A unique approach

Associate Professor Matthew Todd discusses the merits of his open source initiative that is attempting to unify academia and industry in the quest for new antimalarial drugs

Can you outline how the Open Source Malaria Consortium was initiated, and the laws that were set out to underpin it?

I was talking with Tim Wells, Chief Scientific Officer of Medicines for Malaria Venture (MMV), about my previous open project on praziquantel (PZQ) – in which the World Health Organization (WHO) and I took an open approach to improving this important drug – and we realised that this idea could be extended to drug discovery with a commitment to a radical openness that ignored patent protection. Rather than debate the likelihood of success, it seemed more efficient to just do it, and this led to Open Source Malaria (OSM), which got underway in 2011. The core of the project is funded by MMV and the Australian Government, with MMV additionally providing a great deal of scientific leadership alongside access to their screening network.

I established the Six Laws as a set of guidelines based on principles that we learned from the PZQ project. They include the idea that all data and ideas need to be shared openly, anyone can participate and there will not be any patents. The licence behind the project allows anyone to use whatever they wish for any purpose, including making money, as long as the OSM project is cited.

What is the role of industry in this project, and why have big companies like GlaxoSmithKline (GSK) made certain molecules available in the public domain?

Industry is absolutely crucial. The counterintuitive finding of the PZQ project was that there were more contributions from industry than academia – particularly experimentally. The drug discovery landscape has been transformed by recent public depositions from big pharma. OSM, for example, builds on GSK's landmark deposition of malaria data, and one of the current strands of OSM is built on Pfizer compounds that are now in the public domain. The human and technological expertise available in industry puts them at the centre of any realistic drug discovery effort. An open project allows contributions with very little bureaucracy, enabling a company to reap a significant scientific and PR benefit.

How can contributors from outside the world of science contribute to this project?

We have recently started a classification of 'to do' items that includes just this – contributions that can be managed by non-scientists or carried out by pre-PhD researchers. There are clerical issues such as maintaining the master compound list, updating the wiki that describes the project's progress as well as non-science issues such as website design and helping with PR. A major area we have not explored properly is the legal and economic case for open drug discovery. OSM would be strengthened by expertise in those areas. At the other end of the scale we recently showed – with Professor Stefan Debbert from Lawrence University, USA – that students in an undergraduate laboratory class can make molecules for the project and have them evaluated as part of a research publication.

Can you describe the substances you have tested so far for their antimalarial potential?

We've investigated four series of compounds to date, making up about 100 final compounds that have been biologically evaluated. All have been small molecules. The first series, from GSK, exhibited very high levels of potency, and were found to be active against a high-value stage of the parasite (the gametocyte) but ultimately suffered from rapid metabolism that we were unable to slow down. The second series appeared promising, but we were informed that a closed group were looking at the same series, so rather than duplicating efforts, we switched to a third series, also from the GSK set. The compound we used as a starting point was very attractive but we found that the smallest modifications to the structure totally obliterated activity. The current series originated from Pfizer in collaboration with MMV. Following some excellent optimisation of the series, first with Pfizer and then TCG Lifesciences, it was passed to OSM. We have inherited a fair amount of data and it appears that the active compounds may be hitting an interesting target in the parasite.

What will be required for OSM's continuing expansion and success?

A crucial aspect of open projects is ownership. It is important for open research to be driven by people in order to guarantee momentum. However, too much ownership can dissuade people from contributing. Outputs from OSM lack ownership, meaning anyone, including the private sector, may benefit. The main challenge we face in the coming years is to show how we can federate the project properly as part of scale-up. This requires laboratories in different countries being locally funded to carry out research that is all contributing to the same totally open project centre. My lab is the main hub of OSM at the moment, but we dearly hope others will be able to join us for this unusual ride.

The future is **open**

The Open Source Malaria Consortium is a new model of online, transparent and international collaboration with exciting implications for the future of scientific research

WHILE THE FIELD of software development has seen numerous open source success stories, including the Firefox web browser and the Linux operating system, it has until now been less certain whether the same methodologies could be applied to other areas. A new possible application is in medical research, particularly drug discovery, and while this concept is new to laboratory-based research, it is already generating some exciting new advances.

FUNDAMENTAL ALTERATIONS

At the University of Sydney, Australia, Associate Professor Matthew Todd coordinates the Open Source Malaria Consortium (OSM) – a collaborative project aiming to discover a small molecule that constitutes an effective malaria treatment. All of the project's data are shared and its experiments published online; anyone can take part, and there are no patents. It is fresh, exciting thinking and represents a bold new collaborative model of scientific discovery. "Open science must operate in a way that allows anyone to join your research as a full partner," Todd explains. "Everyone needs access to all the data and the ability to help in any way, allowing specialists to contribute spontaneously without being known to the existing team. It is the purest and most inclusive form of collaboration."

Working successfully within this new paradigm necessitates some fundamental alterations in the way research is undertaken, as it requires scientists to be comfortable sharing negative data, false starts, half-thoughts and uncertainties. Once these psychological adjustments are made, however, openness brings significant advantages. Research likely to be unproductive is halted before it begins, saving time and resources. More generally, distributed collaboration in a dispassionate, open arena is well-suited to solving hard problems such as drug discovery, which require the analysis of huge quantities of data.

Market failure has made drug discovery a particularly appropriate application. At one end of the scale there are diseases that provide no incentive for research because there are few financial returns – a market failure based on value – where the limited importance of secrecy makes the case obvious for the open sharing of data and ideas. Conversely, there are 'developed world' diseases such as Alzheimer's, where the basic science is challenging and the disease poorly understood – this is a market failure based on risk. Tackling this requires the basic science to progress quickly, which in turn means scaling up the collaborative process in order to effectively de-risk the market.

LEARNING CURVE

Methodologies and approaches to data management in open source projects such as OSM differ from those used in conventional research. "There must be less worry about ownership; leading an open project is not a right – it is a position that is constantly earned, based on performance," says Todd. "One is forced to abandon email – instead, conversations

Scientists looking back in 50 years' time will be surprised by the insularity of today's researchers

happen in the public domain, where one may of course be wrong, and the error preserved." In many respects, this is how science has always operated, except that traditionally it has been possible to 'smooth over' the rough spots by keeping them secret. Operating in public therefore introduces some challenges, but it also encourages participants to keep high-quality research records.

It has been a steep learning curve for the team leading OSM, as they have realised the new approaches required to run a consortium existing entirely in the public domain. Proprietary tools cannot be used as this would force contributors to buy software – the lab notebook is therefore open source and the coordination tools are either in general public use or repurposed by the team. Solving these technical issues has created a functionally useful platform that helps the community to solve scientific challenges, with researchers across the world contributing their advice, as well as real molecules and assays. The platform both permits and encourages the assembly of talented people to solve scientific challenges as they arise, with remarkably few overheads and no need to move people around the world.

CULTURAL SHIFT

Todd and his colleagues have worked hard to make the Consortium accessible to as wide an audience as possible. "The technical side of the project is completely open, with every experiment written up online in the lab notebook," he remarks. "The biological activity data are also uploaded to ChEMBL – an open database at the European Bioinformatics Institute. All of the data are machine-discoverable so that search engines know which molecules are on each page, our results filtering through to other databases such as PubChem."

The OSM team also ensures that all of the active questions in a project are maintained on the public 'to do' list, disseminating these and other aspects of the project on whichever platforms are the busiest. OSM has a Google+ presence, which allows in-depth discussion with an active scientific community, and also exists on 'lighter', broadcast-type platforms such as Twitter and Facebook, which are providing increasing numbers of scientific responses.

Despite this growing support, however, the scientific establishment has been slow to warm to the concept of open science, with industry being the Consortium's greatest supporter. Academia has been less interested, and Todd believes this is due in part to the pressures faced by academics. "The culture of publishing in academia requires a scientist to be seen to own a certain problem and publish papers as the corresponding author," he reveals. Researchers worry that if they contribute to a larger project they will lose ownership of their work, and moreover their latest ideas might be published by someone else.

Such worries are likely unwarranted, but the necessary cultural shift is going to be a slow one and there are currently few examples of open source research projects. Todd is convinced, however, that it will quickly become apparent that openness accelerates research and that open science will soon be the norm, with scientists looking back in 50 years' time surprised by the insularity of today's researchers.

LOGISTICAL CHALLENGE

Despite existing for just two years, OSM has already made a large number of new molecules available, and the beauty of the open source model means that even if Todd's team chooses not to actively pursue a given series in the lab, the fact that the data are publicly available means anyone else can step in and quickly use the work as a starting point for their own research. "Perhaps most importantly, we have shown how any lab in the world can see what the project requires and contribute as full partners," enthuses Todd. "For example Patrick Thomson, a student at Edinburgh University, completed the synthesis of several molecules needed in Series 1, without needing to meet other members of the team, and the quality of the work was clear because all the data were shared."

This is a model of how research can be done quickly and efficiently in a scalable, global and open way. Going forward, Todd hopes to involve more contributors from malaria-endemic countries, which might prove to be more of a logistical challenge associated with the improvement of basic infrastructure than one of hearts and minds. In any event, OSM's talented team of international collaborators will find ways to solve this problem.

INTELLIGENCE

OPEN SOURCE MALARIA CONSORTIUM

OBJECTIVES

To accelerate the discovery of novel antimalarial drugs by creating an open source system wherein researchers can collaborate and work with academic and industrial partners from around the world to pool their efforts openly.

PARTNERS

The University of Sydney, **The University of Melbourne**, **Monash University**, Melbourne, **Griffith University**, Brisbane, **The Australian National University**, Canberra, Australia • **Medicines for Malaria Venture**, Geneva, Switzerland • **Swiss Tropical and Public Health Institute**, Basel, Switzerland • **The European Bioinformatics Institute**, Cambridge, UK • **University of Edinburgh**, UK • **GlaxoSmithKline**, Madrid, Spain • **University of California**, San Diego, USA • **Lawrence University,** Appleton, USA • **Central Drug Research Institute**, Lucknow, India • **University of British Columbia**, Vancouver, Canada • **TW2Informatics**, Sweden • **Karolinska Institute**, Stockholm, Sweden

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ASSOCIATE PROFESSOR MATTHEW TODD obtained his PhD in organic chemistry from Cambridge University, UK, in 1999 and has previously spent time as Wellcome Trust postdoctoral researcher at The University of California, Berkeley, USA, as college fellow at Cambridge University and lecturer at Queen Mary, University of London, both UK. He is Chair of The Synaptic Leap, a non-profit organisation dedicated to open biomedical research, and currently leads the Open Source Malaria (OSM) consortium. In 2011, he was awarded a New South Wales Scientist of the Year award in the Emerging Research category for his work in open science, and in 2012, the OSM consortium was awarded one of three Wellcome Trust/Google/*PLoS* Accelerating Science Awards.