A child in Tanzania is treated for malaria — a disease that could benefit from an open approach to medical research.

STEPHANIE AGLIETTI/AFP/GETTY

TROPICAL DISEASE

# A neglected cause

*A more open approach to combating tropical diseases may help to overcome a pharmaceutical market failure.*

BY LUCAS LAURSEN

He didn't know it at the time, but when chemist Matthew Todd posted a request for help on The Synaptic Leap, a website devoted to open-source biomedical research, he was sowing the seeds for a rivalry between an open initiative and a contract-research organization hired by the World Health Organization to reach the same goal.

The aim of both projects, run in 2010, was to produce a safer, low-cost version of praziquantel, a treatment for the tropical parasitic infection schistosomiasis. Up until that point, the treatment contained two enantiomers (mirror-image versions of the molecule that have slightly different properties) of praziquantel. One enantiomer has no effect on the parasite, but gives the drug a bitter taste. Eliminating this undesirable form could reduce side effects and help more patients to complete their treatment. The pure drug needed to be affordable. Todd, who is at the University of Sydney in Australia, thought that an open project was the best way to achieve this. "Open is very well-suited for neglected diseases," he says. "The pay-off of secrecy is not very large."

This is because the potential buyers of drugs targeted at rare and neglected diseases, such as schistosomiasis and dengue fever, are often unable to pay the prices that large pharmaceutical companies must charge if their investments are to pay off. Occasionally, these companies have made investments that have no hope of direct commercial return, such as the decision in 1987 by Merck and Co., based in Kenilworth, New Jersey, to offer Mectizan (ivermectin), a drug for onchocerciasis or river blindness, free of charge. But too many of these decisions would risk a company's survival. Although governments have often intervened to promote and fund research in areas with the highest financial risk, diseases that affect the poorest countries or smallest subpopulations remain undertreated and under-researched.

The race to produce a single-enantiomer version of praziquantel finished in late 2010 in an effective tie when both Todd's open group and the contract-research organization posted their different but comparable solutions online. Half a decade later, Todd is aware that his method is still being used to produce the active enantiomer of praziquantel in various labs around the world. Todd points to the work as one of the success stories of open-source medical research. The project matched the results of the conventional approach, but, by collaborating with researchers previously unknown to Todd's team, he says that the project did it faster than it ever could have done in secret.

The research community is embracing the open approach to find treatments for diseases that have little potential to make a profit. By collaborating, drug companies, non-governmental organizations and governments can share the load. Partnerships to handle development and

distribution of treatments for neglected and tropical diseases have already begun, as have efforts to find ways to share data on early-stage research to avoid duplication. And although open-source projects, such as Todd's, remain the exception rather than the rule, they, too, are gaining popularity.

## FASTER SCIENCE

Around the turn of the millennium, a number of organizations were set up to connect industry, government and non-governmental organizations, and to promote the sharing of knowledge about tropical and neglected diseases — Medicines for Malaria Venture (MMV), the TB Alliance and the GAVI Alliance. Pharmaceutical companies, they argued, had compound libraries and dormant intellectual property that, for areas in which they could not expect to reap significant profits, could be shared without threatening their financial prospects.

In 2010, pharmaceutical companies GlaxoSmithKline and Novartis, and St. Jude Children's Hospital in Memphis, Tennessee, publicly released a database, through MMV that contained 20,000 compounds that had shown some antimalarial activity. These 'hits' are an early step on the long path to designing new drugs (see page S65) and are usually proprietary. Researchers began to also ask for samples that they could work with, so, the following year, MMV began offering a selection of the compounds by post. This 'malaria box' offered researchers a common starting point and the organizers hoped that it would accelerate research.

The box meant that researchers did not waste valuable time creating duplicates of compounds already produced by someone else. "People could really focus on understanding novel chemical series," says Jeremy Burrows, head of drug development at MMV based in Geneva, Switzerland. And thanks to MMV's coordination, researchers can divide up the analysis to understand the existing pool of compounds, rather than work in secret and risk overlapping efforts.

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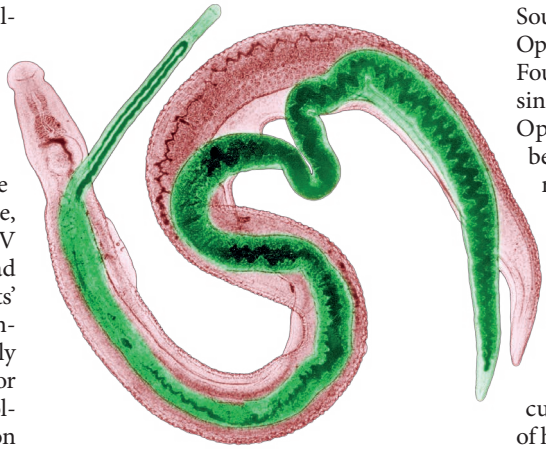
Companies have also begun to share their intellectual property through large international systems, such as the Re:Search project, established in 2011 by the World Intellectual Property Organization (WIPO) to drive innovation around neglected diseases, malaria and tuberculosis. Data and compounds, for example, are made available through research agreements that specify certain requirements, such as assurance that access to any end product is affordable in the 49 least-developed countries. As of March 2016, the programme had 103 members operating under 100 research agreements. Five active antimalarial projects involve compounds in pre-clinical development — one step before human clinical trials — and a WIPO-initiated dengue-fever project is already putting a repurposed compound through clinical trials.

## OPEN REVOLUTION

When business specialist Henry Chesbrough of the University of California, Berkeley, popularized the term open innovation in 2003, his definition was a broad one. It included industrial adoption of academic practices, such as publishing results in journals, and collaborations, within which a select few partners would share information with each other, but maintain secrecy with the wider world. Todd's approach with open-source science was more radical.



NIBSC/SPL

**The female (green) and male parasites that cause the tropical disease schistosomiasis.**

"In drug discovery and development, you have a spectrum," says Burrows. At one end are pharmaceutical firms going about their work in secret, he says. At the other is open source. This model, whereby information is made freely available to a wider community and not just the people directly involved in the collaboration, originated in software development. Central to Todd's project was the decision to make the team's laboratory notes available to the world while they worked. Although this meant that any other teams working towards the same objective were able to see exactly what they were doing, it also opened them up to external help. "The people contributing really knew what they were doing," says Todd. Not only does he say that their input accelerated the research, but also that timely suggestions to change direction kept them away from expensive blind alleys. "We could have wasted the whole grant on something unproductive," he says.

Sharing lab notes can also prevent duplication of effort, says Katy Graef, associate director of BIO Ventures for Global Health in Seattle, Washington. In one case, Graef says, the non-profit organization learned that researchers at Saint Louis University in Missouri were planning to screen inhibitors of the enzyme METAP-1 for antitubercular activity, a test that GlaxoSmithKline had already performed. BIO Ventures put the two parties in contact, and the Saint Louis researchers were able to redirect their research, instead of wasting an estimated three months.

Since his first foray into open-source research, Todd has developed a bigger project: Open Source Malaria. The aim of the project is to find new medicines for malaria. So far, the team has explored several groups of promising compounds, including those released through MMV, and it is currently exploring the potential of a set of molecules that originated with the drug giant Pfizer.

Anyone can contribute to the project, and with all data and ideas posted publicly, this is perhaps the most open approach yet to tackling a tropical disease. The project is part of an emerging trend in drug research. The Open Source Pharma conference, sponsored by the Open Society Foundations and the Rockefeller Foundation, was held in 2014 and 2015. And since 2008, the Indian government-funded Open Source Drug Discovery project has been conducting crowdsourced tuberculosis research with the aim of expanding to other neglected diseases. The project has identified potential molecules for fighting tuberculosis and built infrastructure for coordinating remote efforts on a tight budget.

The global burden of neglected tropical diseases, as defined by the World Health Organization, as well as malaria and tuberculosis is around 5.5% of the total number of healthy years lost to disability, poor health or early death. But research and development spending on neglected diseases in 2010 was only around 1% (about US$2.4 billion) of global-health research spending. And only 4% of therapies registered between 2000 and 2011 were indicated for neglected diseases. The open research initiated in the past decade could begin to address these imbalances.

Not all initiatives to tackle neglected diseases need to be run as publicly as Open Source Malaria to make an impact. The Wellcome Trust, for instance, began offering grants for multicentre, transnational collaborations in 2015, inspired by the ad hoc partnerships that sprang up between labs during the Ebola crisis. "There are a lot of different models out there," says Graef, "and it's good that we have these different approaches to keep things complementary."

Burrows shares her optimism, and points to four promising compounds that emerged from MMV's open work and are included in candidate drugs now in clinical testing. It will be a few more years before any open-origin treatment for neglected diseases makes it from the sharing stage all the way through to commercialization, but that is where everyone, from non-governmental organizations to the largest pharma firms, is placing their bets. "Everyone is aware that opening things up makes them more efficient," Todd says. ■

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