香港藥物基因學網絡
HONG KONG Pharmacogenetics NETWORK

Hong Kong Pharmacogenetics Network
Inaugural Scientific Meeting

Personalised Medicine in Practice

3 March 2011

Kai Chong Tong, Postgraduate Education Centre
Prince of Wales Hospital, Shatin, Hong Kong

Organisers

Faculty of Medicine
The Chinese University of Hong Kong

Centre for Food and Drug Safety

Department of Clinical Oncology

Division of Clinical Pharmacology
Department of Medicine and Therapeutics

The School of Pharmacy

Faculty of Medicine
The University of Hong Kong

Division of Chemical Pathology
Department of Pathology

Division of Clinical Pharmacology
and Therapeutics
Department of Medicine

Hospital Authority, Hong Kong

Chemical Pathology Laboratory
Department of Pathology
Princess Margaret Hospital

Medication Safety Committee

Department of Health
The Government of the Hong Kong SAR

Supported by

Chinese Pharmacogenomics Network

Programme Book

Welcome message from the Secretary for Food and Health

I wish to congratulate the colleagues from both medical schools in Hong Kong, the Hospital Authority and the Department of Health for their joint efforts in establishing the Hong Kong Pharmacogenetics Network (HKPGN). The Network is expected to promote collaboration in translational research, staff training and clinical practice in the fields of pharmacogenetics, pharmacogenomics and personalised medicine.

As we all know, patients can have highly variable responses to medicines, both beneficial and adverse. Serious adverse reactions to drugs remain an important clinical issue, while lack of response to drugs leads to delay in patients receiving appropriate treatment and inefficient use of health care resources. Drug responsiveness and toxicity are affected by genetic variation. Knowledge of the genetic determinants of patients' responses can help improve the safety and efficacy of drugs. Personalised medicine is the tailoring of drug treatments to individual patients based on the likelihood to show beneficial responses and their risks of adverse events. The coordinated efforts of HKPGN should advance our knowledge and help promote the concept of personalised medicine in Hong Kong.

The Inaugural Scientific Meeting of the HKPGN covers important topics in pharmacogenetics, pharmacogenomics and personalised medicine. It provides good examples of how drug therapies can be tailored to the needs of individual patients by maximising their efficacy and reducing the risk of toxicity. I would encourage all health care professionals to participate in this Meeting.

I wish the Meeting every success.

Dr. York Y.N. Chow, GBS, JP
Secretary for Food and Health
The Government of the Hong Kong SAR

Welcome message from the Deputy Director of Health

Watson and Crick's discovery of DNA in 1953 paved the way for the development of genomic medicine. Then, the subsequent discovery of the oestrogen receptor in the 1960s and the introduction of the anti-oestrogen tamoxifen in the 1970s enabled a more individualised approach to the treatment of breast cancer patients. Testing for hormone receptor status has since become a stratification factor.

Indeed, we are now well in the stratified medicine period, leaving behind the blockbuster mode of medical practice and heading towards Langreth and Waldholz's era of personalised medicine.

Genomics hold such promise for public's health that all stakeholders ought to prepare ourselves so as to gain the most from this landmark scientific advance. The Hong Kong Pharmacogenetics Network has been formed in this spirit. Through it, colleagues in Hong Kong's public sector join hands to collaborate in the areas of genomic medicine service, training and research.

Let the Network's position be clearly known from the start. Genetic susceptibility is not health destiny. Genomics can and should be part of any plan to reduce disease and improve health and the Network is committed to this. We thank you for your favourable support and please enjoy our Inaugural Scientific Meeting!

Dr Gloria TAM
Deputy Director of Health
Hong Kong Special Administrative Region

Welcome message from the Organising Committee

On behalf of the Organising Committee and the Organisers, we would like to welcome you to the Inaugural Scientific Meeting of the Hong Kong Pharmacogenetics Network (HKPGN). The HKPGN is a collaboration of the Hong Kong centres with a clinical and research interest in pharmacogenetics, pharmacogenomics and personalised medicine. It is established by a group of clinicians, scientists and public health doctors to promote collaboration among centres in translational research, staff training and clinical practice, to increase the public awareness of the roles of pharmacogenetics, pharmacogenomics and personalised medicine and to provide strategic advice on the optimal use of medicines and drug developments using pharmacogenetics and pharmacogenomics approach. The implementation of genetic data for a better prediction of response to drugs and adverse drug reactions becomes a reality in many clinical fields. The HKPGN is a territory-wide effort to provide the health care system with useful tools and advice that can optimise the effectiveness of drug treatment in individual patients. The impact of personalised medicine is potentially enormous. The establishment of the HKPGN should help translate the research findings into clinical practice. The ultimate aim is to improve patient care and safety in relation to the use of medicines. We wish to thank the representatives from the two medical schools, Hospital Authority and Department of Health for their suggestions in the establishment of the HKPGN.

The HKPGN will organise an annual scientific meeting to provide the updates for health care professionals on pharmacogenetics, pharmacogenomics and personalised medicine. The meeting provides a platform for participants to meet the experts and exchange knowledge in these subject areas. The topics in the Inaugural Scientific Meeting well illustrate the clinical applications of pharmacogenetics and pharmacogenomics and personalised medicine should become a reality for many patients.

We wish to thank all the speakers, chair persons, participants and supporting units for their contributions to the success of this Meeting.

Prof. Thomas Y.K. Chan
Prof. Anthony T.C. Chan
Prof. Ching Wan Lam
Dr. Joseph Lui
Dr. Raymond S.M. Wong
Dr. Albert Y.W. Chan
Prof. Bernard M.Y. Cheung
Dr. Heston Kwong
Prof. Vincent H.L. Lee
Prof. Brian Tomlinson
Prof. Hong-Hao Zhou

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Hospital Authority, Hong Kong

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Medication Safety Committee

Department of Health, The Government of the Hong Kong SAR

Supporting Organisation

Chinese Pharmacogenomics Network

Organising Committee

Prof. Thomas Y.K. Chan (Co-Chairman)

Prof. Bernard M.Y. Cheung (Co-Chairman)

Prof. Anthony T.C. Chan

Prof. Ching Wan Lam

Dr. Joseph Lui

Dr. Raymond S.M. Wong

Dr. Albert Y.W. Chan (Secretary)

Dr. Heston Kwong

Prof. Vincent H.L. Lee

Prof. Brian Tomlinson

Prof. Hong-Hao Zhou

Keynote Speaker

Prof. Hong-Hao Zhou

Member of the Chinese Academy of Engineering

Chairman, Chinese Pharmacogenomics Network, and

Professor and Director

Pharmacogenetics Research Institute, Institute of Clinical Pharmacology

The Central South University, China

Local Speakers

Dr. Albert Y.W. Chan

Consultant Chemical Pathologist, Department of Pathology

Princess Margaret Hospital

Hospital Authority, Hong Kong

Prof. Bernard M.Y. Cheung

Clinical Professor, Division of Clinical Pharmacology and Therapeutics

Department of Medicine

Li Ka Shing Faculty of Medicine

The University of Hong Kong

Dr. Patrick K.L. Kwan

Associate Consultant, Department of Medicine and Therapeutics

Prince of Wales Hospital

Hospital Authority, Hong Kong

Prof. Ching Wan Lam

Clinical Professor, Division of Chemical Pathology

Department of Pathology

Li Ka Shing Faculty of Medicine

The University of Hong Kong

Prof. Brian Tomlinson

Professor of Medicine and Therapeutics, and

Head of Division of Clinical Pharmacology

Department of Medicine and Therapeutics

The Chinese University of Hong Kong

Prof. Winnie Yeo

Professor, Department of Clinical Oncology

Faculty of Medicine

The Chinese University of Hong Kong

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Programme

8:15 – 8:45 Registration

8:45 – 9:15 Opening Ceremony

Welcome Remarks

Prof. Thomas Y.K. Chan, JP
Coordinator, Hong Kong Pharmacogenetics Network

Opening Address

Dr. York Y.N. Chow, GBS, JP
Secretary for Food and Health
The Government of the Hong Kong SAR

Prof. Hong-Hao Zhou
Member of the Chinese Academy of Engineering
Chairman, Chinese Pharmacogenomics Network, and
Professor and Director
Pharmacogenetics Research Institute
Institute of Clinical Pharmacology
The Central South University, China

9:15 – 10:15 Plenary Lectures on Personalised Medicine

Chair Persons:

Prof. Brian Tomlinson

Prof. Bernard M.Y. Cheung

9:15 – 09:45 Personalised Medicine in China

Prof. Hong-Hao Zhou

09:45 – 10:15 **Making Cancer Treatment Safer and More Effective**

Prof. Winnie Yeo

10:15 – 10:30 ***Tea Break***

10:30 – 12:10 **USING PHARMACOGENETICS TO IMPROVE DRUG SAFETY AND EFFECTIVENESS**

Chair Persons:

Dr. Patrick C.K. Li

Dr. Joseph Lui

10:30 – 10:55 **Maximising the Efficacy and Safety of Statins Therapy**

Prof. Brian Tomlinson

10:55 – 11:15 **Pharmacogenetic Algorithms to Individualise Warfarin Dosing**

Prof. Bernard M.Y. Cheung

11:15 – 11:35 **Pharmacogenetics in Epilepsy Treatment**

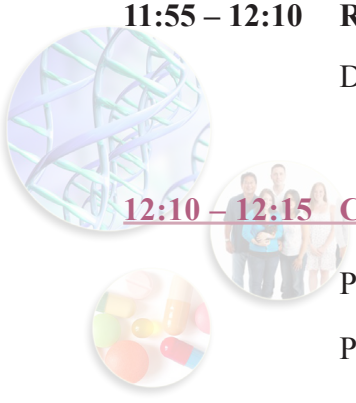
Dr. Patrick K.L. Kwan

11:35 – 11:55 **Personalised Medicine and Molecular Diagnostics**

Prof. Ching Wan Lam

11:55 – 12:10 **Role of Clinical Laboratory in Patient and Drug Safety**

Dr. Albert Y.W. Chan



12:10 – 12:15 **CLOSING REMARKS**

Prof. Brian Tomlinson

Prof. Bernard M.Y. Cheung

Personalised Medicine in China

Prof. Hong-Hao Zhou, The Central South University, China

The standard "trial and error"method for determining the choice of drug and dose of the drug has contributed to millions unsafely or ineffective drug prescriptions annually. One of the promises of pharmacogenetics is to personalize the delivery of medical treatment by providing safer and more effective therapies based on individual genetic polymorphisms in certain genes that ultimately determine how one might respond to a particular drug. Accordingly the pharmacogenics testing has drawn increasing attention by the promise of delivering individualized therapies and preventing adverse drug reactions. To translate pharmacogenetics knowledge to the treatment of patients, a Tailored Therapy Center was founded in October, 2004 at the Third Affiliated Hospital and Institute of Clinical Pharmacology, Central South University. Soon after, The Xiangya Medical Lab was established in September, 2010 for the major purpose of translating pharmacogenetics to personalized pharmacotherapy. The Center and the Lab are pioneering the use of patient tailored therapy and the use of state-of-the-art research facilities to perform advanced testing of a patient's genotype to determine which medications are effective against it, and what dosage levels are needed to treat it, and then devise a treatment regimen that is unique to each individual patient. Several thousands patients including cancer, hypertensive, organ translation patients were served through the Center and the Lab. To optimize the personalized medicine we need more clinical data, more outcome studies, drug labeling changes, more well- identified genetic testing products and well-trained personalized management personnel and teams.

Making Cancer Treatment Safer and More Effective

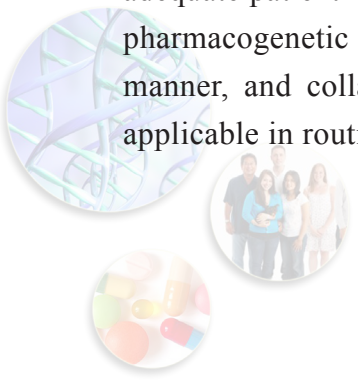
Prof. Winnie Yeo, The Chinese University of Hong Kong, Hong Kong

Oncological treatment commonly involves the use of conventional chemotherapeutic agents as well as targeted biological agents. Efficacy and toxicity of individual agents used are being affected by tumour biology as well as host response to treatment.

Treatment related toxicity is, in general, influenced by multiple genetic factors and non-genetic factors. The manifestations of adverse drug reactions differ between individuals. To add to the complexity of the situation, it is known that there exist inter-ethnic or population differences in toxicity and clinical outcome following treatment with anticancer drugs. Such variations have been shown to be clinically relevant in oncology practice. These differences arise from complex interactions involving varied distribution of genetic polymorphisms that affect DNA-repair enzymes, drug-metabolising enzymes, and cellular transporters of cytotoxic chemotherapy. These genetic variants are often single nucleotide polymorphisms (SNPs) and haplotypes (combinations of SNPs that are inherited together), which can be phenotypically associated with altered enzymatic activity and pharmacokinetics of anticancer drugs.

There is also inter-ethnic variability in the expression of drug targets and receptors that may predict the efficacy of a particular group of drugs. One of the best known examples of selecting patients for appropriate anti-cancer therapy would be that based on lung cancer model. It is now known that there is a high prevalence of epidermal growth factor receptor (*EGFR*) mutations in pulmonary adenocarcinoma in Asian patients (including China, Japan and Korea) who are non-smokers, which predict sensitivity to EGFR tyrosine kinase inhibitors.

Most data currently available have been based on retrospective studies and commonly lacks adequate patient number to establish confirmatory results. It is therefore pertinent to assess pharmacogenetic profiles in a specific ethnic or geographic population in a prospective manner, and collaborative effort is required to obtain meaningful results that could be applicable in routine clinical practice.



Maximising the Efficacy and Safety of Statins Therapy

Prof. Brian Tomlinson, The Chinese University of Hong Kong, Hong Kong

The HMG-CoA reductase inhibitors or statins are one of the most widely used groups of drugs and their benefits are supported by extensive evidence from large clinical trials showing they effectively reduce LDL cholesterol and cardiovascular events. They are generally very well tolerated and most side effects are mild and rapidly reversible on cessation of therapy. However, the adverse effect of muscle damage resulting in myalgia, myopathy or rhabdomyolysis is the most serious problem and this has resulted in the withdrawal from the market of one of these drugs, cerevastatin, and contributed to the withdrawal of mibefradil, which interacted with the statins to increase the risk of muscle damage. The exact cause of statin-induced muscle damage is not clear but it is usually associated with a high systemic exposure to the statin related to drug interactions or pharmacogenetic effects. The more lipophilic statins are subject to considerable metabolism by cytochrome P450 (CYP) enzymes, acting principally on the statin lactones and producing various active and inactive oxidative metabolites within both enterocytes and hepatocytes. The most common relevant CYP variant is probably in CYP3A5 and this has been shown to influence the pharmacokinetics of statins such as simvastatin, but its effects on safety and efficacy have been less consistent. Drug transporters may be more important than enzymes with the hydrophilic statins and the active acid forms of lipophilic statins. Most of the statins are substrates for the hepatic uptake transporter organic anion-transporting polypeptide 1B1 (OATP1B1, or SLCO1B1) and a single nucleotide polymorphism (SNP) in the gene for this transporter was the only significant genetic determinant of the risk for myopathy with high dose simvastatin in a genomewide association study. Efflux transporters such as multidrug resistance protein (MDR1, or ABCB1) and breast cancer resistance protein (BCRP, or ABCG2) appear to play an important role in the disposition and efficacy of some statins. A common polymorphism in the gene for the ABCG2 transporter is the most important genetic determinant discovered so far for the higher plasma concentrations of rosuvastatin in East Asian as compared to Caucasians. Subjects with the ABCG2 variant also show greater reductions in LDL cholesterol with rosuvastatin treatment. There are considerable differences between individuals in the reduction in LDL cholesterol with statin treatments. Part of this can be attributed to the degree of adherence to drug therapy and to variations in dietary intake but the variability appears to remain high even when these are controlled. This may be related to genetic differences in the lipid metabolism pathways or other factors influencing cardiovascular outcomes. The large clinical studies with statins suggest that despite aggressive treatment a substantial portion of cardiovascular risk persists. It remains to be proven whether this can be improved by personalised choice of the particular statin or dose to achieve the maximum reduction in LDL cholesterol or some other risk marker such as high-sensitivity C-reactive protein. It seems unlikely that statin treatment

can overcome all the cardiovascular risks related to dyslipidaemia and the addition of other lipid modifying drugs is likely to be necessary in certain cases. There is considerable potential for improving therapy to reduce cardiovascular risk by selecting the most appropriate drug and dose of the statin for individual patients or by using drug combinations in carefully selected individuals.

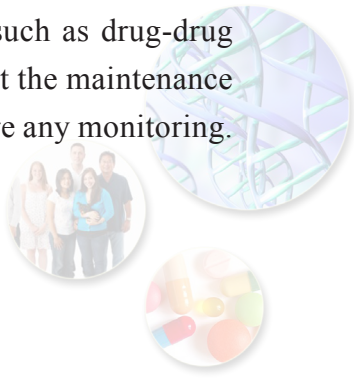
Pharmacogenetic Algorithms to Individualise Warfarin Dosing

Prof. Bernard M.Y. Cheung, The University of Hong Kong, Hong Kong

The oral anticoagulant warfarin is indicated for the prevention of thrombosis and embolism in patients who have atrial fibrillation, artificial heart valves, deep vein thrombosis or pulmonary embolism. Warfarin was historically a rat poison and so not surprisingly, it has to be used with great care in man. It has a narrow therapeutic index, meaning that the correct therapeutic dose is quite close to toxic dosages. Moreover, there is a several-fold variation in the maintenance dose among different individuals. Thus, warfarin is a drug that requires careful dose titration and frequent therapeutic monitoring of the international normalised ratio (INR).

Genetic studies in the last decade have shown that the INR response to warfarin is to a large extent determined by a few genes, including the genes that encode vitamin K epoxide reductase complex 1 (VKORC1) and CYP2C9, a key cytochrome P450 enzyme. Single nucleotide changes in these genes lead to an enhanced response to warfarin, and therefore lower doses are required to reach the target INR. These genetic polymorphisms can now be tested easily and have been shown to help determining the dose of warfarin required. Such algorithms usually incorporate information on age, weight and if possible, an estimated vitamin K intake. The utility of these algorithms depends on the prevalence of these genetic polymorphisms in the population. Clearly, if the minor allele is exceedingly rare, testing for it may not be very useful. In Chinese, variants in CYP2C9 that lead to increased INR are rare compared to Caucasians. In contrast, the vast majority of Chinese have a version of the VKORC1 gene associated with lower enzyme activity, making them more sensitive to warfarin. In one study in Hong Kong, genotyping the two polymorphisms mentioned helps to identify the 5% of patients who require very low doses and 7% of patients who require extra high doses of warfarin.

Enthusiasm for genetic testing to determine the dose of wafarin must be tempered by the fact that there are many non-genetic factors affecting warfarin dosage, such as drug-drug and drug-food interactions. Monitoring of the INR is still needed to adjust the maintenance dosage. Finally, there are now direct thrombin inhibitors that do not require any monitoring.



Pharmacogenetics in Epilepsy Treatment

Dr. Patrick K.L. Kwan, Prince of Wales Hospital, Hospital Authority, Hong Kong

Advances in genetic research over the past decade have led to the development of targeted diagnostics and therapeutics that leverage the knowledge of an individual's genetic makeup, promising a more personalised approach to healthcare. Through screening of genetic variations it is now possible to predict an individual's susceptibility to certain diseases as well as response to particular medications ("pharmacogenomics"), and match patients with the right medications given at the right doses. As such pharmacogenomics has the potential to eliminate the use of treatments that are destined to be ineffective or harmful for that individual, and to inform the choice of more efficacious and safer treatments, leading to improve health outcomes.

In antiepileptic drug (AED) pharmacogenomics, the greatest progress has been an improved definition of the role of HLA-related genes as predictors of serious cutaneous reactions. This has led to the recommendation that subjects of Asian ancestry be tested for the *HLA-B*1502* allele, in order to identify those at high risk of developing Stevens-Johnson syndrome and toxic epidermal necrolysis after administration of carbamazepine and, possibly, phenytoin and other AEDs. Progress in predicting seizure response, however, has been painstakingly slow. It has been suggested that one of the reasons for this is the heterogeneous definitions used by different groups in phenotyping drug response. Recognising pharmacogenomics as one of key research priorites/benchmarks, the International League Against Epilepsy has set up a special task force to faciliate research in this field with the aim of, among others, developing consensus definitions of drug response phenotypes. Further work is also needed to translate research findings to point-of-care testing as personalised medicine becomes increasingly consumer driven.

Personalised Medicine and Molecular Diagnostics

Prof. Ching Wan Lam, The University of Hong Kong, Hong Kong

Personalized Medicine and Molecular Diagnostics or Theranostics has been hailed as driving an impending revolution in medicine; indeed, the technology platforms and assay formats needed to provide patients and their physicians with better therapeutics using pharmacogenomic information have matured to the stage at which they can be utilized routinely. The combination of single nucleotide polymorphism (SNP) database and high-density SNP array allows the use of SNP as informative polymorphic markers for theranostics. These molecular diagnostic assays are expected to guide the therapeutic treatment of many diseases, by informing physicians about molecular subtypes of disease that require differential treatment, which drug has the greatest probability of effectively managing the disease, and which individual patients are at the highest risk of experiencing adverse reactions to a given drug therapy. Progress made in recent years suggests that pharmacogenomic biomarkers have the potential to provide physicians with clinically useful, actionable information that can improve patient care through increased individualization of treatment, particularly in the management of life-threatening disease.

Role of Clinical Laboratory in Patient and Drug Safety

Dr. Albert Y.W. Chan, Princess Margaret Hospital, Hospital Authority, Hong Kong

It is a global trend to move beyond poisoning / toxicity, to safety / efficacy and personalized medicine. However, in the drug safety loop in HK, there are weak links which will hamper the development and impact of the other efforts. In particular, the relative lack of development in laboratory services to support the monitoring of the safety and efficacy of therapeutic agents.

The role of Therapeutic Drug Monitoring (TDM) is recognized and service is routinely available in hospital laboratories. However, many important drugs are not provided for in HK. Invariably, these other drugs require the use of more sophisticated analytical platforms for analysis and appropriate logistics to render the service affordable and user-friendly. While the concept of TDM is simple, it may not be enough for all patients, for the efficacy and safety issues very much depend on the genetic makeup of individuals. The role and potential of pharmacogenetics / pharmacogenomics is therefore well recognized. However, development and general adaptation in the routine lab services has been slow and limited as only a very small number of PG tests is available in HK.

In order to realize the full benefit of therapeutics and personalized medicine, such bottle-necks should be removed. It seems logical therefore to establish one or more Patient & Drug Safety Labs in HK. The objectives and rationale will be deliberated in more details in the presentation.

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