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Public-private partnership: From there to here

Simon L. Croft*

Drugs for Neglected Diseases Initiative (DNDi), 1 place Saint Gervais, 1201 Geneva, Switzerland

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Summary Major changes in research and development (R&D) for drugs to treat tropical and neglected diseases have occurred in the past five years. Public-private partnerships for product development (PD PPPs) have emerged since rising drug development costs pushed pharmaceutical companies out of R&D for these diseases of the developing world and are now having an impact on the discovery and development of new medicines to treat them. PD PPPs can be an efficient model for bridging the translational research gap between basic research and clinical development by bringing together expertise from academia, the pharmaceutical industry and the public sector. Sustainability of funding is a serious problem. At present, one or two key philanthropic organisations provide a large proportion of the funding. Drug development typically takes 10 years and only 10 per cent of initial projects making it into the clinic. The partnerships need to widen their funding base and ensure that the funders understand the high level of attrition. Public-private partnerships have proved that they can move compounds quickly through the R&D pipeline. The challenge is to ensure that the products are delivered to the people who need them and to ensure that scientists in endemic countries are involved in the whole process.
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1. Introduction

At the close of the last millennium, drug research and development (R&D) for diseases of the developing world was at a virtual standstill (Pécoul et al., 1999; Trouiller and Olliaro, 1999). Of the 1393 new pharmaceuticals marketed between 1975 and 1999, only 13 were for tropical diseases (Trouiller et al., 2002).

This neglect of diseases that kill and disable millions of the world's poorest populations every year was the result of two historical trends. The development of most of the drugs still used today to combat tropical diseases was driven by the needs of colonialism during the first half of the twentieth century (Janssens et al., 1992), by veterinary needs and by wars in endemic regions. Interest waned with the end of colonialism, changes in the structure of the pharmaceutical industry, the rising cost of drug R&D and increasing regulation.

The legacy of this neglect is all too apparent. There are no available vaccines against many tropical diseases. Existing drugs are inadequate, toxic, often require parenteral administration, need long treatment courses and increasingly fail due to resis-

* Tel.: +41 22 906 9230.
E-mail address: scroft@dndi.org.

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tance (Sundar, 2003; White, 2004). The picture for diagnostics for some of these diseases is equally grim. Many techniques are invasive, non-predictive, complex and employ poor markers.

By the 1990s it was clear that, without drastic action, this unhappy situation was set to continue. Although the problems of drug development for neglected diseases had been raised previously (Taylor, 1986), and in some cases acted upon (Vane and Gutteridge, 1985), increasing R&D costs meant that pharmaceutical companies were unwilling to develop products specifically for diseases which disproportionately afflict populations with no purchasing power. Although the WHO Special Programme for Research and Training in Tropical Diseases (WHO/TDR) took over much of the burden in the 1990s, it became clear that a new model was needed to stimulate the discovery and development of new medicines for tropical diseases.

The result was the emergence of public-private partnerships for drug development, the so-called product development partnerships (PD PPPs). These partnerships are now starting to make an impact and are largely responsible for the seismic shift in R&D for tropical diseases that has occurred within the last five years (Nwaka and Ridley, 2003).

2. Product development partnerships: more than the sum of their parts

Public-private collaboration in product development is not a new idea. The Special Programme for Research and Training in Tropical Diseases, has been active on this front for many years (see Nwaka and Ridley [1993] and below) and has included partnerships with the pharmaceutical companies since the 1980s (Vane and Gutteridge, 1985).

What is different about today's situation, however, is the sheer number and diversity of PPPs targeting tropical diseases. Many are focused on vaccines, microbicides and diagnostics (see Widdus, Public-private partnerships: an overview, this supplement). In this review, the focus will be on PD PPPs working on the chemotherapy of malaria, leishmaniasis, human African trypanosomiasis and Chagas disease.

The important thing about PD PPPs is that the whole is more than the sum of the parts. None of the individual players — the public sector institutions and academia, the pharmaceutical industry, the biotech sector, contract research organisations (CROs), or the not-for-profit organisations — have all the skills and resources necessary to discover and develop products which are needed by millions of people but for which there is no commercially viable market.

Within PD PPPs, there are key roles for both the public sector and the pharmaceutical industry. After all, it is the public sector through academia and other institutions that has provided, and still provides, much of the technology and ideas from the genome to the structural biology that enables rational drug design. It is in the public sector that the repository of disease expertise is still to be found, whilst within the pharmaceutical industry the strength lies in translating this knowledge into safe and effective medicines.

One of the key roles for the pharmaceutical industry lies in bridging the translational research gap. This is the gap between the basic research and the formal drug development process — the evolution of an idea, for example an enzyme inhibitor, through to a drug and the development of that drug into a product. Here industry, in the form of big or small pharmaceutical companies or contract research organisations provides vital expertise. Translational research needs pharmacology, assay development, toxicology, scale-up chemistry and formulation done to the highest standards and quality to ensure that the potential drug can move to clinical trials and ultimately be registered for patient use. This is not, after all, just an academic exercise.

Translational research is a multidisciplinary step (Figure 1). It requires focus, coordination and, something that cannot be over-emphasised, good management. There must also be something else. In all the complexity of translational research, there must be the commitment and determination to 'get this drug through'. Success is not just about money, it is not just about having a system; it is about building positive interactions

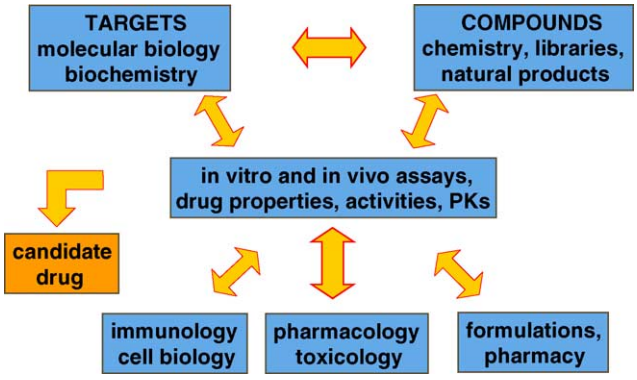

Figure 1 R&D process needs focus and coordination of multidisciplinary discovery and pre-clinical translational phases.

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between the chemists, biochemists, microbiologists and pharmacologists to achieve a common goal and managing that interaction proactively (Omura, 1986). Several organizations are committed to this process.

3. The Special Programme for Research and Training in Tropical Diseases

The Special Programme for Research and Training in Tropical Diseases is not, strictly speaking, a PPP. However, it has been involved in public-private collaboration for product development since its creation in 1975. The TDR was established by the WHO, the World Bank and the United Nations Development Programme and is managed through the WHO. It is funded primarily through international, governmental and philanthropic contributions.

The TDR has been a major funder of drug discovery and development, even during the 'hard' times of the 1990s when there was little interest in this area, and has developed a productive relationship with the pharmaceutical industry. The TDR also plays an important role in clinical trials involving public-private consortia and in the management of drug development though product development teams (PDTs). These teams guide the overall development programme, including timelines, budget, study design and protocols. They consist of pharmaceutical company experts, TDR members, clinical investigators and other external experts.

Two of TDR's most recent registration successes are miltefosine with Zentaris for visceral leishmaniasis in 2002 and chlorproguanil—dapsone with GlaxoSmithKline (GSK) for malaria in 2003.

Both miltefosine and eflornithine, a drug used for human African trypanosomiasis, were originally developed as anti-cancer drugs. The approach of 'therapeutic switching' or drug repositioning can deliver new drugs more quickly and at lower cost as much of the development work has already been done (Ashburn and Thor, 2004).

4. The 'portfolio' partnerships

4.1. Medicines for Malaria Venture

The Medicines for Malaria Venture (MMV) was one of the first PD PPPs to be established. An independent, not-for-profit foundation based in Geneva, Switzerland, it was founded in 1999. The MMV's mission is to discover new, affordable antimalarial medicines through public-private partnership. It is funded mainly by philanthropic foundation contributions as well as by international and governmental agencies.

Within five years, MMV has built up a portfolio of 10 pre-clinical and clinical and 11 discovery projects. The MMV model is that of a 'virtual' pharmaceutical company. It employs the sort of management systems required in a pharmaceutical company and, like most PD PPPs, has adopted a 'portfolio' approach to product development. Here, however, the similarity ends, as no pharmaceutical company would have 21 projects on malaria going through at the same time.

This portfolio approach encourages an immense synergy between projects. Knowledge, ideas and skills can be shared. It allows MMV to concentrate its energies on promising projects and to cut those which are considered to be failing to achieve milestones.

For example, using this approach, MMV ensured that novel synthetic peroxides were developed and reached clinical trials just four years after starting from basic chemistry funded by TDR. This was achieved by a project spanning four time zones and involving centres in places as far flung as Nebraska, USA, Europe and Australia (Vennestrom et al., 2004).

One of the keys to success was teamwork. Members of the synthetic peroxide project team identified regular team interaction; human factors such as loyalty, commitment and the enjoyment of working together; the regular interaction with MMV and with industry, and the clear objectives as important factors for success. These factors were also those identified in an earlier discussion on establishing strategic collaborations in public — private partnerships (Reich, 2000).

4.2. Institute for OneWorld Health

The Institute for OneWorld Health (IOWH) is a not-for-profit pharmaceutical company with an entrepreneurial business model based in San Francisco, USA. Founded in 2000, IOWH is funded mainly through the Gates Foundation. Its development pipeline covers both drugs and vaccines.

The IOWH has a portfolio that includes projects in leishmaniasis, Chagas disease, malaria, schistosomiasis and diarrhoeal diseases. It concentrates on licensing late-stage development candidates and on drug development, rather than on drug discovery. The IOWH has just completed Phase III trials in India of paromomycin, an antibiotic originally developed for oral use against gut pathogens, as an injectable for use in visceral leishmaniasis.

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4.3. TB Alliance (Global Alliance for TB Drug Development/GATB)

Tuberculosis (TB) is, of course, not an exclusively tropical disease. However, it is a neglected disease that disproportionately affects the poor in the developing world. The TB Alliance is a not-for-profit foundation based in New York, Brussels and Cape Town — the last a TB endemic area. Founded in 2000, its mission is the discovery of fast-acting and affordable drugs to fight TB. The TB Alliance is funded mainly through government and charitable foundations.

The TB Alliance has a portfolio of 11 projects including quinolones, nitroimidiazoles and macrolides, three of them in pre-clinical and clinical development. Importantly, however, the TB Alliance is also investing in upgrading the research tools required, including animal models, surrogate markers, databases and clinical trial capacity. Upgrading research tools is an issue that must be tackled, and not ignored, with other chronic diseases such as trypanosomiasis and Chagas disease.

The fact that the TB Alliance has established part of its operation in a TB endemic area in Africa is important. If PD PPPs are to achieve a long-term health impact, it is vital that scientists in disease-endemic countries are fully involved in the discovery and development process.

4.4. Drugs for Neglected Diseases Initiative

The Drugs for Neglected Diseases Initiative (DNDi), established in 2003, has addressed the issue of disease-endemic country involvement in a fundamental way. Four of its founding partners are research institutions from the developing world — the Oswaldo Cruz Foundation from Brazil, the Indian Council for Medical Research, the Kenya Medical Research Institute and the Ministry of Health in Malaysia. The other partners are Médecins Sans Frontières (MSF), the Pasteur Institute from France; and the TDR.

The DNDi, which is principally funded through MSF, already has a portfolio of nine projects targeting leishmaniasis, trypanosomiasis, Chagas disease and malaria (Figure 2).

At the discovery stage, DNDi is working to identify inhibitors of the kinetoplastid enzymes trypanothione reductase, dihydrofolate reductase and protein farnesyltransferase and is carrying out high throughput screening on whole cell trypanosomes to identify novel lead compounds.

In pre-development, DNDi is assessing possible combinations of existing drugs for both visceral leishmaniasis and second-stage human African trypanosomiasis, the latter in collaboration with the TDR and Bayer.

Also at the development stage, DNDi, in partnership with seven medical institutes around the world, is developing two fixed-dose artesunate combination therapies (FACT). These are artesunate—amodiaquine and artesunate—mefloquine for use against chloroquine-resistant malaria in Africa and Asia respectively.

It is essential that DNDi collaborates with IOWH and the TDR where they share interests in the discovery and development process for these neglected diseases.

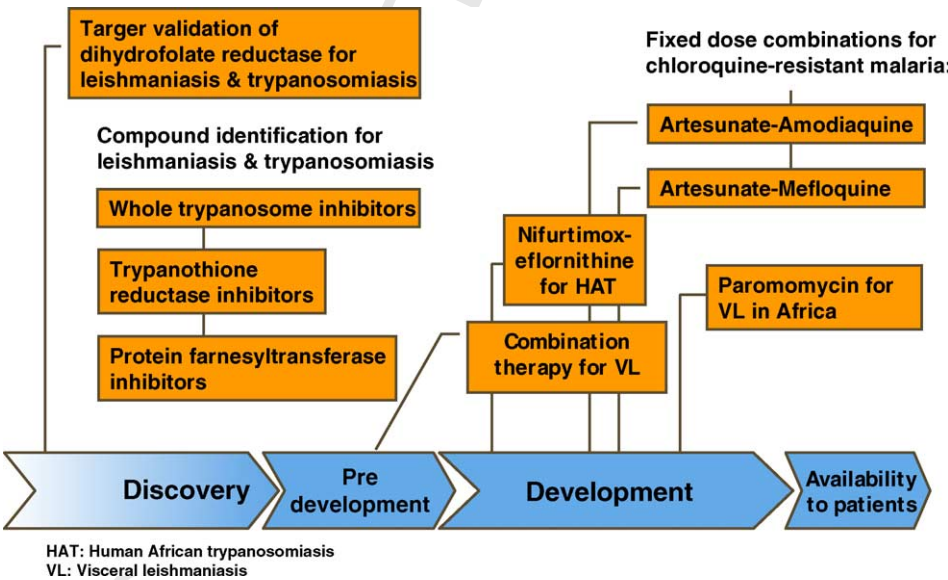

Figure 2 Nine ongoing projects.

5. Small but effective

The increased involvement of major pharmaceutical companies in PD PPPs is to be welcomed, but partnerships do not necessarily need 'big pharma' to bridge the translational research gap. Small companies of six to eight people with the right knowledge can be very successful at helping to manage the development process from basic research though clinical development.

A good example of this is to be found in the University of North Carolina-led Consortium to develop New Drugs for African Sleeping Sickness and Leishmaniasis, a smaller PPP funded chiefly by the Gates Foundation. The consortium has eight drug discovery partners and four partners dealing with drug development. These development partners include a small company called Immtech International from Illinois, which has played an important role in driving the science through into a potential product. The consortium has successfully moved diamidine derivatives to treat early-stage African trypanosomiasis from academic groups at the University of North Carolina and Georgia State University through to Phase II clinical trials.

6. Discussion

So, in the midst of all this activity, how do we measure success? Do PD PPPs actually work? Is this a successful new model for drug discovery and development?

6.1. Measures of success

Answering the following questions helps clarify the level of success so far.

6.1.1. Has there been development of portfolios?

Yes. As outlined above, several PD PPPs are taking a portfolio approach for specific diseases. This is important as it gives partnerships the ability to synergise across portfolios and even across PD PPPs where there are shared projects and ideas.

However, within these portfolios it is important to maintain a sufficient number of early-stage projects because the attrition rate in drug discovery is huge — only 10% of initial projects are going to reach the clinic.

6.1.2. Are PD PPPs a new model for producing drugs/treatments?

In terms of treatments, it is too early to say. Most of the PD PPPs for drugs have only been around for up to five years, and drug discovery and development can take 10 years or more. Sustainability of funding is the key issue here. At present, there is a limited range of funding with one or two key philanthropists, such as the Gates Foundation and MSF, making very large contributions. In future, there must be a greater spread of funding to ensure that projects are supported for the full 10 years.

6.1.3. Are PD PPPs time and cost effective in the development of new products/treatments?

Yes. PD PPPs, both large and small, have already shown that they are capable of making decisions and of moving compounds along the development pipeline very quickly. As stated above, it is too early to judge what the outcome of this will be in terms of new treatments for patients as there will, inevitably, be failures in the clinical trial stages. It will be up to the PD PPPs to ensure that the funders understand and accept the high attrition rate.

6.1.4. Have PD PPPs engaged the pharmaceutical and biotech sectors?

Yes, up to a point. A few major companies, for example GSK and Novartis, have made a high level of commitment, as have a number of smaller and medium-sized enterprises. However, overall, the number of companies becoming involved is very small.

6.1.5. Has there been re-building of expertise?

Yes, up to a point. GSK has built the Tres Cantos R&D unit in Spain specifically for malaria and TB. Meanwhile, the Novartis Institute in Singapore is already developing other facilities and expertise for TB and dengue.

However, a recent FDA report, *Innovation or Stagnation?* (FDA, 2004), concludes that a large proportion of the cost of drug development is due to the use of inadequate models and screens to move things through the discovery and pre-clinical stages. According to the report, drug discovery and development models have not kept up with advances in technology and basic science. Obviously, we need better models, and this is another area on which PPPs and pharmaceutical companies can collaborate.

6.1.6. Are PD PPPs achieving a public health impact?

Again, it is too early to form a judgement, and there are significant problems to overcome. There is a significant lack of clinical trial capacity for many tropical and neglected diseases, and procurement

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and delivery systems for drugs in many disease-endemic countries are poor.

6.1.7. Is there disease-endemic country involvement?

Some. As outlined above, two partnerships, DNDi and TB Alliance, are taking a proactive role and other PD PPPs must follow this lead. It is extremely important in the long run that scientists in disease-endemic countries actively participate in the discovery and development process.

In conclusion, it is probably fair to say, even at this early stage of the new model's evolution, that had PD PPPs existed in the early 1990s they would probably have reduced the journey from discovery to development for some products by up to five years. Public-private partnerships for product development for tropical and neglected diseases have made a good start. However, there are many challenges ahead. Not least of these are the necessity to broaden the funding base and the difficulty of keeping those funders on board throughout the long, and often disappointing, process of drug discovery and development. It remains to be seen how many of the PD PPP projects now underway are successfully translated into products and delivered to those populations who need them.

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