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Impact of non-profit organizations on drug discovery: opportunities, gaps, solutions

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Non-profit organizations (NPO) play an increasingly important role in drug discovery and development for diseases that are neglected by the pharmaceutical industry because of low or absent commercial incentives. Governments and major private foundations such as the Wellcome Trust and the Bill & Melinda Gates Foundation increasingly step in to provide strategic direction, communication platforms and major resources, motivated by the fact that major healthcare problems remain unsolved. Drug discovery in the field of neglected diseases is fraught with complexities since, in many cases, important tools are lacking including readily available diagnostics, molecular epidemiology, appropriate model systems, representative strain collections, biomarkers, up-to-date trial methodologies and regulatory strategies. On top of this, the high hurdles addressing novel drug targets must be cleared.

Business model of the established pharma industry

Traditionally, drug discovery has been the domain of the established pharmaceutical industry, including (since the eighties) the biotech industry, either in partnership with the pharmaceutical industry via licensing deals or via outright takeovers of the junior partners. Increasingly, the biotech industry drives development activities independently, including regulatory submissions, and in some cases regional or even worldwide marketing of products.

All of these companies have adopted a profit-driven business model, which has led to practically all major innovations in the pharmaceutical industry over the past 3–4 decades. Unfortunately there is little incentive for these companies to invest in diseases with low or negligible commercial potential [1], because R&D of novel therapeutics has become a high stakes gamble where successes are scarce and failures are the norm [2]. This business model is driven by very ambitious revenue and profit goals that are set quarterly by the representatives of the capital market.

Within the framework of this business model the pharmaceutical industry is currently investing annually >US$ 60 billion in drug discovery and development. It is a fair estimate that about one third of these funds (i.e. ~US$ 20 billion) flow into drug discovery alone. However, we are witnessing a decline in output of dramatic proportions. In 2005 there were 20, and in 2006 only 17, FDA-approved drugs. Estimates for R&D costs for a single new drug (taking into account failed projects) range between US$ 800 million to US$ 1.5 billion [3,4].

The pharmaceutical industry is scrambling for answers to reduce the inherent risks of this endeavor and is attempting to shorten the timelines of the R&D process, while minimizing attrition through stringent quality controls at all levels. Despite all these efforts, the uncertainties and the huge financial risks remain high, translating into enormous pressure on pharmaceutical companies.

Neglected diseases/tropical diseases – a new landscape of funding mechanisms to address unmet medical needs

Given the aforementioned constraints, it is practically inconceivable that the Pharma industry allocates any resources to indications without proven or plausible commercial potential [1]. This is the case for most of the tropical diseases, which are often referred to as 'Neglected Diseases'. Examples of neglected diseases include malaria, tuberculosis, Buruli ulcer, Dengue fever, leishmaniasis, trypanosomiasis, diarrheal diseases, among many others. To some extent, HIV/AIDS has also become a tropical disease because of the fact that Western medicines, which have radically changed the outlook for patients in the developed world, are still largely

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1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2008.02.005

inaccessible in Africa and South/South-East Asia despite huge financial efforts by the Global Fund, UNAIDS, WHO and several other institutions [5].

Clearly, to address these unmet medical needs, new solutions must be found. Through a convergence of interests of many different partners, it has indeed been possible to forge alliances and consortia that are driving drug discovery and development in a way that was inconceivable ten years ago.

Examples for government-funded activities are framework programs of the European Community, the Small Business Innovation Research (SBIR) and the Small Business Technology Transfer (STTR) program of the US government, the Singapore Economic Development Board, the Innovation Promotion Agency (CTI) of the Swiss Science & Technology Council and many others). These agencies can fund activities that are devoted to seeding drug discovery activities aiming at the creation of start ups on the basis of the discoveries in academic laboratories. These initiatives seek to build and expand the life science industry, enabling academic scientists of the respective countries to gain access to major funding that supports goal-oriented projects in the biomedical arena. These initiatives can be 'non-profit', at least initially, but ultimately the countries or regions hosting these initiatives want to participate in the strengthening of the life science industry by generating new technology platforms, new target classes, or entirely new avenues of research such as stem cell technologies. In some cases, however, it is directed in part, or entirely, at solving the problems of neglected diseases (for example, the European Developing Countries Clinical Trials Partnership, EDCTP).

Major private foundations have stepped in to complement these funding streams. In particular, the Wellcome Trust (WT) and the Bill & Melinda Gates Foundation (BMFG) play a dominant role as funders in setting the agenda and priorities, in giving strategic direction and providing resources in an unprecedented fashion. The program 'Grand Challenges in Global Health', undertaken jointly by the NIH and the BMFG, is a striking example. A new landscape has emerged of drug discovery consortia linking academic groups, industrial partners and donors effectively addressing the largely unmet medical needs of tropical diseases.

Possible models for drug discovery organizations addressing neglected diseases

The experience of the pharmaceutical industry suggests that successful R&D for any disease (including neglected diseases) requires highly specialized know how, experienced project management and large investments. The times when one or two labs were able to generate drug candidates are long past. Today, any serious effort must encompass a portfolio of projects, professional project management and a multi-year financial commitment. Because the pharmaceutical industry cannot shoulder this burden, the only viable way forward for R&D in neglected diseases seem to be non-profit organizations (NPO). Several models are currently being explored:

a. *Non-government organizations* (NGOs) active in a particular disease area fund drug discovery and development in academia, the biotech industry and Pharma. Typically, such NGOs will create consortia addressing a particular disease, combining academic groups with industrial partners. Examples include Medicines for Malaria venture (MMV) [6] (http://www.mmv.org), Global Alliance for TB Drug Development (GATB) [7] (http://www.tballiance.org), the institute for One-World Health (iOWH) [8] (http://www.oneworldhealth.org) and the Drugs for Neglected Diseases initiative (DNDi) [9] (http://www.dndi.org). MMV has arguably the most developed network of all, drawing funds from governments as well as major private foundations such as the Wellcome Trust (WT) or BMGF. MMV is funding drug discovery activities in academia, biotech and the pharmaceutical industry including GSK and Novartis (see http://www.mmv.org). Another example is the partnerships of the Special Programme for Research and Training in Tropical Diseases (TDR) of the World Health Organisation (WHO) with Pfizer, Serono and Pharmacopeia. (see http://www.who.int/tdr/publications/tdrnews/news77/drug.htm).
b. *Public-private partnerships* (PPPs) are possible when the interests of the public sector overlap with those of industry. An example is the Novartis Institute for Tropical Diseases in Singapore (NITD), which is funded jointly by the Singaporean government and Novartis [10]. This institute has as its mission the aim to discover and drive the early development of drug candidates for treatment of Dengue fever, tuberculosis and malaria. Products that reach the market will be made available to poor patients in developing countries at cost. For the Singaporean government it is useful to attract a major pharmaceutical company with its technologies and expertise for training and education of young scientists, and for Novartis it is important to gain a foothold in a region of emerging markets with their talent pools, their drive to scientific and technological excellence, and to gain first-hand experience working with the communities of clinicians and regulatory authorities of this emerging region.
c. *Academic, open-source networks* driving drug discovery have sprung up recently to organize drug discovery around a particular target, a technology or disease in the absence of any industrial partners. Examples include The Sandler Center for Basic Research in Parasitic Diseases (http://wwwedu/mckerrow/slide.html) and the tropical disease initiative at the University of Dundee (http://www.drugdiscovery.dundee.ac.uk/tropical/overview/) and the Rosberg Institute.

In practice there is considerable overlap between points a and b [11]. Both models of NPOs are drifting toward PPPs that bring together governments, funding agencies, NGOs and industry players. Model (c) attempts to reproduce some of the infrastructure of the pharmaceutical industry in an academic setting, but whether such institutes can be productive in the longer term needs to be seen. In our mind an ideal situation would be a PPP that also includes academic scientists (in effect a combination of points a, b and c).

The business model of a NPO is then quite complex. Currently, we see consortia of funders driving the work of consortia of researchers in academia and industry. The composition of these consortia can vary over time, with new and different funders entering the fray over the drug discovery and development process. This can be illustrated as follows (Figure 1).

Advantages and disadvantages of NPOs in neglected disease drug discovery

Because the available budgets are not comparable to the pharmaceutical industry, NPOs have developed innovative (but so far

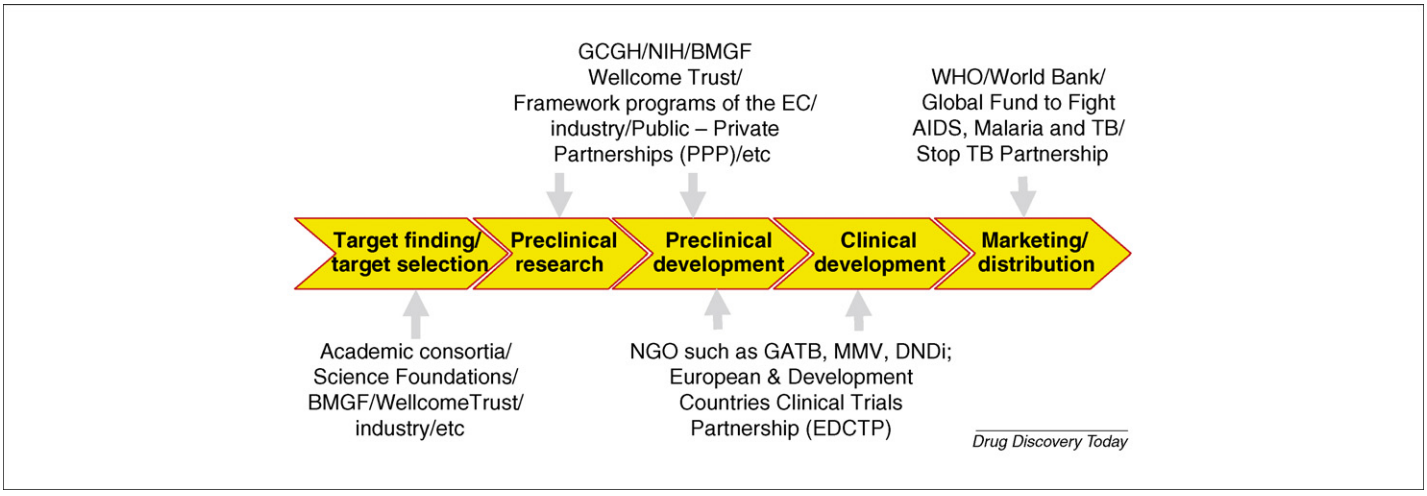

FIGURE 1

Outline of the drug discovery and development process and some key consortia involved at the different stages. The composition of consortia comprising researchers from academia and industry can vary over time.

unproven) approaches [12] to drug discovery and development. They work with very low overhead, minimal infrastructure and by systematically outsourcing expensive activities such as medicinal chemistry to countries with lower labor cost (India, China, countries of the former Eastern Bloc). They are also willing to adapt their project portfolio and their resource commitments to the vagaries of variable funding streams, which would be unacceptable for a large pharmaceutical company.

There are inherent shortcomings in such loosely structured collaborative networks. Because funding is usually limited to a fixed time frame there is very little opportunity and financial strength to cope with unforeseen difficulties. This is especially relevant in the area of infectious diseases where drug discovery is far from straightforward and setbacks are common [12]. To work in this area is pioneering by necessity, if the goal is to come up with new, safe and efficacious medicines in a useful time frame. Patience of funders has its limits, and if no tangible progress is seen over 5–10 years funding may cease.

Another serious downside is the lack of institutional memory of such an organization. For drug discovery it is absolutely vital that experiences are shared and that past mistakes are not repeated. Because very few scientists are working in neglected diseases and the funding is limited, this is even more important than in more commercially attractive diseases.

Despite these challenges, some important successes have come from such efforts including Coartem, the first Artemisinin-based fixed dose combination therapy for malaria (Novartis/WHO; [13]), and several others [14]. In this particular instance, Novartis as a profit-based institution has chosen to set aside funds for work that is not-for-profit, that is has acted as a NPO in a segment of its activities, similarly as in its initiative to set up NITD (see above).

Gaps in drug development

The term 'neglected' already suggests that very little scientific and/or drug discovery work has been done in these diseases, and therefore huge gaps exist in all aspects of drug discovery and development. It would be a mistake to think that R&D for neglected tropical disease is simply a question of money. NPO can only be successful through a combination of scientific and technological advances with proper project management based on pharmaceutical know how.

To understand the hurdles that NPO are facing we need to first evaluate the state of the art in these disease areas.

This starts with the drugs that are currently used for neglected diseases. Often they are old and have severe side effects and more modern therapies are only slowly emerging [14,15].

For example, no new drug has been developed for TB in thirty years [16], no specific drug exists for Dengue fever [17], and anti-malarial drugs are uniquely dependent on the safety and efficacy of artemisinin-based fixed-dose combination. If resistance were to develop against the Artemisinins, malaria would be largely devoid of cheap and effective treatment options [18]. Moreover, although Artemisinins are effective against blood stages of *P. vivax*, relapses occur because of chronic liver cell infections that can currently only be treated with primaquine [19], a drug that must be used for at least a fortnight and has several disadvantages, most notably toxicity in patients with Glucose-6-phosphate dehydrogenase (G6PD) deficiency [20].

Major gaps are also associated with treatment schedules. TB is a striking example, where patients must enroll in a so-called 'Directly Observed Treatment, Short-course' (DOTS) regimen which imposes daily combination treatment at a treatment center for at least six months. Often, these treatment centers are far away from where patients live, in regions with no (or scarce) public transport. This leads to serious compliance issues [21]. Compliance problems are even encountered with the three day schedule used to treat uncomplicated malaria. When the fever drops after one day, treatment is sometimes stopped prematurely. This leads to relapses and is an obvious way to generate resistance. A one-dose cure would be an ideal solution.

Resistance against TB drugs has recently become a serious issue, with the extremely resistant TB (xdr-TB) that is resistant to all first line drugs, and sometimes even to some second line drugs [21]. TB, in particular multi drug resistant TB (mdr-TB), is the major killer of people with HIV/AIDS, and a determined effort to find new drugs with novel mechanisms of action is needed [22–24].

From the above examples it is evident that there are major needs in the field of neglected diseases, in terms of

- Diseases without any specific treatments, such as Dengue fever
- Diseases for which there are drugs that are either not really effective, have met with resistance, and/or have safety problems such as *Plasmodium vivax* malaria, mdr- and xdr-TB
- Drug combinations that require schedules with severe (DOTS) or moderate (ACT) compliance problems
- Drugs where cost-related issues and access problems exist, severely restricting access of poor populations (second line drugs for HIV/AIDS)
- Preventative use of drugs such as prevention of HIV transmission from mother to child during birth and breast feeding, or prevention of vaginal transmission of HIV during intercourse through microbicides.
- Epidemiology, in particular the precise mapping of the molecular epidemiology of bacteria, viruses and parasites despite major progress in this area
- Understanding the pathophysiology of neglected diseases

Because of the lack of progress in many of these areas, the community is ill prepared for clinical trials of new drugs. If the current worldwide resurgence in neglected disease drug discovery is to bear fruit, new tools are urgently needed to support clinical researchers. Rapid feedback on the performance of drug candidates in clinical trial is essential, since improvements in efficacy and safety can be engineered into backup or follow-up compounds, if timely information is provided to drug discovery scientists.

To enable this information flow clinical researchers need fast, reliable and cheap diagnostics and biomarkers capable of measuring pharmacokinetic and pharamacodynamic endpoints in proof-of-concept studies [25].

Gaps in drug discovery

One of the most surprising gaps for a newcomer to drug discovery in neglected diseases is the lack of targets with demonstrated essentiality, epidemiology and, most crucially, druggability. Druggability is one of the most important hurdles in drug discovery and the source of major attrition in all disease areas. It is often ignored by academic scientists, but the most extensively validated drug target will be useless if no small molecular weight lead can be identified [26].

Lead finding is a major bottleneck in all infectious diseases [27], leading to an acute lack of good chemical starting points for lead optimization. Especially High-throughput Screening (HTS) using biochemical assays is often unsuccessful [12]. The reasons for this lack of success are manifold and include the absence of suitable targets, but other issues, too, need to be considered in this context.

Screening libraries consist of collections of compounds that have been designed to interact with human proteins. It is therefore not surprising that hit rates for bacterial, viral and parasite proteins are often quite low. Commercial and corporate libraries seem to contain few compounds that are suitable as inhibitors of microbial proteins [12]. Unfortunately, our knowledge of the chemical space required to interact with such proteins is rudimentary at best, and we urgently need more data to be able to construct libraries that promise more success.

HTS campaigns with the currently available libraries are complicated by a large number of false-positive hits because of inhibition by colloidal aggregates [28]. These so called promiscuous inhibitors make the identification of chemically tractable hits very difficult and time consuming. In a telling experiment Shoichet and co-workers screened library compounds, from the NIH Chemical Genomics Center, against β-lactamase. Of 1274 identified inhibitors, >94% were aggregate-based inhibitors and therefore false-positive hits [29].

Finally, significant gaps exist in the later stage of the drug discovery process. For example, the predictive power of animal models for human disease is largely unknown [28]. While the modeling of simpler parameters such as Dengue viremia in a mouse model is feasible, the modeling of a complex disease process such as Dengue hemorrhagic shock is elusive at best. Similarly, parasitemia in a mouse model of malaria is a useful parameter in the drug discovery process but will not capture drug efficacy in real life situations in humans. Hence, the predictive power of animal models is largely unknown and species differences need to be much better understood regarding human disease [30].

Solutions

As an important starting point we need to accept that drug discovery in the field of neglected diseases remains as difficult as ever, exacerbated by the absence of an extensive basis in molecular epidemiology, pathophysiology and clinical practice. Discovering and developing drugs for TB, leishmania or *P. vivax* is more challenging than comparable work in diseases that are dominant in the northern hemisphere, because many of the basic tools that scientists use every day are simply not available and know-how specific to these neglected diseases is lacking even in the pharmaceutical industry. There is no easy path to new drugs for neglected diseases [8].

Fortunately, the tide is starting to turn and especially the creation of PPPs [31,32] has stimulated all aspects of neglected disease R&D attempting to close the gaps listed above. Important progress can and will be made through funding streams that were not available in the past. Consortia of academic scientists and industrial partners are able to tackle fundamental questions of strategic significance [31,32]. The best known example is the initiative known as 'Grand Challenge for Global Health' under the patronage of NIH and funded by BMGF and WT (http://www.gcgh.org/channels/gcgh).

While funding of R&D in neglected diseases is improving and more and more academic and industrial scientists are joining the search for new drugs, it is important to remember that financial resources are limited. As a consequence, it would be advantageous to focus efforts on a few promising targets and employ rigorous project management to reach fast go/no-go decisions. If a vibrant pipeline is desired, there is no way around a management structure with seasoned drug discovery experts as key decision makers.

The rapid and successful discovery of efficacious anti-AIDS drugs in the mid eighties through the combined efforts of NIH, NCI and NIAID has taught us several valuable lessons. Central agencies can spearhead the creation of databases, central repositories of cell lines and biochemical tools and targeted workshops where unpublished results can be shared among groups of active scientists.

Such a coordinated effort should be started for all neglected diseases, so that an attempt can be made to create an institutional memory which supports collective learning and reduces duplication. We need to clearly recognize, however, that competitive groups targeting identical targets were the major force behind rapid gains in the field of HIV/AIDS. This is unlikely to happen in the field of neglected diseases, with the possible exception of malaria, and the scarcity of funds will require judicious and coordinated, long-term funding.

At the operational level, a concerted effort should be made to make laboratory tools available for scientists in the field, including strain collections of epidemiologically representative wild-type strains and resistant strains, cDNAs, antibodies and crystal structures. Assays should be standardized and be made available to other groups of researchers, either by technology transfer or by permitting access of outside groups to have their compounds screened.

A particular challenge is the chemical libraries, which need to be built around microbial targets. There is little consensus on how to create such focused libraries and only a concerted effort by the whole community can solve this problem. A special funding scheme to bring together computational and medicinal chemists as well as screening experts to generate a hypothesis would be of enormous value. In addition, it would be necessary to screen the newly created 'antimicrobial' library against several targets and compare the results with traditional screening campaigns.

Cellular screening has been routinely used for antimicrobial drug discovery since the start of the 20th century. While this has led to the discovery of all our currently available antimicrobial drugs, it is not a very productive way to search for leads, if done in a traditional sense. Nevertheless, interesting compounds may be identified through screening of libraries in specialized phenotypic screening systems that mimic specific aspects of a disease. In TB, for instance, microbial cultures can be used for drug screening under low oxygen tension or low nutrient concentration. Such screens can yield important tool compounds for biologists and sometimes leads for drug discovery. Such efforts can be highly informative if the mechanism of action of the hits is examined using microarrays [33] and resistant mutants are sequenced to find the target proteins [34].

Animal models are useful tools to understand the therapeutic potential of drug candidates. However, the plethora of animal models that are available for testing the efficacy of selected molecules in disease models of TB and malaria and the uncertainties about their predictive value complicates the progression of drugs into preclinical development. For instance, it is relatively straightforward to look for active compounds in a model of viremia [35]. It is, however, much more difficult to screen for therapeutic activity in models that accurately reflect the human disease. Such models should be reviewed very critically for their value. This can be attempted through a careful, quantitative and comparative analysis of the (immuno)histopathology of the animal model and human disease. The models should be standardized and tested with a battery of clinically used drugs. This will then allow determination of what kinds of questions can be asked with any level of predictive power.

Conclusions

Neglected diseases that were underserved for decades by the established pharmaceutical industry are now receiving considerable attention through new funding streams from private sources and governments. NPOs are marshaling collaborative efforts in several important neglected diseases and the prospects for new drugs have brightened considerably. While this is a good start, success is not guaranteed and several gaps in discovery and development need to be addressed. Lessons learned over several decades in the areas of cancer and HIV/AIDS drug discovery need to be applied forcefully and the technologies that have become available introduced in the area of neglected diseases. Target selection, lead finding and animal models of efficacy need to receive greater attention. This is a unique opportunity that must be seized but there must be tangible successes for the efforts to be sustainable.

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