleeding are particularly high in the presence of stigmata of recent hemorrhage (SRH), namely adherent clots, non-bleeding visible vessels and active bleeding. Patients with aspirin induced ulcer bleeding must stop taking aspirin because of substantial risk of rebleeding, which may predispose to breakthrough occurrence of stroke and heart attack.

Potent acid suppression to maintain a pH of more than 6 has been shown to promote platelet aggregation and stabilizes blood clots *in vivo*. We have previously demonstrated that high-dose intravenous infusion of proton pump inhibitor (IVPPI), as an adjuvant to endoscopic therapy, reduced recurrent bleeding and the need for second

endoscopy or surgery. However, whether IVPPI can allow these patients to resume aspirin early after ulcer bleeding is still unclear. Due to the potent stabilizing effect on newly formed blood clot, we hypothesize that IVPPI can effectively prevent rebleeding even if aspirin is continued during the initial course of ulcer bleeding.

This is a double-blind, randomized controlled trial in which consecutive patients admitted for high risk aspirin induced peptic ulcer bleeding are recruited and randomly assigned to IV pantoprazole infusion in addition to aspirin or IV pantoprazole plus placebo. The primary outcome measure is rebleeding rate at 30 days. Other outcomes include occurrence of stroke and cardiovascular event, transfusion requirement and mortality.

(MD02933)

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**Efficacy and Tolerability of a Maintenance Treatment over 6 Months with Pantoprazole 20mg o.d. vs. Esomeprazole 20mg o.d. in Patients with Healed GERD**

✉ SUNG Joseph Jao Yiu • WU Che Yuen Justin • LEUNG Wai Keung • CHAN Ka Leung Francis • LEE Yuk Tong • HUNG Cheung Tsui • HUI Aric Josun

□ 1 April 2003

❖ Altana Pharma, Asia

The aim of the study is to investigate the relapse of a maintenance treatment over 6 months as well as the safety of pantoprazole 20mg daily in comparison to esomeprazole 20mg daily in patients who suffered from reflux esophagitis. This study consists of Acute Phase and a Maintenance Phase, in which acute phase involves open-label treatment with pantoprazole 40mg daily for 4-8 weeks. The acute phase is followed by a randomized, double-blinded,

parallel-group comparison of maintenance daily treatment with pantoprazole 20 mg and esomeprazole 20 mg. The treatment endpoints include relapse of erosive esophagitis and symptom.

(MD02874)

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**Molecular Biology of Peritoneal Fibrosis and Peritoneal Dialysis Failure - A Study of Transforming Growth Factor Beta and Its Downstream Mediators by a Cell Culture Model**

✉ SZETO Cheuk Chun • WONG Teresa Y. H.\*

□ 1 September 2002

❖ Research Grants Council (Earmarked Grants)

*Introduction.* Peritoneal dialysis (PD) is the first-line treatment of kidney failure in Hong Kong. Peritoneal fibrosis is the major cause of treatment failure in PD patients. Peritoneal mesothelial cell (PMC) is important in maintaining peritoneal function by regulating inflammation and fibrosis via the production of cytokines. Previous studies found that transforming growth factor (TGF) plays a cardinal role in peritoneal fibrosis, but the underlying mechanism is unknown. *Hypothesis.* TGF acts on PMC via two downstream mediators, namely vascular endothelial growth factor (VEGF) and connective tissue growth factor (CTGF). The selective expression of either mediator is affected by exogenous factors. *Method.* Primary culture of rat PMC is used. Up-regulation of VEGF and CTGF in TGF-stimulated PMC has been documented. Firstly, the mechanisms of this VEGF and CTGF up-regulation will be determined by selective inhibition of the cellular pathways. Secondly, we will evaluate the role of VEGF and CTGF in the mediation of the known TGF effects on PMC. PMC will be cultured with TGF; collagen synthesis, proliferation and apoptosis will be quantified. The



effect of VEGF and CTGF in the above cellular functions will be examined by blocking experiments. Finally, determinants of the relative expression of VEGF and CTGF in TGF-stimulated PMC will be studied by addition of inflammatory or components of conventional PD solution. *Significance.* Identifying the key determinants of peritoneal fibrosis will establish a firm scientific foundation for further development of therapeutic strategies.

(CU02122)

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**Oxidative Stress in Patients with Type 2 Diabetes: Are There Benefits from Antioxidant Supplements?**

✉ TOMLINSON Brian • THOMAS Neil G (School of Pharmacy)# • BENZIE Iris F F\* • LAM Wai Man Wynn (Dept of Diagnostic Radiology & Organ Imaging) • GRIFFITH James Francis (Dept of Diagnostic Radiology & Organ Imaging) • HAINES Christopher John (Dept of Obstetrics & Gynaecology) • LAM Wai Kei Christopher (Dept of Chemical Pathology) • CHAN Chung Ngor Juliana

☐ 1 January 2003

❖ CUHK Research Committee Funding (Direct Grants)

Oxidative stress contributes to the development of atherosclerosis and subsequent vascular disease. Studies have suggested that antioxidants can reduce the risk of vascular disease, but findings remain inconsistent. Type 2 diabetic patients are at high risk of developing vascular disease, particularly when hypertensive, and have increased oxidative stress. Supplementation of Type 2 diabetic patients with vitamins C and E has been reported to improve glycaemic control and delay the onset of complications. Interventional data investigating the

effects of antioxidants on blood pressure are limited, yet blood pressure correlates with certain indices of oxidative stress. As the prevalence of diabetes is increasing rapidly in Hong Kong, primary prevention becomes increasingly important. Antioxidant supplements may be a potentially important and safe method to delay or prevent the development of vascular disease in diabetic patients. In this longitudinal study we propose to increase the understanding of the relationship between antioxidants and vascular disease in a high-risk group of hypertensive diabetics, using a more in depth panel of antioxidant markers and a series of endocrine markers of inflammation and vascular function. We will treat these patients either with vitamin C alone or in combination with vitamin E in a 3 way cross-over study of periods of 3 months randomised, placebo-controlled, double-blinded treatment and will primarily investigate the impact of treatment on blood pressure, and in addition assess glycaemic control and surrogate markers of vascular disease. This increased understanding of the long term role of these antioxidants will help to plan more definitive outcome studies and nutritional strategies to maintain health, to lower the risk or delay the onset of vascular disease, and to promote healthy ageing.

(MD02339)

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**A Prospective Observational Study of Acute Major Organ System Failure in Septic Patients**

✉ TOMLINSON Brian

☐ 1 January 2003

❖ GlaxoSmithKline

This study is a multi-center, international, prospective observational study of hospitalized septic patients. The study will be conducted at approximately 60 centers worldwide. Approximately 1,200 subjects

will be evaluated daily for 28 days or until discharge for occurrence of acute organ system failure, requirement for organ support interventions, hospital length of stay and mortality. Data will be collected from the patients' charts. No study medication will be administered. No protocol-specified laboratory or clinical assessments will be required for the study.

The objectives of the study are:

- (1) describe the occurrence of acute major organ system failures among subjects with sepsis among varying levels of organ system dysfunction at baseline;
- (2) describe the occurrence of acute major organ system failures among subjects with either gram-negative or gram-positive sepsis;
- (3) test for group differences in occurrence of acute major organ system failures among three levels of organ dysfunction at baseline;
- (4) test for group differences in occurrence of acute major organ system failures between gram-positive and gram-negative infections;
- (5) compare the requirement for new organ support interventions between gram-negative and gram-positive subjects, and among varying levels of organ system dysfunction at baseline; and
- (6) explore the significance of baseline physiologic, laboratory and clinical assessments as possible prognostic indications of subsequent major organ system failure.

Clinic charts will be reviewed daily for each enrolled subject. Physiologic, laboratory and clinical parameters associated with sepsis, occurrence of acute major organ system failure and the requirement for organ system support will be monitored through discharge from hospital. No study-specific assessments or procedures will be performed with the exception of a 28-day follow up by telephone call in discharged subjects.

(MD02422)

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### The Participation of the Cytoskeleton in Insulin Action in Human Skeletal Muscle

✉ TONG Peter Chun Yip • COCKRAM Clive Stewart

☐ 1 September 2002

❖ Research Grants Council (Earmarked Grants)

Diabetes mellitus affects up to 10% of our population. Insulin resistance, manifested by a reduction in glucose uptake in skeletal muscle following insulin stimulation is a key feature of the disease. Besides its metabolic effects, insulin induces morphological changes by reorganizing the cytoskeleton. The function of cytoskeleton includes cell motility, vesicle transport, endocytosis and secretion. Our previous work has established the importance of actin microfilaments in modulating insulin action in rat skeletal muscle cells. A functional cytoskeleton is required for propagation of insulin signaling molecules, translocation of glucose transporters to the plasma membrane and consequently glucose uptake following insulin stimulation. Intriguingly, *in vitro* induction of insulin resistance with high glucose and insulin is associated with diminished insulin-mediated cytoskeletal remodeling and glucose uptake.

We propose to investigate the participation of the cytoskeleton in glucose homeostasis and insulin resistance in human skeletal muscle. Primary culture of human skeletal muscle will be developed from muscle biopsies of insulin resistant nondiabetic siblings of Type 2 diabetic subjects and from nondiabetic control individuals. Remodeling of the cytoskeletal proteins, redistribution of insulin signaling molecules as well as glucose transporters following insulin stimulation will be examined by immunofluorescence and laser confocal scanning

microscopy. Perturbation of the cytoskeletal network by chemical agents will be performed to establish the causal relationships between cytoskeletal remodeling and glucose transport in human skeletal muscle cells. If defect in cytoskeletal reorganization is evident in muscle from insulin resistant subjects, it will provide a novel explanation for the development of insulin resistance and progression to diabetes.

(CU02124)

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**A Rapid System for Studying the Translatability of Human IGF-I and IGF-0I Binding Protein-3 Gene in Plants**

✉ TONG Peter Chun Yip • SUN Sai Ming Samuel  
(Dept of Biology)

□ 1 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

Insulin-like growth factor-I (IGF-I) modulates fuel metabolism and participates in the homeostasis of glucose metabolism. Administration of the recombinant IGF-I improves glycemic control and insulin sensitivity in patients with diabetes. The lack of sufficient quantity of IGF-I limits our understanding of the role of IGF-I in the management of diabetes. To increase the yield of IGF-I, we aim to synthesize IGF-I using plant as a bioreactor. In this proposal, we test the feasibility of introducing chimeric gene products of IGF-I and its binding protein-3 into the plant (tobacco and soyabean) using the particle bombardment method. B-glucuronidase fusion gene will be used as a marker to demonstrate the correct usage of codon of the chimeric genes. To confirm the proper translation of the start codon, a frame-shift mutation approach will be employed. The success of translation of the chimeric gene in the

plant system will provide a solid foundation for us to explore the possibility of using plant to manufacture proteins of therapeutic importance.

(MD02308)

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**An Open-label Extension Trial to Access the Safety of Galantaine HBr in the Treatment of Vascular Dementia**

✉ WONG Ka Sing Lawrence • KWOK Chi Yui Timothy • MOK Chung Tong Vincent • HUI Andrew Che Fai • HO W S Wency\*

□ 5 August 2002

❖ Janssen Pharmaceutica, a division of Johnson & Johnson (HK) Ltd.

The safety and tolerability of galantamine (8 or 12 mg twice daily [b.i.d.]) will be evaluated in a 6-month open-label extension trial for subjects with vascular dementia who completed either trial GAL-INT-17 or GAL-INT-26. All subjects will receive galantamine hydrobromide (HBr). All subjects, regardless of previous treatment will have their dose retitrated to 8 or 12 mg b.i.d. Safety will be assessed by adverse event reports, laboratory evaluations, physical examinations, and electrocardiograms (ECGs). Cognitive and functional abilities will be evaluated by means of the Alzheimer's Disease Assessment Scale-Cognitive subscales (ADAS-cog), Neuropsychiatric Inventory (NPI), and Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) Inventory.

(MD02510)

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**An Open-label, Long-term, Flexible-dose Study of Safety, Tolerability, and Therapeutic Response of PNU-95666E in Patients with Parkinson's Disease**

✉ WONG Ka Sing Lawrence • MOK Chung Tong  
Vincent • YEUNG Hon Ming Jonas

□ 1 September 2002

❖ Pharmacia Singapore Pte. Ltd.

This is an open-label flexible-dose, non-randomized, multicentre and multinational study. The treatment consists of up to 11 weeks of escalation, up to 4 years of maintenance and 1-week taper. This study is being conducted to assess the long-term safety tolerability, and therapeutic effect of sumanirole (D2 receptor agonist) in patients with Parkinson's disease who have previously participated in a double-blind sumanirole Parkinson's Disease trial. It aimed to assess the long-term safety and tolerability of the solid oral dosage form of sumanirole given twice daily in involved patients. Moreover, to assess the long-term therapeutic response to sumanirole and whether sumanirole shows an effect on key dimensions of quality of life and healthcare economics in those patients. The primary endpoints are the occurrence of treatment-emergent adverse events rates for postural hypotension, nausea and vomiting, hallucinations and dyskinesias, electrocardiogram (ECG) measurements, laboratory safety variables, the Epworth sleepiness Scale scores and vital signs. Secondary efficacy endpoints that will be examined are the Modified Hoehn and Yahr Scale, the combined sum of UPDRS parts II and III scores, daily levodopa dose, the Goetz Dyskinesia Scale and the Schwab & England Activities of Daily Living Scale. Secondary endpoints pertaining to Quality of Life (QoL) will be evaluated by assessing changes in scores over time as demonstrated by the Functional Status Questionnaire (FSQ), the Parkinson's Disease Questionnaire (PDQ39) and the EuroQoL (EQ). Both summary and domain scores will be reviewed. Healthcare economics endpoints will be assessed through the use of information

contained in the Patient Productivity, Expenditure and Satisfaction Questionnaire (PPESQ). Correlations between these scores and other variables, such as the UPDRS scores, the Hoehn and Yahr score, the Modified Schwab and England score, the Goetz Dyskinesia score and the Epworth Sleepiness Scale may also be assessed.

(MD02481)

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**Genetic Factors in the Etiology of Middle Cerebral Artery Stenosis in Chinese with Diabetes and Hypertension**

✉ WONG Ka Sing Lawrence • THOMAS Neil G  
(School of Pharmacy)# • TOMLINSON Brian •  
KAY Li Chi Richard

□ 1 October 2002

❖ CUHK Research Committee Funding (Direct  
Grants)

Stroke is one of the commonest causes of disability and death worldwide. Despite the advances in the field of molecular biology, the progresses in studying the genetic factors of stroke have been limited. Furthermore, genetic study on Chinese stroke patients has not been published. Stroke is a heterogeneous condition with very different stroke mechanisms: ischemic versus hemorrhagic; cardioembolism versus large artery stenosis versus small artery disease; intracranial versus extracranial stenosis. Therefore, the phenotype of the study population need to be well-characterised. In Chinese, intracranial larger artery stenosis is the commonest vascular lesion identified in stroke patients, while extracranial carotid stenosis is the commonest lesion found in Caucasians. Genetic factors may play an important role in this observed differences. With a previous RGC-supported grant studying the prevalence of asymptomatic middle cerebral artery stenosis in Hong

Kong Chinese, we have identified 100 patients with both hypertension and diabetes. We propose to recruit 200 more to study a total of 300 patients with MCA stenosis. 300 patients with both hypertension and diabetes but without MCA stenosis will be recruited as control. We plan to compare the difference in the prevalence of polymorphism of common genes.

(MD02317)

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**Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA)**

✉ WONG Ka Sing Lawrence • HUI Andrew Che Fai • MOK Chung Tong Vincent • LEUNG Wai Hong Thomas • LIANG K S Eric\* • LI Sin Hung\*

☐ 28 February 2003

❖ Sanofi-Synthelabo Hong Kong Limited

*Study Objectives:* (1). *Primary objective:* to assess whether clopidogrel 75mg daily is superior to placebo in preventing the occurrence of major ischemic complications (stroke, MI, cardiovascular death) in high-risk patients aged 45 years or older, who are receiving background therapy including low-dose aspirin. (2). *Secondary objective:* to evaluate the safety of clopidogrel in this population, and more specifically the incidence of fatal or severe bleeding (including primary intracranial haemorrhage), in order to estimate the global benefit of clopidogrel in this patient population.

*Study Design:* Phase III, multicentre, multinational, randomized, parallel group, double-blind trial of clopidogrel versus placebo, on background therapy including low-dose aspirin.

*Study Population:* (1). *Main selection criteria* – (i) Combination of two major or three minor or one

major and two minor atherothrombotic risk factors: (a) Major atherothrombotic risk factors: [diabetes mellitus nephropathy, ankle-brachial index <0.9, carotid plaque ± stenosis ≥70%] (b) Minor atherothrombotic risk factors [hypertension, primary hypercholesterolemia, current smoker and age ≥ 65 in male and ≥70 in female]. (ii) Documented cerebrovascular disease. (iii) Documented coronary disease. (iv) Documented symptomatic peripheral vascular disease. (2). *Total expected number of patients:* At least 15,200 (7,600 per study group).

*Evaluation Criteria:* (1). *Primary efficacy endpoint:* The first occurrence of any component of the following cluster: (i) non-fatal or fatal myocardial infarction, (ii) or non-fatal or fatal stroke, (iii) or cardiovascular death (as validated by the Clinical Events Adjudication Committee). (2). *Primary safety endpoint:* Fatal or severe bleeding (GUSTO definition), including primary intracranial hemorrhage.

*Assessment schedule:* (1). Clinic visits scheduled at baseline and at 1, 3, 6 months, then every 6 months until study end date for efficacy endpoints and bleeding or adverse events / serious adverse events reporting. (2). Intermediate phone calls scheduled at 9, 15, 21 months, then every 6 months until final visit.

*Duration of Study Period (per subject):* This is an event-driven trial. The estimated study duration that served as the hypothesis for sample size calculations is 42 months, but the final duration per subject will be driven by the total number of primary events. Randomization is initially planned for at least 15,200 patients. However, patient recruitment will continue beyond this number until a total of 1,040 primary events are projected to have occurred at which time a study end date will be defined.

(MD02626)

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**A Pilot Study in the Application of Telemedicine in Community Care of the Elderly**

✉ WOO Jean • KWOK Chi Yui Timothy • LEE Tze Fan Diana (The Nethersole School of Nursing) • ZHANG Xuejie (Dept of Community and Family Medicine)

□ 3 January 2003

❖ S K Yee Medical Foundation

Currently many elderly people with physical or mental impairment live at home, alone or with family members who have difficulty in caring for them. They cannot afford private residential home care and need to wait a few years for government subvented places.

This project seeks to develop a model of care in the community that would improve health care support for this group of elderly, and reduce inappropriate use of acute hospital facilities. To improve holistic health care for frail elderly people living in the community, by developing a new model of care using telemedicine, and at the same time reduce utilization of acute hospital beds and attendances at Accident and Emergency Departments.

(MD02718)

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**Consultancy on Health Care Services in Home and Community Based Model**

✉ WOO Jean • HUI Elsie

□ 1 April 2003

❖ Tung Wah Group of Hospitals

The project will provide expertise guidance and support on health-related issues in our daily operation, such as formulating care plans and dealing with geriatric problems. A nurse with training in community geriatrics, based at Shatin Hospital, will

liaise with our team.

(MD02827)

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**A Novel Homocysteine-lowering Strategy for Atherosclerosis Prevention in China: Diet, Hyperhomocysteinaemia and Atherosclerosis**

✉ WOO Kam Sang

□ 1 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

Atherosclerosis (heart attacks and stroke) is an important medical problem of the 21<sup>st</sup> century, but traditional risk factors, including lipid disorders, could only account for 50% of the problem. In testing our hypothesis of hyperhomocysteinaemia (high homocysteine blood level) contributing to atherogenesis process beyond the lipid effect, we have documented two unique (low blood lipid) and novel clinical models of hyperhomocysteinaemia in Hong Kong (voluntary vegetarian) and in northern rural Chinese (obligatory vegetarian). This project will aim to consolidate our homocysteine hypothesis among bigger vegetarian samples in Hong Kong, and to evaluate the impact of homocysteine-lowering strategies on surrogate markers of early atherosclerosis (vascular reactivity FMD, and inner wall thickness IMT) in both localities. 150 strict vegetarians (vegans) in Hong Kong and 360 rural Shanxi (Yu County) villagers will be recruited. FMD of brachial (arm) artery and carotid (neck artery) IMT will be measured by ultrasonography and compared with normal database (Hong Kong vegans vs normal control southern Chinese; rural northern vs rural southern Chinese). Oral vitamin B-12 (0.5mg/day) supplementation or placebo capsule will be given for 12 weeks to 50 eligible hyperhomocysteinaemic and 50 matched

normohomocysteinaemic vegetarians in Hong Kong, in double-blind randomized cross-over fashion, with 10 weeks' placebo washout before cross-over. In Yu County, vitamin B-12 (0.5mg/day)  $\pm$  folic acid (5mg/day) will be given to 200 hyperhomocysteinaemic villagers, using double-blind placebo-control 2x2 factorial design. In both places, open-label vitamins (folic acid and/or vitamin B-12)  $\pm$  double-blind vitamin C (500mg/day) will be given for 12 more months in the later stage. Ultrasound study and blood tests will be repeated before and after each treatment period, with improvement in brachial FMD and carotid IMT as primary end points and changes in blood homocysteine, folate and vitamin B-12 as secondary endpoints. A successful result of this project will establish a firm scientific foundation to embark on larger interventional trial and eventually the evidence-base, for long-term folic acid supplementation intervention programme for primary and secondary prevention of stroke and coronary events in China.

(MD02967)

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**Epidemiological Study of the Correlation Between the Intima-media Thickness of the Common Carotid Artery and Absolute Cardiovascular Risk**

✉ WOO Kam Sang • CHOOK Ping • KUM Chi Chiu Leo

☐ 1 December 2002

❖ Pfizer Corporation Hong Kong Limited

Carotid intima-media (inner wall) thickening has emerged as a good surrogate marker of subclinical atherosclerosis in western population, but its value in non-western populations remains unproven.

This study will compare the carotid intima-media thickness in different Asian, Latin American and African populations and relate these to traditional

atherosclerotic factors (for assessment of absolute atherosclerosis risk).

96 subjects (48 normal control and 48 subjects with hypertension and high blood-cholesterol) in Hong Kong will be screened and studied. They will be invited to visit the Prince of Wales Hospital once for clinical review of atherosclerosis risk according to Framingham scale assessment, including blood pressure, height and weight measurement, smoking and diabetes status, and blood taking (10ml) for lipid and glucose profiles. Ultrasound scanning (noninvasive) of both carotid artery will be performed, using predetermined uniform methods and intima-media thickness of common carotid artery (IMT) will be measured off-line, using a uniform and validated automatic edge-detecting and measurement computer software. The carotid IMT will be correlated to presence of traditional atherosclerotic risk factors and Framingham scale absolute atherosclerosis risk. A subgroup analysis will be performed on 168 Chinese subjects to be recruited (96 from Hong Kong, 32 from Beijing and 32 from Shanghai).

(MD02798)

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**Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA)**

✉ WOO Kam Sang • SANDERSON John Elsby • YU Cheuk Man • WONG Ka Sing Lawrence • CHAN Chung Ngor Juliana • CHAN W M Wilson\* • TSE Kin Kei Lawrence\* • CHAN Anna\* • YIP Wai Kwok Gabriel\* • WU Eugene Brian\* • WONG John\* • KUM C.C. Leo\* • FUNG W H\* • CHAN C K\* • KWONG Shu Keung\* • CHAN Yau Sung Joseph\* • YU Tak Hung\* • KWOK Hing Yiu\* • YIP W C\*

□ 1 December 2002

❖ Sanofi-Synthelabo Hong Kong Limited

*Study Objectives:* (1) Primary objective: to assess whether clopidogrel 75mg daily is superior to placebo in preventing the occurrence of major ischemic complications (stroke, MI, cardiovascular death) in high-risk patients aged 45 years or older, who are receiving background therapy including low-dose aspirin. (2) Secondary objective: to evaluate the safety of clopidogrel in this population, and more specifically the incidence of fatal or severe bleeding (including primary intracranial haemorrhage), in order to estimate the global benefit of clopidogrel in this patient population.

*Study Design:* Phase III, multicentre, multinational, randomized, parallel group, double-blind trial of clopidogrel versus placebo, on background therapy including low-dose aspirin.

*Study Population:* (1) Main selection criteria – (i) Combination of two major or three minor or one major and two minor atherothrombotic risk factors: (a) Major atherothrombotic risk factors: [diabetes mellitus ± nephropathy, ankle-brachial index <0.9, carotid plaque ± stenosis ≥70%] (b) Minor atherothrombotic risk factors [hypertension, primary hypercholesterolemia, current smoker and age ≥ 65 in male and ≥ 70 in female]. (ii) Documented cerebrovascular disease. (iii) Documented coronary disease. (iv) Documented symptomatic peripheral vascular disease. (2) Total expected number of patients: At least 15,200 (7,600 per study group).  
*Evaluation Criteria:* (1) Primary efficacy endpoint: The first occurrence of any component of the following cluster: (i) non-fatal or fatal myocardial infarction, (ii) or non-fatal or fatal stroke, (iii) or cardiovascular death (as validated by the Clinical Events Adjudication Committee). (2) Primary safety endpoint: Fatal or severe bleeding (GUSTO

definition), including primary intracranial hemorrhage. *Assessment schedule:* (1) Clinic visits scheduled at baseline and at 1, 3, 6, months, then every 6 months until study end date for efficacy endpoints and bleeding or adverse events / serious adverse events reporting. (2) Intermediate phone calls scheduled at 9, 15, 21 months, then every 6 months until final visits.

*Duration of Study Period (per subject):* This is an event-driven trial. The estimated study duration that served as the hypothesis for sample size calculations is 42 months, but the final duration per subject will be driven by the total number of primary events. Randomization is initially planned for at least 15,200 patients. However, patient recruitment will continue beyond this number until a total of 1,040 primary events are projected to have occurred at which time a study end date will be defined.

(MD02828)

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### **Influence of *H. pylori* Infection on Management of Gastroesophageal Reflux Disease in Hong Kong**

✉ WU Che Yuen Justin • SUNG Joseph Jao Yiu •  
CHAN Ka Leung Francis • LEUNG Wai Keung

□ 18 December 2001

❖ Hong Kong Society of Gastroenterology

The aim of this project is to study various effects of *H. pylori* infection in management of GERD in Hong Kong. The project begins with evaluation of the use of reflux symptom analysis as diagnostic tool for GERD in a population with high prevalence of *H. pylori* infection. The second study of the project is evaluation of the role of esophageal motility dysfunction in reflux patients with *H. pylori* infection. And the third study aims to evaluate the changes in oesophageal acid exposure, reflux symptoms and the



severity of esophagitis after eradication of *H. pylori* in patients with GERD.  
(MD01934)

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**Is Visceral Hyperalgesia the Culprit of Noncardiac Chest Pain in Chinese?**

✉ WU Che Yuen Justin • CHAN Ka Leung Francis  
• FUNG Wing Hong • LEUNG Wai Keung •  
MOK Chung Tong Vincent • SUNG Joseph Jao  
Yiu • WONG Ka Sing Lawrence

□ 1 September 2002

❖ Research Grants Council (Earmarked Grants)

Noncardiac chest pain (NCCP) is a common clinical problem worldwide. In Hong Kong, it has been estimated that about 20% of patients with chest pain are misdiagnosed to have coronary heart disease. Despite its benign nature, this condition causes anxiety, impairs quality of life and consumes a substantial amount of healthcare resources. While acid reflux and motility disorder in the esophagus are often attributed as the cause of NCCP, visceral hyperalgesia of esophagus is now recognized to play a central role in the pathogenesis of this condition.  $\gamma$ -Aminobutyric acid (GABA), an inhibitory neurotransmitter, modulates visceral sensation and might be able to alleviate NCCP. This research project aims to evaluate the role of visceral hyperalgesia in Chinese patients with NCCP. In the first study, NCCP patients will be evaluated for the prevalence of gastroesophageal reflux disease and esophageal motility disorder by endoscopy, manometry and pH study. The visceral sensory and pain thresholds of these patients will be compared with asymptomatic controls. In the second study, the effect of baclofen (GABA<sub>B</sub> agonist), diltiazem (muscle relaxant) and placebo will be compared in a double-blinded randomized study for the treatment of

NCCP. Cerebral cortical, brainstem and spinal evoked potentials before and after treatment will be evaluated. Results of this study will shed lights on pathogenesis and treatment of NCCP in Chinese.  
(CU02127)

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**Treatment of Diastolic Heart Failure: The Role of Blockade of the Renin-Angiotensin System. A Comparison of Diuretics with an Angiotensin Converting Enzyme Inhibitor, Angiotensin Receptor Blockade or Diuretics Alone**

✉ YU Cheuk Man • SANDERSON John Elsby

□ 29 April 1999

❖ Sanofi-Synthelabo Hong Kong Limited

This study aims at comparing the relative benefits of 3 classes of drugs for the treatment of diastolic heart failure. They included angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor antagonists (AIIA) and diuretics. We will be recruiting patients that have had symptoms and signs of heart failure with documented evidence of pulmonary congestion on the chest x-ray and a left ventricular ejection fraction >45% on echocardiogram. Patients are randomized to diuretics alone, diuretics plus AIIA, or diuretics plus ACEI. The endpoints include mortality, quality of life score and hospital re-admissions.

The study is still ongoing at the moment.

(MD98666)

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**Assessment of Left Ventricular Remodeling and Myocardial Viability with Echocardiography in Patients after Myocardial Infarction: A Comparative Study with Contrast-enhanced Magnetic Resonance Imaging**

✉ YU Cheuk Man • SANDERSON John Elsby • LAM Wai Man Wynn timer (Dept of Diagnostic Radiology & Organ Imaging) • ZHANG Yan

□ 1 July 2001

❖ Collaboration Project with Dept of Diagnostic Radiology & Organ Imaging, PWH

*Background:*

- (1) Cardiac remodeling after myocardial infarction is an important process that leads to progressive ventricular enlargement and heart failure.
- (2) it is not clear what impact an area of myocardial infarction will have on electro-mechanical synchronicity of the whole ventricle especially early after the infarction.
- (3) if electro-mechanical asynchrony is present it may have an important on left ventricular (LV) systolic and diastolic function, increasing wall stress and hastening the process of adverse remodeling.

*Aims of the study:*

To assess the degree of overall LV synchrony in patients with acute myocardial infarction and to relate this to the size and extent to the infarction measured by MRI.

To determine the physiologic mechanisms underling the long term functional remodeling of infarct and peri-infarct myocardium.

To identify key novel physiologic imaging parameters that may accurate predict cardiac remodeling and potentially guide therapy after myocardial infarction.

(MD01950)

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**The Effect of Angiotensin Receptor Blockade Alone or in Combination with Spironolactone on the Process of Ventricular Remodeling in Chronic Heart Failure**

✉ YU Cheuk Man • SANDERSON John Elsby • CHAN Kin Yin • YEUNG Leata Y.C.\* • WONG John\* • WU Eugene Brian\* • LAM Wai Man Wynn timer (Dept of Diagnostic Radiology & Organ Imaging)

□ 1 October 2001

❖ Takeda Chemical Industries (Taiwan), LTD.

This is a double-blind randomized trial of an angiotensin receptor blocker (ARB) (Candesartan) alone or candesartan with spironolactone 25 mg daily in patients taking an angiotensin converting enzyme inhibitor (ACEI). The aim is to assess the effect of a combination versus candesartan alone on long-term outcome and in particular on the process of ventricular remodeling assessed by magnetic resonance imaging. 50 patients with typical chronic congestive heart failure with left ventricular ejection fraction <40% who have been taking standard therapy with an angiotensin converting enzyme inhibitor for more than 6 months will be recruited. Ejection fraction will be measured by MRI and 2 D echocardiography at baseline, 6 months and 12 months.

This study will provide useful information on the effect of ARB alone or in combination with spiro lactone on the ventricular remodeling process in patients already on long-term ACEI therapy. Since aldosterone is increasingly recognized to be an important factor in determining the outcome in heart failure these results could have significant clinical implications if it is demonstrated that ARB is more effective in combination with spironolactone in reducing ventricular volume. In addition, we will be able to determine the effect of long-term ARB therapy on plasma aldosterone levels in patients already on long-term ACEI therapy.

The study is still ongoing.

(MD01512)

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**Atherosclerotic Plaque Burden Reduction in Native and Intervened Coronary Arteries as Well as in Other Major Arteries by High Dose Atorvastatin Therapy (ANIMATE)**

✉ YU Cheuk Man • CHAN Wai Man Wilson • SANDERSON John Elsby

□ 1 December 2002

❖ Pfizer Corporation Hong Kong Limited

This study is a double blind, randomized, controlled study compared the effect of high dose vs conventional dose statin therapy in the regression of atherosclerotic plaque in the coronary and carotid arteries. It also assess if endothelial function is improved in the high dose arm.

The end points include carotid intimo-medial thickness assessed by B-mode ultrasound, coronary plaque volume assessed by intravascular ultrasound, as well as endothelial function by vascular ultrasound.

The study is still on-going.

(MD02551)

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**A Multi-centre, Multinational, Long-term, Extension Study to Assess the Safety and Tolerant of Subject Optimised Treatment Regimens of Oral Sildenafil for Pulmonary Arterial Hypertension in Subjects Who Have Completed Study A1481140**

✉ YU Cheuk Man • KONG Shun Ling • MA Wing Yan • YIP Wai Kwok Gabriel • WANG Zheng (Dept of Ophthalmology and Visual Sciences)# • WONG Wing Cheong (Dept of Ophthalmology and Visual Sciences) • WONG Tai Hung John • KUM Chi Chiu Leo • LAI Hong Yee Connie\*

□ 1 February 2003

❖ Pfizer Corporation Hong Kong Limited

Pulmonary hypertension can affect all age groups. Many pathologies can cause pulmonary hypertension. Primary pulmonary hypertension is a rare aggressive disease leading to right heart failure and death. The historical survival rate is 29% at 4 years. Transplantation of the lungs or heart and lungs is the treatment of last resort and 40% of patients receiving heart/lung transplant will survive at 5 years post transplant. Orally administered vasodilating drugs are used, however, the response rate (functional capacity) to individual drugs is usually only around 25% and they are not selective for the pulmonary circulation. Prostacyclin has been shown to be efficacious in patients with pulmonary arterial hypertension, but has to be given by continuous infusion through a central line for life. Recently, the endothelin antagonist, bosentan has provided patients with the first oral treatment available for this life threatening disease. However, there are some concerns around the safety profile of this class of compounds, in particular the hepatotoxicity and teratogenicity.

There is a clear need for a more effective oral therapy to increase functional capacity in these subjects. Pre-clinical and early clinical studies indicate that sildenafil is a selective dilator of the pulmonary vessels. This extension to the 12 week placebo controlled study (A1481140) will investigate the long term safety of oral formulation of sildenafil in treating pulmonary hypertension where chronic therapy is needed.

Sildenafil is marketed for male erectile dysfunction (MED). Adverse events experienced with use of sildenafil in MED (with incidence >1%) are:

Cardiovascular: Headache (12.8%), Flushing (10.4%), Dizziness (1.2%)

Digestive: Dyspepsia (4.6%)

Respiratory: Nasal congestion (1.1%)

Special senses: Altered vision (1.9%; mild and transient, predominantly colour tinge to vision, but also increased perception of light or blurred vision)

In fixed dose studies, dyspepsia (12%), and altered vision (11%) were more common at 100mg than at lower doses. In addition, there were reports of muscle aches when sildenafil was administered more frequently than the recommended dosing regimen. In postmarketing surveillance priapism has been reported. Adverse reactions were mild to moderate in nature and the incidence and severity increased with dose.

(MD02489)

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**A Multinational, Multi-centre, Randomised, Double-blind, Double-dummy, Placebo-controlled study to Assess the Efficacy and Safety of 20, 40 and 80 mg TID Sildenafil in the Treatment of Pulmonary Arterial Hypertension in Subjects Aged 18 Years and Over**

✉ YU Cheuk Man • KONG Shun Ling • MA Wing Yan • NG Siu King Joan (Dept of Ophthalmology and Visual Sciences) • YIP Wai Kwok Gabriel\* • TAM Lai Shan\* • LAI Hong Yee Connie\* • WONG Wing Cheung\*

☐ 1 February 2003

❖ Pfizer Corporation Hong Kong Limited

Pulmonary arterial hypertension is a disease with significant morbidity and mortality. Although it is not a very common condition, sufferers of the disease will have severe symptoms that limit their exercise capacity and quality of life; with shortness of breath on exertion and even result in repeated hospitalization for decompensation. Pulmonary hypertension could be a primary disease (primary

pulmonary hypertension), or secondary to other conditions such as collagen vascular disease including systemic lupus erythematosus and scleroderma etc. The elevation of pulmonary arterial pressure and related events of cardiopulmonary damage is the main target of therapy. A few therapeutic modalities have been tried for this condition with some symptomatic relief, such as calcium channel blockers, nitric oxide inhalation, endothelin antagonist or prostaglandin analogue. However, patients either remain symptomatic or the therapeutic agents are very expensive. Some of them may not be available in Hong Kong, such as endothelin antagonist. The current study will investigate the role of oral sildenafil in the treatment of primary or secondary hypertension by a multinational, multi-centre, randomised, double-dummy, placebo-controlled study. The safety and effectiveness of the drug will be assessed, and its benefit in exercise capacity, quality of life and pulmonary arterial pressure will be compared with placebo.

(MD02780)

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**Please refer to previous issues of this publication for more details of the following ongoing research at the department:**

<u>Edition</u>	<u>Title/Investigators</u>
2000-01	Establishment of a Catalogue of Chinese-specific Genetic Markers for Obesity, Diabetes and Diabetic Kidney Disease (MD20020) ✉ CHAN Chung Ngor Juliana • NG Chor Yin • LEE Shao Chin (Dept of Clinical Oncology)# • COCKRAM Clive Stewart • TONG Peter Chun

- Yip • TOMLINSON Brian • CHAN Yan Keung Thomas • THOMAS Neil G (School of Pharmacy)# • CRITCHLEY Julian A J H#
- 2001-02 Diabetes Mellitus, Obesity and Cardiovascular Risk Factors in Hong Kong Adolescents (MD01055)  
 ✉ CHAN Chung Ngor Juliana • COCKRAM Clive Stewart • LEE Shao Chin (Dept of Clinical Oncology)# • NG Chor Yin • TONG Peter Chun Yip • WONG Wing Kin Gary (Dept of Paediatrics)
- 2001-02 A Multicentre, Double-blind, Randomised, Placebo- and Active-controlled Parallel Study to Evaluate the Glucose and Lipid-altering efficacy and Safety of L-410198 in Patients with Type 2 Diabetes (MD01943)  
 ✉ CHAN Chung Ngor Juliana • TONG Peter Chun Yip • SO Wing Yee
- 2001-02 Cyclooxygenase-2 in Human Gastric Ulcers: Biological and Clinical Perspectives (MD01056)  
 ✉ CHAN Ka Leung Francis • LEUNG Wai Keung • SUNG Joseph Jao Yiu • SZETO Cheuk Chun • TO Ka Fai (Dept of Anatomical & Cellular Pathology)
- 2001-02 Cyclooxygenase and Trefoil Peptides in Stomach - Biology & Clinical Diseases (MD01711)  
 ✉ CHAN Ka Leung Francis • LEUNG Wai Keung • YU Jun# • SUNG Joseph Jao Yiu • NG Enders Kwok-wai (Dept of Surgery) • CHUNG Sheung Chee Sydney (Dept of Surgery) • TO Ka Fai (Dept of Anatomical & Cellular Pathology) • CHEN M H\* • HU P J\*
- 2001-02 Clinical Protocol for a Randomized, Double-blind, Placebo-controlled Study of the Efficacy and Safety of Celecoxib (SC-58635) in the Prevention of Colorectal Sporadic Adenomatous Polyps (PRESAP) (MD01879)  
 ✉ CHAN Ka Leung Francis • SUNG Joseph Jao Yiu • LEUNG Wai Keung • LEE Yuk Tong • CHAN Lik Yuen • WU Che Yuen Justin • HUI Yui • HUNG Cheung Tsui • HUI Aric Josun
- 2001-02 Prevention of Ulcer Bleeding in High-risk Patients: Is the Enthusiasm for COX2 Selective NSAIDs Justified? (MD01406)  
 ✉ CHAN Ka Leung Francis • LEUNG Wai Keung • SUNG Joseph Jao Yiu • LUK Yiu Wing\* • LAI Moon Sing\* • LEUNG King Sun Vincent\*
- 2001-02 A Multi-national, Multi-centre, Randomised, Open-labelled, Parallel Group Trial to Compare Glycaemic Control of Biphasic Insulin Aspart 30 in Combination with Pioglitazone to Biphasic Insulin Aspart 30 Monotherapy and Pioglitazone in Combination with Sulphonylurea in Subjects with Type 2 Diabetes (MD01549)

- ✎ CHOW Chun Chung Francis •  
 COCKRAM Clive Stewart • MA  
 Ronald\* • OZAKI R\*
- 2001-02 Multi-centre, Multinational,  
 Open-labelled, Randomised, Parallel,  
 Controlled Trial in Type 2 Diabetic  
 Subjects Inadequately Controlled on  
 Repaglinide, to Compare the Efficacy  
 and Safety of Repaglinide Combined  
 with Bedtime NPH Insulin versus Twice  
 Daily NPH Insulin (MD01661)  
 ✎ CHOW Chun Chung Francis •  
 COCKRAM Clive Stewart • MA  
 Ronald\* • OZAKI R\*
- 2001-02 A 24 Week, Open, Controlled,  
 Randomized, Multinational, Multicenter,  
 Phase IIIb Clinical Study to Investigate  
 the Efficacy and Safety of Lantus®  
 Insulin Analogue (Once Daily at Bedtime)  
 Plus Amaryl® (Glimepiride) and NPH  
 Basal Insulin (Once Daily at Bedtime )  
 Plus Amaryl® in 440 Patients with Type 2  
 Diabetes Mellitus Who Fail Good  
 Metabolic Control with Oral Antidiabetic  
 Drugs (OADs) (MD01709)  
 ✎ CHOW Chun Chung Francis •  
 COCKRAM Clive Stewart • SO W  
 Y\* • OZAKI Risa • CHAN Wing  
 Bun
- 2001-02 A Randomised, Multi-centre,  
 Double-blind, Double-dummy, Parallel  
 Group Trial of Two Doses of NNC  
 61-0029 in Combination with  
 Glibenclamide versus Glibenclamide  
 Monotherapy and versus Combination  
 Therapy of Glibenclamide and
- Metformin in the Treatment of Type 2  
 Diabetic Subjects (Phase IIIa)  
 (MD01754)  
 ✎ CHOW Chun Chung Francis •  
 COCKRAM Clive Stewart • SO W  
 Y\* • CHAN W B\*
- 2001-02 A 12-week, Multi-centre, Double-blind,  
 Randomised, Placebo-controlled Trial on  
 Low Dose Repaglinide for the Treatment  
 of Impaired Glucose Tolerance in Asian  
 Subjects (MD01479)  
 ✎ CHOW Chun Chung Francis •  
 COCKRAM Clive Stewart • MA  
 Ronald\* • CHAN W B\*
- 1999-00 Nocturnal Nasal Positive Pressure  
 Ventilation Plus Oxygen Therapy versus  
 Oxygen Alone in Severe Stable Chronic  
 Obstructive Pulmonary Disease  
 (MD99017)  
 ✎ HUI Shu Cheong David
- 2000-01 The Effects of Nasal Continuous Positive  
 Airway Pressure on Platelet Activation,  
 Fibrinolysis and Activities of the  
 Sympathetic Nervous System and Renal  
 Kallikrein-kinin System in Obstructive  
 Sleep Apnoea (CU00147)  
 ✎ HUI Shu Cheong David • CHENG  
 Gregory
- 2001-02 Reference Lung Function Values and the  
 Effects of Smoking on Lung Function in  
 Chinese Adults in Hong Kong  
 (MD00494)  
 ✎ HUI Shu Cheong David • CHAN  
 Tung# • CHOY Ka Leung Dominic

- CHAN Pui Yu\* • LEUNG Mei Yi\* • TONG Wai Ching\*
- 2001-02 The Effects of Nasal Continuous Positive Airway Pressure Treatment on Cardiac Structure, Function and Cardiac Natriuretic Peptide Levels in Obstructive Sleep Apnoea (MD01436)  
 ✉ HUI Shu Cheong David • SANDERSON John Elsby
- 2001-02 Evaluation of Subjective Sleepiness and Prevalence of Obstructive Sleep Apnoea and Sleep Disordered Breathing in a Population of Commercial Drivers (MD01948)  
 ✉ HUI Shu Cheong David
- 2000-01 Quality of Life and Handicap of Stroke Survivors in Hong Kong (MD20055)  
 ✉ KWOK Chi Yui Timothy • WOO Jean • KAY Li Chi Richard • YU Ly Mee Ashley (Centre for Clin. Trials & Epidemiological Research)#  
 • LEUNG Kwok Fai\* • Lo Raymond\*
- 2001-02 A Comparative Study of the Long-term Outcomes of Two Orthopaedic Services with and without Geriatric Liaison in Older Hip Fracture Patients (MD01886)  
 ✉ KWOK Chi Yui Timothy • WOO Jean • LAU Edith Ming Chu (Dept of Community and Family Medicine)  
 • LEUNG Ping Chung (Dept of Orthopaedics & Traumatology)
- 2001-02 Histologic and Cell Kinetic Changes of Premalignant Gastric Lesions with Helicobacter Pylori Eradication and Cyclooxygenase-2 Inhibition (MD01061)  
 ✉ LEUNG Wai Keung • CHAN Ka Leung Francis • CHAN Wing Yee (Dept of Anatomical & Cellular Pathology) • CHUNG Sheung Chee Sydney (Dept of Surgery) • NG Enders Kwok-wai (Dept of Surgery)  
 • SUNG Joseph Jao Yiu • YU Jun#
- 2001-02 A Multicentre, Randomised, Double-blind, Placebocontrolled Dose-finding Phase II Study of Subcutaneously Administered Onercept in the Treatment of Patients with Active Crohn's Disease (Protocol: 22523) and Long-term Follow-up of Crohn's Disease Patients Having Completed Serono protocol 22523, Allowing for Re-treatment with Open-label Onercept (Protocol: 23054) (MD01458)  
 ✉ LEUNG Wai Keung • LEONG Rupert Wing Loong# • CHAN Ka Leung Francis • HUNG Cheung Tsui
- 2001-02 A Randomized, Double-blind Study of Treatment with LdT, Lamivudine, or the Combination of Both Agents in Adult Patients with HbeAg-positive Chronic Hepatitis B (MD01585)  
 ✉ LEUNG Wai Yee Nancy
- 2001-02 Endothelial Dysfunction as an Early Index of Atheromatous Disease in Systemic Lupus Erythematosus and Its Association with Markers of Oxidative Stress and Inflammatory Mediator (MD01333)

- ✎ LI Kwok Ming Edmund • THOMAS Neil G (School of Pharmacy)# • TOMLINSON Brian • TAM Lai Shan\*
- 2001-02 Salvage of Infarcted Myocardium by an Extract of Dagencao with Dual Effects on Angiogenesis and Cardiomyogenesis and Investigation of the Molecular Mechanism Involved in Dagencao Induced Angiogenesis & Cardiomyogenesis (MD01972)
- ✎ LI Ming • SANDERSON John Elsby • LEE Ka Ho Kenneth (Dept of Anatomy) • LEUNG Ping Chung (Dept of Orthopaedics & Traumatology)
- 1999-00 The Effect of Adrenergic Receptor Blockade on Myocardial Collagen and Ventricular Remodeling in Heart Failure Post Myocardial Infarction (CU99340)
- ✎ SANDERSON John Elsby • CHOW Tsun Cheung Louis (Dept of Anatomical & Cellular Pathology) • CHOW Sing Sum Moses (School of Pharmacy) • WOO Kam Sang
- 2000-01 Identification and Isolation of a Chinese Herbal Medicine that Could Enhance Cardiac Muscle Revascularization and Healing Following Heart Muscle Infarction (MD00667)
- ✎ SANDERSON John Elsby • LI Ming
- 2001-02 Heart Failure in Hong Kong: Epidemiology, Aetiology and Determinants of Prognosis (MD01892)
- ✎ SANDERSON John Elsby • WOO Kam Sang
- 2001-02 TRANSCEND - Telmisartan Randomized AssessmentNt Study in aCE iNtolerant Subjects with Cardiovascular Disease Trial (MD01729)
- ✎ SANDERSON John Elsby • YEUNG Leata Y.C.\* • CHAN Kit Wan Skiva • WU Eugene Brian\* • WONG John\* • CHAN Anna\* • MA Wing Yan
- 2001-02 ONTARGET - Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (MD01796)
- ✎ SANDERSON John Elsby • YEUNG Leata Y.C.\* • CHAN Kit Wan Skiva • WU Eugene Brian\* • WONG John\* • CHAN Anna\* • MA Wing Yan
- 1999-00 A Double-blind Placebo Controlled Clinical End-points of Lamivudine in Patients with Hepatitis B Related Cirrhosis (MD98164)
- ✎ SUNG Joseph Jao Yiu • CHAN Ka Leung Francis • TSANG W C Steven\* • CHAN Lik Yuen • HUI Y\*
- 2000-01 Eradication of H. Pylori in Gastro-esophageal Reflux Disease: A Clinical and Pathophysiological Study (MD00307)
- ✎ SUNG Joseph Jao Yiu • WU Che Yuen Justin • CHAN Ka Leung Francis



- 2000-01 A Randomised, Double-blinded, Placebo-controlled Trial of Lamivudine Treatment in HbeAg Negative Chronic Hepatitis B Patients (in Asia) (MD20060)  
 ✍ SUNG Joseph Jao Yiu • CHAN Lik Yuen • CHAN Ka Leung Francis • LEUNG Wai Yee Nancy • HUI Y\*
- 2001-02 A Phase II Study of Lamivudine Compared to Lamivudine Plus Adefovir Dipivoxil for Patient with Chronic Hepatitis B (MD00505)  
 ✍ SUNG Joseph Jao Yiu • CHAN Lik Yuen • CHAN Ka Leung Francis • LEUNG Wai Yee Nancy
- 2001-02 Multicenter Open Label Expanded Access Program Of Peg-Interferon Alfa 2a (Ro-25=8310) And Combination Therapy With Ribavirin (Ro-20-9963) In Patients With Hepatitis C (MD01964)  
 ✍ SUNG Joseph Jao Yiu • CHAN Lik Yuen • CHAN Ka Leung Francis • LEUNG Wai Yee Nancy • HUNG Cheung-tsui Lawrence\*
- 2001-02 Genomic Study of Viral Hepatitis B to Predict Development of Cancer and Response to Therapy (MD01639)  
 ✍ SUNG Joseph Jao Yiu • CHAN Lik Yuen • LEUNG Wai Yee Nancy • MOK Shu Kam Tony (Dept of Clinical Oncology) • JOHNSON Philip James (Dept of Clinical Oncology) • TSUI Kwok Wing (Biochemistry) • WAYE Mary Miu Yee (Biochemistry) • LEUNG Kwong Sak (Dept of Computer Science and Engineering) • HENG Pheng Ann (Dept of Computer Science and Engineering) • LEE Kin Hong (Dept of Computer Science and Engineering)
- 2000-01 Correction of Metabolic Acidosis in Continuous Ambulatory Peritoneal Dialysis Patients with Borderline Dialysis Adequacy-effect on Nutritional Status, Systemic Inflammatory Response & Patient Morbidity (MD20027)  
 ✍ SZETO Cheuk Chun • LI Kam Tao Philip\*
- 2001-02 Physiological Control of Peritoneal Permeability: A Study of the Interactions between Leukocytes, Mesothelial and Endothelial Cells (MD01550)  
 ✍ SZETO Cheuk Chun • LI Kam Tao Philip\* • WONG Yuk Hwa, Teresa\*
- 1998-99 A Multicenter, Double-Blind, Randomized, Parallel, 36-week Dose Escalating Study to Evaluate the Efficacy and Safety of Simvastatin 40 and 80 mg/day Versus Atrovastatin 20, 40 and 80 mg/day in Patients with Hypercholesterolaemia (International) (MD98121C)  
 ✍ TOMLINSON Brian
- 2000-01 Molecular Biology of Hypertension: A Study Investigating Genetic Markers and Possible Underlying Pathogenic Mechanisms of Hypertension in Chinese (CU00095)  
 ✍ TOMLINSON Brian • CHAN Chung Ngor Juliana • THOMAS Neil G (School of Pharmacy)#

- 2001-02 Accelerated Atherosclerosis in Chinese Patients with Systemic Lupus Erythematosus: The Effects of Methionine Loading-induced Hyperhomocysteinaemia on Platelet and Endothelial Function and Oxidative Stress (MD01577)  
 ✉ TOMLINSON Brian • THOMAS Neil G (School of Pharmacy)# • HAINES Christopher John (Dept of Obstetrics & Gynaecology) • LI Kwok Ming Edmund • YIM So Fan\* • TAM Lai Shan
- 2000-01 Epidemiology of Cardiovascular Problem in Chinese Continuous Ambulatory Peritoneal Dialysis Patients: Prevalence, Severity & Risk Factors (MD20005)  
 ✉ WANG Yee Moon Angela • SANDERSON John Elsby • CHAN Kam Wing (Dept of Diagnostic Radiology & Organ Imaging)# • LUI Siu Fai
- 1999-00 A Pilot Study of Early and Aggressive Lipid-lowering Therapy for Atherosclerotic Stroke (MD99041)  
 ✉ WONG Ka Sing Lawrence • LO See Kit Raymond\* • TOMLINSON Brian • LAM Wai Man Wynnie (Dept of Diagnostic Radiology & Organ Imaging) • LAM Wai Kei Christopher (Dept of Chemical Pathology) • KAY Li Chi Richard
- 2000-01 A Prospective Study of the Long Term Outcome of Patients with Intracranial Arterial Occlusive Disease (MD00869)  
 ✉ WONG Ka Sing Lawrence • LAM Wai Man Wynnie (Dept of Diagnostic Radiology & Organ Imaging) • LI Huan# • KAY Li Chi Richard
- 2000-01 A Randomized 26-week, Double-blind, Placebo-controlled Trial to Evaluate the Safety and Efficacy of Galantamine in the Treatment of Dementia Secondary to Cerebrovascular Disease (MD00553)  
 ✉ WONG Ka Sing Lawrence • HUI Andrew Che Fai • MOK Vincent\*
- 2001-02 Genetic Factors in the Etiology of Middle Cerebral Artery Stenosis in Chinese with Diabetes and Hypertension (MD01965)  
 ✉ WONG Ka Sing Lawrence • THOMAS Neil G (School of Pharmacy)# • TOMLINSON Brian • KAY Li Chi Richard
- 2001-02 Management of Atherothrombosis with Clopidogrel in High-risk Patients with Recent Transient Ischemic Attack or Ischemic Stroke: A Randomised, Double-blind Study, with 18 Months of Follow-up (MD01361)  
 ✉ WONG Ka Sing Lawrence
- 2001-02 A Phase III, Double-blind, Placebo-controlled, Randomised Study Comparing the Efficacy, Safety, and Tolerability of Sumanrole versus Placebo or Ropinirole, as an Adjuvant to Levodopa, in Patients with Advanced Parkinson's Disease (MD01488)  
 ✉ WONG Ka Sing Lawrence • MOK Chung Tong Vincent

- 2001-02 Long Term Care for the Elderly in Hong Kong - What Constitutes Quality and What Resources are Needed to Achieve (MD01402)  
 ✉ WOO Jean • CHI Iris\* • PHILLIPS David\* • CHAN Alfred\*
- 1999-00 Chinese Atherosclerosis in the Aged and Young (Cathay Study) (MD96224)  
 ✉ WOO Kam Sang • WOO Jean • SANDERSON John Elsby • CRITCHLEY Julian A J H# • CHENG Gregory • LAM Ching Wan (Dept of Chemical Pathology) • LAU Tak Fai Joseph (Centre For Epidemiology & Biostatistics)
- 1999-00 A Multicenter, Randomized, Controlled, Double-blind Trial to Investigate the Clinical Efficacy and Tolerability of Early Treatment with Simvastatin 40mg Daily for 30 Days, Followed by Simvastatin 80mg Daily thereafter in Tirofiban-Treated Acute Coronary Syndrome Patients Who have been Randomized to Receive Enoxaparin or Unfractionated Heparin in Conjunction with Aspirin. (A to Z study) (MD99072)  
 ✉ WOO Kam Sang • SANDERSON John Elsby • FUNG Wing Hong\* • CHAN W M Wilson\*
- 2000-01 An Open Prospectively Randomised Comparison of Hirulog Versus Heparin in Patients Receiving Aspirin and Thrombolysis (Streptokinase) for the Treatment of Acute Myocardial Infarction - The Hirulog Early Reperfusion/Occlusion (HERO-2) Trial (MD97341)  
 ✉ WOO Kam Sang • SANDERSON John Elsby • YIP Wai Kwok Gabriel
- 2000-01 Tolerability and Clinical Application of Platelet Glycoprotein IIb-IIIa Inhibitor (Epifibatide) Therapy in Hong Kong Chinese (MD20063)  
 ✉ WOO Kam Sang • SANDERSON John Elsby • CHAN Wai Man Wilson • TSE Kin Kee • CHAN C K\* • CHAN S K\*
- 2001-02 A Novel Strategy to Prevent Atherosclerosis in Predialysis Renal Failure: A Clinical Model of Accelerated Atherosclerosis (MD01070)  
 ✉ WOO Kam Sang • CELERMAJER David S\* • LAU Tak Fai Joseph (Centre For Epidemiology & Biostatistics) • LUI Siu Fai • METREWELI Constantine (Dept of Diagnostic Radiology & Organ Imaging)# • SANDERSON John Elsby • SZETO Cheuk Chun • YU Wai Yin Alex
- 2001-02 A Non-randomized Evaluation of the Multi-link Rx Vision™ Coronary Stent System in the Treatment of Patients with *De Novo* Native Coronary Artery Lesions (MD01334)  
 ✉ WOO Kam Sang • CHAN Wai Man Wilson • TSE Kin Kei Lawrence\*
- 2000-01 Omapatrilat versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) (MD20068)

✍ YU Cheuk Man • YEUNG Leata  
Y.C.\* • CHAN Kit Wan Skiva •  
SANDERSON John Elsby

## RESEARCH PROJECTS

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### **Molecular Characterization of Group B Streptococcus (*Streptococcus agalactiae*) in Hong Kong**

✉ IP Margaret • LYON D J\* • CHENG Fun Bun Augustine

☐ 1 April 2003

❖ CUHK Research Committee Funding (Direct Grants)

Invasive *Streptococcus agalactiae*, or group B streptococcal (GBS) infections have emerged in recent years as an important cause of morbidity and mortality among adults. GBS is a major cause of bacterial meningitis and bacteraemia in neonates. In adults, it is often associated with pregnancy and in those who are immunocompromised. Recently, however, increasing frequency of invasive GBS disease in previously healthy adults has been seen worldwide and severe with high mortality had been associated with certain serotypes eg Type V. Similarly, an increasing number of invasive GBS infections have also been observed recently in Hong Kong. Data on the epidemiology of GBS in Hong Kong has been lacking. The objectives of this study are to characterize Hong Kong isolates of GBS by the antibiotic susceptibility profile, serotyping and molecular typing by pulsed-field gel electrophoresis and to build up a database on the clinical and epidemiological background of GBS in Hong Kong. A collection of 700 GBS isolates from the ten-year period, 1993-2002, will be studied. This includes isolates obtained from invasive GBS disease; soft tissue infections; and colonized GBS from the mucosae of neonates and from the vaginal and rectal

flora of pregnant mothers. The patient demographics and relevant clinical data from which these isolates were isolated will be recorded. The basic clonal structure of the GBS strains causing invasive disease and those of the human flora will be examined. The study will provide a database on GBS in Hong Kong to enable further genomics to be investigated in detail and will facilitate further understanding of the epidemiology of invasive GBS as an emerging pathogen and thus enable steps to be devised toward implementation of strategies for prevention.

(MD02329)

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### **Genetic Characterization of *Escherichia coli* Mutants Resistant to the Fluoroquinolones**

✉ LING Mei Lun Julia

☐ 1 April 2003

❖ CUHK Research Committee Funding (Direct Grants)

Fluoroquinolones are broad-spectrum antimicrobial agents that target against type II and type IV topoisomerases. These enzymes introduce negative supercoils into covalently closed DNA and decatenate the chromosome before cell division, respectively. Since the older fluoroquinolones such as ciprofloxacin and ofloxacin, have limited activity against respiratory pathogens such as *Streptococcus pneumoniae* and other Gram-positive bacteria, newer fluoroquinolones that were targeted against these organisms were developed. Our study “The ability of different antimicrobial agents to induce and select resistant mutants of *Escherichia coli* and *Pseudomonas aeruginosa*” showed that different fluoroquinolones, including these newer fluoroquinolones, had different abilities to select resistant mutants irrespective of their antimicrobial

susceptibilities. Antibiotic-organism combinations were also different. In order to elucidate the resistance mechanisms of the resistant *E coli* mutants, we aimed to study the mutations in the quinolone resistance determining region of *gyrA*, *gyrB*, *parC*, and *parE* of *E coli* to follow changes in mutations resulting from the selection. This has important clinical implications. The primary target site of different fluoroquinolones could be identified. The sequential development of mutations in different genes as a response to exposure to different concentrations of different drugs could be followed. Drugs that induce more than one mutation even at low concentrations could be identified. Such as understanding of the molecular mechanisms of resistance would aid in the design of drugs that could decrease the development of resistant strains and in the prediction of cross resistance to other members of this group of drugs.

(MD02514)

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**A Prospective, Randomized, Double Blind, Placebo-controlled, Trial to Assess Safety, Efficacy, Tolerability and Immunogenicity of Influenza Virus Vaccine, Trivalent, Types A & B, Live Cold-adapted, Liquefied Formulation (CAIV0T), Administered Concomitantly with a Combination Live, Attenuated, Mumps, Measles, and Rubella Vaccine in Healthy Children Aged 11-24 Months**

✉ TAM Siu Lun John • CHENG Fun Bun Augustine • FOK Tai Fai (Dept of Paediatrics) • SUNG Yn Tz Rita (Dept of Paediatrics) • NELSON Edmund Anthony Severn (Dept of Paediatrics) • CHAN Kay Sheung Paul • MA Kwok Chiu\* • CHEUNG Kam Lau\* • WONG William C F\* • YAM Man Ching\* • LEE

Karen\* • MOK Geoffrey\* • LO Amy\* • WAN Helene\*

□ 1 October 2002

❖ Wyeth Pharmaceuticals, Inc.

Influenza is an acute viral respiratory illness characterized by abrupt onset of fever, myalgia, non-productive cough, headache, sore throat, nasal congestion, and malaise. In Asia, influenza rates also appear to be highest in young children. In residential kindergartens in Beijing, China, 19% of acute respiratory infections of children aged 6 months to 7 years were confirmed by culture to be attributed to influenza. In community surveillance of children under 5 years with acute lower respiratory infections in Manila, Philippines, and Dhaka, Bangladesh, influenza was confirmed by culture as the probable etiology in 22% and 14%, respectively.

The purpose of this study is to determine the effect of Influenza Virus Vaccine, Trivalent, Types A & B, Live Cold-Adapted (CAIV-T) on other live viral vaccines in a diverse Asian population aged from 11 months to less than 24 months, in tropical and temperate climates. In addition, the trial provides the opportunity to investigate the efficacy and safety of CAIV-T over a single influenza seasons in each of the respective countries. It is expected that approximately 1200 subjects will be enrolled at multiple study sites in Asia. In Hong Kong 100 subjects will be enrolled as part of this multi-centered trial. Each subject will be required to participate for approximately 9 months. All subjects will be monitored for respiratory illnesses with culture confirmation for viruses.

(MD02994)

Please refer to previous issues of this publication for more details of the following ongoing research at the department:

✉ FUNG Sau Chun Kitty • HOUANG Ting Sou Elizabeth • LEE Albert (Dept of Community and Family Medicine) • LYON Donald James

<u>Edition</u>	<u>Title/Investigators</u>
2000-01	Development of a Rapid <i>in vitro</i> Drug Susceptibility Test Method for Mycobacterium Tuberculosis Using Metabolic Markers (CU00097) ✉ CHAN Chiu Yeung Raphael
2001-02	Association between Human Leukocyte Antigens and Progression of Oncogenic Human Papillomavirus Infection of the Cervix (MD01071) ✉ CHAN Kay Sheung Paul • CHANG Alexander Russell (Dept of Anatomical & Cellular Pathology)# • CHENG Fun Bun Augustine • CHEUNG Tak Hong (Dept of Obstetrics & Gynaecology)
2000-01	A Survey of Drug-resistance Genes in Clinical Isolates of Mycobacterium Tuberculosis and Its Direct Application to the Detection of Drug-resistant M. Tuberculosis in Clinical Specimens (CU00098) ✉ CHENG Fun Bun Augustine • CHAN Chiu Yeung Raphael • HUI Mamie
2001-02	Household Transmission of Methicillin-Resistant Staphylococcus Aureus (MRSA) in Hong Kong - Incidence and Risk Factors (MD01743)
2001-02	Development of a Molecular Typing Method for the Study of Invasive <i>Candida Albicans</i> Infection (MD01456) ✉ HUI Mamie • CHENG Fun Bun Augustine
2001-02	The Epidemiologic Typing of Methicillin-Resistant <i>Staphylococcus aureus</i> (MRSA) in Hong Kong (MD01646) ✉ IP Margaret • CHENG Fun Bun Augustine • LYON D J* • ENRIGHT M*
2000-01	Mechanisms of Fluoroquinolone-resistance in Salmonellae in Hong Kong (CU00049) ✉ LING Mei Lun Julia
2001-02	The Ability of Different Antimicrobial Agents to Induce and Select Resistant Mutants of <i>Escherichia Coli</i> and <i>Pseudomonas Aeruginosa</i> (MD01384) ✉ LING Mei Lun Julia • CHAN Wai Chi
2000-01	Virus Isolation in Association with a Multicentre Clinical Trial on the Safety and Efficacy of Influenza Virus Vaccine, Trivalent, Types A & B, Live Cold-Adapted (CAIV-T) in Healthy Children in Asia (MD00369)

- ✍ TAM Siu Lun John • FOK Tai Fai  
(Dept of Paediatrics) • CHENG Fun  
Bun Augustine
- 2000-01 A Prospective, Randomized,  
Double-blind, Placebo-controlled Trial to  
Determine the Safety and Efficacy of  
Influenza Virus Vaccine, Trivalent Types  
A & B, Live Cold-Adapted (CAIV-T) in  
Healthy Children (MD00691)
- ✍ TAM Siu Lun John • FOK Tai Fai  
(Dept of Paediatrics) • CHENG Fun  
Bun Augustine • NELSON Edmund
- Anthony Severn (Dept of Paediatrics)  
• NG Pak Cheung (Dept of  
Paediatrics) • CHAN Kay Sheung  
Paul • LEUNG Ting Fan (Dept of  
Paediatrics) • MA Kwok Chiu (Dept  
of Paediatrics) • CHENG Pik Shun  
(Dept of Paediatrics) • LI Man Chim  
Albert Martin (Dept of Paediatrics) •  
FUNG Lai Wah Eva (Dept of  
Paediatrics) • MOK Chi Fung  
Geoffrey (Dept of Paediatrics)



## RESEARCH PROJECTS

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### Psychosocial and Physical Factors Predicting Handicap

✉ CHAU Pak Chun Janita • WOO Jean (Dept of Medicine & Therapeutics) • CHANG Anne Marie\* • MACKENZIE Ann E\*

☐ 15 October 2002

❖ Health Care & Promotion Fund, Hospital Authority

#### Objectives:

- (1) Examine differences in the levels of social support, depression, self-esteem, functional ability and handicap over the 3 stages of data collection;
- (2) Determine the association among demographic data, social support, depression, self-esteem, functional ability and handicap;
- (3) Identify factors predicting handicap at 1 year following discharge from a rehabilitation unit.

*Design:* A prospective, longitudinal design will be used to collect data on 3 occasions from stroke patients over a period of 1-year following discharge from a rehabilitation unit.

*Setting:* A regional rehabilitation hospital and patient's homes.

*Subjects:* 265 patients discharged from a stroke rehabilitation hospital.

*Main outcome measures:* The Barthel Index (BI), London Handicap Scale (LHS), Geriatric Depression Scale (GDS), State Self-esteem Scale (SSES), Social Support Questionnaire (SSQ6).

*Data Analysis:* Differences in each of the variables over time will be determined using ANOVA. Pearson's correlation coefficient will be used to

determine the relationships among continuous variables and point biserial correlation will be used to examine the relationship between dichotomous and continuous variables. *Analysis of covariance for discrete outcome measurements, as well as multiple regression models and standardized partial correlation coefficients for continuous outcome variables, will be used to evaluate the independent effects of each determinant, corrected for other determinants.*

*Results:* for dissemination in conferences and in local and international refereed journals.

*Conclusion:* The findings will provide information on the psychosocial and physical factors influencing the level of handicap post-stroke thereby providing direction for health promotion interventions by nurses in hospital and community settings.

(MD02482)

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### Establishing Psychometric Properties of the Childbirth Self-Efficacy Inventory among Chinese Pregnant Women

✉ IP Wan Yim

☐ 30 June 2003

❖ CUHK Research Committee Funding (Direct Grants)

The lack of a reliable and valid Chinese measure of self-efficacy for childbirth is one of the major drawbacks in the development of childbirth education program and related research in Hong Kong. The Childbirth Self-Efficacy Inventory (CBSEI) developed by Lowe (1993) has been psychometrically tested in the West to measure women's confidence for childbirth. The aim of this study is to translate the CBSEI into Chinese and to establish the psychometric properties of the CBSEI among Hong Kong Chinese pregnant women. A

panel of experts will establish the equivalence and content validity of the translated CBSEI. The Chinese version of the General Self-Efficacy Scale (CGSE) will be used to establish concurrent validity of the translated CBSEI. Construct validity will be determined by factor analysis. A convenience sample of 310 Chinese pregnant women at their third trimester of pregnancy will be recruited at Li Ka Shing Specialist Clinic. After giving an informed consent, the eligible women will be asked to fill in the translated CBSEI and CGSE in an interview room. The re-testing of the translated CBSEI will be carried out at 2 weeks later in the same clinic. Data will be analyzed using SPSS program. Descriptive statistics, Confirmatory factor analysis and Pearson/Spearman correlations according to the level of data will be used to determine the relationships among variables.

(MD02670)

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**Developing a Culturally Relevant Theoretical Framework of Successful Aging for Chinese Elders**

✉ LEE Tze Fan Diana

□ 1 November 2002

❖ Research Grants Council (Earmarked Grants)

Assisting older people to age successfully is one of the main goals of gerontological practice. However, there is little consensus as to what constitutes successful aging. A large body of research focuses heavily on what is believed as necessary for successful aging without ever defining the concept. Moreover, little is known about elderly people's subjective views of successful aging and the strategies they use when striving to age successfully. Still less is known of this aspect in Chinese elderly people.

This study is to develop a culturally relevant theoretical framework of successful aging for Chinese elderly people. Approximately 100 elderly persons from 18 elderly community centres of Hong Kong will be invited to participate in an in-depth interview to identify what successful aging means to them, what are necessary for successful aging and what prevent successful aging. Their aging experience in terms of these concepts of successful aging will also be explored. Results of this study will (1) produce a sound theoretical basis for health care professionals to identify and evaluate appropriate interventions to promote successful aging and (2) provide a Chinese cultural perspective to understanding elderly people's successful aging experiences.

(CU02228)

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**Translation and Validation of Two Disease-specific Instruments in Chinese Patients with Coronary Heart Disease**

✉ LOPEZ Violeta • THOMPSON David Robert

□ 1 May 2003

❖ CUHK Research Committee Funding (Direct Grants)

*Background:* Coronary heart disease (CHD) is a major cause of death and disability in Hong Kong and there is growing evidence that its prevalence in Hong Kong and mainland China is increasing. Modern treatments of CHD focus not only on improving life expectancy but also symptoms, function and quality of life. Health-related quality of life measures that are disease-specific are important to address the needs and the multiple aspects of the quality of life especially with CHD patients that generic measures may not be able to address. Translation and validation of developed

instruments are critical steps if used in a linguistically different population as errors in translation could distort that original intent of the instrument and compromise its reliability and validity.

*Aim:* To translate into Chinese and validate the Cardiac Limitations and Symptoms Profile (CLASP) and the Myocardial Infarction Dimensional Assessment Scale (MIDAS).

*Method:* A methodological design will be used. A total of 390 subjects will be recruited (130 per group of patients diagnosed with myocardial infarction, heart failure, unstable angina); Subjects will be recruited from the coronary care units and medical wards of the New Territories East cluster hospitals. Reliability and validity tests will be conducted. Convergent validity tests will also be conducted between CLASP and MIDAS with two existing Chinese versions of quality of life instruments (SF-36 and Sickness Impact Profile). Sensitivity and specificity (gender effect) will also be examined.

*Significance:* The validated instruments will also be used by the researchers in the major study to assess the health status and quality of life of Chinese Hong Kong patients with CHD. It is anticipated that using the valid and reliable instruments will identify symptoms and functional limitations as well as the overall health status of patients with CHD that would enable nurses in planning appropriate and culturally-sensitive intervention for these group of patient. These instruments will also add to the pool of valid and reliable instruments that could be accessed and used by clinicians and other researchers in Hong Kong.

(MD02421)

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**Establishing Reliability and Validity of the Chinese Version of the Caregiver Strain Index and the Center for Depression**

✍ LUI How Lin • LEE Tze Fan Diana

☐ 1 June 2003

❖ CUHK Research Committee Funding (Direct Grants)

*Objectives:* The aim of this study is to establish the reliability and validity of the Chinese version of the Caregiver Strain Index (CSI) and the Center for Epidemiologic Studies Depression Scale (CES-D).

*Design:* Prospective, descriptive study

*Subjects:* Main family carers of stroke survivors and stroke survivors

*Setting:* Rehabilitation hospitals, stroke clubs and carer support centers

*Main Outcome Measures:*

Caregiver Strain Index (CSI) and the Center for Epidemiologic Study for Depression Scale (CES-D). The Cost of Care Index (CCI) and the Geriatric Depression Scale (GDS) will be used to determine the validity of the CSI and CES-D.

*Data Analysis:* Spearman's rank-order correlation coefficient between the translated CSI and the CCI; and between the translated CES-D and GDS will be calculated to determine the concurrent validity of the translated CSI and the translated CES-D.

Factor analysis will be used to determine the construct validity of these translated tools. Any difference The Cronbach's alpha and Intraclass Correlation Coefficient will be calculated to determine the internal consistency and test retest reliability of the translated tools. For all analysis, any difference identified at  $p < 0.05$  will be accepted as significant.

*Conclusion:* Development of reliable and valid Chinese versions of the CSI and CES-D is the cornerstone in a currently planned study that evaluates the effectiveness of an education to family carers who look after their stroke relative in the community with the aim to reduce their burden.

The translated CSI will be used to determine the extent such intervention reduce carer burden while the translated CES-D helps to measure depression of stroke survivors.

(MD02761)

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**Preparation for Surgery in Patients Awaiting Coronary Artery Bypass Surgery**

✉ THOMPSON David Robert • GILL Furze\* • ROBERT Lewin\* • STEVEN Griffin\* • JOHN Caplin\*

☐ 1 February 2003

❖ British Heart Foundation

Waiting for open-heart surgery can be a frightening experience for patients and their families. Research has shown that education, exercise and relaxation can all help, resulting in them having fewer complications and a faster discharge and recovery. This research will develop and test a 'preparation for surgery programme' (comprising education, exercise and relaxation) that is home-based and supervised by telephone calls from a hospital-based facilitator.

(MD02865)

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**Increasing Knowledge and Uptake of Screening for Cervical Cancer amongst Hong Kong Chinese Women over 40 Years: An Evaluation of a Community Health Promotion Campaign**

✉ TWINN Sheila Frances • HOLROYD Eleanor Anne • DICKINSON James Arthur (Dept of Community and Family Medicine)# • FABRIZIO Cecilia\*

☐ 23 September 2002

❖ Health Care & Promotion Fund, Hospital Authority

The aims of this study are to investigate the knowledge and uptake of screening for cervical cancer amongst Hong Kong Chinese women aged 40 years and older and to evaluate the effectiveness of a community health promotion campaign targeted at increasing knowledge and uptake of cervical screening amongst this target group. A mixed method two-phase design has been selected to meet the aims of the study. A sample of 515 women aged 40 years and over drawn from a random sample of 12000 residential telephone numbers will be used for Phase I of the study. A volunteer sample of pathology laboratories will be employed. Purposive sampling drawn from the women completing the structured telephone interview will be used for Phase II. A pre and post campaign coded confidential structured telephone interview will measure the effectiveness of the campaign in changing women's knowledge as well as intention and uptake of cervical screening. The number of cervical smears received by the selected laboratories three months prior and three months post campaign will also be assessed. Semi-structured telephone interviews will be used to understand the processes involved in women's responses to the campaign and contribute to an understanding of any changes in women's knowledge as well as their intention and uptake of screening. A major outcome of this study will be improved understanding of older women's knowledge and uptake of cervical screening and the information and stimuli that facilitate change in their screening practice. Such data will enable health providers to target more specifically the needs of older women and improve cervical screening rates amongst its vulnerable population.

(MD02557)

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**The Beliefs and Attitudes of Chinese Women about Cervical Screening Programme in Hong Kong**

✉ TWINN Sheila Frances • HOLROYD Eleanor Anne

□ 21 October 2002

❖ Dept of Health, HKSAR Government

Well-organised population based cervical screening programmes are an important method of reducing the mortality and morbidity associated with cervical cancer. However, for these programmes to be effective women need to attend regularly for screening. Attendance rates for cervical screening in Hong Kong are low compared to other countries. The aim of this study is to investigate women's views and opinions about attending for cervical screening. The objectives for the study include how women's attitudes and beliefs influence their decision to attend for screening, women's knowledge and opinions of the effectiveness of past and present cervical screening publicity campaigns and women's opinions of the ways in which they are notified about their smear result and how this personal information is used to inform a population-based screening programme. This study will use a qualitative research design to achieve the aims and objectives of the study. Data collection methods will consist of focus groups targets at three age groups of women: 25-34, 35-49 and 50-64 years. In each age group there will one focus group for women who have attended at least once for cervical screening and one group for women who have never attended for cervical screening. Each focus group will last approximately one and half-hours and will be held at a time and place convenient to women. A gift of \$100 will be given to every woman attending the group. The group discussion will be audio-taped

and all information will be treated confidentially. Data collection and thematic analysis of the data will be undertaken simultaneously. Categories will be developed to conceptualize women's opinions and views about cervical screening and the factors that influence the success of such screening programmes. A comparison of the thematic analysis of the data from each group will be undertaken to identify any similarities and differences in the findings from the three groups.

(MD02862)

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**Beliefs of Older Hong Kong Chinese Women and Medical Practitioners about Mammography Screening: An Explanatory Model Approach**

✉ TWINN Sheila Frances • HOLROYD Eleanor Anne • SHIU Tak Ying

□ 1 November 2002

❖ Research Grants Council (Earmarked Grants)

Breast cancer is the most common cause of cancer and a significant cause of mortality amongst women in Hong Kong. Research has shown that early detection of the disease significantly reduces mortality rates, particularly amongst women aged 50 to 69 years. Mammography has been identified as the most effective method of screening for this age group. Locally, however, attendance rates are low with surveys indicating rate below 30%. Factors identified that influence women's attendance for mammography include their beliefs about screening and the disease, socio-demographic factors, cost and the influence of the practitioner. Evidence from the United States suggests that cultural beliefs about the disease may influence Chinese women's attendance for screening. The aim of this study is to examine the beliefs of older Hong Kong Chinese women and practitioners about mammography screening and to

examine the implications for any differences in those beliefs in determining screening practices. Beliefs will be explored using a framework of explanatory models to provide an understanding of the significance of breast cancer and mammography screening in the context of women's and medical practitioners' screening practice. A qualitative research design has been selected using ethnographic interviews as the method of data collection. Interviews will be undertaken with approximately 50 practitioners and 100 women aged between 50 and 69 years (50 who have attended and 50 who have never attended for mammography screening). It is anticipated that the findings will contribute to an understanding of screening practices and the development of culturally specific health promotion strategies to maximize attendance for screening amongst this age group.

(CU02229)

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**An Evaluation of Nursing Practice and Advance Nursing Roles in Five Pilot Clinics in Primary Care Settings Managed by the Hospital Authority**

✉ TWINN Sheila Frances • LOPEZ Violeta • THOMPSON David Robert • LEE Tze Fan Diana • SHIU Tak Ying

☐ 1 December 2002

❖ Hospital Authority

Nursing practice in primary care settings internationally has developed both in complexity and the contribution to patient care in particular within the context of patient outcomes and satisfaction. In Hong Kong developments in nursing practice have focused on the clinical nurse specialist and the contribution to patient care. The aims of this study are therefore to examine the contribution of advanced nursing practice and other nursing roles to the quality

of patient care provided in five pilot clinics in the primary care settings managed by the Hospital Authority (HA). The objectives of the study include: identifying the contribution of nursing practice and advanced nursing practice to patient outcomes, identifying appropriate skill mix amongst nursing staff to achieve required outcomes of patient care and identifying the perceptions of nurses, family physicians, allied health staff and patients of advanced nursing practice to patient outcomes and the quality of care. In order to achieve the aims and objectives a multiple case study design has been selected consisting of five case studies. Each case study consists of one pilot HA clinic in a primary care setting (General Out Patient Clinic {GOPC}). The focus for each case study will include the collection of data on the structure, process and outcomes of care. A total population of nursing staff in each case study will complete a questionnaire about their perceptions of nursing roles from which a purposive sample of 4 participants will be selected for face-to-face semi-structured interviews. A purposive sample of allied health professionals will also participate in a face-to-face semi-structured interview. An opportunistic sample of patients in each case study will be asked to complete a patient satisfaction survey form from which a purposive sample of 10 patients in each case study will be asked to complete a face-to-face semi-structured interview. Observations will also be completed in each case study. Data analysis will consist of two researchers independently developing categories from the qualitative data to identify similarities and differences within and across the case studies. The use of descriptive statistics will be used to analyze the quantitative data. As with case study design the analysis will allow theoretical generalizations of the findings to similar practice settings.

(MD02665)

Please refer to previous issues of this publication for more details of the following ongoing research at the department:

<u>Edition</u>	<u>Title/Investigators</u>
2001-02	Adherence to Phase II Cardiac Rehabilitation Programme & Psychosocial Outcomes of Clients with Acute Coronary Syndrome (MD01339) ✉ CHAN Dominic Shung Kit • CHANG Anne Marie# • CHAU Pak Chun Janita
2000-01	An Evaluation of the Effectiveness of a Multisensory Environment on Clients with Learning Disability (MD00708) ✉ CHAN Wai Chi Sally • CHIEN Wai Tong • TO Yuen Fung Maggie*
2001-02	Effectiveness of Interventions for Reducing Breathlessness, Fatigue & Anxiety in Chinese Patients Undergoing Lung Cancer Radiotherapy in Hong Kong (MD01833) ✉ CHAN YIP Carmen Wing Han • CHANG Anne Marie# • LEUNG Sing Fai (Dept of Clinical Oncology) • MAK So Shan*
2001-02	Effectiveness of Mutual Support and Psychoeducational Group Interventions for Family Caregivers of Patients with Schizophrenia (MD01337)
2000-01	Preparation for Pregnancy, Labour & the Early Postpartum Period: An Evaluation of a Hospital Based Antenatal Education Program (MD20028) ✉ HOLROYD Eleanor Anne • IP Wan Yim • TWINN Sheila Frances
2001-02	Validation of Chinese Versions of Measures of Stress Incontinence and the Intrinsic Motivation Inventory (MD01466) ✉ LOPEZ Violeta • CHANG Anne Marie# • YIP Shing Kai Alexander (Dept of Obstetrics & Gynaecology) • SIU LS Katherine*
2001-02	To Assess the Effectiveness of a Nurse-led Sexual Health Promotion Project amongst Hong Kong Adolescents (ED01702) ✉ TWINN Sheila Frances • LEE Albert (Dept of Community and Family Medicine) • HOLROYD Eleanor Anne • CHENG YAM Fung Khing Frances (Dept of Community and Family Medicine) • SHIU Tak Ying

## RESEARCH PROJECTS

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### Identification of Metastasis Related Genes in Ovarian Carcinoma by cDNA Arrays

✉ CHUNG Kwok Hung Tony • CHEUNG Tak Hong • CHIN Khew Voon\* • WONG Yick Fu • YU Mei Yung (Dept of Anatomical & Cellular Pathology)

☐ 1 December 2002

❖ Research Grants Council (Earmarked Grants)

A large-size primary tumor suggests a delay in diagnosis and higher chance of tumor spread. However, metastasis can occur in patients with small primary tumor and patients with large-size tumor may not have metastasis. It remains to be determined whether there are genetic alterations that are important for the metastatic process. Genetic changes of proteinases, adhesion molecules, angiogenesis and others have been studied in relation to metastasis. As only a few genes were evaluated in each of the early studies, it has not been possible to acquire a global understanding of metastatic process relative to the genetic changes during tumorigenesis. cDNA microarrays which measure quantitatively the expression of thousands of genes simultaneously in a tumor sample could address this limitation.

We propose to determine the gene expression profiles of ovarian carcinomas with metastasis using cDNA microarrays. Tissues retrieved, both from primary and metastatic sites, will be subjected to microarray analysis. By comparing genetic profiles in primary and metastatic sites, genes changes crucial to the metastatic process may be identified. For comparison, additional ovarian carcinomas, which have not metastasized (Stage I), will also be

examined in order to determine whether there are differences in the expression profiles between early and late stage (Stage II –IV) ovarian carcinoma. Our research findings can provide key information on genetic changes that are important for metastasis and help choose potential targets for gene therapy.

(CU02133)

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### Proteomic Approach to the Serological Markers of Pre-eclampsia

✉ LEUNG Tse Ngong • POON Chuen Wai (Dept of Clinical Oncology) • WANG Chi Chiu • LAU Tze Kin • ROGERS Michael Scott

☐ 1 June 2003

❖ CUHK Research Committee Funding (Direct Grants)

Pre-eclampsia is multi-system disorder unique to pregnant women, occurring almost exclusively after 20 weeks of gestation. The pathogenesis of this condition is not fully understood but recent evidences suggests that circulatory factors are released from the placenta into the maternal circulation, which in turn result in an excessive maternal inflammatory response and subsequently generalized vascular endothelial dysfunction. Sera of pre-eclamptic women have been shown to cause endothelial damage *in vitro* and alter its function. Various circulatory factors, including cytokines, activin A, inhibin, lipid peroxides and syncytiotrophoblast microfragments have been proposed to be involved in the pathogenesis of the clinical syndrome but the exact mechanism still needs to be better delineated. The recently available proteomic approaches, commonly used for cancer research, are likely to be useful in displaying the differential protein expression profiles from the sera of pre-eclamptic and non-pre-eclamptic women. The information will



facilitate the understanding of the pathogenesis of this disease. It also helps develop the serological markers for identifying pregnant women susceptible to pre-eclampsia before its clinical manifestation. Better understanding of the pathogenesis and an accurate identification of high-risk subjects may allow the development of preventive measures at the subclinical phase of this condition and this will be of great clinical relevance.

(MD02649)

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**Expression of Leptin and Leptin Receptor in Pathological Pregnancies**

✉ LI Hang Wun • WONG Yick Fu • YU Mei Yung (Dept of Anatomical & Cellular Pathology)

□ 1 January 2003

❖ Hong Kong Obstetrical and Gynaecological Trust Fund

Leptin, a product of the *ob* (obese) gene, is a polypeptide hormone which was originally found to control energy metabolism. It was subsequently also found to play important roles in the regulation of a wide range of physiological processes including reproduction and pregnancy.

During pregnancy, studies have demonstrated that the placenta is an important source of leptin production, as well as a target for its action, as both the *ob* gene and its receptor gene (*ob-R*) has been demonstrated to be expressed in placental trophoblasts. There were studies which suggested that leptin and leptin receptor both have a promoting role in the invasive processes of the cytotrophoblasts by modulating the expression of MMPs. These results may also imply that altered expression of leptin and leptin receptor may be involved in the development of pathological conditions characterized by insufficient (e.g.

pre-eclampsia and intrauterine growth retardation) or excessive (e.g. gestational trophoblastic diseases) trophoblastic invasion.

We propose to study the expression of placental leptin and leptin receptor in pre-eclampsia and gestational trophoblastic diseases, using placental tissue from gestational age-matched normal pregnancies as controls.

We shall study the expression of leptin and leptin receptor (long isoform) (*ob-R<sub>L</sub>*) using the techniques of immunohistochemistry and reverse transcriptase-polymerase chain reaction (RT-PCR).

(MD02301)

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**The Effect of Interactions between Genetic and Environmental Factors and History of Gestational Diabetes on the Incidence of Diabetes and Metabolic Syndrome in Hong Kong Chinese Women**

✉ TAM Wing Hung • CHAN Chung Ngor Juliana (Dept of Medicine & Therapeutics) • TONG Peter Chun Yip (Dept of Medicine & Therapeutics) • COCKRAM Clive Stewart (Dept of Medicine & Therapeutics) • ROGERS Michael Scott • KO Tin Choi Gary\* • NG Chor Yin (Dept of Medicine & Therapeutics)

□ 1 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

Gestational diabetes mellitus (GDM) is a well recognized risk factor for progression to diabetes (DM) in later life. Despite the high prevalence of diabetes in Hong Kong Chinese of over 10%, thus far, there have been no prospective study on the natural history of progression from GDM to DM in our local population. Furthermore, our previous studies have demonstrated that autoimmune and genetic factors

may play particular important roles in these young women and that their predisposition to DM was unmasked during a stressful period such as pregnancy.

Using a consecutive cohort of 942 pregnant women with documented glycaemic status based on 75 gram OGTT in the year 1992-1993, we have identified 130 women with gestational diabetes at the time. These women had been recalled for re-evaluation of progression to DM and metabolic syndrome. We also aimed to examine the interactions of autoimmune, genetic and environmental factors in the development of diabetes amongst these high risk women.

The progression of DM will be determined using both history (including use of medications) or 75 gram OGTT. Glycated haemoglobin, insulin, C peptide, lipid profile and autoimmune markers (antibodies to glutamic acid decarboxylase) will be examined in these individuals. DNA extraction and genetic analysis on glucokinase and mitochondrial DNA mutations and polymorphisms will also be performed. A detailed history of environmental factors will be documented through a structured questionnaire including family history of DM, levels of physical activity, tobacco and alcohol intake, occupational and leisure activities. The antenatal, intrapartum and perinatal history of the index pregnancy will be retrieved from the 1992-93 research database. Maternal weight gain, glycaemic status, blood pressure and any history of pre-eclampsia will be recorded. The interactions between these factors will be examined using standard univariate and logistic regression analysis to determine the predictors for progression to DM in these women.

(MD02964)

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#### Molecular Neurogenesis of Down's Syndrome

✉ WANG Chi Chiu • ROGERS Michael Scott • KAZUHO Ikeo\* • TAKASHI Gojobori\*

□ 30 June 2003

❖ CUHK Research Committee Funding (Direct Grants)

An extra copy of human chromosome 21 (hChr 21) causes Down's syndrome in mankind, which is characterized by mental retardation and congenital heart disease. Identification of gene dosage effect and characterisation of the gene function is an essential step towards understanding complex neurodevelopmental abnormalities in the clinical syndrome. Systematic studies of prenatal development cannot be carried out in human. We conducted a pilot study to investigate abnormalities in gene expression in neuronal stem cells and progenitor cells from a mouse embryonic stem cell line TT2F containing a single human chromosome 21 (TT2F/hChr 21) *in vitro*. The results correlated the dysregulation of the neuron-restrictive silencer factor and some of the neurological deficits. We propose to further the neurogenesis study in the developing prenatal brain *in vivo* from the embryos of chimeric mice containing an intact hChr 21. Differential temporal and spatial expression profiles of the defective neurogenesis will be displayed with mouse cDNA arrays and confirmed by whole mount *in situ* hybridisation and quantitative real-time PCR. It will provide new insights into mechanisms underlying the complex neurodevelopmental abnormalities associated with Down's syndrome.

(MD02548)

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#### High Density Allelotypes on Chromosome 1 in a Large Set of Microdissected Cervical Neoplasms and Their Clinicopathological Significance

✉ WONG Yick Fu • CHEUNG Tak Hong •  
CHUNG Kwok Hung Tony (CU02138)

□ 1 December 2002

❖ Research Grants Council (Earmarked Grants)

Cervical cancer continues to be the most common gynaecologic malignancy in Hong Kong women. The involvement of several oncogenes in cervical cancer has been demonstrated but no cervical cancer related tumor suppressor genes (TSGs) have been well characterized so far. One of the effective approaches in locating TSGs is through studying patterns of loss of alleles in tumors known as loss of heterozygosity (LOH) analysis. If a LOH within the given region contributes to the development and/or progression of a subgroup of a cancer, it may be useful as a prognostic parameter in cancer.

In cervical cancer, chromosome 1 aberrations have been one of the most commonly reported karyotypic changes. In moderate density allelotyping in cervical carcinomas, we have found the incidence of LOH at multiple loci on chromosome 1 exceeded 35%.

In this project we propose to perform a comprehensive high density and high resolution allelotyping on chromosome 1 in a large set of cervical neoplasms including cervical intraepithelial neoplasia and cervical squamous cell carcinoma using short tandem repeat polymorphism and single nucleotide polymorphism analysis in combination with microdissection and whole genome amplification techniques. With this research, we can obtain a detailed estimate of chromosome 1 loci involvement in cervical carcinogenesis for future identification of critical cervical TSGs. In addition, we will search for potential molecular prognostic markers in cervical cancers by correlating the allelic imbalances with their clinicopathological characteristics.

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**A Randomised Controlled Trial Comparing Different Protocols of Postnatal Pelvic Floor Exercised Program and Their Effectiveness in Prevention of Pelvic Floor Dysfunction after Delivery**

✉ YIP Shing Kai Alexander • PANG Man Wah Selina\* • CHAN Lin Wai Daniel\* • YIU Raymond\*

□ 1 April 2003

❖ CUHK Research Committee Funding (Direct Grants)

*Aims:* To assess whether routine postnatal pelvic floor exercise (PFE), when applied to a general obstetric population, is able to prevent the development of pelvic floor dysfunction. The study also aims to evaluate the efficacy and subject acceptance to different PFE protocols.

*Design:* Prospective randomised evaluator-blinded study.

*Setting:* The postnatal wards of a university teaching hospital plus another tertiary hospital.

*Sample:* 600 postpartum women who have had vaginal delivery.

*Methods:* The subjects will be randomised into four groups (150 subjects per group). Each group will be given different protocols of PFE in the postnatal period. *Group 1:* Control with no intervention; *Group 2:* Written instructions on PFE; *Group 3:* Individual initial assessment and training with feedback within 3 days, and then 6 weeks after delivery by a research nurse; *Group 4:* Individual initial assessment and training with feedback within 3 days, and then 6 weeks after delivery by a research nurse + weekly group exercise supervised by the research nurse for 6 weeks. The subjects in Groups

2, 3, and 4 will be given a standardised set of PFE routines, despite the different protocols.

*Outcome measures:* There are four outcome categories: (1) Clinical (vaginal squeeze pressure, symptoms of pelvic floor dysfunction); (2) Quality of life (general and disease-specific); (3) Sexual function; and (4) Client satisfaction. Validated Chinese versions of psychometric instruments will be used in categories (2), (3) and (4).

*Significance:* To develop a PFE program that is clinically efficacious and acceptable to postnatal women with minimal added cost for intervention. (MD02698)

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**Please refer to previous issues of this publication for more details of the following ongoing research at the department:**

Edition      Title/Investigators

2000-01      Microsatellite Instability in the Evolution of Cervical Neoplasm and Its Clinical Association (MD00784)

✉ CHUNG Kwok Hung Tony • WONG Yick Fu • CHEUNG Tak Hong • YU Mei Yung (Dept of Anatomical & Cellular Pathology)

2001-02      Global Protein Profiling of Cervical Cancer Using a Novel Protein Biochip Technology: A Pilot Study (MD01480)

✉ CHUNG Kwok Hung Tony • WONG Yick Fu • CHEUNG Tak Hong • MOK Samuel C\*

2000-01      A Randomized, Double-blind Placebo-controlled Crossover Study of the Effect of Livial (tibolone) on the Dyadic

Relationship of Chinese Couples (MD00939)

✉ LAM Po Mui • SHEK Tan Lei Daniel (Dept of Social Work) • LEE Tak Shing Dominic (Dept of Psychiatry) • CHEUNG Wai Yan Grace\*

2001-02      A Study on Placental Transfer of Rosiglitazone (MD01681)

✉ LAU Tze Kin • YEUNG Hok Keung John (Dept of Pharmacology) • SIU Shing Shun Nelson • CHAN Yik Si Louis

2000-01      Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study (MD98171)

✉ LI Chi Yin • ROGERS Michael Scott • NG Pak Cheung (Dept of Paediatrics)

2000-01      To Assess the Predictive Value of Ultrasonic Assessment of Umbilical Cord Morphology for Intrapartum Fetal Distress (MD20007)

✉ ROGERS Michael Scott • IP Wan Yim (The Nethersole School of Nursing) • LAU Tze Kin • PANG Chi Pui Calvin (Dept of Ophthalmology and Visual Sciences)

2001-02      Evaluation of Green Tea Polyphenols in Pregnancy (MD01077)

✉ ROGERS Michael Scott • CHU Kai On • HAINES Christopher John • LAU Tze Kin • PANG Chi Pui Calvin (Dept of Ophthalmology and Visual Sciences) • WANG Chi Chiu

- 2001-02 To Compare the Levels of Oxidative Stress in Pregnant Women with Varying Degrees of Carbohydrate Intolerance (MD01081)  
 ✍️ ROGERS Michael Scott • LI Chi Yin • NG Pak Cheung (Dept of Paediatrics) • PANG Chi Pui Calvin (Dept of Ophthalmology and Visual Sciences) • TAM Wing Hung • WANG Chi Chiu
- 2001-02 Effect of Maternal Emotional Status During Pregnancy on Neonatal Birthweight (MD01082)  
 ✍️ SAHOTA Daljit Singh • LAU Tze Kin • LEE Tak Shing Dominic (Dept of Psychiatry) • LEUNG Tse Ngong • YIP Shing Kai Alexander
- 2001-02 The Effect of Interactions Between Genetic and Environmental Factors and History of Gestational Diabetes on the Incidence of Diabetes and Metabolic Syndrome in Hong Kong Chinese Women and Their Offspring (MD01482)  
 ✍️ TAM Wing Hung • CHAN Chung Ngor Juliana (Dept of Medicine & Therapeutics) • KO Tin Choi (Dept of Medicine & Therapeutics) • NG Chor Yin (Dept of Medicine & Therapeutics) • TONG Peter Chun Yip (Dept of Medicine & Therapeutics) • COCKRAM Clive Stewart (Dept of Medicine & Therapeutics) • ROGERS Michael Scott
- 2001-02 A Prospective Observational Study on the Prevalence of Group B Streptococcus in Hong Kong Pregnant Women and Its Associated Factors (MD01945)  
 ✍️ TSUI Hang Yuet Michelle • LEUNG Tse Ngong • IP Margaret (Dept of Microbiology)
- 2000-01 Methylation Profiling of Gene Promoter CpG Islands In Cervical Neoplasm (MD00701)  
 ✍️ WONG Yick Fu • CHUNG Kwok Hung Tony • CHEUNG Tak Hong
- 2001-02 Gene Expression Profiles in Cervical Neoplasms in Hong Kong Chinese Women: Analysis by cDNA Array Hybridization (MD01084)  
 ✍️ WONG Yick Fu • CHEUNG Tak Hong • CHUNG Kwok Hung Tony • TSAO George\*
- 2001-02 A Randomized Controlled Evaluator-blinded Intervention Study of Psychological Counselling on the Outcomes of Miscarriage (MD01803)  
 ✍️ YIP Shing Kai Alexander • LEE Tak Shing Dominic (Dept of Psychiatry) • TAM Wing Hung • SHEK Tan Lei Daniel (Dept of Social Work) • CHUNG Kwok Hung Tony

## RESEARCH PROJECTS

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### Study of *RPI* Mutations Causing Autosomal Dominant Retinitis Pigmentosa

✉ CHAN Wai Man • PANG Chi Pui Calvin • LAM Shun Chiu Dennis • FAN Shu Ping Dorothy

□ 1 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

Retinitis pigmentosa (RP) represents a group of inherited human retinal diseases which involve degeneration of photoreceptor cells. It is the most widely recognized retinal dystrophy with an estimated prevalence of ~1 in 4000. Individuals affected with RP exhibit night blindness, constricted visual fields, pigment deposition in the outer retina. It is a progressive degenerative retina disease, often leading to blindness. RP occurs as autosomal dominant (ADRP), recessive, X-linked or digenic mode of inheritance.

Several genes have been identified for the different hereditary pattern of the RP. Molecular genetic studies to date have identified mutations associated with ADRP in four genes. RP1 was the one recently identified. The information and data related to the *RPI* gene in causing the RP in Chinese are currently lacking in the literature. Our preliminary study has shown a specific mutation pattern of *RPI* in Chinese RP patients when compared to Caucasians. We propose a study to determine the types and frequencies of RP1 mutation that are responsible for the RP. We shall investigate sequence alterations of all coding exons of *RPI* in RP patients, their family members and control subjects for identification of

causative *RPI* mutations. Such genotypic information and phenotype features, including onset and severity of the RP, will provide information to understand more about the molecular etiology and pathogenesis of the disease. Our results will also be helpful in making the phenotype-genotype correlation and early diagnosis. This may hopefully throw light to the future genetic therapy in this group of disease. (MD02618)

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### A Randomized, Controlled Trial of Photodynamic Therapy with Verteporfin for Choroidal Neovascularization in Pathologic Myopia in Chinese

✉ CHAN Wai Man • FAN Shu Ping Dorothy • KWOK Kwan Ho • LAM Shun Chiu Dennis

□ 1 November 2002

❖ Research Grants Council (Earmarked Grants)

Myopia is a common eye problem in Hong Kong. Eye that has refractive error equal to or greater than -6.0 diopters is classified as pathologic or high myopia. The estimated figure in the general population of Hong Kong having pathologic myopia is about 8 % while that in US is 2%. Choroidal neovascularization (CNV) is characterized by abnormal blood vessels that grow under the center of the retina in high myopia due to the elongation of the eyeball. It generally occurs among people of their young or middle age and results in a permanent, severe loss of vision. The worldwide incidence of CNV due to pathologic myopia is estimated to be 50,000 new cases per year, more are expected in the Asia due to a higher prevalence of pathologic myopia. In the past, both laser photocoagulation and surgery gave unsatisfactory outcomes. Photodynamic therapy (PDT) is a two-step procedure involving first, intravenous infusion of the drug and then, the

application of low-energy diode laser in activating the drug. This is a new modality of treatment for the CNV; however, the calculated laser energy delivered is fixed and predetermined based on the clinical response of the eyes in Caucasian. The different amount of pigment in Chinese eyes may have different energy absorption and reaction. Our pilot study shows some differences in clinical responses and outcomes, but still there is no randomized controlled study on the safety and efficacy of this treatment in Chinese or Asian eyes. Data generated from this study will provide not just important information regarding role of PDT in treating CNV in high myopia, but also pave the way for future investigations of other related ocular conditions.

(CU02140)

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**Effects of Preoperative Keratometry on Postoperative Refractive Outcomes and Corneal Curvature in Patient with Myopic LASIK**

✉ CHENG Chak Kwan Arthur • LAW Wai Kee • LAM Shun Chiu Dennis

□ 1 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

Although laser in situ keratomileusis (LASIK) has been shown to be safe and effective for the treatment of myopia, greater outcome variability has been reported in higher degrees of myopia. Factors reported to influence the predictability of LASIK include patient age, optic zone diameter, epithelial hyperlasia, and preoperative keratometry. We have previously analyzed the results of patients undergoing LASIK at our center to assess the relationship between preoperative keratometry and postoperative refraction. Our results indicate that preoperative keratometry does affect outcome predictability in

LASIK.

Our data reveals the occurrence of greater undercorrection after LASIK in eyes with less preoperative keratometry. The effect of preoperative keratometry on the final refractive outcome appears also to be greater in eyes with higher myopia, and these differences were clinically significant in eyes with myopia > -10D.

However, the exact underlying mechanism for such an observation remained obscured. The current study is designed to look at the postoperative corneal topographical changes in relation to postoperative refractive outcome in patients with myopic LASIK. Patients with flat, average and steep cornea will be individually compared.

(MD02372)

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**A Multi-center, Randomized, Double-masked, Controlled Study to evaluate the Safety and Efficacy of an Intravitreal Fluocinolone Acetonide (0.5 or 2 mg) Implant in Patients with Non Infectious Uveities Affecting the Posterior Segment of the Eye**

✉ LAM Shun Chiu Dennis • CHAN Wai Man • WONG Tak Hung • FAN Shu Ping Dorothy • CHAN Kar Mun Carmen

□ 26 July 2002

❖ Bausch & Lomb Incorporated

Sight-threatening uveitis is poorly treated with current therapy. Bausch & Lomb, Incorporated and Control Delivery Systems (CDS) have developed an implantable, sustained release drug delivery system that delivers the corticosteroid, fluocinolone acetonide, directly into the vitreous cavity of the eye. This system has the potential to maintain therapeutic drug levels in the eye while reducing systemic exposure to the drug to negligible levels. This

approach is based on experience with Vitrasert®, an intravitreal sustained-release delivery system for ganciclovir, approved by the FDA in 1996 for the treatment of AIDS-related cytomegalovirus retinitis.

Preliminary results of Phase I/II trials of the 2.0 mg and 6.0 mg fluocinolone acetonide implants suggest that this approach may be effective.

The objectives of this study are:

- (1) To evaluate the safety and efficacy of intravitreal fluocinolone acetonide implants in the management of patients with non-infectious uveitis affecting the posterior segment of the eye.
- (2) To compare the safety and efficacy of 2 doses of fluocinolone acetonide (0.5, or 2 mg) delivered by an intraocular/intravitreal implant in patients with non-infectious uveitis affecting the posterior segment of the eye.

This prospective, randomized, controlled study was designed to demonstrate the safety and efficacy of this implantable, sustained release drug delivery system, and to determine the optimal dose to be delivered in the treatment of posterior uveitis.

(MD02525)

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**Intraocular Pressure Profile, Endothelial and Nerve Fibre Analysis in Patients on Systemic Steroid**

✍ LAM Shun Chiu Dennis • FOK Tai Fai (Dept of Paediatrics) • CHIK Ki Wai (Dept of Paediatrics)  
• LI Tsz Ha Randa

☐ 1 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

Systemic steroid is mainstay of treatment for many paediatric diseases, such as nephrotic syndrome, leukaemia and various haematological and autoimmune diseases. One major ophthalmic

complication of steroid is ocular hypertension that may result in irreversible ocular damage. However, steroid induced glaucoma is usually symptom-free until significant damage has been done to the eye.

To date, reports on ocular hypertensive response to systemic steroids are few. However, different conclusions have been made based on heterogenous groups of patients receiving different dosages of steroids. Prospective and continuous surveys are needed to systematically examine the condition in order to ensure the practice evidence-based. This is especially important to patients requiring repeated courses of high dose steroid over an extended period. In order to determine the safety threshold for ophthalmic screening, more information is required with regard to: the incidence of ocular hypertension in children receiving high dose systemic steroid; temporal relationship between elevation in intraocular pressure and systemic steroid administration; and other possible associated ocular damage.

Results of this prospective study are essential for achieving safe and cost-effective management plan for patients receiving systemic steroid. If the incidence and magnitude of ocular hypertensive response are low and associated damage is minimal, we can save the effort and cost of unnecessary ophthalmic screening. However, if the incidence and magnitude are high or the associated damage is significant, the detail information obtained from this study can help clinicians to determine the timing and frequency of ophthalmic monitoring for patients receiving high dose of steroid.

(MD02783)

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**A Second Year of Treatment in a One Year, Multi-center, Double-masked, Placebo-controlled, Safety and Efficacy Study of 2% Pirenzepine Ophthalmic Gel in Children with Myopia**



**-Amendment 2 (13 February 2002) Open Label Safety Study**

✍ LAM Shun Chiu Dennis • FAN Shu Ping Dorothy • LAM Robert Fung • CHENG Chak Kwan Arthur • CHAN Kar Mun Carmen

☐ 15 February 2003

❖ Valley Forge Pharmaceuticals, Inc.

Myopia is the commonest eye problem in Hong Kong. The health-relatedness of myopia treatment has taken on a sense of urgency because of the increasing prevalence in school children. Atropine, a nonselective antimuscarinic agent, was proven to be effective in preventing myopic progression. However, it was associated with a number of side effects including pupil dilatation, photophobia and loss of accommodation. Newer type of selective antimuscarinic agent (pirenzepine) was developed. The preliminary result on this agent was promising. We are conducting a study to examine the safety and efficacy of pirenzepine treatment in preventing o myopic progression in school children in Hong Kong. A randomized trial has been instituted and the endpoints are the refractive error and the axial length after 2 years of treatment. The study will be completed by 2003. We proposed to continue the study to the third year. In this open-labeled study, all the eligibility subjects who completed the 2-year study will receive the active gel. No control group is involved.

With data collected from this study, more information on the treatment regimes in preventing myopic progression can be obtained. Thus devastating diseases associated with myopia including open-angle glaucoma, cataracts, retinal detachment, and age-related macular degeneration can be prevented.

(MD01805)

**A Randomized, Controlled Pilot Study to Evaluate the Safety and Efficacy of an Intravitreal Fluocinolone Acetonide (0.5 or 2 mg) Implants in Patients with Clinically Significant Diabetic Macular Edema**

✍ LAM Shun Chiu Dennis • CHAN Wai Man • CHAN Kar Mun Carmen • WONG Tak Hung • LI Kai Wang Kenneth • TSANG Chi Wai • FAN Shu Ping Dorothy • LI Siu Hung

☐ 24 February 2003

❖ Bausch & Lomb Incorporated

Diabetic macular edema refers to thickening of the retina due to the accumulation of fluid typically in the middle portions of the retina. It is one of the important causes of blindness in patients with diabetes mellitus. If macular edema is defined as thickening of the retina within one disc diameter of the fovea then the prevalence rate for the diabetic population as a whole is approximately 10%. The prevalence of macular edema is related to the severity of retinopathy and types of diabetes. In young onset diabetics approximately For older onset diabetics requiring insulin approximately 40% will 30% will have macular edema after 20 years. Macular edema can be subdivided into two general categories – focal and diffuse and was treated by focal laser and grid laser photocoagulation. In patients with edema involving the center of the macular the risk of losing 3 lines of vision was 13% in the treatment are compared with 33% in the observation group. Macular laser photocoagulation is effective in reducing the incidence of visual loss however it is not ideal for several reasons: (1) the likelihood of improved visual acuity is low following treatment, approximately 16% for the treatment group as a whole; (2) Laser treatment only reduces the risk of

visual loss by 50%, suggesting that an alternate therapy is needed. Over 10% of the patients in the treatment arm had a doubling of the visual angle at 3 years indicating significant visual loss; (3) Macular laser photocoagulation in more advanced cases of retinopathy is not as efficacious and this population of patients is at high risk for severe visual loss. Recently considerable attention in diabetic retinopathy has been focused on the role of vascular endothelial growth factor (VEGF). The secretion of VEGF is stimulated by hypoxia in retinal tissue and the levels of VEGF have been shown to be increased in patients with diabetic macular edema. Steroids are extremely effective in inhibiting inflammation and in turning off the gene for the production of VEGF. We propose the use of a sustained delivery formulation of the steroid fluocinolone acetonide, which can be implanted into the vitreous cavity of the eye and slowly release fluocinolone acetonide over approximately 3 years. This implant has been used in over 225 diabetic patients demonstrating a favorable risk/benefit ratio. Thus, this implant provides a means of long-term delivery of a drug known to inhibit inflammation and VEGF with favorable risk/benefit ration for DME.

(MD02973)

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**A Prospective Randomized Comparative Study on the Role of Anterior Capsular Polishing (ACP) Technique in the Subsequent Formation of Post-operative Posterior Capsule Opacification (PCO) in Senile Cataract Surgery**

✉ LAW Wai Kee • LAM Shun Chiu Dennis • CHENG Chak Kwan Arthur

☐ 1 January 2003

❖ CUHK Research Committee Funding (Direct Grants)

Posterior capsule opacification (PCO) is an important, common but yet unresolved cause of visual deterioration after a successful operation on senile cataract. The medical and economical implications are huge but the conventional treatment using Nd:YAG laser is costly and is not without complications. Serious and visual threatening complications like retinal detachment, cystoid macular edema, uveitis and secondary glaucoma do occur.

Various theories have been proposed for the formation and progression of the PCO. It is generally agreed that PCO results from the aggregation, proliferation, and transformation of the residual lens epithelial cells and the resultant deranged aggregates and the fibrosis induced will render the transplant posterior capsule opaque. These result in an unacceptable, high incident rate of PCO in the range of 18-50%.

(MD02906)

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**Gene Expression Profiling of Glaucoma**

✉ PANG Chi Pui Calvin • LEUNG Yuk Fai# • LAM Shun Chiu Dennis • FAN Shu Ping Dorothy

☐ 1 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

Glaucoma is a severe cause of visual impairment, characterized by optic nerve damage. Primary open angle glaucoma (POAG) is a common form of glaucoma and a leading cause of visual field defects and blindness in developed countries, affecting about 2% of the world's population. POAG is often associated with high intraocular pressure (IOP) due to increased resistance to aqueous humor outflow, although there are also normotensive cases. It is

multifactorial in etiology, with strong genetic susceptibility. The *MYOC* and *OPTN* are the only 2 confirmed causative gene for POAG, but together they account for less than 15% of cases. The trabecular meshwork (TM), a small network of cells rimming the junction of the iris and cornea, aids in regulating the aqueous drainage. Presence of excessive or mutated MYOC protein in the TM causes POAG, although we have shown that absence of MYOC does not lead to glaucoma. Other genes over- or under-expression in the TM of patients are involved in the etiology of POAG. We and other groups have detected over-expression of specific proteins in TM cells, and their roles in POAG are to be ascertained. We propose to study the gene expressions of TM cells from POAG patients with high IOP and to compare with the profile from people with normal IOP. We plan to obtain TM tissue from POAG and normal tension glaucoma patients after trabeculectomy, and extract RNA from specimens prepared by micro-dissection. Gene expression will be studied by human cDNA microarray. (MD02455)

**Please refer to previous issues of this publication for more details of the following ongoing research at the department:**

<u>Edition</u>	<u>Title/Investigators</u>
2001-02	Mutations in <i>ABCA4</i> ( <i>ABCR</i> ) Gene in Chinese Patients with Age-Related Macular Degeneration (MD01994) ✉ CHAN Wai Man • PANG Chi Pui Calvin • LAM Shun Chiu Dennis • FAN Shu Ping Dorothy • KWOK Kwan Ho • BAUM Lawrence

	William (Dept of Medicine & Therapeutics)
2001-02	Endolaser and Internal Limiting Membrane Removal around Macular Holes Causing Retinal Detachment in High Myopes (MD01509) ✉ CHAN Wai Man • LAM Shun Chiu Dennis
2001-02	TIGR Gene Mutations and Their Association with Primary Open Angle Glaucoma (MD00631) ✉ CHUA Kien Han John • LAM Shun Chiu Dennis • PANG Chi Pui Calvin • FAN Shu Ping Dorothy • BAUM Lawrence William (Dept of Medicine & Therapeutics)
2001-02	A Twelve-week, Double-masked, Parallel Group, Primary-therapy Study of the Safety and Efficacy of Travoprost 0.004% Compared to Latanoprost 0.005% in Patients With Chronic Angle-closure Glaucoma (MD01398) ✉ CHUA Kien Han John • LAM Shun Chiu Dennis • LAI Shiu Ming Jimmy • THAM Chee Yung Clement • POON Shuet Yan • YEUNG Yat Ming Barry • CHIU Yee Hang Thomas • NG Wai Chung Philip
2000-01	Safety of Intravitreal Injection of Various Concentrations of Indocyanide Green Dye (MD00325) ✉ KWOK Kwan Ho • LAM Shun Chiu Dennis • PANG Chi Pui Calvin •

- YAM Hin Fai# • LAI Yuk Yau Timothy
- 2000-01 Use of Conjunctival-limbal Autografts Versus Intraoperative Application of Mitomycin-C in Treatment of Recurrent Pterygium in Hong Kong (CU00052)  
 ✎ LAM Shun Chiu Dennis • RAO Srinivas Kamalakar# • YU Yau Woon Edward# • LAW Wai Kee
- 2000-01 A Randomized Trial to Investigate the Ocular-hypertensive Response to Different Dosages of Topical Steroid (0.1% Dexamethasone) in Chinese Children (CU00050)  
 ✎ LAM Shun Chiu Dennis • FAN Shu Ping Dorothy • NG Siu King Joan • YU Bing On Christopher
- 2000-01 A One-year Multi-center, Double-masked, Placebo-controlled, Parallel, Safety and Efficacy Study of 2% Pirenzepine Ophthalmic Gel in Children with Myopia (MD00996)  
 ✎ LAM Shun Chiu Dennis • FAN Shu Ping Dorothy • LAM Robert Fung
- 2000-01 A One Year Multi-center, Double-masked, Placebo-controlled, Parallel, Safety and Efficacy Study of 2% Pirezepine Ophthalmic Gel in Children with Myopia (MD20040)  
 ✎ LAM Shun Chiu Dennis • FAN Shu Ping Dorothy
- 2001-02 A Prospective Randomized Comparative Study on the Safety and Efficacy of Argon Laser Peripheal Iridoplasty (ALPI) versus Systemic Intraocular Pressure Lowering Medications for the Immediate Management of Acute Attack of Primary Angle Closure Glaucoma (PACG) (MD01090)  
 ✎ LAM Shun Chiu Dennis • CHUA Kien Han John • LAI Shiu Ming Jimmy • POON Shuet Yan • THAM Chee Yung Clement
- 2001-02 A Randomized Controlled Trial to Determine the Optimal Laser Power Setting for Argon Laser Trabeculoplasty (ALT) in Chinese Eyes with Primary Open-angle Glaucoma (POAG): 300 mW versus 500 mW (MD00727)  
 ✎ LAM Shun Chiu Dennis • THAM Chee Yung Clement • CHUA Kien Han John • LAI Shiu Ming Jimmy • POON Shuet Yan
- 2001-02 PIR207A - A Second Year of Treatment in a One Year Multi-center, Double-masked, Placebo-controlled, Parallel, Safety and Efficacy Study of 2% Pirenzepine (MD01995)  
 ✎ LAM Shun Chiu Dennis • FAN Shu Ping Dorothy • LAM Robert Fung • CHENG Chak Kwan Arthur
- 2000-01 An Observer-masked, Parallel Group, Randomized, 7-day Environment Study of Patanol versus Loratadine in Asian Patients from Hong Kong with Perennial Allergic Conjunctivitis (MD20052)  
 ✎ LAW Wai Kee • LAM Shun Chiu Dennis • LEUNG Tai Shing

- 2001-02 Retinal Nerve Fibre and Corneal Endothelial Cell Damage in Children with Previous Systemic Steroid Therapy (MD00706)  
✍ NG Siu King Joan • CHIK Ki Wai (Dept of Paediatrics) • LAM Shun Chiu Dennis • LEE K.P.\* • LI Tsz Ha Randa
- 2001-02 Identification of DNA Methylation Sites in Cancer-related Genes in Retinoblastoma Genome (MD01091)  
✍ PANG Chi Pui Calvin • CHOY Kwong Wai • FAN Shu Ping Dorothy • LAM Shun Chiu Dennis • LO Kwok Wai (Dept of Anatomical & Cellular Pathology) • TO Ka Fai (Dept of Anatomical & Cellular Pathology) • YU Bing On Christopher
- 2000-01 Role of the Putative Promoter of the *TIGR* Gene on Development of Primary Open Angle Glaucoma (MD00439)  
✍ PANG Chi Pui Calvin • LAM Shun Chiu Dennis • FAN Shu Ping Dorothy • CHUA Kien Han John • BAUM Lawrence William (Dept of Medicine & Therapeutics)

## RESEARCH PROJECTS

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### **A Study of Tendon Healing in Sports Injury: The Manipulation of Transforming Growth Factor beta (TGF- $\beta$ ) on Matrix Deposition**

✉ CHAN Kai Ming • WONG Wan Nar Margaret • FU Sai Chuen Bruma (Lee Hysan Clinical Research Laboratories) • LEE Kwong Man Simon (Lee Hysan Clinical Research Laboratories)

☐ 1 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

Tendon injury is a common sporting injury from the epidemiological perspective. The diversity of tendon injury can be classified broadly as acute traumatic tendon rupture and chronic overuse type of injuries very often loosely termed tendonitis or tendinopathies. There has not been a significant breakthrough in the management of tendon injuries, in particular intervention to enhance the natural healing process. However, the current understanding on tendon healing process is still too scarce to enable such as justified treatment. Transforming growth factor beta (TGF- $\beta$ ) is a cytokine which serves as local paracrine to mediate inflammatory responses, fibroblastic proliferation, neovascularization and matrix deposition, i.e., all stages in soft tissue healing. The association of elevated TGF- $\beta$  to healing disturbances in soft tissues indicates that manipulation of TGF- $\beta$  may be crucial to ensure a successful healing response. The study will reveal if altered TGF- $\beta$  activity leads to healing disturbances and it will serve as a basis to devise strategies to treat healing disturbances in tendon as

well as to promote tendon healing.

Therefore, the main objective of this research is to study the tendon healing process, focused on the effect of TGF- $\beta$  on matrix deposition was affected by the contextual milieu in healing tendons. We will use tendon fibroblast culture to assess if the effect of TGF- $\beta$  on matrix production is modulated by different extracellular matrix substrata.

(MD02851)

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### **The Effect of Weight of School Bag on Subjects with Adolescent Idiopathic Scoliosis: A Biomechanical and Physiological Study**

✉ CHENG Chun Yiu Jack • CHOW Hung Kay, Daniel\* • YAO Y D Fiona\* • WONG Man Sang\*

☐ 1 October 2001

❖ RGC-Central Allocation Scheme - Group Research (collaboration with PloyU)

Scoliosis is a serious deformity that can affect any part of the spine. Among the various causes, the most common group is Adolescent Idiopathic Scoliosis (AIS) which typically affects growing adolescent girls between the age of 10 to 16. Surveys show that the prevalence of AIS in Hong Kong is growing and higher than that in other countries. Scoliosis deformity when not treated or improperly treated may deteriorate progressively leading to significant cosmetic problems and functional disabilities. Despite extensive research, the etiology of AIS is still unclear. However, abnormal external loading is known to be one of the possible factors that may exacerbate the deformity. It is a common phenomenon in Hong Kong that the school bag carried by the primary school students is quite heavy and disproportionate to their size in comparison to other countries. A previous survey

showed that the average school bag weight of Hong Kong primary school students was well over the 'recommended' level. As an 'overweight' school bag can impose abnormal biomechanical and physiological stress on the spine and may affect the growth of the spine, it is important to know whether this is associated with the growing prevalence of AIS in Hong Kong. In this proposed study, the effects of weight loading, in the form of school bag, on the static and dynamic trunk balance and cardiopulmonary functions in children with AIS during walking will be examined and compared with normal age-matched controls. The outcome of this study will be useful for establishing guideline for prescribing proper school bag for children with AIS as well as normal children.

(MD01907)

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**Formative Assessment Case Studies (FACS):  
Establishing Life-Long Learning Skills in Health  
Science Students**

✉ CHENG Chun Yiu Jack • KUMTA Shekhar  
Madhukar

☐ 1 July 2002

❖ UGC Teaching Development Grants

The Information Age has created unprecedented challenges for tertiary education, and particularly so for programmes responsible for educating health care professionals. The increasing rate in the growth of information and readily available technology for accessing these burgeoning data by most of society has given rise to an increasingly informed public that holds higher expectations for its health care providers to be well versed in the latest scientific and clinical evidence.

To cope with these societal developments, health care educators have attempted to reduce coverage in basic

and clinical science content to the necessary core and have expanded their curricula to develop better process skills of life-long learning.

This TDG's goal is to augment on-going efforts to develop life-long learning skills in undergraduate medical and occupational therapy in Hong Kong. It follows closely the strategic and action plans set out by the two involved Universities (as well as their Faculties) in defining and in developing life-long learning skills which are regarded as the key attribute for addressing the challenges presented by the Information Age.

We propose to use a browser-based utility (Formative Assessment Case Studies (FACS)) that we developed. FACS enable students to proceed along learning pathways using case problems, accompanying resource materials and formative assessments (not unlike traditional programme learning models). However, feedback is automated and in the form of reflective questions and suggestions as students make decisions. Various on-line resources facilitate students undertaking further analysis and finding alternate solutions. Students cannot proceed unless these appropriate resources are accessed and time taken to reflect (the tracking of which is automated). Data pertaining to the number of unsuccessful learning cycles and additional paths students take to reach a solution are generated automatically. These data facilitate in-person teaching interventions for helping students most in need.

The formative protocol is designed to reinforce independent, successful learning and develop commitment to using independent, resourceful skills on a continuing basis (i.e. life long learning).

(ED01398)

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**The Biology and Efficacy of Low-intensity Pulsed  
Ultrasound Treatment on Posterior Spinal  
Fusion – A Study in Rabbit Model**

✉ CHENG Chun Yiu Jack • QIN Ling • LEE Kwong Man Simon (Lee Hysan Clinical Research Laboratories) • HU Yun Yu\*

□ 1 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

Spinal deformities and degenerative diseases are very common conditions in orthopaedics. Many of which would require surgical stabilization with instrumentation and posterior spinal fusion (PSF). Decortication of the vertebral lamina and other posterior structures followed by implantation of autologous bone grafts harvested from the patient's own iliac crest are standard operation procedures. However there are multiple inherent problems and disadvantages associated with the surgical procedures. In the past decade, synthetic hydroxyapatite-tricalcium phosphate (HA-TCP) has been used as a bone substitute to cut down the requirement for autograft in PSF. Recent clinical studies has demonstrated that low-intensity pulsed ultrasound (LIPUS) could significantly enhance fracture healing of the upper and lower extremities. To explore the potential clinical application of LIPUS in PSF, the study will investigate the biology and efficacy of LIPUS in PSF enhanced with HA-TCP, with or without decortication in our well established rabbit model. The research outcome of this project will significantly enhance the success of posterior spinal fusion and improve the surgical outcome. By using a combination of synthetic bone substitute and low intensity pulsed ultrasound without decortication, the necessity of the additional surgical procedure of autologous graft harvest and the associated complications at the donor site could be avoided. The quality and supply of the graft material can be

secured. Non-decorticated spinal fusion further reduces the operation time and the intra- and post-operative blood loss. The project can also provide better understanding of the biology and efficacy of low intensity pulsed ultrasound stimulation on bone formation and fusion in PSF. (MD02873)

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### **A Prospective Randomized Study on Two Methods of Mobilization After Flexor Tendon Repair**

✉ HUNG Leung Kim • WONG Man Wah • HO Pak Cheong • AU Kin Ming\* • CHAN Ping Tak\*

□ 1 June 2003

❖ Hong Kong College of Orthopaedic Surgeons

Early assisted mobilization after flexor tendon repair is a standard rehabilitation protocol. It can reduce adhesion and ensure a satisfactory recovery of movement. The Kleinert splint is widely used for this purpose.

Previously the authors practiced an active mobilization programme which did not require the use of the rubber band, a typical feature of the Kleinert splint. The advantages of this modification are reduced patient discomfort, reduced flexion contracture of the injured fingers, better flexor digitorum profundus gliding, and the feasibility to use it for combined extensor and flexor tendon injuries.

In this study the two splinting protocols are compared prospectively. Adult patients (age range 16 to 60) who had simple flexor tendon injury in their hands are randomized into using either one of the two splinting protocols. In either group the protective dorsal splint is used. In the Kleinert group, the injured finger is flexed with a rubber band. The patient extends the finger against the pull of the



rubber band. In the active mobilization group, no rubber band is used. The patient follows careful instructions to move the fingers and wrist.

The patients are assessed at regular intervals after surgery and will be evaluated for pain, scar tenderness, joint stiffness, both passive and active range of movement, grip strength, and the incidence of rupture of the tendon repair, other secondary surgical procedures and other complications.

The main outcome measures of the project are the range of movement in particular movement in the distal interphalangeal joint, the incidence of rupture of the tendon repair, other complications, and patient satisfaction.

(MD02742)

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### The Learning Objects Initiative

✉ KUMTA Shekhar Madhukar • HART Ian\* • CHAN Rita\* • Blurton, Craig\*

☐ 1 September 2002

❖ UGC Teaching Development Grants

The proliferation of e-Learning courses world-wide has resulted in considerable duplication of effort and a proliferation of modular materials that vary in quality and pedagogical effectiveness

The Learning Objects Initiative is a mechanism for the identification and development of internet-based, re-usable, updateable and accessible curriculum materials (learning objects) in a variety of disciplines (or cross-discipline) that will be made available on the Internet to all UGC-supported institutions and learners in Hong Kong. The modular materials will be designed and produced to the highest technical and pedagogic standards and evaluated by both content and education experts. It will both seek out existing materials that may have been produced under earlier

grants and support the development of new materials that conform to the Learning Object paradigm.

The Learning Object Initiative is: (1) a proactive consortium promoting the use of Learning Objects for web-based teaching and student-directed learning; (2) a funding body which facilitates the identification and development of suitable learning objects by Hong Kong academics; (3) an accreditation body that provides peer-review and evaluation and an efficient form of dissemination through the application of internationally-agreed metadata.

(ED02513)

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### Fall and Fractures Prevention Program for the Elderly

✉ LEUNG Kwok Sui • CHEUNG Wing Hoi • CHAN Tan Jessica • WONG Josephine\* • LAU Herman\*

☐ 1 August 2002

❖ S K Yee Medical Foundation

Fall is a very common accident among old people, particularly those who are under privileged, have chronic diseases and living in a crowded environment. Fall in old people often results in serious consequences, that are fractures. These fractures cause significant disabilities and even death. In fact, the commonest operation in any orthopaedic department in Hong Kong is fixing the hip fracture among elderly after fall accident. The commonest fractures we treat in fracture clinics are fractures around the wrist. We strongly believe that fall is a *preventable accident*. The goal of this project is to help the elderly to understand the risk of fall and introduce preventive measures in the daily living to minimize fall incidences, thus helping them to live a healthier and happier life. The project consists of educational program to help the elderly to understand

risk factors leading to fall accident. Home visits to identify risk factors and introduce methods to modify living habit and the environment. Exercise that helps to improve co-ordination and muscle strength will also be taught. It is hope that these programs put together will help to decrease fall incidence and thus the serious consequences from these accidents.

(MD02439)

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**Augmentation of Bone Mineral Acquisition in Osteoporotic Bone by Low-intensity Pulsed Ultrasound - A Study with Osteoporotic Goat Model**

✉ LEUNG Kwok Sui • CHEUNG Wing Hoi • LEE Kwong Man Simon (Lee Hysan Clinical Research Laboratories) • QIN Ling • SIU Wing Sum#

□ 1 September 2002

❖ Research Grants Council (Earmarked Grants)

Osteoporosis is very common among old people. Due to the change in bone mineral content and the altered microstructures, osteoporotic bone fractures easily after fall accident. Osteoporotic fractures are the commonest clinical problem that orthopaedic surgeons have to manage everyday. It is one of the major medico-social problems in the coming years. Fractures in the wrist and the hips are the commonest debilitating osteoporotic fractures. While there are many approaches to handle this common problem, we postulate that if the local bone mineral content can be improved and maintained by a non-invasive method, the incidence of fracture may decrease.

In this research project, we propose to study the effect of low-intensity pulsed ultrasound on osteoporotic bone with an osteoporotic goat model we developed in our laboratory. The low-intensity pulsed ultrasound is applied to the thigh bone around

the knee after pre-treated with shock-wave to initiate the bone forming process. We postulate that the bone forming cells (osteoblasts) may be stimulated by ultrasound directly and by the regulatory mechanism from the osteocytes activated after shock-wave pre-treatment. The changes of bone mineral content of the treated bone are monitored regularly with DXA. Bone specimens after treatment will be studied with pQCT for the bone mineral content; new bone formation pattern will be studied by histomorphometry; the change in the micro-structure with the Micro-CT and the mechanical property by indentation test with a material testing machine. The study will be conducted in four groups of animals with different treatment protocols to confirm the effect according to strict statistical analysis. The *in vivo* animal study will be further supported by the *in vitro* laboratory studies with cultured bone cells stimulated by the ultrasound and shock-wave. Their effects on bone forming cells (osteoblast) will be studied to depict the biological mechanism involved.

It is hoped that this study will help to confirm the positive effect of the use of low-intensity pulsed ultrasound on bone mineral acquisition and the possible mechanism involved in osteoporotic bone. The results of the research may be useful in the design of a simple and effective machine for prevention of osteoporotic fractures for everyday use. (CU02153)

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**The Effectiveness of a Fall Prevention Program for the Elderly Living in the Community**

✉ LEUNG Kwok Sui • CHEUNG Wing Hoi • CHAN Tan Jessica

□ 1 January 2003

- ❖ CUHK Research Committee Funding (Direct Grants)

Hip fractures are among the most common, and costly medical problems facing the elderly. An essential element in preventing hip fractures at old age is the achievement of normal peak bone mass at young age and fall prevention when the person gets old. Therefore, educational programs which can encourage old subjects to prevent falls will be beneficial.

The study aims to examine the effectiveness of a fall prevention program for the elderly living in the community using a randomized controlled trial. One hundreds and eighty elderly aged over 60 years will be recruited from the elderly centres in Shatin. They will be randomly allocated into two groups (treatment and control). For the treatment group, a fall prevention program including health education and home safety assessment will be given while the control group will receive no treatment. The rate of falls will be monitored prospectively for a year. During this period, two home visits will be conducted for the treatment group to reinforce their idea. Questionnaires on their attitude towards the risks of fall, balancing power and the muscle strength tests will be administered at baseline and 12 months after the program. The study results will provide objective and scientific basis for the use of fall prevention program in the elderly. Our study is expected to show that fall prevention educational program can effectively increase the consciousness of elderly about the impact of fall and hip fracture, reduce the incidence rate, improve their quality of life and finally reduce the financial burden of Hong Kong Health Care System.

(MD02347)

### Development and Biomechanical Characterization of Tissue Engineering Scaffolds for Articular Cartilage Regeneration

✉ QIN Ling • MAK F T Arthur\* • VUNJAK-Nova Kovic G\* • YAO K D\*

☐ 1 September 2001

- ❖ Research Grants Council (Coll. with PolyU ERG)

Articular cartilage covers the ends of articulating bones. It plays important biomechanical roles in facilitating joint movement and in transmitting joint loading to the underlying bone structure. Surface lesions on articular cartilage exhibit little propensity to heal by themselves. Subsequent tissue degeneration could lead to severe disability and major interventions such as total joint replacement. There are few successful methods that could arrest the progression of cartilage lesions in early stages before clinical joint destruction.

In the past decade, tissue engineers have been attempting to regenerate biological tissues using biodegradable scaffolds seeded with cells and other bioactive factors. It is hoped that such tissue-engineered constructs could fulfill the functional demands when placed in-situ. For musculoskeletal tissues such as articular cartilage, much of their functional demands are biomechanical in nature.

The objectives of this research are: (1) to develop and fabricate tissue-engineering scaffolds with and without a specific biomimetic feature that reflects the ultrastructural heterogeneity of normal articular cartilage (Arthur, it would be essential if we may highlight that we have successfully developed this materials, to avoid the challenge of our potential to continue rest part of research); (2) to characterize and compare the biomechanical properties of these

biodegradable scaffolds; and (3) to evaluate the subsequent tissue-constructs after different culturing and loading periods in a specially developed tissue bioreactor. The biomechanical experimental data will be analyzed using a mixture theory specially developed for hydrated biological tissues such as articular cartilage.

(BL00359)

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**Processing and Properties of Hydroxyapatite Coatings on Porous Metal Implants**

✉ QIN Ling • LENG Yang\* • FU Sai Chuen Bruma\* • FUNG Kwok Pui (Biochemistry) • SHI Yin Yu\*

□ 1 September 2001

❖ Research Grants Council (Coll. with HKUST ERG)

This proposed study aims at developing methods of hydroxyapatite (HA) coatings on titanium (Ti) substrate using a new approach involving both electrochemical and plasma spray techniques. This study focuses on improvements of mechanical properties and bioactivity of HA coated Ti implants.

Currently, Ti implants with HA coating are widely used in orthopedic and dental applications due to their better biocompatibility and bioactivity than that of pure Ti implants. It is known that implant surface morphology plays a crucial role in bioactivity and mechanical stability. Porous surfaces of implants is desirable because they promote bone cell growth into the pores and form a strong adhesion between bone and implants, since the adhesion between metal substrates and HA coatings relies on mechanical interlocks. Plasma spray is an efficient method to produce the HA coating on metal substrates, but the plasma spray is linear in nature, i.e., coatings can only form on surfaces exposed to the spray sources.

Electrochemical deposition is non-linear which can produce HA coating on surfaces inside the pores. Also, the electrochemical process can be tightly controlled, and produce desired coating morphology. However, the electrochemical processing is less efficient and its coatings adhesion to metal substrates is poorer than that of plasma spray. In this project, we plan to combine electrochemical and plasma spray methods to produce HA coating on porous Ti implants is to achieve a synergistic effect. Our goal is to obtain HA coatings on inside and outside surfaces of porous Ti implants, and also to have surface HA morphology with better bioactivity. In addition, we will investigate the method for improving adhesive strength by generating chemical gradient on porous surfaces using controlled plasma spray. The long-term objectives are to build up biomedical materials research and development, and to promote the high value-added industry of bioengineering in Hong Kong.

(BL00700)

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**Engineering Titanium Surfaces for Hard Tissue Implants**

✉ QIN Ling • LENG Yang\*

□ 1 September 2002

❖ Research Grants Council (Coll. with HKUST ERG)

This proposed study aims at developing a new type of titanium surfaces with special surface geometric patterns and chemistry which will improve bioactivity and interfaces between Ti implant and bone tissues.

Biocompatibility and bioactivity are the key factors for achieving success in biomedical materials applications. The reactions between the biomedical materials and nature tissues mainly occur at the their

interfaces. It remains as a challenge to improve the biocompatibility and bioactivity by modifying the surface chemistry and morphology of orthopedic materials.

Titanium as one of major implants materials for orthopedic and dental applications has been the major focus of research. The recent development in engineering titanium surfaces including changing the surface bioactivity by chemical treatments and modifying the surface morphology by using porous titanium or by machining surface grooves.

In this proposed project, we will use a method of combining micro-fabrication and chemical treatment to engineer the titanium surfaces. We will employ techniques of micro-fabrication techniques and electrochemical processing to produce regular pits on titanium surfaces. After chemical and heat treatment, the bioactive titanium surfaces with two dimensional array of micro-pits will promote bone ingrowths into titanium. (If possible, please emphasize the "wordings" that this method has been well established by the PI etc!) We expect that this type of surfaces improve bone integration and adhesion at the titanium/bone interfaces. This proposed study will be a part of joint and long-term efforts in bioengineering research between an engineering school and a medical school in two Hong Kong tertiary institutions.

(BL01373)

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**Ultrasonic Characterization of the Transient and Inhomogeneous Swelling Behavior and Progressive Degeneration of Articular Cartilage**

✉ QIN Ling • ZHENG Yong Ping\* • MOW Van C\* • LU MH\*

☐ 1 September 2002

❖ Research Grants Council (Coll. with PolyU ERG)

Articular cartilage is a biological weight-bearing tissue covering the bony ends of articulating joints. Subtle changes in structure or composition can lead to degeneration of cartilage such as in osteoarthritis, and ultimately to loss of functions. Currently, there is a lack of reliable diagnostic techniques for early signs of osteoarthritis. It has been documented that the swelling behavior of articular cartilage is related to the tissue ultrastructure and composition. Such swelling, particularly at the superficial zone near the articular surface, has been recognized as an early sign of cartilage degeneration. However, the inhomogeneous swelling behaviors of articular cartilage have been measured only in a destructive manner using optical methods. Biomechanical theories like triphasic models have been used to describe the transient swelling behavior of cartilage. However, there is a lack of experimental validations for those models in intact cartilages.

The objectives of this project are to use ultrasound to probe the transient inhomogeneous swelling and progressive degeneration of cartilage in vitro, and thus to develop a new approach for the early assessment of osteoarthritis. Our preliminary studies have demonstrated that ultrasound can be used to reliably measure the transients of inhomogeneous strain field during swelling and the progression of enzymatic digestion through the cartilage depth. Such transient inhomogeneous behavior of cartilage measured in a non-contact and non-destructive manner would be very useful in the biomechanical modeling and assessment of articular cartilage.

In this study, the transient inhomogeneous swelling behavior of cartilage specimens from bovine patellae treated with enzyme and from rabbit femoral

condyles with experimental osteoarthritis will be investigated by varying the ionic concentration of the bathing solution. The results of ultrasonic measurement will be compared with those measured with optical microscopic methods. They will be correlated with the corresponding quantitative histological profiles. The inhomogeneous mapping of the material properties of cartilage through its thickness will be derived from the strain distribution induced by swelling, together with a multi-phasic mixture theory.

(MD01891)

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**Biophysical Intervention for Enhancing Bone-Tendon Junction Repair during and after Immobilization - An Partial Patellectomy Model in Rabbits**

✉ QIN Ling • GUO Xia\* • LEUNG Kwok Sui • ZHENG Yong Ping\*

□ 1 December 2002

❖ Research Grants Council (Earmarked Grants)

This investigation employs the established partial patellectomy model in rabbits to study the effect of Low Intensity of Pulsed Ultrasound (LIPUS) on accelerating bone-tendon junction (BTJ) repair after surgery and cyclic tensile force induced by FES on quadriceps muscles as an active BTJ repair rehabilitation program. The results obtained will help us to modify our clinical treatment protocols, which may lead to shortening of immobilization period and an active functional rehabilitation of the operated knee for avoiding associated complications. The potential beneficial effects from this study can also be generalized to other regions involving direct bone to tendon junction repair such as ankle and shoulder. The significance of this study will be particularly important in the following aspects: (1)

from the performance perspective, because injured athletes strive to return to training and competition as early as possible; and (2) from the public health perspective, it should be stressed that some tissues may not fully recover after immobilization, which may cause morbidity, particularly among the elderly individuals.

(CU02155)

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**Ultrasound Elastomicroscopy**

✉ QIN Ling • LENG Yang\*

□ 1 January 2003

❖ Research Grants Council (Coll. with PolyU ERG)

Bone fractures caused by osteoporosis have been one of the big socioeconomic problems in the world. To avoid such fractures, it is necessary to know the factors determining the bone fracture risk. This is of prime importance in the assessment of fracture risk, prevention of osteoporotic fracture and the measurement of efficacy of therapeutic interventions in bone disease. The influence of age or disease related bone loss, bone remodeling and bone adaptation on the mechanical behavior of trabecular bone is dependent on the internal bone architecture and the loads externally applied on the structure. This study aims at developing micro-finite element models to predict the trabecular bone fracture risk. The micro-architecture of trabecular bone will be obtained by 3D reconstruction of the MicroCT images. The mechanical properties of bone tissues and whole specimen will be measured experimentally. The quantitative results obtained by model simulation will provide the critical information regarding bone biomechanics and outcome assessment of drug or surgical treatment.

(BL02792)

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**Development of Micro-Finite Element Model for Quantifying Mechanical Properties of Trabecular Bone**

✉ QIN Ling • GUO Xia\* • ZHANG Min\* • SHI San Qiang\*

□ 1 February 2003

❖ POLYU ICRG Research Grants for Interdisciplinary / Collaborative Research 2003

Bone fractures caused by osteoporosis have been one of the big socioeconomic problems in the world. To avoid such fractures, it is necessary to know the factors determining the bone fracture risk. This is of prime importance in the assessment of fracture risk, prevention of osteoporotic fracture and the measurement of efficacy of therapeutic interventions in bone disease. The influence of age or disease related bone loss, bone remodeling and bone adaptation on the mechanical behavior of trabecular bone is dependent on the internal bone architecture and the loads externally applied on the structure. This study aims at developing micro-finite element models to predict the trabecular bone fracture risk. The micro-architecture of trabecular bone will be obtained by 3D reconstruction of the MicroCT images. The mechanical properties of bone tissues and whole specimen will be measured experimentally. The quantitative results obtained by model simulation will provide the critical information regarding bone biomechanics and outcome assessment of drug or surgical treatment.

(BL02993)

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**The Effect of Glucocorticoid on Human Tendon Explant – A Biomechanical Study**

✉ WONG Wan Nar Margaret • CHAN Kai Ming • FU Sai Chuen Bruma (Lee Hysan Clinical Research Laboratories) • LEE Kwong Man Simon (Lee Hysan Clinical Research Laboratories)

□ 1 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

Glucocorticoid injections are used in a wide spectrum of soft tissue disorders and inflammatory conditions. The potent anti-inflammatory action often gives rapid clinical response. There are a number of reports on spontaneous tendon ruptures with previous glucocorticoid injection in the literature. However, an association or cause-effect relationship has never been established. A clarification of its effect is needed to allow practice with evidence based medicine.

Our group have demonstrated cytotoxic and cytostatic effects, and also suppressed 35-sulphur uptake, indicating decreased proteoglycan synthesis by dexamethasone (a glucocorticoid) on human tendon fibroblast cultures. The cell culture system lacks the extracellular matrix and three-dimensional structure of normal tendons, which affects the response to stimuli. We propose to further investigate the link between glucocorticoid and eventual tendon ruptures using human tendon explant tissue culture. Using tendon explant culture has the advantage of controlled *in vitro* experiment, yet maintaining the three dimensional structure of tendons and the presence of extracellular matrix.

The proposed study will examine the effect of a commonly used glucocorticoids (dexamethasone) in human tendon explant culture, testing its effect on the biomechanical properties.

The result of this study will clarify the link between glucocorticoid injections, effect on mechanical

properties and possible eventual link to spontaneous tendon ruptures. Evidence based recommendations on the proper use of local steroid may then be devised. The findings also form basis for future studies to search for ways to allow the continuous use of this useful therapeutic regime, while limiting its adverse effects.  
(MD02366)

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**Please refer to previous issues of this publication for more details of the following ongoing research at the department:**

Edition      Title/Investigators

2000-01      Low Intensity Pulsed Ultrasound Retained Change of Bone Mineral Content of Complex Tibial Fractures (MD00354)

✉ CHAN Chun Wai\* • LEUNG Kwok Sui • TSUI Hon For# • LEE Wing Sze

2000-01      Low Intensity Pulsed Ultrasound Enhanced Bone Mineral Content of Tibial Lengthening (MD00579)

✉ CHAN Chun Wai\* • LEUNG Kwok Sui • CHENG Chun Yiu Jack • NG Kin Wah Bobby • LEE Wing Sze • HUNG Wing Yin Vivian

2001-02      A Study of the Potential of a Semi-purified Total Flavone Extract from Chinese Medicine Hippophae Rhamnoides in Promoting Tendon Healing (MD01092)

✉ CHAN Kai Ming • FU Sai Chuen Bruma (Lee Hysan Clinical Research

Laboratories) • FUNG Kwok Pui (Biochemistry) • GAO Jin\* • LI Jingxian\*

2001-02      To Promote Tai Chi as an Exercise to Enhance the Health Promotion Aspect of Osteoporosis (MD01740)

✉ CHAN Kai Ming • QIN Ling • LI Jingxian (Dept of Sports Science & Physical Education) • HONG Youlian (Dept of Sports Science & Physical Education) • LAU Edith Ming Chu (Dept of Community and Family Medicine) • WOO Jean (Dept of Medicine & Therapeutics)

2000-01      Re-defining the MRI Reference Level for Cerebellar Tonsil - A Study of 225 Adolescents - Normal vs Idiopathic Scoliosis (MD00378)

✉ CHAU Wai Wang • CHENG Chun Yiu Jack • GUO Xia • CHAN Y. L.\*

2000-01      The Implications of Preoperative Somatosensory Evoked Potential (SSEP) in Adolescent Idiopathic Scoliosis Patients (MD00430)

✉ CHAU Wai Wang • FU Lap Kun • GUO Xia • CHENG Chun Yiu Jack

1998-99      Low Volumetric Bone Mineral Density in Adolescent Idiopathic Scoliosis (MD98136)

✉ CHENG Chun Yiu Jack • QIN Ling • GUO Xia • LEE Kwong Man Simon (Lee Hysan Clinical Research Laboratories) • NG S W Edmond\*



- 1999-00 Osteoporosis in Adolescent Idiopathic Scoliosis - A Study of the Genetic Markers, Bone Mineral Turnover and Their Correlation with Severity and Progression of the Spinal Deformity (CU99336)  
 ✍ CHENG Chun Yiu Jack • LEE Kwong Man Simon (Lee Hysan Clinical Research Laboratories) • QIN Ling • GUO Xia
- 2000-01 "Subacute Synovitis of the Hip in Children" A distinct Entity? - A Follow-up Study of 84 Cases (MD99384)  
 ✍ CHENG Chun Yiu Jack • YUNG Shu Hang Patrick • NG Kin Wah Bobby • LAM Tsz Ping
- 2000-01 An Immunohistochemical Study on Expression of Decorin and Biglycan in Bone of Osteopenic Adolescent Idiopathic Scoliosis Girls (MD00734)  
 ✍ CHENG Chun Yiu Jack • TANG Shengping • GUO Xia • LEE Kwong Man, Simon\* • QIN Ling
- 2000-01 Can Exogenous Vascular Endothelial Growth Factor (VEGF) Enhance Angiogenesis and Osteogenesis in Posterior Spinal Fusion? (CU00140)  
 ✍ CHENG Chun Yiu Jack • CHOW Pak Ham Patricia (Dept of Anatomy) • GUO Xia • LEE Kwong Man Simon (Lee Hysan Clinical Research Laboratories) • TABATA Yasuhiko\*
- 2000-01 Sternocleidomastoid Pseudotumor of Infants (SCMPOI) and Congenital Muscular Torticollis (CMT): The Relation Between Spontaneous Regression and Apoptosis (MD00523)  
 ✍ CHENG Chun Yiu Jack • TANG Shengping • LIU ZQ\* • QuanXM\* • QIN JZ\* • ZHANG DW\*
- 2000-01 Virtual Reality (VR) Based Systems for Training on Endoscopic Surgery and Diagnostic Ultrasound Procedures (EE20028)  
 ✍ CHENG Chun Yiu Jack • HENG Pheng Ann (Dept of Computer Science and Engineering) • CHAN Kai Ming • CHUNG Chi Kit Ronald (Dept of Auto. & Computer-Aided Engin.) • CHUNG Sheung Chee Sydney (Dept of Surgery) • LAU Tze Kin (Dept of Obstetrics & Gynaecology) • LEUNG Kwong Sak (Dept of Computer Science and Engineering) • SUNG Joseph Jao Yiu (Dept of Medicine & Therapeutics) • TSUI Hung Tat (Dept of Electronic Engineering) • WONG Tien Tsin (Dept of Computer Science and Engineering) • XU Yangsheng (Dept of Auto. & Computer-Aided Engin.) • YIM Ping Chuen Anthony (Dept of Surgery) • SHI Peng Cheng\* • TSO Shiu Kit\*
- 2000-01 Osteopenia in Adolescent Idiopathic Scoliosis (AIS): Preliminary Ultrastructural Study (MD00374)  
 ✍ CHENG Chun Yiu Jack • TANG Shengping • GUO Xia • LEE Kwong Man, Simon\* • QIN Ling

- 2001-02 Percutaneous Intramedullary Kirschner Wiring for Displaced Disphyseal Fractures in Children (MD99476)  
 ✍ CHENG Chun Yiu Jack • YUNG Shu Hang Patrick • NG Kin Wah Bobby • LAM Tsz Ping
- 2001-02 Promoting a safer Household Environment: A Volunteer-based Home Visit Programme (MD01665)  
 ✍ CHENG Chun Yiu Jack • CIPRA members\*
- 2001-02 Correlation of Calcium Absorption and Homeostasis with Severity and Progression of Spinal Deformity in Growing Adolescents with Idiopathic Scoliosis (MD99370)  
 ✍ CHENG Chun Yiu Jack • LEE Tak Keung Warren • LEE Kwong Man, Simon\* • GUO Xia
- 2001-02 Relationship between Postural Balance, Somatosensory Evoked Potential and the Progression of Scoliotic Deformity in Adolescent Idiopathic Scoliosis - A Longitudinal Study (MD01864)  
 ✍ CHENG Chun Yiu Jack • HUI Chan W Y Christina\* • GUO Xia\*
- 2001-02 Electromotive Antibiotic Delivery to Bone by Iontophoresis (MD01360)  
 ✍ HUNG Leung Kim • CHAN Chiu Yeung Raphael (Dept of Microbiology) • WU Hay Tong
- 2000-01 Towards Understanding the Molecular Events of Histogenesis and Biological Behaviour of Giant Cell Tumour of Bone - The Significance of Urokinase Type Plasminogen Activating System and Osteoclast Regulatory Factors (CU00142)  
 ✍ KUMTA Shekhar Madhukar • CHOW Tsun Cheung Louis (Dept of Anatomical & Cellular Pathology) • LEE Kwong Man Simon (Lee Hysan Clinical Research Laboratories) • LEUNG Ping Chung • ZHENG Ming Hao\*
- 2001-02 A Web-based Self Assessment Programme for Final Year Orthopaedic Students (MD01680)  
 ✍ KUMTA Shekhar Madhukar
- 2001-02 Promotion of Experience Sharing and Sharing of Good Teaching and Learning Practices in CUHK 2001 - Teacher Focused Workshops to Enable the Development of Interactive Web-based Strategies Designed to Foster Critical Thinking in Students (ED01533)  
 ✍ KUMTA Shekhar Madhukar • CHENG Chun Yiu Jack • HUNG Leung Kim
- 2001-02 Bisphosphonates Induce the Healing and Consolidation of Osteolytic Secondary Bone Tumors (MD01649)  
 ✍ KUMTA Shekhar Madhukar • YEO Winnie (Dept of Clinical Oncology) • GRIFFITH James Francis (Dept of Diagnostic Radiology & Organ Imaging) • CHOW Tsun Cheung Louis (Dept of Anatomical &

- Cellular Pathology) • HUANG Lin • CHENG Yuen Yee#
- 2000-01 Monteggia Fracture in Children - A Review of 30 cases (MD00535)  
 ✎ LAM Tsz Ping • MA RF\* • NG Kin Wah Bobby • CHENG Chun Yiu Jack
- 2000-01 Anterior Spinal Fusion with Halm-Zielke Instrumentation System in Adolescent Idiopathic Scoliosis (MD00788)  
 ✎ LAM Tsz Ping • NG Kin Wah Bobby • CHENG Chun Yiu Jack • MA RF\*
- 2000-01 Calcium Intakes in Patients with Adolescent Idiopathic Scoliosis (AIS) (MD00838)  
 ✎ LEE Tak Keung Warren • CHEUNG Siu King • LAM See Way Sylvia (Dept of Community and Family Medicine) • LEE Ching Shun Christine\* • CHAU Wai Wang • CHENG Chun Yiu Jack
- 1999-00 The Effect of Non-invasive Low Intensity Pulsed Ultrasound on the Consolidation of Osseous Tissue after Callotasis - The Biological Basis and Its Potential Clinical Application (CU99257)  
 ✎ LEUNG Kwok Sui • LEE Kwong Man Simon (Lee Hysan Clinical Research Laboratories) • FUNG Kwok Pui (Biochemistry) • CHAN Chun Wai (Lee Hysan Clinical Research Laboratories)
- 2000-01 The Biological Mechanism of Neo-osteogenesis with Callotasis - A Study of the Effect of External Mechanical Stimulation on Biological System and Its Potential in Clinical Modulation (MD00652)  
 ✎ LEUNG Kwok Sui • FUNG Kwok Pui (Biochemistry) • LEE Kwong Man Simon (Lee Hysan Clinical Research Laboratories) • LUI Po Yee Pauline# • CHAN Chun Wai (Lee Hysan Clinical Research Laboratories)
- 2000-01 Reconstruction of Damaged Physis with 3-D Chondrocytes Pellet Culture (MD20039)  
 ✎ LEUNG Kwok Sui • LUI Po Yee Pauline# • LEE Kwong Man Simon (Lee Hysan Clinical Research Laboratories) • CHEUNG Wing Hoi
- 2001-02 The Biological Mechanism of Neo-Angiogenesis with Callotasis - A Study of the Effect of External Mechanical Stimulation on Biological System and Its Potential in Clinical Modulation (MD01806)  
 ✎ LEUNG Kwok Sui • LEE Kwong Man Simon (Lee Hysan Clinical Research Laboratories) • FUNG Kwok Pui (Biochemistry) • LUI Po Yee Pauline#
- 2000-01 Development and Clinical Trials of Compound Yun Zhi (Jiang Su) and Danshen (He Nan) Products (MD20043)  
 ✎ LEUNG Ping Chung • FUNG Kwok Pui (Biochemistry) • LAM Wai Kei

	Christopher (Dept of Chemical Pathology)	2001-02	Low Intensity Pulsed Ultrasound for Accelerating Bone-tendon Junction Repair (MD01098)
2001-02	Herbal Formula for Prevention and Treatment of Osteoporosis - A Rat Model (MD01097)		✍ QIN Ling • LEE Kwong Man Simon (Lee Hysan Clinical Research Laboratories) • LENG Yang* • WONG Wan Nar Margaret
	✍ LEUNG Ping Chung • FU Sai Chuen Bruma (Lee Hysan Clinical Research Laboratories) • FUNG Kwok Pui (Biochemistry) • QIN Ling • SHI Yin Yu*	2000-01	Treatment of "Floating Elbow" in children (MD00960)
2001-02	Chinese Medicine Research and Further Development (MD01714)		✍ TANG Ning • NG Kin Wah Bobby • CHENG Chun Yiu Jack
	✍ LEUNG Ping Chung • FUNG Kwok Pui (Biochemistry) • SUNG Joseph Jao Yiu (Dept of Medicine & Therapeutics) • HAINES Christopher John (Dept of Obstetrics & Gynaecology) • SUNG Yn Tz Rita (Dept of Paediatrics) • WOO Kam Sang (Dept of Medicine & Therapeutics) • CHE Chun Tao (School of Chinese Medicine) • CHAU F T* • TSIM Karl W K* • FONG W F*	2000-01	Bacterial Adherence to Gentamicin-PMMA Beads (MD20030)
			✍ WONG Wan Nar Margaret • HUI Mamie (Dept of Microbiology)
		2000-01	Bio-engineered Chondrocyte Pellet as Interposition Material for Acceleration of Bone-tendon Junction Healing and Restoration of Junctional Fibrocartilage Zone (MD00373)
			✍ WONG Wan Nar Margaret • QIN Ling • LEE Kwong Man Simon (Lee Hysan Clinical Research Laboratories)
2000-01	Associated Osteoporosis of the Host Bone in Tibial Lengthening (MD00633)	2001-02	The Effect of Glucocorticoid on Human Tendon Explant: The Link with Tendon Rupture (MD01921)
	✍ NG Kin Wah Bobby • HUNG Wing Yin Vivian • CHENG Chun Yiu Jack		✍ WONG Wan Nar Margaret • FU Sai Chuen Bruma* • LEE Kwong Man Simon (Lee Hysan Clinical Research Laboratories) • CHAN Kai Ming
2000-01	Application of Low Intensity Pulsed Ultrasound for Bone-tendon Junction Repair (MD00844)	2000-01	Culture of Rabbit Chondrocytes Released from Rib Cage on Calcium Phosphate
	✍ QIN Ling • WONG Wan Nar Margaret • LEE Kwong Man, Simon* • LEUNG Kwok Sui		

Ceramic and Collagen Sponge  
(MD98751)

✉ YEUNG Hiu Yan • LEE Kwong  
Man, Simon\* • CHEUNG Wing Hoi  
• LAW Lai Pang (Institute of

Chinese Medicine)# • TABATA  
Yasuhiko\* • CHENG Chun Yiu Jack

## RESEARCH PROJECTS

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### **Application of Hematopoietic Growth Factors in the Protection and Repair of the Central Nervous System: An Experimental Study in Neonatal Rats with hypoxic-ischemic Brain Damage**

✉ CHIK Ki Wai • YANG Mo • FOK Tai Fai • LI Kwai Har Karen

☐ 1 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

Erythropoietin (EPO) has been known as a neuro-protective factor. However, its effect on neonatal brain damage has not been investigated. We hypothesize other hematopoietic growth factors such as thrombopoietin (TPO) and angelica polysaccharide (APS) as well as EPO may have neuronal regeneration effect. We will analyze and compare their effects on neuro-protection and neuronal regeneration in neonatal rat model with hypoxic-ischemic brain damage and mitogenic effects on *in vitro* cultured neurons. The brain repair effect of EPO, TPO and APS, if proven in this neonatal model, may open up new clinical applications for hypoxic-ischemic brain damage.

(MD02440)

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### **Randomised Controlled Trial of the Use of Colloid and Crystalloid in the Treatment of Hypotension in Preterm Very Low Birth Weight Newborns**

✉ FOK Tai Fai • NG Pak Cheung • SO King Woon Alan

☐ 30 June 2003

❖ CUHK Research Committee Funding (Direct Grants)

Hypotension is a common complication of preterm infants. The condition may damage vital organs including the brain, kidney, heart, and intestine. Standard treatment of hypotension is rapid expansion of the blood volume by intravenous infusion of fluid which may be a salt solution (crystalloid) or a salt solution with added albumin (colloid). Theoretically, albumin may stay in the blood vessels for a longer time, and have a more sustained effect in supporting blood pressure. For this reason many neonatal units are using albumin as the first line treatment of hypotension in newborns. However, sick preterm infants have permeable capillary wall which allows the leakage of infused albumin into the surrounding tissues. In preterm infants with lung disease such as respiratory distress syndrome, leakage of protein into the air spaces may result in inactivation of surfactant and inflammatory changes that may lead to the development of chronic lung disease. The use of crystalloids is not associated with this complication. Studies in critically ill hypotensive adults have shown that when compared to crystalloids, colloids are not more effective in restoring blood pressure, and its use is associated with higher mortality. There is only one study comparing the use of colloids and crystalloids in preterm infants. This study, reported by us in 1997, showed that 0.9% sodium chloride solution (a crystalloid) and 5% albumin (a colloid) had similar effect in stabilizing blood pressure, but the use of albumin was associated with a possible increase in mortality and chronic lung disease. The differences were however not statistically significant due to the relatively small number of infants studied, and albumin continues to be used in many neonatal units as the standard solution for the treatment of

hypotension. By enrolling a large enough sample of infants, the following multi-centre study is designed to determine conclusively the relative benefits and harms of using 5% albumin or 0.9% sodium chloride solution in the treatment of hypotensive preterm newborns. The findings may provide the rationale for neonatologists to use the more effective and safer treatment modality in these infants.

(MD02796)

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**Identification of Predisposition Genes for Atopic Dermatitis in Chinese Children**

✉ HON Kam Lun • LEUNG Ting Fan • TANG Leung Sang Nelson (Dept of Chemical Pathology) • MA Kwok Chiu\* • LAM Wai Kei Christopher (Dept of Chemical Pathology)

□ 4 April 2003

❖ CUHK Research Committee Funding (Direct Grants)

Atopic dermatitis is a relapsing and disabling disease associated with allergen exposure. This atopic disorder affects up to 20 percent of Hong Kong children. Parallel to asthma and allergic rhinitis, advances have been made in both clinical and laboratory grounds in understanding the pathophysiology of atopic dermatitis. Inherited predisposition and a variety of environmental influences are implicated in the development of these atopic disorders. Unlike asthma, however, little has been done in studying the genetics of atopic dermatitis. The relevant literature in Chinese subjects has been particularly deficient. This study, aiming to identify the predisposition genes for atopic dermatitis in Chinese families using the transmission disequilibrium approach, will delineate whether these predisposition genes also act as disease-modifying loci that regulate the severity of atopic dermatitis in

the Chinese population. In addition, the relationship between these predisposition genes and the susceptibility to develop sensitisation to food allergens will be defined. Our research may enable us to identify young children at risk of having atopic dermatitis early so that appropriate drug therapy as well as non-pharmacologic management (e.g. allergen avoidance) for this common disease can be instituted.

(MD02691)

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**A Pilot Study of Exhaled Chemokines as Novel Non-invasive Inflammatory Markers for Childhood Asthma**

✉ LEUNG Ting Fan • WONG Wing Kin Gary • WONG Chun Kwok (Dept of Chemical Pathology) • LAM Wai Kei Christopher (Dept of Chemical Pathology)

□ 1 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

Asthma is the most prevalent chronic childhood disease worldwide. Immunologically, asthma is characterised by an overproduction of cytokines and chemokines from type-2 T helper (Th2) lymphocytes. The disease severity of asthma is traditionally assessed by spirometry as well as a number of tedious and insensitive clinical scoring systems. The measurement of a number of inflammatory markers in peripheral blood is advocated as an accurate and reproducible means of monitoring asthma control. However, the painful procedure associated with blood taking prohibits clinicians from repeating these inflammatory markers too frequently especially in children. The quantitation of nitric oxide and non-volatile chemicals such as hydrogen peroxide in exhaled breath is currently investigated for their

usefulness in assessing asthma severity. It will be of great impact to everyday clinical practice if we can establish that these exhaled inflammatory markers, when measured serially, can 'predict' the worsening of asthma control. Our group is amongst the first to report increased plasma concentration of TARC, a Th2-specific chemokine, in children with asthma. This marker also correlated with spirometric indices of asthma severity. The main aim of this study is to investigate whether Th2-specific chemokines can be detected in exhaled breath and to study the utility of these important chemotactic factors in assessing airway inflammation in children with asthma.

(MD02947)

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***In vitro* Induction of Human Embryonic Stem Cells into Functional, Multi-potent Hematopoietic Stem Cells**

✍ LI Kwai Har Karen • TSANG Kam Sze Kent  
(Dept of Anatomical & Cellular Pathology)

□ 1 May 2003

❖ CUHK Research Committee Funding (Direct Grants)

A major breakthrough in stem cell research was reported by Thomson *et al* (1998), who successfully established the human embryonic stem cell line (ESC) H1 from preimplantation blastocytes. ESC can be maintained in culture indefinitely as undifferentiated cells. They also, in principle, have the capacity to commit into cell types of all germ layers, and thus becoming a valuable source of pluripotent stem cells for replacing defective tissues of the body. However, there are significant challenges to be overcome before ESC can be applied in the clinic. The prime concern is to generate sufficient numbers of the desired cell type in a pure form. In this study, we propose to adopt a novel approach to induce

human ESC to the hematopoietic lineage. The H1 line will be co-cultured (contact and non-contact) with matrix/stromal cells established from murine AGM, fetal liver and bone marrow. Using the appropriate growth factor supports, we shall study the *in vitro* development of the hematopoietic system, using lineage and developmental specific markers by flow cytometry (CD34, CD133, CD38, CD31, CD41, CD45, CD3) and functional clonogenic cells (CFU-GEMM, BFU-E, CFU-GM, LTC-IC and CAFC) by colony forming assays. The homing and multi-potent capacity of these human cells will be evaluated by their engraftment in the non-obese diabetic (NOD)/severe immunodeficient (SCID) mouse transplant model. Results obtained from this project would contribute to better understanding the mechanism of human hematopoiesis as well as to the much-needed technology for the induction of human ESC to a targeted lineage suitable for clinical applications.

(MD02937)

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**The Role and Mechanism of Stem Cells in Regenerative Medicine**

✍ LI Kwai Har Karen • NG Ho Keung (Dept of Anatomical & Cellular Pathology) • CHAN Chung Ngor Juliana (Dept of Medicine & Therapeutics) • CHAN Hsiao Chang (Dept of Physiology) • SUNG Yn Tz Rita • FOK Tai Fai

□ 1 June 2003

❖ CUHK Strategic Research Program

Stem cells, the fundamental building blocks of human development, are abundant in early embryogenesis. In an adult, some stem cells such as those replenishing the blood system and skin tissues remain robust throughout life. Others, such as neural and cardiomyocytic stem cells, have been considered as



either absent or inactive. This traditional view on stem cells and thus their potential clinical applications, however, have recently been revised by two revolutionary concepts: stem cell plasticity and human embryonic stem cells. In principle, these technologies could lead to the induction of multi-potent stem cells for replacing defective tissues of the body, such as those manifested in Parkinson's diseases, Type 1 diabetes and myocardial infarction.

The present Strategic Program represents a concerted effort combining the experience and expertise of basic and clinician scientists to develop this innovative and crucial technology of stem cell therapy which are of theoretic values and clinical relevance. In this series of interlinked project, bone marrow, embryonic and fetal stem cells will be induced to various tissues including pancreatic islets, neurons, epithelium and hematopoetic cells by the use of traditional Chinese medicines, cytokines and growth factors. The methodology employed would include the identification of cell types using different markers, molecular technology to examine gene expressions and animal models for *in vivo* functional assessment of the derived cell types and clinical protocols. Specifically, the following resources will be established: (a) stem cell/ fetal cell banks, (b) stem cell marker bank, (c) immune-deficient NOD/SCID animal models for engrafting various cell types and (d) molecular techniques and database.

(MD02328)

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### **An Epidemiological Study of Obstructive Sleep Apnoea Syndrome in Hong Kong Chinese Children**

✉ LI Man Chim Albert Martin • FOK Tai Fai • LAM Chuen Kwong (Dept of Surgery) • LAU Tak Fai Joseph (Centre For Epidemiology &

Biostatistics) • WING Yun Kwok (Dept of Psychiatry)

□ 1 October 2002

❖ Research Grants Council (Earmarked Grants)

Childhood obstructive sleep apnoea syndrome (OSAS) is a common and serious condition. It can result in significant morbidity and possibly mortality if left untreated. Early reports documented such complications as failure to thrive, systemic hypertension, pulmonary hypertension and neuro-cognitive deficits. 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. Previous studies 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 the United States and Indian descendants 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 this information allow further cross-ethnic comparison; the study will also lay the foundation for establishing an epidemiological approach to paediatric sleep disorders in general. 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 condition and to foster the development and research of paediatric Sleep Medicine in Hong Kong.

(CU02161)

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**Assessment of Daily Glycaemic: A Pilot Study**

✉ NELSON Edmund Anthony Severn • SUNG Yn Tz Rita • WONG Wing Kin Gary

☐ 1 January 2003

❖ CUHK Research Committee Funding (Direct Grants)

The dramatic global increase in the prevalence of obesity is reaching epidemic proportions, in both developed and developing countries. However, the role of dietary composition on body weight regulation remains unclear. This pilot study aims to investigate the feasibility of using the Glucowatch to measure oral glucose tolerance test (OGTT), food glycaemic index (GI), and postprandial blood sugar profiles and food intake in obese and normal weight adolescents and adults. The results of this study will be used to assess the feasibility of using the Glucowatch to study the OGTT and glycaemic profiles of normal weight and obese adolescents and adults following the ingestion of high and low GI meals. Two obese adolescents and four normal weight adults will be evaluated on two occasions. Participants will follow different dietary schedules on each occasion according to a defined schedule. Blood glucose levels will be recorded using the Glucowatch. The Glucowatch obtains glucose measurements on subcutaneous glucose samples by using reverse iontophoresis. Blood glucose data from the Glucowatch will be compared with blood samples and dietary records.

(MD02429)

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**A Multicentre, Randomised, Double Blind, Controlled Study of Oral Erythromycin for Treatment of Gastrointestinal Dysmotility in Preterm Infants**

✉ NG Pak Cheung • CHENG Fun Bun Augustine (Dept of Microbiology) • CHOW C B\* • FOK Tai Fai

☐ 1 December 2002

❖ Research Grants Council (Earmarked Grants)

Gastrointestinal dysmotility manifested as feed intolerance is a common problem in very low birth weight (VLBW) infants requiring intensive care. Slow advancement in enteral feeding often leads to prolonged use of parenteral nutrition which may predispose to cholestatic jaundice and hepatic dysfunction, nosocomial bacterial and fungal infection, and prolonged hospitalisation. As cisapride is no longer suitable for clinical use, there is currently no approved medication recommended for treatment of this condition. This randomised controlled study is, thus, necessary to determine that oral erythromycin is an useful drug in promoting enteral feeding in VLBW infants, and it may also reduce the incidence of parenteral nutrition induced cholestatic jaundice which is potentially serious and life-threatening. Earlier achievement of full enteral feeding may also translate into shorter duration of parenteral nutrition, lesser hyperalimentation associated traumatic procedures (e.g. long line placement) and complications, and may result in shorter duration of hospitalisation.

(CU02163)

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**Generation of Cardiomyocytes from Bone Marrow Stromal Cells: The Effect of Serotonin**

✉ SUNG Yn Tz Rita • YANG Mo • LI Kwai Har  
Karen • YI Qi Jian\*

□ 1 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

Myocardial infarction is a highly fatal disease caused by the irreversible damage of tissues and the subsequent impairment of cardiac function. As the remaining myocytes are unable to reconstitute the necrotic tissue, the post-infarction heart function deteriorates with time. Recent *in vivo* studies have suggested that bone marrow cells possess the capacity to differentiate into cardiomyocytes, which potentially could repair damaged cardiac muscles. In this study, we aim to establish an *in vitro* culture system that generates functional cardiomyocytes from murine bone marrow stromal cells. We propose that serotonin, which is a neural transmitter as well as a factor for heart development, would enhance the production of cardiomyocytes. Our read-out system of cardiomyocyte formation and functions includes the measurement of ultrastructure by transmission electron microscopy; cardiomyocyte-specific gene expressions by RT-PCR and Southern blot; cardiomyocyte-specific protein expressions by immunostaining; and electrophysiology of cardiomyocytes by action potential recording. The transplant of cultured, autologous cardiomyocytes would theoretically incur little adverse complications caused by immune reactions of allogeneic tissue transplants. The generation of myocardial progenitors from bone marrow stromal cells would be potentially applicable to the treatment of myocardial infarction and degenerative diseases.

(MD02591)

### A Randomised Trial on the Effects of Rope Skipping in Normal Weight and Overweight Children

✉ SUNG Yn Tz Rita • WOO Kam Sang (Dept of Medicine & Therapeutics) • LAU Wing Chung Patrick\*

□ 1 February 2003

❖ Hong Kong College of Cardiology

*Objectives:* To test the hypotheses that both normal weight and overweight children may become physically and psychologically fitter after rope skipping exercise. Overweight children may have additional benefits of lowered blood pressure, lipid & insulin levels and improved exercise capacity and endothelial function.

*Design:* Randomised controlled trial of a rope-skipping program compared with no intervention.

*Participants:* Eighty 8 to 12-year old normal weight children with body mass index (BMI) between 3rd and 75<sup>th</sup> percentile of the age- and sex- specific local BMI charts and 80 overweight children (BMI between the 85<sup>th</sup> and 95<sup>th</sup> percentile) will be recruited.

*Interventions:* Rope skipping exercise led by 2 professional sport instructors, three 30 min sessions per week, will be given to exercise group for 4 months.

*Main outcome measures:* Anthropometric measurements (weight, height, waist and hip circumference); body composition (lean body mass, fat mass and % total body fat, bone mineral density) measured by dual energy x-ray absorptiometry (DEXA); blood lipid, glucose and insulin levels by standard laboratory procedures; cardiopulmonary fitness by treadmill test (VO<sub>2-peak</sub>), self perception of competence with physical appearance and social acceptance by Marsh's Physical Self-description

Questionnaire for Children.

*Result:* The analysis will be based on intention to treat. Baseline comparisons of variables will be made using t-test or Mann-Whitney test. The baseline values will be subtracted from the values obtained 4 months after the intervention to obtain change scores. The effects of treatment on the outcome will be measured by means of analysis of covariances with adjustment made for baseline score. (MD02719)

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**Is the Prevalence of Childhood Asthma Increasing in Chinese Children?**

✉ WONG Wing Kin Gary • CHEN Yu Zhi\* • LEUNG Ting Fan

□ 1 October 2002

❖ Research Grants Council (Earmarked Grants)

Asthma is one of the most common chronic disorders in childhood. Phase I of the International Study of Asthma and Allergies (ISAAC) developed simple standardized written and video questionnaires for measuring prevalence of childhood asthma, allergic rhinitis and atopic eczema for meaningful international comparison. Phase I study revealed that asthma is relatively less common in Chinese children when compared with Caucasians. Within the Chinese population, the prevalence rate was found to be highest in Hong Kong Chinese children. Although there has been suggestion that there might be an increasing trend of childhood asthma in Hong Kong, the use of different methodologies and increased community awareness of asthma might have contributed to the observed increase. Phase I ISAAC study was performed 6 years ago. This study is to investigate the current prevalence of asthma and atopic disorders in Chinese schoolchildren from Beijing and Hong Kong using

the same standardized methodology as in the Phase I study. A group of subjects will also be recruited from the rural area of Beijing to assess the possible protection of farming environment from asthma and allergies.

(CU02165)

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**A 24-Week Randomized, Double-Blind, Active-controlled, Multicenter Study to Evaluate the Safety and Efficacy of Rosiglitazone when Administered to Pediatric Patients with Type 2 Diabetes Mellitus**

✉ WONG Wing Kin Gary • FOK Tai Fai

□ 3 December 2002

❖ GlaxoSmithKline

Type 2 diabetes mellitus is becoming increasing more common in children. No agents are currently approved for use in treating type 2 diabetes in paediatric patients. The current study will investigate the effect of rosiglitazone monotherapy in paediatric patient with type 2 diabetes.

(MD02480)

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**A 12-week, Randomized, Double-blind, Parallel-group, Multicentre, Phase-III Study to Compare the Efficacy and Safety of Symbicort pMDI (budesonide/formoterol 80/4.5 mcg 2 actuations bid, delivered dose) with that of Pulmicort pMDI (budesonide 100 mcg 2 actuations bid, metered dose) and Symbicort Turbuhaler (budesonide/formoterol 80/4.5 mcg 2 inhalations bid, delivered dose) in Children with Asthma**

✉ WONG Wing Kin Gary • LEUNG Ting Fan • FOK Tai Fai

	<u>Edition</u>	<u>Title/Investigators</u>
<p>❑ 3 December 2002</p> <p>❖ AstraZeneca Hong Kong Limited</p> <p>Childhood asthma is a common condition. The role of long-acting beta agonist in the management of asthma is still not clear. This is a randomized trial to assess the efficacy of budesonide/formoterol combination in the treatment of childhood asthma. (MD02815)</p>	2001-02	<p>Effects of Oxygen-induced Lung Damage on Megakaryocytopoiesis in Neonates Receiving Mechanical Ventilation (MD01554)</p> <p>✉ FOK Tai Fai • LI Kwai Har Karen • YANG Mo</p>
<hr/> <p><b>A 52-Week Multicenter, Randomised, Double-blinded, Double Dummy, Placebo-controlled Parallel Group Study to Compare the Efficacy and Tolerability of Salmeterol/Fluticasone Propionate Combination (Seretide™) 50/100mcg once Daily in the Morning with Fluticasone Propionate 100mcg Twice Daily and Placebo (Short-acting β<sub>2</sub>-agonist as Required only) Twice Daily, All via the Accuhaler™ as Initial Maintenance Therapy in Mild Asthmatic Subjects</b></p>	2001-02	<p>The Assessment of Disease Severity of Atopic Dermatitis in Chinese Children Using Clinical Scores and Laboratory Markers (MD01484)</p> <p>✉ HON Kam Lun • LEUNG Ting Fan • LAM Wai Kei Christopher (Dept of Chemical Pathology) • WONG Chun Kwok (Dept of Chemical Pathology) • MA Kwok Chiu*</p>
<p>✉ WONG Wing Kin Gary • LEUNG Ting Fan</p> <p>❑ 20 January 2003</p> <p>❖ GlaxoSmithKline Research and Development Limited</p>	1999-00	<p>Study of Varicella-zoster Virus Immunization in Paediatric Haematopoietic Stem Cell Transplantation (MD99087)</p> <p>✉ LEUNG Ting Fan • CHAN Kay Sheung Paul (Dept of Microbiology) • LI Chi Kong*</p>
<p>Asthma is a common condition. The use of inhaled corticosteroid (ICS) treatment is well established for mild asthma. It is not clear that whether the addition of long acting beta agonist can further reduce the dose of ICS. This randomized controlled trial will address this question. (MD02908)</p>	2000-01	<p>A Multicenter, Double-blind, Placebo-controlled, Randomized, Parallel-group, Study to Determine the Efficacy of Montelukast in the Prevention of Exacerbations in Asthmatic Patients Aged 2-to-5 Years (MD00738)</p> <p>✉ LEUNG Ting Fan • LI Man Chim Albert Martin • WAN Helene</p>
<hr/> <p><b>Please refer to previous issues of this publication for more details of the following ongoing research at the department:</b></p>	2001-02	<p>Characterization of Immunologic Profiles Associated with Hepatitis B Virus Immunoprophylaxis Following</p>

- Allogeneic Haematopoietic Stem Cell Transplantation (MD01630)  
 ✉ LEUNG Ting Fan • CHAN Kay Sheung Paul (Dept of Microbiology)  
 • LI Chi Kong\*
- 2000-01 The Effect of Continuous versus Pulsed Maternal Corticosteroid Treatment on Neonatal Pituitary-adrenal Function (MD00593)  
 ✉ NG Pak Cheung • LAM Wai Kei Christopher (Dept of Chemical Pathology) • FOK Tai Fai
- 1998-99 Human Stem Cell Technology: *ex vivo* Expansion of Cord Blood Stem/Progenitor Cells and Applications (MD98070)  
 ✉ LI Kwai Har Karen • HUANG POON Wai Sin Dolly (Hong Kong Cancer Institute) • TSANG Kam Sze Kent (Dept of Anatomical & Cellular Pathology)\*
- 2001-02 A Multicentre, Randomised, Double Blind, Controlled Study of Two Corticosteroid Regimens for Treatment of Systemic Hypotension in Preterm Infants (MD01104)  
 ✉ NG Pak Cheung • CHOW Chun Bong\* • FOK Tai Fai • LAM Wai Kei Christopher (Dept of Chemical Pathology)
- 2001-02 Thrombospondin-1: Antileukemia Effects and Mechanism of Apoptosis (MD01598)  
 ✉ LI Kwai Har Karen • LI Chi Kong • CHIK Ki Wai • YANG Mo
- 2001-02 Thyroid Volumes in Chinese Children (MD01520)  
 ✉ WONG Wing Kin Gary • LAM Wai Kei Christopher (Dept of Chemical Pathology) • AHUJA Anil Tejbhan (Dept of Diagnostic Radiology & Organ Imaging)
- 1998-99 WHO/GSTF Maternity Advice Study (MD98123)  
 ✉ NELSON Edmund Anthony Severn • COWAN S\* • MANGIATERRA V\* • CAFFERATA M.\*
- 2000-01 A Hospital-based Study on Disease Burden and Health Costs of Rotavirus Associated Diarrhoea in Hong Kong (MD00598)  
 ✉ NELSON Edmund Anthony Severn • TAM Siu Lun John (Dept of Microbiology) • FOK Tai Fai • CHAN Kay Sheung Paul (Dept of Microbiology) • POON K H\* • NG C H\* • IP K S\* • YU Ly Mee Ashley (Centre for Clin. Trials & Epidemiological Research)#
- 2000-01 Effects of Oxygen Toxicity on Megakaryocytopoiesis and Thrombopoietin Production in Neonates - A Rat Model (CU00137)  
 ✉ YUEN Man Pan Patrick • FOK Tai Fai • LEE Kwong Man Simon (Lee Hysan Clinical Research Laboratories) • LI Kwai Har Karen • YANG Mo

2001-02 The Direct Role of the Pro-inflammatory  
Cytokine IL-1 $\beta$  on Megakaryocytopoiesis:  
the Signal Transduction Response and  
Stimulation of Cytokine Response  
(MD01778)

✍ YUEN Man Pan Patrick • LI Kwai  
Har Karen • FOK Tai Fai • YANG  
Mo

## RESEARCH PROJECTS

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### **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 Ventr**

✉ KWAN Yiu Wa • LIU Wing Keung Ken (Dept of Anatomy) • TSUI Kwok Wing (Biochemistry)

☐ 1 December 2002

❖ Research Grants Council (Earmarked Grants)

Activity of mammalian heart is continuously under the influence of autonomic nervous system. Catecholamine released from sympathetic nerves through binding to the membranous receptor such as  $\beta$ -adrenoceptor ( $\beta$ -AR) leads to an increase in heart rate and force of contraction. It has been known that there are two  $\beta$ -AR subtypes ( $\beta_1$ -AR and  $\beta_2$ -AR) in heart and these receptors are responsible for the excitatory effect of catecholamine. Recent pharmacological and molecular biological studies, however, suggest the presence of another  $\beta$ -AR subtype (atypical or  $\beta_3$ -AR) in cardiac muscle. In stark contrast to  $\beta_1$ -AR and  $\beta_2$ -AR, activation of this atypical  $\beta$ -AR in human heart preparation resulted in a decrease in cardiac muscle contraction. Influx of  $\text{Ca}^{2+}$  through the  $\text{Ca}^{2+}$  channels ( $I_{\text{CAL}}$ ) is important in the excitation-contraction coupling of the heart. However, the relationship of  $\beta_3$ -AR activation,  $I_{\text{CAL}}$  activity and heart muscle contraction has not been established in details. A decrease in contraction upon the activation of  $\beta_3$ -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  $\beta_3$ -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. Results obtained in this study will provide important information for a better understanding of the physiological functions of this atypical  $\beta$ -AR and assist future drug development for an effective treatment of heart failure.

(CU02166)

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### **Neural Mediation of Inflammatory Joint Disease**

✉ LAM Fu Yuen

☐ 1 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

The contribution of the peripheral nervous system to inflammatory processes remains unclear. Previous research has provided evidence for a contribution from both sympathetic postganglionic efferent fibres and sensory C fibres. However, these experiments assessed the inflammatory response in terms of oedema formation, which lags behind changes in vascular caliber. The hyperaemia that occurs early in the inflammatory process of a rat model of acute monoarthritis appears to be entirely neurally mediated as chronic peripheral nerve section abolishes this response. Whether this neurogenic inflammatory response is mediated by neuropeptides in sensory C nerve fibres or by sympathetic efferent fibres is unknown at present and would be investigated by selective chemical ablation of the sympathetic or sensory innervation. A further aim of the study is to determine the extent to which the early phase of inflammatory hyperaemia is mediated via sensory neuropeptides such as substance P (SP)



and calcitonin gene-related peptide (CGRP), or modulated by vasoactive intestinal peptide (VIP) and/or nitric oxide (NO). This proposed study into the mechanisms underlying inflammatory hyperaemia will provide new insights into the first few critical hours of an inflammatory response. A clearer understanding of these hyperaemic factors may, in turn, lead to the development of novel anti-inflammatory therapies, which may prove applicable to many vascular beds.

(MD02658)

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**Pharmacological Characterisation of Cyclic Nucleotide Phosphodiesterases in Rat Peritoneal Mast Cells**

✉ LAU Hang Yung Alaster

□ 1 May 2003

❖ CUHK Research Committee Funding (Direct Grants)

Allergic reactions and the underlying inflammation are often initiated by the activation of mast cells. Hence control of mast cell activation is an important anti-allergic property of pharmacological agents. Substantial literature has reported that pharmacological elevation of intracellular cyclic adenosine 3', 5'-monophosphate (cyclic AMP) and to a lesser extent guanosine 3': 5'-monophosphate (cyclic-GMP) can inhibit the release of mediators from mast cells. Among these agents are non-selective inhibitors of cyclic nucleotide phosphodiesterase (PDE) such as theophylline. Recent advance in phosphodiesterase research has identified 11 isoforms for the enzymes. Currently, isoform selective inhibitors for PDE I to V are now available commercially and facilitate the pharmacological characterization of PDE in various biological systems. Previous studies investigating

the effects of a limited number of selective PDE inhibitors on mast cells had produced contradicting results. It is hence the aim of the present study to evaluate the effects of a full range of isozyme selective PDE inhibitors on immunologically activated rat peritoneal mast cells. The observed effects will further be correlated with the ability of the PDE inhibitors in modulating intracellular levels of cyclic nucleotides. Results from this study will be important for identifying the PDE isoforms present in mast cells and to define the group(s) of selective PDE inhibitors which may possess anti-allergic potency.

(MD02396)

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**Research and Development for a New TCM-based Product with Antitussive Activity**

✉ LIN Ge • CHUNG Hoi Sing • HON Po Ming (Institute of Chinese Medicine) • LI Song Lin

□ 1 November 2002

❖ Bright Future Pharmaceutical Laboratories Ltd.

Based on our previous systemic studies of several traditional Chinese medicinal (TCM) antitussive herbs, researchers in the CUHK and experts in the Bright Future Pharmaceutical Laboratories Limited would like to joint together to develop a new TCM-based anti-cough herbal product. An appropriate formulation containing at least two most commonly used traditional Chinese antitussive herbs will be developed as the proposed new TCM-based anti-cough product, in which the action mechanisms of the active ingredients in these herbs involve different pathways. Although both herbs have been well studied individually, there are several areas, which need for further studies in more depth, including quality control of plant sources, toxicology and stability studies of the formulation, and clinical

trials. Furthermore, it has not yet been elucidated whether or not there are synergistic or antagonistic activities when these two or more herbs were formulated together. Indeed these are all essential investigations, which need to be accomplished for facilitating the promotion of our preclinical inventions to the next stage of commercial production as the TCM-based product. The proposed TCM-based product will be made in Hong Kong with well-controlled and clarified chemical and pharmacological bases for its therapeutic uses.

The detailed studies includes (1) identification of the correct plant sources and appropriate locations; (2) preparation of the herbal extract and formulation; (3) development of analytical method for quality control and stability study of the herbal formulation; and (4) preclinical study.

(MD02561)

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**Investigation of Chuanxiong Herbal Materials with GAP Standard**

✉ LIN Ge • LI Songlin • CHUNG Hoi Sing

□ 1 April 2003

❖ Sichuan Green Pharmaceutical Technology Development Co. Ltd.

The aim of this collaborative research is to identify and investigate the appropriate plant species of Chuanxiong herbal materials with GAP standard. The resultant herbal materials will be used as the plant sources for Chuanxiong, which is the Chinese medicinal herb investigated in our research project supported by ITF matching grant (UIM/034).

(MD02951)

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**Development of a Model of Cisplatin-induced Acute and Delayed Kaolin Consumption in *Suncus murinus***

✉ RUDD John Anthony • TAKEDA Noriaki\* • YAMATODANI Atsushi\*

□ 1 January 2003

❖ CUHK Research Committee Funding (Direct Grants)

Chemotherapy using cisplatin-containing regimens may induce episodes of acute and delayed nausea and emesis in man. The acute response occurs on the first day of treatment and is particularly sensitive to 5-HT<sub>3</sub> receptor antagonists such as ondansetron. The delayed phase occurs on days 2-5 and may be less sensitive to the action of 5-HT<sub>3</sub> receptor antagonists. The control of both phases is improved by the combination of anti-emetics with glucocorticoids such as dexamethasone. However, no single agent is effective to satisfactorily reduce delayed nausea and vomiting in man. The project will develop a novel model of acute and delayed emesis in *Suncus murinus* that also simultaneously assesses kaolin consumption as an indicator of nausea. Ondansetron and dexamethasone will be used as reference anti-emetic drugs that reduce both chemotherapy-induced nausea and emesis in man. Studies will also assess the role of the substance P NK<sub>1</sub> tachykinin receptor in the mechanism of motion-induced emesis and kaolin consumption. The studies will be the first to investigate simultaneously emetic and pica behaviour that may be relevant to the detection of novel drugs to prevent both nausea and vomiting in man.

(MD02667)

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**Growth Hormone Secretagogue Receptors: Cell Signalling and Receptor Oligomerization**

✉ WISE Helen • CHENG Hon Ki Christopher (Biochemistry)

□ 16 September 2002

❖ Research Grants Council (Earmarked Grants)

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 signaling 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 signaling. 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 resulting complexity warrants elucidation if we are to understand and manipulate these processes for the development of better therapeutic agents.

The mechanisms underlying GPCR dimerization and the consequences for cell signaling may not be the same for all types of GPCRs. In this proposal our attention is focused 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 signaling of GHSR, and to determine the extent and importance of interactions between these two receptor subtypes.

(CU02267)

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**A Study to Investigate the Mechanisms of the Drug Interaction between Warfarin and Danshen**

**(*Salvia Miltiorrhiza*): Effects on Specific Human Cytochrome P450 Isoforms**

✉ YEUNG Hok Keung John

□ 1 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

This study aims to make use of current Cytochrome P450 technology for assessing the safety and efficacy of drugs to investigate the mechanisms involved in the clinically important drug interaction between Danshen (*Salvia Miltiorrhiza*) and warfarin. The effects of Danshen, and some of its active components, on specific human CYP isoforms will be determined to investigate the pharmacokinetic interactions of these compounds. Results of this study should provide scientific evidence that may be used to enable awareness by clinicians and the general public in the safe use of Traditional Chinese Medicine (TCM), either alone or in combination with Western medicine.

(MD02444)

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**Please refer to previous issues of this publication for more details of the following ongoing research at the department:**

<u>Edition</u>	<u>Title/Investigators</u>
2000-01	Mapping Signal Transduction Networks by Multidisciplinary Approach (BL99452) ✉ JONES Robert Leslie • WISE Helen • HUANG Yu (Dept of Physiology) • IP Y Nancy* • WONG Yung-hou* • TSIM Karl W K* • BARNARD

- Eric A\* • POON Y C Randy\* • SUCHER Nikolaus\* 2001-02 Development of TCM-based Products with Known Active Ingredients and Verified Oral Absorbability (MD01857)
- 2001-02 The Mechanisms Responsible for the Exaggerated Excitatory Effect of Acetylcholine in the Pulmonary Artery of Spontaneously Hypertensive Rats (MD01107)  
 ✎ KWAN Yiu Wa • GURNEY A M\*
- 2000-01 Investigation of the Mechanisms and Significance of Altered Neurogenic Responses in Arthritic Rat Knee Joints (MD00464)  
 ✎ LAM Fu Yuen • CHEW CHENG Siew Boon (Dept of Physiology)
- 2001-02 Investigation of the Mechanisms and Significance of Altered Neurogenic Responses in Arthritic Rat Knee Joints (MD01988)  
 ✎ LAM Fu Yuen
- 2000-01 The Roles of Mast Cells in the Pathogenesis of Aspirin Sensitive Asthma (CU00064)  
 ✎ LAU Hang Yung Alaster • LEUNG Po Sing (Dept of Physiology) • NAGAKURA Toshikazu\* • OBATA Toru\* • SAITO Hirohisa\* • WU Young Yuen Adrian\*
- 2000-01 Identification of Brain Areas Involved in Emesis Control in the Ferret (CU00066)  
 ✎ RUDD John Anthony • YEW Tai Wai David (Dept of Anatomy)
- 2001-02 Investigation of Johnson and Johnson Pharmaceutical Research and Development Compounds to Inhibit Both the Acute and Delayed Phases of Cisplatin-Induced Emesis in a Ferret Model (MD01607)  
 ✎ RUDD John Anthony
- 1998-99 Metabolic Studies of a Series of Drugs in Horses (MD98082)  
 ✎ YEUNG Hok Keung John • WONG Nai Ching Henry (Dept of Chemistry)

## RESEARCH PROJECTS

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### Development of an *In Vitro* Model for Oral Mucosal Drug Delivery – A Preliminary Investigation

✍ CHOW Sing Sum Moses • ZUO Zhong • BURD David Andrew Ross (Dept of Surgery) • YIN Qiping • TOMLINSON Brian (Dept of Medicine & Therapeutics)

☐ 1 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

The primary objective of this proposal is to investigate an *in-vitro* model for screening of drugs suitable for oral mucosal (buccal/sublingual) delivery or administration. It is well known that oral mucosal drug delivery has the advantage of better bioavailability and more rapid onset of action compared to the conventional oral intestinal delivery. However, the number of drugs for buccal/sublingual administration is very limited at present due to lack of a good screening method to identify drugs suitable for such administration. Thus, we propose to develop an *in-vitro* screening method (model) by using a buccal cell line (TR146) which has recently been shown to be suitable for studying buccal drug permeability.

The present study will investigate drug permeability from TR146 cell line and correlate to buccal and sublingual tissue permeability. To initially test this model, a series of beta-blockers and calcium channel blockers will be evaluated. Based on their *in-vitro* results, those drug with good, medium and low permeability or rate of absorption will be further validated using pharmacokinetic studies in human

subjects following buccal or sublingual administration.

Successful establishment of this *in-vitro* model can provide a “new” avenue in drug delivery leading to improvement in therapeutic modality of many drugs, e.g. better bioavailability as well as convenient and rapid onset of action. Such effect can be important to many patients, especially those with life-threatening urgent medical conditions.

(MD02378)

### A Pharmacokinetic-Genomic Approach for Predicting Herb-Drug Interactions : An Initial Evaluation Using Ginkgo Biloba

✍ CHOW Sing Sum Moses • TOMLINSON Brian (Dept of Medicine & Therapeutics) • WAYE Mary Miu Yee (Biochemistry) • ZUO Zhong

☐ 15 December 2002

❖ Research Grants Council (Earmarked Grants)

The long-term goal of the present proposal is to develop a pharmacokinetic-genomic approach to predict herb-drug interactions in individual human subjects. The specific objectives of this project are (1) to verify a “high-throughput” pharmacokinetic “cocktail” approach for screening the activities of drug-metabolizing enzymes in Chinese subjects; (2) to apply and assess the predictability of potential herb-drug interactions using such an approach; (3) to relate individual herb-drug interaction data to respective genotype in each subject.

Ginkgo biloba (EGb761) will be used to serve as a prototype herb in this proposed study. Its effect on drug metabolizing enzymes will be screened in 18-24 healthy subjects using a “high-throughput” pharmacokinetic approach previously developed by the principal investigator. Based on the screening results, the potential for interaction will be predicted

and subsequently verified by actual interaction study with one “western” drug. In addition, the magnitude of individual interaction will be correlated to the genotype in each subject.

If the results of the present proposed study are positive, this pharmacokinetic-genomic may serve as a tool for predicting and assessing many herb-drug interactions. Such data can be potentially utilized to design herb-drug combination therapy scientifically leading to improved therapy and/or reduced toxicity for individual patients.

(CU02180)

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**Novel TCM-Platinum Compounds : New Mechanism(s) of Antitumor Action?**

✉ HO Yee Ping • AU-YEUNG Chik Fun Steve  
(Dept of Chemistry)

☐ 1 November 2002

❖ Research Grants Council (Earmarked Grants)

A novel series of TCM-based platinum compounds has been developed that combines a modified active chemical component from a traditional Chinese medicine (TCM), demethylcantharidin (DMC), which has been used to treat liver cancer, with a platinum (Pt) moiety. In pre-clinical evaluations, the novel TCM-Pt compounds demonstrated excellent antitumor activity and exhibited no cross-resistance with cisplatin, a platinum drug that is commonly used in cancer chemotherapy. The deliberate integration of the modified TCM, demethylcantharidin into the novel compounds has apparently introduced a novel dual mechanism of antitumor action that is reflected in the observed liver selectivity, enhanced cytotoxicity and significantly, circumvention of acquired resistance. Our previous studies have strongly suggested that the novel TCM-Pt compounds operate under a different mechanism of action,

distinct from the classical Pt-based drugs such as cisplatin or carboplatin. We propose that this novel mechanism comprise of the DMC providing an inhibition effect on the enzyme protein phosphatase 2A (PP2A), and interference of DNA synthesis by the Pt moiety.

The aim of this project is to elucidate fully the role of DMC in eliciting the apparent new mechanism of antitumor action, and to provide evidence that the inhibition of PP2A by TCM-Pt compounds directly influences the circumvention of resistance and liver selectivity. If the new mechanism is substantiated, the novel compounds will be a *new class of antitumor drugs* with enormous potential in the clinical treatment of cisplatin-refractory tumors. This study should also highlight the powerful prospects of combining traditional Chinese medicine with western medical practices.

(CU02181)

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**Clinical Impact of Genetic Polymorphism in the Cytochrome P450 CYP2C9 on the Management of Warfarin in Chinese Patients**

✉ LEE Wing Yan Vivian • YOU Hoi Sze Joyce •  
LEE Kwing Chin Kenneth • WAYE Mary Miu  
Yee (Biochemistry) • CHENG Gregory (Dept of  
Medicine & Therapeutics)

☐ 1 April 2003

❖ CUHK Research Committee Funding (Direct  
Grants)

Warfarin has been widely used in the management of different thromboembolic disorders. It is a drug with narrow therapeutic index that requires close monitoring. It is metabolized by hepatic microsomal enzyme CYP 2C9. Various studies have demonstrated that genetic polymorphisms of CYP 2C9 would alter the warfarin dose requirements.

However, the direct association between the genetic variation and the clinical outcomes of warfarin therapy is yet to be established especially in Chinese patients. The objective of the current prospective cohort study is to determine the association between genetic polymorphism in the cytochrome P450 2C9 isoenzyme and clinical outcomes of the warfarin management in Chinese patients.

Men or Women aged 18 or older who require warfarin therapy for > 3 months will be recruited from the anticoagulation clinic at the Prince of Wales Hospital. A blood sample will be obtained for genotyping of CYP 2C9. The primary clinical outcome measurement is the anticoagulation status including (1) time to therapeutic INR; (2) rate of above-range INRs; (3) time to stable warfarin dose; and (4) stable maintenance warfarin dose. Other clinical information will also be recorded such as patient demographics, past medical history, warfarin indication and concurrent medications.

The findings of this study will identify the clinical significance of CYP 2C9 polymorphism in dosing, safety and efficacy of warfarin therapy for Chinese patients.

(MD02882)

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**Comparison of a Clinical Pharmacist-managed Anticoagulation Service with Routine Medical Care - Impact on Clinical Outcomes and Healthcare Costs**

✉ YOU Hoi Sze Joyce • CHENG Gregory (Dept of Medicine & Therapeutics) • CHAN Yan Keung Thomas (Dept of Medicine & Therapeutics)

□ 1 October 2002

❖ Health Care & Promotion Fund, Hospital Authority

*OBJECTIVES:* To compare the effects of a clinical pharmacist-managed anticoagulation service with routine medical care on clinical outcomes of warfarin therapy in an ambulatory care setting in Hong Kong and to determine the cost-effectiveness of the clinical pharmacist-managed anticoagulation service from the perspective of a public health organization.

*DESIGN:* Prospective, randomised clinical trial.

*SETTING:* Anticoagulation clinic of a teaching hospital.

*SUBJECTS:* Men or women aged 18 or older who require warfarin therapy for >3 months.

*INTERVENTIONS:* Patients will be randomised to the routine medical care group or to the clinical pharmacist-managed care group.

*MAIN OUTCOME MEASURES:* Clinical outcomes: Anticoagulation control measured by the international normalized ratio (INR), and, the incidence of thromboembolic and hemorrhagic events associated with warfarin therapy.

*ECONOMIC OUTCOMES:* Incremental cost-effectiveness ratio comparing the costs and clinical outcomes of the clinical pharmacist-managed care group with those of the routine medical care group.

(MD02441)

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***In-vitro* Evaluation of Glucuronidation of Selected Flavonoids in Gut and Liver**

✉ ZUO Zhong • LIN Ge (Dept of Pharmacology)

□ 1 May 2003

❖ CUHK Research Committee Funding (Direct Grants)

The bioavailabilities of flavonoids, no matter in the form of aglycone or glycosides, were not as high as expected from their favorable lipophilicity. Such discrepancy is believed to be mainly due to the

extensive first-pass metabolic effect. Metabolic glucuronidation seems to be the major metabolic pathway for flavonoids. The proposed study is designed to utilize the *in-vitro* methods to interpret the glucuronidation in gut and liver of a series of structurally related flavonoids from the flavone subgroup, namely flavone, 3-hydroxyflavone, 5-hydroxyflavone, 6-hydroxyflavone, 7-hydroxyflavone, 2'-hydroxyflavone, 3'-hydroxyflavone and 4'-hydroxyflavone, respectively. The intestinal mucosa transport and metabolism will be studied by the *in-vitro* Caco-2 cell monolayer model to investigate the transepithelial transport and metabolic glucuronidation. In addition, by incubation of the selected flavonoids with human pooled liver S9 fraction, the possible glucuronides formed, their formation rates and the enzyme responsible for the biotransformation will be delineated. Combined the results obtained from the above two *in-vitro* models, a Structure-Activity-Relationship (SAR) will be established for the glucuronidation of the selected flavonoids in gut and liver.  
(MD02576)

**Please refer to previous issues of this publication for more details of the following ongoing research at the department:**

<u>Edition</u>	<u>Title/Investigators</u>
2000-01	Establishment of a University Based Drug Development Centre for Anticancer and Cerebro/Cardio-vascular Drugs (MD20024) ✍ CHOW Sing Sum Moses • HO Walter K. K. (Biochemistry) • JONES Robert Leslie (Dept of

Pharmacology) • HO Yee Ping • LAU Bik San Clara • LIN Ge (Dept of Pharmacology) • JAMES Anthony Edward (Laboratory Animal Services Centre) • CHOW Hee Lum Albert

2001-02 Development of a Ganoderma (Lingzhi) and Coriolus (Yunzhi) Formula as an Anti-cancer Agent (MD01301)

✍ LAU Bik San Clara • ZUO Zhong • CHOW Sing Sum Moses • FUNG Kwok Pui (Biochemistry) • LEUNG Kwok Nam (Biochemistry) • LIN Ge (Dept of Pharmacology) • JAMES Anthony Edward (Laboratory Animal Services Centre) • SHAW Pang Chui (Biochemistry) • BUSWELL John Anthony • LIEBERMAN Ron\*

2000-01 The Effect of Orlistat and Rosiglitazone on Insulin Action in a Group of Chinese Patients Affected by the Metabolic Syndrome - A Randomized, Single-blinded and Placebo-controlled Study (CU00069)

✍ LEE Kwing Chin Kenneth • CHAN Chung Ngor Juliana (Dept of Medicine & Therapeutics) • TOMLINSON Brian (Dept of Medicine & Therapeutics) • YOU Hoi Sze Joyce

2001-02 Direct Medical Cost for a Cohort of Chinese Patients with Chronic Hepatitis B and Its Complications in Hong Kong (MD01434)



- ✍ LEE Kwing Chin Kenneth •  
KWONG Kai Sun Sunny (Dept of  
Economics) • CHAN Yan Keung  
Thomas (Dept of Medicine &  
Therapeutics) • LAU Tak Fai Joseph  
(Centre For Epidemiology &  
Biostatistics) • SUNG Joseph Jao  
Yiu (Dept of Medicine &  
Therapeutics) • WONG Ian C K\*
- 2001-02 Absorption of Active Components from  
Hawthorn and Green Tea - *in vitro* and *in  
vivo* Relationship (MD01122)
- ✍ ZUO Zhong • CHOW Sing Sum  
Moses

## RESEARCH PROJECTS

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### Development of Globally Marketable Proprietary Natural Products for Treating Insomnia

✉ CHAN Hsiao Chang • ZHANG Zhi Yan\*

☐ 1 June 2003

❖ Bright Future Pharmaceutical Laboratories Ltd. • University-Industry Collaboration Prog.: Matching Grant for Joint Research, ITF, Innovation & Tech. Commission

Insomnia is the most common sleep disorder requiring appropriate recognition and management. Because of the side-effects commonly associated with conventional drugs, herbal and other natural sleep aids are gaining popularity. However, most of the natural products available are herbal mixtures with very little understanding of their action mechanisms, and thus few are proprietary products. The present project aims to develop proprietary natural alternative treatment for insomnia and other sleep related disorders, by using new and innovative techniques to investigate the sleep-inducing characteristics and mechanism pathways of a novel herb identified by the research team to have potential hypnotic qualities. The project will adopt two strategic approaches: (1) to develop a herbal health supplement with defined pharmacological action; (2) with further purification and detail chemical analysis, to identify the active fractions/compounds with in depth understanding of the pharmacological mechanisms which will enable further development of a proprietary fine pharmaceutical with global market potentials.

(MD02645)

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### Protection against Neuronal Apoptosis by the cGMP/protein Kinase G Pathway: Protein Phosphorylation and Quantitation of DNA Fragmentation Using Novel Ultrasensitive CE-LIF Technology

✉ FISCUS Ronald Ray • SHAW Pang Chui (Biochemistry)

☐ 1 September 2002

❖ Research Grants Council (Earmarked Grants)

Neuronal apoptosis in the brain occurs in Alzheimer's and Parkinson's diseases, resulting in neurological deficits. We showed that atrial & brain natriuretic peptides (ANP & BNP) inhibit apoptotic DNA fragmentation, increasing the survival of stressed neural (PC12) cells, via cGMP/protein kinase G (PKG) signal transduction pathway (Fiscus, Tu & Cheng Chew, *NeuroReport* 12: 185-189, 2001). Our recent data suggest that even basal levels of cGMP have anti-apoptotic effects and are required to prevent entry into a pro-apoptotic pathway. The working hypothesis of this project is: ANP, BNP and nitric oxide (NO), at low, physiological concentrations, elevate cGMP, activate PKG and phosphorylate BAD, CREB and Raf-1, protecting against neural apoptosis. cGMP may cross-activate protein kinase A (PKA), already known to phosphorylate BAD, CREB and Raf-1, contributing to inhibition of apoptosis. The proposed project will determine: (1) if ANP, BNP and NO activate PKA and/or PKG in cultured neural cells (PC12, NG108-15 and N1E-115 cells and primary cultures of hippocampal neurons), utilizing an assay, previously developed by the PI, that simultaneously measures the intracellular activation of both PKA and PKG; (2) phosphorylation of BAD (ser112, 136 & 155), CREB (ser133) and Raf-1 (ser43) by Western blot; (3) relative contribution of PKA and PKG in

cGMP-mediated phosphorylations and anti-apoptotic effects; and (4) involvement of NO synthase (NOS) in anti-apoptotic actions using primary neurons isolated from eNOS-, iNOS- and nNOS-knockout mice. Apoptotic DNA fragmentation will be quantified by a novel ultrasensitive technique, using capillary electrophoresis/laser-induced fluorescence (CE-LIF), developed by the PI. This new information should help development of more effective treatments for prevention/therapy of Alzheimer's and Parkinson's diseases.  
(CU02169)

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**Mechanisms of Vasorelaxation Induced by the Novel Ca<sup>2+</sup> Channel Blocker Cilnidipine and Metabolites of Cytochrome P450 in Coronary Vasculature**

✉ HUANG Yu • GOLLASCH Maik\* • YAO Xiaoqiang

☐ 1 December 2002

❖ Research Grants Council (Earmarked Grants)

Dihydropyridine (DHP) Ca<sup>2+</sup> antagonists, including nifedipine, blocking L-type voltage-sensitive Ca<sup>2+</sup> channels are widely used in the management of chronic stable angina due to coronary artery disease in humans. However, nifedipine and possibly other short-acting, 1<sup>st</sup> generation Ca<sup>2+</sup> channel blockers have been recently found to increase mortality in the patients with coronary artery disease. The deleterious mechanism is actually unknown but may involve the interaction with second messengers in smooth muscle cells and/or endothelium regulating vessel tone, *e.g.* protein kinase C, and/or reflex tachycardia because of very rapid Ca<sup>2+</sup> channel inhibition in arterial smooth muscle. On the other hand, cilnidipine, a novel and unique dihydropyridine Ca<sup>2+</sup> channel blocker that possesses a slow-onset,

long-lasting vasodilating effect, is effective as a once-daily antihypertensive agent and has little influence on heart rate in patients with essential hypertension. This effect may offer the clinical advantages of cilnidipine over the short-acting, 1<sup>st</sup> generation Ca<sup>2+</sup> channel blockers for the treatment of coronary artery disease. However, no studies have examined the vascular action of cilnidipine on coronary vasculature, which may account for its potential cardiac protective action. Our hypotheses propose that (1) cilnidipine is a slow-acting channel blocker that induces a channel state-dependent block of complex, multi-subunit vascular L-type voltage-sensitive Ca<sup>2+</sup> channels in small, resistance-sized rat coronary arteries; (2) "classical" dihydropyridine L-type Ca<sup>2+</sup> channel blocker (nifedipine) may interfere with protein kinase C and, thereby, inhibits the sustained contractile phase of small, resistance coronary arteries by both reducing Ca<sup>2+</sup> influx through Ca<sup>2+</sup> channels and inhibiting protein kinase C, while cilnidipine inhibits sustained contraction by reducing Ca<sup>2+</sup> influx through Ca<sup>2+</sup> channels but not by inhibiting protein kinase C; (3) cilnidipine releases endothelium-derived relaxing factors such as cytochrome P450 metabolites to induce endothelium-dependent relaxation of small, resistance-sized coronary arteries by activating smooth muscle K<sup>+</sup> channels. The primary objective of this proposal is to investigate these hypotheses, presenting the cellular and ionic mechanisms linking the cilnidipine-induced action in endothelium and vascular smooth muscle to decreased coronary contractility in comparison with other DHP drugs. The proposed study should provide experimental evidence supporting the clinical advantages of using cilnidipine over other DHPs against coronary heart disease.

(CU02170)

**Stimulatory Effect of Scutellariae Radix (Huangqin) and Its Major Flavonoids on Electrolyte Transport in Rat and Human Colonic Epithelia**

✉ KO Wing Hung • HUANG Yu

□ 1 August 2002

❖ Research Grants Council (Earmarked Grants)

*Scutellariae Radix* (Huangqin), the root of *Scutellaria baicalensis* Georgi, has been frequently used in combination with other herbs in Kampo medicines (Chinese herbal medicines) for centuries. Pharmacological activity of *Scutellariae Radix* has been shown to be anti-inflammatory, anti-pyretic, anti-allergic, anti-convulsant, and anti-tumor, etc. Our pilot studies indicated that the total extract of *Scutellariae Radix* and its three major flavonoids, baicalein, baicalin and wogonin, stimulated chloride secretion across rat colonic epithelia. More interestingly, baicalein also potentiated chloride secretion across human colonic epithelia. Therefore, the physiological basis of the therapeutic effect of *Scutellariae Radix* on colonic electrolyte transport has not been reported and the mechanism of action is still unclear. The purpose of the present proposal is to investigate whether the total extract and the three major flavonoids (baicalein, baicalin and wogonin) derived from *Scutellariae Radix* cause chloride secretion in rat and human colonic epithelia and examine the mechanism of this response using microspectrofluorimetric and electrophysiological approaches. Experiments will also be conducted using a “combined approach”, that allow real-time measurement of intracellular  $[Ca^{2+}]_i$  or [cAMP] and transepithelial ion transport simultaneously in a polarized epithelium. The information obtained from this study will give us a better understanding of the cellular mechanisms of these flavonoids with

respect to their specific effect(s) on intracellular signaling events and electrolyte transport in rat and human colonic epithelia. This should enhance an understanding of the therapeutic mechanisms of *Scutellariae Radix*, which in term could lead to clinical applications.

(CU02171)

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**Angiotensin IV Receptors AT<sub>4</sub>: Its Expression, Regulation and Potential Role in Chronically Hypoxic Carotid Body**

✉ LEUNG Po Sing

□ 1 January 2003

❖ CUHK Research Committee Funding (Direct Grants)

Our recent studies shown that AT<sub>1</sub> receptor modulate the excitability of the carotid chemoreceptors. Hence angiotensin II elevates the intracellular calcium level of glomus cells and the carotid afferent activity that activate the chemoreflex pathway. This action could be essential for the physiological response to hypoxia and the maintenance of salt and water balance. In this regard, chronic hypoxia is associated with an enhanced sensitivity of chemoreceptor activities to angiotensin II via an upregulation of AT<sub>1</sub> receptor expression. The regulation may be subject to a control by a local rennin-angiotensin system in the carotid body. Such a modulation may be important for the adaptation of the carotid body functions in the hypoxic ventilatory response, for purpose of enhancing the cardiorespiratory response and adjusting for electrolyte and water homeostasis during the stress of chronic hypoxia. Besides angiotensin II, emerging data have shown that another biologically active peptides of the RAS, such as Ang (1-7) and Ang IV, are currently and actively emphasized. Of particular

interest in this context is the demonstration of bioactive Ang IV, which binds to distinct AT<sub>4</sub> receptor in order to exert its specific functions. In spite of its diverse functions and importance, no data of AT<sub>4</sub> receptor is available for the carotid body. The present study therefore aims at unraveling the cellular localization and regulated expression of AT<sub>4</sub> receptor in our chronically hypoxic model using *in-vitro* autoradiography, emulsion light microscopic autoradiography and fluorescence-labelled assay for Ang IV. The results of the current project should give new insights into the localization, regulation and potential role of AT<sub>4</sub> receptors, which may have functional and physiological relevance to the carotid body during the stress of chronic hypoxia.

(MD02805)

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**The Role of Angiotensin and Endothelin in the Regulation of Fibrogenic/Anti-fibrogenic Factors in Hepatic Kupffer Cells: Its Clinical Implications for Hepatic Fibrosis**

✉ LEUNG Po Sing • IP Siu Po (School of Chinese Medicine) • WONG Tung Po • SCHUPPAN Detlef\*

□ 1 January 2003

❖ Germany/Hong Kong Joint Research Scheme

A close association of the renin-angiotensin system (RAS) and hepatic stellate cells (HSC), the major collagen producing cells in fibrosis, in the pathogenesis of liver fibrosis and cirrhosis has been well documented. However, the potential role of RAS in Kupffer cells (KC) in the regulation of fibrogenic and anti-fibrogenic cytokines are largely undefined. This is of particular relevance, since KC constitute about 80-90% of the resident liver macrophages and are a major source of cytokines. In addition, we recently showed that KC express the

angiotensin II receptor AT<sub>1</sub>, which may regulate HSC activation in liver fibrosis. The present study aims at elucidating the role of RAS and the endothelin (ET) system in the regulation of fibrogenic cytokines and their association with HSC activation in the evolution of liver fibrosis. The results should shed new insight into the following aspects:

- (1) Role of the AT receptor in KC and its modulation of the fibrogenic/antifibrogenic cytokine response;
- (2) Role of the ET<sub>B</sub> receptor in KC and its modulation of the fibrogenic/antifibrogenic cytokine response;
- (3) The association of hepatic KC and HSC with the hepatic fibrosis and liver cirrhosis; and
- (4) The AT and ET systems in KC as a potential target for future therapy of liver fibrosis such as cirrhosis.

(MD02871)

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**Angiotensin-converting Enzyme Genotype in High-altitude Populations of Yunnan, China**

✉ LEUNG Po Sing • TAM Michael S C • ZHENG Yong Tang\* • HUGH Montgomery\*

□ 15 March 2003

❖ University College London Medical School

Specific genetic factor that strongly influences human performance have been reported. In this regard, a polymorphism of the gene encoding angiotensin-converting enzyme (ACE) may be associated with elite endurance performance among high-altitude mountaineers. As a result, we hypothesize that the frequency for the insertion allele (I) and deletion allele of ACE is subjected to changes with altitude in populations of the same racial origin, who are resident at these altitudes for ideally > 20 generations. Accordingly, we test this hypothesis by examining the changes of genotype profiles of

ACE and its downstream signalers including angiotensin II receptors, AT<sub>1</sub> and AT<sub>2</sub>, and bradykinin receptors, BK<sub>1</sub> and BK<sub>2</sub> in various levels of high-altitude inhabitants living in the province of Yunnan, China.

We need to study unrelated individuals of the same racial background, resident in isolated communities for > 20 generations with minimal out-breeding over a range of altitudes. Ideally, we would use a range of altitudes from lowest possible to highest possible, given the constraints above. The greater the range of altitudes is the greater the number of communities, and the better. DNA can be collected from mouth swabs. Extraction of DNA and genotype will be performed in the U.K. The results from the present project will provide an insight onto the genotype profiles of the rennin-angiotensin system and related system in high-altitude inhabitants of the province of Yunnan thus its implications for high-altitude physiology.

(MD02436)

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**Functional Genomics on the Sexual Differentiation of the Rat Brain**

✉ WONG Chun Cheung

☐ 1 January 2003

❖ CUHK Research Committee Funding (Direct Grants)

Gene expressions during sexual differentiation of the sexual dimorphic nuclei of the pre-optic area (SDN-POA) and accessory olfactory bulb (AOB) are used to study the functional genomics of the sexual differentiation of the rat brain. Expression of genes in SDN-POA and AOB of male, female and masculinized female rats are compared to look for gene candidates that are essential for the sexual differentiation. High free estrogen levels around the

mentioned brain regions control an unknown program to produce bigger SDN-POA and AOB in the males than those in the females. Aromatase, the enzyme that converts testosterone to estradiol – 17 β and the high affinity estrogen binding protein α-fetoprotein are the other two key factors that control the local free concentrations of estrogens. In this study, the SDN-POA and AOB from all three kinds of rats will be cut from cryo-sections using a laser-assisted micro-dissector and total RNAs of pooled sections are prepared with a re-fined technology to support the following real-time PCR procedures for the detection of gene transcriptions. Using this approach, we can specifically determine gene control on the differentiation of sexual dimorphic brain regions. Other than the reported sexual differentiation related genes, we would further examine marker genes for various cell types in both brain regions as well as genes for axon guidance and synapse formation. Genes with distinct sexual dimorphism and are altered in masculinized female are considered as potential candidates for genes for the sexual differentiation of the brain.

(MD02363)

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**The Role of Organic Anion Transporters (OAT) in the Accumulation of Antifertility Drugs by the Rat Epididymis**

✉ WONG Patrick Yee Ding

☐ 1 September 2002

❖ Research Grants Council (Earmarked Grants)

Our laboratory has recently reported that some indazole carboxylic acid derivatives are potent blockers of the cystic fibrosis transmembrane conductance regulator-chloride channels (CFTR-Cl<sup>-</sup>) in the epididymis. As these ion channels play a central role in the secretion of fluid into the lumen,

blocking these channels by these compounds should in principle lead to disruption of the epididymal milieu with the ensuing decrease in sperm functions and fertility. Before these compounds can block the channels they have to enter the epididymal lumen to reach the luminal membrane of the epididymal cells where the CFTR-Cl<sup>-</sup> channels are located. Spermatozoa inside the epididymal duct are shielded from external chemical influence by the blood-epididymis barrier (a partition formed by the cell layer lining the duct) which restricts the passage of foreign compounds into the lumen. The barrier, however, has a specialized transport system which can accumulate selective drug molecules into the ductal lumen. We speculate that the indazole compounds can avail themselves of this system to enter the lumen where they can act on the CFTR-Cl<sup>-</sup> channels. To gain an understanding of the specialized transport system, we propose to characterize an important component of the system, viz the organic anion transporters, using physiological and molecular approaches that have been successfully used on the kidney tubules. It is hoped that this project will help understand (1) how environmental sperm-toxic xenobiotics (pollutants) gain access to the epididymal microenvironment. These compounds are thought to cross the blood-epididymis barrier via the organic anion transporters, and (2) the feasibility of exploiting the organic anion transporters for drug delivery into the epididymal lumen to disrupt the sperm microenvironment. The latter has impact on the development of new contraceptive methods for the male.

(CU02268)

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**Functional Roles of Trp (Transient Receptor Potential) Channels in Vascular Endothelial Cells**

✍ YAO Xiaoqiang

☐ 1 November 2002

❖ Research Grants Council (Earmarked Grants)

Numerous humoral and physical stimuli cause vascular endothelial cells to secrete relaxing and contracting factors such as nitric oxide, prostacyclin (PGI<sub>2</sub>), and endothelium-derived hyperpolarizing factor (EDHF), which modulate smooth muscle tone and blood pressure. In many cases, the initial response of endothelial cells to these diverse signals involves an increase in intracellular Ca<sup>2+</sup> concentration. Up to now, however, the molecular nature of these Ca<sup>2+</sup> influx channels has not been revealed. One likely candidate responsible for different Ca<sup>2+</sup> influx pathways in endothelial cells is transient receptor potential (Trp) channel. Previous studies from my research group already demonstrated the presence of six Trp isoforms in human vascular endothelial cells. In this proposal, we plan to determine the particular Trp isoform(s) that is(are) responsible for each distinct Ca<sup>2+</sup> influx pathway in vascular endothelial cells. The results from this study should provide crucial mechanistic background for rational design of anti-hypertensive and anti-atherosclerotic drugs that are targeted at Trp channels.

(CU02174)

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**Subunit Composition, Spatial Distribution and Pharmacological Profiles of GABA-A Receptors in Globus Pallidus Neurons : Correlation with Different Synaptic Inputs**

✍ YUNG Wing Ho • YUNG Kin Lam Ken\*

☐ 1 December 2002

❖ Research Grants Council (Earmarked Grants)

Parkinson's disease is an age-related neurodegenerative disorder; it afflicts roughly 1 in 1000 adults. Human and animal studies have shown that parkinsonism results from the degeneration of the nigrostriatal dopaminergic pathway. The therapeutic strategies for treating Parkinson's disease are limited. The use of the dopamine precursor L-DOPA has been the major and most widely used treatment, but with severe limitations. Recent neurosurgical approaches revealed that the motor symptoms of Parkinson's disease could be relieved by selective lesioning of the globus pallidus-subthalamic nucleus complex. Similar results have been obtained in rodent and primate models of parkinsonism. Indeed, the neuronal activity of globus pallidus under this pathological state was found to be abnormal. Therefore, elucidating the signal processing mechanism in globus pallidus is essential not only in understanding its normal function, but also its role in basal ganglia disorders. In this proposal, we focus on examining the spatial distribution, subunit composition and pharmacology of GABA-A receptors in rat globus pallidus, with an emphasis on their relationship with different synaptic inputs, which are crucial in determining the pattern of the activity of these neurons. Electrophysiological and anatomical methods will be applied to address the issue. The results generated should provide the much needed information about the GABAergic signaling in this critically important, yet under-studied, basal ganglia nucleus.

(CU02175)

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**Please refer to previous issues of this publication for more details of the following ongoing research at the department:**

<u>Edition</u>	<u>Title/Investigators</u>
1998-99	Research in Epithelial Cell Biology (MD98084) ✉ CHAN Hsiao Chang • CHEW CHENG Siew Boon • FISCUS Ronald Ray • LEUNG Po Sing • WONG Patrick Yee Ding • YAO Xiaoqiang
1999-00	Innovation Development of Chinese Medicine-based Health Care Products for Women of All Ages (MD99127) ✉ CHAN Hsiao Chang • BUT Pui Hay Paul (Dept of Biology) • LI K Y*
2000-01	Functional Studies of a Novel Epididymis-specific Gene, Bin-1b: Role in Epididymal Host Defense and Male Fertility (CU00070) ✉ CHAN Hsiao Chang • CHEN Xu* • ZHANG Yong Lian*
2001-02	Epithelial Cell Biology and Functional Genomics (MD01001) ✉ CHAN Hsiao Chang • CHEW CHENG Siew Boon • CHOW Pak Ham Patricia (Dept of Anatomy) • FISCUS Ronald Ray • LEUNG Po Sing • WONG Patrick Yee Ding
2001-02	Apoptotic DNA Fragmentation in Uterine Epithelial Cells: Cellular Mechanisms and Quantification by Capillary Electrophoresis with Laser-induced Fluorescence (MD01386) ✉ FISCUS Ronald Ray • CHAN Hsiao Chang • CHEW CHENG Siew Boon



- 1998-99 Physiological Role of Membrane Potential in Regulation of Resistance Arterial Tone (MD98008)  
 ✍ HUANG Yu • CHAN Leung Franky (Dept of Anatomy) • NELSON Mark T\* • GOLLASCH Maik\*
- 2000-01 Investigation into Mechanisms of Vascular Action of Purified Neferine from *Nelumbo nucifera* Gaertn in Rat and Mouse Arteries (MD20025)  
 ✍ HUANG Yu • CHAN Wood Yee (Dept of Anatomy) • CHEN Zhenyu (Biochemistry) • KO Wing Hung • YAO Xiaoqiang • YEW Tai Wai David (Dept of Anatomy) • TSANG Suk Ying
- 2001-02 Investigation Into Mechanisms of Cerebral Vasodilator Effects of *Ligustrum Purpurascens* Extract and Purified Phenylethanoids in Normotensive and Stroke-Prone Spontaneously Hypertensive Rats (MD01620)  
 ✍ HUANG Yu • CHEN Zhen Yu (Biochemistry) • YAO Xiaoqiang • TSANG Suk Ying\*
- 2001-02 Mechanisms of Arterial Smooth Muscle Relaxation by the Novel Calcium Antagonist Cilnidipine and Metabolites of Cytochrome P450 (MD01679)  
 ✍ HUANG Yu • GOLLASCH Maik\* • TSANG Suk Ying
- 2001-02 Regulation of Ion Transport in Rat and Human Colonic Epithelia: Cellular
- 2000-01 Association between Pancreatic Angiotensin System and Pancreatic Blood Flow and Ductal Secretion: The Significance of Changes by Chronic Hypoxia in the Rat Pancreas (CU00075)  
 ✍ LEUNG Po Sing • FUNG Man Lung\* • NOBILING Rainer\*
- 2000-01 Regulated Expression and Function of Pancreatic Renin-angiotensin System: Its Significance in Transplanted Pancreatic Islets (MD20057)  
 ✍ LEUNG Po Sing • CARLSSON Per-Ola\*
- 2001-02 Activation of Pancreatic Renin-angiotensin System: Its Role in the Regulation of Reactive Oxygen Species and Apoptosis in Pancreas (MD01116)  
 ✍ LEUNG Po Sing • IP Siu Po (School of Chinese Medicine)
- 1999-00 To Investigate the Feasibility of Blocking Epididymal Anion Channels as a Novel Method for Male Fertility Regulation (MD99014)  
 ✍ WONG Patrick Yee Ding
- 2001-02 The Role of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) in Spermatogenesis (MD01670)  
 ✍ WONG Patrick Yee Ding

- 2000-01 Nucleotide Modulation of Non-selective Cation Channels in Vascular Endothelial Cells (MD00479)  
✉ YAO Xiaoqiang • GARLAND Christopher\*
- 2000-01 Protein Kinase G-sensitive Ca<sup>2+</sup> Influx in Endothelial Cells and Its Role in Vasoregulation (CU00079)  
✉ YAO Xiaoqiang • HUANG Yu • YEW Tai Wai David (Dept of Anatomy)
- 2001-02 The Regulation of Store-operated Ca<sup>2+</sup> Influx by Vesicle Fusion and Protein Kinase G (MD01429)
- ✉ YAO Xiaoqiang • KWAN Hiu Yee
- 2001-02 Role of Vesicle Fusion and Protein Kinase G in Regulating Store-operated Calcium Influx (MD01340)  
✉ YAO Xiaoqiang • VILLAZ Michel\*
- 2000-01 Analysis of GABAergic Neurotransmission in Rat Globus Pallidus: Correlation of Electrophysiology with Ultrastructural Immunocytochemistry (CU00080)  
✉ YUNG Wing Ho • BOLAM John Paul\* • YUNG Kin Lam Ken\*

## RESEARCH PROJECTS

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### A Telephone Survey on Perception of the Public on SARS-related Issues

✉ LEE Sing • CHAN Yu Yee • MAK Ka Hi • TONG Bianca\*

☐ 18 June 2003

❖ Equal Opportunities Commission

The SARS outbreak has brought enormous social, economic and health impacts in Hong Kong. According to the Department of Health of the Hong Kong Special Administrative Region, there have been over 1755 and 297 accumulated SARS infected and death cases respectively since its outbreak in Hong Kong in March. One emergent dimension of the outbreak has been related to discrimination towards people who have suffered from SARS or are considered at high risk of having contracted SARS. However, there has been little research on stigma related to the new global threat of SARS in both international and Hong Kong perspectives. Available information in Hong Kong suggested that SARS has caused work-related difficulties and discrimination in goods & services provisions and certain members of the public hold negative perceptions towards people considered to be at risk of SARS. The proposed study will focus on the stigmatizers' angle and examine the attitudes of the general public toward understanding the complex subject of discrimination related to SARS. Given the overlapping visions of reducing social stigma and promoting the well being of people in work and other domains of living, the Hong Kong Mood Disorders Center proposes to collaborate with the Equal Opportunities Commission (EOC) in conducting a

timely and much needed study on the perception of the public on SARS-related issues. The objectives of the present study are (1) to depict the general perceptions on employment and goods & services provision issues arising from the SARS crisis; (2) to examine behavioural issues, such as how people react to, manage, and resolve the problems arising from the SARS crisis; and (3) to determine SARS-related discriminatory attitudes and experience in the employment and non-employment settings. The proposed study will include two focus groups and a telephone survey. Ideas generated from the two focus groups and literature review will be used for designing a questionnaire that consists of 15-18 items for the telephone survey. The survey, to be carried out by the Telephone Survey Research Laboratory at the Hong Kong Institute of Asia-Pacific Studies, will enroll about 1,000 respondents aged 15-65. Difference among groups will be examined using chi-square test.

(SS02373)

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### Poststroke Depression in Hong Kong Chinese Patients

✉ TANG Wai Kwong • UNGVARI Gabor Sandor • SZE K H Frank\* • WOO Jean (Dept of Medicine & Therapeutics) • KAY Li Chi Richard (Dept of Medicine & Therapeutics) • CHIU Fung Kum Helen • AHUJA Anil Tejbhan (Dept of Diagnostic Radiology & Organ Imaging)

☐ 15 January 2003

❖ CUHK Research Committee Funding (Direct Grants)

Stroke is common in Hong Kong. Poststroke depression (PSD) was found to be present in up to 39% of survivors of stroke. PSD adversely affects

morbidity, suicide, speed of recovery, length of stay in hospital, functional outcome, and quality of life. Although PSD is frequently unrecognized and untreated, its treatment leads to improvement inpatients' mood, psychological well-being, cognitive functions and activities of daily living. Despite its significance, there is still a lack of consensus about the prevalence and underlying pathophysiology of PDS. Data on PSD in Chinese patients are very limited.

The present proposal aims to examine the frequency of PSD among Hong Kong Chinese patients, the risk factors for PSD and its one-year course and outcome. The study will provide valuable information on PSD in Chinese patients and enhance early detection and treatment by identifying patients at high-risk.

Patients with acute stroke will be recruited from the stroke unit of a general hospital. PSD will be detected by a screening test followed by a structured psychiatric interview conducted by psychiatrist. Patients will be reassessed at 6 and 12 months after their stroke. Vascular lesions will be measured by CT scan of the brain and analyzed by a radiologist.

(MD02628)

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### **A Family and Genetic Study of Narcolepsy in Chinese**

✍ WING Yun Kwok

☐ 1 March 2003

❖ CUHK Research Committee Funding (Direct Grants)

Narcolepsy is an under-diagnosed and under-treated sleep disorder that affects 0.034% of the general population in Hong Kong. Characterized by excessive daytime sleepiness, cataplexy, nocturnal sleep disturbance and other REM sleep related phenomenon such as sleep paralysis and hypnagogic

hallucination clinically; narcolepsy is a lifelong crippling sleep disorder with conspicuous physical and psychosocial complications. Familial studies of narcolepsy reported an increase in the prevalence of excessive daytime sleepiness and idiopathic hypersomnia which suggested that a spectrum of phenotypes existed across cataplexy-narcolepsy, non/atypical cataplexy-narcolepsy, and idiopathic hypersomnia. Based on limited studies, the familiar risk of a first-degree relative was 0.9%-2.3% for narcolepsy-cataplexy, which was 20-70 times higher than the prevalence in the general population. However, despite the confirmation of familial contribution in narcolepsy, questions remained on the exact mode of genetic transmission, the degree of heritability, relative importance of genetic and environmental influences, incomplete phenotypes and the possible involvement of genes other than HLA and hypocretin system. Some of the uncertainties arise from the limitation in the methodologies of previous studies in other ethnic groups, for example, the lack of individual clinical and laboratory investigation in each relative. By detail investigation of the Chinese narcoleptics and their family members, we aim to explore for the first the familial transmission of narcolepsy in Hong Kong Chinese. Not only will the Chinese database of HLA association in narcolepsy to be obtained allow further cross-ethnic comparison, the study will also shed some light on wider issues between mode of transmission and diseases. The finding should help to understand the mode of transmission and its relationship with HLA typing of narcolepsy.

(MD02428)

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**Please refer to previous issues of this publication for more details of the following ongoing research at the department:**

<u>Edition</u>	<u>Title/Investigators</u>	
		2001-02 A Mutli-centre Efficacy Trial of Naltrexone Maintenance Therapy in Hong Kong (MD01462) ✍ LEE Tak Shing Dominic • CHEUNG Kin Leung Ben • LEUNG Shun Pun* • WONG Chi Keung* • CHAN Ronald* • LAM Ming
2001-02	"Life Clinic", 3-Tier Coordinated Service Model, Joint Project on Prevention of Elderly Suicide (MD01324) ✍ CHIU Fung Kum Helen • LAM Chiu Wa	
2001-02	Association Between Pro-inflammatory Genotypes and Alzheimer's Disease in Chinese (MD01538) ✍ LAM Chiu Wa • TANG Leung Sang Nelson (Dept of Chemical Pathology)	2001-02 Poststroke Dementia in Hong Kong: A Pilot Study (MD01380) ✍ TANG Wai Kwong • CHAN Sau Man Sandra • UNGVARI Gabor Sandor • CHIU Fung Kum Helen • SZE Kai Hoi Frank* • WOO Jean (Dept of Medicine & Therapeutics)
2000-01	Attitudes toward and Cultural Meanings of Suicide in Contemporary Chinese Society (CU00380) ✍ LEE Sing • Arthur KLEINMAN* • Michael PHILLIPS*	2000-01 Prospective Memory in Patients with Schizophrenia and Its Relationship with Retrospective Memory, Executive Functions, and Daily-life Adjustment (CU00330) ✍ UNGVARI Gabor Sandor • AU Wing Cheong* • CHU Man Keung* • TANG Wai Kwong • SHUM H K David*
2001-02	Antenatal Depression among Hong Kong Chinese Women (MD01120) ✍ LEE Tak Shing Dominic • CHUNG Kwok Hung Tony (Dept of Obstetrics & Gynaecology) • YIP Shing Kai Alexander (Dept of Obstetrics & Gynaecology)	2001-02 Psychological Morbidity in Burn-injured Patients in Hong Kong Chinese - A Prospective Follow-up (MD01663) ✍ WING Yun Kwok • HO Wai Sun* • KAM Irene* • YING SY*
2001-02	A Database on Traditional Chinese Medicine Treatment for Drug Addiction (MD01884) ✍ LEE Tak Shing Dominic • LEUNG Ping Chung (Dept of Orthopaedics & Traumatology) • XU Min*	

## RESEARCH PROJECTS

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### Survey on Direct to Consumer Advertising of Prescription Pharmaceuticals

✉ MAO Jing • NG Sian\*

☐ 1 July 2002

❖ AstraZeneca Hong Kong Limited

The study was to investigate the attitude towards Direct to Consumer Advertisement of prescription pharmaceuticals among public and private doctors. (MD02962)

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### Asthma Control in Asia-Pacific: The Asthma Insights and Reality in Asia-Pacific Study

✉ WONG Ming Chung • LAI Kei Wai Christopher  
(Dept of Medicine & Therapeutics)

☐ 10 September 2002

❖ GlaxoSmithKline

*Background and objective:* Few data on asthma management are available for the Asia-Pacific region. This study examined asthma symptoms, healthcare utilization and management in Asia-Pacific.

*Methods:* Cross-sectional survey, followed by administration of a questionnaire in a face-to-face

setting in the respondents' homes, in their language of choice. Urban centers in eight areas were surveyed: China, Hong Kong, Korea, Malaysia, The Philippines, Singapore, Taiwan and Vietnam.

*Results:* A population sample of 3207 respondents with physician-diagnosed asthma was identified by screening 108,360 households. Daytime asthma symptoms were reported by 51.4% of respondents, and 44.3% reported sleep disturbance due to asthma in the preceding 4 weeks. At least two in every five respondents (43.6%) had been hospitalized, attended a hospital emergency room or made unscheduled emergency visits to other healthcare facilities for their asthma during the previous 12 months. Overall, 15.3% of respondents reported that they had required admission to hospital for their asthma. Asthma severity correlated with the frequencies of hospitalizations and emergency visits for asthma in the past year. Even in those with severe persistent asthma, 34.3% regarded their disease as being well or completely controlled. Current use of an inhaled corticosteroid was reported by only 13.6% of respondents, while 56.3% used quick-relief bronchodilators. Absence from school and work in the past year was reported by 36.5% of children and 26.5% of adults.

(MD02849)

## RESEARCH PROJECTS

### Switching from Sildenafil Citrate to Tadalafil in Treatment of Erectile Dysfunction: Multinational Assessment of Treatment Preference

✉ CHAN Lung Wai • CHAN Shu Yin Eddie\*

☐ 27 June 2003

❖ Eli Lilly (Asia) Inc.

Tadalafil is a selective and potent inhibitor of phosphodiesterase type 5 (PDE5). PDE5 inhibitors are believed to enhance erectile response in patients with erectile dysfunction (ED) by mediating the relaxation of vascular smooth muscle of the penis. Tadalafil is currently being developed by Lilly ICOS LLC as a treatment for ED.

This study is a multicenter, open-label study that will evaluate patient choice of either tadalafil or sildenafil citrate as a treatment to be administered for ED, and to assess sexual encounter attributes and the safety and tolerability of both medications.

The objective of this study is:

- (1) to determine the proportion of patients who will choose tadalafil as the treatment to be administered during the extension phase of the study
- (2) to assess sexual encounter attributes (time pressure, romance, sexual self-esteem) as measured by the Psychological And Interpersonal Relationship Scales (PAIRS) in patients taking sildenafil and subsequently tadalafil
- (3) to assess the safety and tolerability of tadalafil and sildenafil for the treatment of men with ED

(MD02735)

### Development of Bid Recombinant Adenovirus and Its Application in Induction of Apoptosis in Hepatocellular Carcinoma Cells

✉ CHEN Gong George • MIAO Ji

☐ 6 January 2003

❖ CUHK Research Committee Funding (Direct Grants)

Our recent studies have shown that the expression of pro-apoptotic Bid is significantly decreased in liver tumor tissues than non-tumor liver tissues from HCC patients and that decreased expression of Bid is related to x protein of hepatitis B virus, which is positive in more than 90% of HCC patients in China including Hong Kong. These results suggest that a deficiency in the expression of Bid may contribute to the development of the imbalance of anti-apoptosis and pro-apoptosis in HCC. The proposed study will attempt to correct the low level of Bid in HCC using Bid recombinant adenovirus. 80% of HCC will produce alpha-fetoprotein (AFP) and for near 40 years, AFP has been a specific marker for diagnosis of HCC. Taking advantage of this unique feature, a gene under the direction of AFP enhancer/promoter should be only delivered to the cell positive for AFP. Therefore, Bid recombinant adenovirus will be such designed that the enhancer/promoter of alpha-fetoprotein (AFP) will be fused with Bid gene and used to direct the expression of Bid. By doing so, Bid will selectively target AFP-producing HCC tumor cells. The proposed study is to construct such a Bid recombinant adenovirus and to test it on AFP-producing HCC tumor cells.

(MD02472)

### Linezolid for the Treatment of Suspected or Proven Gram Positive Skin and Soft Tissue Infection - An Open-label Trial

✉ CHUNG Sheung Chee Sydney • NG Enders Kwok-wai • CHENG Fun Bun Augustine (Dept of Microbiology) • CHAN YUNG Man Yee • SUEN Bing Yee

□ 13 August 2001

❖ Pharmacia Asia Limited

This open-label study will evaluate the efficacy (clinical and microbiologic), safety, and tolerance in the treatment of Skin and Soft Tissue Infection:

- IV linezolid (600mg every 12 h) for entire treatment period or switched during treatment period to linezolid PO (600 mg every 12 h).

Hospitalized (includes chronic care facilities) patients will be eligible for this protocol if they have known Skin and Soft Tissue Infection. Patients with endocarditis, CNS infections, and osteomyelitis will be excluded from the study.

Patients enrolled will begin treatment with intravenous study medication but should switch to the oral treatment when appropriate as determined by the discretion of the investigator. Efficacy assessments and clinical and microbiological evaluations will be performed/monitored as will safety assessments, including adverse events, vital signs, and laboratory assays.

(MD01444)

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**Function of Potassium Channels in the Coronary/Pulmonary Arteries and Myocardium during Heart/Lung Surgery: Clinical Implications**

✉ HE Guo Wei

□ 1 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

Potassium channels (PC) in the coronary/pulmonary artery and the myocardium play important roles in the function of heart and lung. These are many subtypes of PC including calcium-activated PC ( $K_{Ca}$ ) and ATP-sensitive PC ( $K_{ATP}$ ).  $K_{Ca}$  is mainly related to the endothelium-dependent and  $K_{ATP}$ , the endothelium-independent hyperpolarization and relaxation. The endothelium-dependent hyperpolarization may be related to nitric oxide (NO) and a chemically unidentified endothelium-derived hyperpolarizing factor [EDHF].

In the myocardium,  $K_{ATP}$  plays important role in myocardial contractility. In the coronary circulation, both  $K_{ATP}$  and  $K_{Ca}$  play a role in maintaining the coronary tone that is critical in myocardial perfusion.  $K_{Ca}$  regulates coronary endothelium-smooth muscle function through endothelium-derived relaxing factors (EDRFs), particularly NO and EDHF, to maintain the normal function of the coronary circulation. During open heart surgery or heart/lung transplantation, the heart (or lung) is subject to ischemia-reperfusion injury that is the main cause of subsequent alteration of the heart/lung function. Our previous work demonstrated that hyperkalemic cardioplegia or organ preservation solutions reduce the EDHF-mediated relaxation and membrane hyperpolarization in coronary arteries and that this function may be restored by hyperpolarizing cardioplegia using potassium channel openers. However, the mechanism have not been understood at the level of single ion channels. Further, little is known in the coronary/pulmonary arteries about 1) the effect of important ions ( $K^+$ ,  $Mg^{2+}$ , exc.) and other components in cardioplegia/organ preservation solutions on PC; 2) the effect of ischemia-reperfusion on PC. We propose this study to answer the above questions. The study is designed mainly at the cellular and single ion channel level. The single PC studies will be carried out by patch-clamp technique.



Myocytes and coronary/pulmonary arteries from pig hearts/lungs will be examined. The study will be also conducted in isolated coronary/pulmonary arteries in organ chambers and myographs. Direct measurements of the membrane potential in a single cell will be performed.

(MD02451)

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**IMASH - Intravenous Magnesium Sulfate in Aneurysmal Subarachnoid Hemorrhage (Does Intravenous Magnesium Sulfate Improve Clinical Outcome?)**

✉ POON Wai Sang • CHAN Matthew Tak Vai (Dept of Anaesthesia & Intensive Care) • LAM Ming Kuen Joseph • BOET Ronald

□ 1 July 2002

❖ Research Grants Council (Earmarked Grants)

Vasospasm secondary to aneurysmal subarachnoid hemorrhage (ASAH) still significantly contributes to a poor outcome in this group of patients. The main pathophysiological pathway through which this occurs is focal neurological ischemia. In current clinical practice, several modalities are employed to prevent and treat vasospasm and resulting ischemic injury. The methods of treatment that are generally accepted as useful in the management of cerebral vasospasm secondary to ASAH are the following: the routine use of calcium blockers i.e. nimodipine, so-called TRIPLE-H therapy which includes a combination of hemodilutional, hypervolemic and/or hypertensive strategies and lastly in centers that have the facilities, endovascular techniques such as vasodilator infusion and balloon dilatation in cases of resistant vasospasm. Despite these treatment options, patients still regularly suffer severe morbidity and mortality. Besides nimodipine several other neuroprotective agents have been

investigated though none of these have as yet been included in routine clinical protocols.

Magnesium is known to block N-methyl-D-aspartate (NMDA) receptors and thereby have a neuroprotective effect. Literature evidence suggests that magnesium can improve outcome after neurological injury by improving general cellular metabolism and function while at the same time blocking NMDA-receptor regulated calcium influx into injured neurons. We wish to perform a randomized, placebo-controlled, double-blinded, multi-center trial to evaluate the effect that intravenous magnesium sulfate infusion has on the clinical outcome of patients with ASAH.

(CU02183)

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**Glioblastoma Cell-targeting Vaccination Generated by Tumour Lysate-pulsed Macrophages Engineered to Produce Tumour Necrosis Factor Alpha (TNF $\alpha$ ) and Interferon Gamma (IFN $\gamma$ )**

✉ POON Wai Sang • CHEN Gong George • NG Ho Keung (Dept of Anatomical & Cellular Pathology)

□ 1 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

Malignant gliomas are highly proliferative and invasive tumor with poor prognosis. It is incurable with currently available treatments. Our study has demonstrated that the growth of glioma cells is significantly inhibited when incubated with macrophages or supernatant obtained from the activated macrophages. We further identified two cytokines, TNF $\alpha$  and IFN $\gamma$  released from macrophages, which are responsible for the inhibitory effect via an increase in the production of apoptotic

molecules. Adjusted by these data, we reason that the immunotherapy with gene-modified macrophages is one of the promising approaches in treatment of glioblastoma. Furthermore, the gene-modified macrophages pulsed with tumor lysate will specifically guide the effector cells towards glioma tumor cells, thus it will prevent any possible side effects associated with over-production of TNF $\alpha$  and IFN $\gamma$  on normal cells and tissues. This novel approach, if successful, will provide us with a novel venue to control and to inhibit malignant gliomas.

(MD02710)

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### **The Establishment of the Chinese Rhinitis Symptom Utility Index (RSUI)**

✉ VAN HASSELT Charles Andrew • TONG Chi Fai Michael • LO Suk Yee Phoebe • WOO Kong Sang John • LAM Chuen Kwong • LEE Ching Chyi (Dept of Decision Sciences and Managerial Economics) • REVICKI Dennis\*

□ 1 May 2003

❖ CUHK Research Committee Funding (Direct Grants)

The Rhinitis Symptom Utility Index (RSUI) as developed by Revicki et al. (1998) is to-date the only available preference-weighted outcome measure for evaluation of rhinitis. This study aims to establish a multiattribute health status classification system and its scoring formula for the use of RSUI in the Chinese population. A secondary goal is to validate the Chinese RSUI with reference to its multiattribute utility function. As an initial step, a modified double-back translation method will be applied to establish linguistic validation of the Chinese RSUI. In the pre-testing phase, the acceptability of RSUI by the Chinese patients and the trial of computer-interactive interviews for preference

measures will be examined. The field-test will involve 100 subjects who are diagnosed as allergic rhinitis. Participants will be requested to (1) see two ENT specialists for symptom severity determination, (2) administer two questionnaires, i.e. RSUI and 36-item Short-Form Health Survey (SF36), and (3) be interviewed for preference measures. Respondents will also repeat administering RSUI in two weeks time for the purpose of test-retest reliability evaluation. The preference measures will use visual analogue scale (VAS) and standard gamble (SG) technique through computer-assisted administration. Results obtained will be used to determine the multiattribute utility function (scoring formula) and its related coefficients for the rhinitis status classification system. Scores obtained from RSUI and SF-36 will be tested for reliability and validity. It is expected that the RSUI would become a useful rhinitis assessment tool for both classical clinical trials and economic evaluation studies.

(MD02323)

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### **The Nuclear Localization of NF Kappa B and p53 in Laryngeal Squamous Cell Carcinoma Infected with HPV16**

✉ VLANTIS Alexander Chris • CHEN Gong George • VAN HASSELT Charles Andrew

□ 1 March 2003

❖ CUHK Research Committee Funding (Direct Grants)

The pathogenesis of human laryngeal squamous cell carcinoma is linked to infection by HPV16. The E7 of HPV16 is one of main oncoproteins produced by the virus. The interaction that occurs between the HPV16 (or its oncoprotein E7) and other cell growth factors such as p53 and NF kappa B in laryngeal cancer is not clearly understood. The aim of this

study is to examine the expression of these three proteins in tumor and non-tumor laryngeal tissues from patients with laryngeal squamous cell carcinoma. Since NF kappa B is a survival signal which can act as an upstream molecule in the transduction pathway of HPV16-related growth factors (Rb, p21 and Bcl-2), whose levels are known to be abnormal in laryngeal cancer, the nuclear co-localization of HPV16 oncoproteins and NF kappa B is believed to be pathologically significant. Therefore, knowing how the HPV16 oncoprotein (such as E6 and E7) interacts with other cell growth factors such as p53 and NF kappa may provide us with some useful data for both pathological use and for understanding the development of human laryngeal squamous cell carcinoma.

(MD02687)

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**Open Label Extension and Long Term Safety Study of Tolterodine PR Capsules in Children 5 to 11 Years of Age with Symptoms of Urge Urinary Incontinence Suggestive of Detrusor Instability**

✍ YEUNG Chung Kwong • SIHOE Dart Yin Jennifer\* • SHIT Kam Yee Frances\*

□ 25 September 2002

❖ Pharmacia Singapore Pte. Ltd.

Tolterodine is a muscarinic receptor antagonist that may increase functional bladder capacity by diminishing unstable detrusor contractions. Previous studies have demonstrated that it is safe and effective for treating symptoms of overactive bladder (OAB) such as urge urinary incontinence, frequency, and urgency in adults. Symptoms of OAB may also affect children aged 5 years and above. The clinical pharmacology of tolterodine has been studied in children 5 to 10 years of age (tolterodine immediate release (IR)) and in children 11 to 15 years of age

(tolterodine prolonged release (PR)). In a previous placebo-controlled safety and efficacy trial in children 5-10 years of age, all subjects with urge urinary incontinence were enrolled with a urinary frequency of > 2 micturitions/24 hours. The greatest efficacy was noted among children who did not demonstrate an infrequent micturition pattern, those patients with 6 micturitions per day.

DETAPE-0581-008 was designed to provide additional efficacy and safety data of tolterodine PR capsules (2 mg qd) in the same age group, 5-10 years, but including only those children with a mean micturition frequency of 6 micturitions per 24 hours. This study will provide open label extension treatment and long-term safety data on all patients completing study DETAPE 0581-008 who would like to continue on a regimen of tolterodine PR capsules.

(MD02921)

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**Effects of Insufflation of the Bladder with Carbon Dioxide (Pneumovesicum) on Renal and Cardio-respiratory Physiology in an Animal Model**

✍ YEUNG Chung Kwong • METREWELI Constantine (Dept of Diagnostic Radiology & Organ Imaging)# • AUN Sui Tee Cindy (Dept of Anaesthesia & Intensive Care) • KARMAKAR Manoj Kumar (Dept of Anaesthesia & Intensive Care)

□ 1 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

Transvesical reimplantation of the ureter is one of the most common operations performed in paediatric urology. However, this procedure involves a significant abdominal incision and a large vesicotomy. This inevitably results in considerable post-operative

pain and also may interfere with subsequent bladder function. We propose that it would be possible to perform such operations completely intravesically without opening the abdomen and the bladder by employing minimally invasive surgical (MIS) techniques previously applied to working in other small cavities of the body, and with the help of insufflation of the bladder using carbon dioxide (CO<sub>2</sub>). This new concept evolves on the fact that the bladder is a natural bodily cavity that is potentially distensible, and is intuitively suitable for application of the keyhole surgery, or MIS techniques, after CO<sub>2</sub> insufflation. Pilot studies using piglets in our unit have indeed shown that an intravesical ureteric reimplantation could be easily achievable without opening the bladder by using MIS techniques under CO<sub>2</sub> pneumovesicum. This new technique therefore has a huge potential for successful clinical application for a wide range of urological conditions in both children but perhaps more so in adults, that would normally require an open bladder, or intravesical, operation.

However, as with all new procedures, we must ensure that the technique is safe to perform and does not have any unforeseen adverse side effects, particularly on the kidneys and bladder, that may either be transient or more persistent. Previous studies in our unit have shown that insufflation of the peritoneum with CO<sub>2</sub> had a greater deleterious effect on the cardio-respiratory system of infant pigs than adult pigs. It becomes mandatory therefore that we should confirm that this new MIS technique is safe by testing them in an animal model before actual clinical application in human subjects.

(MD02818)

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**Role of Angiogenesis in Mediating the Inhibitory Effect of the External Stent on Porcine Vein Graft Thickening**

✉ YIM Ping Chuen Anthony • WAN Song • JEREMY Jamie\* • BAKER Andrew\* • ARIFI Ahmed A\*

□ 1 November 2002

❖ CUHK Research Committee Funding (Direct Grants)

In a porcine model, we have demonstrated that external placement of a non-restrictive, porous stent around saphenous vein grafts significantly reduces neointima formation and total wall thickness, one month after implantation. These stented vein grafts are characterised by the rapid formation of a highly organised “non-adventitia” in the space between the graft and stent, which in turn is infiltrated by an extensive network of microvessels. We therefore proposed that the external stent, by virtue of promoting angiogenesis, influences neointimal thickening by providing adequate oxygenation to the adaptively thickening graft. In order to explore this hypothesis further, a porcine model of stented and unstented saphenous vein – carotid artery interposition grafts will be investigated at different times over one month. Grafts will be excised and oxygenation status and the distribution of angiogenic factors in the neoadventitial-microvessel complex assessed using immunocytochemistry. In order to test whether angiogenesis is the key to the effectiveness of the external stent, microvessel growth will be arrested in vein grafts with gene transfer of angiostatin and drug treatment using lavendustin A and the effect of this treatment of graft thickening assessed. Ultimately, the project will lay the foundation for a rational and practical approach to the promotion of angiogenesis as a therapeutic strategy in reducing venous graft disease and failure.

(MD02883)

Please refer to previous issues of this publication for more details of the following ongoing research at the department:

Edition      Title/Investigators

2001-02      Biological Effects of Laser Energy on Post-Burn Keloid Fibroblast Cells (MD01802)

✉ BURD David Andrew Ross

2001-02      Apoptosis in Infiltrating Mononuclear Cells of Colorectal Cancer is a Novel Mechanism for Tumor Escape (MD01624)

✉ CHEN Gong George • LEE Fung Yee Janet

2000-01      Altered Expression and Mutations of the HBV Transactivator X Gene in Hepatocellular Carcinoma and Liver Cirrhosis (MD00305)

✉ CHUI Ka Keung Albert • CHEN Gong George • LAU Wan Yee Joseph

2000-01      A Multi-centered Randomized Controlled Trial Comparing Standard Oesophagectomy Versus Primary Chemo-irradiation without Surgery as the Treatment for Squamous Oesophageal Cancer (CU00084)

✉ CHUNG Sheung Chee Sydney • CHAN Chi Wai Angus • GRIFFITH James Francis (Dept of Diagnostic Radiology & Organ Imaging) • KWOK Po Yin Samuel • LEONG Heng Tat • LEUNG Sing Fai (Dept

of Clinical Oncology) • ONG Lina Lilian • LI Ka Wah Michael

2000-01      A Randomized Trial on the Need for Cholecystectomy in Elderly Patients after Endoscopic Sphincterotomy for Bile Duct Stones (MD00455)

✉ CHUNG Sheung Chee Sydney • LAU Yun Wong James • CHAN Chi Wai Angus • SUNG Joseph Jao Yiu (Dept of Medicine & Therapeutics) • LAU Wan Yee Joseph • NG Enders Kwok-wai

2001-02      Isolation and Characterisation of the Nitrite Reductase Gene of Helicobacter Pylori and Its Role in Gastric Carcinogenesis (MD01126)

✉ CHUNG Sheung Chee Sydney • CHAN Chiu Yeung Raphael (Dept of Microbiology) • CHENG Fun Bun Augustine (Dept of Microbiology) • LEUNG Wai Keung (Dept of Medicine & Therapeutics) • LING Kin Wah Thomas (Dept of Microbiology) • NG Enders Kwok-wai • SUNG Joseph Jao Yiu (Dept of Medicine & Therapeutics)

1999-00      Protection of Coronary Endothelium-smooth Muscle Function During Cardiac Surgery (CU99246)

✉ HE Guo Wei

2001-02      The Interaction between Endothelium and Smooth Muscle/Cardiac Myocytes During Heart Surgery and Clinical Significance (MD01127)

- 1997-98    2000-01    A Systematic Review of the Effectiveness of Ofloxacin Otic Solution for the Treatment of Suppurative Otitis Media (MD20013)  
 2001-02    Prospective Study on the Relationship of Central Venous Pressure and Blood Loss During Hepatectomy (MD96217)  
 2001-02    Activation of NF- $\kappa$ B and NF-IL6, the Common Pathway Towards Angiogenesis of Hepatitis-B-Related Hepatocellular Carcinoma (MD01511)  
 2001-02    Expression of Double-stranded RNA-activated Protein Kinase in Hepacellular Carcinoma with Hepatitis B Virus Infection (MD01468)  
 2001-02    Which Traumatic Intracerebral Haematoma should be Surgically Evacuated? An Autoregulation and Neurochemical Monitoring Study (MD01947)  
 1995-96    Video Assisted Thoracic Surgery (MD92192)
- 2001-02    Primary Nocturnal Enuresis in Young Adults in Hong Kong: An Epidemiological, Hormonal Cystometric and Somnographic Study (MD01812)  
 2001-02    Children's Continece Care Centre (MD01896)  
 2001-02    A Phase III, Randomized, Double Blind, Multicenter and Multinational Study to Determine the Efficacy and Safety of Tolterodine Prolonged Release Capsules in Children 5 to 10 Years of Age with Symptoms of Urge Urinary Incontinence, Suggestive of Detrusor Instability (MD01597)
- 2001-02    LAI Bo San Paul • CHUI Po Tong (Dept of Anaesthesia & Intensive Care) • LEOW Chon Kar# • LAU Wan Yee Joseph  
 2001-02    LAI Bo San Paul • CHEN Gong George • LAU Wan Yee Joseph  
 2001-02    LAU Wan Yee Joseph • CHEN Gong George  
 2001-02    POON Wai Sang • CHAN Matthew Tak Vai (Dept of Anaesthesia & Intensive Care) • GIN Tony (Dept of Anaesthesia & Intensive Care) • LAM Wai Man Wynn (Dept of Diagnostic Radiology & Organ Imaging) • NG CP\* • LAM Joseph MK\*  
 2000-01    HE Guo Wei  
 2001-02    TONG Chi Fai Michael • Generoso T Abes\* • Noel L Espallardo\*  
 2001-02    YEUNG Chung Kwong • VAN HASSELT Charles Andrew • LAU Tak Fai Joseph (Centre For Epidemiology & Biostatistics)  
 2001-02    YEUNG Chung Kwong • BOWER Wendy Fiona • SIT K Y Frances\* • YEW Siu Yin\*  
 2001-02    YEUNG Chung Kwong • SHIT Kam Yee Frances\* • Sihoe, Deary Yin Jennifer\*  
 2001-02    YIM Ping Chuen Anthony

2000-01 Novel Strategies for the Treatment of Vein Graft Failure: Investigations Using a Porcine Model (CU00091)

✍ YIM Ping Chuen Anthony • ARIFI Ahmed A\* • JEREMY Jamie\* • WAN Song

and Hypercholesterolaemia and Novel Approaches to Therapy Using Gene Transfer in a Porcine Model" (MD01133)

✍ YIM Ping Chuen Anthony • ARIFI Ahmed A\* • HE Guo Wei • JEREMY Jamie\* • NEWBY Andrew C\* • WAN Song

2001-02 "Homocysteine, Oxidant Stress and Vein Graft Failure: Interactions with Diabetes

## RESEARCH PROJECTS

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### Plasma Nucleic Acids as a Non-invasive Marker of Severity in Acute Coronary Syndrome

✉ RAINER Timothy Hudson • LO Yuk Ming Dennis (Dept of Chemical Pathology) • WOO Kam Sang (Dept of Medicine & Therapeutics) • CAMERON Peter Alistair#

☐ 1 October 2002

❖ CUHK Research Committee Funding (Direct Grants)

*Background:* Ischaemic Heart Disease is the leading cause of death worldwide and associated with cellular ischaemia and death. Nothing is known of the release of DNA and RNA into the circulation after myocardial ischaemia.

*Study Design:* Prospective, observational trial investigating patients with chest pain or electrocardiographic abnormalities suggestive of myocardial ischaemia and comparing them with healthy controls.

*Participants:* 120 adult patients will be recruited from the Emergency Department of the Prince of Wales Hospital.

*Laboratory methods :* After single and/or serial blood samples are withdrawn from the patients, centrifuged plasma will be used for quantitative analysis of DNA and RNA by real-time polymerase chain reaction and real-time reverse transcriptase polymerase chain reaction.

*Outcome measure:* Plasma nucleic acid concentrations in patients who develop angina, myocardial infarction.

(MD02581)

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Please refer to previous issues of this publication for more details of the following ongoing research at the department:

<u>Edition</u>	<u>Title/Investigators</u>
2001-02	Cost-effectiveness Analysis of Oral Paracetamol, Diclofenac and Indomethacin for the Treating Pain After Soft Tissue Limb Injuries: A Randomized, Controlled Trial (MD01438)  ✉ MAN Shin Yan • WOO Wing Keung • RAINER Timothy Hudson • COCKS Robert Anthony (Dept of Surgery) • LAM Kwok Wai (Centre for Clin. Trials & Epidemiological Research)# • JACOBS Philip* • NG Ying Chu*
2001-02	Role of Plasma DNA and Other Markers in the Prediction and Development of Post-traumatic Complications 1224/1202 (MD01839)  ✉ RAINER Timothy Hudson • LO Yuk Ming Dennis (Dept of Chemical Pathology) • JOYNT Gavin Matthew (Dept of Anaesthesia & Intensive Care)



## RESEARCH PROJECTS

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### Data Management and Data Analysis for the Clinical Trials on Nasopharyngeal Carcinoma

✍ LAU Tak Fai Joseph • XU Liying (School of Public Health)

☐ 1 January 2002

❖ Ho Hung Chiu Medical Education Foundation

Contracted services to manage data and perform analysis for the clinical trials on nasopharyngeal carcinoma.

(MD01551)

### Research on Cross-border Substance Abuse Problem Among Hong Kong Residents

✍ LAU Tak Fai Joseph • LAU Man Chun Mason

☐ 1 June 2002

❖ Action Committee Against Narcotics

According to the information collected from various studies and the drug seizure statistics from the Police and the Customs and Excise Department, 'cross-border substance abuse' has demonstrated an upward trend in recent years. With regard to the increasing number of newly recruited cross-border drug-abusers among young people in Hong Kong, the Action Committee Against Narcotics (ACAN) has commissioned the Centre for Clinical Trials and Epidemiological Research (CCTER) at the Chinese University of Hong Kong to employ scientific methods to investigate the problem of cross-border substance abuse among Hong Kong Residents. The study aims to obtain the demographic profiles of cross-border substance abusers, provide a better

portrait on the patterns, knowledge, attitudes, and reasons concerning cross-border drug abuse, and recommend appropriate strategies to tackle the problems. It is expected that findings of this study will lead to a better understanding of the problem and its associated factors, which may assist the Government in formulating relevant preventive education and strategies.

(SS01686)

### Evaluation of the Adolescent and family Counselling Service

✍ LAU Tak Fai Joseph • LEUNG Kit Sang (School of Public Health) • LAI Yee Ching Kelly (Dept of Psychiatry) • LAU Man Chun Mason

☐ 12 July 2002

❖ Education & Manpower Bureau, HKSAR Government

The Adolescent and Family Counselling Service (AFCS) is a major component of the Understanding Adolescent Project (primary) commissioned by the Education Department in 2002. As the UAP proper is designed to foster the general resilience of primary four students who have been identified as being at risk of developing certain psychosocial maladjustments, the AFCS aims to explore the feasibility of providing intensive psychosocial interventions to those who have salient psychosocial problems. In the AFCS, therapeutic interventions will be conducted at the family level where family members of the client students will be invited to participate in therapeutic interviews. Adopting the cognitive-behavioural and familial approaches, the AFCS also attempts to foster both internal and external resources of the perspective clients in terms of optimism, competence, and sense of belonging.

The AFCS will be evaluated independently by the Center of Clinical Trials and Epidemiological Research of the Chinese University of Hong Kong. The evaluation study adopts a longitudinal pre-post study design. The outcome effectiveness of the AFCS will be evaluated through the changes in overt behaviours, attitudes, as well as perceived sense of belonging, optimism, and competence.  
(SS02390)

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**Needs Assessment of Unemployed Youth in Hong Kong**

- ✉ LAU Tak Fai Joseph
- 1 September 2002
- ❖ The Hong Kong Jockey Club Charities Trust

The project investigates the situations of the unemployed youths, a population which has been under studied. It consists of two studies. In the first study, with assistance of the Labour Department, random samples of adolescents who were of age 15-19 were drawn from two youth pre-employment scheme (Youth Work Experience and Training Scheme & Youth Pre-employment Training Program) and with assistance of the Hong Kong Council for Social Services, a random sample was drawn from all clients of the 15 outreaching social service teams. These were compared to a full time student group of the same age range. The employment and unemployment history, quality of life, stress, services needs, resilience etc. of these youths were measured. In the second study, unemployed youths of 18-24 were studied and compared to a control group who were either full time students or full time workers. Similar topics were investigated.  
(ED02794)

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**Data Analysis for the Project "AIRAIP"**

- ✉ LAU Tak Fai Joseph • WONG Wai Eric (Dept of Community and Family Medicine)#

□ 1 March 2003

- ❖ GlaxoSmithKline Asia Pacific

Contracted services to manage data and perform analysis for a project for GlaxoSmithKline Asia Pacific  
(MD02894)

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**Consultancy Project for CK Life Sciences Development Inc.**

- ✉ LAU Tak Fai Joseph • XU Liying (School of Public Health)
- 26 March 2003
- ❖ CK Life Sciences Development Inc.

The consultation includes: review of a study protocol, provide training in GCP clinical trials and data analyses on clinical data.  
(MD02992)

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**Surveillance and Intervention Research for Different Communities in Hong Kong**

- ✉ LAU Tak Fai Joseph • KIM Jean Hee
- 1 April 2003
- ❖ Council for the AIDS Trust Fund

The entire program comprises five individual projects. Two behavioural surveillance surveys on two high-risk groups, male clients of female sex workers and Hong Kong –mainland China cross-border sex-networkers, will be conducted to keep track of the risk behaviours practiced by these groups and associated risk factors. These two series of study are continuation of a 3-year and a 4-year long

projects respectively. The third surveillance project is a very unique series of surveillance for awareness, knowledge, discriminatory attitudes, etc. among the general public in Hong Kong (8 rounds of studies have been since 1994). The fourth project is a seroprevalence surveillance on female sex workers and their clients in Hong Kong. It aims to obtain prevalence data on HIV/STD and behavioural data (e.g., frequency of condom use) on female sex workers and their clients. The fifth project is an innovative intervention program for men who have sex with men (MSM), making use of the internet platform. The project will make use of a randomized clinical trial study design, a stringent evaluation method. The feasibility of using internet for prevention in Hong Kong will be examined and it is expected that the intervention would reduce unprotected sex by 20-25% and increase the rate for HIV antibody testing.  
(MD02369)

**Please refer to previous issues of this publication for more details of the following ongoing research at the department:**

<u>Edition</u>	<u>Title/Investigators</u>
2001-02	Understanding Adolescent Project 4 (ED01367) ✉ LAU Tak Fai Joseph • LEUNG Kit Sang (School of Public Health) • LAU Man Chun Mason
2001-02	Evaluation of the Primary Preventive Programs of the Understanding the Adolescent Project (UAP) in Secondary Schools (ED01748) ✉ LAU Tak Fai Joseph • LEUNG Kit Sang (School of Public Health) • LAU Man Chun Mason

## RESEARCH PROJECTS

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### Functional Studies of a Putative Peroxisomal Regulating Gene, *BRE* - Its Roles in Cellular Survival, Immune System and Tumorigenicity

✉ CHUI Yiu Loon • CHAN Yeuk Hon John\* • CHING Kar Keung • LEE Ka Ho Kenneth (Dept of Anatomy)

☐ 1 September 2002

❖ Research Grants Council (Earmarked Grants)

This research is aimed at elucidating the function of a human gene *BRE*, which can, through alternative splicing, generate multiple minor isoforms. *BRE* is highly conserved throughout evolution, and can be found in organisms all the way from humans to fish, and from insects to plants. The highly conserved nature of the gene suggests that it is playing a fundamental role on which nearly all life forms depend. Indeed, the importance of the gene in life and death has been evidenced in our preliminary studies. We have shown that in both the transgenic and cell line systems, blocking the endogenous expression of *BRE* using antisense DNA could lead to apoptosis *in vivo* and *in vitro*. On the other hand, transfecting the sense *BRE* to a mouse tumor clone enhanced its tumorigenicity upon transfer to the mouse hosts. Thus, up-regulation and down-regulation of *BRE* expression can positively and negatively affect cell survival, respectively. Our other data on sequence, expression and functional analysis of *BRE* strongly point to the likelihood that the life-essential role of *BRE* could be attributed to its possible function in regulating peroxisomal activities. Peroxisomes are known to perform a wide range of functions, the effects of

which extend to steroidogenesis, cell and organelle membrane physiology, especially that of the nervous system and the cardiac tissue, as well as to the redox state that in turn can influence myriad signal transduction and cell cycle control pathways. These pathways affect many cellular processes, not least the immune responses and oncogenesis. Here we propose to 1) consolidate the above transgenic and cell line findings by improving the experimental designs and scaling up the size; 2) extend the functional study to include the functions of the isoforms; 3) extend the scope of investigation from apoptosis to other functions related to the peroxisomal activities, such as the redox regulation, and its effects on redox-sensitive pathways, among others; and 4) study the cellular basis on which *BRE* enhances tumor survival *in vivo*. Given the extensive homeostatic role of peroxisomes at cellular and systemic levels, we envisage that our study of *BRE* will provide new insights to medical problems that include neurodegeneration, heart diseases, reproduction and hormonal disorders, immune disorders, as well as aging and cancers.

(CU02090)

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### Crystallisation of a Carrier-specific Antibody and Its Reconstruction as a Bona Fide Antibody Fragment

✉ LIM Pak Leong • SUTTON Brian\*

☐ 1 October 2002

❖ Research Grants Council (Earmarked Grants)

Antibodies are extremely useful reagents for the diagnosis and treatment of diseases, and as probes in biological investigations. A recent technological advancement has allowed these proteins to be produced conveniently in bacteria rather than in people or in animals. A simpler and smaller form

(scFv) is produced by this means. Although clinically useful scFvs have been produced to-date, we have found from a scFv we have constructed previously that the fine specificity of these proteins may not be exactly like that of the native antibody. This particular feature (carrier specificity) has not been examined by investigators previously. We hope to genetically re-construct the scFv in various ways to find out how to restore this specificity. We will use various methods of analysis including X-ray crystallography to look at the 3-dimensional structure of the scFvs and the native antibody. Understanding how antibodies bind to their target at the molecular level is not only academically challenging but is also biotechnologically important because this helps in the design of more specific and effective scFvs.

(CU02092)

**Please refer to previous issues of this publication for more details of the following ongoing research at the department:**

<u>Edition</u>	<u>Title/Investigators</u>
2001-02	Molecular Mechanism of Somatic Hypermutation and Its Potential Clinical Application (MD01659) ✉ CHUI Yiu Loon • CHING Kar Keung
2001-02	Crystallization of a Carrier-Specific Antibody (MD01325) ✉ LIM Pak Leong

