

Wanted: social entrepreneurs

Scientists-turned-entrepreneurs are resuscitating the research and development of drugs for neglected diseases. Researchers, administrators and funders should contribute their expertise to help these initiatives — or set up their own.

The all-embracing open-source encyclopedia Wikipedia doesn't have a dedicated page on kala-azar, or visceral leishmaniasis. But who cares? After all, the disease only transforms vast numbers of people in developing countries into walking skeletons carrying bellies bloated by an enlarging liver and spleen. With drugs costing up to US\$200 a course, it often goes untreated, causing some 200,000 deaths each year. In the research and development (R&D) chains that lead to drugs, more attention is devoted to silicone breast implants and pills for erectile dysfunction than to the roughly 8,000 orphan diseases. These neglected diseases each touch up to just 2,000 people, but together they affect millions.

The root cause is that the markets for these diseases are too small to seriously interest the large pharmaceutical companies, which are involved in partnerships to address them but must also answer to their shareholders. What can be done to redress this balance by the many stakeholders along the route from research to product?

A round table on neglected diseases, co-organized by *Nature* at the BioVision World Life Sciences Forum in Lyon, France, last week, left a depressing sense of how far we have all got to go to seriously address neglected diseases — but also provided some encouraging sparks of enlightenment, and pointers to possible ways forward.

The meeting was held to celebrate the 50th anniversary of the approval of a polio vaccine. Polio is on the brink of being eradicated, something that would have been impossible without the March of Dimes, which courageously supported key basic research into the disease, and the Rotary Foundation, which got the vaccine into the field by raising more than \$500 million and providing volunteers. They addressed critical bottlenecks, and won. As a result, most people reading this will be unaware that just a few decades ago, polio was a disease that every parent feared.

New leaders

A new generation of 'social entrepreneurs' are testing imaginative ways to tackle neglected diseases. One small step for Victoria Hale, for example, may be a giant leap for mankind: the founding of a San Francisco-based not-for-profit drug company, the Institute for OneWorld Health. At the Lyon meeting she told of clinical-trial results that could lead to a safe and effective cure for kala-azar for just \$10 a course.

Instead of trying to develop a new drug from scratch, Hale started knocking on university and company doors, looking for drug leads lying in drawers, prescribed for something else or abandoned somewhere along the drug pipeline. She arm-twisted companies to give her promising candidates for such diseases as schistosomiasis and Chagas' disease, and went on to raise philanthropic funds for their clinical development.

The \$10 kala-azar drug is paromomycin, an off-patent antibiotic dating from the 1950s. With the help of funding from the Bill & Melinda Gates Foundation, Hale's company took it through the expensive clinical development and trials that no one else had ever bothered doing, to test and market it for kala-azar. Delivery will be achieved with the help of a generic-drug manufacturer in India.

A similar approach is being taken by the Geneva-based Drugs for

Neglected Diseases Initiative, instigated by Doctors without Borders, for a host of other neglected diseases. As well as testing and reformulating existing drugs, such initiatives are bridging the abyss between research and clinical development by focusing on leads that would otherwise have remained in the lab for lack of an industry sponsor.

Another key bottleneck in the pipeline is preclinical research in animal models or cell cultures. Genomics has revealed the molecular basis of some 1,200 orphan diseases, as well as major ones such as malaria and tuberculosis, revealing new drug targets. This is opening up many orphan diseases to possible cures for the first time. If the molecular basis involves the expression of interleukin A, for example, then existing interleukin A inhibitors might make potential drugs. But the many drug analogues needed by academic researchers to test this plethora of emerging targets are found only in industry.

So French gene therapist and social entrepreneur Alain Fischer is trying to persuade companies to give researchers access to the wealth of relevant drugs they hold but have not developed. The fledgling European Rare Disease Therapeutic Initiative gives the company the right of first refusal to market a promising molecule for a neglected disease. If it declines, the researchers can take it to another company or funder to take it to the clinic.

Persistence for change

The catch is that all these initiatives are relatively small. Funding is a big issue, but Hale is bullish. The money is out there, she says, provided that scientists, doctors and social entrepreneurs build awareness and argue their case. Robert Scott, who spearheads the Rotary campaign against polio, agrees, pointing out that governments, companies and research institutes change: someone who says 'no' today may say 'yes' tomorrow. Dogged persistence pays off.

Ironically, getting rights and molecules from universities is often harder than obtaining them from companies. University technology offices tend to patent aggressively, look no further than generating income, and often fail to include provisions beneficial to tackling orphan diseases in their licensing deals with companies. More scientists and their institutions should sign up to organizations such as the Centre for the Management of Intellectual Property in Health Research and Development, Biological Innovation for Open Society, and the Science Commons, which help academics to exploit their research and intellectual property for social ends.

The scale of the market failure in neglected-disease R&D is staggering, and awareness of the scale of the problem is chronically low among many research and health stakeholders. Sustained and inspired leadership is needed from those who shape research agendas or can bend the ear of funders, both individual and institutional, private and public.

Scientists, retired industry execs, fundraisers and others can volunteer research and expertise to the Institute for OneWorld Health (www.oneworldhealth.org/how) and other social entrepreneurs, or they can network at OrphanXchange (www.orphanxchange.org) and the US National Institutes of Health's Office of Rare Diseases (www.rarediseases.info.nih.gov). And, of course, they can highlight the challenge by adding the appropriate pages to Wikipedia. ■