ผู้ดำเนินการอภิปราย: *รองศาสตราจารย์ ดร. วิจิตรา ทัศนียกุล*
ภาควิชาเภสัชวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

10.15 – 10.30 น.   พักรับประทานอาหารว่าง

10.30 - 12.00 น.   ชมและตัดสินการแสดงผลงานวิชาการ โปสเตอร์
โดย คณะกรรมการประกวดผลงาน

12.00 – 13.00 น.   พักรับประทานอาหารกลางวัน

13.00 – 14.30 น.   **Session 5: Drug Design By Molecular Modeling**

Drug Design Approaches: Molecular Modeling, Computational Chemistry
and Combinatorial Chemistry
ศาสตราจารย์ ดร.สุภา หารหนองบัว
คณะวิทยาศาสตร์ มหาวิทยาลัยเกษตรศาสตร์

Drug Discovery: Pharmacokinetic/Pharmacodynamic Fitting and Simulation
รองศาสตราจารย์ ดร.กอบธัม สถิรกุล
คณะเภสัชศาสตร์ มหาวิทยาลัยมหิดล
ผู้ดำเนินการอภิปราย: *รองศาสตราจารย์ ดร.กอบธัม สถิรกุล*
คณะเภสัชศาสตร์ มหาวิทยาลัยมหิดล

14.30 – 14.45   พักรับประทานอาหารว่าง

14.45 – 16.15   **Session 6: Chemotherapy and Discovery of Chemotherapeutic Agents: Research on Natural Products**

From Herbal Medicine to Modern Medicine: New Leads for Infectious and Cancer
Chemotherapy
รองศาสตราจารย์ ดร.อรุณพร อิฐรัตน์
คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์

Marine Compounds as Sources of Chemotherapeutics
ผู้ช่วยศาสตราจารย์ ดร. คณิต สุวรรณบริรักษ์
คณะเภสัชวิทยา จุฬาลงกรณ์มหาวิทยาลัย
ผู้ดำเนินการอภิปราย: *รองศาสตราจารย์ ดร. อรุณพร อิฐรัตน์*
คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์

16.15 – 16.30   พิธีมอบรางวัลการเสนอผลงานวิจัยดีเด่น
ปิดการประชุม

Chiravat Sadavongvival Memorial Lecture

The challenge of identifying novel antimalarial drug candidates

Steve Ward

Liverpool School of Tropical Medicine, University of Liverpool, UK

The need for the next generation of novel antimalarials is highlighted by the reports of reduced parasite susceptibility to the artemisinins emerging from the Thai Cambodian borders as early as 2003 and finally confirmed in 2009 (Dorndorp et al 2009, Cui and Su 2009). After the demise of chloroquine and pyrimethamine/sulphadoxine and the loss of efficacy of mefloquine, the use of drug combinations containing an artemisinin was heralded as a very timely solution to the burgeoning malaria problem worldwide. In fact leading scientists of the day when asked about potential resistance to this new drug class were quoted as saying "not in our life-time" Sadly this seems now to have been naïve and over-optimistic. If history tells us anything it is that the malaria parasite is more than well equipped with the evolutionary equipment to thwart our efforts at chemotherapy. Having said that we should not underestimate the huge impact the artemisinin - based combinations are having and will continue to have in the control and treatment of malaria globally over the short to medium term. However it is clear we now need a Plan B.

The Antimalarial drug development path, as with any drug development path, is both time-consuming and expensive. In reality any screening hit identified today would take 10-15 years before it became a therapeutic reality for patients in malaria endemic countries using the accepted drug development paradigm. So it is important that at the outset we are clear on what type of drug we want to develop, often referred to as the Target Product Profile (TPP). The TPP will differ depending on the end use of the drug e.g. treatment of non - severe *falciparum* disease, prophylaxis, radical cure etc. and several organisations including WHO and MMV have TPP's for malaria published on their websites (Wells et al 2009). This has become increasingly important in the so-called "malaria eradication era". The drugs that will be required to eradicate malaria will not necessarily have the same TPP as drugs needed in the control and treatment phases of this programme.

Through the efforts of organizations such as the Medicines for Malaria Venture (MMV), the antimalarial drug development pipeline is as healthy as at any time in recent history. However a cursory glance at the molecules in the portfolio reveal some causes for concern. There are very few drugs that genuinely target novel parasite processes, there is a heavy reliance on variations of existing themes including in the peroxide based drug class and there is a dearth of drugs that are being developed with a view to eliminating liver stage parasites including hyponozoites, gametocytes and other species most notably *P. vivax*. That being said, these specific areas are being specifically targeted for funding as we move forward (Wells et al 2009).

Efforts to rationally develop antimalarial drugs against specific and novel parasite targets has so far proven difficult without a single successful example in the clinic. The malaria genome has been in the public domain for nearly a decade (Gardner et al 2002). Yet despite significant scientific endeavour the number of truly validated is small (Wells et al 2009, Olliaro and Wells 209, Aguero et al 2008). There are many factors that contribute to this but the difficulty in developing a condition knock out strategy for falciparum malaria and a genome where almost half the genes have no know function are significant contributors.

Faced with this poor return on effort, the community has moved towards whole cell *P. falciparum* screening of chemical libraries as a source of new parasite specific antimalarial

"hits". This approach, sponsored in large part by MMV, has proven spectacularly successful. To date some 5 million individual compounds have been screened and up to 20,000 different compounds have been identified that kill *P. falciparum in vitro* with IC50 values in the sub-nanomolar range (Wells et al 2008). The *P.falciparum* genome has approximately five and a half thousand genes and from extrapolation with other cellular systems it might be reasonable to expect that less than 5% of these genes would represent genuinely druggable targets. Based on this argument, many of the 20,000 novel hits must target a common gene product.

This is a fantastic new resource for the community, but there are many hurdles before these hits become drug candidates and then ultimately drugs in the clinic. Even for the biggest of pharmaceutical companies working in one of the "block-buster" therapeutic areas, it would be impossible to rationally triage 20,000 compounds into a hit to lead programme even if substantial singletons can be clustered based on some a priori feature. To do the data justice will require input from the whole malaria community with partnerships between academia and industry. The first challenge will be to ensure that this data reaches the public domain, which unfortunately has not been the case to date.

The development pathway to a drug registration is well established yet attrition rates remain very high. Data presented by Wells and Oliarro (2009) suggest the need for 7 to 10 molecules entering phase I clinical trials in order to ensure one new antimalarial drug combination into the clinic. Consequently we will need all the hits available in order to ensure that the early discovery and development is sufficiently robust to deliver this number of clinical candidates. The fact that this is a significant challenge cannot be overstated. An interesting example of the unforeseen challenges that lie ahead can be exemplified by the isoquine and CDA projects both supported by MMV. In the case of isoquine this was a drug from a known class, the 4-aminoquinolines, that had been rationally redesigned to overcome resistance and idiosyncratic toxicity based on a reactive metabolite (O'Neill et al 2009). Despite over 50 years of successful clinical experience with the drug class, the pre-clinical development programme repeatedly uncovered unexpected toxicities in animal models. When the drug eventually entered phase I trials, a drug associated serious adverse event finally terminated the programme. In the case of CDA, another drug using well-established clinical drugs, it was only at the phase III clinical trial stage, using a very focused protocol design looking at hemotoxicity in detail, that an unexpected hemotoxicity in G6PD deficient patients was uncovered which precluded its development as a treatment for non-severe malaria (Tiono et al 2009). The fact that working with so called well understood drugs and drug classes can still fail to met all the requirements for modern drug registration, stresses the need for greater filtering at the early discovery stage to see if as much risk as possible can be eliminated from the molecules being taken forward. This concern is not restricted to antimalarial development but is a pharma industry wide problem. It is now standard practice to look for toxic and metabolic alerts and dispositional liabilities in lead molecules very early and certainly before they progress to candidates. Specifically for antimalarials, the potential for resistance development is also considered early in development. Although to date it is not clear what would constitute a no-go decision based on resistance acquisition. Finally and with reference to the outputs from whole cell screening we are encouraged to establish a mechanism of action. Although lack of this information isn't a barrier to development and registration, it does pose difficulties and slows the progress of the development process. Additional challenges for the malaria community are the lack of adequate predictive models to assist in the candidate selection process. In the case of *P. falciparum* there are excellent *in vitro* models and a humanized mouse model. There are no robust *in vitro* assays for *P. vivax* and this is major hinderence to developing drugs against this malaria species. Equally we await a validated *in vitro* hypnozoite assay and a truly validated gametocyte assay (*P.*

falciparum in the first instance) that is predictive of transmission blocking activity. All of these are opportunities for new development and research investment.

In conclusion it is clear that we urgently need new antimalarial drugs with novel mechanisms of action that can effectively treat parasite populations resistant to existing drugs. We are now in a unique position with respect to P. falciparum with several thousand in vitro nanomolar "hits" and the challenge will be to efficiently triage these hits to leads onto candidates and then eventually into clinical drugs. We will also need to look beyond drugs to treat non-severe falciparum malaria and severe malaria as we plan the development programmes that will deliver in 10-15 years. We will need to consider other malaria species and other applications such as radical cure, intermittent presumptive treatments, mass drug administration etc and modify our TPP's accordingly.

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