



Programmes

Over the past year, the Faculty has continued to focus on building up the fundamental strengths that underpin its research enterprise. A key initiative which was launched to capitalise on these fundamentals was the active promotion of programmatic research within the Faculty.

Currently, there are a total of 16 programmes registered with the Faculty. Below is a summary highlight of these 16 programmes.

Asthma and Allergy Research Programme

http://www.med.nus.edu.sg/progrsch/Allergy_and_Asthma_Research_Programme.htm

Research Theme: The development of diagnostic and immunotherapeutic reagents for the asthma and allergic diseases - with reference to allergens in the tropics.

Programme Members:

Assoc Prof Lee Bee Wah (Coordinator), Assoc Prof Chua Kaw Yan, Dr Chew Fook Tim, Dr Cheong Nge, Dr Wang De Yun, Dr Liew Lip Nyin, Dr Shek Pei Chi Lynette, Dr Goh Yam Thiam Daniel.

Programme Activities:

Dust mite allergens

Cloning of *Blomia tropicalis* (B t) mite allergens. Two methods are used simultaneously for this project. One deals with the screening of the *Blomia tropicalis* Uni-ZAP cDNA library by plaque immunoassay method and the other using the SMART RACE cDNA amplification Kit. We had isolated cDNA encoding for ten allergens. These cDNA are being expressed as recombinant allergens and their allergenicity is being evaluated. Catalogue of expressed sequence tags from the allergen producing dust mites, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* and *Blomia tropicalis*. Mass excision and pilot expressed sequence tagging (EST) of the *Blomia tropicalis* and *Dermatophagoides farinae* libraries has been carried out and 3500 EST has been achieved. In addition, cDNA microarray for *Blomia tropicalis* and *Dermatophagoides farinae* have been prepared.

Immunopathogenesis of allergic disease

Research work was focused on the establishment of a mouse model for atopic dermatitis and allergic asthma by epicutaneous sensitisation with dust mite allergen. Epicutaneous allergen patching resulted in localized dermatitis characterized by epidermal hyperplasia and spongiosis, which was associated with infiltration of eosinophil, neutrophils, degranulated mast cells, CD8+ dendritic cells, and CD4+ and CD8+ T cells. Th2-polarised allergen-specific T cells were detected in skin and spleen indicating local and systemic allergen sensitisation. Allergen-specific serum IgE and IgG1 were also detected. Allergen challenge induced airway inflammation, coupled with bronchial hyperresponsiveness on methacholine challenge. This disease model closely resembles the human allergic diseases.

DNA vaccines for allergic diseases

Preclinical studies to evaluate had been performed for a number of major mite allergens. New plasmid vectors had been tested for increased vaccine efficacy. A collaboration was set up with the Bioengineering group of Johns Hopkins Singapore to develop novel gene delivery system to improve vaccine efficacy. Animal models for asthma and atopic dermatitis with recombinant allergens have been established and used for vaccine evaluation.

Tropical spore allergens

The cDNAs encoding several allergenic components from *Elaeis guineensis* have been isolated and characterised. In addition, we had developed a software program for image capture and rapid quantification of biometric parameters of spores and pollen and a pilot validation study is currently on-going.

Genetic of asthma and allergies

Using polymorphic genetic markers, our work on 88 families with asthma and allergies has shown that specific genes located in the chromosome 5q31-33 region influence the susceptibility to asthma and atopy in our population. We are currently evaluating genetic polymorphisms in the promoter or other non-coding regions of linked candidate genes to determine their role in conferring susceptibility to the asthma/atopy phenotype.

Gerontology Research Programme (GRP) http://www.med.nus.edu.sg/progrsch/Gerontology_Research_Programme.htm

The Gerontology Research Programme (GRP) in the Faculty of Medicine grew from the work of a small group of doctors who conducted a study on depression and dementia in the 1990s.

In 1998, a team of medical and related professional groups interested in the elderly, namely, dental surgeon, dietician, physiotherapist, psychologist, epidemiologist, architect and economist met and discussed and a GRP was formally registered in February 1999 with the Faculty of Medicine.

It is one of two programmes in NUS on research on the elderly, the other is in the Faculty of Arts and Social Sciences.

Research Theme:

The GRP has 5 objectives:

- Basic research on ageing
- Applied research in geriatric medicine
- Development of treatment strategies
- Promotion of policies on care, services and education of the elderly; and
- Identification of problems and opportunities in the elderly

Programme Members:

Assoc Prof Goh Lee Gan (Coordinator), Prof Kua Ee Heok, Dr Calvin Fones, Ms Jasmine Lam.

The members in partnership in the longitudinal study of the elderly are:

Prof Kua Ee Hock, Assoc Prof Das De, Assoc Prof Tan Chay Hoon, Assoc Prof Goh Lee Gan, Dr Calvin Fones, Dr Hillary Thean, Assoc Prof Jim Harrison, Mr Kenneth Parker.

Helicobacter pylori http://www.med.nus.edu.sg/progrsch/HELICOBACTER_PYLORI1.htm

Research Theme: To identify molecular mechanisms of pathogenesis and improve treatment.

Programme Members:

Assoc Prof Yeoh Khay Guan (Coordinator), Assoc Prof Ho Bow, Assoc Prof Lim Seng Gee, Assoc Prof Gwee Kok Ann, Assoc Prof Quak Seng Hock, Assoc Prof Teh Ming, Assoc Prof Ho Khek Yu.

Programme Activities:

The NUS Helicobacter pylori Research Programme is a multi-disciplinary programme which coordinates research work in the medical faculty on the gastric pathogen Helicobacter pylori which is the most important cause of gastroduodenal diseases, including peptic ulcer disease and gastric cancer.

Key findings have been:

1. Challenging the widely held tenet that putative virulence genes (eg cagA) are associated with bacterial pathogenicity and disease, our genotyping studies showed that these bacterial genes are in fact equally prevalent in Asia patients with or without disease.
2. Molecular mimicry in the form of shared antigens such as Lewis blood group antigens may favour selective persistence and disease in susceptible hosts.
3. Dimorphism of H pylori and evidence that the latent coccoid stage may be a dormant phase to survive unfavourable environments, yet viable and with the potential to transform to the active spiral form. This is thought to have implications in bacterial transmission and possibly recrudescence of infection after antibiotic treatment.
4. Our clinical treatment studies showed that a low dose combination triple therapy overcame metronidazole resistance and is now a standard cost-effective treatment used locally.

Research Theme: Intestinal lactic acid bacteria as probiotics and vectors for gene therapy.

Programme Members:

Assoc Prof Lee Yuan Kun (Coordinator), Assoc Prof Bay Boon Huat, Prof Chan Soh Ha, Dr Christopher Cheng, Dr Hu Huai Zhong, Dr Ratha Mahendran, Dr Lim Chor Kiang, Dr Ooi Eng Eong, Assoc Prof Poh Chit Laa, Dr Song Keang Peng, Assoc Prof Tan Hai Meng.

Programme Activities:

A grant entitled "Lactic acid bacteria as animal probiotics" was awarded (Investigators: Assoc Prof Lee Y K and Assoc Prof Tan H M).

Five Honours year Microbiology science students (Ms Lim BK, Ms Low YL, Mr NBA Rahim, Seow SW, Lai OL) and two postgraduate students (Ms Chen H, Ms Puong KY) are involved in the programme.

The NUS Research Programme has linked up with the Functional Foods Development Centre at the University of Turku, Finland.

Research Theme: Basic and clinical investigations of leukocyte function.

Programme Members:

Assoc Prof Lee Szu Hee (Coordinator), Dr Lu Jinhua, Dr Hu Huaizhong, Dr Loh Foo Hoe, Dr Lim Sai Kiang, Dr Gan Yunn Hwen.

Programme Activities:

Members of the group have diverse research interests in leukocyte biology. These include the role of integrins in monocyte/macrophage adhesion, migration and activation, T cell homing in murine acute graft versus host disease, IL-12 and IL-18 expression and regulation, clonality analysis using X-linked polymorphisms, analysis of apoptosis and DNA ploidy, effects of peritoneal macrophages in endometriosis and the role of haptoglobin in haemolysis, inflammation and atherosclerosis, use of mycobacteria bovis hsp65 as adjuvant and/or chaperone to enhance tumour antigen presentation by macrophages/dendritic cells. There is much active collaboration between members of the group, which held eight programme seminars last year.

Introduction

The Medical Informatics Programme (MIP) was jointly funded by the National Science and Technology Board and the Ministry of Education in September 1996 to focus on upstream basic research into the tools and techniques that will enhance the understanding, communication and management of information in medical practice, education and research.

Aims of the MIP:

- To undertake upstream basic research in medical informatics
- To lead midstream projects by forming strategic partnerships with the healthcare and IT industries
- To build a critical mass of medical informatics to meet long-term research goals and to effect technology transfer to the health sector of Singapore
- To provide the leadership role for consensus building in matters relating to medical informatics technology and policy in Singapore

Health Information Systems Group (Assoc Prof Kenneth Ong, E-mail: eleongk@nus.edu.sg)

This research group's focus is on developing systems that help in collecting, retrieving, organising and analysing patient data and medical knowledge.

Aims:

- Advanced techniques in human-computer interface
- Rapid-prototyping methods for medical expert systems
- Intelligent generation and management of electronic medical records

Clinical Decision Systems Group (Assoc Prof Leong Tze Yun, E-mail: leongty@comp.nus.edu.sg)

This research group's focus is on developing tools and techniques for supporting complex medical decisions. Relevant information from distributed sources is integrated to provide decision recommendations in a timely manner.

Aims:

To provide a comprehensive medical decision making framework that includes:

- An expressive language for effective specification of decision factors and objectives
- Methodologies for automated acquisition of decision information from human experts and on-line databases
- Techniques for reasoning with complex decisions under resource constraints

Medical Education Systems Group (Assoc Prof K C Lun, E-mail: kclun@nus.edu.sg)

This research group's focus is on developing new paradigms and tools for learning and knowledge acquisition as well as to promote and hone clinical problem-solving skills for better patient management.

Aims:

- Develop techniques and systems that teach general problem-solving skills and strategies to support the training of medical students and the continuing education of practising physicians
- Research into new strategies for the search, acquisition and delivery of electronic medical information across wide-areas networks
- Investigate the use of desk-top virtual reality systems in the development of knowledge and psychomotor skills in medical student training

Medical Networking, Applications Development & Integration Framework (Assoc Prof Pung Hung Keng, E-mail: punghk@comp.nus)

This research group's focus is on investigating networking issues pertaining to the development and integration of next-generation Medical Informatics applications systems on high-speed communication networks.

Aims:

- Establish a high-speed backbone network domain testbed-The Medical Informatics Network Testbed (MINT)
- Rapid prototyping in developing health care and medical applications of collaborative and mission/time critical nature
- Implement a prototype of advanced image interpretation system on the network

Technopreneurship

The MIP, currently in its 4th year is targeting project deliverables for commercialization which is in line with the government's drive to encourage technopreneurship. Presently, the MIP has one spin-off company and another is being actively explored. Several of its research products are also ready for commercialization.

Neurodegeneration

<http://www.med.nus.edu.sg/progrsch/Neurodegeneration.htm>

Research Theme: To study factors which contribute to, or modulate, degeneration in the nervous system.

Programme Members:

Assoc Prof Ong Wei Yi (Coordinator), Prof Barry Halliwell, Assoc Prof Benjamin Ong, Assoc Prof Lim Tit Meng, Dr Henry Yu, Assoc Prof Sheu Fwu-Shan, Dr Anthony Liou, Assoc Prof Marcelo Ang.

Programme Activity:

Collaborative projects carried out between members of the research group, resulting in several published papers and papers in press.

Neuropsychopharmacology

<http://www.med.nus.edu.sg/progrsch/Neuropsychopharmacology.htm>

Research Theme: The pharmacology of drugs that may exert neural, psychological and behavioural changes in animals and human.

Programme Members:

Assoc Prof Tan Chay Hoon (Coordinator), Assoc Prof Ong WY, Dr Ng YK, Dr Ho KH, Assoc Prof Lee HS, Assoc Prof P Wong, Dr Zhu YZ, Prof Kua EH, Dr C Fones and Dr B Yeo, Assoc Prof Lim TM, Dr P Lee, Dr Chong SA, Dr Ratha Mahendran and Dr A Chan.

Programme Activities:

Meetings: There were 14 formal and informal meetings with various programme members to discuss collaboration. New members from Neurology Department, NUH put up their proposals in the area of electro-physiology and repetitive Transcranial magnetic stimulation.

- Assoc Prof Ong from Dept of Anatomy collaborated with Assoc Prof Lim from the Biological Sciences
- Assoc Prof Tan from Dept of Pharmacology, Prof Kua, and Dr B Yeo from the Dept of Psychological Medicine and Dr Tan EC from IMCB completed the study on Genotype of Chinese Heroin Dependence and published a paper in Molecular Psychiatry. Collaboration with Malaysia and Thailand researchers on different ethnic groups is being proposed
- Dr C Fones from Dept of Psychological Medicine and the team members including Assoc Prof Tan had completed the prospective randomized multi-centre double clinical trial on Illoperidone in Schizophrenic patients

- Dr Chong SA, Angie Chan and Rathi Mahendran from Institute of Mental Health, Assoc Prof Tan and Dr Tan EC from IMCB had completed 2 clinical studies on Genotype of Unipolar depression and schizophrenia
- Dr Zhu, Assoc Prof Wong and Assoc Prof Lee HS from Dept of Pharmacology have collaboration with the Defence Medical Research Institute (DMRI) on neuroscience project. New research grant was funded
- Assoc Prof Ong from Dept of Anatomy and Assoc Prof Tan are studying the effects of some drugs on the cytosolic calcium response in hippocampal neurons

Nitric Oxide (NO) Study Group [http://www.med.nus.edu.sg/progrsch/Nitric_Oxide_\(NO\)_Study_Group.htm](http://www.med.nus.edu.sg/progrsch/Nitric_Oxide_(NO)_Study_Group.htm)

Research Theme: Distribution, functions and biochemistry of NO.

Programme Members:

Prof Leong Seng Kee (Coordinator), Assoc Prof Adaikan P Ganesan, Assoc Prof Wong Chong Thim, Assoc Prof Yeoh Khang Guan, Assoc Prof Lim Tit Meng, Assoc Prof Lee Kang Hoe, Prof Ong Choon Nam, Assoc Prof Kaur Charanjit, Prof Barry Halliwell, Dr Lee Hui-Hoa, Psyche, Dr Ng Yee Kong, Assoc Prof Ong Wei Yi, Dr Shabbir M Moochhala, Dr Liu Haiping, Assoc Prof Yeo Jinn Fei, Prof Ang How Ghee, Dr Ruan Runsheng, Assoc Prof Khoo Hoon Eng, Dr Cheah Li Sam, Assoc Prof Samuel Tay, Dr Li Shengnan, Assoc Prof P.T.-H. Wong, Prof Robert Pho, Assoc Prof Wong Hee Kit, Dr He Xiao Hua.

Programme Activities:

A total of 6 seminars were conducted in 1999 as part of this programme. 3 given by members of the Study Group (Ang How Ghee, Leong Seng Kee and Ruan Runsheng), 2 given by Professor Forstermann, a distinguished visitor from Germany passing by Singapore, and 1 large scale seminar in which 3 international speakers (Bredt D, Chiueh C.C. and Kalyanaraman B) and 3 locals (Barry Halliwell, Leong Seng Kee, and Shabbir M Moochhala) took the plenary sessions and 7 other locals gave the symposium lectures. There were also 6 free paper presentations and 11 poster presentations.

Oxidants and Antioxidants Research Group http://www.med.nus.edu.sg/progrsch/Oxidants_and_Antioxidants_Research_Group.htm

Research Theme: To study the molecular and cellular biology of the action of oxidants and antioxidants and their role in human disease and nutrition. The Oxidants/Antioxidants programme also liaised with the Nitric Oxide Group and Neurodegeneration programme, since nitric oxide is a free radical, and free radicals are involved in neurodegeneration.

Programme Members:

Prof Barry Halliwell (Coordinator), Prof Ong Choon Nam, Prof Frank Watt, Dr Marie-Veronique Clement, Assoc Prof Shazib Pervaiz, Dr Lim Sai Kiang, Assoc Prof Kenneth Hughes, Dr Robert Yang Hongyuan, Assoc Prof Benny Tan Kwong Huat, Assoc Prof Ong Wei Yi, Assoc Prof Nikolai Kocherginsky, Dr Matthew Whiteman, Dr Shen Han-Ming.

Programme Activities:

The programme has developed rapidly into a powerful interdisciplinary research grouping. For example, Prof Ong Choon Nam, Ong Wei Yi, Halliwell and Dr Lim Sai Kiang are collaborating to study the histochemistry, biochemistry and changes in gene expression in transgenic animals lacking selected antioxidant defences, such as haptoglobin. Prof Watt, Halliwell and Tan are using nuclear microscopy to research the role of iron in atherosclerosis. Prof Tan and Halliwell are studying oxidative stress in diabetes. Dr Yang is providing molecular biology expertise to Prof Ong Wei Yi in the field of excitotoxic neurodegeneration and also in a project in Prof Halliwell's group examining why defects in the sulphite oxidase gene cause massive neurodegeneration and early death in humans. Prof Ong Choon Nam, Whiteman and Halliwell are collaborating on developing techniques for measuring oxidative DNA damage and applying them to human tissues, as well as to the transgenic mouse tissues provided by Dr Lim Sai Kiang. Drs Clement and Pervaiz have developed new concepts about the role of free radicals in causing apoptosis in malignant cells, and are working with Prof Halliwell to study apoptosis induced by antioxidants. Prof Ong Wei Yi and Halliwell are continuing neuroanatomical, histochemical and biochemical approaches to dissect out the role of free radicals in neurodegenerative diseases using rodent models, and it is planned to extend this to the transgenic animals provided by Dr Lim Sai Kiang.

The group hosted several seminars by visiting scientists during the year. In particular 2 seminars were given by Prof GN Wogan, a distinguished visitor from MIT (based in COFM with Prof Ong Choon Nam). The group is playing a major part in organizing and presenting papers at the UNESCO meeting "Micronutrients and Health", to be held in July 2000. All members of the programme gave invited seminars overseas during 1999. The group also held extensive discussions with Prof B Kalyanaraman when he visited Singapore for the NUS Nitride Oxide Symposium.

Programme In Environmental Microbiology http://www.med.nus.edu.sg/progrsch/Programme_in_Environmental_Microbiology.htm

Research Theme: Biochemistry & Molecular Biology of Environmental Microorganisms.

Programme Members:

Assoc Prof Poh Chit Laa (Coordinator), Assoc Prof Khoo Hoon Eng, Dr Theresa Tan May Chin, Dr Karina Gin, Dr Gamini Kumarasinghe, Dr Paul Thambiyah, Dr Antonius Suwanto.

Programme Activities:

- Collaboration between members of the Research Programme on topics of mutual interest
- Collaboration involving co-supervision of postgraduate students
- Collaboration focused on research speciality areas of members
- Seminars and regular exchange of research information and bacterial strains

Programme In Infectious Diseases (PID) http://www.med.nus.edu.sg/progrsch/Programme_in_Infectious_Diseases.htm

Research Theme: Molecular strategies for the diagnosis, epidemiology and prevention of infectious diseases.

Programme Members:

Assoc Prof Vincent T K Chow (Coordinator), Prof Chan Soh Ha, Assoc Prof Poh Chit Laa, Assoc Prof Mary Ng Mah Lee, Dr Song Keang Peng, Dr Hu Huai Zhong, Dr Mark Taylor, Dr Kevin Tan, Dr Ooi Eng Eong, Dr Chao-Koh Woon Puay.

Programme Activities:

Since its official registration in February 1999, a number of joint projects have been initiated and are progressing well. More than 40 geographically- and temporally-separated strains of enterovirus type 71 (EV71) causing hand-foot-mouth disease ranging to encephalitis, have been characterized by RT-PCR, nucleotide, amino acid sequence and phylogenetic analyses. These data revealed two new EV71 genogroups designated D and E. Furthermore, these results facilitate the identification and cloning of suitable targets for EV71 DNA vaccine candidates.

Another joint project is the development of DNA vaccines against dengue. Work is on-going to clone DNA constructs containing structural and non-structural genes of dengue viruses. Experiments are also being conducted to analyze and develop immunological assays to monitor host immune responses to dengue infections and vaccines. Collaborating partners include Johns Hopkins Singapore and Defence Medical Research Institute. A novel human papillomavirus (HPV) type, HLT7474-S, has been isolated, whose complete nucleotide sequence, genomic organization and phylogeny indicate its close relationship with the A7 group of genital HPVs that confer high risk of genital carcinogenesis. Other projects include cloning of the elongation factor Tu gene of *Bartonella henselae*; the seroepidemiology of *Chlamydia pneumoniae* infections in Singapore (in conjunction with the Ministry of Health and the NUS Department of Community, Occupational and Family Medicine); PCR detection and sequence analysis of *Burkholderia pseudomallei* in clinical specimens (together with the Departments of Medicine and Pharmacology), and apoptosis in Blastocysts.

Tissue Engineering in Orthopaedic Surgery http://www.med.nus.edu.sg/progrsch/Tissue_Engineering.htm

Research Theme: Musculoskeletal tissue regeneration and repairs.

Programme Members:

Prof E H Lee (Coordinator), Assoc Prof James Goh, Prof K Satkunanatham, Assoc Prof S DasDe, Prof Casey Chan, Assoc Prof H K Wong, Dr James Hui, Dr Suresh Nathan, Assoc Prof Teoh Swee Hin, Assoc Prof SL Toh, Assoc Prof TE Tay.

Programme Activities:

The core capabilities developed are as follows:

Isolation and Culture of Mesenchymal Stem Cells

We have successfully isolated mesenchymal stem cells from several sources. Immunohistochemistry has been performed to confirm the mesenchyme lineage of the isolated cells. There is tremendous potential application of the MS cells in the repair and regeneration of damaged cartilage, bone, muscles as well as ligament.

Functional Tissue Mechanics

We have set up a facility for the objective evaluation of regenerated and repaired tissues and more importantly for in-vitro engineered tissues. Furthermore, in conjunction with the NUS Dept of Mechanical Engineering, theoretical models using computational bioengineering techniques to predict loading stresses have been developed.

Human Clinical Trial

We have developed a protocol for a human clinical trial on repair and regeneration of articular cartilage in the knee joint. There are 4 main stages in carrying out the study, ie patient selection and consent, preparation of mesenchymal stem cells, transplantation of autologous MSCs and assessment of clinical results.

Several projects are currently on-going in the Dept of Orthopaedic Surgery. One of the project aims to determine the best source of mesenchymal stem cells and to study the effects of mesenchymal stem cells on the repair and regeneration of physcal and articular cartilage defects with and without the use of chondroinductive agents such as glucocorticoids, members of TGF-B superfamily and component of collagen extracellular matrix. In collaboration with the Laboratory of Biomedical Engineering, we are working to develop a bioresorbable scaffold specifically designed for articular bone/cartilage tissue substitutes. The objective of this project to develop a cell culture system that allows the tissue engineering of cartilage attached to subchondral bone. We are also working on the development of a tissue-engineered ligament. An important consideration is to induce fibroblast formation with the cell aligned longitudinally. In addition, the group is designing and developing an apparatus to provide cyclic tensile stimulus to enhance orientation of the cells and collagen fibers for engineering ligaments. We are also working on the development of a spinal implant for fusion based on a bioabsorbable material seeded with osteoblasts or mesenchymal stem cells and loaded with bone growth factor.

Transcription Factors In Human Health and Diseases

http://www.med.nus.edu.sg/progrsch/Transcription_Factors_in_Human_Health_and_Disease.htm

Research Theme: To apply the expertise of core group members to the study of transcription factors and their associated co-factors that regulate tissue-specific gene expression.

Programme Members:

Assoc Prof Yong Eu Leong (Coordinator), Dr Stephen Hsu I Hong, Dr Wang Nai-Dy, Dr Lim Sai Kiang, Dr Lu Jinhua.

Programme Activities:

Since its inception in 1998, the programme has played a crucial role in gelling researchers in the transcription factor fields in the faculty together. One of the most important effects is the cross-collaborations and synergies obtained because of the different expertise and competencies of the members of the programme.

- Dr Hsu and Yong have produced a collaborative work on regulation of the prostate specific antigen (PSA) promoter, which may have important implications for the mechanism of acquired resistance of prostate cancer to anti-androgen therapy
- Dr Lim KS and Yong are collaborating on a project to characterize estrogen receptor subtypes in uterine fibroids. This project has resulted in a poster presentation at the 3rd ASM of NUS-NUH
- Dr Lu and Yong are using the yeast two-hybrid system to identify novel interacting proteins important in prostate cancer. Several novel proteins have been pulled out and they are now been characterized
- Dr Hsu and Lu are characterizing novel transcription factors identified in screening for integrins

These cross-collaborations has translated into many publications in prestigious journals, numerous awards won, and a new website. Regular seminars have been organized. The fruits of the programme can only increase in the future with more funding and administrative support.

Tumour Biology and Proteomics

http://www.med.nus.edu.sg/progrsch/Tumour_Biology_and_Proteomics.htm

Research Theme: Focus on Hepatocellular Carcinoma, Hepatitis B virus, Hepatitis C virus, Nasopharyngeal carcinoma, Epstein Barr virus.

Programme Members:

Assoc Prof Ren Ee Chee (Coordinator), Prof Chan Soh Ha, Assoc Prof Maxey Chung, Assoc Prof Leow Chon Kar, Dr Caroline Lee.

Programme Activities:

1. Identification of a specific mutation at nt1752 of the hepatitis B virus which is correlated with high levels of serum HBV DNA in chronic carriers. As this nucleotide falls within the enhancer II region of the viral genome, we cloned a 131 bp fragment of the enhancer into a luciferase-promoter vector to determine function. The results showed that having an "A" at nt1752 had high activity while having a "C", "G" or "T" substituted by site-directed mutagenesis, showed a 50% reduction in activity. This clearly demonstrates the effect of a single base change in a location of the enhancer that is crucial for its function.

We have also found that the nt1752A variant is preferentially associated with HCC cell lines. Our lab's effort is focused currently on sequencing 200 paired HCC tumour and non-tumour samples obtained from Assoc Prof CK Leow. In order to determine the HBV strain that has integrated into the HCC genome. It is possible that the nt1752A variant elicits chronic inflammation to the host liver due to its efficient replication, leading to increased risk of cirrhosis mediated by immune damage. Together with the availability of higher levels of HBx within these hepatocytes, the combined factors result in driving the liver towards development of HCC.

2. The proteomics effort headed by Assoc Prof Maxey Chung looks at the proteome of HCC cells lines and tumour tissue resected from HCC patients. So far more than 1000 individual proteins have been identified in the 2D gel analysis, followed by tryptic digest analysis, MALDI-TOF and

bioinformatics searches. Of these protein 2 were of particular interest given that they are altered significantly in the HCC state vs non-tumour. The first is called P-151 and the second P-242. Antibodies to recombinant P-151 have been produced and when applied to stain HCC cells by immunofluorescence, the protein was found to be localised in the cytoplasm.

3. In the area of NPC, we have cloned 2 subfragments of the BRLF-1 gene of the EBV for use as an early diagnostic marker of the disease. Antibodies to these 2 protein fragments are found in high titers in the sera of NPC patients. This test is far superior to the existing "gold standard" of immunofluorescence testing of IgA-EA and Ig-VCA.

An ELISA test kit was produced using recombinant proteins from the C terminal of the BRLF gene. 39/47 NPC patients sera tested were shown to be positive for IgG to these proteins. 6/47 normal sera were also positive, with 2 sera showing relatively high levels. We are currently screening 700 NPC sera and also improving on the ELISA to reduce background even further. The next step is to get this test kit into a multi-centre evaluation and then turning into a commercial product.

Venom and Toxin Research Programme (VTRP) http://www.med.nus.edu.sg/progrsch/Venom_and_Toxin_Research_Programme.htm

Research Theme: From Venoms to Drugs, From Toxins to Therapeutics.

Programme Members:

Prof P Gopalakrishnakone (Coordinator), Prof Matthew CE Gwee, Assoc Prof HE Khoo, Assoc Prof CH Tan, Assoc Prof K Jeyaseelan, Assoc Prof Maxey Chung, Assoc Prof Mulkit Singh, Dr Kerwin Low, Dr M M Thwin, Dr Z E Emmanuel, Mr Shang Hui Shen, Dr A Armugam.

Programme Activities:

Purification, biochemical and pharmacological characterization as well as molecular aspects of research involving cloning, sequencing and expression of new toxins are actively being done by the academic staff with the help of research fellows, research assistants and postgraduate students. A range of novel toxins from different species of scorpions, spiders and cone shells have been isolated, purified, sequenced and the synthetic toxins being screened for novel biological activities. Several channel toxins, specific for sodium, potassium or calcium channels, have been extensively studied with respect to their structure, mode of action, and localization of the functional site. On detection of toxins, the working prototype on ISFET has been established, miniaturized and packaged. Solid phase Micro Extraction (SPME) techniques are also being established and used to detect marine toxins in collaboration with the Defence Science Organization. Crystallographic studies are in progress on stonustoxin and phospholipase A2 toxins from an Australian Elapid. A novel antitoxic and anti-inflammatory protein has been discovered from a non-venomous snake serum, which forms the basis for cloning studies, leading to production of a recombinant protein that is proven useful as a therapeutic agent for snake envenomation and inflammatory diseases. Further studies are in progress to develop this protein with therapeutic potential into a potent anti-inflammatory drug or as an investigative tool for structure-function studies.