Unique collaboration finds the wizard of OZ

How academic and industry researchers joined forces to develop a much-needed antimalarial drug.

Sophie Petit-Zeman

As the fight against malaria took a huge stride forward with publication of a potential synthetic antimalarial candidate (Vennerstrom, J. L. *et al. Nature*, 430, 900–904 (2004)), so too has the value of research collaborations between industry and academia that tackle developing world diseases.

The antimalarial compound, OZ277/RBx11160 — known as 'OZ' — is a synthetic version of the most effective current antimalarial, artemisinin, and is cheaper and easier to produce. Developed by the Indian pharmaceutical company Ranbaxy, OZ is now in Phase I trials in the United Kingdom.

The R&D journey that brought OZ to this stage involved a unique partnership of academic and industrial groups from across the globe, sponsored by the non-profit foundation Medicines for Malaria Venture (MMV). With international private and public backers, MMV enables academics and the drug industry to re-engage in this notoriously under-resourced field.

According to Hugues Matile, senior scientist at the major industry partner Hoffmann-La Roche, the project began when his company, which was already collaborating with Jonathan Vennerstrom at Nebraska University, decided to stop malaria research.

"Our management gave us the opportunity to continue work with external institutions," says Matile. "Two of us got sabbaticals: Robert Ridley, now at the World Heath Organization, went to Geneva to support building up the MMV; and myself, together with my technician Jacques Chollet, transferred know-how and technology from Roche to the Swiss Tropical Institute. Robert arranged contacts with Bill and Susan Charman from Monash University [Melbourne, Australia] for pharmacokinetic studies and with Sarah Arbe-Barnes from Fulcrum Pharma Developments [UK] for project management."

The full team comprised chemists working with Vennerstrom (as chief investigator), the pharmacokinetic group at Monash, parasitologists in Switzerland and managers in the UK. Expertise also came from scientists, such as Matile at Hoffmann-La Roche, but, perhaps surprisingly, the company has no interest in the clinical development and marketing of the drug. As Matile says: "Cooperation from the Roche side was a pure goodwill action by the company and scientists involved."

According to Vennerstrom, a key early obstacle was the "identification of compounds with both good antimalarial activities and good biopharmaceutical properties", and Charman recalls the hurdle of "establishing management systems, data and people, and clear project objectives that were both quantitative and qualitative."

Calls for trial to assess genetic and environmental interactions in disease

Study welcomed but there are worries that logistical issues might hamper ambitious proposal.

Courtney Peterson

The time is right for an ambitious trial that could provide long-sought-after information on how environmental factors influence many common diseases, according to one of the visionaries of the Human Genome Project.

Study could identify how environmental factors such as smoking influence common diseases.

Francis Collins, Director of the US National Institute for Genomic Research, has outlined proposals for a US-wide study that would follow 200,000 people for two or more years to uncover how genes and the environment interact to contribute to the 40 most common diseases, such as how food intake influences in obesity and diabetes (*Nature* 429, 475–477 (2004)).

There are similar, but smaller, studies being conceived or carried out in other countries. However, Collins says that the US should seriously consider undertaking its own study, because other minority groups, such as African-Americans, Latinos and Native Americans, are likely to have different environmental risk factors.

A prospective cohort study that collects data on groups of subjects over time on this scale has several logistical hurdles, such as requiring large sample sizes, detailed characterization at the beginning of the study and prolonged follow-up for disease occurrence. But the payback is that this will provide additional information to the case-control approach used, for example, in standard randomized clinical trials, says Collins.

"If what you want is an accurate estimate of the quantitative risk that's contributed by a particular genetic variant or a particular environmental exposure, the prospective study design will give you that," he says. "The case-control approach tends in general to overemphasize the more severe end of the spectrum of the disease."

Although many researchers are excited by Collins's proposals, they fear that any efforts to get this study off the ground could be restricted by current logistical limitations.

"I'm personally in favour of not getting started on it yet," says Christopher Carlson, an epidemiologist at the University of Washington. "Right now, we're almost ready to do the genotypes; in a few years, we'll be ready to do some of the phenotypes; but the clinical stuff, I just don't see that being cheap enough yet."

Carlson says that many environmental influences are difficult, if not impossible, to measure. Added to that, the more elaborate the phenotyping, the more expensive the study. Carlson estimates that finely phenotyping several hundred thousand individuals will boost the cost of the study into the billion dollar mark.

Similarly daunting, says William Evans, Scientific Director of St. Jude Children's Research Hospital, Memphis, Tennessee, will be

Regarding the keys to success, the academics cite learning from each other, enjoying working together, laughter, regular telephone calls, e-mails and group meetings, and trust and commitment. Charman adds: "It was hard work, challenging, with all the good bits of working in the drug industry without the politics and endless meetings. It was a real project and we were determined to succeed."

"Collaboration between the groups was excellent," says Matile, "mainly due to MMV's full support, so the major problem of finance for universities was not an issue, and because of personal friendship between team members." Really no tensions in drawing together such diverse partners? "Not existent," Matile says.

Doubtless encouraged by this story of philanthropic bonhomie, public–private partnerships are cited as the way ahead in the fight against malaria. Propelled by umbrella bodies such as MMV, the disease described as keeping poor people poor, and which affects almost half the world's population, is under concerted attack from academics and industry — even though it's unlikely to make them rich.

the construction of a highly sophisticated data-management system to assemble and analyse the data. "Such a system has remained out of reach to date," says Evans, "even when [the] scope of interest is much more narrow than the 100,000-patient prospective cohort study."

But even if the study proves scientifically and technically feasible, informed consent, recruitment, public support and the cost pose significant challenges to getting the project off the ground. "The most important thing to do will be to convince a number of communities that this is the right thing to do, especially given the price tag," says Aravinda Chakravarti, Director of the Institute of Genetic Medicine at Johns Hopkins University. "But the prospect is important and exciting enough to warrant such an effort," he says.

At the moment, Collins stresses that all of those issues are in flux. "I would hope that by the end of the year, that they would coalesce into something that could be put in front of an interested audience — the government, leading scientists, and the public — and then [we'd] let them decide whether they think it makes sense or not."

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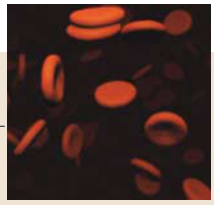

NEWS IN BRIEF

Setback for anticoagulant drug

AstraZeneca has received a blow with the news that an FDA advisory committee raised concerns about the safety and efficacy of its anticoagulant ximelagatran (Exanta). The treatment, the first alternative to warfarin for more than 60 years, had been granted European approval in May 2004 for the prevention of blood clots in patients undergoing knee-replacement surgery, but briefing documents released by the FDA highlighted previously unheard-of problems. Trial data for the three indications in which AZ sought approval — prevention of blood clots in knee-replacement surgery, prevention of strokes in patients with atrial fibrillation, and long-term secondary prevention of blood clots following standard treatment of a clot — left too wide a margin in showing equivalence to warfarin. Concerns were raised about the previously reported increase in liver-enzyme levels with ximelagatran — including three deaths related to liver failure — and what seemed to be a signal of increased cardiac events with even short-term exposure.

Demands grow for clinical trials registry

Moves to establish an independent database for clinical trials have advanced. First, GlaxoSmithKline settled its case with New York Attorney General Eliot Spitzer for US $2.5 million, and it has agreed to publish results of its drug trials in a registry. The Pharmaceutical Research and Manufacturers of America (PhRMA) trade group announced plans for an online database starting 1 October 2004 (http://www.clinicalstudyresults.org/). This voluntary scheme will contain results of all controlled clinical trials — mainly Phase III and IV studies — completed since October 2002. But editors of 11 major medical journals say that this is not enough, and have announced that from July 2005 their journals would no longer publish any trial results that have not been registered in advance in an independent database that is freely accessible to the general public.

China revokes patent on Viagra

Another country has stepped up efforts to overturn its patent on sildenafil citrate (Viagra; Pfizer). The Chinese State Intellectual Property Office (SIPO) revoked patent protection for insufficient disclosure on the drug, arguing that Pfizer's application had failed to accurately explain the use of the drug's key ingredients. Pfizer has already lost patent protection for Viagra through similar challenges in Colombia and Venezuela. The patent in China, which expires in 2014, faces further pressure as a result of the announcement of an alliance between 17 Chinese pharmaceutical companies to produce a generic version of the drug.

Partnership struck between Bayer and Schering

Bayer and Schering-Plough announced an agreement under which Schering will have marketing rights to Bayer's primary care products, such as its antibiotics, in the United States. But the driving force behind the deal involves the company's biggest products. Schering will now have a Japanese marketing partner for its cholesterol absorption inhibitor, ezetimibe (Zetia), which is under regulatory review. Bayer now has help in the US commercialization of its erectile dysfunction drug vardenafil (Levitra), and in establishing an oncology business unit in the US, in which it will be able to commercialize its renal cell carcinoma drug, BAY 43-9006, that is currently in Phase III trials.

Initiative to apply nanotechnology to cancer

The US National Cancer Institute (NCI) has launched a new five-year initiative to develop engineered nanoparticles to treat cancer. Around $144 million will be spent on The NCI Alliance for Nanotechnology in Cancer, with the largest chunk — $90 million — going towards funding several Centers of Cancer Nanotechnology Excellence. NCI plans to release a call for applications for these centers this autumn, and expects to have at least five of them set up by summer 2005. NCI plans to collaborate with National Institute of Standards and Technology to work on the characterization of nanomaterials and with the FDA to define pathways to get nanotechnologies into clinical testing.

Society to assess potential of pharmacogenetics

The Royal Society, the United Kingdom's academy of science, will examine the potential of developing personalized medicines and how well equipped the UK is to proceed with it. The group, chaired by David Weatherall of the University of Oxford, will look at whether pharmacogenetics is, or when will it become, a scientifically achievable aim. It will also look at whether healthcare systems in the UK and other countries have the resources to implement such technologies, and what the pharmaceutical industry's assessment is of the significant investment needed to try and develop them in the first place. The Royal Society report will be published in summer 2005, and individuals and organizations are invited to provide evidence by 12 November 2004 (http://www.royalsoc.ac.uk/policy/pharmacogenetics.htm).