



AntiMal News



December 2009

Issue 4

AntiMal At The World's Largest Malaria Conference



The 5th Pan-African MIM conference was held at the Kenyatta Centre in Nairobi, Kenya from the 2nd to the 6th November. AntiMal took the podium, hosting two symposia on antimalarial drug development. The consortium was represented by 28 members, each presenting either an oral or poster presentation during the symposia.

The first symposium focussed on early stage drug discovery and the invited speaker was Kelly Chibale from the University of Cape Town who discussed the challenges and opportunities of discovering and developing antimalarial drugs in Africa by Africans. This was followed by another 8 presentations from students and researchers within the consortium.

The second symposium was dedicated to later stage antimalarial drug discovery. The invited speaker was Jose Garcia Bustos from GSK who was followed by 6 speakers from the AntiMal consortium. This session described current research activities associated with the development of a range of antimalarial drugs

Both sessions were well attended and well received. Further details can be obtained at:-

<http://www.tropika.net/svc/specials/mim2009/session-reports/symposium-13>

<http://www.tropika.net/svc/specials/mim2009/session-reports/symposium-38>

Forthcoming Events



14-15th December 2009

ESAC Review, Liverpool, UK

18th May 2010

Management Committee Meeting, University of Milan, Italy

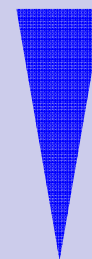
7-9th September 2010

IP and Clinical Trials Workshop, Gabon

28-29th September 2010

Joint Cluster Meeting, St Georges Hospital School, London

INSIDE THIS ISSUE:



AntiMal at MIM	1
Forthcoming Events	1
ESAC Review	2
Good news story	2
Leadership Course	3
Traditional Healers in Burkina Faso	3
PhD Student spotlight	4
ADMET Course	4

ESAC Review March 2009

The goal of the AntiMal project is to establish a portfolio of new antimalarial drugs from the scientific community and to select candidates from within the portfolio for progression to "first into man" studies within the 5 year programme.

An external scientific advisory committee (ESAC) was established to assess the scientific progress of the individual work packages on an ongoing basis. The committee consists of eight experts in the field of malaria and drug development who are independent of the scientific research funded by AntiMal.

The second AntiMal review was held on the 3rd and 4th March 2009. The feedback from ESAC and the EU Commission on the progress of the AntiMal project was very positive. Many workpackages have progressed well since the last review and the African capacity building initiative was highlighted as a very positive aspect of the programme.

As a result of the review, the following work packages were selected for further funding until the end of the project

Cluster	PI	Work Package	Title
1	Steve Ward	4.1.1.1	Novel 4-aminoquinolines 1
	Donatella Taramelli	4.1.1.2	Novel 4-aminoquinolines 2
	Collen Masimirembwa	4.1.1.4	Strengthening the DMPK platform at AiBST and medicinal chemistry at UCT
2	Paul O'Neill	4.1.2.1	Synthetic peroxides
	Souleymane Sanon	4.1.2.5	Assessment of the antimalarial activity of medicinal plants used by traditional healers in Burkina Faso
	Chris Parkinson	TTC2	Novel antimalarials from natural products
3	Henri Vial	4.1.3.1/2	Discovery and selection of an orally-potent bithiazolium antimalarial
4	Christian Doerig	4.1.4.1	Protein kinase targets: validation, screening and structure
	Michael Lanzer	4.1.4.5	Development of novel bisarylurea compounds with high efficacy against Plasmodium falciparum
	Arsalan Kharazmi	4.1.4.7	Novel chalcones as antimalarials
	Alexis Nzila	TTC1	Novel antifolate based antimalarials
5	Livia Vivas	4.1.5.8	Platform for efficacy studies and potential drug combinations to delay resistance development

The next ESAC review will be held in Liverpool on the 14th and 15th of December 2009

Good News Story...



Congratulations to Sara Finaurini and family.

On behalf of the AntiMal Consortium we would like to welcome our newest AntiMal baby, Anna Bonifacio. Sara Finaurini, who is one of our AntiMal PhD students gave birth to Anna on the 7th November 2009 weighing 3.4 kilos.



Leadership Workshop



Teamwork in action

In October 2009 twenty-one members of the AntiMal consortium converged on the little village of Les Diablerets in the Swiss Alps for a leadership course. The group was made up from several Institutes across the consortium, including the University of Nairobi, the University of Milan and CNRFP in Burkina Faso. Delegates with a variety of skill sets were each looking for a new way to lead and cultivate their teams.

From the very first evening all the participants were told to throw away all inhibitions and prepare to live outside their comfort zone for the following 72 hours. The course was designed to be a highly interactive and practical skills development workshop, for academic professionals keen to improve their personal effectiveness, influencing skills, strategic thinking and leadership capabilities.

The workshop was aimed at both junior and senior members of AntiMal, investigating working relationships already in place and how to invest time, and energy into the improvement of those relationships. Over the three days each delegate took part in a variety of activities which included looking at personality types, working under pressure and ways of communicating with others.

Interspersed were some fun team building exercises, which encouraged bonding, and friendship, amongst the team.

By the end of the course, everyone felt better equipped to deal with the day to day management of their labs, and teams. The tools each participant took away from this course will help toward the smooth running and ultimate success of the AntiMal project.

Traditional healers in Burkina Faso



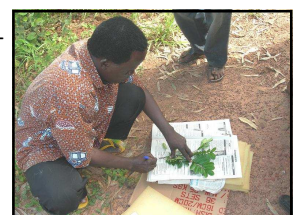
Scientists from the Centre National de Recherche et de Formation sur le Paludisme (CNRFP) in Burkina Faso are currently investigating the antimalarial activities of plants routinely used by traditional healers. The plant materials used in this investigation have been screened after ethnobotanic and socio-anthropologic surveys performed in the Province of Comoé, South-West of Ouagadougou, Burkina Faso. This part of the country is well known for the wide utilisation of medicinal plants to treat various diseases. It is one of the regions where there is a well organised network of traditional healers working in partnership with local health care centres.

The CNRFP team in collaboration with

the associations of traditional healers, local population and the health regional staff of Comoé province has obtained the list of traditional healers operating in the area. Based on this list they randomly selected 45 out of 312 traditional healers to take part in the preliminary investigation.

A total of 176 plants were cited in the treatment of malaria by the traditional healers and 31 of them were cited more than once. Those 31 plants have been identified by the study botanist through the local name in Dioula Mooré and by physical examination with the presence of a traditional healer. Amongst the 31 plants, 8 plants have never been studied for their pharmacological activities (*in vitro* efficacy assays using resistant strain). These plants were *Cassia sieberiana*, *Entada africana*, *Entada sudanica*, *Sarcocephalus latifolius*, *Zanthoxylum zanthoxy-*

loides, *Vitex doniana*, *Anogeissus leocarpus*, and *Combretum molle*. A specimen of each plant was kept in the CNRFP herbarium. Parts of plants used in traditional medicine according to the traditional healers, were collected washed, dried and pulverized. The powder obtained was used to prepare crude extracts with different polarity solvents. The crude alkaloids extract was also prepared since these types of chemical entities often exhibit pharmacological activities. These various crude extracts are being studied at CNRFP to assess antiplasmodial activity *in vitro* against *Plasmodium falciparum* resistant and sensitive strains.



PhD Student Projects Spotlight Victoria Jeffers

I moved from my native country, Ireland, to the Netherlands to start my PhD with AntiMal through the European Malaria Graduate School. Based at the Biomedical Primate Research Centre working with Dr. Clemens Kocken, I began to investigate the role of the chloroquine resistance transporter (CRT) in chloroquine resistance. The proposed mode of action of chloroquine is the disruption of haem polymerisation in the food vacuole, resulting in a build up of this toxic by-product causing death of the parasite. This compound has now become almost useless in treating malaria due to the emergence of resistant strains of *Plasmodium*. However the mutations in a transporter-like molecule (PfCRT) that are closely associated with chloroquine resistance (CQR) in *P. falciparum* are not found in resistant *P. vivax*, suggesting a different resistance mechanism in *P. vivax*. Indeed, a recent study suggests that *P. vivax* parasites are most sensitive to chloroquine at a completely different stage in the asexual cycle than *P. falciparum*, hinting at perhaps a different mechanism of action of the drug in the species. Studies on *P. vivax* are difficult as routine *in vitro* culture of this species is not possible due to its dependency for invading reticulocytes. The non-human primate malaria *P. knowlesi* can be used as a good model for *P. vivax*. It is phylogenetically related to *P. vivax* and infects humans as well as the experimental host, the rhesus macaque, used for *in vivo* studies. *In vitro* culture and transfection is possible and the full genome sequence has recently been published, making this parasite very amenable to genetic manipulation.

In the initial stages of these studies I noticed that there appeared to be some distinct differences between the

food vacuole morphology of *P. knowlesi* and that of *P. falciparum*. Using an acidotropic stain which accumulates and fluoresces in acidic compartments such as the food vacuole, I noticed that *P. knowlesi* parasites contained a number of small individual acidic compartments in contrast to *P. falciparum* which has only one. This extends to another primate malaria closely related to *P. vivax*, *P. cynomolgi*. I found these developments intriguing and set out to further characterise the food vacuole morphology of *P. knowlesi*. I have created a number of transfectant parasites which express a protein fusion consisting of known food vacuole proteins with fluorescent protein tags. In collaboration with Prof. Michael Lanzer's lab at the University of Heidelberg and applying their experience in the imaging of *P. falciparum* food vacuoles to *P. knowlesi*, I am working to elucidate the biogenesis of food vacuoles in *P. knowlesi* by visualisation of the fluorescently tagged proteins throughout the erythrocytic cycle.

Using *P. knowlesi* as a model for *P. vivax*, I hope to characterise some differences between the food vacuoles of these parasites and those of the well studied *P. falciparum*. Should there be fundamental differences between the food vacuoles of these *Plasmodium* species, it could have important implications for antimalarial drug development. The unique nature of the food vacuole makes it an important target for new antimalarial compounds. A detailed understanding of this organelle is required in both *P. falciparum* and *P. vivax* if a drug is to be developed which is effective against both species and is able to delay the onset of drug resistance for as long as possible.

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ADMET DMPK Course May 2009

During the period 25-29th May 2009, biologists and chemists interested in drug discovery and development participated in an intense course in which they learnt the latest strategies in the integration of ADMET (absorption, distribution, metabolism, excretion and toxicity) in Medicinal Chemistry. The course involved lectures and hands on exercises in computational modeling and attracted participants from different countries and biomedical research backgrounds. They included senior scientists, postdoctoral fellows and PhD students, a balanced mix that encouraged intellectual exchange of ideas and experiences.

The course was presented by lecturers with both academic and industrial experience in the sciences and technologies of drug discovery. These included, Prof. Kelly Chibale (UCT), Prof. Guy Kip (St Jude's Childrens Research Hospital, USA), Prof. Ismael Zamora (Lead Discovery Ltd, Spain), Prof. Ian Gilbert (University of Dundee, UK) Dr. Lourdes Cucurull-Sanchez (Pfizer) and Dr. Collen Masimirembwa (AiBST).

The course design was such that each day's lectures included an introductory lecture on the biological aspects of the DMPK parameter(s) of interest followed by a medicinal chemistry perspective of the parameter(s) and computational modeling approaches to addressing the various ADMET issues.

The overwhelming positive feedback from the participants was the ultimate measure of the success of the course. Comments from the delegates proved that this was a timely and relevant course in addressing the gap in knowledge on the importance of ADMET in drug discovery and an introduction to the tools of how to address ADMET issues in projects.

