Report of the Clinical Division of IUPHAR

August 2008 – January 2009

1) REPORT OF THE PAEDIATRIC SUB-COMMITTEE OF THE IUPHAR CLINICAL PHARMACOLOGY DIVISION 2008-2009
18.1.2009

The term (2004-2008) of the Paediatric Sub-committee consisting of: *Kalle Hoppu* (Finland, chairman), *Gabriel Anabwani* (Botswana), *Madlen Gazarian* (Australia), *Gregory L. Kearns* (USA), and *Hidefumi Nakamura* (Japan) ended on 30 July 2008.

IUPHAR Clinical Division Paediatric Sub-committee (2004-2008) the first and only time together during the CPT2008 in Quebec after the symposium 'Better Medicines For Children" it organised on 30 July 2008. From left: Gabriel Anabwani, Madlen Gazarian, Kalle Hoppu, Hidefumi Nakamura, and Gregory L. Kearns

The new Paediatric Sub-committee for the term 2008-2014 consists of: *Kalle Hoppu* (Finland, chairman), *Gabriel Anabwani* (Botswana), *Facundo Garcia-Bournissen* (Argentina/Canada), *Madlen Gazarian* (Australia), *Gregory L. Kearns* (USA), *Hidefumi Nakamura* (Japan), and *Shalini Sri Ranganathan* (Sri Lanka).

After the most significant political development in children's medicines in 2007 important concrete actions already started to take place in 2008. Following is an abbreviated summary of the main activities where the IUPHAR Sub-committee has been involved.
WHO related activities where the IUPHAR Paediatric Sub-committee has helped by providing expertise either in the form of experts attending and/or preparing documents for the meeting or by providing presentations requested by the WHO:

- Second Meeting of the WHO Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines 29 Sept – 3 Oct 2009, and the proposed 2nd WHO Model List of Essential Medicines for Children (K. Hoppu and G Kearns invited as Expert Subcommittee Members, G Kearns served as raporteur of the meeting)

- The WHO is currently working to review the evidence supporting current formulation and dosage guidelines for paediatric TB drugs in to develop recommendations for optimal FDC:s of the most important TB medicines. As a first step an Expert Meeting on TB Medicines for Children took place at the WHO Headquarters, Geneva, Switzerland, 8-9 July 2008. K. Hoppu and G Kearns were invited as experts to the meeting, and are continuing to provide expert work for the project.
- Innovative Paediatric Formulations ad hoc teleconference group initiated by the IUPHAR Paediatric Sub-committee in February 2008 and chaired by K Hoppu led to an Informal Expert Meeting on Dosage Forms of Medicines for Children, WHO Headquarters, Geneva, Switzerland 15-16 December 2008 (K. Hoppu invited as expert and chaired the meeting). The work of the teleconference group continues.
- WHO / FIP Training Workshop on Pharmaceutical Development, with a Focus on Paediatric Formulations, Mumbai, India, April 2008 (K Hoppu invited as speaker)
- ICDRA (International Conference for Drug Regulatory Authorities) Pre-Conference 'Better Medicines for Children: The Way Forward', 14-15 September 2008, Berne, Switzerland. (K Hoppu invited as speaker)

IUPHAR meetings where the Paediatric Sub-committee has provided assistance in planning and delivering the paediatric pharmacology content:

- The IXth World Conference on Clinical Pharmacology and Therapeutics CPT2008, July 27 – August 1, 2008 Québec City, Canada" (Symposium 'Better Medicines For Children' organized by Paediatric Sub-committee)
- IUPHAR CPT 2008 "The Toronto Satellite in Pediatric Pharmacology", July 25-26, 2008, Toronto, Canada (K Hoppu member of the program committee)

Other meetings related to advocacy for global paediatric medicines actions

- Ministry of Health of Ukraine Academy of Medical Sciences of Ukraine State Pharmacological Center MoH Ukraine International Foundation for Clinical Trials, Second Scientific and Practical Conference In memory of Vladimir I. Maltsev, Clinical Trials of Medicines in Ukraine, Kiev, Ukraine, October 23-24, 2008, Topic 1. Clinical development of medicines Lections (Session), Pediatric formulations, (K Hoppu invited as speaker)
- The EFGCP (European Forum for Good Clinical Practice) Children's Medicines Working Party 4th Annual Conference 'EU & US Paediatric Legislation: What is Changing in Practice in Paediatric Drug Treatment, Research & Development?' 26 November 2008, Brussels, Belgium, (K Hoppu invited as speaker)

Other actions:

- The IUPHAR Paediatric Sub-Committee together with the IUPHAR member society ESDP has submitted a proposal for a focused stream in paediatric clinical pharmacology and proposals for plenary lectures on paediatric pharmacology for WorldPharma 2010.
- The IUPHAR Paediatric Sub-Committee has together with Dr Shinya Ito from Toronto, Canada and Dr Emilio Sanz from Tenerife, Spain been working since 2007 to set up a Paediatric Pharmacology e-learning Pilot Course, primarily aimed at middle to low income country participants which is planned to be ready for enrolment in 2009.
- In its work for children's medicines in the global setting, the IUPHAR Paediatric Sub-Committee has collaborated with IPA (International Pediatric Association). Sub-committee members Kalle Hoppu was appointed by the IPA as a Technical Advisor and co-chair of the IPA program committee, and Madlen Gazarian a member of the IPA program committee for the area of Better Medicines for Children in April 2008. This will give an unprecedented

opportunity for IUPHAR to work together wit IPA globally for paediatric medicines and therapeutics.

Report on EU Legislation of Drug Evaluation in Children

We have agreed with the Chair of the EU Legislation of Drug Evaluation in Children, Hannsjörg Seyberth that since the EU Paediatric regulation came in force into January 2007 it is no longer meaningful to report separately on the effects of this permanent legislation. Any relevant EU developments will from now on be included in the Paediatric Sub-committee report.

In 2008 the EU regulatory authorities, particularly the EMEA (European Medicines Agency), and the pharmaceutical industry have been at the centre of the activities stimulated by the EU Paediatric regulation. Between August 2007 and December 2008 the Paediatric Committee (PDCO) has received altogether 356 validated PIPs (Paediatric Investigation Plans) or Waiver applications for new medicinal products or extensions for products still under patent protection. The PIP and waiver applications covered 597 indications. During these first 1.5 years, when it has been possible to submit such applications, the PDCO has given a positive decision on 58 full waiver applications, and 83 PIPs including deferrals. Four negative opinions have been adopted and 5 positive opinions given on compliance with PIP at the stage of submission of a Market Authorisation Application.

The approved Paediatric Investigations Plans have not yet lead to a significant increase in paediatric clinical trials, as in all cases, unless the product is exclusively for children, the PDCO has agreed to a deferral until the benefit:risk in adults is positive. There has been no requirement to study a product before authorisation if it is not specifically for children. It is therefore expected that the real increase in paediatric clinical trials will occur from 2010 onwards.

On 15 January 2008 the EMEA Management Board adopted the strategy for establishment of the EU network of Paediatric networks mandated by the Paediatric regulation. However, the first meeting of the networks, centres, and investigators of paediatric research was delayed due to the workload of the EMEA and will take place on 16 February 2009 in London.

DRAFT IUPHAR PAEDIATRIC CLINICAL PHARMACOLOGY WORK-PLAN 2009-2014

The Paediatric Sub-Committee of the Division of Clinical Pharmacology of the IUPHAR has developed a Work-plan 2009-2014 as a direct continuum of its efforts in the years 2004-2008, and based on the current very positive and dynamic developments in the field of paediatric medicines.

- The aim is to provide children all over the world better access to safe, effective and appropriately formulated medicines, to be used in a rational way to maintain and improve children's health.
- The methods to be used include advocacy at all levels, educational activities aimed at capacity building in paediatric clinical pharmacology and therapeutics, and improving rational use of paediatric medicines.
- Advocacy efforts will be done globally while the main focus of the educational and capacity building activities will be in the developing world and other countries lacking paediatric pharmacologists.
- In practise the IUPHAR Paediatric Sub-Committee will work by continuing to show leadership and providing paediatric clinical pharmacology experts for key international activities.

- To achieve the aim, the IUPHAR Paediatric Sub-Committee will work in collaboration with IUPHAR member societies and other organisations sharing this aim, like the WHO, the International Pediatric Association (IPA), the International Pharmaceutical Federation (FIP) among others.
- In addition the IUPHAR Paediatric Sub-Committee will work with IUPHAR member societies to explore the possibility of establishing an international scientific organisation of persons interested in research within the area of paediatric pharmacology/paediatric medicines to foster international networking of existing paediatric clinical pharmacologist and facilitate co-operation in research, and exchange of information.

Some specific action currently underway or in planning:

1. Pilot project on web-based distance learning course on paediatric pharmacology currently being developed in co-operation with Prof. Shinya Ito (Toronto, Canada) and Prof. Emilio Sanz.
2. Assistance in planning and delivering the paediatric pharmacology content of WorldPharma2010 and WorldPharma2014.
3. Discussions with the IUPHAR Member Society ESDP (European Society for Developmental, Perinatal and Paediatric Pharmacology) and other members of the international paediatric pharmacology community on feasibility of establishing a virtual network which can effectively link physicians, pharmacologists and pharmacists working in the field of paediatric clinical pharmacology and thereby, create a global community of professionals dedicated to improving therapeutics for infants, children and adolescents.
4. Contacting together with the International Pediatric Association (IPA) the International Pharmaceutical Federation (FIP) with the aim of setting up collaboration for global advocacy for children's medicines and helping the WHO in its activities within the 'make medicines child size' –program (which all three organisation have endorsed)
5. Assisting the International Pediatric Association (IPA) in setting up its new activities within the area of paediatric medicines.
6. Helping the WHO in its activities related to paediatric medicines, especially with WHO Model List of Essential Medicines for Children, and the new three-year programme of work to promote application of the List and treatment guidelines commencing in 2009 for which the WHO has received donor support from the Government of the Netherlands and the Bill & Melinda Gates Foundation. Other activities like those related to TB Medicines for Children, and to defining and fostering development and manufacturing of dosage forms most suitable for children globally are also continuing to be supported by providing paediatric clinical pharmacological expertise.

Kalle Hoppu
Chairman of the Sub-Committee for Paediatric Clinical Pharmacology

2) REPORT SUB-COMMITTEE OF PHARMACOGENETICS OF THE IUPHAR CLINICAL PHARMACOLOGY DIVISION 2008-2009
12.1.2009

Working report 2008
Members of the Sub-Committee
Ingolf Cascorbi, Kiel, Germany (Chair)
Laurent Becquemont, Paris, France
Kim Brøsen, Odense, Denmark
Ingolf Cascorbi, Kiel, Germany
Ann Daly, Newcastle upon Tyne, United Kingdom
Magnus Ingelman-Sundberg, Stockholm, Sweden
Julia Kirchheiner, Ulm, Germany
Deanna Kroetz, San Francisco, CA, USA
J. Steven Leeder, Kansas City, MO , USA
Adrian Llerana, Badajoz, Spain
Vural Ozdemir, Montreal, Quebec, Canada
Matthias Schwab, Stuttgart, Germany
Toshiyuki Someya, Niigata, Japan
Andrew Somogyi, Adelaide, Australia
Guilherme Suarez-Kurtz, Rio de Janeiro, Brazil
Bryn Williams-Jones, Montréal, Québec, Canada

PhD course on Pharmacogenetics Denmark
The PhD course was organized by Kim Brøsen on behalf of the Danish Clinical Intervention Research Academy in cooperation with IUPHAR and with support of the EACPT. It took place in Helsingør, Denmark, from 20.-22. August 2008. In addition to other distinguished Danish scientists, the subcommittee members Laurent Becquemont, Kim Brøsen, Ingolf Cascorbi, Ann Daly and Matthias Schwab contributed with several lectures to this successful PhD course, which was attended by 36 participants from nine European countries.

São Paulo Research Conference on Molecular Medicine and Pharmacogenetics
This joint meeting of the IUPHAR Sub-Committee on Pharmacogenetics and the Brazilian Pharmacogenetics Network tookplace in São Paulo, Brazil, from September 18-20, 2008.
Conceived as a series of meetings to explore the frontiers of knowledge in medicine, biology and social sciences, the São Paulo Research Conferences adopted an original format in their 11th edition by focusing on two major topics, namely Molecular Medicine and Pharmacogenetics/-genomics (PGx). This concept attracted a broad audience of about 450 participants, the vast majority from Brazil, comprising academic scientists, clinicians, representatives of the pharmaceutical industry and the national drug regulatory agency, as well as many graduate and undergraduate students. About 250 participants attended the symposia on pharmacogenetics. The scientific program included plenary sessions on topics of general interest - including a keynote lecture by Prof. Oliver Smithies, recipient of the 2007 Nobel Prize for Medicine – and parallel activities directed to either the PGx or Molecular Medicine audiences. Prof. Boris Vargaftig (Universidade de São Paulo, São Paulo, Brazil), who created the SPRC in 2003, was the conference chair.

The conference was sponsored mainly by the University of Sao Paulo; IUPHAR supported financially the meeting giving travel grants to four of the invited speakers. Overall, nine member of the Sub-Committee were present: Ingolf Cascorbi, Ann Daly, Magnus Ingelman-Sundberg,

Deanne Kroetz, Steven Leeder, Adrian Llerana, Vural Özdemir, Matthias Schwab, Andrew Somogyi, and Guilherme Suarez-Kurtz.

The IUPHAR Sub-Committee on Pharmacogenetics met at the last day of conference and it was unanimously agreed that the conference format provided a valuable model for future educational initiatives of the committee directed at increasing the global awareness of the role of PGx in personalized drug therapy. Overall, the conference was a hallmark for promoting PGx research in Brazil.

A detailed conference report was published:
G. Suarez-Kurtz and I. Cascorbi: São Paulo Research Conference on Molecular Medicine and Pharmacogenetics, A Joint Meeting with the IUPHAR Sub Committee on Pharmacogenetics and the Brazilian Pharmacogenetics Network, São Paulo, Brazil, September 18-20, 2008. Current Pharmacogenomics & Personalized Medicine 2008; 6: 234-238.

A short version appeared in the December issue of the IUPHAR journal "Pharmacology International".

Further Activities
It was unanimously agreed that the work of the IUPHAR Subcommittee of Pharmacogenetics as such helps to link the large networks such as the US PharmGKB network, the Pacific Rim Association for Clinical Pharmacogenetics and European activities. Possible further meetings could take place in early 2010.

Next Sub-Committee meeting
The 9th conference of the European Association of Clinical Pharmacology and Therapeutics (EACPT) was identified as a large conference, where a significant number of members will be present. It will take place from Sunday 12th to Wednesday 15th July 2009.in Edinburgh, Scotland, UK.

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São Paulo Research Conference on Molecular Medicine and Pharmacogenetics, A Joint Meeting with the IUPHAR Sub-Committee on Pharmacogenetics and the Brazilian Pharmacogenetics Network, São Paulo, Brazil, September 18-20, 2008

Guilherme Suarez-Kurtz[*,1] and Ingolf Cascorbi[2]

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Abstract: Pharmacogenetics/-genomics (PGx) was a major topic of the XI edition of the São Paulo Research Conferences (SPRC, 18-20 September, 2008), sponsored jointly by the Sub-Committee on Pharmacogenetics of the International Union of Basic and Clinical Pharmacology (IUPHAR) and the Brazilian Pharmacogenetics Network (Refargen), in collaboration with the University of São Paulo, Brazil. Conceived as a series of meetings to explore the frontiers of knowledge in medicine, biology and social sciences, the SPRC covered in previous editions a broad range of topics, such as Cancer, Drug Addiction, Evolution and the Origin of Life, Infections and Vaccines, Memory, and Molecular Biology. The PGx program of the XI SPRC comprised a keynote lecture on *Clinical aspects of pharmacogenetics: Promises and future*, four symposia, poster exhibits and an oral communication session. Two symposia focused on PGx in clinical practice, and covered recent developments in the PGx of analgesics, cancer chemotherapy, anti-HIV drugs, statins and oral anticoagulants. The two other symposia focused on PGx in special populations (pediatric patients, Amerindians, Hispanic populations and admixed populations), ethical aspects of PGx and recent developments in the PGx of CYP450 drug metabolizing enzymes and drug transporters. The IUPHAR Sub-Committee on Pharmacogenetics met at the last day of conference and it was unanimously agreed that the conference format provided a valuable model for future educational initiatives of the committee. Finally, the launching of an online pharmacogenetics database for the Brazilian population at Refargen´s internet site (www.refargen.org.br) was announced at the conference.

INTRODUCTION

Conceived as a series of meetings to explore the frontiers of knowledge in medicine, biology and social sciences, the São Paulo Research Conferences (SPRC; http://www.eventus.com.br/bioconferences/sprc11/) adopted an innovative format in their 11th edition, held in São Paulo, Brazil (18-20 September, 2008), by focusing on two major topics, namely Molecular Medicine and Pharmacogenetics/-genomics (PGx). This concept attracted a broad audience of nearly 450 participants, the vast majority from Brazil, comprising academic scientists, clinicians, representatives of the pharmaceutical industry and the national drug regulatory agency, as well as many graduate and undergraduate students. The scientific program included plenary sessions on topics of general interest - including a keynote lecture by Prof. Oliver Smithies, laureate of the 2007 Nobel Prize in Physiology and Medicine – and parallel activities directed to either the PGx or Molecular Medicine audiences. The conference was chaired by Prof. Boris Vargaftig (Universidade de São Paulo, São Paulo, Brazil), who created the SPRC in 2003 and has presided over previous editions, in which a broad range of topics, such as Cancer, Drug Addiction, Evolution and the Origin of Life, Infections and Vaccines, Memory, and Molecular Biology were explored.

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The present conference report aims to provide an overview of the SPRC PGx program, which was jointly organized by the Sub-Committee on Pharmacogenetics of the International Union of Basic and Clinical Pharmacology (IUPHAR, www.iuphar.org) and the Brazilian Pharmacogenetics Network (Refargen, www.refargen.org.br). The IUPHAR subcommittee (http://www.iuphar.org/clin_pharma.html) was founded in 2006 to promote the exchange of pharmacogenetics knowledge and to evaluate the clinical impact of pharmacogenetics. Its international members, coming from Europe, USA, Canada, Brazil, Japan and Australia cover a broad spectrum of this discipline. In particular the subcommittee aims to support education and the development of pharmacogenetics research in emerging countries. It co-operates with the Pacific-Rim Association for Clinical Pharmacogenetics and focuses its initiatives in the organization and intellectual support of regional meetings dedicated to strengthen individualized medicine.

To deal with the specificities of PGx in the heterogeneous Brazilian population, Refargen, a collaborative network of researchers from various institutions distributed over the country´s five geographical regions was established in 2004 [Suarez-Kurtz G. 2004]. Refargen´s mission (www.refargen.org.br) is to promote close scientific interaction among its members, to establish a multi-centered repository of biological samples for PGx studies, to create a PGx database for the Brazilian population, to provide a forum for public debate of topics pertaining to PGx and to play an active role in educational programs directed to the health science students, pro-

1875-6921/08 $55.00+.00

fessionals and public health officials. Co-sponsoring the SPRC on Pharmacogenetics and Molecular Medicine fulfils Refargen´s mission and provided a unique opportunity for promoting PGx interest and knowledge in Brazil. Also represented in the conference was the Ibero-American Network of Pharmacogenomics (RIBEF, www.ribef.org), a multi-national initiative that congregates research groups from Latin America and the Iberian peninsula with the mission to promote PGx training and collaborative research in these world areas.

The PGx program was comprised of a keynote lecture, four symposia, poster exhibits, an oral communication session and a meeting of the IUPHAR Subcommittee of Pharmacogenetics.

EXPERT OVERVIEW OF THE CONFERENCE

The PGx program was opened by an excellent keynote lecture delivered by **Matthias Schwab** (Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, Germany) on **Clinical aspects of pharmacogenetics: Promises and future**. He outlined the limited efficacy of major pharmacotherapy regimens and discussed how PGx-guided decisions may amend this therapeutic predicament. As major examples of application of PGx in clinical practice, Matthias Schwab presented highly interesting and timely data on the haematotoxicity of 6-mercaptopurine due to TPMT deficiency, on the importance of cytochrome P450 (CYP) 2D6 polymorphisms for the dose requirement of the HIV drug effavirenz to avoid CNS toxicity, and finally on the association of HLA B5701 with hypersensitivity to abacavir treatment in HIV-infected subjects. The increasing evidence that prevention of stent thrombosis by clopidogrel is subject to CYP2C19 activity was also highlighted. Poor metabolizers, carrying the *CYP2C19*2* allele, display lower formation rates of the active metabolite of clopidogrel, thus having a higher risk of stent thrombosis. As a complement to therapeutic significance of human variation in DNA sequence and genetic polymorphisms, Matthias Schwab then presented data on gene expression analysis in the treatment of different forms of childhood leukemia that led to a significant improvement of efficacy and safety. He cautioned that although genome wide analyses may identify new susceptibility factors, its use in clinical practice remains subject to further investigation and will benefit from next generation sequencing technologies at lower cost and faster resolution. Future developments in PGx will also encompass information on epigenetics, microRNA silencing and further assessment of environmental factors.

The **first symposium**, entitled "**Pharmacogenetics in clinical practice**" was chaired by **Ingolf Cascorbi** (University of Kiel, Germany) and dealt with the impact of PGx on cardiovascular diseases and on the genetic background of adverse drug events in HIV treatment. **Heyo Kroemer** (Institute of Pharmacology, University of Greifswald, Germany) presented data on **pharmacogenomics of statin transport and action**. Lipid lowering agents are among the most frequently used drugs and a wealth of evidence supports the beneficial effects of statins in particular for prevention of myocardial infarction. There is evidence that the uptake of statins by hepatocytes is mediated by OATP transporters, especially OATP1B1. Genetic polymorphisms in *SLCO1B1*, in particular the 388A>G and 521C>T SNPs account for diminished hepatic uptake and elevated plasma concentrations of statins, which lead to relatively modest impact in these drugs´ hypocholesterolaemic effect but might increase the risk of adverse side effects. Very recently, a genome wide analysis disclosed a strong association of the risk of statin-associated myopathy with a tag-SNP of 521C>T in *SLCO1B1*. Heyo Kroemer presented new data on the impact of *OATP1B1* polymorphism on statin effects in a large population cohort (Study of Health in Pommerania, SHIP). Interestingly, the influence of OATP1B1 variants on the LDL-level was detectable after inclusion of patients into the study, but was less pronounced after 10 years of treatment with increasing dosages of statins. **José Eduardo Krieger** (University of São Paulo, Brazil) delivered a talk on the **impact of pharmacogenetics in the treatment of cardiovascular diseases**. He pointed out that, although recent development of high throughput screening technologies identified several genetic markers that may predict inter-individual variability of drug response in chronic cardiovascular diseases, PGx will only be incorporated into clinical practice when it becomes part of clinical decision-making models capable of using PGx information in a cost-effective way. The importance of availability of reliable PGx markers and their incorporation into therapeutic decisions was emphasized and illustrated with data for the insertion/deletion polymorphism of the angiotensin-convertion enzyme in relation to blood pressure control, and on the *CYP2C9* and *VKORC1* genes for warfarin anticoagulation. The latter topic was further developed by **Ann Daly** (University of Newcastle, Newcastle, United Kingdom) in her talk on **pharmacogenetics of oral anticoagulation.** Vitamin K antagonists including warfarin, acenocoumarol and phenprocoumon are among the most widely prescribed drugs worldwide, but require dose individualization on the basis of clinical response. Ann Daly emphasized the 200-fold interindividual variation in the warfarin dose required to achieve adequate anticoagulation, and discussed the patient-specific factors, both genetic and non-genetic, that contribute to this variability. *CYP2C9* and *VKORC1* genotypes are the best studied genetic factors, which together with age and either height or body weight account for approximately 55% of variability in warfarin dose requirement in several retrospective studies in European populations. Recent genome-wide approaches disclosed only minor contributions from other genes, such as *APOE4*, *CYP4F2* and the genes encoding coagulations factors VII and X. Ann Daly is a member of the International Warfarin Pharmacogenetics Consortium (IWPC) that is presently pooling data for a total of >5000 patients worldwide, with the purpose of developing warfarin dosing algorithms that might be applied globally to different populations. **Vanessa S. Mattevi** (UFRS, Porto Allegre, Brazil) presented data concerning the identification of **genetic markers associated with highly active antiretroviral therapy (HAART) adverse effects in HIV-infected patients**. Therapeutic advances in AIDS treatment have changed the perception of this disease from a fatal to a chronic condition. Importantly, Brazil pioneered the universal access of HIV drugs to infected patients, and thereby provides large cohorts for studying the PGx of the drugs used in highly-active antiretroviral

treatment (HAART). HAART combines at least three antiretroviral drugs to maximally suppress HIV virus replication and halt disease progression. Adverse effects associated with HAART include dyslipidemia and the lipodystrophy syndrome, characterized by metabolic complications, altered fat distribution and increased risk of developing cardiovascular disease. Current data indicate a multifactorial pathogenesis of the lipodystrophy syndrome. Vanessa Mattevi reported on lipodystrophy candidate genes including those involved in pharmacokinetics and pharmacodynamics of antiretroviral agents. In particular, *ApoB* variants were associated with lipodystrophia, whereas SNPs in genes encoding TNFα and SREBP1c (3322C>G) showed significant associations that require further confirmation and functional elucidation.

The second symposium chaired by **Magnus Ingelman-Sundberg** (Karolinska Institute, Stockholm, Sweden) dealt with **pharmacogenetics in special populations**. The peculiarities of **Pharmacogenetics in Pediatric Patients** were discussed by **J. Steven Leeder** (Children's Mercy Hospitals and Clinics, Kansas City, MO, USA), and examples were given of how characterization of drug metabolizing phenotypes may provide important insights into the interaction of PGx and human development across the age continuum in pediatric patients. As a concrete example of forward applications of pediatric pharmacogenetics, Steven Leader showed data on the association of acetaminophen taken by pregnant women with gastroschisis, a rare congenital defect of the abdominal wall that causes the abdominal contents to develop outside the abdominal cavity. Investigation of drug metabolizing enzymes involved in the formation of major acetaminophen toxic metabolites (e.g. APAP-S) led to the identification of certain sulfotransferases, such as SULT1A3 and SULT1E1 that are not expressed after birth, and to a strong association of the maternal *SULT1A1* genotype with gastroschisis. Another example of the impact of the maternal genotype on drug toxicity was provided by the fatal opioid poisoning in a breastfed neonate whose codeine prescribed mother was a CYP2D6 ultra-rapid metabolizer. Steven Leeder also presented data on the time course of acquisition of functional drug metabolism in infants, studied with the CYP2D6 probe dextromethorphan (DM). Although CYP2D6 phenotype was consistent with *CYP2D6* genotype by two weeks of age and did not change appreciably throughout the first year of life, a second metabolic pathway for DM in adults, *N*-demethylation, increased dramatically during the same period of time. Finally, the variability in the response of montelucast and fluticasone in asthma therapy in pediatric patients was reviewed. **Population diversity** in PGx was discussed in three lectures, and perhaps not surprisingly for a meeting held in Brazil, the focus was on the peoples of the Americas. **Eduardo Tarazona-Santos** (Federal University of Minas Gerais, Belo Horizonte, Brazil) dealt with the **Pharmacogenetics of Native American**, a highly heterogeneous population that is greatly under-represented in PGx studies. Data on the haplotype structure of drug-metabolizing enzymes (exemplified by NAT2), drug-transporters and drug-targets in different Native American populations were discussed in relation to geographical patterns of genetic diversity across different populations and the evolutionary factors that have influenced these patterns. Tarazona-Santos emphasized the importance of controlling for population stratification in PGx association studies in Native Americans, especially in the case of large differences in allele frequencies across Native American and other populations. The **Pharmacogenomics in Hispanic populations,** including people living in Spanish-speaking countries of the Americas as well as those categorized as Hispanic/Latino in the United States was reviewed by **Adrian Llerena** (University of Extremadura, Badajoz, Spain). The diversity of these peoples by their country of origin or residence, culture and genetic ancestry is reflected in the frequency distribution of pharmacogenetic polymorphisms. For example, the frequency of the CYP2D6 poor metabolizer (PM) phenotype associated with deficient *CYP2D6* alleles was shown to range from 3.2 – 10% in Hispanics compared to 5-7% in Spaniards. Among Native Americans living in Spanish-speaking countries, the CYP2D6 PM phenotype was not detected in the Cuna of Panama and Tepehuano of Mexico, but is present in 2.2 – 4.4% of Ngawbe and Embera groups of Panama and Colombia. Dr. Llerena reported the intriguing observation that personality differences in Spaniards and Cubans are associated with CYP2D6 metabolic capacity, and concluded his presentation by a description of the Ibero-American Network of Pharmacogenomics (RIBEF, www.ribef.org), a multi-national initiative that congregates research groups from Latin America and the Iberian peninsula with the mission to promote PGx training and collaborative research in these world areas.

The third symposium, chaired by **Heyo Kroemer** (University of Greifswald), was devoted to **Pharmacogenetics in clinical practice** to allow a deeper appreciation of the recent advances in clinical applications of pharmacogenetics science**.** The **pharmacogenomics of opioids** was initially discussed by **Andrew Somogyi** (University of Adelaide, Adelaide, Australia). Opioid analgesics have been the mainstay of pain control for centuries and are also widely used for treatment of opiod addiction, but there is substantial interpatient variability in efficacy and toxicity. The contribution of genetic factors to such variability has been investigated at both the pharmacokinetics - including drug metabolizing enzymes such as CYP2D6 and efflux transporters such as P-glycoprotein - and pharmacodynamics - including the μ-opioid receptor and signaling elements such as ß-arrestin levels. Andrew Somogyi discussed the impact of *CYP2D6* polymorphisms on the clinical response to codeine, oxycodone and tramadol, and pointed out the increasing knowledge of the genetic interplay between pain and opioid analgesia that resulted in identification of new pharmacogenomic factors (e.g., cytokines) contributing to variability in opioid effectiveness and adverse effects. **Ingolf Cascorbi** (University of Kiel, Kiel, Germany) gave a presentation on the **Pharmacogenetics of chronic pain treatment**. Response to the treatment of chronic pain is subject to broad interindividual variability, part of which is believed to be associated with polymorphisms in genes, affecting pain perception, transmission and processing, but also the pharmacokinetics and –dynamics of analgesics. Well established are pronounced effects of impaired or accelerated CYP2D6-mediated metabolism of opioids such as codeine or of the tricyclic antidepressant amitriptyline. From a pharmacodynamic standpoint, frequently occurring variants in the opioid receptor gene *OPRM1* lead to lesser affinity of opioids and lower

efficacy. Furthermore, there is increasing evidence that catechol amine *O*-methyltransferase (COMT) variants are associated to decreased opioid dose requirements. More recently, variants in transient receptor potential cation channels were identified. There is *in vitro* evidence that variants of the heat-sensitive receptor *TRPV1* significantly affect protein function and expression, whereas *in vivo* data are conflicting. To this end, Ingolf Cascorbi reported on the impact of variants in *TRPA1, TRPV1* and *TRPM8* on quantitative sensory testing (QST) in 296 patients with neuropathic pain and 255 healthy volunteers. Although the association was not significant when the composite overall phenotype was evaluated, significant differences were observed at subscale levels when evaluating various scores of the twelve QST parameters. Moreover, variants in the *OPRM1* receptor affected mechanical pain threshold. These results contributed to the knowledge that pain perception and transmission are modulated by genetic factors, as it is most pronounced in individuals having deleterious mutations in the *SCN9A* gene, coding for the α-subunit of the voltage-gated sodium channel. **Matthias Schwab** (Institute of Clinical Pharmacology, Stuttgart, Germany) discussed the **Pharmacogenetics in Cancer,** and emphasized that variation in drug disposition and response among patients is a major concern in anticancer therapy, especially for chemotherapeutic agents that have a narrow therapeutic window. Cancer chemotherapy provides several appreciable examples on the clinical value of PGX-informed decisions. One of the best examples is the thiopurine methyltransferase polymorphism (TPMT) and its clinical relevance for 6-mercaptopurine therapy in children with acute lymphoblastic leukemia. TPMT deficiency, which associates with increased risk of bone marrow suppression may be prevented by *TPMT* genotyping and adjustment of the prescribed dose of 6-mercaptopurine. Another example discussed by Matthias Schwab referred to the impact of *CYP2D6* polymorphism on the efficacy of tamoxifen in breast cancer: CYP2D6 catalyzes the conversions of tamoxifen into its active metabolite endoxifen, and women who are CYP2D6 poor metabolizers have reduced endoxifen plasma concentrations and a poorer outcome when receiving tamoxifen adjuvant therapy. Despite these two notable examples of the major impact of single gene polymorphisms on the outcome of cancer chemotherapy, it is likely that more comprehensive '-omics appoaches' (e.g., genomics, transcriptomics, proteomics) will identify additional putative genes, pathways and targets that modulate the individual response to cancer chemotherapy. For instance, microarray technology in childhood ALL has been shown to be informative in redefining cancer diagnosis and predicting tumor response to specific drugs.

The fourth symposium, chaired by **J. Steven Leeder,** (Children's Mercy Hospitals and Clinics, Kansas City, MO, USA) focused on **Pharmacogenetics of drug disposition,** but addressed also ethical aspects of ethnicity and genetic diversity. An overview of **Recent developments in the pharmacogenetics of cytochrome P450 (CYP) enzymes,** by **Magnus Ingelman-Sundberg** (Karolinska Institutet, Stockholm, Sweden) focused on clinically relevant examples, where pharmacogenetics provided significant information for improved drug therapy. Evolutionary aspects of the global distribution of polymorphism in *CYP* genes, and the contribution of genetic drift and selection due to environmental stress were reviewed. Data were presented on recently identified variant alleles in *CYP2C19* (particularly the fast **17* allele), *CYP2B6* and *CYP3A7* and on novel mechanisms for control of expression of CYP enzymes by gene methylation (exemplified by CYP2W1) and by the action of specific micro RNAs regulating the extent of enzyme translation, which contribute to the inter-individual variability in CYP activity. It was suggested that predictive genotyping in the future will be of benefit in 20-30% of drug treatments and thereby allow for prevention of drug adverse reactions, which are estimated at 100 billion USD and over 100,000 deaths per year. The **Pharmacogenomics of ATP-Binding Cassette** (**ABC) transporters**, a superfamily of membrane transporters involved in the efflux of a wide range of xenobiotic and endogenous substrates was reviewed by **Deanne Kroetz** (University of California San Francisco, USA). Data from a multi-investigator project, in which the coding and proximal promoter regions of major *ABCB, ABCC* and *ABCG* transporters involved in drug efflux were resequenced in ethnically diverse populations revealed that genetic diversity is greater at synonymous sites than non-synonymous sites in the coding region, suggesting some degree of selective pressure to limit changes in transporter function. Surprisingly, for some transporters, genetic variation is greater in the proximal promoter region (-250 to +50 bp) than in the coding region. Computational prediction of polymorphisms most likely to alter function combined with heterologous expression systems provided a dearth of information on transport of clinically relevant ABC-substrates. In many cases, the impact of the genetic polymorphisms on ABC transporter activity is substrate-dependent, which has significance in the design and interpretation of clinical association studies. In his talk on **Race As a Variable in Pharmacogenomics Science: From Empirical Ethics to Publication Standards, Vural Ozdemir** (Université de Montreal, Montreal, Canada) approached population pharmacogenetics from an ethicist´s perspective. Contrasting what he perceives as a lack of in-depth discussion on "race-based" pharmacogenomics with research fields such as public health and anthropology where the use of race as a variable has been contested and debated rigorously, Vural Ozdemir advocated the use empirical ethics research methodologies (e.g., interviews, focus groups, surveys, etc) to better understand the intersection of "race" and pharmacogenomics. It was proposed that empirical ethics may be particularly useful to discern gaps and 'blind spots' between scientific practice and attendant socio-ethical standards and to reveal the diverse perceptions, attitudes and knowledge towards race-based pharmacogenomics among its potential user groups, towards the development of meaningful publication standards and science policy. Finally**, Guilherme Suarez-Kurtz (**National Cancer Institute, Rio de Janeiro, Brazil) offered an overview of **Pharmacogenetics in Admixed Populations** focusing on the impact of genetic admixture in Brazil, where five centuries of intermarriage between Amerindians, Europeans and Africans, resulted in the extensive population heterogeneity observed presently. The effectiveness of phenotype-based and marker-based biogeographical ancestry classifications in typing polymorphisms of pharmacological relevance was compared using logistic regression modeling. Data from

nearly 400 healthy subjects indicate that the PGx diversity among Brazilians has become highly individual and is best described as a continuum. Specifically, the odds of having alleles *CYP3A5*3*, *GSTM3*B* and *GNB3 825T* increases continuously, whereas the odds of having the *GSTM1-null* polymorphism decreases continuously as the estimated individual proportion of African ancestry increases within the Brazilian population, irrespective of self-reported racial/color identity. These distribution patterns argue strongly against the use of racial/ethnic criteria as a guidance to drug therapy in Brazilians. It was emphasized that admixture must be dealt with as a continuous variable, rather than proportioned in arbitrary sub-categories for the convenience of data quantification and analysis.

A session on **Short oral communications** was designed to provide PhD students with the opportunity to present their research projects. Four projects were selected for presentation by Alice. C. Rodrigues ("Alterations of the expression of typically ABC and SLC transporters in hyperlipidemia under artovastatin treatment"), Jamila A. Perini (Pharmacogenetics of warfarin treatment in Brazilians"), Vinicius. A. Sortica ("Influence of functional SNPs of SLCO1B1 and 1B3 on the efficacy and safety of simvastatin treatment") and Mariana S. Silva ("Pharmacogenetics studies in patients with temporal lobe epilepsy"). The SPRC traditionally awards prizes for the best posters exhibited at the conference to recognize and encourage outstanding scholarship among trainees. An adjudicating committee, composed of Ingolf Cascorbi (University of Kiel, Germany), Adrian Llerena (University of Extremadura, Spain) and Rosane Vianna-Jorge (Brazilian National Cancer Institute) selected the following two posters for the prizes:

- J. A. Perini, I. S. C. Santana, E. Silva-Assunção, F. Rangel, E. B. Ojopi, E. Dias-Neto, C. Struchiner & G. Suarez-Kurtz: Pharmacogenetics of warfarin treatment in Brazilians
- E. F. Costalonga, A. Sonir, G. Guerra-Júnior, B. B. Mendonça, I. J. P. Arnhold, A. A. L. Jorge: An allele at position -202 in the promoter region of the IGFBP-3 gene is associated with higher serum levels of IGFBP-3 and higher growth rate after growth hormone (GH) treatment of children with severe GH deficiency.

CONCLUSIONS AND FUTURE OUTLOOK

The conference was a hallmark for promoting PGx research in Brazil, and provided a model for future educational initiatives directed at increasing the global awareness of the role of PGx in personalized drug therapy. The participation of leading international investigators, including nine members of the IUPHAR Subcommittee of Pharmacogenetics contributed to the successful outcome of the event, which must be credited also to the motivated involvement of Refargen, the Brazilian Pharmacogenetics Network, and to the successful history of the São Paulo Research Conferences over the last 5 years. With the current international expansion of PGx research, population diversity worldwide must be acknowledged and dealt with, in order for PGx to impact positively on global public health and to avoid the risk of creating a genomics divide between nations or regions. Initiatives such as the SPRC represent significant steps towards these goals.

ACKNOWLEDGEMENT / CONFLICT OF INTEREST

None declared.

REFERENCE

Suarez-Kurtz, G. (2004) Pharmacogenomics in admixed populations: The Brazilian Pharmacogenetics/pharmacogenomics network – REFARGEN. *Pharmacogenomics J.* **4**, 347-348.

Received: 28 September, 2008 Revised: ?????????????, 2008 Accepted: 2 October, 2008

3) REPORT ABOUT THE IUPHAR-WHO COLLABORATION 2006-2008

The most recent plans for the collaboration between IUPHAR and WHO were worked out at a meeting in Geneva in October 2006 (minutes have been submitted earlier). The meeting was organized by the two liaison scientists between WHO (Dr Lembit Rägo) and IUPHAR (Prof. Folke Sjöqvist). The recently elected chairman (Prof. Lars Gustafsson) of the Subcommittee for clinical pharmacology in developing countries within the Clinical Division, IUPHAR, accompanied Prof. Sjöqvist to this meeting.

Activities during 2007-2008

1. Core curriculum in Clinical Pharmacology (CP) and renewal of WHO Technical Report Series No. 446 (TRS 446).

The highest priorities for the work during 2007-2008 have been to develop a core curriculum in CP and to renew the 1970 WHO recommendations in clinical pharmacology (TRS 446). For these purposes a meeting was arranged in November 2007 in Copenhagen with participants from WHO and the Clinical Division, IUPHAR, particularly representatives of its Subcommittee for clinical pharmacology in developing countries. The meeting was supported by grants from WHO, IUPHAR and the Karolinska Institutet. Prof. Kim Brøsen volunteered as local host for the meeting.

A second meeting was held in Stockholm in September 2008. The deliberations at this meeting (enclosure 1) resulted in a final disposition of a new IUPHAR-WHO booklet on CPT (enclosure 2). This meeting was supported by grants from IUPHAR, EACPT and The Swedish Foundation for Clinical Pharmacology and Therapeutics.

In January 2009 the majority of the suggested chapters have been submitted to the editor.

The final draft will be submitted for revision to the Clinical Division in good time before World Pharma in Copenhagen in 2010. The booklet will be presented during this congress.

2. Supporting the development of clinical pharmacology in Egypt.

Between 2005 and 2008 the TEMPUS organisation within EU has supported a project entitled "Clinical Pharmacology for Rational Drug Prescription in Egypt". The project was initiated by Prof. Mohamed Ibrahim, Menoufia and supported by Prof. Mohamed Khayyal, Cairo, member of the IUPHAR executive committee. Through the two professors TEMPUS asked Professor Folke Sjöqvist at the Karolinska Institutet in Stockholm to organize a Danish-Swedish-Egyptian task force to assist Egypt in its ambition to develop clinical pharmacology. Denmark has been represented by Prof. Kim Brøsen, Odense, Sweden by Professors Sjöqvist, Anders Rane, Lars Gustafsson and Ulf Bergman, and Egypt by Professor Ibrahim and Prof. Mahmoud Khayyal. Thirteen Egyptian universities have participated in the project, which has had three major aims:

a) To develop clinical pharmacology in the undergraduate teaching of medical students and in the continued training of physicians.
b) To introduce the concept of Drug and Therapeutics committees (DTC:s) guiding drug selection and rational drug use (RUD).
c) To introduce drug utilization (DU) studies and pharmacoepidemiology as bases for RUD.

The program has included bilateral visits to the participating countries, advanced courses in clinical pharmacology, initiation of research projects in Egypt and introduction of clinical pharmacology in the teaching of medical students in Egypt.

The advanced courses in CP have focused on methods and principles in drug utilization research and principles in drug evaluation. The former course was held in Cairo in May 2007 in collaboration with the WHO Collaborating center for drug statistics in Oslo (Head Dr Marit

Rönning) and the WHO Collaborating Center for Drug Utilization Research and Clinical Pharmacological Services in Stockholm. At this course about 25 Egyptian physicians and pharmacists were examined and approved. Programs for monitoring drug use have been introduced in two university hospitals in Cairo.

One week courses in drug evaluation have been given both in Stockholm and Cairo for Egyptian professors in pharmacology. In October 2007 an intense research oriented course was held in Stockholm for five selected Egyptian professors. Rating scales for evaluation of the quality of clinical drug trials have been introduced.

In June 2008 a final Egyptian-Swedish workshop on teaching methods in clinical pharmacology was held in Cairo at Ain Shams University under the chairmanship of Prof. Ahmed M. Abdel-Tawab and 20 participating Egyptian teachers. Drs Ylva Böttiger and Georgios Panagiotidis were responsible for the European input.

The project has not only had considerable effects on Egyptian pharmacology but has also awakened an interest in other Arabic countries such as Jordan.

The Eastern Mediterranean office of WHO (EMRO) in Cairo has participated in several of the meetings in Cairo and the project leaders have had continuous contacts with and paid visits to this office, particularly Dr. Zafar Mirza and the regional director Dr. Abell Aziz Saleh. Dr Mirza considers that this program is suitable for introducing the principles of RUD both in health care institutions and academic medicine in the EMRO region.

In the midst of these activities the Egyptian coordinator Prof. Mohamed Ibrahim, a member of the clinical division IUPHAR, died suddenly and was replaced by Prof. Mahmoud Khayyal. The collaboration is expected to continue as an academic effort after the support from Tempus has ended. Prof. Mahmoud Khayyal was subsequently elected a member of the council of the Clinical Division, IUPHAR

3. Various activities
During my tenure I have continuously supported IUPHAR related activities in the developing world when consulted. An important example is continued support of projects in paediatric clinical pharmacology and drug use in children guided by Prof. Kalle Hoppu, Helsinki, Finland. Contributions have also been made to the WHO Drug Information Journal, edited by Dr. Lembit Rägo, head of Drug Monitoring at WHO, Geneva.
Stockholm in January 2009

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Enclosure #1

NOTES OF THE MEETING OF THE WHO-IUPHAR GROUP HELD AT THE SHERATON HOTEL IN STOCKHOLM AT 09.00 HOURS ON SUNDAY SEPTEMBER 28TH 2008.

Present were Prof.Folke Sjöqvist (FS) (in the chair), Prof. Lars Gustafsson (LG), Dr. Simon Maxwell (SM) and Prof. Michael Orme (MO).

Apologies were received from Prof. Kim Brøsen, Prof. Ingolf Cascorbi, Dr. Lembit Rägo and Prof. Sir Michael Rawlins.

The progress with updating of the 1970 WHO document on Clinical Pharmacology and Therapeutics (CPT) was reported. In brief three main manuscripts had been received from Prof. Lars Gustafsson, Prof. Sir Michael Rawlins and Prof. Tony Smith and two shorter chapters from Prof. Folke Sjöqvist. A number of e-mails had been exchanged among the group concerning the definition of a Clinical Pharmacologist with a variety of expressed views. It was agreed here that a Clinical Pharmacologist was a medical specialist whose training in pharmacology and medicine permitted them to promote and take responsibility for the rational use of drugs in individual patients and in the population at large. The full text of the definition agreed is appended. The format of the proposed document was examined and after dues discussion certain changes were agreed:

1. There would be a short introduction to be produced in due course by the General Editor (Michael Orme).

2. The teaching part of the document would be altered. The first two parts Undergraduate education and Continuous education for all doctors would be the prime responsibility of Dr. Simon Maxwell but for the undergraduate section he would be supported by Dr. David Nierenberg (USA) and Dr. Ylva Böttiger (Sweden).
    a. The section on the education and training of specialist clinical pharmacologists would, it was hoped, be taken on by Dr. Marcus Reidenberg (USA) and Prof. Folke Sjöqvist would be approaching him as soon as possible. It was suggested that the UK document on specialist training in CPT, updated in 2007, could be used as the model but wit all UK specific items deleted in the end result.
    b. The two Addenda would be included within a single Appendix as free standing sections. It was agreed to release Prof. Kim Brøsen from his initial responsibility for the production of Addendum II on Specialist Training now to be done (hopefully), by Dr. Marcus Reidenberg.

3. The section on training (item 7 in the November 2007 document) would be deleted as now being unnecessary but its author (Prof. Paul Waako) would be consulted about Addendum II once it was in draft form.

   Prof. Folke Sjöqvist would amend the original document and send this out to all parties.

   (ACTION FS).

4. It was agreed that colour pictures and data pictures (eg. bar graphs) could be used in the text of manuscript where this was relevant in order to improve the initial impact of the final document.

NEXT STEPS

The original deadline for the production of manuscripts (September 15th 2008) was regarded as unrealistic because a number of authors had not been informed fully about their tasks following the November 2007 meeting. It was confirmed that the new deadline for the receipt o the completed manuscripts /by Prof. Sjöqvist and Prof. Orme) was December 15th 2008 and a reminder would be sent to all authors who failed to hit this deadline. It was considered essential to have all manuscripts received by January 1st 2009 or the programme would inevitably slip.

The long term aim, after much consultation, was to present the final version of the booklet at the World Pharma congress in Copenhagen in July 2010.

Once all manuscripts had been received the editorial process could be started in order to produce a single coherent document. There would be an ebb and flow of discussion about manuscripts in January and February 2009 but the aim was to produce the first draft of the completed document in mid March 2009. This would be circulated to all authors and to selected individuals for critical review.

The first aim would be to hold a meeting just after Easter (April 15th and 16th 2009) in Florence to discuss the document. The meeting on April 15th would be just for authors of the document and the meeting on the 16th would involve authors as well as selected individuals. The Executive Committee of the European Association for Clinical Pharmacology and Therapeutics (EACPT) was due to meet in Florence on April 17th and 18th for its regular spring meeting. The host for this EACPT meeting was Prof. Piero Geppetti (Prof. of CPT in Florence) and he wold be asked to reserve additional hotel rooms for the nights of April 15th and 16th. (ACTION MO). It was hoped that some members of the EACPT Executive Committee would be able to come a day early to Florence to help in the review and it was also hoped to invite individual key people from other parts of the world to help the review on April 16th. These would be senior office holders in CPT Associations in Africa, SE Asia, Japan, Australasia, North America and Central (and South) America who would be expressing their personal views at this stage. (Once the document had been corrected it would be sent out for formal critical review to IUPHAR, WHO and World CPT Associations). It was possible that representative views could be obtained without bringing people long distances (eg. Prof Joan-Ramon Laporte may be able to give an initial view on behalf of Central and South America). MO agreed to write to key individuals to try to identify the best people to come from outside Europe (eg. Prof. Felix Bochner in Australia, Profs. Paul Waako and Andrew Waluboa in Africa (with a copy to Mahmoud Khayyal in Egypt).

FUNDING OF THE PROCESS

This was a difficult area and while limited funds might be available from some organisations we would need to write to Lembit Rägo at WHO for clarification on this matter since the final document would be a WHO one.

MANUSCRIPT REVIEW

The three main manuscripts that had been received were then examined for their general content. In general they covered their topics well with inevitable repetition that will be addressed in the overall editorial process but it is not proposed to remove all repetition. Comments were made about all three which were in the process of being fed back to the original authors.

The meeting concluded at 12.15 hours

07.10.2008

Michael Orme

Enclosure #2

The IUPHAR-WHO booklet on CPT

– suggestions September 2008 at a meeting in Stockholm

The document should have an Executive summary (1 page) and not exceed 50 pages (double spaced).

It was discussed and agreed that the document should have the following Chapters (the proposed author and length of each individual Chapter are given in brackets).

1. **Introduction** (Prof. Michael Orme)
   Definition of Clinical Pharmacology and Therapeutics (Professor Folke Sjöqvist – 0.5 page, a draft has been delivered)
   History of Clinical Pharmacology (Professor Folke Sjöqvist – 2.5 pages)
   Global Medicines Scene (Professor Michael Rawlins – 4 pages, a draft has been delivered)

Drug Scene Globally is changing and the following issues were pointed out during the discussions. Costs for new drug research and development are increasing. Non-affordable drugs (such as new generation of HIV/AIDS to fight emerging resistance) may challenge Global public health needs. Increasing complexity and safety concerns of new biological medicines. Changes in the disease pattern and turning focus from communicable diseases as the biggest killer to non-communicable diseases. Unavailability of medicines continued to be a problem. Unintended events and increased complexity of new medicines create new challenges - increased use of fixed dose combination (FDC) medicines; effects of Direct to Consumer (DTC) marketing; weak health care systems and service delivery in many resource poor/limited countries; changing Global regulatory environment; market forces contradicting health care needs and "market failure"; role of Public Private Partnerships (PPPs) in research and development for medicines for which there is no market; continuing irrational use of medicines in all of its forms including polypharmacy; the ADR problems appear to increase.

2. **Roles of Clinical Pharmacology**

   5.1 *Research* (Professor Kim Brösen – 5 pages)
   5.1.1. Biomedical
   5.1.2. Clinical
   5.1.3. Society
   5.2. *Teaching* (Professor Simon Maxwell – 4 pages)
   5.2.2. Undergraduate
   5.2.3. Postgraduate (continuous education)
   5.2.4. Specialty training in clinical pharmacology, overview (Paul Waako, 2 pages)
   5.3. *Patient care* (Professor Lars L. Gustafsson – 5 pages, a draft has been delivered)
   5.3.1. Individual
   5.3.2. Special Populations and Diseases
   5.3.3. Society level – clinical pharmacologists as experts to address issues raised by politicians. Pharmacoepidemiology, pharmacovigilance, drug utilization, drug and therapeutics committees, ethics committees.
   5.4. *Industry* (Professor Donald Birkett – 4 pages)
   Role of clinical pharmacologists in research and development including new therapies.
   5.5. *Governments* (Dr. Lembit Rägo – 4 pages)
   Regulatory authorities, insurance – drug reimbursement boards, national drug policies, input for creating scientifically useful electronic patient health records, electronic prescription databases and other databases.

3. **Organization** (Professor Kim Brösen – 3 pages)

4. **Relationship to other drug experts** (Professor Folke Sjöqvist – 2 pages, a draft has been delivered)
   - Clinicians (pharmacotherapeutic experts)
   - Pharmacists
   - Drug analytical expertise
   -
5. **Emerging Roles of CPT** (Professor Petra Thürmann; Professor Ingolf Cascorbi – 3 pages)
   - Biologicals and biosimilars
   - Use of new types of data, drug informatics
   -
6. **The Contribution of Clinical Pharmacology to the Global Public Health** (Professor Anthony Smith 5 pages, a draft has been delivered)

7. **Conclusions** (General Editor – 2 pages)

The following suggestions were made regarding the Addenda.

Addendum I. Model Core Curriculum in Clinical Pharmacology for Undergraduate Training: Professor Simon Maxwell in collaboration with Dr. David Nierenberg, USA and Dr. Ylva Böttiger, Sweden.

Addendum II. Model Curriculum for Specialization in Clinical Pharmacology. Marcus Reidenberg, USA, (to be invited) together with Andrew Waluboa.

From: IUPHAR
Subject: Proposal concerning IUPHAR relations to WHO

-----Message d'origine-----
De : Sam Enna[mailto:SENNA@kumc.edu]
Envoyé : 20 janvier 2009 10:47
À : Sue Duckles; Du Souich Patrick
Cc : Kalle Hoppu; Kalle Hoppu; Folke.Sjoqvist@ki.se; IUPHAR@kumc.edu; ragol@who.int

Patrick - This will be placed on the Exec. Comm. agenda for Cairo, with you as the discussant.

Thanks

Sam

>>> "Du Souich Patrick" <patrick.du.souich@umontreal.ca> 1/19/09 12:33 PM >>>

Dear Sue and Sam,
The three points raised by Kalle are of great importance and should be included in the agenda and be discussed/voted upon at the EC meeting in Cairo.
1. Expand the contract between WHO and IUPHAR made under the rules of NGOs to include the activities of the Paediatric Sub-Committee of the Clinical Division,
2. Discussion about other programs of WHO where IUPHAR could be implicated,
3. I propose that Kalle be nominated for an alternate contact with WHO
Cheers,
Patrick

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-----Message d'origine-----
De : Kalle Hoppu [mailto:kalle.hoppu@fimnet.fi]
Envoyé : 18 janvier 2009 16:26
À : Sue Duckles; Sam Enna; Du Souich Patrick; Folke Sjöqvist
Cc : Kalle Hoppu; Lembit Rägo
Objet : Proposal concerning IUPHAR relations to WHO

Dear Sue, Sam, Patrick and Folke,

I have had recently several opportunities to meet people representing the WHO and to work together with members of the IUPHAR Paediatric Subcommittee to help the WHO by providing paediatric clinical pharmacology expertise for various activities of the 'Better medicines for children' -resolution and the 'make medicines child size' program. Much of this has been made possible by the network of paediatric clinical pharmacologists available through the IUHAR Paediatric Subcommittee, and your help. Also the status of IUPHAR as an NGOs in official relations with WHO has helped, even been the key that allowed me to attend the WHO Executive Board meeting and the World Health Assembly in 2007 when the 'Better medicines for children' resolution was discussed and adopted. I also have had several times in recent years the pleasure to discuss the IUPHAR-WHO relations with Lembit Rägo, who is the official contact of IUPHAR at the WHO (whom I copy on this message also).

I want now to share my experience and opinions on the IUPHAR and WHO relationship for the Executive committee to consider. I know the important work that has been done under the leadership of Folke together with the WHO to define clinical pharmacology globally, and to train clinical pharmacologists in various parts of the world, which both are continuing. These activities have, as far as I understand, been covered by the contract between the IUPHAR and the WHO. However, the paediatric activities, which in the last few years have been substantial, and are likely to remain so, have not been in any official agreement.

For the activities themselves it is of no consequence, whether they are covered by a IUPHAR-WHO contract or not, but it could be of value for the IUPHAR to have also the paediatric activities covered by the contract to maintain its official NGO position. The WHO Principles Governing Relations with Nongovernmental Organizations (attached) state that:
The WHO Executive Board, through its Standing Committee on Nongovernmental Organizations, shall review collaboration with
each NGO every three years and shall determine the desirability of maintaining official relations. The Board's review
shall be spread over a three-year period, one-third of the NGOs in official relations being reviewed each year.

The Board may discontinue official relations if it considers that such relations are no longer appropriate or necessary in the light of changing programmes or other circumstances.
In the discussions with WHO people it has become clear, that a NGO who has little official collaboration in its contract and in the yearly reports it has to provide to the WHO on its activities, may risk loosing its NGO status. Therefore it would be of benefit for the IUPHAR to add to its activities done under the official contract with the WHO, and an easy way would be to add the paediatric activities in the contract.

So my proposal now is for the IUPHAR to consider suggesting the WHO that discussions to expand the contract between WHO and IUPHAR made under the rules of NGOs having official relationships with the WHO should be initiated as soon as possible, especially as the WHO Gates project may offer additional opportunities for agreed collaboration. I would also propose, that while Folke should continue as the official contact person to the WHO from the side of IUPHAR, it should be explored if one of the Paediatric Subcommittee members could be named as an alternative contact.

I also would urge the IUPHAR to consider making better use of the status of a NGO in official relations to WHO. There are at least a couple of other programs, in addition to 'Better medicines for children', the WHO has which are, or in my mind at least should be, of importance for the world basic and clinical pharmacologists, which are listed in the new WHO Medicines strategy.

Kind regards

Kalle

IUPHAR - RE: Proposal concerning IUPHAR relations to WHO

From: IUPHAR
Subject: RE: Proposal concerning IUPHAR relations to WHO

>>> "Rago, Lembit" <ragol@who.int> 1/23/09 3:00 AM >>>
Dear Kalle,

Thank you for this e-mail and sorry for the delay in answering. First, about the facts we have today about the status of IUPHAR as regard to WHO. I have traced down inside WHO what the official status is as per today and I am happy to confirm that the records show that IUPHAR is in official relations with WHO and that I am the designated technical officer (DTO) for IUPHAR. Please also note that IUPHAR will be contacted later this year to submit a report on the IUPHAR collaboration with WHO during the past three years. It would perhaps be already now good time to start Woking on the report and collect all examples of collaboration together. The report will be a very good opportunity to reflect also on the work done in the area of children medicines. Our official records also show that Professor Folke Sjöqvist is the only focal point mentioned in the records.

I think we should perhaps use some of the opportunities to discuss with IUPHAR how to have a better structured cooperation in the future and perhaps seeking IUPHAR official contacts for several specific areas of work. I think we also would need from WHO side increase the number of professionals involved but so far I have had limited success to bring others on board. We as WHO are very interested to be also informed about all the arrangements that IUPHAR has with developing country representatives. I have had some informal contacts but clearly there needs to be more structured approach for the future.

Perhaps we could also from WHO side provide IUPHAR some materials that would help IUPHAR to understand how WHO is structured and working. IUPHAR might also consider contacting when needed our regional advisers on medicines. Contact list can be easily provided.

Best wishes,

Lembit

From: Kalle Hoppu [mailto:kalle.hoppu@fimnet.fi]
Sent: 18 January 2009 22:26
To: Sue Duckles; Sam Enna; Patrick du Souich; Folke Sjöqvist
Cc: Kalle Hoppu; Rago, Lembit
Subject: Proposal concerning IUPHAR relations to WHO

Dear Sue, Sam, Patrick and Folke,

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Kind regards

Kalle

10 February, 2009

Letter to African Pharmacology Socities/Pharmacologists

Dear colleague,

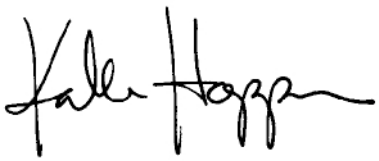
The International Union of Basic and Clinical Pharmacology, in collaboration with our colleagues in paediatrics and paediatric pharmacy, is exploring a project with the World Health Organization to implement the new WHO Essential Medicines List for Children (1) and guidelines for the rational use of medicines. WHO has suggested 14 potential African sites for attention, namely Cameroon, Chad, Congo, DRC, Ethiopia, Ghana, Kenya, Mali, Nigeria, Rwanda, Senegal, Tanzania, Uganda and Zambia.

The IUPHAR Pediatric Subcommittee is seeking countries from this list of fourteen, where the National Pharmacological Societies or some other group of pharmacologists would be interested in collaborating with this project. This project is an important endeavour, which will address the needs for the children of your country and of all countries for safe and effective medicines. The IUPHAR has been helping for some years now the WHO in its endeavour for Better Medicines for Children and we feel this new Essential Medicine List and the accompanying initiative in rational drug use represent a step forward for children everywhere. We also feel that in the coming actions for education and capacity building in relation to paediatric medicines, the active participation of national pharmacologists would be important.

Please let us hear from you as soon as possible if your Pharmacological Society and/or you are interested in collaborating with this project. Please reply to kalle.hoppu@hus.fi (Kalle Hoppu, Chairman, Sub-Committee for Paediatric Clinical Pharmacology, IUPHAR Division Of Clinical Pharmacology).

We hope to hear from you soon if you are interested in being part of this exploratory project.

With kind regards and best wishes,



Kalle Hoppu

1. http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf

Kalle Hoppu, MD. PhD
Chairman, Sub-Committee for Paediatric Clinical Pharmacology
IUPHAR Division Of Clinical Pharmacology
Medical Director
Poison Information Centre, Helsinki University Central Hospital

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