

DRUG DEVELOPMENT FOR PARASITIC DISEASES
2nd COST B22 CONGRESS
University of Siena, Siena – Italy
29 September – 01 October 2005

One hundred and forty participants attended the congress. Although the majority of the participants came from EU- or other countries, which have signed the memorandum of understanding, we were very glad to welcome several scientists from the USA, from various African (Burkina Faso, Nigeria and South Africa) and other overseas countries (Australia, Brazil, Chile, Venezuela, Hong-Kong, Iran, Thailand). Eight participants from developing countries attended the conference under scholarships provided by the IOCD (International Organization for Chemical Sciences in Development). The congress was opened by the local organizer Prof. Giuseppe Campiani, and consisted of 5 sessions, during which 47 oral presentations were given. Furthermore, 57 posters were presented. These posters could be viewed by the participants during the coffee and lunch breaks. Additionally, a special session was dedicated to the best 5 posters selected for short oral presentations by a scientific committee formed by the chairpersons of the different sessions.

The title of the first session was “Drug Discovery and Development for Parasitic Disease in 2005: State of the Art”. To this session contributed Piero Olliario (WHO, Swiss) who highlighted how can publicly and privately funded research contribute effectively to the discovery and development of drugs for neglected diseases, pointing out the complexity of the drug development process for parasitic infections. Additionally Daniel Brasseur (EMA, chairman) was invited to speak about the function and structure of the European Medicines Evaluation Agency (EMA) and he discussed the whole process of registration, marketing authorization and certification of drugs for human use and in particular against neglected diseases. This session then continued with scientific communications, and interesting new data were given by the speakers on drug development especially against malaria. Mark Hamann (USA) was invited to speak about the manzamine alkaloids and their implications on future drug discovery and development efforts. This class of marine natural antiparasitic-antibiotics is highly promising for the control of malaria. Efficacy, pharmacokinetics, fermentation kinetics, metabolic stability, and toxicology studies of these metabolites has provided valuable insight into their potential utility as antimalarial-leads. Hamann illustrated the significant potential the oceans hold for the discovery and development of novel antiparasitic agents. Other antimalarials, such as bisquaternary ammonium compounds were also discussed. Several other speakers dealt with the development of anti-leishmanial and antimalarial drugs.

The second session was entitled “From Parasite Proteomic to Drug Discovery” . The invited speakers in this session mainly discussed the investigation of novel targets for drug development against parasitic diseases such as the sterol biosynthesis in trypanosomes, the dUTPase as a potential target in trypanosomes, leishmania and plasmodium, the enzyme of the trypanothione metabolism as antitrypanosomal drug targets, the ornithine decarboxylase, another potential antileishmanial drug target, and the microtubule system as an antimalarial target. The second part of this session dealt with Leishmania and trypanosomes. Several unique aspects of lipid and amino acid metabolism were discussed. Interesting information were presented about the drug-induced modulation of the Entamoeba Histolytica proteome and transcriptome, the development of ether phospholipids, the identification of new hits against Tripanosoma cruzi pteridine reductase 1 through rapid screening technologies and the gene expression changes during Leishmania donovani differentiation.

The theme of the third session was “Discovery, ADME and Toxicology: Establishing Drug Likeness Early on”. George Mihaly (Australia) was invited to speak on

managing the gap between Research and Development, pointing out the role of Academia in discovery and innovation in medicine, arisen from basic research, although the translation of these medical discoveries into therapeutic entities requires fulfilment of disciplined and systematic development processes, carried out in commercial operations. A case study on ADME + T was introduced by Gabriele Cruciani, a speaker invited to discuss the importance of high-throughput physicochemical techniques and in silico virtual screening in pharmacokinetic lead optimisation. The other speakers of the second part of the session dealt with drug development strategies for antimalarials: the investigation of chloroquine and amodiaquine analogues with optimized dynamic and kinetic properties, the investigation of the mode of action of ferroquine, the development of novel quinolizidinyl derivatives of quinolines, the discovery of novel endoperoxides from marine organisms.

At the end of the session interesting data on the use of antimalarial drugs in pregnancy were presented, together with the definition of the effects of artemisinin on reproduction in mice. In the fourth session, entitled "Artemisinins, Combination Therapy and Drug Resistance", the speaker Nick White (Thailand) presented the exciting story of the clinical development of artemisinin compounds in artemisinin combination treatment of malaria. In particular he reported data on the advantage of the combination of artemisinin compounds with piperaquine (artekin). The artemisinin component given for three days ensures rapid therapeutic response, prevents gametocyte formation (thereby reducing transmission potential), and reduces the parasite biomass. The partner drug eliminates the residual parasites ensuring a high cure rate (> 90%). There is mutual protection against the emergence of resistance. The session continued with Sanjid Krishna who proposed a mechanism of action of artemisinins based on inhibition of the function of a Ca²⁺-ATPase orthologue encoded by *P. falciparum* (PfATP6) and having SERCA-like properties, while Richard Haynes from Hong Kong proposed a different mechanism, based on radical formation, and discussed an interesting set of SARs that led to the development of non-neurotoxic derivatives of artemisinin. Other speakers also discussed the potential role of artemisinin in schistosomiasis and the trematocidal activity of artemisinin analogues. Formulation of artemisinin was also discussed. J. Golenser introduced the treatment of murine malaria by intranasal administration of dihydroartemisinin in a permeation enhancing carrier.

In the second part of the session another clinician from India, Syham Sundar, was invited to speak about the treatment of visceral leishmaniasis and drug resistance. In particular he focused on the situation of leishmania in India and Nepal where the phenomenon of resistance appears to be spreading and the treatment strategies should turn on efficacious multidrug treatment of VL in order to improve compliance and prevent development of resistance. The invited speaker from Thailand, Yongyuth Yuthavong, focused on the dihydrofolate reductases as targets for antiprotozoal drugs. A number of crystal structures of *Trypanosoma brucei* and *T. cruzi* DHFR determined in his laboratory: information from these structures, plus modeled structures of the enzyme from other species, may be in fact exploited for drug development. Other speakers dealt with drug resistance in tripanosomiasis and in leishmaniasis in Africa, Asia and Latin America.

A special session was dedicated to short communications from selected posters and was chaired by Carl Craft and Reto Brun. K. Stuart discussed the mitochondrial function as a target for drugs against trypanosomes, while L. Leon presented the development of novel pyrazole derivatives to treat leishmaniasis. A. Gego presented the development of a new approach for the high-throughput screening of drug activity on *Plasmodium* liver stages in vitro. D. Bonnet-Delpon illustrated novel fluoro artemisinins, hydrolytically more stable than artemether, and H. Jomaa

discussed the identification of an apicoplast-localized electron transfer pathway that is involved in the isoprenoid biosynthesis of Pf.

The fifth and last session was about “International Cooperation for Drug Development”. To this session participated Dr. Carl Craft (MMV), Dr. Else Torrelee (DNDi), Dr. Stephen Matlin (Global Forum for Health Research), who gave us some stimulating thoughts and a comprehensive overview of the obstructions and opportunities for the development of new drugs against parasitic diseases for developing countries. Dr. Mark Felton (GSK) discussed the challenges for R&D for the developing world, while Dr. Gilles Roche (Impact Malaria) spoke about the interaction between big pharma companies and international cooperation for antimalarial drug development.

The congress was closed by the chairman of the COST B22 action, F. Opperdoes, who invited all participants to the next annual conference, which will take place in Athens, Greece. Siena, 20 October 2005

Giuseppe Campiani
Chairman Organising Committee