The 2nd Latin American Pharmacogenomics and Personalized Medicine Congress, attended by a broad audience of nearly 200 participants, mostly from Brazil, but also Argentina, Chile, Colombia, Costa Rica, Cuba, Ecuador and Mexico, opened with a presentation by Julie A Johnson (University of Miami, FL, USA) on ‘Translating pharmacogenomics to clinical practice’, in which the goals and achievements of the Pharmacogenomics Research Network (PGRN) [101], Clinical Pharmacogenetics Implementation Consortium (CPIC) [102] and Pharmacogenomics Knowledge Base (PharmGKB) [103] were reviewed. CPIC, one of the consortia that has arisen from the PGRN, evaluates the evidence for clinical implementation of pharmacogenetics and provides guidelines for using genetic information in drug prescription; to date, six guidelines have been published. PharmGKB is a valuable web-based information source for pharmacogenomics, with content ranging from basic information on SNPs and genes to clinical annotations for pharmacogenomics. The clinical adoption of pharmacogenomics-informed prescription was further discussed in two debate sessions, the first of which focused on psychiatry and was chaired by Mauricio Silva de Lima (Roche, SP, Brazil). The discussants, Mara Hutz (Universidade Federal do Rio Grande do Sul, RS, Brazil) and Adrian LLerena (Universidad de Extremadura, Extremadura, Spain), agreed that application of pharmacogenetics into clinical psychiatry practice holds great promise, but is hindered by clinical (i.e., diagnostic uncertainty, heterogeneous presentation, the chronic nature of psychiatric disorders and the common occurrence of comorbidities) as well as drug-related factors (i.e., active drug metabolites and the lack of well defined pharmacokinetic–pharmacodynamic relationships). The second debate, chaired by LLerena, covered clopidogrel and warfarin. The high levels of evidence for the association between genotype and dose (warfarin) or drug response (clopidogrel) were reviewed by Johnson, who coauthored the CPIC guidelines for both drugs. Guilherme Suarez-Kurtz (Instituto Nacional do Câncer, RJ, Brazil) discussed the performance of warfarin dosing algorithms across populations, with an emphasis on the differential distribution of the relevant polymorphisms in CYP2C9 and VKORC1, and the controversial use of ethnic/racial labels that do not encompass human diversity worldwide.

A symposium on ‘New Tools and Technologies in Pharmacogenomics Research’ was chaired by Karen Weck (University of North Carolina, NC, USA), who initially reviewed the required analytical attributes of pharmacogenomic tests, the impact of differential prevalence of pharmacogenetic polymorphisms across ethnic groups, and postanalytic factors such as clinical validity and clinical utility. Weck then discussed the advantages and challenges associated with the advent of multiplexed microarray technologies and newer next-generation sequencing platforms. The rapid pace at which these technologies continue to move at Ion Torrent at Life Technologies (CA, USA), was highlighted by Pat Brooks (Ion...
Torrent), who introduced new products such as the Proton™ instrument, to be launched later this year, and the Proton I and Proton II chips.

Issam Zineh (US FDA, MD, USA) chaired the second symposium, entitled ‘Personalized Medicine: Across the Drug Development, Utilization and Regulation Continuum’. José Fernando Perez (Recepta Biopharma, SP, Brazil) described the development by Recepta Biopharma of a monoclonal antibody for the treatment of ovarian cancer that has recently received approval for clinical trials from both the FDA and Anvisa (Brasilia, Brazil), the Brazilian drug regulatory agency. Frank Scappaticci (Genentech/Roche, CA, USA) described two types of innovation in biologics that Roche is undertaking; the first exemplified by a new antibody–drug conjugate agent that is showing promise in Her2-positive metastatic breast cancer and the second related to the development of surrogate end points for clinical oncology trials, such as minimal residual disease for chronic lymphocytic leukemia and pathologic complete response rate in neoadjuvant breast cancer. George Patrinos (University of Patras, Patras, Greece) reported the activities of the European Regional Center of the Pharmacogenomics for Every Nation Initiative [104], and the Golden Helix Institute of Biomedical Research [105], including recruitment of DNA samples from healthy volunteers, organization of education activities, surveying the pharmacogenomic environment in European developing countries and the establishment of guidelines and recommendations for integrating pharmacogenomics in these countries’ healthcare systems. The last two talks in the symposium dealt with drug regulatory issues. Marcelo Moreira, from the Anvisa [106], went on to review the drug regulatory legislation in Brazil, with an emphasis on its impact in pharmacogenomics research. In his talk ‘On a Decade of Personalized Medicine at the US FDA’, Zineh argued that personalized medicine has represented an area of progression at the FDA over the past 10 years, evident in initiatives such as the Critical Path Initiative, the Critical Path Opportunities List and the most recent Advancing Regulatory Science Initiative. The use of pharmacogenomics to enhance mechanistic drug development translated in many FDA-approved new molecular entities in 2011 having a pharmacogenomic component as part of the development program. Zineh concluded by offering a perspective on the next 10 years. He focused on enhanced intercenter communication at the FDA, the development of guides to industry relevant to personalized medicine drug development and the importance of considering novel applications for pharmacogenomics in the context of globalized drug development.

In his keynote lecture, entitled ‘Pharmacogenomic and Pharmacoepigenomic Biomarkers for Drug Therapy’, Magnus Ingelman-Sundberg (Karolinska Institutet, Stockholm, Sweden) initially described the importance of adverse drug reactions in the clinical setting and the prevention of such reactions by utilizing validated pharmacogenomics biomarkers. This was followed by excellent overviews of the role of DNA methylation and 5-hydroxymethylation for the control of gene expression and the development of epigenetic drugs, particularly for cancer treatment. Ingelman-Sundberg concluded his talk with a vision of the use of pharmacogenomic and pharmacoepigenomic markers, where labeling of specific drugs for pharmacogenetic testing provides a useful instrument for a more effective and safer drug therapy in the future.

The symposium on ‘Pharmacogenomics in Oncology’, chaired by Howard McLeod (University of North Carolina) started with Alfredo Hidalgo-Miranda (National Institute of Genomic Medicine, DF, Mexico) presenting results of the Slim Initiative of Genomic Medicine (SIGMA) project of characterization of different cancer types. Whole-exome sequencing identified loss-of-function mutations in the NOTCH family of genes in head and neck tumors, and mutations and deletions of the CBFB transcription factor in breast tumors. In 7% of triple-negative breast tumors, somatic translocation involving MAGI3 and AKT3 leading to constitutive phosphorylation activity and cellular transformation was detected. Notably, the activity of the fusion protein could be abrogated by a small-molecule inhibitor of AKT, which might prove to be of
Scappaticci offered an overview of key issues and challenges in the development of biologics including biosimilars, highlighting the complexity of biologic protein drugs and manufacturing challenges. The recently released FDA guidelines for biosimilar agents were discussed and a case example of two anti-CD20 targeted biologics showing different safety profiles after Phase III trials were completed was provided, to emphasize the need for rigorous clinical studies to ensure the safety of any new biologics. In the following talk, entitled ‘Discovery is necessary, but not sufficient’ (to fulfill the pharmacogenomics’ promise of individualized drug therapy), McLeod argued that, after finding the ‘right’ biomarkers and validating them in robust data sets, it is imperative to apply this knowledge in the clinical setting. Examples were provided of clinically relevant associations of pharmacogenetic polymorphisms with the efficacy and toxicity of cancer drugs, including CYP2C8*3 and paclitaxel-induced neuropathy, CYP2D6 phenotype and relapse-free survival in breast cancer, and the influence of the TSER genotype on the proportion of complete response to chemoradiation (5-fluorouracil based) of rectal tumors.

Hutz chaired a symposium dedicated to ‘Pharmacogenomics in Latin America’. Jorge Duconge (University of Puerto Rico, PR, USA) presented a physiogenomic analysis of the Puerto Rican population ancestry and described a pharmacogenetic-driven warfarin dosing algorithm. A distinct feature of this algorithm is an admixture vector component, which, per se, accounted for 5.7% of the warfarin dose variance in Puerto Rican patients, and for 67% of this variance when combined with five other covariates. Hidalgo-Miranda presented data from the PGENI Mexican Regional Center on the distribution of 1936 polymorphisms in 225 pharmacogenes, among different Mexican, including Amerindian groups, and argued that differences in allele distribution across the groups will be valuable to inform public health decisions regarding specific drug use in Mexico. The next two talks dealt with pharmacogenomic networks in Latin America. Suarez-Kurtz introduced the Brazilian network Refargen [107], a consortium of 18 research groups, with the mission to provide leadership in pharmacogenomic research and education in Brazil, with an impact on population health. Results from a Refargen study on the influence of biogeographical ancestry on the frequency distribution of 60 pharmacogenetic polymorphisms in Brazilians showed that: first, the frequency distribution of polymorphisms varies across geographical regions and within self-reported color categories and second, that ‘racial/ethnic/color’ categories do not capture the diversity of the Brazilian population, which must be dealt with as a continuous variable. LLerena went on to describe the Iberian American Network of Pharmacogenetics and Pharmacogenomics (Ribef) [108], a consortium of researchers in 16 Latin American countries, Spain and Portugal and the Consorcio Europeo e IberoAmericano de Farmacogenetica de Poblaciones (CEIBA). Studies from both consortia have so far focused mainly on genotyping CYP2D6 genetic polymorphisms and measuring the metabolic ratios of CYP phenotype probes (i.e., dextromethorphan, debrisoquine, losartan, caffeine and omeprazol) in various Latin American populations.

Matthias Schwab (Institute of Clinical Pharmacology, Stuttgart, Germany) chaired the symposium on ‘Recent Progress in the Pharmacogenomics of Drug Transporters’. Genetic control of ABC transporter expression was discussed by Deanna Kroetz (University of California San Francisco, CA, USA). A specific example with ABCG2 detailed the combined bioinformatic and experimental approaches to identify enhancer regions that control the expression of ABCG2 in the human liver and kidney. This gene-centric analysis was in contrast to a family-wide expression quantitative trait loci analysis of ABC transporter expression in the human kidney. The long-term goal of these studies is to assemble a panel of SNPs that can be considered markers of variable drug response and toxicity. Ingolf Cascorbi (Christian Albrechts University, Kiel, Germany) discussed recent evidence from his group showing that deregulated miRNA expression patterns of tumor cells may interfere with drug response. In one study, downregulation of certain miRNAs...
abolished imatinib resistance of BCR/ABL-overexpressing K-562 cells through upregulation of ABCG2. In another study, induction of ABCC2 protein by rifampicin was counteracted by miRNA 379 in HepG2 cells, an observation that might contribute towards explaining the discrepancies between mRNA and protein expression following external stimuli though PXR ligands. Schwab focused on the influence of DNA methylation on interindividual differences in drug response, best studied in cancer patients. Tissue-specific DNA methylation alters the expression of pharmacokinetic genes encoding CYP450 enzymes as well as drug transporters. As an example, DNA methylation of the hepatic SLC22A1 (OCT1) uptake transporter was shown to be associated with downregulation of SLC22A1 in hepatocellular carcinoma, which might be a novel biomarker for diagnosis and prognosis as well as a target for demethylating agents such as decitabine for therapy of hepatocellular carcinoma.

In his keynote lecture entitled ‘Turning Genetic Diversity into Rational Drug Policy’, McLeod presented the rationale, purposes, organization and achievements of PGENI, a worldwide consortium that comprises two regional centers in Latin America (Rio de Janeiro, Brazil and Mexico City, Mexico). McLeod showed results for the differential distribution of pharmacogenomic polymorphisms among PGENI countries and discussed the use of these data for medication prioritization for individual countries and to identify population subgroups at higher risk of toxicity and treatment failure. Importantly, PGENI provides support for building local infrastructure in the participating countries for future pharmacogenetic research studies. McLeod emphasized that modern medical therapy is a key component of improved health, that requires integration into clinical practice and into public health policy to be successful.

Abstracts of the oral presentations and posters are available at the Refargen website [107]. At the closing ceremony, it was announced that the 3rd Latin American Pharmacogenomics and Personalized Medicine will be held in Mexico, in 2014.

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