



AntiMal News



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Issue 2

New African Partners Join the AntiMal Consortium

The AntiMal consortium will expand to 34 partners very soon, with the integration of three new partners from Africa. The principle aim of this expansion is to increase the volume and diversity of the AntiMal portfolio.

The Council for Scientific and Industrial Research (CSIR), based in South Africa is one of the leading research and development, technology and innovation institutions in Africa and undertakes approximately 10% of all research and development on the continent. CSIR Biosciences will conduct research into novel antimalarials from natural products. South African botanical material will be screened for antimalarial activity and active molecules will be isolated for further analysis and

development. The Principle Investigator (PI) of this group and workpackage is Dr Chris Parkinson.

The Kenya Medical Research Institute (KEMRI) group under the leadership of Dr Alexis Nzila represents international expertise in antifolate antimalarial drugs with a proven track record in molecular and biochemical studies as well as field investigations. His research has so far been used to fight malaria in Kenya and Nigeria. Both cancer cells and the malaria parasite multiply readily and rely upon the availability of folates in order to grow. Dr Nzila has provided evidence that low and non-toxic antifolate anticancer drugs, such as methotrexate could be used in combination with folate mole-

cules to treat malaria. By comparing the role of folates in cancer cells to their function in malaria, Dr Nzila was able to understand their function more clearly - particularly their role in causing resistance to a popular malaria drug. Dr Nzila will work with Dr Maina Ngotho from the Institute of Primate Research (IPR) on a new workpackage to investigate novel antifolates as antimalarial agents.

These three new partners will add two new exciting drug discovery/development initiatives to the AntiMal consortium in areas underrepresented in the current portfolio. The EU contribution to the AntiMal consortium will increase by 250,000 Euros as a result of these new initiatives.



CSIR team with Dr Chris Parkinson, back row, last on right

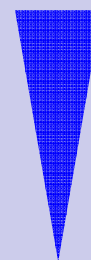


KEMRI team with Dr Alexis Nzila, second from right



IPR team with Dr Ngotho, second left

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September Review

The goal of the AntiMal project is to establish a portfolio of new antimalarial drugs from within the European scientific community, to manage this portfolio through an industry standard, pre-clinical evaluation and select candidates from within the portfolio for progression to "first into man" studies.

In order to achieve this goal a major review of the AntiMal portfolio will be conducted in

September 2007. An External Scientific Advisory Committee (ESAC) of ten experts in the field of malaria drug development and African public health has been established to conduct this review in an independent and transparent manner.

The aim of the review process is to selectively fund those projects that are most likely to achieve the AntiMal goal over the remaining three years of the project.

As a result of this review the composition of the consortium will change as a smaller number of the most promising drug development programmes will be fast tracked over the remaining years of the project.

All of the research groups within the consortium are currently working very hard to produce the pivotal results to present to ESAC at the September review.

Workshops Scheduled for 2007

A workshop on Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) will be held in Liverpool in the second quarter of 2007. This three-day residential course will be available to members of the AntiMal consortium and a limited number of non-consortium individuals.

A Project Management workshop will be held in Nairobi, Kenya on the 19th, 20th and 21st of September 2007. This will also be a three-

day residential workshop covering the basic principles of project management including project management tools together with people and team skills. The workshop will also include exercises and case studies.

Further course details and the process for application through the secure website will be made available soon by the Management Office in Liverpool



PhD Student Projects Spotlight



Sara Finaurini from Italy is working on a project to investigate the cellular basis for quinoline/peroxide antimalarial interactions and their implications for drug efficacy and toxicity. "This work will be the result of training in three laboratories, under the supervision of Professor Donatella Taramelli and Dr Diego Monti (University of Milan,

Italy) and Professor Steve Ward (Liverpool School of Tropical Medicine). Artemisinin combination therapy (ACT) is strongly recommended by WHO guidelines especially as an oral treatment of uncomplicated *P. falciparum* malaria. Consequently, different combinations of quinoline/artemisinin derivatives are currently under evaluation. The mechanism and site(s) of action of both classes of drugs are still controversial and the interactions of these compounds when used in combination have not been completely elucidated.

The aims of this project are to investigate the basis of these drug/drug interactions from three points of view:-

1. Chemical interactions: the different chemical reactivity of quinoline/artemisinin

derivatives will be tested in the presence of reducing agents and their interactions with heme in infected red blood cells and/or a cell free system will be evaluated.

2. Antimalarial drug interactions: the role of the association of drugs on *P. falciparum* culture will be analysed to determine the efficacy and possible synergism/antagonism and define the best ACT for clinical tests.

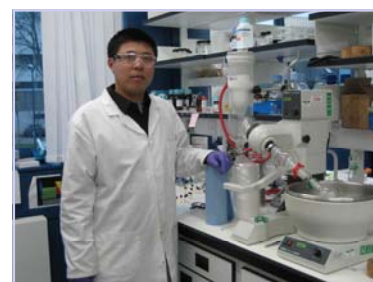
3. Toxicity and drug interactions: although generally considered safe, the artemisinins do carry a potential reprotoxic effect and their safety in pregnancy is still not well documented. For this purpose, we are using a new method to study embryo toxicity with cell lines of erythroid origin. The effects of artemisinins and the potential modifying role of the quinolines will be evaluated."

Huaqing Cui is working in the laboratory of Professor Ian Gilbert at the University of Dundee on the project entitled "Nucleoside Drug Targets in *Plasmodium falciparum*". This project is run in collaboration with Professor González-Pacanoska in Granada in the field of Proteomics and Huaqing will also carry out molecular biology experiments with Professor Francis Mulaa at the University of Nairobi.

Huaqing explained that "pyrimidine nucleotide biosynthesis inhibition in the parasite is a major route for therapeutic intervention against the disease. In the last two decades, much work has focused on making inhibitors against enzymes involved in the pyrimidine metabolism pathway. Meanwhile, proteomics has emerged and vastly improved.

As a new but matured technique, the proteomics approach has been widely used in the biological field, from the analysis of full protein expression profiles of certain organisms to the identification of single unknown proteins. The aim of our recent work is to test the technical possibility of chemical proteomics in the identification of novel nucleoside drug targets.

We have synthesized a number of nucleoside probes which will be used in chemical proteomics studies in order to identify new pyrimidine binding proteins. The first stage of the work has been completed in Dundee and the nucleoside analogues will now be used in Granada, where they will be coupled to solid supports to allow isolation of binding proteins. Proteins which bind to these



nucleoside analogues will be identified by a combination of SDS-PAGE/MALDI-TOF Mass Spectroscopy or 2D/MALDI-TOF Mass Spectroscopy.

A second aspect of our work is the characterization of known enzymes in pyrimidine metabolism with the aim of exploring their potential as drug targets for Medicinal Chemistry".



PhD Student Projects Spotlight (Continued)



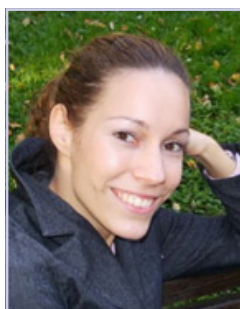
Patrice Mimche from Cameroon is working at the Immunology Unit of the London School of Hygiene and Tropical Medicine under the direction of Dr Livia Vivas and the Department of Public Health Microbiology-Virology of the University of Milan with Prof Donatella Taramelli.

Patrice explained that "malaria continues to be a major public health problem in the developing world and the

situation has worsened as a result of widespread drug resistance. To curb this trend, new and affordable drugs with a wide range of mechanisms of actions are urgently needed. My project is focusing on the modulation of CD36 expression and monocyte/macrophage function by antimalarial drugs, ultimately enhancing parasite clearance by non-opsonic phagocytosis of *Plasmodium falciparum*-infected erythrocytes (PE). CD36 is a class B scavenger receptor under the transcriptional control of the Peroxisome Proliferator Activated Receptor-Retinoic Acid Receptor (PPAR γ -RXR), a nuclear hormone receptor involved in lipid transport and metabolism that has been shown to be up-regulated by thiazolidinedione agonists, enhancing PE phagocytosis and inhibiting NF κ B and the production of proinflammatory cytokines. Currently available antimalarial drugs

and those developed under the AntiMal program will be screened for their capacity to specifically up-regulate monocyte/macrophage CD36, PPAR γ -RXR, expression, phagocytosis of PE and downregulate pro-inflammatory cytokines involved in malaria pathophysiology. These effects will be measured on monocytic cell lines (THP-1 and U937), peripheral blood mononuclear cells and dendritic cells from different donors.

This "host-targeted approach" will ultimately demonstrate an additional mechanism of action of antimalarial drugs that will complement their direct anti-parasitic effect due to interference of specific parasite biological processes. In addition, the effects of anti-malarial drugs on infected and uninfected red blood cell membranes and their susceptibility to phagocytosis will be also explored with the aim of finding adjunct therapies to ameliorate anaemia".



Ksenija Slavic is involved in the project entitled "Functional analysis of metabolite and drug carrier systems in *Plasmodium falciparum*". "I joined this project as a PhD student in Professor Sanjeev Krishna's group at St. George's Hospital Medical School in London. It was this group that first identified and functionally characterized the hexose transporter PfHT in *Plasmodium*

falciparum. Our aim is to further investigate PfHT and provide its genetic validation as a novel drug target. Furthermore, exploiting tools of genetic engineering we aim to rationally target PfHT with the ultimate goal of identifying new classes of animalarials". This PhD project is run in collaboration with Professor Michael Lanzer at the University of Heidelberg.



Francesc Marti from Spain is working with Professor Giuseppe Campiani at the European Research Centre for Drug Discovery and Development, NatSynDrugs at the University of Siena in Italy. "The project will focus on the development of a synthetic strategy to produce novel endoperoxides structurally related to Plakortin and will be run in collaboration with the University of Liverpool and CNRS in Toulouse".

Francesc explained that "causing about 2 million deaths every year and affecting more than 500 million people, malaria is one of the major causes of mortality around the world. The increase of resistance to chloroquine (CQ) by *Plasmodium falciparum* (Pf), one of the parasites responsible for malaria, and the limited number of available and effective drugs against it makes the discovery of new animalarials a crucial challenge. Artemisinin is a sesquiterpene endoperoxide derived from *Artemisia annua* and along with its derivatives has proved to be very potent against Pf. Its antimalarial activity is mainly due to its endoperoxide pharmacophore. Another natural source of stable cyclic endoperoxides is marine organisms. One of these organisms, the Caribbean sponge *Plakortis simplex*, has turned out to be a source of several of these cycloperoxides. Several natural endoperoxides isolated from

Plakortis species were investigated *in vitro* for antimalarial properties and the six-membered endoperoxides plakortin and dihydroplakortin proved to be the most potent against CQ-resistant Pf strains, although 50 times less active than artemisinin. The goal of our study is the development of a versatile synthetic strategy for plakortin-related derivatives with simplified structure by means of stereoselective and regioselective reactions in order to obtain the desired chiral products.

One of the key issue in this process is the stereoselectivity of the reactions and the formation of the chiral 1,2-dioxane skeleton. Combining Sharpless asymmetric epoxidation to the Mukaiyama-Isayama Co(II)-catalyzed regioselective hydroperoxysilylation of an alkene we synthesized a key intermediate to generate a new class of synthetic analogues of plakortin."



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Gender Action Plan for AntiMal by Professor Donatella Taramelli

The resolution of the European Council regarding Women in Science in 2001 suggested several initiatives to promote gender equality in science and to increase the participation of women in science in EU Member states through the Research Framework Programmes. Since then, contractors of FP6 integrated projects or network of excellence are requested to develop a Gender Action Plans (GAP) as part of their projects.

As a first step, a diagnosis of the situation regarding women's participation to the AntiMal consortium was performed. A questionnaire was sent out to all work-

package (WP) managers and 16 reports were received. Results showed that of the 155 participants recorded in the reports, there are 73 (47%) men and 82 (53%) women, with a minimal female majority. However, the distribution between male and female changes significantly with respect to position and function within the AntiMal programme (Fig 1). In leading positions or elevated work levels, a male majority is found (manager, team leader, experienced researcher), whereas young researchers and technicians are predominantly female. The percentage of female workers is 23% among the WP managers and rises to 72% of the

technical staff and to 80% of the administrative staff. The 23% of female WP managers is slightly lower than the gender distribution reported in FP6 for evaluation panels, advisory groups, programme committees which are 27%, 27% and 25%, respectively (EU-25-2004). As in other fields, there is the need to increase the number of women in leading positions.

Using the questionnaire, a database of names and e-mail addresses of female AntiMal participants was also completed. It will be used to distribute information and a calendar of initiatives related to the AntiMal gender implementation programme.

Fig 1 Gender representation within the AntiMal consortium. (2006 survey)

