Programme at a glance

<table>
<thead>
<tr>
<th>Morning Session</th>
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<tbody>
<tr>
<td>8:00 - 9:00</td>
<td>Registration</td>
</tr>
</tbody>
</table>

**Lecture Theatres 3 & 4**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>9:00 - 9:15</td>
<td>Opening Ceremony</td>
</tr>
<tr>
<td>9:15 - 9:55</td>
<td>Keynote Lecture I: Prof RH Aebersold</td>
</tr>
<tr>
<td>9:55 - 10:25</td>
<td>Tea Break (at Foyer)</td>
</tr>
<tr>
<td>10:25 - 12:45</td>
<td><strong>Lecture Theatre 1</strong></td>
</tr>
<tr>
<td></td>
<td>Keynote Lecture II: Prof RS Bresalier</td>
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<td>Keynote Lecture IV: Dr BCY Wong</td>
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<td></td>
<td>Keynote Lecture VI: Dr SY Leung</td>
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<td></td>
<td>Keynote Lecture VIII: Prof NE Reiner</td>
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<tr>
<td>12:45 - 14:00</td>
<td><strong>Lecture Theatre 2</strong></td>
</tr>
<tr>
<td></td>
<td>Keynote Lecture III: Prof RG Gosden</td>
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<td>Keynote Lecture V: Prof JRW Masters</td>
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<td></td>
<td>Keynote Lecture VII: Dr DF Newgreen</td>
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<tr>
<td></td>
<td>Keynote Lecture IX: Prof Samuel HH Chan</td>
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**Afternoon Session: Scientific Meetings of the Centres of Excellence and Departments**

<table>
<thead>
<tr>
<th>Time</th>
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<tbody>
<tr>
<td>14:00 - 15:30</td>
<td><strong>Lecture Theatre 1</strong></td>
</tr>
<tr>
<td></td>
<td>Keynote Lecture X: Prof HR Anderson</td>
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<td></td>
<td>Keynote Lecture XI: Dr SH Kagan</td>
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<td></td>
<td>Telomedicine Centre</td>
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<tr>
<td></td>
<td><strong>Lecture Theatre 3</strong></td>
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<td></td>
<td><strong>Lecture Theatre 4</strong></td>
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<tr>
<td></td>
<td><strong>Seminar Rooms 1 &amp; 2</strong></td>
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<tr>
<td></td>
<td><strong>Lecture Theatre 2</strong></td>
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<tr>
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<td><strong>Seminar Room 5</strong></td>
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<td></td>
<td><strong>Seminar Room 6</strong></td>
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<tr>
<td>15:30 - 15:50</td>
<td>Tea Break (at foyer/Fan Pui Garden)</td>
</tr>
<tr>
<td>15:50 - 17:40</td>
<td>Keynote Lecture XII: Prof PM Hawkey</td>
</tr>
<tr>
<td></td>
<td>Keynote Lecture XIII: Prof RP Harvey</td>
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</tbody>
</table>

- 7 -
# Scientific Programme

## Morning Session

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
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<tbody>
<tr>
<td>8:00 - 9:00</td>
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<tr>
<td>9:00 - 9:15</td>
<td><strong>Opening Ceremony</strong></td>
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<tr>
<td></td>
<td>- Officiating address by Professor Lap-Chee Tsui, Vice-Chancellor</td>
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<tr>
<td></td>
<td>- Welcoming address by Professor SK Lam, Dean of the Faculty of Medicine</td>
</tr>
<tr>
<td>9:15 - 9:55</td>
<td><strong>Keynote Lecture I</strong></td>
</tr>
<tr>
<td></td>
<td><em>Quantitative proteome analysis: New technology and applications</em></td>
</tr>
<tr>
<td></td>
<td>Professor RH Aebersold</td>
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<td></td>
<td>Institute for Systems Biology, USA</td>
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<tr>
<td>9:55 - 10:25</td>
<td>Tea Break (at Foyer)</td>
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<table>
<thead>
<tr>
<th>Time</th>
<th>Lecture Theatre 1</th>
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<tbody>
<tr>
<td>10:25 - 11:00</td>
<td>Chairpersons: Professor RH Aebersold</td>
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<tr>
<td></td>
<td>Dr RTP Poon</td>
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<tr>
<td></td>
<td><strong>Keynote Lecture II</strong></td>
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<tr>
<td></td>
<td><em>Pharmacologic chemoprevention of colorectal cancer</em></td>
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<td></td>
<td>Professor RS Bresalier</td>
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<tr>
<td></td>
<td>University of Texas MD Anderson Cancer Centre, USA</td>
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<tr>
<td>11:00 - 11:35</td>
<td><strong>Keynote Lecture IV</strong></td>
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<tr>
<td></td>
<td><em>Chemoprevention of gastric cancer</em></td>
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<td></td>
<td>Dr BGY Wong</td>
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<td></td>
<td>Department of Medicine</td>
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<tr>
<td>11:35 - 12:10</td>
<td><strong>Keynote Lecture VI</strong></td>
</tr>
<tr>
<td></td>
<td><em>Variation in gene expression patterns in gastric cancer and discovery of prognostic biomarkers</em></td>
</tr>
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<td></td>
<td>Dr SY Leung</td>
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<tr>
<td></td>
<td>Department of Pathology</td>
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<tr>
<td>12:10 - 12:45</td>
<td><strong>Keynote Lecture VIII</strong></td>
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<tr>
<td></td>
<td><em>Intracellular pathogens as Trojan horses: Lessons learned from Leishmania</em></td>
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<td></td>
<td>Professor NE Reiner</td>
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<tr>
<td></td>
<td>University of British Columbia, Canada</td>
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<tr>
<td>12:45 - 14:00</td>
<td>Lunch (at Fan Pui Garden)</td>
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<thead>
<tr>
<th>Time</th>
<th>Lecture Theatre 2</th>
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<tbody>
<tr>
<td>10:25 - 11:00</td>
<td>Chairpersons: Professor RP Harvey</td>
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<tr>
<td></td>
<td>Dr MH Sham</td>
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<td></td>
<td><strong>Keynote Lecture III</strong></td>
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<tr>
<td></td>
<td><em>Oocyte and ovarian tissue cryopreservation</em></td>
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<td></td>
<td>Professor RG Gosden</td>
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<td></td>
<td>Eastern Virginia Medical School, USA</td>
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<tr>
<td>11:00 - 11:35</td>
<td><strong>Keynote Lecture V</strong></td>
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<tr>
<td></td>
<td><em>Human prostate epithelial stem cells</em></td>
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<td></td>
<td>Professor JRW Masters</td>
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<td></td>
<td>Royal Free and University College Medical School, UK</td>
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<tr>
<td>11:35 - 12:10</td>
<td><strong>Keynote Lecture VII</strong></td>
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<tr>
<td></td>
<td><em>From neural crest to enteric nervous system: a paradigm for the co-dependence of basic and clinical research</em></td>
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<td>Dr DF Newgreen</td>
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<td></td>
<td>The Murdoch Children’s Research Institute, Australia</td>
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<tr>
<td>12:10 - 12:45</td>
<td><strong>Keynote Lecture IX</strong></td>
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<td></td>
<td><em>Understanding brain death: From intensive care unit to laboratory</em></td>
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<td>Professor Samuel HH Chan</td>
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<td>National Sun Yat-sen University, Taiwan</td>
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</table>
# Afternoon Session 1

## Lecture Theatre 1

1. **Scientific Meeting of the Public Health Group and Medical Education Unit**

   Chairpersons: Professor HR Anderson  
   Dr. ANY Cheung

14:00 - 14:30

**Keynote Lecture X**

*Global health impact of outdoor particulate air pollution*

Professor HR Anderson, St George’s Hospital Medical School, UK

14:30 - 14:50

*Impact of sulphur on respiratory health: air pollution in Hong Kong 1989-2000*

Professor AJ Hedley, Department of Community Medicine

14:50 - 15:10

*Will mammography screening do more harm than good in Hong Kong Chinese?*

Dr. GM Leung, Department of Community Medicine

15:10 - 15:30

*Breast cancer surgery for Hong Kong women - taking a gamble?*

Dr. WWT Lam, Department of Community Medicine

15:30 - 15:50

Tea Break (at Forey)

15:50 - 16:10

*Tomorrow’s doctors: what is new?*

Professor F Lieb-Mak, Medical Education Unit

16:10 - 16:30

*Quality assurance in teaching and learning*

Professor YS Chan, Department of Physiology

16:30 - 16:50

*Quality assurance in assessments, or assessing assessments*

Dr. JM Nicholls, Department of Pathology

16:50 - 17:10

*Integration of PBL and PBT (Problem based teaching) in clinical years*

Dr. NG Patil, Department of Surgery and  
Professor TH Lam, Department of Community Medicine
### Afternoon Session 2

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>14:00 - 14:20</td>
<td>2. Scientific Meeting of the Department of Nursing Studies</td>
</tr>
<tr>
<td></td>
<td>Chairpersons: Dr SH Kagan</td>
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<td></td>
<td>Professor PL Sullivan</td>
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<td></td>
<td>Mrs AKL Lau</td>
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<tr>
<td>14:20 - 14:40</td>
<td><em>The knowledge, attitudes, and practice of nurses in smoking cessation</em></td>
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<td>Dr SSC Chan, Department of Nursing Studies</td>
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<tr>
<td>14:40 - 15:00</td>
<td><em>Detecting depression by doctors working in geriatric wards</em></td>
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<td>Ms ACK Lee, Department of Nursing Studies</td>
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<tr>
<td>15:00 - 15:30</td>
<td><em>Couples walking through depression after delivery</em></td>
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<td>Dr SSK Leung, Department of Nursing Studies</td>
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<tr>
<td>15:30 - 15:50</td>
<td><strong>Keynote Lecture XI</strong></td>
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<tr>
<td></td>
<td><em>Theoretical and methodological opportunities for gerontology research in aging societies</em></td>
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<td>Dr SH Kagan, University of Pennsylvania, USA</td>
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<tr>
<td>15:50 - 16:10</td>
<td><em>Management of central venous catheters and related issues</em></td>
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<td>Dr EKY Loh, Department of Nursing Studies</td>
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<tr>
<td>16:10 - 16:30</td>
<td><em>Fatigue-relieving strategies for patients after bone marrow transplantation</em></td>
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<td>Ms W So, Department of Nursing Studies</td>
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<tr>
<td>16:30 - 16:50</td>
<td><em>The prevalence of domestic violence among pregnant Chinese women</em></td>
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<td>Dr AFY Tiwari, Department of Nursing Studies</td>
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<tr>
<td>16:50 - 17:10</td>
<td><em>The association of critical thinking disposition and problem solving: A phenomenographic approach</em></td>
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<td>Dr FYuen &amp; Dr AFY Tiwari, Department of Nursing Studies</td>
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<tr>
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<tbody>
<tr>
<td>15:30 - 15:50</td>
<td>Tea Break (at Foyer)</td>
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</table>
### Afternoon Session 3

#### Lecture Theatre 3

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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</thead>
<tbody>
<tr>
<td>14:00 - 14:20</td>
<td>An emerging diarrheal pathogen&lt;br&gt;Professor KY Yuen, Department of Microbiology</td>
</tr>
<tr>
<td>14:20 - 14:40</td>
<td>The role of Helicobacter pylori in bronchiectasis&lt;br&gt;Dr KWT Tsang, Department of Medicine</td>
</tr>
<tr>
<td>14:40 - 15:00</td>
<td>Human metapneumovirus - a new respiratory pathogen&lt;br&gt;Dr S Chin, Department of Paediatrics and Adolescent Medicine</td>
</tr>
<tr>
<td>15:00 - 15:20</td>
<td>The origin and evolution of H5N1 influenza viruses from poultry in Southern China&lt;br&gt;Dr Y Guan, Department of Microbiology</td>
</tr>
<tr>
<td>15:20 - 15:50</td>
<td>Tea Break (at Foyer)</td>
</tr>
</tbody>
</table>

#### Chairpersons

- Professor PM Hawkey
- Professor YL Lau
- Professor NE Reiner
- Professor KY Yuen

#### Keynote Lecture XII

- **Emerging antibiotic resistance mechanisms in Gram negative bacteria**<br>Professor PM Hawkey, University of Birmingham, UK
- **Treatment of melioidosis - clinical and genetic perspectives**<br>Dr PL Ho, Department of Microbiology
- **Immunopathogenesis of human H5N1 infection**<br>Professor JSM Peiris, Department of Microbiology
- **The role of regulatory T cells in small bowel transplantation**<br>Dr I Tian, Department of Surgery
- **B cell selection during development and its implication in autoimmunity**<br>Dr I Lu, Department of Pathology
<table>
<thead>
<tr>
<th>Time</th>
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<tbody>
<tr>
<td>14:00 - 14:20</td>
<td>Clinical assessment of ovarian reserve in ART   [Chairpersons: Professor RG Gosden, Dr WSB Yeung]</td>
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<tr>
<td>14:20 - 14:40</td>
<td>In vitro culture and maturation of rat preantral follicles [Dr WS O, Department of Anatomy]</td>
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<tr>
<td>14:40 - 15:00</td>
<td>Organ morphogenesis via regulation of cell migration and matrix interaction [Dr KL Chow, Hong Kong University of Science and Technology]</td>
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<tr>
<td>15:00 - 15:20</td>
<td>Sonic hedgehog in enteric nervous system development [Dr VCH Lui, Department of Surgery]</td>
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<tr>
<td>15:20 - 15:50</td>
<td>Tea Break (at Foyer)</td>
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<tr>
<td>15:50 - 16:10</td>
<td>Epidermal growth factor as a biologic switch in hair growth cycle? [Chairpersons: Dr DF Newgreen, Dr SK Chung]</td>
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<tr>
<td>16:10 - 16:30</td>
<td>Hoxb3(^{−/−}): A mysterious knockout mutant [Dr MH Sham, Department of Biochemistry]</td>
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<tr>
<td>16:30 - 16:50</td>
<td>A mouse with two tales [Dr D Chan, Department of Biochemistry]</td>
</tr>
<tr>
<td>16:50 - 17:10</td>
<td>An essential role for type IIA procollagen in heart development [Professor KSE Cheah, Department of Biochemistry]</td>
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</tbody>
</table>
| 17:10 - 17:40 | Keynote Lecture XIII  
Cardiac NKX2-5 homeobox gene pathways in development, evolution and disease \[Professor RP Harvey, University of New South Wales, Australia\] |
### Afternoon Sessions 5 & 6

#### Seminar Rooms 1 & 2 (G/F)

<table>
<thead>
<tr>
<th>Time</th>
<th>Session Title</th>
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</table>
| 14:00 - 14:20 | Study of different approaches to enhancing tumor immunity in hepatocellular carcinoma immunotherapy  
Dr Y Xie, Hong Kong University of Science and Technology |
| 14:20 - 14:40 | Li-Cadherin, a tumor suppressor or biomarker for GI Cancer?  
Dr JMC Luk, Department of Surgery |
| 14:40 - 15:00 | Genome-wide expression profiles of liver cancers  
Dr ST Cheung, Department of Surgery |
| 15:00 - 15:20 | Rescue of marginal graft by novel nitric oxide donor FK409 in liver transplantation  
Dr K Man, Department of Surgery |

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>15:20 - 15:50</td>
<td>Tea Break (at Fan Pui Garden)</td>
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</tbody>
</table>
| 15:50 - 16:10 | New concepts in improving long-term outcomes of organ transplantation  
Dr TV Tsui, Department of Surgery |
| 16:10 - 16:30 | Crypt fission in colonic diseases  
Dr WM Wong, Department of Medicine |
| 16:30 - 16:50 | Gastric effects of sleep deprivation  
Dr MWL Koo, Department of Pharmacology |

#### Lecture Theatre 2

<table>
<thead>
<tr>
<th>Time</th>
<th>Session Title</th>
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</table>
| 14:00 - 14:20 | Initiation proteins for DNA replication as potential anticancer targets  
Dr CC Liang, Hong Kong University of Science and Technology |
| 14:20 - 14:40 | Biomimetic combinatorial synthesis of cyclic peptide libraries for drug discovery  
Dr ZH Guo, Hong Kong University of Science and Technology |
| 14:40 - 15:00 | Genetic analysis of polyol pathway in diabetic complications in mice and humans  
Dr SSM Chung, Institute of Molecular Biology |
| 15:00 - 15:20 | Oral gene therapy: Potential and challenge  
Dr RX Xu, Institute of Molecular Biology |

<table>
<thead>
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<tr>
<td>15:20 - 15:50</td>
<td>Tea Break (at Foyer)</td>
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</table>
| 15:50 - 16:10 | Genetic analysis of thyrotoxic periodic paralysis (TPP)  
Professor AWC Kung, Department of Medicine |
| 16:10 - 16:30 | Endothelial dysfunction in diabetes  
Dr KCB Tan, Department of Medicine |
| 16:30 - 16:50 | A health-related definition of childhood overweight  
Professor JPE Karlberg, Clinical Trials Centre |
### Afternoon Sessions 7 & 8

**Seminar Room 5 (LG1)**

<table>
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<th>Time</th>
<th>Session</th>
<th>Chairpersons/Auditors</th>
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<tbody>
<tr>
<td>14:00 - 14:20</td>
<td><strong>7. Scientific Meeting of the Department of Anaesthesiology and Department of Orthopaedic Surgery</strong></td>
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<tr>
<td></td>
<td><strong>Perioperative bleeding</strong></td>
<td>Dr WW Lu, Dr MRC Rodrigo</td>
</tr>
<tr>
<td>14:20 - 14:40</td>
<td><strong>Tissue engineering in Orthopaedics</strong></td>
<td>Dr WY Ip, Department of Orthopaedic Surgery</td>
</tr>
<tr>
<td>14:40 - 15:00</td>
<td><strong>Sr-HA bioactive bone cement characterization and pre-clinical trials</strong></td>
<td>Dr WW Lu, Department of Orthopaedic Surgery</td>
</tr>
<tr>
<td>15:00 - 15:20</td>
<td><strong>Anterior release in scoliosis by chymopapain injection: Increase in spinal flexibility is dose-dependent</strong></td>
<td>Dr DS Lu, Department of Orthopaedic Surgery</td>
</tr>
<tr>
<td>15:20 - 15:50</td>
<td><strong>Tea Break (at Fan Pui Garden)</strong></td>
<td></td>
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<tr>
<td>15:50 - 16:10</td>
<td><strong>Generalised artificial finger joint design process employing reverse engineering techniques</strong></td>
<td>Dr I Gibson, Department of Mechanical Engineering</td>
</tr>
<tr>
<td>16:10 - 16:30</td>
<td><strong>Time-frequency analysis: A new technique for intraoperative somatosensory evoked potential monitoring</strong></td>
<td>Dr Y Hu, Department of Orthopaedic Surgery</td>
</tr>
<tr>
<td>16:30 - 16:50</td>
<td><strong>Cancer self-remission and tumour instability</strong></td>
<td>Dr L Wang, Department of Mechanical Engineering</td>
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**Seminar Room 6 (LG1)**

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<tr>
<th>Time</th>
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<tbody>
<tr>
<td>14:00 - 14:20</td>
<td><strong>8. Scientific Meeting of the Department of Physiology</strong></td>
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<tr>
<td></td>
<td><strong>Plasticity of vestibulo-cardiovascular interactions</strong></td>
<td>Professor YS Chan, Department of Physiology</td>
</tr>
<tr>
<td>14:20 - 14:40</td>
<td><strong>Some aspects of the control of blood pressure and blood flow in acute systemic hypoxia</strong></td>
<td>Dr HJ Ballard, Department of Physiology</td>
</tr>
<tr>
<td>14:40 - 15:00</td>
<td><strong>Is atrinomedullin a cardiac depressant in septic shock?</strong></td>
<td>Dr JP Bourreau, Department of Physiology</td>
</tr>
<tr>
<td>15:00 - 15:20</td>
<td><strong>Hypoxia - matters from molecules to physiology</strong></td>
<td>Dr ML Fung, Department of Physiology</td>
</tr>
<tr>
<td>15:20 - 15:50</td>
<td><strong>Tea Break (at Fan Pui Garden)</strong></td>
<td></td>
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<tr>
<td>15:50 - 16:10</td>
<td><strong>Modulation of volume sensitive chloride current by tyrosine kinases in human atrial myocytes</strong></td>
<td>Dr GR Li, Department of Medicine</td>
</tr>
<tr>
<td>16:10 - 16:30</td>
<td><strong>Adrenergic control of nasal venous vasculature</strong></td>
<td>Dr MARY Lung, Department of Physiology</td>
</tr>
<tr>
<td>16:30 - 16:50</td>
<td><strong>Use of opioid as a cardioprotective agent</strong></td>
<td>Professor TM Wong, Department of Physiology</td>
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</table>
Keynote Speakers

Professor RH Aebersold  
Professor and Co-founder  
Institute for Systems Biology, Seattle, USA

Professor HR Anderson  
Professor of Epidemiology and Public Health  
Chairman of Department of Public Health Sciences  
St George’s Hospital Medical School, UK

Professor RS Bresalier  
Professor of Medicine and Chairman  
Department of Gastrointestinal Medicine and Nutrition  
University of Texas MD Anderson Cancer Center, USA

Professor Samuel HH Chan  
Vice-President (Academic Affairs)  
Director, Center for Neuroscience  
National Sun Yat-sen University, Taiwan

Professor RG Gosden  
The Howard & Georgeanna Jones Professor of Reproductive Medicine  
The Jones Institute for Reproductive Medicine  
Eastern Virginia Medical School, USA

Professor RP Harvey  
Head, Developmental Biology Unit  
Victor Chang Cardiac Research Institute  
University of New South Wales, Australia

Professor PM Hawkey  
Professor of Clinical and Public Health Bacteriology  
University of Birmingham, UK

Dr SH Kagan  
The Doris R. Schwartz Associate Professor of Gerontological Nursing, School of Nursing  
Gerontology Clinical Nurse Specialist, Hospital of the University of Pennsylvania  
Secondary Faculty, Department of ORL-HNS; University of Pennsylvania, USA

Dr SY Leung  
Associate Professor, Department of Pathology  
The University of Hong Kong  
Recipient of the 2000-2001 Outstanding Young Researcher Award of HKU

Professor JRW Masters  
Professor of Experimental Pathology  
Director, Prostate Cancer Research Center  
Royal Free and University College Medical School, UK

Dr DF Newgreen  
Group Leader  
Embryology Unit  
The Murdoch Children’s Research Institute, Australia

Professor NE Reiner  
Professor of Medicine, Microbiology and Immunology  
Head, Division of Infectious Diseases  
University of British Columbia, Canada

Dr BCY Wong  
Associate Professor, Department of Medicine  
The University of Hong Kong  
Recipient of the 2001-2002 Outstanding Young Researcher Award of HKU
Keynote Lectures
Keynote Lecture I
Quantitative Proteome Analysis: New Technology and Applications

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Professor RH Aebersold obtained his PhD degree at the University of Basel, Switzerland, in 1983. He joined the Department of Molecular Biotechnology of the University of Washington in 1993 after working as a professor at the University of British Columbia in Vancouver and completing a fellowship at the California Institute of Technology. As the co-founder of the Institute for Systems Biology at Seattle, USA, he is internationally recognized for his work in analytical protein biochemistry and proteomics, and leads a research crew that is focused on developing new methods and technologies for understanding the structure, function and control of complex biological systems. He also leads the development of high-throughput facilities that enable the Institute for Systems Biology to take on very large projects, including research to identify proteins that are selectively expressed in cancer cells and understand how white blood cells trigger immune responses.

A number of powerful technologies now permit the determination of complete genome sequences as well as the systematic and quantitative measurement of gene expression at the mRNA and protein levels. It is the premise of “functional genomics” technologies that they will significantly contribute to the mechanistic understanding of biological processes, either by themselves, if applied in a discovery mode, or in combination with traditional hypothesis-driven research approaches. Proteomics is a preferred functional genomics technology because its focus is proteins: the most significant class of molecules affecting biological structure, function, and control.

In this presentation, we will discuss a new approach to quantitative proteome analysis and show results from selected applications of the technology to microbial and mammalian cell systems. The technology is based on a new class of chemical reagents termed isotope coded affinity tags (ICAT) (Gygi SP, Rist B, Gerber SA, Turecek F, Gelb MH, Aebersold R, Nature Biotechnol 1999; 17:994-9). The reagents and the tandem mass spectrometry-based analytical process allow the precise quantitation and identification of large numbers of proteins in complex mixtures rapidly and sensitively. The need to separate and analyze extremely complex peptide mixtures challenges the separation sciences. Optimized peptide separation protocols connected on-line with mass spectrometers will be discussed. The applications will document the performance of the method to examine changes in protein profile in yeast cells induced by metabolic shifts, to measure quantitative differences in the cell surface protein profile in mammalian cells, and to detect and quantify changes in protein phosphorylation profiles in cell lysates.
Keynote Lecture II
Pharmacologic Chemoprevention of Colorectal Cancer

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Professor Robert S Bresalier, MD, received his GI Fellowship training at the University of California, San Francisco where he was a faculty member for many years. He is currently Professor of Medicine and Chairman of the Department of Gastrointestinal Medicine and Nutrition at MD Anderson Cancer Center, Texas, USA. Professor Bresalier has been a leading investigator in the area of gastrointestinal tumor biology, and specifically the role of glycoproteins and carbohydrate-binding proteins in tumor progression and metastasis. He leads active NIH-funded research programs in cancer screening, early detection, and prevention. He is member of the National Steering Committee and Chair of the Colorectal Cancer Subcommittee of the Prostate, Lung, Colon, and Ovarian Cancer Screening Project. He is Associate Editor for the journal Cancer, member of the Editorial Boards of many international journals, and author and editor of over 200 articles, chapters, and reviews in Gastrointestinal Oncology.

Colorectal cancer is a major cause of cancer-associated mortality worldwide. Globally it is the fourth most common cancer in males and third most common in females with mortality paralleling incidence. Chemoprevention involves the use of natural or synthetic agents to reverse, suppress, or prevent the occurrence of cancer. The most studied pharmacologic agents for chemoprevention of colorectal cancer are nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical case-control and cohort studies have shown a 40%-50% reduction in colorectal cancer-related mortality in individuals taking aspirin and other NSAIDS on a regular basis compared with those not taking these agents. Animal and laboratory studies indicate that this effect is biologically plausible. The precise mechanism for cancer protection is unknown but appears to relate to altered synthesis of arachidonic acid metabolites that include prostaglandins, thromboxanes, leukotrienes, and hydroxyecosatetraenoic acids. These compounds modulate signal transduction pathways that affect cellular adhesion, growth, and differentiation. Cyclooxygenase (COX) or prostaglandin endoperoxide synthase) oxidizes arachidonic acid to prostaglandin G₂, reduces prostaglandin G₂ to prostaglandin H₂, and is the key enzyme responsible for production of prostaglandins and other eicosanoids. The COX-2 isomer is induced by cytokines, mitogens, and growth factors and its levels are elevated in 85% to 95% of colorectal cancers and in experimental colorectal tumors. COX-2 inhibition leads to prevention of cancer development during both the initiation and promotion/progression stages of carcinogenesis. Knockout of COX-2 through genetic manipulation or through the use of specific inhibitors reduces tumor formation in animal models. A potential mechanism includes inhibition of gene activation by the nuclear hormone receptor peroxisome-proliferator-activated receptor (PPAR-α). PPAR-α activates genes involved in cellular growth, differentiation and apoptosis after exposure to a variety of ligands including eicosanoids. COX-2 inhibition also leads to alterations in cellular adhesion to extracellular matrix proteins, inhibition of angiogenesis, reduction in carcinogen activation, and increases in programmed cell death (apoptosis). Preclinical studies of COX-2 inhibitors in animal models of familial adenomatous polyposis (FAP) such as the Apc<sup>−/−</sup> mouse demonstrate significant dose-dependent reductions in polyp number and size, alterations in polyph morphology and accompanying reductions in proliferation, membrane-bound vascular endothelial growth factor (VEGF) and angiogenesis at blood levels achieved in humans with a clinical anti-inflammatory drug dose (rofecoxib).
Human clinical trials in patients with FAP have shown significant reductions in adenoma number in patients treated with the NSAID sulindac and the COX-2 inhibitor celecoxib, leading to approval of the latter by the U.S. Food and Drug Administration as an adjunct to usual care in this group. Prospective clinical trials of NSAIDS and specific COX-2 inhibitors for prevention of adenoma recurrence in patients with sporadic adenomas are in progress. Data from a large randomized prospective trial using aspirin in this group will soon be reported, and demonstrate a significant chemopreventive effect of low-dose aspirin on adenomas in the large bowel. There is growing evidence that NSAIDS including COX-2 inhibitors may be effective chemopreventive agents for adenomas and cancer occurrence in the colon, either alone or in combination with other agents. Assessment of their full potential awaits additional trials designed to further elucidate their mechanisms of action and to confirm their efficacy in both average and high-risk groups.
Keynote Lecture III
Oocyte and Ovarian Tissue Cryopreservation

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Professor Roger Gordon Gosden is the Howard and Georganna Jones Professor of Reproductive Medicine and Scientific Director of the Jones Institute for Reproductive Medicine, Eastern Virginia Medical School. Professor Gosden completed his PhD at the University of Cambridge in 1974 and was awarded DSc by the University of Edinburgh in 1989. He has won a number of prizes and published a lot of chapters and research papers in renowned journals such as Nature, Nature Genetics and Lancet. Professor Gosden is the world expert in ovarian tissue cryopreservation and oocyte cryopreservation, a very difficult but a very important area for fertility conservation.

Cryopreservation of ovarian tissue and oocytes is a promising technology which is still under development. Several dozen children have been born after IVF of freeze-thawed oocytes, and ovarian tissue banking has produced so far only short-term hormonal benefit after autotransplantation for a few patients. Optimizing these technologies will require understanding the principles of low temperature biology and knowledge of biophysical variables, including membrane permeability to water and cryoprotective agents. Most progress to date has been the result of adapting protocols through empirical studies and extrapolation from animal models. On top of the problems of freezing and thawing is the sensitivity of oocytes to chilling before reaching freezing point. These effects may be less serious with ovarian tissue, which presents other problems for cryopreservation - notably, cellular heterogeneity compromising the development of an optimal protocol throughout the tissue. It is hoped that vitrification can overcome problems with equilibrium cooling methods, though it requires potentially toxic concentrations of solutes. Ice fish proteins, choline substitution and cytoskeletal inhibitors have been claimed to be beneficial but, as elsewhere in the field, limited availability of fresh human oocytes and ovarian tissue has delayed research progress.
Keynote Lecture IV
Chemoprevention of Gastric Cancer

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Dr BCY Wong, Associate Professor in the Department of Medicine, is the recipient of the 2001-2002 Outstanding Young Researcher Award of The University of Hong Kong.

Gastric cancer is the second commonest cancer in the world. There is a strong association between *Helicobacter pylori* (*Hp*) and gastric cancer. A recent prospective study from Japan showed that gastric cancer developed in around 3% of *Hp* carriers over a mean follow-up of 7.8 years, including those with a normal endoscopy/histology at the beginning. Those with precancerous histology were at a significantly higher risk. Several studies were designed to address if eradication of *Hp* could reverse pre-malignant lesions (intestinal metaplasia and dysplasia) or prevent gastric cancer. Our prospective randomized placebo controlled study in Fujian, China showed that after a follow-up of 7.5 years, the overall gastric cancer incidence in the *Hp* eradication and placebo groups were similar. In the subgroup of patients with no precancerous lesions (intestinal metaplasia or dysplasia) on entry in 1994, there is a significant prevention in development of gastric cancer (P<0.014). We conclude that *H. pylori* eradication prevents the development of gastric cancer only in subjects without pre-existing precancerous lesions. For subjects with intestinal metaplasia and dysplasia, most previous intervention studies using various agents achieved only 10-30% chance of regression.

Epidemiological studies have shown that chronic aspirin or non-steroidal anti-inflammatory drug (NSAID) users have 30-50% reduction in incidence of gastric and colon cancer. NSAID inhibited the enzymes cyclooxygenase-1 and -2 (COX). Overexpression of COX-2 was demonstrated in a high percentage of both gastric and colon cancer. Our laboratory showed several COX-dependent and -independent mechanisms for anti-tumour property of COX-2 inhibitors. Translating these information to bedside, we have recently started another chemoprevention study aiming at evaluating the role of *H. pylori* eradication and use of specific cyclooxygenase-2 inhibitor in inducing regression of precancerous lesions and preventing gastric cancer. Screening endoscopic study was completed in April 2002 for 2700 subjects in Shandong, PR China. Subjects with precancerous lesions (intestinal metaplasia, dysplasia) and positive for *H. pylori* infection will be randomized to receive *H. pylori* eradication, specific cyclooxygenase-2 inhibitor (3 years), combination or placebo. Endoscopic follow up of precancerous lesions and overall cancer incidence will be evaluated in future.
Keynote Lecture V
Human Prostate Epithelial Stem Cells
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Professor John Masters received his PhD in Cancer Research from The University of London, United Kingdom, in 1974. He joined the Institute of Urology and Nephrology, University College London in 1976 as a Lecturer and was promoted to Reader in 1994. In 1999, he was made a Professor of Experimental Pathology in the University College London, UK. Professor Masters has published over 100 peer-reviewed articles in a variety of medical journals in the fields of human pathology, molecular cancer biology and molecular mechanisms responsible for chemodrug sensitivity in human cancer. Recently, he established the Prostate Cancer Research Centre in the UK and has been focusing on prostate cancer research and prostatic stem cell study.

Stem cell theory suggests that in every tissue there is a small self-renewing population of cells that survives throughout life and gives rise to all the other cells within that tissue. Normal prostate epithelial stem cells are the most likely progenitor for prostate cancer cells, and growth dysregulation of prostate stem cells may result in benign prostatic hyperplasia. Our aim was to isolate and characterise prostatic epithelial stem cells.

Samples of benign prostatic hyperplasia were digested overnight with collagenase, the prostatic acini separated by differential centrifugation and a single cell suspension obtained by trypsinisation. The freshly isolated epithelial cells were cloned in vitro on 3T3 feeder layers in serum-free PrEGM medium (Gibco) at low density (10^3-10^4 cells per 5 cm dish).

Two types of colony developed over a 14 day culture period, termed type I and type II. Type I colonies were small, irregular and contained a loose mixture of differentiated and undifferentiated cells. In contrast, type II colonies were large, round and homogeneous, consisting almost exclusively of small undifferentiated and dividing cells. The colony forming efficiency was 5.8% ± 1.8% for freshly isolated epithelial cells. There were approximately 10 times as many type I as type II colonies and, overall, approximately 1 in 200 of the plated cells was capable of forming a type II colony.

We used differential adhesion to try to isolate the putative stem cells. Freshly isolated epithelial cells were plated on collagen-coated dishes. After 5 minutes the unattached cells were transferred to a separate dish. Within 5 minutes, 50% of the cell capable of forming colonies had attached to the collagen-coated dish, but there was no enrichment for type II colonies.

In order to study the proliferative heterogeneity of the cells, the number of cells in each colony containing at least 32 cells (equivalent to 5 population doublings) was counted in 3 separate experiments (approximately 50 colonies per experiment). The type I colonies underwent a maximum of 13 population doublings, and there was little overlap with the type II colonies, which underwent between 12 and 15 population doublings in the 14 day culture period.

In order to study the potential of the type II colonies to differentiate into the other cell types within the prostate epithelium, individual colonies were grown in three dimensional culture on Matrigel. The type II colonies produced structures reminiscent of prostate epithelium, with luminal cells expressing markers of prostate epithelial differentiation. In the subrenal capsule assay, the morphology of the xenografts containing type II colonies was similar to that of benign prostatic hyperplasia.

On the basis of their proliferative characteristics and capacity for differentiation, the type II colonies may be the progeny of stem cells and the type I colonies of a more differentiated transit amplifying population.
Keynote Lecture VI
Variation in Gene Expression Patterns in Gastric Cancer and
Discovery of Prognostic Biomarkers

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Dr SY Leung, Associate Professor in the Department of Pathology, is the recipient of the 2000-2001 Outstanding Young Researcher Award of The University of Hong Kong.

Gastric cancer is the 2nd most common cancer worldwide. Most patients with gastric cancer present at advanced stages with poor survival. There is an urgent need for new markers effective in early detection, treatment and prognostication. Using cDNA microarrays representing about 30,300 genes, we have profiled the gene expression of 90 gastric adenocarcinomas, 14 paired lymph node metastasis and 22 non-neoplastic gastric mucosa. We found diversity of gene expression reflecting intrinsic properties of tumour and normal cells, tumour-stroma interaction and host immune response. The gene expression patterns can clearly distinguish tumour from non-tumour gastric tissue. Thousands of genes were found differentially expressed in gastric cancer compared to non-neoplastic gastric mucosa. Of genes expressed in a high level in gastric cancer, many represent primary events such as chromosomal amplification or altered signal transduction pathways. Detailed analysis revealed specific markers that correlate with patient survival. The association can be confirmed in an independent set of patient samples using quantitative RT-PCR. In conclusion, gene expression profiling with linked molecular, pathological and clinical data is a powerful approach to identify genes involved in different pathways of gastric carcinogenesis and elucidate prognostic biomarkers.
Keynote Lecture VII
From Neural Crest to Enteric Nervous System: A Paradigm for the Co-dependence of Basic and Clinical Research

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Dr DF Newgreen’s current research interest is in the identification of genes involved in the development of the neural crest cells, a population of stem cells which have significant impact on morphogenesis. Defects in neural crest development cause the most common malformations at birth. Dr Newgreen has instrumentally developed a cell culture system for morphogenetic studies. He has made significant contributions in our current understanding of the migration and cellular interactions of the neural crest, and in craniofacial birth defect. He has been the Group Leader of the Embryology Unit, Murdoch Children’s Research Institute, Melbourne, since 1991.

One of the keys to current progress in understanding of the development of the Enteric Nervous System (ENS) has been the description of a principal abnormality of ENS development: Hirschsprung’s Disease (HSCR) in humans, and more recently similar abnormalities in animals. A key feature of HSCR is a relatively constricted terminal bowel segment, usually the distal colon, immediately oral to which the intestine is grossly distended. Although recognised and named in the 19th century as a cause of congenital intractable constipation, it was presumed that the distended segment was abnormal. It was only well into the 20th century that the true site and nature of abnormality was realised: the defect lay in the terminal segment. This region was defective in peristalsis due to the regional absence of an ENS, whereas the distended segment was relatively normal in ENS presence and function. This correct interpretation led to rapid advances in surgical treatment and understanding of the causes.

Many genes are now known which, when mutated or deleted, may cause defects of ENS development. Many of these genetic abnormalities in animal models give a phenotype similar or identical to HSCR, and these genes were discovered by studies of both humans and of mouse mutants with similar defects. The most important of these genes are those coding for molecules in the Glial cell line Derived Neurotrophic Factor (GDNF) intercellular signalling system, and those coding for molecules in the Endothelin-3 (ET-3) signalling system. In particular these are the genes for GDNF itself, its receptor Ret and co-receptor GFRα1, and the genes for ET-3 itself, its receptor Endothelin receptor B (ETB) and the activating protease Endothelin Converting Enzyme (ECE).

However, a range of other genes for different signalling systems and for transcription factors, when they are deleted or mutated in humans or animals, also disturb ENS formation. These include the Smad Interacting Protein 1 (SIP1), Indian Hedgehog (Ihh), Sonic Hedgehog (Shh), Sox10, Pax3, Pax2b and Hox11.1 genes, the latter giving a phenotype in mice resembling not HSCR but rather a more contentious form of constipation in humans called Intestinal Neuronal Dysplasia type B. In addition Mash-1, when deleted in mice, gives an intestinal dysplasia regionally inverse to that of HSCR, in that the ENS in the foregut is missing but that of the more distal gut is present.

The roles of these genes in ENS disease are in many cases subtle, marked by incomplete penetrance and large variations in severity even for identical mutations. Many of these genes seem to cross regulate, although the precise connections are not fully described. Moreover, a large proportion of HSCR cases have not been ascribed to the currently known genes, suggesting that additional genes for ENS development await discovery.
Enumeration of the genes which when mutated give rise to ENS disorders is not sufficient to give an understanding of how these abnormalities arise. The indirect link between genotype and phenotype lies in the early embryonic development of the ENS. The ENS precursor cells originate mostly from cells in the roof of the hindbrain neural tube, these are the so-called vagal neural crest cells. In early embryogenesis, these cells migrate to the nearby foregut and then become distributed progressively oro-anally along the midgut and hindgut until the entire gastrointestinal tract is colonized. A much smaller population of ENS precursor cells also originates in the lumbar-sacral neural crest, and these cells migrate ano-orally into the hindgut and distal midgut.

Experimental evidence on the controls of ENS formation is derived from classic embryological, cell culture and molecular genetic approaches. The first and perhaps most crucial of these experiments was reported in the 1950’s, whereby ablation of the entire vagal neural crest in chick embryos led to complete absence of the ENS, whereas partial ablation produced a terminal lack of ENS only in the distal regions, similar to HSCR. This pointed to a key role of neural crest cell numbers in driving the colonization of the gut by ENS precursors. A brief sketch will be presented of current notions on the developmental processes between the genes and the morphogenesis of the ENS, and of how the known genetic abnormalities might result in the ENS phenotype observed in HSCR.
Keynote Lecture VIII
Intracellular Pathogens as Trojan Horses: Lessons Learned from Leishmania

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Professor Neil F Reiner is Professor of Medicine and Head of the Division of Infectious Diseases at the University of British Columbia. His research has focused on host defense and macrophage cell biology with particular relevance to intracellular pathogens such as Leishmania donovani, and more recently, Mycobacterium tuberculosis. He has investigated mononuclear phagocyte activation and cell-signalling pathways and the strategies deployed by intracellular parasites such as Leishmania for immune evasion. For example, his research group found that Leishmania inhibits the interferon gamma mediated activation of both JAK and JAK2 tyrosine kinases and STAT1.

The human leishmaniases are persistent infections of macrophages caused by protozoa of the genus Leishmania. The chronic nature of these infections is in part related to induction of macrophage deactivation, linked to activation of the Src homology 2 domain containing tyrosine phosphatase-1 (SHP-1) in infected cells (Infect. Immun., 1999, 67:4055-4063.) To investigate the mechanism of SHP-1 activation, lysates of Leishmania donovani promastigotes were subjected to SHP-1 affinity chromatography and proteins bound to the matrix were sequenced by mass spectrometry. This resulted in the identification of leishmania elongation factor-1α (EF-1α) as a SHP-1-binding protein. Purified leishmania EF-1α, but not host cell EF-1α, bound directly to SHP-1 in vitro leading to activation of the phosphatase. Leishmania EF-1α was detected in promastigote culture filtrates by Western blotting (not accounted for by parasitic lysis) and, cytosolic fractions prepared from macrophages infected with 35S-labeled promastigotes also contained leishmania EF-1α (in the absence of phagolysosome disruption). Furthermore, confocal, immunofluorescence microscopy using species-specific antibodies detected leishmania EF-1α in the cytosol of infected macrophages. These findings suggested that leishmania EF-1α is exported from the phagosome thereby enabling targeting of host proteins. Indeed, co-immunoprecipitation showed that leishmania EF-1α associated with SHP-1 in vivo in infected cells. Finally, introduction of purified leishmania EF-1α, but not the corresponding host protein into macrophages activated SHP-1 and blocked the induction of inducible nitric oxide synthase expression in response to interferon-γ. Thus, leishmania EF-1α is identified as a novel SHP-1-binding and activating protein that recapitulates the deactivated phenotype of infected macrophages. These findings suggest a new paradigm in which an intracellular pathogen exports virulence factors from the phagosome. Targeting of host regulatory proteins disrupts intracellular signaling and brings about cell deactivation.
Keynote Lecture IX
Understanding Brain Death: From Intensive Care Unit to Laboratory

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Professor Samuel HH Chan is no stranger to this Faculty, especially to the preclinical Departments. He was a lecturer in the Department of Physiology from 1973 to 1976. He is now the Vice-President (Academic Affairs), Professor of Biological Science, and Director of the Center for Neuroscience of the National Sun Yat-sen University in Kaohsiung, Taiwan. He has been a national chair professor since 1997, a title shared by only a few basic scientists in Taiwan. He has won many awards and honours including the appointment as Secretary General of the Southeast Asia-Pacific Regional Federation of Pharmacologists in Sydney, Australia. He has been invited to deliver plenary lectures at many international conferences and symposia and has proved himself to be an excellent speaker with insight and great humour.

Life and death is a phenomenon that has intrigued people of all walks of life since time immemorial. With the current legal definition that links death to brain stem death, one fundamental issue that requires attention is to define the cellular and molecular mechanisms that underlie alterations in the activity of brain stem neurons during the transition from life to death.

Clinical studies from our laboratory revealed in patients who succumbed to systemic inflammatory response syndrome, severe brain damage or organophosphate poisoning that death is invariably preceded by a dramatic reduction or loss of the low frequency components (0.004 to 0.15 Hz) in the spectrum of systemic arterial pressure (SAP) signals. This commonality among deceased patients affords a potentially new clinical marker for “life and death”, and provides the foundation for mechanistic evaluations.

We traced the origin of the low frequency components of the SAP spectrum in animal studies to the premotor sympathetic neurons at the rostral ventrolateral medulla (RVLM), which are responsible for the maintenance of stable SAP. In a rat model of endotoxemia, we determined that the progressive prevalence in molecular synthesis and functional expression of the inducible nitric oxide synthase and the resultant overproduction of nitric oxide in the RVLM is a crucial determinant for the loss of sympathetic vasomotor tone and eventual death. Instead of cGMP, the formation of peroxynitrite via interaction between nitric oxide and superoxide anions is primarily responsible for eliciting fatality. Parallel studies indicated that dysfunctions of mitochondrial respiratory chain in RVLM neurons take place during the transition from life to death, and that coenzyme Q10, confers protection against mortality during endotoxemia.

Based on a proteome map that we recently established for the rat RVLM, we are currently in the process of identifying additional pro-life and pro-death protein entities that may be up- or down-regulated during the progression towards death.
Keynote Lecture X
Global Health Impact of Outdoor Particulate Air Pollution

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On behalf of the Outdoor Air Pollution Working Group of the WHO Global Burden of Disease Comparative Risk Assessment Project

Working Group Members: H Ross Anderson (Chair), Aaron Cohen (Co-Chair), Kersten Gutsche, Michal Krzyzanowski, Nino Kunzli, Bart Ostro, Kiran Pandey, Arden Pope, Isabelle Romieu, Jonathan Samet, Kirk Smith

Professor Ross Anderson is professor of epidemiology and public health and chairman of the Department of Public Health Sciences at St George’s Hospital Medical School. He is co-founder of the steering group of the International Study of Asthma and Allergies in Childhood (ISAAC) and a member of the Review Committee of the Health Effects Institute in the USA. He was recently a member of the US Academy of Sciences Committee on Air Pollution. He is currently chair of the World Health Organization Expert Group examining the outdoor air pollution’s contribution to the Global Burden of Disease. He has been collaborating with the Department of Community Medicine, The University of Hong Kong on air pollution research for more than 5 years.

The serious consequences of exposure to high levels of ambient air pollution were made clear in the mid-20th century when cities in Europe and the United States experienced air pollution episodes, such as the infamous 1952 London fog, that resulted in a sharp increase in mortality and other acute health problems. Subsequent clean air legislation and other actions reduced ambient air pollution in many countries. However, recent epidemiological studies, using sensitive designs and analyses, have identified important health effects of combustion-derived air pollution even at the low ambient concentrations typical of Western European and North American cities (1-6). At the same time, the populations of the rapidly expanding megacities of Asia, Africa and Latin America are increasingly exposed to levels of ambient air pollution that rival and often exceed those experienced in developed countries in the first half of the 20th century (7).

Urban air pollution is largely and increasingly the result of the combustion of fossil fuels for transport, power generation and other human activities. All combustion processes produce particles that are small enough to be inhaled into the lung, either as primary emissions, such as from diesel engines, or via subsequent atmospheric transformation, such as when sulphur dioxide, produced by the oxidation of sulphur in fuel combines with ammonia to form sulphate particles.

Air pollution from combustion sources is associated with a broad spectrum of acute and chronic health effects (3,4), the nature of which may vary with the pollutant constituents. Particulate air pollution is nevertheless consistently and independently related to the most serious effects, including lung cancer and other cardio-pulmonary mortality (1,5,6). This paper describes a project which aimed to estimate attributable deaths and estimated life-years lost due to particulate outdoor air pollution in all major cities of the world.

The availability of measurements of ambient concentrations of particulate matter (PM) varies widely across the globe, making a comprehensive estimation of annual average concentrations in all cities a considerable challenge. We collected as much available PM measurement data as possible, but in order to provide estimates all 14 WHO regions, we relied on models developed by the World Bank to estimate PM10
(particulate matter with aerodynamic diameter <10 micrometres) using econometric data and the available PM10 measurements (available for several hundred cities) for 3226 cities with populations greater than 100,000 plus capital cities. These PM10 estimates were converted to PM2.5 (fine particles that tend to penetrate more deeply into the lung) using available information on geographic variation in the ratio of PM2.5 to PM10. Data on the percentage of urban dwellers was used to derive population-weighted annual averages for each PM metric.

We calculated four estimates of impact: mortality from cardio-pulmonary causes in adults, mortality from lung cancer, mortality from all-natural causes in adults and in children 0-5, mortality from acute respiratory infections in children 0-5. Risk coefficients from a large US cohort study of adults (1) were used to calculate attributable numbers of deaths and years-of-life lost for adults and children (<5 yr.). Impact estimates were calculated over a range of annual average concentrations of PM2.5 between 7.5 and 50 micrograms per cubic metre. The uncertainty of the estimates was quantified by propagating the errors in the estimates of annual average concentration and the relative risks. Additional uncertainty due to assumptions about the shape of the concentration-response function and the ratio of PM2.5 to PM10 was assessed in sensitivity analyses. An additional estimate of attributable deaths was calculated from time-series studies of daily mortality, based on results of a meta-analysis of the world literature.

The preliminary and provisional analyses on which this presentation was based estimate that, globally, ambient air pollution causes about 1% of cardiorespiratory disease and 3% of lung cancer globally. This amounts to about 0.6 million (1.2%) premature deaths and 7.4 million (0.5%) years of life lost. This burden predominantly falls on cities in developing countries.

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Keynote Lecture XI

Theoretical and Methodological Opportunities for Gero-Oncology Research in Aging Societies

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Dr Sarah H Kagan holds the Doris R Schwartz Term Chair in Gerontological Nursing with her primary academic appointment as Assistant Professor—Clinician Educator with two clinical appointments. Dr Kagan’s primary clinical appointment is as a Gerontology Clinical Nurse Specialist in Medical Nursing at the Hospital of the University of Pennsylvania. Dr Kagan’s secondary faculty appointment is in the Department of Otolaryngology: Head and Neck Surgery, where she consults on clinical research and the management of patients who have head and neck cancers and are suffering complex wounds and other symptoms. Dr Kagan teaches students in the undergraduate nursing program where she directs the required course “Nursing Care of the Older Adult”. She also lectures in the Gerontology and Oncology Master’s degree programs and precepts graduate students and Geriatric Medicine fellows in acute care gerontology and symptom management. Dr Kagan’s program of clinical research is centered on symptom management in older adults with an emphasis on symptom management with older adults who have cancer.

Purpose: This paper analyzes theoretical and methodological opportunities to address the challenge of designing and implementing gero-oncology research in aging societies.

Background: Attention to cancer and aging as a distinct field has grown steadily since the 1980’s. Current calls for research lack specificity in theoretical and methodological direction and fail to support research with cultural and social relevance that create impact across aging societies.

Analysis and Conclusions: Gero-oncology has only recently become a priority within nursing and biomedicine. Sparadic papers in the last 20 years created attention for age-related research but did little to refine inquiry. Current calls for research, centered through a strong voice from biomedicine, draw attention to complex problems of co-morbidity, treatment tolerance, and survival analysis. Nursing, with less articulated voice, lags behind in arguing for a focus on the responses of older cancer patients.

Implications: The name gero-oncology affords the distinction of using gerontology—with emphasis on age, health, and function—to lead research development. Borrowing theory used in gerontology accentuates human development: physical, cognitive, and emotional function; and decision making. While existing research uses quality of life (QOL) as both theory and method, approaches to QOL that reflect the unique nature of older’s lives in culturally disparate communities and aging societies must be delineated. Several disease and treatment specific models (e.g prostate cancer, radiation therapy) are used but do not consider larger epidemiological, genetic, and cultural concerns imbedded within them. For example, prostate cancer is a limited global model given the low incidence of that disease in Asia. New models must feature integration of age-related disease (i.e. non-melanoma skin cancer), demography, and epidemiology with attention to genetics and culture, with function status, QOL, and resource use. Measures of survival, tolerance, and treatment effects are complex and must be dissected quantitatively and qualitatively. Survival methods and accommodation for attrition are useful in redefining population outcomes research for this group in which survival may not stand alone. Redefining tolerance to include function and co-morbidity are important to advancing measurement. Highlighting symptoms of co-morbid disease and the experience of chronicity may be better addressed through qualitative work. Finally, the full scope of gero-oncology seems best explored through collaborative interdisciplinary work that pioneers new directions in theory and methods leading to developments on this frontier.

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Emerging Antibiotic Resistance Mechanisms in Gram Negative Bacteria

Peter M Hawkey
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Professor Peter M Hawkey is Professor of Clinical and Public Health Bacteriology at the University of Birmingham, United Kingdom. His research has been on the epidemiology and molecular biology of antibiotic resistance factors of Gram-negative bacteria. He is one of the leaders of the University of Birmingham Antimicrobial Research Group where his work is particularly focused on the molecular evolution of extended-spectrum beta-lactamases and carbapenemases. While at the University of Leeds, he was involved in launching a multidisciplinary research centre involving 43 academic members of staff with interests in antimicrobial research.

The treatment of infections caused by Enterobacteriaceae was revolutionised in the early 1960s with the introduction of semi-synthetic penicillins notably ampicillin. Within a very short time of the introduction of these agents resistance by virtue of the production of TEM type beta-lactamases became rapidly established and disseminated and in some parts of the world resistance rates due to this mechanism in E. coli can exceed 60%. The success of this beta-lactamase in conferring resistance to ampicillin is no doubt in large part due to the fact that the genes encoding this beta-lactamase are present on a transposon which is frequently found on conjugative plasmids which carry resistance determinants to other antibiotics thus resulting in the maintenance of high levels of carriage of blaTEM due to co-selection. A major advance in this area was made by the introduction in the 1980s of third generation cephalosporins which had good stability to degradation by TEM beta-lactamases. However, the selection of variants of the blaTEM and also blashV genes carrying just one or two altered amino acids conferred resistance to third generation cephalosporins. Counter-intuitively this process emerged and although initially isolates of so called extended-spectrum beta-lactamases were rare, it is now apparent that some 20 years after the first introduction of third generation cephalosporins, this has become a major mechanism of resistance, particularly in the Far East, Europe and South America. A very large number of mutations have now been identified and many of these have been mapped to changes enzyme structure, often involving enlargement of the omega loop allowing better access of the substrate to the active site of the enzyme. Because the parental genes are located on a transposon/plasmids rapid horizontal transfer of these genes has occurred together with subsequent micro-evolution of sequences, often in response to the selective pressure of particular geographical locations. More recently we have seen the emergence and dissemination of other serine based beta-lactamases, notably those of the CTX-M class, which have now become the dominant enzymes in China and South America with their apparent importation into North America and the U.K. this year. There is a continued transfer of beta-lactamase genes from commensal and environmental bacteria such as Pseudomonas aeruginosa with, in some parts of the world, an increasing prevalence of enzymes such as the PER series in Pseudomonas aeruginosa and Acinetobacter. The chromosomal broad-spectrum AmpC beta-lactamases of Citrobacter, Enterobacter and Pseudomonas which were formerly thought to be not genetically mobile have also become mobilised onto conjugative plasmids and now over 30 different examples of these enzyme variants which, by a study of their DNA homology can be traced back to chromosomal ancestors have been identified in many parts of the world. When derepressed these enzymes confer broad-spectrum resistance to most cephalosporins including second generation compounds and when present with an ESBL in the bacterium, effectively confer resistance to all beta-lactams with the exception of carbapenems. It is a continuing evolutionary story that in hospital services and locations in the world, intensive use of carbapenems has in turn generated
potentially even more severe problems of resistance. In 1993 in Japan a plasmid mediated zinc dependent β-lactamase which was capable of degrading all carbapenems and most other β-lactam antibiotics was described. This gene has been designated blα35 and a number of variants have now been described in Japan and the gene has spread widely amongst a variety of strains of Enterobacteriaceae, Pseudomonas and Acinetobacter, probably by virtue of its plasmid location and association with Class-I integrons. In turn, there have been a number of reports of the appearance and spread of metallo-β-lactamase genes, predominantly in Pseudomonas and Acinetobacter, notably a large cluster of blα35, carrying Acinetobacter in Hong Kong over a period of some four years. There are now at least 12 variants of blα35 and three variants of blα35 described in a number of different geographical locations. It is clear that in the future we are going to see a wide range of β-lactamases often from comparatively unfamiliar bacterial species moving by horizontal gene transfer into clinically significant bacteria. Depending upon the selective pressure and virulence of those clinically significant bacteria, an unpredictable and potentially untreatable assortment of β-lactamase genes are likely to be encountered in nosocomial Gram negative bacteria in the 21st century.
Keynote Lecture XIII
Cardiac NKX2-5 Homeobox Gene Pathways in Development, Evolution and Disease

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Professor Richard Harvey heads the Developmental Biology Unit at the Victor Chang Cardiac Research Institute, where he is the Sir Peter Finley Professor of Heart Research. His interest in the mechanisms and function of the mammalian heart led him to isolate and study novel mouse genes essential in the heart formation, making significant contributions in the filed. Using tissue-specific gene manipulation in mice and microarrays, he is developing technology to facilitate the dissection of genetic pathways in the developing and adult heart.

Professor Harvey serves on many national and international advisory boards and committees. He is editorial board member of several leading journals, including Molecular Cell. In 2001 he was awarded the Hazel Croke Research Award and the Calross Prize for Scientific Research.

The conserved cardiac homeobox gene Nkx2-5 sits high in a developmental hierarchy governing lineage allocation and morphogenesis in the vertebrate heart. In humans, mutations in NKX2.5 occur in patients with congenital heart disease. Our recent studies relate to the role of Nkx2.5 and other cardiac transcription factors in heart chamber specification. Anatomical, electrophysiological and gene expression data suggest that chamber muscle is formed at the outer curvature of the looping heart as a specialisation of the more primitive and ancient muscle type of the primary heart tube. The integration of anterior/posterior and dorsal/ventral patterning information is required for chamber specification, and in homozygous Nkx2-5 mutant mice, chamber differentiation is blocked at an early stage. The neuregulin1/ErbB2/4 signalling system has previously been shown to be necessary for formation of trabeculae, the spongiform layer of myocytes that forms at the outer curvature of the ventricles. We now have evidence that this signalling pathway is critical for specification and proliferation of chamber myocardium acting, at least in part, through Nkx2-5. Our studies reveal an absolute requirement for the neuregulin system for maintenance of the cardiomyogenic program and thresholds for expression of distinct cardiac genes in different heart chambers.
1. Scientific Meeting of the Public Health Group and Medical Education Unit
Impact of Sulphur on Respiratory Health: Air Pollution in Hong Kong
1989-2000

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Sulphur is one of the most abundant elements in the universe. On earth it is projected into the air we breathe from volcanic eruptions and emissions from burning of fossil fuels. Very high levels of sulphur compounds, mainly sulphur dioxide (SO₂), are discharged in the air from various sources of power generation.

Most epidemiological research has focussed on episodic or short term effects of changes in exposures to air pollution. Prospective cohort studies now indicate that the impact of pollution on health may be greater than previously considered, especially for cardiopulmonary mortality. There is a need for new research particularly on the effects of interventions which lead to marked reductions in pollutants.

On July 1st 1990 the Hong Kong Government Environmental Protection Department (EPD) restricted the sulphur content of fuel to 0.5% by weight. In cohort studies between 1989 and 1992 we demonstrated that the reduction in sulphur pollutants, following the EPD intervention, led to a significant reduction in bronchitic symptoms in both primary school children and their mothers, and in bronchial hyper-responsiveness in the children.

A new study, published in the Lancet in November 2002, has examined the impact of the July 1990 fuel restriction on mortality in the Hong Kong population. The analyses demonstrate that the reductions in SO₂ were associated with an immediate reduction in deaths including a short term decline in cool season deaths and longer term reduction in the annual trend in deaths overall.

In the first cool season period following the intervention, cardiopulmonary and all-causes mortality were lower than expected. Cool season deaths in years 2 and 3 were increased and then returned to the expected seasonal pattern. This pattern suggests that pollution episodes advance the deaths of many who would otherwise have survived for much longer periods. Over the five year period post-intervention the annual proportional increase in deaths in Hong Kong declined by 2.2% overall and by 2.8% for respiratory deaths in the elderly. The decline in mortality risk over the five years of the study equates to 3000 deaths avoided, or 50,000 person years of life saved.

As the intervention did not lead to changes in the other criteria pollutants, fine particles (PM₁₀), NO₂ or O₃, the health benefits can be directly attributed to control of sulphur in fuel. Reductions in other air pollutants are likely to yield similar benefits to those observed with the decline in SO₂. Although the concentrations of SO₂ have been much reduced, we have shown that current levels of SO₂ in ambient air in Hong Kong are still strongly associated with risks of both hospital admissions and deaths.

The results of these research enquiries have clear implications for environmental policy making in Hong Kong and provide a strong evidence-base for air quality controls and other environmental legislation in the HKSAR.

References


Will Mammography Screening do more harm than good in Hong Kong Chinese?

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Although mammographic screening for women over 50 years has become routine practice in many Western countries, there are no data about its efficacy in Chinese women for the early diagnosis of cancer. Despite this lack of evidence, there have been widespread and unqualified recommendations for whole population screening, and aggressive promotion of mammographic examination in Chinese women. The present situation is the result of the misapplication of scientific logic where proponents for population screening argue that breast cancer has a rising incidence and has recently become the commonest female malignancy, and a test (i.e. mammography) to detect cancer is available, therefore all women should be screened to reduce the burden of morbidity and increase survival.

First, we reviewed the local epidemiology and secular trends of breast cancer. Changes in cancer rates may lead to hypotheses regarding disease aetiology and also predictions of future trends for China. We examined statistics from the Hong Kong Cancer Registry based on 26,566 cases of invasive breast cancer from 1973 to 1999. The trends in breast cancer incidence were studied using log-linear longitudinal models. We further analysed the independent effects of chronological age, time period and birth cohort on incidence trends using age-period-cohort modelling. The average annual percent change of the age-standardised incidence was 3.6% during 1973-1999. Age-period-cohort modelling indicated the incidence development was predominantly a cohort effect, where the rise in relative risk was seemingly linear in successive birth cohorts, showing a two- to three-fold difference when comparing women born in the 1960's with those born around 1900. Our results suggest that direct and indirect consequences of westernisation may have been responsible for most of the observed increase in breast cancer incidence. As China moves towards a more westernised way of life, we can expect an emerging epidemic of breast cancer as Hong Kong’s experience has demonstrated.

Next, we examined overseas evidence of population-based screening for early breast cancer detection through an updated systematic review and meta-analysis of clinical trials evaluating mammography screening. We then applied these results to women in Hong Kong, where 95% of the resident population are ethnic Chinese. The pooled relative risk for breast cancer-related death in the screened group was 0.80 (95% confidence interval = 0.71, 0.90). When applied to Hong Kong this translates into a number needed to screen of 1,302 healthy women screened annually for 10 years to prevent one death. The positive predictive value of mammography was between 1.8% and 13.4%. Therefore, for 100,000 Hong Kong Chinese women aged 50 or over screened annually for 10 years we would expect 8,980 false positive cases, 134 of them would sustain a biopsy-related complication. Only 77 breast cancer-related deaths would be avoided, assuming trial conditions and 100% uptake and follow-up.

We conclude that there is currently insufficient evidence to justify population-based breast cancer screening by mammography for women in Hong Kong and other Asian populations with low breast cancer prevalence. Our discussion has only dealt with mass, population-based mammographic screening of well women. For those at high risk for the disease, careful individual clinical assessment should guide the need for and frequency of mammographic screening. We suggest resources that may be allocated for a comprehensive population screening program in Asian populations would be better directed at raising public awareness of the issues exposed here, along with case-finding in targeted high-risk groups where mammography may be a truly beneficial, and necessary, intervention.
Breast Cancer Surgery for Hong Kong Women - Taking a Gamble?

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Objectives: To (1) describe breast cancer (BC) treatment decision making (TDM) from Chinese women’s perspective, (2) report how often women’s actual roles in TDM matched their preferred roles, and (3) explore the effect of participation congruence (PC) on subsequent satisfaction with TDM.

Methods: Phase I consisted of a qualitative study of 22 women recently completed breast surgery who completed an in-depth interview designed to study Objective 1. Phase II consisted of a quantitative interview-based study designed to study Objectives 2 and 3 with assessment within twelve days after surgery. 134 (89.5%) women who had recently undergone BC surgery at one of six Hong Kong government hospitals provided information on preferred and perceived TDM participation, satisfaction with TDM consultation and difficulties in TDM.

Results: Grounded theory analysis in Phase I showed that discovery of breast abnormality and emotional responses to BC diagnosis influence the TDM process. The experience of TDM, which was likened to gambling, did not end once the decision was made, but unfolded while waiting for surgery and the post-operative report.

Most (80%) of women in Phase II had participated as much as, 13% more than and 6% less than desired. Women reported PC had fewer difficulties in TDM (F = 5.51, p=.005) than women not reporting PC, while over-involved had more doubts about their choice (F = 5.07, p=.004). PC was associated with being offered a treatment option ($\chi^2 = 15.59, p<.001$) and surgeons expressing a surgical preference ($\chi^2 = 6.63, p=.036$). Satisfaction was unrelated to PC.

Conclusion: These findings provide important new information on Chinese women facing BCTDM which can help to optimize clinical care for these women.
This paper is an attempt to apply some degree of clairvoyance on what will medicine and the practice of medicine be like in the next fifty years.

The structure, organization, and texture of healthcare are undergoing a pace of change that is both relentless and revolutionary. This discussion will be divided into three parts: (1) trends in the development of science, technology, politics, and society; (2) the impact of these changes on the clinical practitioner, the medical researcher, the medical administrator, the academician, and the medical profession as a corporate identity; (3) what are the skills, knowledge and attitude that ought to be nurtured to enable doctors to meet tomorrow’s challenges.
Quality Assurance in Teaching and Learning

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Quality assurance (QA) ensures effective running of the medical curriculum in a course that is abreast of current developments in the field. Quality objectives for skills, knowledge and attitudes are explicitly set out and are consonant with the mission of the Faculty and the goals of the curriculum. Under the Faculty's Undergraduate Education Committee (UEC), the QA Sub-Committee is established to coordinate and manage the programmes related to the evaluation and monitoring of the curriculum. Results from the evaluations are reported back to the respective staff member/Department and the UEC, which reviews the contents and structure of the curriculum, modes of teaching and programme operation. The Medical Education Unit also oversees the evaluation results and offers advice/assistance to the relevant colleagues if deemed necessary. All these are conducive to the refinement of the curriculum map according to the changing needs of teaching and learning, research development, and societal demand.

To achieve a thorough, objective and all-round perspective, our curriculum is evaluated in an ongoing fashion and in a long-term context. In the ongoing scheme, we use surveys, electronic voting system, staff-student consultative meetings, learning logbooks and focus group interview to assess every component of the curriculum. On the teaching side, various measures are undertaken to secure different dimensions of teaching effectiveness within our curriculum. Teachers are also evaluated on the basis of a peer review system. We identify and reward our staff in the promotion of good teaching pedagogy. Constant review and improvement of different evaluation processes are adopted. Our experience gained during the implementation of these schemes will be discussed. Certain facets of the evaluation have been transformed into research projects, e.g. students' views on a transitional course in a revised medical curriculum, student feedback improves the quality of paper cases used for problem based learning, clinical skill training, etc.

In the long-term scheme, educational value of our medical curriculum is evaluated. Projects have been launched to compare students in the old and those in the new medical curriculum in terms of their learning behaviors/attitudes, clinical skills, clinical interpersonal skills, and core competencies. Frameworks have also been laid down to monitor progression through the curriculum as well as to evaluate beyond graduation when views of the end-users and practicing colleagues will be solicited. Through various undertakings of research projects on teaching and learning, the Faculty is striving for a long-term strategic direction and hence higher level of excellence in education.
Quality Assurance in Assessments, or Assessing Assessments

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The 10th Ottawa Conference on Medical Education was held in July this year in Ottawa Canada. Over 600 participants from around the world attended to share views on assessment in medical education. There have been 4 major forces leading to significant changes in assessment and these are an assessment of high-stakes program accountability, an emphasis on the investigation of the consequences of assessment, emergence of computer adaptive testing and a pressure for assessments that are performed in context. At the Ottawa meeting a review of submitted abstracts showed approximately 10% of submitted papers dealt with the reliability, validity and reproducibility of assessment methods used in medical curricula.

The process of test construction appears, on the surface relatively straightforward - the domain of knowledge and understanding is specified, the mental tasks or process the student must use in dealing with the subject matter are identified, the test questions that unambiguously assess the students ability to deal with the knowledge domain are written, the test is administered, the item response is analyzed and the raw scores are converted to some meaningful metric (http://www.uts.psru.edu/Test_construction_frame.htm).

In practice each of the above steps is prone to errors to the effect that the usefulness of the academic measurement of the test is inversely proportional to the amount of error it contains. Classical test theory (CTT) is a relatively simple model that is applicable for the fixed length tests we perform in this faculty, CTT allows computation of the measurement error, reliability and validity. Whilst these factors deal with a given test at a given time, further questions arise over item analysis - that is, how good is a test question or item in measuring a learning outcome. Focus should be spent on determining the item difficulty (the probability of a correct response to a question) item discrimination (the strength of relation between a test item and the underlying attitude being measured) and the item-to-item correlation.

In more recent years item response theory (IRT) or latent trait theory has become more popular and the focus of academic research as it provides a more intuitive approach to measurement. In IRT the true score is defined as the latent trait of interest rather than the test. In academic terms we refer to this as ability. Whilst this is easily described, it cannot be measured as easily as something such as height or weight. One of the features of IRT is the relationship between the latent trait and the observed response in the form of a line called the item characteristic curve (ICC). The ICC can be defined mathematically and allows analysis of test bias and tailored testing.

Whilst we have tended to use checklists as assessment tools for our OSCE there is a growing trend towards the use of rubrics for assessment of performance. Two common types of rubrics that are used for performance testing are holistic and analytic rubrics. The former requires the teacher to score the overall process as a whole without judging the component parts separately. In an analytic rubric the teacher scores separate individual parts of the product or performance first then sums the individual scores to obtain a total score. The focus of score reported using a holistic rubric is on the overall quality but gives limited feedback to the student.

Our revised medical curriculum has been in operation for over 5 years. With increasing research into the quality of assessment it is an opportune time to re-examine the methods of assessment we use and determine changes that need to be made to ensure quality, validity and reliability.
Integration of PBL and PBT (Problem Based Teaching) in Clinical Years

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In 1997, the Faculty of Medicine, The University of Hong Kong, introduced PBL as an important element of its curriculum reform to foster the student-centred education, and to cultivate a culture of lifelong learning. PBL tutorials are now well established features of the first three years of MBBS curriculum at the Faculty. Introduction of PBL in clinical years, particularly in the ward setting, has been, however, a challenging proposition since, historically, traditional bedside teaching has provided a powerful and effective tool for Problem Based Teaching (PBT). The integration of PBL and PBT-(PBLT) has provided us with an opportunity to achieve the best of the both of worlds during the clinical clerkships. Authors will highlight the experience of the Faculty and the process of 'PBL in the Wards' at the presentation.
2. Scientific Meeting of the Department of Nursing Studies
The Knowledge, Attitudes, and Practice of Nurses in Smoking Cessation

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Tobacco smoking is the single most preventable cause of premature death, and much is known about the devastating health effects of tobacco. Tobacco control is vital and beneficial to preventing illness and saving health care costs. Nurses have a vital role in tobacco control by providing smoking cessation interventions to patients aiming to promote health and prevent illness. Nurses represent the largest proportion of the health care workforce in the health care system and have the most frequent contact with patients. Therefore, they are in a unique position and should act as leaders to assess, plan, implement, and evaluate smoking cessation interventions to promote, protect, and maintain the health of patients. The aim of this study was to investigate the knowledge, attitudes, and practice (KAP) of nurses in smoking cessation in Hong Kong. The study was a cross-sectional survey using a self-administered questionnaire. All registered nurses working in the clinical areas of the selected hospitals were invited to participate in the study. A total of 1843 nurses completed the questionnaire with a response rate of about 51%. About 91.3% are non-smokers and 3.5% are smokers. Almost all (97%) have not had training in smoking cessation counselling. Preliminary findings showed that most nurses had a general understanding of tobacco and its bad effects on health. However, nearly half are not clear about the extent of health risks associated with smoking, and its comparison to other health hazards such as air pollution. The nurses’ attitudes were quite positive and majority considered they should educate patients to quit smoking. Barriers to nurses’ smoking cessation work included lack of time, heavy workload, unmotivated patients and lack of knowledge. This study has provided some evidence for the development of professional nursing practice in smoking cessation. Nurses should be prepared in both the undergraduate and postgraduate nursing curriculum and be equipped with the appropriate knowledge and skills so that they are competent to provide tobacco control interventions. Furthermore, Adequate resources and support from management would facilitate the delivery of smoking cessation interventions in the clinical setting.
Detecting Depression by Doctors working in Geriatric Wards

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Objectives: To analyze current practice in detecting geriatric depression.

Design: Semi-structured questions in face-to-face interviews.

Setting: Geriatric wards of public hospitals.

Participants: 16 doctors with more than one year working experience in geriatric wards.

Main outcome measures: Doctors' knowledge, skill and attitude towards depressed elderly patients; factors influencing early detection.

Results: Themes were derived using ethnographic approach. Informants all felt moderate to strong level of need over early detection of depression in their setting as well as in the community. Under detection did exist and might be explained by resource and people factors. Doctors' inherent skills in assessing depressed elderly patients and perceived availability of strategies to diagnose depression varied and could be affected by experience, previous interaction with elderly people, level of suspicion and keenness for early detection. Maintaining high level of suspicion and satisfactory doctor-patient relationship showed to be very important promoting factor for improving detection rate of depression. Also, patients' ability and willingness to verbalize depressive symptoms posed another determinant for early detection. Interesting to find, many doctors were quite hesitant to adopt the golden standard, the Diagnostic and Statistical Manual (DSM) IV criteria to diagnose depression and were quite reserved to explicit the diagnosis of depression to patients directly.

Conclusion: Though doctors in geriatric wards generally agreed that depression was prevalent and important health issue, consistent methodology in early detection was still not in place. Evidence on reasons for under detection should be further researched to make early rectification.
Couples Walking through Depression after Delivery

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This is a phenomenology study to describe the essential structure of lived experiences of the couples during the period of postpartum depression. Correlation between postpartum depression and inadequate spousal support was widely supported by the literature. While the literature documented the importance of spousal support, there is little information to guide the spouses to provide effective support. In order to develop effective intervention to advise the depressed women and their spouse to cope with the disorder there is a pressing need to understand the interaction between the depressed women and their partners when they were living with postpartum depression. The study results would particularly be useful to local health care providers to culturally appropriate interventions in addressing the needs of Hong Kong Chinese couples who are affected by postpartum depression.

With phenomenological approach, semi-structured interviews are conducted on a purposive sample of postnatally depressed women and their partners individually. The length and sample size for data collection is determined by saturation of the data. Subjects are recruited from Psychiatric Department of the Queen Mary Hospital and Department of Obstetrics and Gynaecology at the Queen Mary Hospital and Tsan Yuk Hospital. Selection criteria are couples with the wives diagnosed by psychiatrists as suffering from or have had postpartum depression in the past five years, Hong Kong Chinese, married, at the age of 18 or above. Verbatim transcription is performed to transcribe the interview data word by word in Chinese. Data is analysed with a computerized software, NUDIST Vivo using Colaizzi’s (1978) method to develop themes. All transcriptions are read through to get overall feel and then to extract significant statements and phrases. Then the statements are formulated into themes and further aggregated into clusters. Preliminary results with themes emerged from the interview data as well as implication to health care providers will be discussed.
Management of Central Venous Catheters and Related Issues

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Introduction: Central Venous Catheter is a device that has been used to administer parenteral nutrition, chemotherapy, antibiotics, and blood products. However, few researches on central venous catheter have been conducted in Hong Kong. Moreover, there is no publication in Hong Kong to discuss about the types of central venous catheters, the complications caused by using the central venous catheter and the management of these complications. The aim of this paper is to discuss about the current care and management of the complications caused by using central venous catheter in Hong Kong.

Objectives: 1) to investigate the types of central venous catheter used; 2) to identify the complications of using central venous catheter; 3) to examine the management of the complications caused by using central venous catheter in Hong Kong; 4) to compare the care and complication management between Hong Kong and Hawaii; 5) to construct recommendations on what should be done in research about central venous catheters in Hong Kong.

Sample: A sample of ten nursing specialists from private and public hospitals was interviewed in this study by means of snowball sampling technique.

Methods: This study was cross-sectional in design. Two approaches were used to collect data. One of the approaches was literature review. Academic Search Premier, CINAHL, MEDLINE and Internet were used to search for literature. Another approach was individual interviews. By purposive sampling, nursing specialist of haematology was selected to participate in this study. Then, nine more nursing specialists of haematology and bone marrow units were interviewed in terms of snowball sampling. They were interviewed either by face-to-face or telephone interviews.

Results: From the literature, infection (local or systemic), occlusion of catheter, air embolism, migration of the catheter (misplacement or dislodgement) and catheter rupture are the complications caused by the usage of central venous catheters. Less common complications in using central venous line have also been identified in published articles. From the result of the interviews, infection and occlusion of catheter are the main complications in using central venous catheters in Hong Kong and the management of these complications has been implemented according to the hospitals’ protocols.

Conclusions: Issues related to central venous catheters usage and its management in Hong Kong are identified. However, no research has been conducted to verify the effectiveness of central venous lines management in Hong Kong, more evidence-based practice need to be implemented in the future.
Fatigue-relieving Strategies for Patients after Bone Marrow Transplantation

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Introduction: Fatigue is one of the common symptoms for cancer patients receiving active cancer treatments. Several literatures have explored the fatigue-relieving methods, which used by the patients. There is limited knowledge about fatigue in the Chinese population after receiving bone marrow transplantation (BMT) and the effectiveness of fatigue-relieving strategies. It is believed that effective fatigue-relieving strategies can help cancer patients in reducing the level of fatigue and improve their quality of life after BMT. Through exploration of the self-initiated fatigue-relieving strategies, it helps the health care professionals to develop effective fatigue-relieving strategies for relieving patients’ symptom. The aims of this study are to examine fatigue in patients after BMT and to explore patients’ preference for self-initiated fatigue-relieving strategies.

Sample: A convenience sample of 220 cancer patients after receiving the course of BMT in a regional teaching hospital were selected to participate in this study.

Methods: It is a descriptive and cross-sectional study. A validated questionnaire including demographics, the Revised Piper Fatigue Scale, and Fatigue Relief Scale. Also, open questions were used to explore other self-initiated fatigue-relieving strategies and their effectiveness on the patients. Data on other factors thought to affect outcome variables were collected from medical record.

Results: Overall, the subjects experienced a moderate level of fatigue (mean=4.7, SD=1.7). Popular relieve-fatigue strategies used by the subjects are rest and reduced activities. Although massage was not commonly used, it was found to be one of the effective fatigue-relieving strategies. Other self-initiated fatigue-relieving strategies were also suggested by the subjects.

Conclusions: A majority of subjects perceived a moderate level of fatigue after BMT. A variety of self-initiated fatigue-relieving strategies was identified and discussed. It is important for nurses and health care professionals to identify the level of fatigue experienced by patients and their needs for symptom relief so that effective fatigue-relieving strategies can be implemented.
The Prevalence of Domestic Violence among Pregnant Chinese Women

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Objective: To assess the prevalence of intimate partner violence in pregnant women attending the antenatal clinic of a local teaching hospital.

Design: This study derived its findings from a subset of data in a randomized controlled trial project.

Method: All pregnant women attending their first antenatal clinic at Tsan Yuk Hospital between 26 May and 31 October 2002 and who agreed to participate in this research study were assessed for intimate partner violence using the Abuse Assessment Screen (AAS). The Conflict Tactics Scale (CTS) was used to assess the nature and frequency of violence. Demographic factors were collected using a questionnaire.

Results: 941 pregnant women were interviewed, 69 (7.3\%) were abused. Of the abused women, 69 (86.9\%) had been abused in the last year; 41 (59.4\%) had been abused during their current pregnancy. For 46 (66.6\%) of the abused women, verbal aggression was the sole form of abuse. The remaining 25 women (33.3\%) had both verbal and physical abuse. Sexual abuse was reported by 5 women (21.7\%) and co-existed with either verbal or physical abuse. Husband was the perpetrator in 54.9\% of the cases. Interestingly, mother-in-law was named as the sole abuser in 21.6\% of the cases and the abuse was entirely verbal. Also, once the woman became pregnant, the abuse from the mother-in-law was reported to be reduced, and only 12.2\% of the women reported their mother-in-law as the sole abuser. In 10\% of the abused women, both the husband and mother-in-law were named as the abusers. A significantly lower rate of minor physical violence was observed in women whose husbands were professional and clerical workers compared with those with manual worker husbands (\( p < 0.05 \)). A higher though not significant rate of serious physical violence was observed in women whose husbands were manual workers. There was a significantly higher rate of sexual abuse in women whose pregnancy was not planned (\( p < 0.05 \)).

Conclusion: The prevalence of intimate partner violence in this study was lower than that of previous local studies involving pregnant women. Further study should be conducted to investigate the possible reasons for the reported decline in such violence. Mother-in-law as an abuser should be further investigated to provide a better understanding of the effects of family dynamic in domestic violence.
The Association of Critical Thinking Disposition and Problem Solving: A Phenomenographic Approach

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**Objective:** To explore the possible association of critical thinking disposition and problem solving ability in nursing students.

**Design:** Phenomenographic approach.

**Method:** Ten first year university nursing students were interviewed before and after a nursing course during which five of the students were randomly assigned to receive problem-based learning (PBL) and five to conventional lecture method. The students’ critical thinking disposition was assessed using the California Critical Thinking Disposition Inventory (CCTDI). During the pre-intervention and post-intervention interviews, each student was presented with a problem situation and his/her responses were sought.

**Results:** Adopting a phenomenographic approach, the analysis showed that students with a comparatively strong disposition to critical thinking and who were in the PBL group demonstrated obvious to marked improvement in their problem-solving ability. Interestingly, students with a comparatively strong disposition to critical thinking and who were in the lecture group demonstrated some to no improvement in their problem-solving ability. Students with a comparatively weaker disposition to critical thinking demonstrated no to some improvement in their problem solving ability irrespective of whether they were in the PBL or lecture group.

**Conclusion:** Using a phenomenographic approach in analyzing data, it is possible to gain a more in-depth insight into the association between critical thinking disposition and problem solving. Studies should be conducted to further explore the complex picture of students’ critical thinking and problem solving.
3. Scientific Meeting of the Centre of Infection and Immunology Group
An Emerging Diarrheal Pathogen

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Despite extensive clinical and laboratory work-up, a microbiological cause can only be identified in at most about 50% of patients with diarrhea. In 2001, we reported the isolation of a novel bacterium, Lariobacter hongkongensis, HKU1, from a patient with alcoholic cirrhosis and bacteremic empyema. In this study, we describe the isolation of L. hongkongensis in pure culture on charcoal cefoperazone deoxycholate agar from the stool of 6 patients with diarrhea. Three patients were residents of Hong Kong, and 3 of Switzerland. Four and 2 patients were males and females respectively. The median age was 32 (range: 1-63). All patients had community-acquired diarrhea. In none of the stool samples obtained from these 6 patients was Salmonella, Shigella, enterohemorrhagic Escherichia coli, Vibrio, Aeromonas, Plesiomonas, or Campylobacter recovered. Rotavirus antigen detection, electron microscopic examination for viruses, and microscopic examinations for ova and cysts were all negative for the stool samples obtained from the 3 patients in Hong Kong. Unlike L. hongkongensis type strain HKU1, all the 6 strains were motile with bipolar flagellae. All 6 strains were sensitive to amoxicillin/clavulanate, imipenem, and gentamicin, whereas 5 were resistant to ampicillin, cefalothin, and ceftriaxone, and 1 was resistant to levofloxacin and cotrimoxazole. Sequencing of the 16S ribosomal RNA genes of the 6 strains showed that they all had sequences with only 0-2 base differences to that of the type strain. Pulsed field gel electrophoresis of the SpeI digested genomic DNA of the 6 isolates and that of the type strain revealed that the 7 isolates were genotypically unrelated strains. Curved Gram-negative bacilli isolated from charcoal cefoperazone deoxycholate agar and grow in aerobic environment without CO₂ should not be discarded as non-pathogens. Further studies should be performed to ascertain the epidemiology, pathophysiology, optimal treatment, and outcome of L. hongkongensis as a cause of infectious diarrhea or bacteraemia.
The Role of Helicobacter pylori in Bronchiectasis

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Bronchiectasis is very common respiratory disease in Hong Kong and affected patients suffer from distressing regular sputum production, recurrent infective exacerbations and gradual destruction of the airways. There are distinct inflammatory and infective components in the pathogenesis of bronchiectasis. Pro-inflammatory mediators, such as interleukin (IL)-1, IL-8, and tumor necrosis factor (TNF) α are upregulated in the bronchiectatic airways and mediate intense neutrophil infiltration into the tracheobronchial tree, sometimes independent of infection. We have recently reported a high sero-prevalence of H. pylori specific IgG among patients with bronchiectasis (76%) compared with healthy subjects (54.3%; odds ratio 2.8). In addition, H. pylori IgG level correlated with disease activity, namely sputum production, in bronchiectasis. We have further reported that, anti-H. pylori CagA, whose expression indicates virulence of H. pylori, is also raised among patients with bronchiectasis. Although H. pylori cannot be cultured directly from sputum, our aforementioned findings strongly suggest a role for H. pylori in the pathogenesis of bronchiectasis. The high sero-prevalence of H. pylori in the general population strongly suggests that H. pylori is unlikely to be the primary cause of bronchiectasis, but it is highly possible that H. pylori infection somehow contribute to disease activity in bronchiectasis.

Continuous beating of cell surface minute cilia occurs in respiratory mucosa, which keeps the respiratory tract sterile. Many bacteria such as H. influenzae and P. aeruginosa are able to chronically infect the bronchiectatic airways by producing exotoxins which slow down ciliary beating and cause cellular damage. We have, therefore, recently studied the effects of H. pylori culture filtrate on the function and structure of human respiratory mucosa. We mixed bacteria-free culture filtrate, obtained from a strain of H. pylori, with human respiratory epithelial cell suspension obtained from brushing the inferior turbinate of healthy volunteers. Preliminary results show that H. pylori culture filtrate causes slowing of ciliary beating, which is essential to maintain the sterility of the respiratory tract. This slowing of ciliary beat would therefore disrupt mucociliary clearance, which is a vitally important aspect of the host defence mechanism in the respiratory tract. H. pylori culture filtrate also causes disorientation of the central microtubules of cilia, which is quantifiable by state-of-the-art TEM techniques, when examined at high power transmission electron microscopy (TEM), which renders the beating of neighboring cilia uncoordinated and disrupts the efficiency of the mucociliary clearance mechanism. Thirdly, we have found that H. pylori culture filtrate causes severe ultrastructural damage on respiratory epithelial cells in the form of nuclear shrinkage with associated chromatin condensation, formation of vacuoles, mitochondrial damage and sloughing of epithelial cells. Our unpublished results, therefore, suggest that H. pylori is capable of disrupting mucociliary clearance and damaging the integrity of the respiratory epithelium. These in vitro results strongly point to a direct pathological role for H. pylori in bronchiectasis.
Human metapneumovirus (HMPV) is a new member of the *paramyxoviridae* family first identified in the Netherlands in 2001. This virus was found in individuals with respiratory symptoms that ranged from mild symptoms to severe cough and pneumonia. Serologic and clinical data showed that most people are infected by 5 years of age and that repeated reinfection probably happens later in life. Since the initial report, HMPV has been isolated in Australia, Canada, the UK, and Finland. To test the hypothesis that HMPV also causes significant respiratory disease in children in Hong Kong, we conducted a prospective study of children ≤ 18 years of age admitted with acute respiratory tract infection from July 2001 to August 2002. Out of the 587 children studied, 32 (5.5%) children had nasopharyngeal aspirate specimens tested positive for HMPV by RT-PCR. The associated clinical diagnoses were pneumonia (36%), asthma exacerbation (23%), febrile seizures (16.1%), rash (12.9%) or acute bronchiolitis (10%). When compared to respiratory syncytial virus (RSV) infection, wheezing in HMPV-infected children was more likely to represent asthma exacerbation rather than acute bronchiolitis. Children with HMPV infection were also older than those infected with RSV. HMPV viral activity peaked during the spring-summer period in Hong Kong, markedly different from the winter-spring circulation reported in temperate areas. HMPV appeared to be an important respiratory pathogen in children causing a wider spectrum of disease than previously appreciated.
The Origin and Evolution of H5N1 Influenza Viruses from Poultry in Southern China

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The H5N1 influenza viruses with the internal gene constellation of HK/156/97-like virus that infected both chickens and humans have not been isolated since the poultry slaughter in late 1997. However, the donor of its hemagglutinin, the Goose/Guangdong/1/96-like (Gs/Gd/96, H5N1) influenza virus, has established a distinct lineage and continued to circulate in geese. In mid-2000, this virus transmitted to domestic ducks. Subsequently, it has undergone reassortment with those viruses resident in ducks and generated at least 5 different genotypes of novel H5N1 influenza viruses. These new reassortants have gradually replaced Gs/Gd/96-like virus from its reservoir in geese and ducks and have transmitted to terrestrial poultry, including chicken, in May 2001. Phylogenetic analysis of H5N1 and other subtypes of influenza viruses recently isolated from duck, goose, chicken and quail during surveillance in live-poultry markets in southern China suggests that these novel H5N1 influenza viruses are undergoing further reassortment and that interspecies transmission continues to occur between aquatic and terrestrial poultry. These novel reassortants and interspecies transmission events may give rise to new outbreaks in terrestrial poultry, such as that in 2002. These findings highlight the fact that H5N1 influenza viruses continue to provide cause for pandemic concern.
Melioidosis is an important health problem in areas where the disease is endemic. In Hong Kong, the disease was first noticed when an outbreak occurred in 1976 among dolphins just before the opening of the Ocean Park. The first human melioidosis in Hong Kong was identified in 1981. Since then, sporadic cases in terms of several cases per year were reported. Historically, the disease was treated with a combination of cotrimoxazole, doxycycline and chloramphenicol. In 1983, researchers in this University were the first to report successful treatment of melioidosis with ceftazidime. A few years later, ceftazidime was shown to halve the mortality of melioidosis and since then this drug has become the treatment of choice for the disease. Despite these advances in the antimicrobial therapy of melioidosis, mortality for the septicemic form of the disease remains high at 30 to 40%. Breakthrough bacteremia with isolation of ceftazidime-sensitive isolates are known to occur during the first few days of treatment. Resistance to ceftazidime has also been reported during clinical treatment. To try to understand these observations, we cloned and expressed the BPS β-lactamase gene of B. pseudomallei. BPS-1 is a cephalosporinase with an isoelectric point of 7.7. Sequence analysis of the gene revealed conserved motifs typical of class A β-lactamases. Upon analysis of the wild type genes in 71 clinical and environmental isolates, three variants (BPS-1b, 1c and 1d) can be distinguished. Sequence alignment reveals that the amino acid of BPS-1 bears high similarity to members of the extended-spectrum β-lactamase CTX-M family. Like CTX-M enzymes, BPS-1 hydrolyzes cefotaxime efficiently. For certain extended-spectrum β-lactamases, there is a recommendation that bacteria producing these enzymes should be regarded as clinically resistant to the cephalosporins, regardless of the in vitro susceptibility. The concern arise from the observation that many strains producing ESBLs demonstrate an inoculum effect in that the MICs of expanded-spectrum cephalosporins rise as the inoculum increases from 10^3 to 10^5. With BPS-1 in Escherichia coli, we have also found an inoculum effect for ceftazidime in that MIC of ceftazidime rise dramatically at high bacterial inoculum 10^5-10^6. These bacterial densities are reached clinically in the serious forms of melioidosis.

References


Immunopathogenesis of Human H5N1 Infection

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The “bird flu” incident in Hong Kong in 1997 was the first documented instance of respiratory disease and death caused by a purely avian influenza virus (H5N1/97). It was considered to be an incipient pandemic situation. Human disease was unusually severe and associated with an overall case fatality rate of 33%. Underlying disease conditions did not explain the severity of H5N1/97 disease. While the genetic origin and continued evolution of H5N1/97-like viruses have now been elucidated, the biological basis for the severity of disease associated with it remains an enigma. We hypothesized that virus-induced cytokine dysregulation played a role in pathogenesis. Using cDNA arrays, we compared the cytokine gene expression profile of H5N1/97 virus infected primary human macrophages in vitro with that induced by conventional human H1N1 or H3N2 viruses. Quantitative RT-PCR was used to confirm the differentially up-regulated genes. Secretion of one of these cytokines, TNF-α, in virus infected macrophages was studied using ELISA assays. H5N1/97 infected macrophages had dramatically higher levels of pro-inflammatory cytokine gene transcription. For example, the levels of TNF-α mRNA and protein secretion induced by H5N1/97 was more akin to that induced by *E.coli* endotoxin. Using reverse genetics, we demonstrated that the H5N1/97 NS gene contributes to this phenomenon. Others have recently reported that H5N1/97 virus is differentially resistant to the antiviral effects of cytokines such as TNF-α and interferon. However, the hyper-induction of cytokines we demonstrate is not a consequence of the resistance to the antiviral effects of cytokines. The ability of H5N1/97 viruses to hyper-induce cytokines on the one hand, while being resistant to their antiviral effects on the other, may contribute to immunopathogenesis and explain the severity of H5N1/97 disease in humans.
The Role of Regulatory T Cells in Small Bowel Transplantation

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Background: Long term survival is difficult to achieve in small bowel allograft (SBT) compared to other types of vascularized allograft probably due to the heavy load gut associated lymphoid tissues transplanted with the SBT. Surprisingly, using a defined FK506 pre-treatment regimen, we have achieved the indefinite survival for orthotopic small bowel allografts but not for heterotopic cardiac transplant (CT), in high responder strain combination (DA to LEW). The primary aim of this study was to determine if regulatory T cells are induced in rats with long term survival of SB allografts thereby providing information on the underlying mechanisms.

Methods: LEW recipients receiving orthotopic small bowel allograft and heterotopic cardiac transplant from DA rats were treated with FK506 pre-treatment regimen [at 2 mg/kg/d i.m., 3 days before transplantation and 0.3 mg/kg/d, post-transplantation (0-14day)]. Mixed lymphocyte responses (MLR) were performed using splenocytes from orthotopic SBT as responder and inactivated DA or third party (PVG) splenocytes as stimulator. T cells of spleen, peripheral blood cell (PBC) and recipient mesenteric lymph node (LN) were collected from LEW rats with long term SBT, cardiac transplant recipients at the time of sacrifice and age-matched normal LEW rats. The expression of CD4, CD25, and CD45RC was analysed by flow cytometry.

Results: SBT in FK506 treated rats survived indefinitely, however they rejected cardiac graft around 45 days. In MLR, the proliferation to DA splenocytes was suppressed, while the proliferation to third party splenocytes was maintained. Rats with long term SBT, when gated on the CD45RC^hi^ population, showed a reduction in total percentage of CD4+ T cells in spleen, PBC and LN. The percentage of CD4+CD25+ over CD4+ T cells was increased about 50% in spleen and LN but not in PBC. These phenotype changes were not observed in the CT and age-matched normal LEW rat.

Conclusion: Donor specific tolerance may have developed in the rats receiving orthotopic SBT indicated by the suppressed MLR against donor antigens. The indefinite survival of orthotopic SBT was associated with the induction of T regulatory cells in the recipients.
B Cell Selection during Development and its Implication in Autoimmunity

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Apoptosis and its regulation are critical in the development, function and homeostasis of the immune system. Dysregulated apoptosis has been implicated in various disorders including autoimmunity. To maintain immune homeostasis and self-tolerance the tumor necrosis factor (TNF) superfamily plays a crucial role in the regulation of immune responses by modulating lymphocyte proliferation and apoptosis. Two newly identified members of the TNF ligand family, BLyS (B lymphocyte stimulator) and APRIL (a proliferation-inducing ligand) bind to peripheral B cells via three surface receptors (BCMA, TACI and BR3) and exhibit a strong enhancement of B cell survival both in vitro and in vivo. However, it remains unknown whether or in what ways BLyS and APRIL can regulate B cell differentiation and survival during the early stages of B cell development.

In our recent studies, we have examined the expression of BLyS and APRIL in developing B cells from normal mouse bone marrow by RT-PCR. Both BLyS and APRIL mRNA expression were detected in B220-IgM precursor B cells and IgM+ immature B cells. Moreover, developing B cells differentially expressed three receptors, BCMA, TACI and BR3. Precursor B cells expressed high levels of BCMA mRNA whereas TACI expression was upregulated in immature B cells. These data indicate that BLyS and APRIL may influence developing B cells at different stages. To determine if BLyS and/or APRIL can regulate B cell development, our flow cytometric analysis revealed that recombinant BLyS and APRIL suppress B cell apoptosis in short-term cultures of bone marrow cells. This effect was blocked when soluble receptor BCMA-Fc was added in the culture medium. These findings suggest that TNF family cytokines can regulate B cell maturation and survival in the bone marrow. Further studies aim to study whether dysregulated TNF cytokines are implicated in the development of mouse collagen-induced arthritis, a well-established model for human rheumatoid arthritis.
4. Scientific Meeting of the Centre of Human Reproduction and Centre of Human Development and Birth Defects
Clinical Assessment of Ovarian Reserve in ART

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Recruitment and development of multiple follicles in response to gonadotrophin stimulation are the key factors leading to successful treatment by assisted reproductive technologies (ART). Prediction of ovarian responses in ART is useful in counseling patients and helpful in tailoring the dosage of gonadotrophin to individual patients. Different clinical, hormonal and ultrasound parameters are used to improve the prediction. FSH level seems to be a better predictor of ovarian responsiveness to stimulation than the age of women. However, basal FSH levels may vary from cycle to cycle. Recently, ultrasound assessment of the ovarian volume, the number of antral follicles and ovarian stromal blood flow has been used in the prediction of the ovarian responses.

Syrop et al. (1995) found that the total ovarian volume and the volume of the smallest ovary were significant variables predicting peak oestradiol levels and number of oocytes and embryos. Total ovarian volume was a predictor of cycle cancellation while the volume of the smallest ovary was a predictor of clinical pregnancy. The mean ovarian volume prior to the stimulation was shown to be predictive of poor ovarian response (Lass et al., 1997). Ovarian volume is also found to be a better measure of ovarian reserve than basal FSH concentration (Syrop et al., 1999).

By counting the number of antral follicles, the resulting ovarian response could also be predicted (Tomás et al., 1997; Chang et al., 1998). A total of 128 consecutive women, who had no history of ovarian surgery, were non-smokers and undergoing the first cycle using a standard regimen of ovarian stimulation were examined in a prospective study (Ng et al., 2000). The objective of this study was to compare age of women, body mass index, basal FSH level, volume of both ovaries and the number of antral follicles of both ovaries in predicting the number of oocytes obtained. The total number of antral follicles was significantly correlated with age of women, basal FSH level, total ovarian volume, HMG duration and dosage, serum E2 on the day of HCG and the number of oocytes obtained whereas the total ovarian volume was significantly correlated with the total number of antral follicles only. The total number of antral follicles achieved the best predictive value, followed by basal FSH, body mass index and age of women.

Ovarian stromal blood flow assessed by colour Doppler ultrasound may be another new way to predict ovarian responses. The mean peak systolic flow velocity prior to pituitary down-regulation was significantly correlated with the ovarian response, after controlling for patients' age (Zaidi et al., 1996). Those with normal ovarian responses had significantly higher velocity than poor responders (10.2 ± 5.8 cm/sec Vs 5.2 ± 4.2 cm/sec). Similarly, ovarian stromal blood flow velocity after pituitary down-regulation is also predictive of the ovarian responses and the IVF outcome (Engmann et al., 1999). More recently, three-dimensional ultrasound and power Doppler have been used to determine ovarian stromal blood flow, which is also useful in the prediction of ovarian response (Kupesic & Kurjak, 2002).
In vitro Culture and Maturation of Rat Preantral Follicles

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In our laboratory, we have developed a culture system in which rat ovarian follicles can be genetically manipulated and assessed for follicular growth, atresia and ovulation. Preantral/early antral follicles (160-210 μm diameter) cultured for 0-6 days with FSH (100ng/ml) showed significant growth as evident by increases in follicular size, cell number and DNA content. Human chorionic gonadotrophin (hCG; 0.5 IU/ml) was capable of inducing oocyte maturation and ovulation in vitro.

Atresia in ovarian follicles is known to mediate by apoptosis in granulose cells. Whether the etiology of ovarian dysfunction in galactosemic condition is related to an increased atresia of follicles has not been investigated. The possible relationship between Xiap and ovarian follicle development in galactosemic rat was studied using the established in vitro system. Ovarian follicles, isolated from control and 7-week old rats treated for 4 weeks with 50% galactose diet to induce galactosemia were culture for 0-4 days with FSH. In galactosemic follicles, there was a significant retardation in growth and in vitro ovulation rate induced by hCG. Galactosemic and control follicles ovulated at 26% and 58% respectively. A higher apoptotic index and a lower Xiap expression were observed in galactosemic follicles compared with the controls. To up-or down-regulate Xiap expression, follicles cultured for one-day with/without FSH were intramural injected with adenoviral Xiap-sense, Xiapantisense cDNA or LacZ. (control) and then cultured with/without FSH for 3 additional days. They were induced to ovulate on Day 4. In the absence of FSH, neither difference in growth nor ovulation response was observed between galactosemic and control follicles. FSH marked stimulated follicular growth in vitro in both groups although Xiap expression in galactosemic follicles was significantly lower than in controls while a higher apoptotic index was found in the galactosemic group. Overexpression of Xiap abolished the significant difference in ovulatory response to hCG between the galactosemic and the control follicles. A lower apoptotic index and Xiap intensity were observed in galactosemic follicles. Our data suggested that defective expression of Xiap might be an important etiological factor in the pathogenesis of ovarian dysfunction.
Organ Morphogenesis via Regulation of Cell Migration and Matrix Interaction

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Male tail sensory ray differentiation in *C. elegans* is a complex morphogenetic event, where active cell migration takes place within a short developmental window. After the birth of eighteen ray cell groups at the late larval stage, these cells are assembled into bundles, attached to the body surface followed by pulling back of all the cell bodies to establish an array of tentacle-like processes for male-hermaphrodite mating. Taking advantage of a set of mutant and transgenic animals, we have established that the formation of these structures can be dissociated into a number of independent steps, (1) determination of the ray cell identity, (2) the assembly of ray cells into a bundle of processes, (3) retraction of cell bodies leaving behind extension of rays and (4) stabilization of cell and ray shape. The ultimate morphology of these processes is determined by the shape of individual ray cells, which is at least partially determined by an active dorsal anterior cytoplasmic and nuclear migration of the ray cells. Failure of this migration event results in swelling of the ray cells. The same defect can also be observed in mutations of at least four genes, *ram-2, ram-3, ram-4* and *mal-7*. In these mutants, abnormal axonal migration and cell retraction are observed resulting in swelling of individual ray processes. The control of the migration process appears to be modulated by the netrin and netrin receptor, and can be influenced by the posterior body matrix environment surrounding the ray cells, primarily the collagen components. With the definition of molecular identities of some of these components, a model invoking both reciprocal signaling process and matrix-cellular interaction will be presented.
Sonic Hedgehog in Enteric Nervous System Development

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Sonic Hedgehog (Shh) is a secretory glycoprotein and functions as a morphogen in the graded manner to regulate cell fate determination in neural tube and limbs. In the gut, Shh is synthesized and secreted from the endoderm into the mesenchyme, establishing a Shh concentration gradient across the radius of the gut. Studies from others and ours indicate that Shh controls the migration and differentiation of neural crest cells (NCCs) in gut. As an initial attempt to examine the functions of Shh on enteric NCCs, we establish ex vivo gut explants, in vitro dissociated gut cells and immuno-selected NCCs cultures. We exploit unique features of these culture systems to investigate the effects of Shh on the migration, plexus formation and differentiation of NCCs. We use E11.5 embryonic gut explants of transgenic mice (b3-Hha-lacZ) to investigate the NCC migration. The enteric NCCs and mature enteric ganglia of b3-Hha-lacZ mice express lacZ activity and stained blue with X-gal and IPTG. In our ex vivo gut explant culture, NCCs migrate from the gut onto the filter membrane and differentiate into neurons in response to glia cell-line derived neurotrophic factor (GDNF) in the medium. The number of migratory NCCs onto the filter displays a positive dose-dependent response to GDNF. Addition of Shh to the medium drastically decreases the migration of NCCs. In dissociated gut cell culture, NCCs treated with GDNF and Shh aggregate into plexus-like structure earlier than those treated with GDNF alone or without GDNF and Shh suggesting that Shh promotes plexus formation of NCCs. To study the cellular effect of Shh on the NCCs, we culture immuno-selected NCCs of mouse embryonic gut in the presence of GDNF or GDNF plus Shh. Shh inhibits GDNF-induced neuron differentiation of NCCs. Our data suggest that Shh regulates the responsiveness of enteric NCCs to GDNF induction on migration and differentiation. The effects of Shh on NCCs may be mediated by Shh acting directly on the NCCs (direct mechanism) and/or indirectly that Shh regulates the mesenchyme which in turn affects the NCCs behaviour (indirect mechanism).
Epidermal Growth Factor as a Biologic Switch in Hair Growth Cycle?

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The hair growth cycle consists of three stages known as the anagen (growing), catagen (involution) and telogen (resting) phases. This cyclical growth of hair is regulated by a diversity of growth factors. Here we show that continuous expression of epidermal growth factor (EGF) in hair follicles causes alopecia. Whereas normal expression of both EGF and its receptors (ErbB1) are down-regulated after the anagen phase, continuous expression of EGF in hair follicles of transgenic mice arrested follicular development in the anagen phase. Data from immunoprecipitation and immunoblotting showed that EGF signals through erbB1/erbB2 heterodimers in skin. Furthermore, topical application of tyrphostin AG1478 or AG825, specific inhibitors of ErbB1 and ErbB2 respectively, completely inhibited new hair growth in wild type mice but not in transgenic mice. When the transgenic mice were crossed with waved-2 mice, which possess a lower kinase activity of EGF receptors, the alopecia phenotype was completely rescued in the offspring. Taken together, these data suggest that EGF receptor signaling is indispensable for the initiation of hair growth. On the other hand, continuous expression of EGF arrests entry into the catagen phase. We propose that EGF functions as a biologic switch which is turned on and off in hair follicles at the beginning and end of the anagen phase of the hair cycle, guarding the entry to and exit from the anagen phase of the hair cycle.
Hoxb3lacZ: A Mysterious Knockout Mutant

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In mouse and humans, the 39 Hox genes are organized into four different chromosomal complexes. Using gene targeting technology it has been possible to manipulate Hox genes and generate mutants for studying their functional roles during development. To better understand the dynamic expression patterns and the functional roles of the Hoxb3 gene, by conventional gene targeting strategy of positive and negative selection we generated a mutant Hoxb3lacZ. By Southern hybridization using 5' and 3' flanking probes we have confirmed that the mutant carried the targeted Hoxb3lacZ mutation as designed.

Heterozygous Hoxb3lacZ mutant embryos expressed the lacZ reporter gene, but with temporal and spatial patterns of neural expression different from those observed by RNA in situ hybridization study on normal wildtype embryos. In heterozygous Hoxb3lacZ embryos, lacZ starts to express as early as 8.0 dpc at high levels in the presomitic and somitic mesoderm. At later stages, lacZ continues to express in the somites and lateral plate mesoderm. In the neural tube, lacZ expression is not detected until 9.5 dpc and expression is extended from posterior to the mid-trunk region. By 10.5 dpc, the anterior boundary of expression in the spinal cord is located at around the 10th somite, with two additional weak stripes of expression in r1 and r6. This is very different from the expected normal Hoxb3 RNA expression in the neural tube at these stages, which extends from the posterior end to the hindbrain at r5 at 9.5 dpc. By 12.5 dpc, the normal full patterns of neural and mesodermal expression are established and maintained till later stages. In summary, the onset and patterns of neural expression of lacZ in the Hoxb3lacZ mutant are different from those of wildtype Hoxb3 RNA transcripts at early stages, but the mesodermal expression is normal.

We have found that homozygous Hoxb3lacZ mutation is embryonic lethal, homozygous embryos display general oedema by 11.5 and 13.5 dpc and no homozygotes could be recovered beyond 15.5 dpc. To address the cause of oedema we have examined the heart of homozygous mutant by histological sections. In one example of severe abnormality, we observed that there was evident ventricular septal defect, also there was a lack of compact myocardium and only loose network of cells were found in the ventricle. In addition, our analysis of 15.5 dpc homozygous embryo shows clearly that there is strong staining of lacZ in the thoracic body wall, which failed to fuse in the ventral midline.

The phenotypes of the Hoxb3lacZ mutant clearly indicate that Hoxb3 has unique functions which are not compensated by other genes. We hypothesize that in this Hoxb3lacZ mutant, the cardiac abnormalities are probably due to abnormal cardiac neural crest development. Based on the phenotypes observed in the Hoxb3lacZ mutant so far, we shall discuss the possible roles of Hoxb3 during embryogenesis.

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A Mouse with Two Tales

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Bone growth occurs at the growth plates situated near the ends of long bones, at the junction between the epiphyseal cartilage and the growing bone. In this junction, bone is formed by a process called endochondral ossification. Characteristically, this process is accomplished by a coordinated sequence of chondrocyte proliferation, differentiation to hypertrophic chondrocytes, mineralization of the hypertrophic cartilage, and finally, replacement of the mineralized cartilage by bone. Prior to the conversion from cartilage to bone, collagen X is actively synthesized by the maturing hypertrophic chondrocytes and deposited as the major extracellular matrix component. It is then degraded to allow replacement with a bone matrix.

In humans, mutations localized to a conserved carboxy-terminal (NC1) domain of collagen X result is an autosomal dominant chondrodysplasia, Schmid metaphysial chondrodysplasia (SMCD) with primary growth plate abnormalities. The main features are flaring of the metaphyses, bowing of the legs and coxa vara. Transgenic mice (13del-tg) expressing a human equivalent collagen X mutation were generated to understand the pathogenesis of collagen X mutations in SMCD. Five different lines of transgenic mice were generated that showed a similar phenotype with skeletal abnormalities apparent from 4-6 days post-partum. Gross morphology showed the transgenic mice are smaller than the non-transgenic littermates with short limbs, abnormalities of the digits and a prominence of the frontal bridge. Histological analysis of the growth plates showed abnormalities in chondrocyte differentiation with a marked expansion of the hypertrophic zone. Interestingly, 13del-tg mice showed an additional abnormality, which is not observed in SMCD patients. X-ray analysis of transgenic mice between the ages of 5-15 weeks showed a progressive increase in bone density that correlates with a progressive thickening of the cortical and cranial bones. These changes, which affect the whole skeleton, represent a generalized new bone formation consistent with an alteration in bone remodeling favouring bone formation.

Detailed analyses of the impact of the 13del mutation on chondrocyte hypertrophy in the growth plate using molecular markers have revealed insight into the molecular pathology underlying the abnormal chondrocyte hypertrophy. We have established that 13del proteins are accumulated inside the hypertrophic chondrocytes within engorged endoplasmic reticulum, activating the unfolded protein response (UPR). Analysis of cell-cycle progression markers showed that the 13del hypertrophic chondrocytes in the lower part of the zone are arrested in G1/S phase. Cells at the chondro-osseous junction in 13del were smaller compared to wild-type hypertrophic chondrocytes, and displayed characteristics and molecular markers more typical of prehypertrophic cells. Our data provide the first in vivo evidence that impaired secretion and UPR can lead to abnormalities in cell cycle progression and differentiation of chondrocytes. Furthermore, 13del-tg mice have revealed plasticity in chondrocyte terminal differentiation in which "terminally" differentiated hypertrophic chondrocytes can potentially revert to a more prehypertrophic state.

We have shown through a genetic approach that the bone phenotype appeared to be independent of the growth plate expansion, and is specific for the 13del mutation in the mouse. The bone thickening is due to stimulated osteoblast activity, either as a direct or indirect action of the 13del protein. Uncovering the molecular basis for this unexpected bone overgrowth will provide new insights into the biology of bone, with the potential to discover novel therapeutic treatments for conditions with altered bone mass such as osteoporosis.
Col2α1 encodes type II collagen, the major cartilage matrix protein. During embryogenesis Col2α1 is transcribed to give HA mRNA containing an exon encoding a cysteine-rich domain in the amino-propeptide and HB mRNA which lacks this exon. In early embryos, HA mRNA is the major form of Col2α1 transcript expressed in both prechondrogenic and non-chondrogenic tissues and is expressed at very high levels in the developing heart between 8.0 - 10.5dpc. HA procollagen has been shown to be able to bind BMP2 and TGFβ1 and has been shown to have dorsalising activity in Xenopus embryos. To understand the role of HA procollagen in development, we have used homologous recombination in mouse embryonic stem cells to produce mice deficient in HA procollagen by deleting exon 2 of Col2α1. Mice heterozygous for the HA null mutation (HA+/−) are fertile and grossly indistinguishable from wild-type. Mice homozygous for the HA null mutation (HA−/−) display variable heart malformations. In 9.5 dpc HA−/− embryos the heart remains as a tube with the right and left portions aligned rostro-caudally. At birth the heart defects are consistent with prenatal onset of hypertrophic changes in the myocardium. The malformed heart shows a variety of defects including deformed endocardial cushions, undivided ventricular chamber, single atrioventricular canal, a common atrium with rudimentary atrial septum, and defective connection of the ventricles with the outflow tracts. These phenotypes were of variable penetrance and severity of consequence. Some mutants survive to birth and newborn HA−/− mice die of birth probably because of respiratory distress. The spectrum of heart defects include some features of human congenital heart conditions such as the tetralogy of Fallot (ventricular septal defect (VSD), pulmonary valve stenosis, overriding aorta and right ventricular hypertrophy), and the Double Outlet Right Ventricle (where aorta and pulmonary arteries arise wholly or in great part from the right ventricle, with associated ventricular septal defect). We hypothesise that Type II HA procollagen may regulate cardiac patterning by binding and sequestering growth factors or signalling molecules.
5. Scientific Meeting of the Centre for the Study of Liver Disease and Centre of Alimentary Research and Education
Cancer cells evade the body’s immune reaction in part because they do not activate T cells to fight and kill tumors. Tumor cells often lack important surface proteins known as antigen presenting cells (APCs) and rarely exhibit specific tumor-associated antigens (TAAs) on their surfaces. Without efficient presentation of TAAs by APCs, tumor cells are not recognized as “non-self” by the immune system, and are therefore not targeted for destruction. Our laboratory is investigating various methods of stimulating T cell response to human hepatocellular carcinoma (HCC). One approach we are exploring is to fuse dendritic cells (DCs) with HCC TAAs to stimulate the immune response to tumors. Mature DCs, which are the body’s most efficient APCs for TAA presentation, have highly expressed MHC class I, MHC class II, B7-1 and ICAM4 molecules, all of which are essential for activation of T cells. By fusing HCC cells with DCs, tumor-specific T cells are activated to become cytotoxic T lymphocytes (CTLs) that will kill the targeted HCC cells.

Another approach is to pulse heat-shock proteins extracted from HCC cells into DCs to enhance CTL activity. Heat shock proteins (HSPs) derived from cancer cells have been shown to elicit tumor-specific immunity and specific CTL activity. HSPs appear to function as carriers for TAAs, introducing them to MHC class I molecules for presentation.

The third approach is to genetically engineer HCC cells to express the co-stimulatory element B7, which is lacking in all solid tumor cells. Our lab recently established a novel human HCC cell line which expresses B7, which is essential for T cell activation.

These three approaches have promising potential for use in HCC immunotherapy.
Li-Cadherin, a Tumor Suppressor or Biomarker for GI Cancer?

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**CDH17** (locus 8q22.1) is a member of the cadherin superfamily genes that encodes for Ca\(^{2+}\)-dependent, membrane-associated glycoproteins. In contrast to classical cadherins (e.g. E-cadherin), the Li-cadherin protein consists of 7 cadherin domains in the ectodomain, and a transmembrane region but lacks the conserved cytoplasmic domain. The protein is found in the gastrointestinal tract and pancreatic ducts, acting as an intestinal proton-dependent peptide transporter. The protein also plays a role in the morphological organization of the liver and intestines. Unlike the E-cadherin, which has been intensively examined with respect to cancer, the role of Li-cadherin in hepatocarcinogenesis and gastric cancer pathogenesis remains largely unknown. The objective of this study is to investigate the expression of Li-cadherin in the two major gastrointestinal cancers in Hong Kong, and to determine its association with liver tumorigenesis.

For the first time, it was demonstrated that expression of Li-cadherin was increased in gastric cancer tissues, contrary to the reduction of functional E-cadherin in many cancer types. We propose that Li-cadherin may enhance the nutritional transport to the tumor site and/or facilitate the invasion and migration of the cancerous cells. A better understanding of the Li-cadherin expression and its association with tumor stages may shed light on the clinicopathologic implications and allow better management of patients. (Supported by the Research Grants Council of Hong Kong)
Liver cancer is a common cancer worldwide. A better understanding on the molecular basis of the disease is crucial in disease prevention and management. Our recent studies on the genome-wide expression analysis of primary and metastasis liver cancers have identified genes that are differentially expressed in liver cancer compared to normal liver and diseased liver with chronic hepatitis and/or cirrhosis.

We have systematically examined the global gene expression profiles of various liver tissues by cDNA microarray. Over 200 liver samples, including 102 primary liver cancers, 74 tumor adjacent liver tissues (non-tumor), 7 benign liver tumors, 10 metastasis cancers, and 10 cell lines were investigated by the cDNA microarray containing 23,000 clones representing 17,400 genes. The expression patterns varied significantly among the HCC (hepatocellular carcinoma, the major histological type of liver cancer). Some features of the gene expression patterns were associated with specific phenotypic and genotypic characteristics of the HCC tumors, including growth rate, venous invasion, p53 gene mutation and protein over-expression. Consistent expression differences were observed between HCC and their non-tumor liver tissues.

More than 1,600 genes were differentially expressed in HCC versus non-tumor liver samples (P<0.01 by Student’s t test with Bonferroni correction). Some of the genes have the potential to serve as diagnostic markers and/or therapeutic targets for the disease.

Disease recurrence and metastasis are frequently observed in many successfully treated localized cancers, including HCC in which intrahepatic and extrahepatic recurrence (metastasis) is frequently observed after curative resection. We have identified metastasis-associated genes in HCC through the investigation on multi-nodular liver cancers. A total of 22 tumor nodules from 6 patients were investigated by the cDNA microarray, and conventional molecular approaches including p53 gene mutation and protein over-expression, HBV integration, and genetic alterations examined by comparative genomic hybridization. We found that the genome-wide expression data contributed substantial information to elucidate the lineage of individual nodules. Comparing the expression patterns of the primaries to the secondaries tumor nodules, 90 genes were shown to have differential expression levels which were candidate metastasis genes responsible for regulating the growth of disseminated cancer cells. These metastasis-associated genes may provide clues to reveal patients with increased risk of developing recurrence and metastasis.

Genome-wide expression analysis can help to better understand the molecular tumorigenesis and progression of liver cancers. The study can also facilitate identification of genetic markers for early diagnosis, better prognosis and novel therapeutic targets for the disease.
Rescue of Marginal Graft by Novel Nitric Oxide Donor FK409 in Liver Transplantation

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Objective: To investigate the effect of low dose FK 409 (Nitric Oxide donor) in liver transplantation using small-for-size grafts by intragraft genes detection, portal hemodynamics monitoring and ultrastructure examination.

Materials and methods: A rat orthotopic liver transplantation model using small-for-size grafts (40% of recipient liver weight) was used. Inbred Lewis rats (180 - 230 g) were donors and recipients. In the FK group, 2mg/kg of FK409 was given at 30 minutes before graft harvesting in the donor and 1mg/kg FK409 was given immediately after reperfusion in the recipient. The 7-day graft survival rates and portal pressure before and after reperfusion were compared between the rats with or without FK409 treatment (control group). Intragraft Egr-1, ET-1, HO-1, A20, and Hsp-70 levels were compared during the first 24 hours after reperfusion by real-time RT-PCR, western-blot and enzyme immunoassay. The liver biopsies were examined under electron microscope.

Results: The 7-day graft survival rates in the FK group were significantly improved compared to the control group (80% vs. 28.6%, p=0.018). The portal pressure in the FK group was significantly lower at the first 60 minutes after reperfusion. In the FK group, intragraft mRNA levels of HO-1 were significantly increased during the first 24 hours (30 minutes: 216% vs. 35%, p=0.03; 2 hours: 917% vs. 67%, p=0.03; 6 hours: 5493% vs. 881%, p=0.03; 24 hours: 1245% vs. 345%, p=0.03) and mRNA levels of ET-1 were significantly lower at 2 hours (133.5% vs. 67.3%, p=0.03) and 6 hours (77% vs. 492%, p=0.03) after reperfusion. The intragraft protein levels of Hsp-70 were higher at 24 hours after reperfusion (17.7 vs. 12.2 ng/ml, p=0.034). The intragraft expression of Egr-1 was lower and A20 were higher during first 24 hours after reperfusion. Only a few apoptotic cells were found in FK group. The sinusoidal lining cells were intact in the FK group and endoplasmic reticulum and mitochondria were normal.

Conclusion: The low dose FK409 rescues the marginal grafts in liver transplantation by attenuating portal hypertension and prior induction of heat shock proteins accompanied by ameliorating acute phase response.
New Concepts in Improving Long-term Outcomes of Organ Transplantation

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Background: Allograft deterioration is the major obstacle to organ transplantation for long-term treatment of end-stage heart failure. In this study, we transduced the anti-oxidant gene, heme oxygenase-1 (HO-1), to heart grafts using a recombinant adeno-associated viral vector (rAAV) in a rat heart transplantation model and investigated their potentiality in prevention of chronic graft deterioration.

Methods and Results: rAAV/HO-1 was administered to heart grafts through coronary arteries during cold preservation. We investigated the expression patterns and activities of transgene, graft survival and histomorphology, relevance of long-term HO-1 expression on graft survival and chronic graft deterioration, and gene expression profile of the graft on day 100. Long-term allograft survival can be achieved by rAAV/HO-1-mediated stable transgene expression. The development of graft arteriosclerosis and interstitial fibrosis was prevented in rAAV/HO-1-treated allografts on day 100. The stable expression of HO-1 is a prerequisite for both survival of the grafts and prevention of graft arteriosclerosis and interstitial fibrosis. cDNA microarray data showed that rAAV/HO-1-mediated long-term graft protection was accompanied by remarkable down-regulation of genes encoding pro-inflammatory cytokines, growth factors and tissue protease inhibitors, and up-regulation of serine proteases in the grafts.

Conclusions: rAAV/HO-1 gene transfer represents a novel therapeutic approach to prevent chronic allograft deterioration in clinical organ transplantation.
Crypt Fission in Colonic Diseases

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Introduction: Intestinal crypts reproduce by the process of crypt fission, in both colon and small intestine. This process begins by basal bifurcation and the crypt then divides longitudinally. Studies of the spread of mutated clones in animals after administration of carcinogens have shown that the mechanism of the expansion of these mutated clones is by crypt fission. In the multi-step process of colonic carcinogenesis, one of the earlier lesions is a colonic adenoma in which mutation in the adenomatous polyposis coli gene (APC) is common. The major defect in pre-neoplastic intestine of human familial adenomatous polyposis (FAP) and multiple intestinal neoplasia (MIN) mice harbouring APC mutations appears to be elevated rates of crypt fission. Whether the above findings extend to most cases of sporadic colorectal cancer, which account for 85 percent of all colorectal cancers is uncertain.

Methods: Human colorectal adenomas, hyperplastic polyps and normal colorectal mucosa (FAP and HNPCC patients were excluded) were obtained during colonoscopy, and microdissected into individual crypts. The morphology, cell proliferation characteristics and fission indices of crypts isolated from these lesions were then studied.

Results: Crypts isolated from colorectal adenomas and colorectal hyperplastic polyps were significantly larger (P<0.001) than crypts from normal colorectal mucosa. Crypt fission was an uncommon event in normal colonic mucosa but common in crypts isolated from adenomas and hyperplastic polyps (P<0.001). Analysis of the distribution of mitoses suggested an upward expansion of the proliferation compartment in adenomas to the surface of the crypt with no reversal of proliferating cell distribution as has previously been described.

Conclusion: Sporadic human colorectal adenomas and hyperplastic polyps grow by the process of crypt fission. Expansion of the proliferative compartment was demonstrated in crypts from adenomas, consistent with de-regulation of cell cycle control. The study of crypt fission and proliferative characteristics of these early pre-cancerous lesions may provide new clues to the fundamental mechanisms of colorectal cancer development.
The gastric mucosa is most susceptible to stress which has been shown to induce mucosal damage in humans and animals. Sleep deprivation (SD) imposes stress in the body and may contribute to the gastric discomforts experienced by subjects deprived of sleep. This study aims to explore the under-lining mechanisms of SD on gastric functions and its effects on mucosal integrity. Sprague-Dawley rats were partially sleep deprived (PSD) by housing inside a slowly rotating drum which was switched off one hour daily to provide a period of undisturbed sleep. Gastric erosions were found in PSD rats 7 days after SD. Gastric acidity, acid secretion, serum gastrin level were found to be elevated while mucosal mucus layer thickness, gastric mucosal blood flow and serum somatostatin were reduced. Enhanced acid back diffusion may contribute to PSD induced gastric erosion. Gastric tissue contents of superoxide dismutase and glutathione were found to be increased and decreased by PSD, respectively. This correlated to an increase in reactive free radicals accompanied with a rise in malondialdehyde level in gastric samples obtained from SD rats. Gastric level of inducible heat shock protein 70 (iHSP70) was markedly elevated and its expression is positively regulated by gastric acid secretion. Its protective homeostatic role was established by the effects of PSD and sodium arsenite injection on HCl induced gastric damage, since under both conditions the expression of iHSP70 was greatly enhanced. Thus, iHSP70 has a physiological function to play in preventing auto-digestion of the mucosal tissues by acid and SD damages gastric mucosa.
6. Scientific Meeting of the Centre for Cellular Biology and Centre of Endocrinology and Diabetes
Initiation Proteins for DNA Replication as Potential Anticancer Targets

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Eukaryotic cells duplicate their genome in the S phase of the cell cycle by initiating DNA replication at multiple chromosomal sites called origins of DNA replication. Initiation of DNA replication is controlled by the cis-acting DNA elements called replicators and the trans-acting initiation proteins that interact with the replicators. Recent studies on DNA replication in the budding yeast *Saccharomyces cerevisiae* have led to the identification of many initiation proteins for DNA replication and the elucidation of a framework of interactions among initiation proteins and their regulators. Homologs of these initiation proteins from higher eukaryotes, including humans, have also been identified by sequence homology to the yeast proteins and found to be required for DNA replication in the respective organisms. Moreover, some replication-initiation proteins in humans are expressed in cancer cells, but not in non-proliferating normal cells. Therefore, these initiation proteins may present very attractive targets for anticancer drugs.

To develop potential anticancer drugs, we have designed, screened and tested antisense DNA oligonucleotides (oligos) targeted to the mRNA of human DNA replication-initiation proteins. Antisense oligos are known to be able to inhibit gene expression. The primary mechanism of antisense oligos is to bind to the complementary target mRNA and activate the endogenous RNase H to cleave the mRNA. Using the antisense strategy, we have found that down-regulation of replication-initiation proteins not only stops DNA replication, but also induces apoptosis of cancer cells. Each of these oligos can kill from 75 to 90% of cancer cells in culture in two days after a single transient transfection, and the oligos do not kill the corresponding normal cells derived from normal tissues. Furthermore, we have found that siRNA (small interfering RNA) can also inhibit the expression of replication-initiation proteins and induce cancer cell death. We believe that our findings represent a new strategy, new targets, and new drug candidates for treating cancer and other hyperproliferative conditions.

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Biomimetic Combinatorial Synthesis of Cyclic Peptide Libraries for Drug Discovery

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Cyclic peptides are an appealing class of small organic molecules in drug discovery. In comparison with their linear counterparts, cyclic peptides are more stable in vivo and more pharmacogenic as a result of their reduced conformational mobility that allows presentation of diverse functionality in a defined and predictable manner. However, limited availability of diverse cyclic peptide libraries for biological screening hampers their application in biomedical research. To generate such libraries, we choose scaffolds of gramicidin S and tyrocidine A, two similar natural cyclopeptide antibiotics with a rigid β-pleated sheet conformation, for diverse presentation of functionality. Two novel methods have been developed to synthesize the scaffold-based combinatorial libraries. In a chemoenzymatic approach, enzymes in the biosynthesis of the natural products are utilized to cyclize the linear peptide precursors synthesized combinatorially on a solid support. In another biomimetic approach, the self-cyclizing capability of the linear biosynthetic precursors of the scaffold molecules and their analogues is exploited for combinatorial synthesis of the cyclic peptide libraries. Generation of these cyclopeptide libraries and their potential application in pharmaceutical research will be discussed.
Genetic Analysis of Polyol Pathway in Diabetic Complications in Mice and Humans

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Diabetes mellitus is a serious health concern worldwide. Long-term diabetes often leads to secondary diseases such as cataract, retinopathy, neuropathy, nephropathy, and cardiovascular diseases. While hyperglycemia is recognized as the primary cause of these diseases, the mechanism(s) remains controversial. Polyol pathway has been implicated in the pathogenesis of some of these diseases. The first enzyme of the pathway, aldose reductase (AR) reduces glucose to sorbitol with the aid of its co-factor NADPH, while the second enzyme sorbitol dehydrogenase (SDH) converts sorbitol to fructose. Inhibitors of AR (ARIs) were effective in preventing some of these diabetic complications in animal models. However, clinical trials of these drugs were disappointing, casting doubt on the role of AR in these diseases. Since the specificity of ARIs in vivo is not clear, we used genetic approach to vigorously test AR's role in the development of these diseases. We developed transgenic mice that overexpress AR in their lenses and showed that they became susceptible to develop diabetic cataract, and we developed AR gene knockout mice and found that they became resistant to develop diabetic neuropathy. These studies clearly demonstrated that AR is crucial to the pathogenesis of these diseases. Using SDH deficient mice, we demonstrated that osmotic stress, from the accumulation of sorbitol, is the major cause for diabetic cataract but not neuropathy. Oxidative stress, due to the AR induced depletion of the major cellular antioxidant GSH, is most likely the major contributing factor for diabetic neuropathy. In human studies we have identified a highly polymorphic (AC)n dinucleotide repeat sequence in the promoter region of the AR gene and showed that one of the alleles in this locus is strongly associated with early onset diabetic retinopathy in type 2 diabetes in the Chinese population in Hong Kong. Since then a number of studies have confirmed similar associations between this AR gene marker and various diabetic complications in type 1 and type 2 diabetes in different populations. These genetic studies in mice and humans strongly indicate that AR is an important target for the prevention of diabetic complications, and they provide impetus to develop more effective ARIs for the prevention of these diseases.
Oral gene therapy: Potential and Challenge

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Gene therapy, developing rapidly as a result of advances in molecular biology and the Human Genome Project, is now highlighted as a most hopeful technology of the 21st century.

It is well recognized that, at its current level, gene delivery technology is a major obstacle to the success of gene therapy. Efficiency, stability, specificity, safety and convenience are the key factors for an optimal gene delivery system. Substantial progress has been made in recent years in gene delivery systems, delivery routes and targeting. In order to control transgene expression to a desired organ at a desired time and at an appropriate level, many factors need to be considered carefully such as the option of vectors, gene delivery routes and tropism of transgene-vector constructs.

The orally administrated rAAV resulted in two phases of transgene protein generation and secretion. The oral rAAV vectors went through stomach to intestines, where they were taken by the gut as normal food nutrients. Some of rAAV vectors were expression in the gut epithelial cells locally and their products went to the liver through capillaries, small veins, superior mesenteric vein and portal vein, following a similar normal food nutrient intake. On the other hand, those that did not express in the gut epithelial cells also went to liver directly via superior mesenteric vein and portal vein, finally arrived the liver. Being taken by hepatocytes, they expressed transgene proteins in the liver.

The potential advantages of transduction of hepatocytes are notable, since the continuous cycling of gut epithelium required repeatedly oral administration if a long term of gene expression is required. Furthermore, stable level is also difficult to be obtained due to rapidly dividing of gut epithelium cells. Gene transfer to hepatocytes has proved to be practical for gene therapy for diabetes. The utilization of this novel gene therapy strategy is much more widely than our original though. It might be used for the treatment of a variety of diseases, such as liver disease.
TPP has been reported to occur commonly among thyrotoxic southern Chinese men with a prevalence of 25%. It rarely occurs in female patients. Paralysis due to hypokalaemia typically occurs after a high carbohydrate meal. This episodic paralysis will remit with the control of thyrotoxicosis but may recur with relapse of the disease. The cause of this condition remains unclear. However these clinical features of TPP are similar to that of an autosomal dominantly inherited syndrome, familial hypokalaemic periodic paralysis (HPP) which is not associated with thyrotoxicosis. HPP is associated with mutations (R528H and R1239H) at dihydropyridine receptor gene (CACNL1A3) which encodes a subunit of calcium channel in muscle (HPP-1) and mutation (R672G) at muscle sodium channel gene (SCN4A) which encodes the α subunit of adult skeletal muscle voltage-dependent sodium channel (HPP-2). To study whether there are similar mutations occurring among the TPP subjects, we directly sequenced the candidate genes for these three mutations in 98 male TPP patients and 97 normal male subjects. Results showed that none of the TPP patients carry any of these mutations. To determine the association of CACNL1A3 gene with TPP, we sequenced the exonic and the adjacent intronic regions for SNP. 11 SNPs were found in our population with 9 being novel polymorphic sites. The association between the polymorphic sites and the haplotype analysis in TPP patients will be presented.
Endothelial Dysfunction in Diabetes

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Endothelial dysfunction is an early event in atherogenesis and precedes the thickening of the intima and the formation of atherosclerotic plaques. Endothelial dysfunction has also been implicated in the pathogenesis of both micro- and macroangiopathy in diabetes and has been consistently demonstrated in patients with type 1 and type 2 diabetes mellitus. Markers of endothelial dysfunction (e.g., von Willebrand Factor, vascular cell adhesion molecules) are elevated in patients with diabetes mellitus and vasodilation mediated by endothelium-derived nitric oxide is impaired. The aetiology of endothelial dysfunction in diabetes is complex and it has been shown that more than one mechanism is involved. We and others have demonstrated that diabetic dyslipidaemia and the formation of advanced glycation endproducts both play a significant role. Other factors that have been suggested to also contribute to the development of endothelial dysfunction in diabetes include increased oxidative stress, insulin resistance, activation of protein kinase C and chronic low-grade inflammation. Current treatment available like HMG-CoA reductase inhibitors or angiotensin converting enzyme inhibitors are not very effective at reversing endothelial dysfunction in patients with diabetes mellitus. Hence, we need a better understanding of the various mechanisms involved and the relative roles they play in the aetiology of endothelial dysfunction so that new therapeutic strategies can be developed.
A Health-related Definition of Childhood Overweight

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Objective: To compare two new definitions of childhood overweight.

Design: Population representative cross-sectional (US) and longitudinal (Sweden) growth studies.


Subjects: Childhood BMI values of normal children between 3 and 17 years of age.

Main outcome measure: The Cole childhood overweight definition with childhood body mass index (BMI) centile curves drawn at age 18 passed through the cut-off points of 25 kg/m² for adult overweight. The He & Karlberg childhood overweight definition with a probability function predicts a 50% risk of reaching a BMI value over 25 kg/m² at age 18.

Results: The shape of the two overweight cut-off curves was different. The He & Karlberg values gradually fall-off in the relation to the Cole et al curve during childhood and adolescence. The He & Karlberg definition showed an overweight prevalence of 1-3% in the US and Sweden at the age of three. At 10 years, 23.2% of US males had a 50% risk of becoming overweight by the time they reached 18, compared to 14.6% of US females, 11.2% of Swedish females and 10.9% of Swedish males. Based on the Cole definition, childhood overweight prevalence decreases between the ages 3-8 years for the Swedish series, but remains fairly constant among US females.

Conclusions: The He & Karlberg childhood overweight definition is the first to be health-related, rather than being based on statistical criteria and it is superior and more effective than the existing definitions.
7. Scientific Meeting of the Department of Anaesthesiology and Department of Orthopaedic Surgery
Perioperative bleeding

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With the increased awareness of the risks and complications related to allogenic blood transfusion, blood conservation during surgery is becoming more important. The three major strategies that have been applied in reducing allogenic blood use during surgery include minimization of blood loss, adopting a more conservative "transfusion trigger" and using alternatives to allogenic blood such as autologous blood and RBC substitutes.

One of the important issues in minimization of blood loss is to avoid haemostatic dysfunction during the perioperative period. Patients' pre-existing diseases, drugs used in the perioperative period, anaesthetic agents in use and physiological changes in this period may all contribute to haemostatic dysfunction. Traditionally haemostatic function has been monitored by platelet count, prothrombin time (PT) and activated partial thromboplastin time (aPTT). These tests all have important limitations and newer haemostatic monitors such as thrombelastography (TEG) and PFA-100 platelet function analyzer may have important roles in perioperative haemostatic monitoring.

We have previously used the TEG to investigate the effects of mild haemodilution on coagulation. Contrary to common beliefs, haemodilution by normal saline in the order of 10-30% actually accentuates the haemostatic process. This has been shown in an observational study[1] as well as a randomised controlled trial[2]. The mechanism of this change and its clinical significance remains to be evaluated.

Some anaesthetic agents may also adversely affect haemostasis. The intravenous anaesthetic agent propofol has been demonstrated to impair platelet aggregation and increase fibrinolysis in vitro. We have performed another prospective randomised study using TEG which demonstrated there is no clinically important haemostatic dysfunction and no increase in intraoperative blood loss when patients are anaesthetized with propofol compared to when anaesthetized with inhaled isoflurane[3].

Another new inhaled anaesthetic agent sevoflurane have also demonstrated antiplatelet effects in vitro. The effects may be mediated via cyclooxygenase inhibition. We have designed a prospective, randomised trial to compare the effects of sevoflurane vs isoflurane anaesthesia on platelet and other haemostatic functions. The trial will be started shortly in patients undergoing total hip arthroplasty.

Many patients are taking medications that may adversely affect haemostasis in the perioperative period. Non-steroidal anti-inflammatory agents (NSAIDs) are well known platelet inhibitors via their effects on cyclooxygenase enzyme. No reliable test is currently available to monitor the degree of platelet dysfunction, which can be highly variable in these patients. We are currently conducting a trial to investigate the value of a new platelet function analyser (PFA-100) as a perioperative platelet function monitor and predictor of surgical blood loss in patients undergoing total knee arthroplasty.

Perioperative haemostasis is an interesting area of research. It is very important to choose the appropriate monitors and eliminate confounding variables through careful patient selection and study design when conducting research in this area.

References
Tissue Engineering in Orthopaedics

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Introduction

Reconstruction of body tissue after trauma and other pathological conditions, such as congenital deficiencies and massive infection is a difficult problem in medicine. Numerous research has been done to solve this problem. In the 1960s, replantation of body parts was successfully achieved using the microsurgery technique. Since then, reconstruction of tissue loss in various parts of the body relies significantly on these microsurgery techniques. The more dispensable tissues are transferred to reconstruct indispensable tissues. Tissues used in reconstruction include the skin, fascia, subcutaneous tissue, bone, joint, nerve, muscle and blood vessels. However, there is always a limitation of what one can harvest from the body and there is always donor site morbidity.

All living cells, which contain the same set of chromosomes, can divide and proliferate or differentiate to different cell lines and form different tissues. The signal for proliferation or differentiation is not entirely known at the moment. There are families of factors, which control the proliferation, and differentiation of cells.

The need for tissue engineering

In orthopaedics, various tissue loss are frequently encountered. At this point we need to consider how to supply new tissue to the body without sacrificing one’s own body tissue. One preference in the criteria for new tissue is that this supply should be unlimited. Another point to consider in the search for new tissue is the high complication rate with both the allografts and xenografts. Naturally, scientists have thought about creating human tissue to fit the tissue loss perfectly.

Tissue engineering can be defined as an emerging interdisciplinary field that applies principles and methods of engineering and life science towards the fundamental understanding of the structural and functional relationship in normal and pathological mammalian tissue, including human tissue. This is a specialty that develops biological substitutes to restore, maintain or improve the function of human tissues or organs. The biological tissue substitutes can be produced in three ways: in vivo, in vitro, or ex vivo, a technique in which tissue cells are harvested from the body and multiplied in vitro before being implanted back in the body.

Bone Tissue engineering

The therapeutic approach to bone defects may use the implantation of materials that support new bone formation. One method is the implant of an insert scaffold over which host bone spreads and which, ideally, replaces the implant. When osteogenic factors and potential bone cells are loaded into a synthetic material, bone can be successfully regenerated. Some of the synthetic materials being studied include hydroxyapatite, polyglycolic acid and polylactic acid.

Clinically, human segmental defects of long bone can be treated by autograft, allograft, vascularized bone graft and bone segmental transport. Bone defects of a small size can heal spontaneously. However, the body can only regenerate up to a certain point and in fact, there is a critical size of bone defect. From clinical experience, a segmental defect of 2.5 cm in length must be bone grafted and a defect longer than 6-7 cm must be treated by vascularized bone graft.

Bone regeneration with resorbable polylactide membrane and sponge

Our present study set out to investigate whether segmental diaphyseal defects of 20 mm in size in rabbit which exceeds the critical size defect can be healed using this particular type of resorbable microporous
membranes or sponges. The study shown that bone regeneration dispersed across the defects treated with the bioreabsorbable membranes and sponges.

**Tissue engineering of other tissues**

Regeneration of cartilage tendon, ligament, vessel walls and nerve is being research extensively at the moment. The early in vitro results are promising.
Sr-HA Bioactive Bone Cement Characterization and Pre-clinical Trials

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Introduction: It has been reported that using minimally invasive bone cement injection for treating vertebral body fracture or stabilizing osteoporosis has been used clinically in recent years. Conventional poly(methyl methacrylate) (PMMA) bone cement has been used in orthopaedic surgery for over 40 years. However, it does not encourage bone ingrowth, has a high exothermity, and monomer toxicity. New bioactive bone cement was designed to overcome the disadvantage of PMMA. The purposes of this study were to further characterize the new injectable bioactive bone cement designed specifically for spinal surgery and to conduct pre-clinical trials.

Materials and Methods: The bioactive bone cement contains a filler blend and a resin blend. The filler blend contains Strontium-containing hydroxyapatite (Sr-HA), fumed silica, and benzoyl peroxide (BPO). The resin blend contains bisphenol A diglycidyl ether dimethacrylate (Bis-GMA), poly(ethylene glycol) methacrylate (PEGMA) and N,N-dimethyl-p-toluidine. The materials used were less toxic when compared with methyl methacrylate (MMA), which was the major component in conventional PMMA bone cement.

Strontium-containing hydroxyapatite was synthesized by the wet method and was characterized by Fourier Transform Infrared (FTIR) spectroscopy, X-ray diffraction (XRD) spectroscopy, and Electron-dispersive X-ray (EDX) analysis.

New Zealand white rabbits (n=10) were used for animal test. Bone cement was injected into the hole in ilium at rabbits. X-ray film was taken periodically post-operation to observe the bone cement in the ilium. The rabbits were sacrificed 3 months post-operation. Another four rabbits were performed as a control with conventional PMMA bone cement. The bone and bone cement interface was observed by Scanning Electron Microscopy (SEM) and Electron-dispersive X-ray (EDX) analysis. Histology of the bone with bone cement section stain with giemsa and cosin was performed. Other tests related to clinical trials have been conducted both in this Department and also in standard labs in PR China.

Results and Discussion: Strontium-containing hydroxyapatite (Sr-HA) was synthesized successfully. The spectra of Sr-HA from Fourier Transform Infrared (FTIR) spectroscopy and X-ray diffraction (XRD) spectroscopy have the pattern as hydroxyapatite. From Electron-dispersive X-ray (EDX) analysis, strontium, calcium, and phosphorus were found which were elements in Sr-HA.

The bone cement can be seen on X-ray film. The bone cement was not absorbed. By Scanning Electron Microscopy (SEM) and Electron-dispersive X-ray (EDX) analysis, the bone and bone cement interface can be observed clearly. The bone cement is bioactive which bond to the bone without soft tissue separation. The EDX pattern of bone cement was similar to that of bone except peaks of strontium and silica were found in the cement. Histology of the bone with bone cement section stain with giemsa and cosin was examined and the bone in growth on the bone cement interface was observed.

All other tests have also shown the satisfactory results suggested that a clinical trial with this bone cement could be conducted.

Summary: A bioactive bone cement which has many advantages over conventional PMMA bone cement was studied. The bone cement was injectable, with less toxic monomers, have lower setting temperature and reasonable setting time and mechanical strength suitable for Vetrbralplasty surgery.
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References


Anterior Release in Scoliosis by Chymopapain Injection: Increase in Spinal Flexibility is Dose-Dependent

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Introduction: Chemonucleolysis was originally introduced as a treatment for sciatica caused by lumbar intervertebral disc herniation. Destruction of the proteoglycans results in dehydration of the nucleus pulposis, a decrease in intradiscal pressure and may cause spinal instability. Taking advantage of this mechanical effect, we proposed that chemonucleolysis might be a useful tool for spinal flexibility modification in scoliotic deformity. The objective of this study was to examine whether the spinal flexibility increase after chymopapain injection was dose-dependent, and to determine the minimal effective dosage of chymopapain required for spinal flexibility modification in a rabbit lumbar spine model.

Methods: One hundred and thirty eight lumbar intervertebral discs from 46 New Zealand white rabbits were randomly injected with chymopapain at 6.25, 12.5, 25, 50, 75 and 100 picokats/pkats/0.05ml/disc. The rabbits were sacrificed 1 week after the injection and the lateral bending stiffness of the spinal segments without the posterior elements were determined.

Results: The lateral bending stiffness of spinal segments injected with 100 pkats/disc was decreased by 46% compared with those of non-injection controls. The decrease in spinal stiffness was dose-dependent. It was not significant after chymopapain injections of 6.25 and 12.5 pkats/disc, but significant following injections of 25, 50, 75 and 100 pkats (all p<0.05 by post hoc LSD tests). There were no significant differences in the flexibility changes between the four higher dosages.

Discussion: The results suggested that intra-discal chymopapain injection was able to increase spinal flexibility and a relatively lower dosage of 25 pkats or above may have the same spinal releasing effect as a higher dosage. Chemonucleolysis may be potentially useful in modifying spinal flexibility in rigid deformities. In combined anterior-posterior surgery for rigid scoliosis, the flexibility-modifying effect of the anterior release should become particularly obvious after removal of the posterior facets during the second stage posterior procedure.

References
Generalised artificial finger joint design process employing reverse engineering techniques

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A number of artificial finger joint designs have recently come on to the market that supposedly incorporate anatomical shape. These shapes are actually based on geometrical shapes that are approximations of finger joint surfaces. This presentation proposes that captured freeform surfaces can be used to further improve these designs. Laser imaging devices are used to capture the surface geometry of actual finger joints. By decomposing these surfaces into a set of NURBS curves, a technique has been developed that describes these surfaces in a compact way. It is therefore possible to build up a database of finger joints and generalise the results into surfaces that provide a much closer approximation to the actual anatomy. It is suggested that this approach could lead to artificial finger joints with a better range of motion and greater patient comfort. The process and initial results will be described in this presentation.
Time-Frequency Analysis: A New Technique for Intraoperative Somatosensory Evoked Potential Monitoring

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The objective of this study is to investigate the improvement on the reliability of intraoperative spinal cord monitoring by applying time-frequency analysis to somatosensory evoked potentials (SEP). 34 patients undergoing scoliosis surgery were studied. SEP were recorded during different stages of scoliosis surgery. Averaged SEP signals were analyzed intraoperatively by Short Time Fourier Transform (STFT). The time-frequency characteristics of SEP were observed during surgery. The main peak in time-frequency interpretation of SEP was measured in peak time, peak frequency and peak power. The changes in these variables were compared with the changes in latency and amplitude during different surgical stages. During different surgical stages, changes in peak times and peak powers were found to correlate to the changes in latency and amplitude, respectively. Peak time showed more variability than the latency (p<0.01), while peak power showed less variability than the amplitude (p<0.01). The peak frequency of SEP seems to be unchanged during surgery. SEP signals were found to have specific time-frequency characteristics, with the time-frequency distribution of the being located in a certain time-frequency space. In conclusion, time-frequency analysis of SEP waveforms reveals stable and easily identifiable characteristics. Peak power is recommended as a more reliable monitoring parameter than amplitude, even though peak time monitoring was not superior to latency measurement. Applying time-frequency analysis to SEP can improve the reliability of intraoperative spinal cord monitoring.
Cancer Self-remission and Tumor Instability

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The spectacular phenomena of spontaneous cancer remission persists in the medical annals, totally inexplicable but real. From time to time patients turn up with advanced cancer beyond the possibility of cure. The patient is sent home to die, only to turn up again ten years later free of disease. But no one has any idea of how it happens. If thousands of patients have succeeded, medicine can learn to accomplish the same (Dr. Lewis Thomas, MD).

Tumor evolution and its interaction with the immune system form a strongly nonlinear dynamic system. Due to nonlinearity, and like many other dynamic systems, tumor has multiple states. This multiplicity and instability of multiple states are believed to be responsible for the cancer self-remission. We make a numerical study of the tumor multiplicity and stability in an attempt to find the causative factors and clinical applicability of spontaneous regression of malignant tumors without treatment.

Based on recently developed models of tumor dynamics, the discretization is made by the finite volume methods. The discretization equations are solved for parameter-dependence of tumor states by the Euler-Newton continuation method. The solution branches are parameterized by physical parameters for the regular portion of solution branches, and by a local variable, arc-length or pseudo-arc-length for turning limit points. The bifurcation points are detected by the test functions. The branch switching is made by a scheme approximating the difference between branches. The stability of multiple states is assessed by examining their dynamic responses to finite random disturbances through direct transient computations. The Hilbert-Huang transformation is used for the analysis of time-series arising in examining the stability of multiple states. The results agree reasonably well with the experimental results from the temperature-variation therapy, the oxygenation-variation therapy and the multiplicative therapy.
8. Scientific Meeting of the Department of Physiology
Plasticity of vestibulo-cardiovascular interactions

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To test the hypothesis that prolonged vestibular activation could modulate the cardiovascular system, we examined the cardiovascular responses after short-term or sustained vestibular stimulation of adult Sprague Dawley rats. This then served as the framework for delineating the vestibulo-cardiovascular circuitry functionally activated by vestibular stimulation.

In response to electrical stimulation (10 min or 120 min duration) delivered to one labyrinth of urethane anesthetized rats, the basal mean blood pressure (MBP) and the heart rate (HR) remained unaltered. However, these resulted in a significant increase in the phenylephrine-induced baroreflex sensitivity index (ΔHR/ΔMBP) which returned to its original level at 30 min after stimulation. This was not observed in the sham-operated group.

In another series of experiments, natural stimulation in the form of constant velocity off-vertical axis rotation (OVAR), an established stimulus that is known to selectively activate the otolith organs in the inner ear, was delivered to conscious rats. Significant reduction in HR (15%) was observed after OVAR for 3 hr and this returned to the pre-OVAR value at 30 min after the termination of OVAR. These were not observed in labyrinthectomized and stationary controls, indicating that HR is attenuated by extended otolith stimulation. Rats subjected to OVAR for 24 hr showed two types of HR responses. In one group of rats, a progressive decrease in HR was observed during OVAR, reaching a reduction of 43% at 24 hr. Among the other group, a lowest (27%) was observed before the termination of OVAR and then the HR rebounded. These findings suggest that vestibular inputs coordinate cardiovascular adjustments during sustained postural changes but some rats are more resistant to bradycardia induced by prolonged otolith stimulation than others.

To map the neural circuitry that subserves the plastic changes associated with the above vestibulo-cardiovascular interactions, combined Fos immunohistochemistry and anterograde/retrograde tracing were performed in rats that were subjected to OVAR. Neuronal activation was defined by the expression of Fos protein in response to OVAR. Two vestibulo-autonomic pathways were identified. For the vestibulo-parasympathetic pathway, the vestibular nucleus (VN) sends projections to the nucleus tractus solitarius (NTS) and Koclikker-Fuse nucleus. Fos-positive neurons from both areas in turn project to the nucleus ambiguous where bradycardia could be induced with electrical stimulation. For the vestibulo-sympathetic pathway, VN sends projections to the NTS and lateral parabrachial nucleus. Fos positive neurons from both areas in turn project to the rostral ventrolateral medulla where pressor response could be induced with electrical stimulation. Our observations reveal novel circuitries in vestibulo-cardiovascular interactions.

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Some aspects of the control of blood pressure and blood flow in acute systemic hypoxia

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Acute systemic hypoxia activates reflex responses which are directed at constricting the peripheral vessels, so as to raise the blood pressure and maximise the oxygen supply to essential organs such as heart and brain. At the local level, all tissues, including the skeletal muscle, release vasodilator metabolites and hormones during hypoxia. These local vasodilator mechanisms are aimed at maintaining an adequate oxygen supply to the peripheral ("non-essential") organs. In the skeletal muscle circulation, the central and peripheral mechanisms compete.

The centrally-mediated peripheral vasoconstriction in hypoxia is mainly produced by an increase in the sympathetic tone on the peripheral vessels, as the result of stimulation of the peripheral chemoreceptors. Adenosine and potassium are two of the most important local vasodilator metabolites contributing to hypoxic vasodilation in the skeletal muscle circulation. Some of the interactions between these two mechanisms will be presented.
Is Adrenomedullin a Cardiac Depressant in Septic Shock?

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Despite intensive research, septic shock is still the most common reason of death in the surgical intensive care, and its incidence keeps increasing. No curative treatment is yet available. The critical aspect of septic shock is the refractory hypotension that develops during its late phase, which leads to a progressive deterioration of cell and organ functions, and in most instances, to death. During septic shock, following the overproduction of cytokines, many factors such as nitric oxide and adrenomedullin are produced in abnormally large quantities, but our understanding of their contribution to the pathophysiology of sepsis is limited. Here we show that adrenomedullin (22-52), an adrenomedullin receptor antagonist improves the contractility of myocytes isolated from LPS-treated rats, whereas in normal myocytes prolonged incubation with adrenomedullin at high concentration decreases their contractility, acting through an adrenomedullin (22-52) sensitive receptor.

In addition, adrenomedullin anti-serum and inducible NO synthase inhibitor improve the survival of LPS-treated rats.

The data indicate that adrenomedullin is a cardiac depressant factor, which along with NO precipitates ventricular failure during septic shock.

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Hypoxia - matters from molecules to physiology

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The maintenance of oxygen homeostasis is central to aerobic metabolism in organisms from cell to physiological levels. Recently, a surge of new evidence suggests that a heterodimeric transcriptional factor directly induced by cellular or tissue hypoxia, namely hypoxia-inducible factor-1 (HIF-1), is a master controller for the regulation of the gene expression of a spectrum of proteins for the cellular response to hypoxia. These proteins, such as endothelin-1 (ET-1), type II nitric oxide synthase (iNOS) and vascular endothelial growth factor (VEGF), play important physiological roles in the control of vascular tone and angiogenesis. The carotid body (CB) is the major peripheral sensor for detecting chemicals in the arterial blood. In acute hypoxia, carotid chemoreceptors transduce the signal to the brain for triggering reflexive responses of the cardiopulmonary system. The CB enlarges and changes its hypoxic sensitivity in humans and animals living at high altitude or subject to long-term hypoxemia associated with chronic cardiopulmonary diseases or hematological disorders. In the CB, chronic hypoxemia induces remodeling of the vasculature, stimulates proliferation of the chemosensitive cells, and changes their excitability and sensitivity to chemical signals. In addition, HIF-1-targeted genes are expressed in the CB and the expression is modulated by chronic hypoxemia, suggesting an active role for HIF-1 in moderate levels of hypoxic stress. We have examined the role of HIF-1 and its target genes in the vascular and physiological changes in the CB of rats breathing 10% oxygen for 4 weeks. Immunohistochemical studies demonstrated that, in chronic hypoxia, majority of cells in the CB increased the protein expression of HIF-1α, a heterodimeric partner of HIF-1 induced by hypoxia. The increased level of HIF-1α may activate the transcriptional expression of genes encoding vascular endothelial growth factor and its receptors in the CB as indicated by immunohistochemistry findings. These changes may mediate the angiogenesis in the CB for the vascular remodeling during chronic hypoxia. Spectrophotometric studies showed that the intracellular calcium response to ET-1 was augmented in chronically hypoxic (CH) glomus cells with an increased ET-1 protein expression, suggesting an enhancement of paracrine/autocrine functions of ET-1 for increasing excitability and mitotic activity of the chemoreceptors in chronic hypoxia. Moreover, iNOS protein was localized in CB glomericuli of the CH instead of the normoxic group. The NO concentration in the CB during acute hypoxia was higher in the CH than that of the normoxic group. The hypoxia-induced NO generation was attenuated by L-NAME and by S-methylisothiourea, a specific blocker for iNOS. These could potentiate the inhibitory effect of NO on the CB chemoreception during chronic hypoxia. Collectively, our results suggest that chronic hypoxemia induces the transcriptional activity of HIF-1 and regulates the expression of target genes for the structural remodeling and physiological adaptation of the CB in chronic hypoxia.

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Modulation of Volume Sensitive Chloride Current by Tyrosine Kinases in Human Atrial Myocytes

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**Introduction:** Cell stretch or swelling induced chloride current, generally named as volume-sensitive chloride current ($I_{\text{vol}}$), is believed to be activated under cardiac pathologic conditions, eg. dilated cardiomyopathy. However, modulation of $I_{\text{vol}}$ by intracellular signaling is poorly understood in human atrial myocytes. The present study was to examine roles of protein tyrosine kinases (PTKs) in the activation of $I_{\text{vol}}$ in human atrial myocytes. **Methods:** Using whole-cell patch technique, the PTK inhibitors genistein, tyrphostin A23 and A25 and their inactive analogs (daidzein and tyrphostin A63) on $I_{\text{vol}}$ were used to evaluate the roles of PTKs in regulation of $I_{\text{vol}}$ evoked by hyposmotic (0.6T) conditions in human atrial myocytes. **Results:** It was found that $I_{\text{vol}}$ was enhanced by the isoflavone genistein in a concentration-dependent manner ($EC_{50} = 22.4 \text{ mmol/l}$). $I_{\text{vol}}$ was increased by 122 ± 10.6% with 100 μmol/l genistein. In contrast, tyrphostin A23 (100 μM) and A25 (100 μM) significantly inhibited $I_{\text{vol}}$ by 38 ± 4.9% and 40.9 ± 3.4%, respectively. The corresponding inactive compounds daidzein and tyrphostin A63 had no significant effects on $I_{\text{vol}}$. In addition, the protein tyrosine phosphatase (PTP) inhibitor orthovanadate at 1 mmol/l inhibited $I_{\text{vol}}$ by 53.5 ± 4.5% ($IC_{50} = 249.6 \text{ μmol/l}$). Pretreatment with 1 mmol/l sodium orthovanadate significantly antagonized genistein-induced augmentation and A23- or A25-induced inhibition of $I_{\text{vol}}$. **Conclusion:** The results demonstrate the first information that 1) genistein enhances $I_{\text{vol}}$, thus genistein-sensitive PTKs may inhibit the activation $I_{\text{vol}}$ channels; whereas 2) tyrphostin A23 and A25 inhibit $I_{\text{vol}}$, and so tyrphostin-sensitive PTKs stimulate the activation of $I_{\text{vol}}$ channels; 3) orthovanadate suppresses $I_{\text{vol}}$ and prevents genistein- or tyrphostin-induced changes in $I_{\text{vol}}$. Therefore, the present study indicates that PTK-PTP system is involved in the modulation of $I_{\text{vol}}$ channel in human atrial myocytes.
Adrenergic Control of Nasal Venous Vasculature

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In the dog, sympathetic nerve stimulation decreases nasal blood flow and nasal airway resistance (Lung & Wang, 1989). A layer of highly vascular mucosa, comprising of sinusoidal venous plexuses (SM) lines the nasal cavity. Blood from the anterior nasal cavity is drained via the anterior collecting vein (ACV) and dorsal nasal vein (DNV) while blood from the posterior nasal cavity is drained via the lateral, septal and medial collecting veins (LCV, SCV and MCV) and sphenopalatine vein (SPV). The aim of this study is to investigate the adrenergic mechanisms of the nasal venous vasculature as to elucidate their role in controlling nasal airway resistance. In vitro isometric tension of the various vascular segments isolated from the dog nasal mucosa was measured.

Transmural nerve stimulation (TNS) was found to cause constriction in ACV, DNV and SM, primary constriction followed by secondary dilatation in LCV and SCV and dilatation in SPV. Tetrodotoxin (10⁻⁶ M) abolished all responses. Phentolamine (10⁻⁶ M), prazosin (10⁻⁶ M) and rauwolscine (10⁻² M) inhibited the constriction in all vessels. Propranolol (10⁻⁶ M), atenolol (10⁻⁶ M) and ICI 118,551 (10⁻⁵ M) inhibited the relaxation in SPV but not in LCV and SCV. Phenylephrine and clonidine constricted whereas dobutamine and terbutaline relaxed all vessels dose-dependently.

The results indicate that α₁-, α₂-, β₁- and β₂-adrenoceptors are present in both venous systems. TNS causes constriction of anterior venous system, venous sinuses and posterior collecting veins primarily via postjunctional α₁-adrenoceptors but relaxation of posterior outflow vein via postjunctional β₁- and β₂-adrenoceptors. The combined action of the two adrenergic mechanisms can reduce nasal airway resistance in vivo by decreasing vascular capacitance and enhancing venous outflow via the posterior venous system.

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Reference

Use of opioid as a cardioprotective agent

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Opioids have been well established to relate to analgesia, euphoria and sedation. The actions are mediated via the nervous system. Accumulating evidence has shown that endogenous opioid peptides and their receptors are present not only in the nervous system, but also in the peripheral tissues such as the heart. The observation suggests that endogenous opioids may act on the peripheral tissue, which is not mediated by the nervous system. In the past 20 years our laboratory has obtained evidence indicating that kappa-opioid receptors (κ-OR) in the heart plays an important role in the regulation and protection of the heart. We therefore conducted experiments in order to further determine the role and mechanisms of opioid as a cardioprotective agent. We studied the effects of morphine, a mu-opioid receptor (μ-OR) agonist for two reasons. First it is commonly used to kill pain and induce sedation in the treatment of myocardial infarct. Second, it has been shown to act on the heart via κ-OR. We performed two series of experiments. In the first we studied the cardioprotective effect of morphine in the rat in conditions, which mimic the conditions when a patient prepares for an operation. The rat is subjected to starvation and stress before the heart is subjected to ischemic insult. In the second series of experiment we studied the electrophysiological actions of morphine in human atrial tissue with the hope to delineate the mechanisms of the anti-arrhythmic action of the opioid. In the presentation results will be provided on the effects and mechanisms of action of morphine. (Supported by The Research Grant Council, Hong Kong and L.C.S.T (Holdings) Limited)