DOI: 10.1002/cmdc.200700184

Medicinal Chemistry in Parasitology: New Avenues in Drug Discovery

Annalisa Tait*[a]

The European Cooperation in the Field of Scientific and Technical Research (COST) Action B22: Drug Development for Parasitic Diseases was appropriately structured as a multidisciplinary approach to drug discovery and development for neglected diseases. The organization of the expert meeting by working group 1 (drug target identification) and working group 3 (drug evaluation) allowed the presentation of a logical approach to drug development. In this case, medicinal chemistry was selected as the connecting area between the two working groups to perform a continuum landscape within the discovery of new compounds against parasites. Top-ranking scientists in functional genomics, structural biology, and medicinal chemistry had the opportunity to meet and discuss the most important issues related to malaria, African trypanosomiasis, and leishmaniasis. Issues included identification of new drug targets, medicinal chemistry results for lead identification and new strategies adopted to the in vitro development of highly active compounds, the lack of 'shuttle funding' for taking leads from identification to clinical evaluation, funding opportunities from pharmaceutical companies, and government involvement. The crucial issues of intellectual property and effective cost of the final treatment were also discussed.

The expert meeting was attended by 103 scientists:[1] 63 from Italy and the remainder representing 13 different countries around the world, including South Africa and China; the event allowed an intense exchange of information and networking. Fifteen posters were presented. The meeting was divided into three main topics and six sessions.

Participants were mainly from academia and other research centers, with a few representatives from pharmaceutical companies and government institutions, namely Merck Serono (Geneva), Naxospharma (Milan), NEED Pharmaceuticals (Milan), Tydock Pharma (Modena), WHO (Geneva), and CNR-ISTM (Italy). The areas covered by the meeting were molecular biology, functional genomics, established drug targets, compound libraries and screens, inhibitor design, and clinical advances. In addition to well-established researchers, young scientists were also invited as speakers.

Piero Olliaro (WHO-TDR, Geneva) was the keynote presenter and discussed new paradigms for the discovery and development of products for neglected infectious diseases. Miltefosine (Impavido), indicated for the treatment of visceral and cutaneous leishmaniasis, is the only effective drug to have been introduced in recent years, and a number of older drugs, although sometimes very toxic, are still in use. However, in the last three to five years, considerable efforts have been made by foundations and nonprofit research institutions such as the Medicines for Malaria Venture (MMV), Drugs for Neglected Diseases Initiative (DNDI), the WHO, and The Bill and Melinda Gates Foundation to support academic researchers in the development of new drugs. In particular, there has been support for drugs that are nearly ready to enter clinical trials. There is an increasing number of initiatives through private–public partnerships, which involve collaboration between the private sector (such as pharmaceutical companies) and public institutions such as the WHO and other foundations. The new targets addressed are related to the environment of the host–pathogen interaction, and this approach is directed to the identification of proteins that are involved in the internalization of parasites into human cells.

Sessions 1 and 2: drug target identification

The first speaker, M. Navarro (IPB López-Neyra, CSIC, Granada) presented the discovery of mTor protein as a new validated drug target. K. Brown (Imperial College, London) talked about *N*-myristoyltransferase as a potential target for the treatment of parasitic disease. This is a topic related to a collaboration in progress with Pfizer. M. Oullette (Université Laval, Québec) introduced the pteridine reductase enzyme showing unknown function, but with an effective role in drug resistance against folate-related molecules.

In the second session, excellent proteomic work with *Leishmania* spp. was presented by B. Papadopoulou (Université Laval, Québec). Other speakers included D. Gonzalez-Pacanowska (IPB López-Neyra, CSIC, Granada), who presented work related to enzymes involved in uracil nucleotide metabolism as drug targets in protozoa, and A. Fairlamb (University of Dundee), who presented a methodological approach toward target identification and assessment for high-throughput screening.

Sessions 3 and 4: drug development: design and synthesis

The medicinal chemistry session ranged from natural products to synthetic molecules. N. De Kimpe (Universiteit Gent) presented a study on natural, semisyn-

[a] *Prof. A. Tait*
Dipartimento di Scienze Farmaceutiche
Università degli Studi di Modena e Reggio Emilia
Via G. Campi, 183, 41100 Modena (Italy)
Fax: (+39) 059-205-5131
E-mail: tait.annalisa@unimore.it

thetic, and synthetic compounds with antileishmanial activity derived from the Vietnamese plant *Maesa Balansae* Mez. (Myrsinaceae). The structures of the active principles "maesabalides I–VI" were discussed together with results of efforts to standardize the extraction process and SAR on new synthetic derivatives and analogues. T. Calogeropoulou (National Hellenic Research Foundation, Athens) discussed the development of phospholipid analogues as antileishmanial agents. The lecture described CoMFA and CoMSIA activity models for correlation of the antileishmanial activity and stereoelectronic requirements of new ether phospholipids developed from miltefosine, an alkylphosphocholine registered in India for the oral treatment of visceral leishmaniasis. A. Dobbs (Queen Mary, University of London) gave a talk on the development of a new unifying strategy for the total synthesis of several C-aryl glycosides and their corresponding aza analogues. Several examples were reported, such as the total synthesis of centrolobine, an antiparasitic glycoside (which targets *Leishmania amazonensis* promastigotes), obtained in five linear steps with an overall yield of 37%, and efforts toward the total synthesis of kendomycin, a potent endothelin receptor antagonist. S. MacKay (Strathclyde University, Glasgow) described the identification of benzodiazepines as a new structural class of antileishmanial agent with better activity and toxicity profiles than those of clinically used drugs.

G. F. Ruda of Professor Ian Gilbert's research group (University of Dundee) reported the discovery of new potent and selective inhibitors of *T. brucei* 6-phosphogluconate dehydrogenase, the third enzyme of the oxidative branch of the pentose phosphate pathway. These compounds mimic the high-energy intermediate produced in the reaction catalyzed by this enzyme. To improve in vitro activity, a phosphate ester prodrug approach was adopted.

In the fourth session, K. Chibale (University of Cape Town) presented the use of rationally selected promiscuous chemical scaffolds as an approach in antiparasitic drug discovery. A SAR study of thiosemicarbazones that can inhibit multiple disease-causing organisms (*T. cruzei*, *T. brucei*, and *P. falciparum*) with multiple targets including proteases were reported. R. K. Haynes (Hong Kong University of Science and Technology) described the preparation and antimalarial activities of *N*-sulfonyl- and *N*-carbonyl-11-azaartemisins with improved thermal stability. The compliance of these new derivatives with WHO/ICH guidelines for thermal stress testing of drugs required for storage in countries in climatic zones III and IV was emphasized. C. Biot (ENSC, Lille) focused his talk on the mechanism of action of ferroquine, a promising organometallic antimalaria drug candidate. The importance of oxidation pathways involving iron(II) and iron(III) were highlighted. H. P. De Koning (University of Glasgow) presented a library of 62 curcumin derivatives that were tested against *T. brucei*, *L. major*, and *L. mexicana*. The most active compound displays low toxicity and no cross-resistance with existing trypanocides. The mechanism of action was investigated; activity was found to be independent of DNA binding. C. Fattorusso (Università di Napoli) presented two new molecular scaffolds to generate potent antimalarial agents: one is based on the polyaromatic scaffold of clotrimazole, and the other is characterized by a hydrazone linker. Detailed SARs of a series of compounds with a hydrazone moiety linking a polyaromatic structure to various heteroaromatic ring systems were discussed.

Sessions 5 and 6: advanced methodologies in drug discovery for parasitic diseases

These sessions were focused on screening approaches in early phase drug discovery. The ability to predict the in vitro activity of new molecules and to set up innovative analytical methods were presented. R. Brenk (University of Dundee) presented an approach toward the assembly of a screening library designed to discover hits for neglected diseases together with quality assessment. Chemical identity, purity and solubility assessments, and diversity analysis ensure the library's high quality. G. Cruciani (Università degli Studi di Perugia) proposed the use of pharmacophore fingerprints as a tool to drive docking simulations or to compare protein binding sites. A. Cavalli (Università di Bologna) discussed a combined molecular dynamics and docking study on the β-hydroxyacyl-ACP dehydratase (Fab2) of *P. falciparum*.

The final session, introduced by S. MacKay, was left to the presentation of various topics including SAR studies on amphotericin derivatives and new optimized leads effective in vivo that are ready for the pre-clinical phase. J. Golenser (Hebrew University of Jerusalem) presented a new formulation of amphotericin B based on an imine conjugate with modified aldehyde groups. S. Henrich (EML Research, Heidelberg) introduced two methods of analysis: comparative binding energy (COMBINE) and the protein interaction property similarity analysis (PIPSA), together with applications. S. Melato (CNR, Milan) presented a combinatorial approach for the synthesis of novel antimalarial quinoline compounds as analogues of cycloguanil and chloroquine with improved efficacy against both CQ-S and CQ-R strains of *P. falciparum*. The last communication was given by S. Romeo (Università degli Studi di Milano), who discussed novel inhibitors of plasmepsins (PLMs), the aspartic proteases involved in the degradation of hemoglobin during the blood stage of *P. falciparum*. Considering the redundancy of PLMs, it is necessary to design compounds that are able to inhibit two or more members of this enzyme family in order to develop active drugs. Some compounds, designed on the basis of the "double-drug" approach as PLM II inhibitors, inhibited PLMs I, II, and IV in the nanomolar range and were also highly selective for PLMs over human cathepsin D.

Donatella Taramelli closed the meeting with a presentation of the list of research laboratories involved in COST Action B22 and which are available for compound evaluation. She underscored the importance of the network that the present COST action is creating and the particular importance of reinforcing and integrating the screening labs.

The general impact of the meeting was good, and the feedback was positive. The high quality of the science pre-

sented reflected the competence of those who accepted the invitation to speak at this conference. Another positive aspect was the attendance of many young scientists and students. The meeting's success is also a result of the joint efforts of the hosting institution representative, Maria Paola Costi (Università degli Studi di Modena e Reggio Emilia), and Donatella Taramelli (Università degli Studi di Milano), Dolores Gonzalez-Pacanowska (IPB López-Neyra, CSIC, Granada), and Fred Opperdoes as the COST Action B22 representative.

[1] Total registered participants: 103 (male: 47, female: 56), young scientists (under 35): 40, senior: 63; meeting website: http://cdm.unimo.it/home/dipfarm/costi.mariapaola/mcpll_2007_home.html. The congress was sponsored by the COST Action B22 (http://www.icp.ucl.ac.be/cost/costB22), Division of Medicinal Chemistry of the Italian Chemical Society (http://www.soc.chim.it/divisioni/chimica_farmaceutica), Università degli Studi di Modena e Reggio Emilia (http://www.unimore.it).

Received: July 30, 2007
Published online on September 11, 2007

