Conference Scene

Report on the Pharmacogenomics and Personalized Medicine 2011 Conference: Part 1

Pharmacogenomics and Personalized Medicine 2011

Wellcome Trust Genome Campus, Cambridge, UK, 29 September–1 October 2011

The joint Wellcome Trust/Cold Spring Harbor Conference on pharmacogenomics and personalized medicine, held in the UK and USA in alternate years, focuses on the opportunities presented by the growing contribution of genomic information and technologies to interdisciplinary approaches in the study of variable human responses to therapeutic agents. This year's meeting provided in depth discussions on diverse fields that are driving forward the new era of personalized medicine including the use of next-generation sequencing technologies to identify common and rare variants determining response to drugs; the interface of pharmacogenomics and complex disease, including cancer; understanding and managing serious adverse drug reactions and public health pharmacogenetics. This year's meeting followed the UK Pharmacogenetics and Stratified Medicine Network 2011 meeting (Cambridge, UK), and marked the Conference's tenth anniversary. In the first of this two-part conference report, sessions on personalized medicines, public health pharmacogenetics and next-generation sequencing will be discussed.

'Rocky road' and 'tiger country' were just two of the phrases used to describe the current state of the field of pharmacogenomics at this year's Pharmacogenomics and Personalized Medicine conference, held on a sunny Hinxton Campus in Cambridge, UK. Over the 3-day long conference, attendees were warned about the Pandora's box nature of genetic information (following the recently announced FarGen project, which will see all 50,000 Faroe Islands citizens have their human genome sequenced) and cautioned not to "throw out the baby with the bath water" in an *ad hoc* debate on *CYP2D6* genotyping in tamoxifen-treated breast cancer patients between Hiltrud Brauch (Institute of Clinical Pharmacology, Germany) and Paul Pharoah (University of Cambridge, UK). As was forecast at the 2010 Cold Spring Harbor Conference (NY, USA), a shift towards the application of next-generation sequencing technologies in the field is evident and a significant number of pharmacogenetic association findings are still being identified by genome-wide association studies (GWAS).

The meeting brought together researchers, medical, regulatory and ethical experts in a range of disciplines to discuss the current issues facing the clinical implementation of pharmacogenomics, and to offer a look into the future advancements of technologies and the biostatistic and bioinformatic methodologies used to analyze arising complexity. The conference

also explored the potential of working together in new international and interdisciplinary research areas for the benefit of individual patients and highlighted the need to focus more efforts on understanding pharmacogenomic diversity in African populations.

Rocky road of pharmacogenomics: personalized medicines

We are now at a point where genome work has exploded for common complex diseases; the field is sat on a see-saw with sequencing costs significantly decreasing and throughput rapidly increasing. But how much further are we down the path of personalized medicine than we were a decade ago?

Following a welcome and introduction by one of the scientific organizing committee members, Munir Pirmohamed, University of Liverpool, UK, the first session (chaired by Deanna Kroetz, University of California, USA) was kicked off by Lon Cardon, GlaxoSmithKline, USA. Cardon was quick to point out that the translation of findings has been difficult and that progress in the field has not quite matched the enthusiasm and expectations that researchers had in the 1980s, when the future seemed so promising. With its large emphasis on drug discovery and development, Cardon crowned oncology as the poster child of personalized medicine, and the discovery of adverse-event loci as

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its equivalent in pharmacogenomics (highlighting specific examples as abacavir in HIV treatment, the antibiotic flucloxacillin, and lapatinib used in combination therapy for HER2-positive breast cancer). Offering a possible explanation as to why progress has not matched initial expectations, Cardon suggested that sequencing is being hampered, not by the sequencing technology, but the lack of large well-characterized samples that can be sequenced. Going forward, Cardon believes that electronic medical records should be combined with genetics so that disease taxonomy and etiology are re-evaluated and practical decisions on diagnosis and treatment decision can be made; furthermore, he highlighted the importance of the repurposing of existing medicines.

Cardon's opening talk was followed with a presentation by Stephane Bourgeois, Wellcome Trust Sanger Institute, UK, on the results of a genome-wide association meta-analysis of warfarin stable dose in Caucasians conducted by the International Warfarin Pharmacogenetics Consortium. This Consortium, which comprises over 20 research groups from around the world, is a multicenter initiative to develop an algorithm for estimating warfarin dose based on clinical and genetic data from a broad population base. The latest results point at a novel locus in the Factor 7 gene on chromosome 13 as influencing warfarin stable dose. Bourgeois confirmed that fine-mapping studies of this region are now required in order to identify a causal allele and mechanism. The question now is what percentage threshold of explained warfarin dose variance is needed for these findings to be translated into the clinic?

The next talk was given by Ron van Schaik, Erasmus University Medical Center, The Netherlands, who presented results suggesting that a new functional *CYP3A4* intron polymorphism significantly affects tacrolimus pharmacokinetics in kidney transplant recipients; to date, no published *CYP3A4* SNPs have been associated with tacrolimus pharmacokinetics.

Richard Weinshilboum, Mayo Clinic, USA, went on to discuss the topic of whether inheritance contributes to the variation observed in estradiol concentrations in postmenopausal women with early-stage

resected breast cancers. Presenting the results from a GWAS that revealed *TSPYL5* to have a genome-wide significant association with plasma estradiol concentrations, Weinshilboum stressed that we now need to move beyond replication and markers to functional validation, mechanistic insight and novel targets.

The second part of the personalized medicines session started with Leroy Hood, Institute for Systems Biology, USA posing the question of what is the biggest challenge facing biology in the 21st century? His answer: the need to deal with its incredible complexity. In his talk on systems biology, transformational technologies and the emergence of proactive P4 medicine, Hood explained the principles of systems biology: seeing biology as an informational science and taking a holistic rather than atomistic approach to biological complexity. Hood used the example of neurodegenerative (prion) disease and glioblastoma in mice as examples of current efforts at a systems approach to disease, stressing that blood is the fundamental organ that will distinguish health from disease.

Hood believes that this approach, together with emerging technologies and the development of powerful new computational and mathematical tools, will transform medicine over the next 5–20 years from its currently reactive state to a mode that is predictive, personalized, preventative and participatory (P4). Hood went on to explain the nature of P4 medicine and its societal implications for healthcare – essentially the patient becoming the center focus and driving many of the changes.

The session was completed by talks on optimizing response to thiopurine therapy by determining novel genetic markers (Paul Blaker, Guys and St Thomas' Hospital NHS Foundation Trust, UK) and an overview of the PharmGKB new-look website launched the week of the conference [101]. Using the example of clopidogrel, Ellen McDonagh, PharmGKB, Stanford University, USA, took the audience through the new features, including a clinical interpretations box on the homepage and an expanded very important pharmacogene summaries section, which provides succinct

pharmacogenetic-based overviews of the literature of important genes involved in drug response. This is an important online worldwide resource, which helps initiate dosing guidelines based on the impact on drug response, and is contributing to the drive towards personalized medicine for better therapeutics. A future focus of PharmGKB will be host consortia and incorporating natural language processing.

Push & pull forces of bench to bedside: public health pharmacogenetics

A new era of personalized medicine is on the horizon; however, to achieve this promise, the new discipline of public health genomics, which seeks to evaluate the use of emerging genomics information effectively and responsibly to improve the health of individuals and populations is essential. As detailed by Muin Khoury (CDC, USA), this will require an effort organized by society to protect, promote and restore the people's health and also to overcome the genomics evidence gap.

Rachel Tyndale, Centre for Addiction and Mental Health and University of Toronto, USA, opened her talk on the pharmacogenetics of smoking and cessation treatment with some startling figures: 400,000 people are still dying every year from smoking; 500,000,000 of everybody alive will die from smoking; and approximately 20% of the current adult population are smokers. A better understanding of the etiology of smoking behaviors and novel therapeutic approaches to improving smoking cessation outcomes are clearly needed. A heritable association has been found: considerable interindividual variation in CYP2A6 activity (the enzyme responsible for over 90% of the metabolic activation of nicotine to cotinine) has been attributed to variation in the *CYP2A6* gene – with a fast metabolizer genotype being linked to an increased number of cigarettes smoked per day. Large differences are also evident between ethnic populations in the frequency of slow metabolizers, which may contribute to the ethnic differences observed in rates of smoking and incidence of tobacco-related diseases. Tyndale anticipates that phenotyping or genotyping for *CYP2A6* could result in rationale

for improved and individualized smoking cessation treatments in the future.

From one major public health issue to the next, Andrew Somogyi, University of Adelaide, Australia, went on to discuss the association between immune genetic pathway markers and alcohol dependence. Over the past 6 years, the role of immunogenetics in alcohol reward and dependence has emerged, and the results of this recent retrospective case–control study demonstrated for the first time that in addition to *IL-1B* genotype, variability in the loci of multiple genes that control the central immune pathway response to alcohol, contributes to alcohol dependence (of which approximately 60% has already been found to be heritable). A prospective validation study is now needed to expand the cluster of immune genes and to see if glial activation attenuators decrease alcohol dependence.

The next presentation provided an update on the current status and future perspective of pharmacogenetics in African populations. Collet Dandara, University of Cape Town, South Africa, explained how the movement towards personalized medicine is gaining momentum in Africa, that the huge genetic diversity will ultimately help in understanding how much of a role genetic variation plays in treatment response. The results of phenotyping, genotyping and sequencing experiments were presented, highlighting that specific variants are distributed differently between African, and Caucasian and Asian populations. With HIV/AIDS affecting approximately 35 million individuals in sub-Saharan Africa, the association between certain CYP haplotypes and efavirenz plasma levels in HIV/AIDS patients will be a major focus in the future. This was also the focus of Marelize Swart's (University of Cape Town, South Africa) talk on *CYP1A2* and *CYP2B6* as major predictors of efavirenz plasma concentration in South African HIV/AIDS patients.

Pharmacogenetic diversity in African populations was also discussed by Folefac Aminkeng, University of British Columbia, Canada, whose team will now be focusing on US FDA-approved pharmacogenetic biomarkers and establishing the most important differences between African and European populations. Both

Dandara and Aminkeng highlighted the work of The Human Heredity and Health in Africa Project (H3 Africa), established by the Wellcome Trust and the US NIH.

The session also featured a talk on the impact of *CYP2D6* and *CYP2C19* polymorphisms on consumption of healthcare in psychiatric practice (Frederieke van der Baan, University Medical Center Utrecht, The Netherlands). This second talk served to further highlight how the implementation of pharmacogenetic tests in clinical settings is, at present, low. Better information on clinical applications and the availability of tests, as well as increasing clinical value by improving prediction levels and treatment selection, are now required to incorporate pharmacogenetic tests into psychiatric clinics.

Muin Khoury's talk on the promises and challenges of human genomics and pharmacogenomics in medicine and public health provided examples of emerging pharmacogenetic tests in practice (e.g., Human Genome Epidemiology Network and Evaluation of Genomic Applications in Practice and Prevention) and discussed how public health sciences can be used to evaluate their performance in populations. Khoury highlighted the ever present genomics evidence gap brought about by the push and pull forces in genomic medicine. Khoury explained the field's expectation to be pulled by the bedside; however, this is not happening as quickly as researchers would like and it is becoming apparent that we need to stop pushing at the benchside.

The first day of the conference ended with the poster session, where participants who had submitted an abstract presented their work to all participants.

One to watch: next-generation sequencing

The recent sequencing revolution has seen the cost of sequencing decrease 10,000-fold since 1998 and throughput massively increase; this is having a large effect on pharmacogenomics and personalized medicine, yet it remains difficult to interpret this genomic information and researchers are still struggling to explain missing heritability in complex diseases – preventing disease modeling, prevention and precaution. It has been 10 years since the Human Genome Project was drafted,

and we are still asking how genomes will help healthcare.

The first speaker in this session (Chaired by Yingrui Li, Beijing Genomics Institute, China) was Steven Scherer, from the Baylor College of Medicine, USA, whose Human Genomes Sequencing Center has recently become a member of the Pharmacogenomics Research Network's Deep Sequencing Resource. Scherer discussed current projects including capture sequencing GWAS-defined regions in breast cancer samples and a network-wide capture probe set of the most common genes known to influence genome–drug interactions.

Thomas Lang (Dr Margarete Fischer-Bosch-Institut für Klinische Pharmakologie, Germany) went on to present a novel established cell technology that systematically investigates the localization, expression and activity of human membrane transporters. This was followed by a presentation on identifying specific genes as markers of complications in critically injured humans and their applications in personalizing therapeutic interventions in the intensive care unit (Wenzhong Xiao, Stanford University, USA).

Matthew Nelson, GlaxoSmithKline, USA, went on to present a brief technical report on exome resequencing yielding high-quality data for the majority of absorption, distribution, metabolism and excretion genes. However, some genes may still require specialized techniques to map and genotype accurately.

The second part of the next-generation sequencing session was kicked off by Yingrui Li, with his talk on unlocking the secret to understanding human genomics. Li outlined what constitutes missing heritability and proposed two possible explanations for this missing heritability: an excess of rare deleterious SNPs not included in GWAS arrays and extensive structural variations/ individual-specific sequences with potential functional impacts. Li called for continued technical innovations to drive the complete *de novo* assembly of multiple private genomes in order to find the key to human genomics for medical genomics and healthcare.

The session was rounded up by Liewei Wang, Mayo Clinic, USA, with his talk on the pharmacogenomics of mTOR

inhibitors performed with lymphoblastoid cell lines and Julie Bertrand, University College London Genetics Institute, UK, discussing multiple SNP analysis in pharmacogenetics studies with a new model used in conjunction with nonlinear mixed effects models.

Part 2 of this conference report will be featured in the next issue of *Pharmacogenomics*. Sessions on Serious Adverse Reactions, Interface of Common Diseases and Pharmacogenomics: Cancer, Interface of Common Diseases and Pharmacogenomics: Complex Diseases and the *CYP2D6* genotyping debate will be covered.

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No writing assistance was utilized in the production of this manuscript.

Website

- 1 Pharmacogenomics Knowledge Base.
www.pharmgkb.org