ASTRAZENECA

Drugs for a developing world

Diseases affecting the developing world have long been neglected by medical research. But a series of partnerships between governments, charities and pharmaceutical firms finally looks set to change that, says Sarah Houlton

Many of the diseases that kill the most people disproportionately affect the developing world. Whether they are familiar, such as malaria, HIV/Aids and TB (tuberculosis), or neglected diseases like leishmaniasis and sleeping sickness, there is little incentive for big pharma companies to develop drugs as those affected simply do not have the resources to pay for them. As a result, much of the drug discovery effort is funded by philanthropic organisations such as the Wellcome Trust, the Bill & Melinda Gates Foundation and the Medicines for Malaria Venture. However, pharma companies remain the best able to bring a drug through from biological target to marketed compound. Several companies are now working in partnership with these organisations, and some have set up research sites within countries affected by these diseases.

Novartis, for example, established the Novartis Institute for Tropical Diseases (NITD) in Singapore as a public–private partnership with the country's Economic Development Board in 2002. Initially its focus was on TB and dengue, and later on malaria was added. But why Singapore? 'Important criteria when deciding where to put a research centre include accessing talent and basic science, academic infrastructure, the legal environment and intellectual property protection,' explains Paul Herrling, the company's head of corporate research. 'But if you want to make medicines for patients, you need to know their environment – and these diseases don't occur in Basel or Cambridge. We felt that if we were going to work on diseases prevalent in the tropics, we should put the research as close to them as possible, and Singapore fits the bill.'

The Institute is a fully integrated research centre, with chemistry, biology and molecular biology, and access to the company's know-how and technology elsewhere in the world. When it was being set up, the Singapore government was trying to attract biomedical science companies – the country had the research infrastructure for basic sciences, but they wanted to be able to translate it into products. 'They wanted to create biomedical science infrastructure so they could learn from it,' Herrling says.

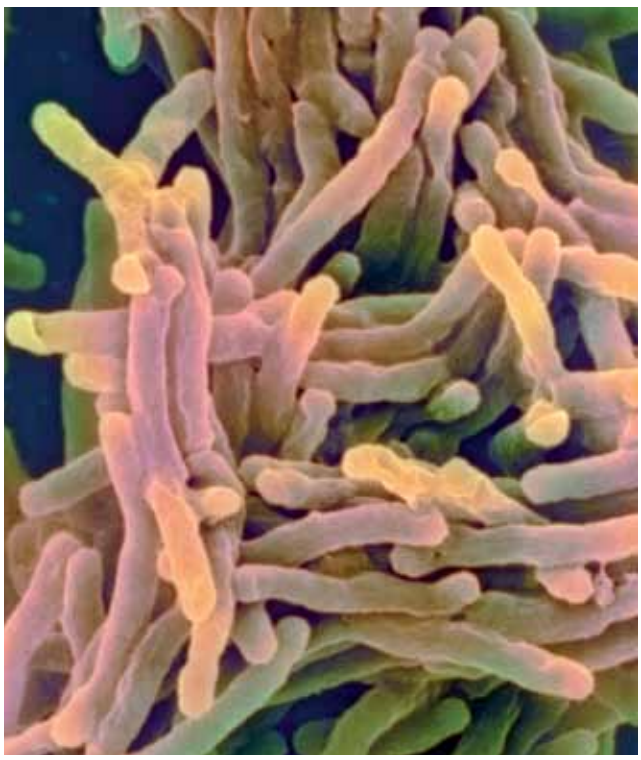
The NITD has also attracted funding from other agencies and charities, such as the Bill & Melinda Gates Foundation. 'Their goal was to foster the creation of new medicines for TB because of resistance, and for dengue as there have never been any,' he says. The Wellcome Trust then asked them to work on malaria, too, and ultimately provided $20 million (£12.2 million) to run the programme, which began 18 months ago. 'We had not selected malaria initially because we already had Coartem [the artemesinin-based combination therapy] – but resistance was starting to appear, and as drug discovery takes 10 to 15 years we needed to start straight away.'

For TB, they are now in the early stage of preclinical development – selecting targets and scaffolds. 'We don't even start any development if the compounds don't work on all the resistant strains,' Herrling says. Things are a little further advanced in dengue, with several projects now in the late stage of preclinical development. 'We found one compound which killed the virus in animal models and still works several days after infection, but the side-effects were prohibitive,' he adds. 'If we can find one that does not affect the host too much, we should be up and running.'

He believes they made the right choice by setting up the NITD in Singapore. 'We assumed it would be easy to recruit brilliant scientists to work there, and we were right,' he says. 'We have about 100 people from 24 nations, and about half of them are locals. And the scientific environment is great – we have many very good collaborations with academic institutions and hospitals which gives us access to patients.'

In short

- **Pharmaceutical firms haven't traditionally focused on developing world diseases**
- **Medical charities and governments are teaming up with pharma companies to tackle these diseases**
- **Drug discovery centres are being set up in the developing world to research medicines for local diseases**
- **Some of the drug leads discovered at these new centres are close to clinical trials**



***Mycobacterium tuberculosis* is particularly prevalent in India**

A DOWSETT, HEALTH PROTECTION AGENCY / SCIENCE PHOTO LIBRARY

Drug discovery culture

AstraZeneca also has a research site in the developing world – in Bangalore, India. It was originally an Astra site working on tropical diseases, and after the Astra–Zeneca merger in 2000, they decided to focus on tuberculosis. 'We've got about a quarter of the world's population of TB patients in India, and we really should do something about it,' says the site's head of R&D, Balganesh Tanjore. 'We looked at the unmet medical need globally, our own infrastructure and expertise, and we had been working in both malaria and tuberculosis as well as parasitic disease, but in 2000 the entire genome sequence of *Mycobacterium tuberculosis* became available, and that of the malaria parasite was still in its infancy. We looked at this as a clear and breaking science, and that made the decision for us.'

India has many advantages for research, he says. 'There is a lot of competence in the scientific base, people are coming back to India because they believe there are now opportunities for them there, the universities are globally competitive, the cost of research is cheaper and, perhaps most importantly, there is access to clinical materials. But it's not just because it's cheaper – building a culture of drug discovery takes time.'

Like the Novartis operation in Singapore, the site can carry out the entire drug discovery process from target identification through to candidate drug, and has access to other AstraZeneca technology such as the central screening facility. 'Our mandate was to have something in the clinic for safety trials by 2010, and we believe we're on schedule,' Tanjore says. 'We have a lead compound in early safety work; it is a new protein synthesis inhibitor which works on drug resistant TB, is orally bioavailable and is compatible with HIV treatment. So it meets the basic requirements we believe are critical for getting a drug into the patient, and we hope it will immediately bring some sort of relief for multi-drug resistant patients.' There is another project in lead optimisation, and he hopes that in the next two years at least two programmes will be in this optimisation stage at any one time.

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Therapeutics for a rainbow nation

South Africa is another country with great unmet medical need and a good science base. This was the rationale behind the decision of a group of chemistry academics – Tony Barrett from Imperial College London, UK, and Steve Ley from the University of Cambridge, UK, and Dennis Liotta from Emory University in Atlanta, Georgia, US – plus George Painter from US anti-viral drug company Chimerix, to set up a start-up company, iThemba Pharmaceuticals, in Johannesburg. As Julian Walsh, director of external affairs for the chemical biology centre at Imperial College and another of the founders, explains, Barrett had started consultancy work in South Africa and had come back impressed at the quality of the people the universities were turning out, and the whole spirit of change in the country.

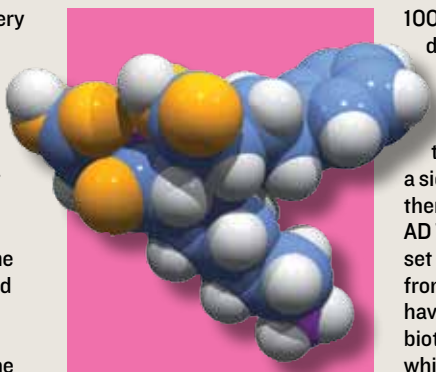
'The initial idea had been to set up a scholarship scheme, but the penny dropped that even if a fantastic scholarship system could be set up, there would be nothing for these people to come back to, at least from the point of view of medicinal chemistry – most decent chemists who stay in chemistry end up working in the oil industry,' he says. 'South Africa's pharma industry was essentially a pills and powders operation. Yet there are huge and growing health needs, particularly because of AIDS, but there was no research-based biotech emerging so the best of the talent was likely to leave the country. We had a Damascene conversion at Cape Town airport over some good wine, and realised that the biggest contribution we could make to South Africa was to found a research-based company.'

Novartis says setting up in Singapore was the right decision

A long search for funding culminated in grants from the South African government via its regional biotech development agencies. The company's business model has two streams, as chief scientific officer Chris Edlin explains. 'One is drug discovery, and we are running a number of projects including one in tuberculosis and a process chemistry project looking for a new route to an antiretroviral drug,' he says. 'But to offset the traditional cash burn associated with drug discovery, we are actively trying to attract custom synthesis projects, in both medicinal and synthetic chemistry. It is low-cost here so we can compete with

Angiodesign

While most of the drug discovery efforts taking place in the developing world are focused on infectious diseases, University of Cape Town's Ed Sturrock is looking at something different – a more selective treatment for high blood pressure. The angiotensin converting enzyme (ACE) inhibitors currently used frequently cause a persistent cough and, more dangerously, angio-oedema, a swelling in the upper respiratory tract that can be fatal. In collaboration with scientists at the University of Bath, UK, they discovered that ACE has two active centres – one at the C end of the protein and the other at the N terminus. The C appears more important for blood pressure regulation, and the N is specific for a substrate that is involved in haematopoeietic stem cell differentiation.



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ACE inhibitors can be unselective

'We've managed to develop inhibitors that show about 100- to 1000-fold selectivity for the C domain,' Sturrock says. And it has local relevance – the Cape Coloured population is genetically much more likely to develop angio-oedema as a side-effect with ACE inhibitor therapy. A spin-out company, AD Therapeutics, has been set up, and has gained funding from Cape Biotech Trust. They have also been working with UK biotech Cresset Biomolecular, which has generated virtual libraries of compounds using some of AD Therapeutics' structures. 'We've been working with our knowledge of the 3D structure to increase the selectivity of the inhibitors,' Sturrock says. 'The next step is preclinical work.'

Asia and India in terms of offering our services to potential clients, and the [intellectual property] laws are as good here as the UK and US so there is a high degree of confidence that the work we do will be protected.'

Meanwhile, at the University of Cape Town, chemistry professor Kelly Chibale is setting up a drug discovery centre he hopes will help South Africa to discover its own drugs in the future. There is a clear strategy from the government to promote innovation and drug discovery, he says, but there are a lot of gaps in knowledge and expertise in the drug discovery chain within South Africa. 'One of them is integrating drug metabolism and pharmacokinetic data into medicinal chemistry, and there is a common misconception that synthesis is the same as medicinal chemistry – it's not!'

What he hopes to achieve is a critical mass of people who understand medicinal chemistry in terms of integrating ADME (absorption, distribution, metabolism and excretion) into drug discovery. 'It's a contribution to delivering quality preclinical drug candidates for infectious diseases, though in principle it could be applied to any area,' he says. 'It has not been done before in South Africa – or in Africa for that matter – and this is the time to transfer that technology. We can learn from the experience of those people who have already embraced drug metabolism, and benefit from what they have learnt.'

SARAH HOULTON

Kelly Chibale is setting up Africa's first drug discovery centre

Chibale has gained experience from several drug discovery efforts in the past, including a collaboration on TB with GlaxoWellcome (now GSK), lead optimisation programmes in malaria funded by the World Health Organization (WHO), and last year he spent four months on sabbatical at Pfizer's labs in Sandwich, UK, learning about drug discovery decision-making and learning how compounds are progressed through the pipeline. 'The WHO projects taught me where I had been going wrong before – I just didn't have this ADME capability, or even know that it was needed to drive medicinal chemistry,' he says. 'This sort of partnership has been very important; people are willing to help if you are willing to help yourself, by knowing what you don't know.' Funding for the ADME component of the centre will come from the Cape Biotech Trust (one of the government's regional biotech agencies) and, he says, the Medicines for Malaria Venture is willing to help him build a platform using malaria projects as a starting point.

'This is Africans initiating something in Africa, rather than looking to people from outside to come and do it for us. We need to have success stories to show that drug discovery can be done in Africa, by Africans!' he says. 'And Africans don't need to stay in the US or Europe to make a difference. I believe in something I once heard from a church pastor. He said there are three types of people – 3 per cent make things happen, 5 per cent watch while it happens, and the rest wonder what happened. I want to be part of the 3 per cent.'

Sarah Houlton is a freelance science journalist based in London, UK

Finding funding

While various academics and not-for-profit organisations are developing early stage drug candidates, the cost of progressing them from the lab to the market is enormous. And the risk of failure during trials is substantial. Novartis' Paul Herrling says that over the past seven years or so, an investment of maybe $1 billion (£600 million) has generated many different early stage projects, but to fund even a few of those through full development will cost more like $1 billion a year for the next decade. 'None of the charities or current funders, including big pharma, can sustain that because there are no returns, and the risk of failure is too great,' he says.

While the patent pools that have been proposed are all very well, he says, they don't solve the problem of paying for development, and a patented drug can only help patients once it has been licensed for use. He proposes a model which shifts the risk of failure into a new fund for R&D in neglected diseases, with much of the money coming from governments. Anyone with a compound for a neglected disease can apply to the fund, and it will be assessed from a scientific and medical standpoint.

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Paul Herrling has a plan

'If they decide to fund the project, it will only be to the next decision point [whether or not to progress the compound to the next stage of trials] – a milestone-driven system rather than providing all the funding up-front – to make the use of the money as efficient as possible,' he explains. 'In return for that money, the researchers must allocate the fund with an exclusive licence for neglected disease indications. It works within the patent system, and also guarantees that the patent system cannot be abused to stop affordable access to the drugs.'

Reference

P L Herrling, *Nat. Rev. Drug Discovery*, 2009, **8**, 91
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