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PERSPECTIVES

OUTLOOK

Can open-source R&D reinvigorate drug research?

Bernard Munos

Abstract | The low number of novel therapeutics approved by the US FDA in recent years continues to cause great concern about productivity and declining innovation. Can open-source drug research and development, using principles pioneered by the highly successful open-source software movement, help revive the industry?

Open-source research, which started as a counterculture movement in the software industry 15 years ago, has since grown into a business model whose best-known product, Linux, has become a credible alternative to Microsoft's Windows. Now, with biology increasingly becoming an information-orientated science, some have suggested that what worked for software might be part of the answer to the spiralling cost of drug R&D. With this in mind, this article examines the relevance to pharmaceutical R&D of the open-source model developed by the software industry. In this context, open-source no longer refers to source code, but instead to the open origin of contributors.

Open-source R&D has already made inroads into bioinformatics and research tools for drug hunters. However, key differences between software and biology, such as regulatory requirements, have limited its application to drug development. Nevertheless, in the past 5 years a new breed of organizations called public–private partnerships (PPPs) have adapted the open-source concept and combined it with outsourcing to create a new, low-cost business model, which they have applied with encouraging results to the discovery of new treatments for neglected diseases.

Advances in data mining, visualization and networking now make it feasible to go one step further. It is possible to offer scientists a computerized toolbox that lets them harness the creativity of numerous volunteers to address the key questions that are holding back innovation. For example, what is the aetiology of a disease? What are the pathways involved? What are the better targets? Once these questions are answered, laboratory and clinical studies can be outsourced to institutions with the requisite capacity through the help of matchmaking software.

The resulting model is a hybrid in which a part of R&D is open-sourced while the rest is outsourced. To function, however, it needs strong project leadership and expertise in the minutia of drug R&D, which mostly exist in big pharmaceutical firms. This suggests that, far from being a threat to conventional drug R&D, open-source could be a way to leverage big pharma's capabilities in order to tackle challenges that the blockbuster model cannot address economically, such as neglected diseases. As pharmacogenomics takes hold, it might also be a way to address market niches that cannot support blockbusters.

A brief primer on open-source

Open-source R&D is a novel approach to research that lets scientists join hands freely across organizations, disciplines and borders to solve problems in which they share an interest. The movement's icon is Linux, the operating system started in the early 1990s by student Linus Torvalds, who used the nascent Internet to circulate it to fellow computer enthusiasts. Soon they were busy adding features and improving the code, with Torvalds overseeing the process. Fifteen years later, this grassroots experiment has blossomed into a new culture that is spreading to other disciplines. It is most prominent in computer software development, for which dedicated websites such as such as SourceForge or Subversion help over a million people collaborate on more than 100,000 projects. But other areas, such as life sciences, have spawned open-source initiatives of their own.

The impetus to create open-source software often comes from developers looking for challenge. They agree on an attractive project, form a team and produce a 'bare-bones' program with basic functionality. Then, they offer it at no cost on the Internet under a public-domain license (there are many different types of open-source license; some, notably the 'copyleft' or General Public License (GPL), require those who download a program to share any improvements they make). If the project draws interest, others add features and post their code on the project's webpage for fellow programmers to critique. New code of sufficient quality is added to the authorized version of the program.

Open-source's chief benefit is to cross-fertilize minds and tap creativity quickly, cheaply and on a scale that is beyond the reach of scientists working in the 'ivory towers' of academia or behind the 'corporate moats' of industry. Hollingsworth[1,2] has shown that innovation spikes when diverse minds interact frequently in an unstructured manner. By drawing talent from all around the world, open-source research takes these dynamics to a new scale. And by making innovation immediately available to all, it speeds up the accumulation and application of knowledge.

Outsiders are often puzzled by the open-source idea. Why would anyone work for free? Simply put, because some people value non-cash compensation more than money. They volunteer their expertise to satisfy idealism or curiosity, seek new challenges, hone skills, build a reputation or enhance careers. Feldman[3] quotes the example of Australian programmers who, within hours of Netscape's release of its browser code, attached an 'add-on' to enable secure internet transactions. No money changed hands, but the authors received respect from the programming community and the satisfaction of turning out an elegant and useful piece of software.

Companies are learning to use open-source to their advantage, and many now allow their employees to participate on company time. They might use it to gain market share against entrenched competitors, or

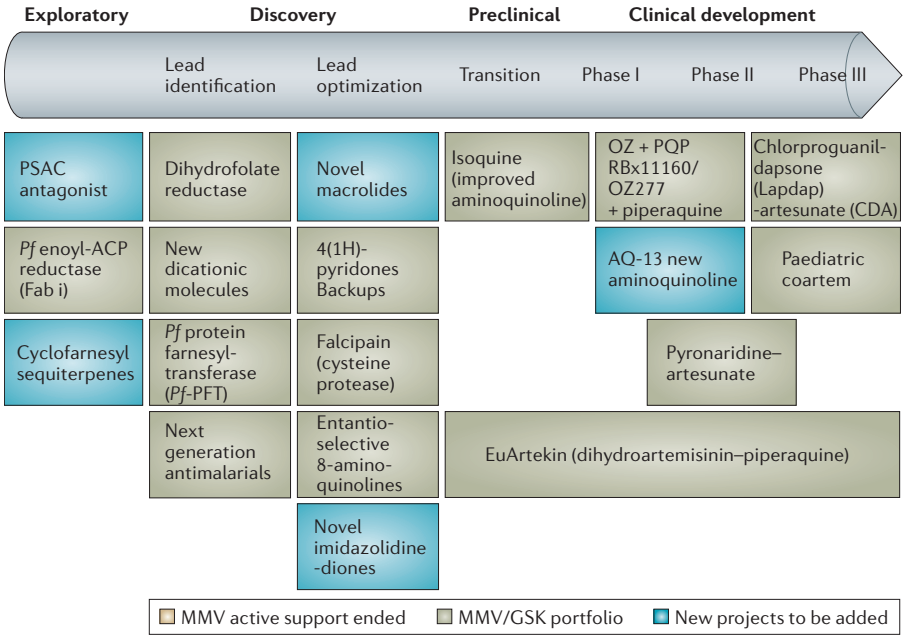


Figure 1 | **Portfolio of the Medicines for Malaria Venture.** PSAC, plasmodial surface anion channel.

to entice developers to create applications for their product, possibly in the hope of turning it into a 'platform'. Some of them have been quite successful at turning open-source into profits. Red Hat, for instance, has attained a US$5-billion market cap from selling support services for Linux.

Can it work for drugs?

If biomedical scientists could adapt the open-source model, it could make a huge difference to such projects as developing drugs for neglected diseases, for which needs are great but funds are scarce[4]. Only 10% of R&D resources are spent on illnesses that represent 90% of the burden of disease. Open-source drug R&D might not change that equation, but could make it possible to get much more from that 10%.

There are, however, significant barriers to the deployment of open-source approaches to drug R&D[5]. One is economic. All it takes to write open-source software is a laptop and an internet connection. With drug research, someone must pay for laboratory expenses and clinical trials. And the costs are high, at more than US$800 million for the discovery and development of a novel drug by most estimates.

Research dynamics between the two industries also differ. Software development does not have a discovery phase. Once the objective is set, programmers set to work and make steady progress towards their goal. By contrast, drug discovery cannot flourish until a certain amount of knowledge about the target disease has been accumulated. That knowledge acquisition can take years or decades, with no way to know at the outset whether the store of knowledge at hand is nearly sufficient or will require years of painstaking additional research before innovation can thrive.

Software development is also simpler: it spans only a few disciplines and has no equivalent to clinical trials. For the most part, a single programmer can master all the skills needed to write a program from start to finish. By contrast, drug development requires coordination of multiple specialties with little overlap. Biomedical knowledge, which grows at the rate of 1,000 publications per day, must be peer-reviewed and replicated before it is accepted. All this is slow and enormously expensive.

Drug R&D can go off-track more easily than software programming. Biologists can get mired in the complexity of biology without ever making much progress towards a drug — chemists handed the wrong target cannot do much good no matter how hard they try; inadequate toxicology can derail a compound late in development, or even after launch. One misstep along the way can render all downstream work useless.

In contrast to drug developers, software publishers are lightly regulated. They do not need FDA approval. The quality standards they face are far less onerous than the minutia of Good Laboratory Practice (GLP), Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP). One sloppy programmer seldom jeopardizes the achievements of others, and errors can be patched without requiring the rewrite of the whole program. With drugs, one careless worker can compromise years of work costing tens of million of dollars.

Finally, the two industries follow different intellectual property regimes. Software is protected by copyrights that arise automatically as code is written, even if nothing is filed. Drug research is protected by patents that are costly to file and maintain, and for which meeting the legal standards that define innovation is much harder.

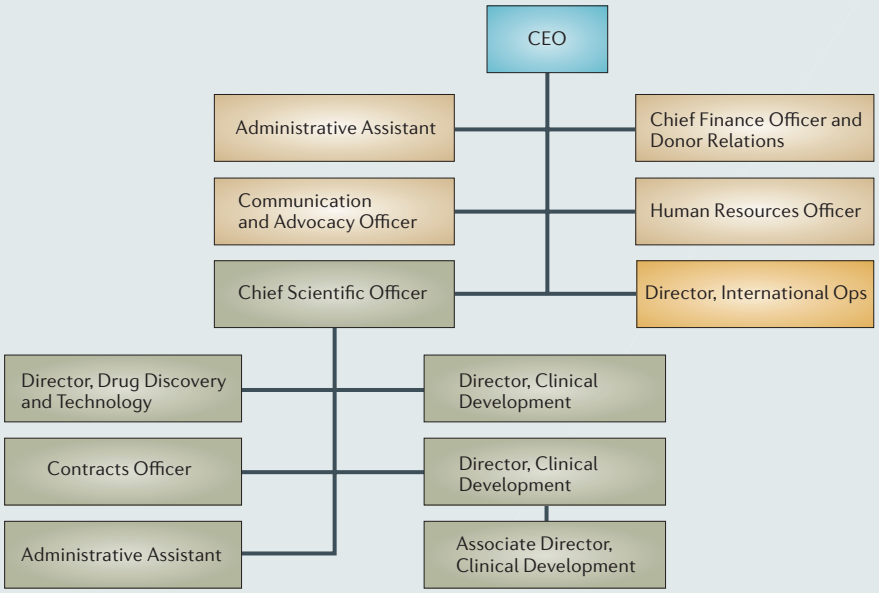
Open-source biomedical research

Early efforts. Despite these differences, the open-source idea has entered biomedical research[6]. The first inroads were made in bioinformatics[7,8], as might have been expected. These efforts resulted in a collection of programs such as Biojava, BioPerl, BioPython, Bio-SPICE, BioRuby and Simple Molecular Mechanics for Proteins[9], and inspired other initiatives such as the Human Genome Project, the SNP Consortium, the Alliance for Cellular Signaling, BioForge, GMOD and Massachusetts Institute of Technology's BioBricks (some of these have the transparency and feel of open-source, although the resources needed to get involved do not allow all volunteers to participate; however, we still call them 'open-source').

An old idea. One could argue that there has long been an active, if invisible, collaborative process akin to open-source in drug development, as, for some diseases, half of all prescriptions are for off-label uses[10]. Somehow, physicians share their ideas and experiences informally to uncover novel uses for existing medicines. For instance, oncologists routinely use drugs approved for one kind of cancer to treat other types. In a recent study, DeMonaco[11] found that 59% of drug therapy innovations were discovered by practicing clinicians via field discovery. The way by which physicians uncover these new indications is quick and inexpensive compared with Phase III trials. From an economic and medical standpoint, there would be merit in exploiting these clinical observations and sharing them with physicians as a complement to, or replacement for, some of the traditional clinical development.

Public–private partnerships. Taking a different approach, a new kind of organization, known as the public–private partnership (PPP), has recently developed a clever virtual business model that emulates the collaborative features of the open-source concept[12]. An example is

Box 1 | **The Medicines for Malaria Venture**



Management team

The Medicines for Malaria Venture (MMV) is run by a staff of 13. Its CEO reports to a Board of 12 Directors who represent funding organizations. An Expert Scientific Advisory Committee, which includes chemists, biologists, clinicians, malariologists and drug development experts, advises on project selection and research strategy. The Management Team's responsibilities are to:

- Encourage the submission of research proposals
- Select proposals and negotiate with partners
- Set up project-management teams and monitor progress
- Organize manufacturing and marketing
- Earn appropriate returns from marketed products
- Raise funds
- Communicate with government agencies

Backers

- Gates Foundation
- BHP Billiton
- ExxonMobil
- Global Forum for Health Research
- International Federation of Pharmaceutical Manufacturers Associations
- Netherlands Minister for Development Cooperation
- Rockefeller Foundation
- Swiss Agency for Development and Cooperation
- United Kingdom Department for International Development
- United States Agency for International Development
- World Bank
- Wellcome Trust
- World Health Organization

the Medicines for Malaria Venture (MMV), which was established in 1999 to discover and develop new, affordable antimalarial drugs. Established as a nonprofit entity with a staff of only 13 people, it has assembled a portfolio of 19 projects ranging from discovery to Phase III (FIG. 1).

MMV gets its projects through open calls — anyone with an idea can contribute. An Expert Scientific Advisory Committee reviews the submissions and selects the projects that will be funded. Each is managed by a project manager who outsources the R&D to a network of 300 scientists at 40 institutions (universities, big pharma, biotechs and research institutes). Funding comes from public and philanthropic partners (BOX 1). After each step, the Scientific Advisory Committee reviews the data and decides whether to proceed or terminate the project. MMV's cumulative spend from 2000 through 2005 is about US$100 million, 90% of which funded actual research. MMV plans to outsource manufacturing to low-cost partners, sell drugs at cost to developing countries, and market them through partners in developed markets (for example, to treat travellers). Its alliance with GlaxoSmithKline supports 25 scientists funded equally by the partners.

The Initiative on Public–Private Partnerships for Health reckons that there are about 24 PPPs engaged in drug and vaccine R&D (TABLE 1). Most of them were created in the past 7 years and share a common profile[13]. First, they focus on neglected diseases. Second, they operate as virtual drug companies, with a small staff getting project ideas from outside, vetting them through a committee of experts and outsourcing R&D to a network of institutions. Third, they manage growing portfolios of projects ranging from discovery through to Phase III trials. Fourth, they have been able to function on lean budgets with a cumulative spending that seldom exceeds US$50 million. This makes them attractive vehicles to fund research in areas that are not economical for traditional drug R&D.

By the end of 2005, PPPs had attracted funding in excess of US$1.5 billion. Foundations have given about US$1.15 billion (with the Gates Foundation alone contributing more than US$950 million), governments US$244 million and private entities US$36 million. In addition, donors have committed another US$3.5 billion which will be disbursed as needed by The Global Fund to Fight AIDS, Tuberculosis and Malaria.

Open-source versus alliance networks. It can be argued that the 25,000 alliances wrought by the 8,000 pharma and biotech companies over the past 15 years add up to a vast open-innovation system that mimics the collaborative features of the open-source model. Some scholars have countered, however, that alliances are less effective than open-source research at promoting innovation. This is because open-source networks are richer in 'weak links' (loose relationships), whereas alliances pride themselves on the strength of the connections between partners. DeBresson[14] has shown that weak links bring novel ideas into the fray whereas strong links tend to reinforce orthodoxies.

PPPs and big pharmas. TABLE 2 lists some of the projects and organizations coordinated by PPPs. As can be seen, GlaxoSmithKline features prominently, with Bristol-Myers Squibb, Novartis, Bayer, Sanofi-Aventis and Ranbaxy involved to a lesser extent.

Lessons learned

PPPs have advantages and drawbacks compared with traditional R&D[15]. Advantages include the following.

Table 1 | **Public–private partnerships engaged in drug and vaccine development**

Name	Focus	Year created
Aeras Global TB Vaccine Foundation	Tuberculosis	1997
BIO Ventures for Global Health	Biotech drugs for neglected diseases	2004
Consortium for Industrial Collaboration in Contraceptive Research	Development of new contraceptives	1995
Contraceptive Research and Development	Improving reproductive health in developing countries	1986
Dengue Vaccine Project	Dengue fever	1989
Drugs for Neglected Diseases Initiative	Sleeping sickness, visceral leishmaniasis, Chagas disease	2003
European Malaria Vaccine Initiative	Malaria	1998
Gates Foundation–UNC Partnership for Development of New Drugs	African trypanosomiasis, leishmaniasis	2000
Global Alliance for TB	Tuberculosis	2000
Global Microbicide Project	New microcides for women	2000
Human Hookworm Vaccine Initiative	Hookworm	2000
Infectious Disease Research Institute	Tuberculosis, leishmaniasis, Chagas disease, malaria, leprosy and Buruli ulcer	1993
Institute for One World Health	Visceral leishmaniasis, cutaneous leishmaniasis, Chagas disease, paediatric secretory diarrhoea	2000
International AIDS Vaccine Initiative	AIDS	1996
International Partnership for Microbicides	HIV	2002
Japanese Pharmaceutical, Ministry of Health, WHO Malaria Drug Partnership	Malaria	1999
Lapdap Antimalarial Product Development	Malaria	1998
Lassa Fever Initiative	Lassa fever	2001
Malaria Vaccine Initiative	Malaria	1999
Medicines for Malaria Venture	Malaria	1999
Meningitis	Meningitis	2001
Microbicides Development Programme	HIV	2001
Pediatric Dengue Vaccine Initiative	Dengue	2001
PneumoADIP	*Pneumococcal* vaccines	2004

UNC, University of North Carolina; WHO, World Health Organization.

Agility. Virtual R&D makes it easier to terminate projects that no longer look promising. The project manager does not have to deal with entrenched advocates manoeuvering to save their project or move it underground.

Creativity. PPPs enable experts from different countries, specialties and styles of thought to leverage each other's ideas. They harness the problem-solving skills of a much greater population than is typically available to traditional research organizations.

Focus. PPPs focus on one or few diseases. This helps them build deep expertise for better decisions (for example, target selection).

Risk sharing. The open-innovation model of PPPs makes it easier for scientists to collaborate on pre-commercial research such as biomarkers or cell signalling.

Affordability. PPPs lower the critical mass required to be a pharmaceutical company. By leveraging external expertise and capabilities, they allow small organizations to do much of what was once the domain of large companies.

Impact. PPPs engage scientists in developing nations who have first-hand experience in many neglected diseases. It helps them build their clinical research capacity, which in turn leverages the effectiveness of their public health systems.

Speed. Lean PPPs can decide quickly, partly because they do not have layers of committees to satisfy. In addition, because they tap their partner's unused capacity, they can advance swiftly as there is often a qualified laboratory somewhere that can do the work without having to wait in someone else's queue.

There are also some disadvantages to PPPs, which include the following.

Funding. US$5 billion has been committed to PPPs ($1.5 billion disbursed). However, despite the thriftiness of PPPs, there is concern that these funds will be stretched as more projects move into late, expensive clinical development.

Sustainability. PPPs have not demonstrated the sustainability of their business model. Some of their projects come from companies that had shelved them because of insufficient commercial prospects. To survive, PPPs will need to replenish their portfolios. There are also worries that, in some areas of science, the pool of contributors might be too thin to perform the work that must be done.

TABLE 3 shows that the PPP R&D model has worked reasonably well. Some of this success comes from targeting low-hanging fruits in diseases that have long been neglected, but it also suggests that the PPP model can be a potent tool in finding new cures. Whether the PPP business model becomes a transformational force or remains a non-threatening niche depends on how it ultimately performs against traditional pharmaceutical R&D. To succeed, it must go beyond tools and software and tackle large projects where it will rival the big firms that are helping it today. Yet, this rivalry need not be a zero-sum game. On the contrary, there is a place for collaborative and proprietary research in drug R&D, just as in software[16]. If open-source drug R&D takes hold, what will probably emerge is not the replacement of one model by another, but an ecology in which big pharma, biotech and collaborative research compete and collaborate at the same time, feeding off each other synergistically, while moving towards therapies along their own distinctive paths.

A template for open-source drug R&D

Can the PPP model succeed beyond neglected diseases? To answer this, it helps to break down drug R&D into knowledge-based activities and rule-based tasks.

Knowledge-based work requires lots of intelligence and intuition, but little infrastructure. Examples include identifying targets, understanding metabolic networks, and designing clinical trials or computerized disease models. It is about scientists leveraging each other's ideas, and using tools to gain deeper insights that might lead to breakthroughs. This work is ideally suited to the open-source model.

Rule-based work requires physical assets (laboratories, equipment, patients and so on) and money. It is tightly scripted and must conform to rigid regulatory requirements. It is about organization, discipline and implementation. Examples include toxicology studies, Chemistry Manufacturing and Controls (CMC) studies, and the conduct of clinical trials. Rule-based work is ideally suited to outsourcing, and much of it is already outsourced to contract research organizations.

This division of labour suggests a business model template in which part of the R&D value chain is open-sourced, while the rest is outsourced, with the following features.

Table 2 | **Public–private partnerships and their partners**

Project	Industry partner	University/public health partner	Other PPP
Medicines for Malaria Venture			
Improved 4-aminoquinoline	GlaxoSmithKline	University of Liverpool	
Farnesyl transferase inhibitors	Bristol-Myers Squibb	University of Washington	
Manzamine derivatives		University of Mississipi	
Cysteine protease inhibitors	GlaxoSmithKline	UCSF	
Fatty acid biosynthesis inhibition		Texas A&M, A. Einstein, Jacobus	
Pyridone	GlaxoSmithKline		
New di-cationic molecules	Immtech	University of North Carolina	
Dihydrofolate reductase inhibition	Biotec Thailand		
Artesunate derivatives	GlaxoSmithKline, Shin Poong		TDR, DNDi
Artemisone	Bayer	University of Hong Kong	
Synthetic peroxide	Ranbaxy	University of Nebraska	
Intravenous artesunate		Walter Reed	
Coartem in infants	Novartis		TDR
TB Alliance			
Pyridones and quinolizines	Taejon, Yonsei		
Isoniazid analogue		Wellesley College	
PA-824		NIH, Johns Hopkins	
Mocifloxaxin	Bayer	CDC, Johns Hopkins	
Institute for One World Health			
Paromomycin			TDR
Azole		Yale	
TDR			
Miltefosine	Zentaris		
Oral eflornithine	Aventis		

CDC, Centers for Disease Control and Prevention; DNDi, Drugs for Neglected Diseases Initiative; NIH, National Institutes of Health; TDR, UNICEF–UNDP–World Bank–WHO Special Programme for Research and Training in Tropical Diseases.

Template features: operating principles

Open-sourcing. The open-source part of our model should allow anyone who can contribute to join. Volunteers should be able to log on to a website, find the page(s) that matches their area of expertise, peruse challenges to be solved, review others' contributions, download computerized tools and start working towards contributions of their own. As they progress, they can publish their findings in scientific journals and discuss their insights in on-line forums. Over time, the better ones will gain authority and become the *de facto* leaders of their open-source community.

Outsourcing. Work to be outsourced should be posted on a website for all to see. Scientists and organizations qualified for the job can bid, and the sponsor picks the best candidate for each task.

Template features: procedures

Governance. Three decision-making bodies provide leadership and guidance: the Board of Directors, the Steering Committee and the Scientific Advisory Committee. The Board of Directors includes senior executives and outsiders who represent shareholders and stakeholders. It approves strategy and ensures that management performance is consistent with the organization's mission. The Steering Committee is a group of senior executives that rules on important operational issues such as fundraising, budgets, project funding, key hires and selection of partners. It also approves recommendations from the Scientific Advisory Committee. The Scientific Advisory Committee (SAC) is a group of external experts from academia and industry. It sets R&D strategy, proposes new projects, reviews existing ones and recommends termination of those that no longer deserve support.

Scope. This template calls for focusing on single diseases or related illnesses. An organization working on unrelated diseases should establish separate websites for each one.

Projects origination. There is a permanent open call for new projects. Scientists are invited to submit ideas online for review by the SAC.

Portfolio management. The SAC is responsible for maintaining an adequate and balanced pipeline of projects.

Project management. Each project is managed by a Project Team led by a member of the organization, and staffed by external experts in drug discovery, clinical research and regulation. The Project Team is responsible for developing the budget and timeline, overseeing outsourced tasks and ensuring compliance with GxP. One of its crucial duties is selecting what will be open-sourced

Table 3 | **Public–private partnerships lower the critical mass required to discover and develop new cures**

Organization	Focus	Staff	Pipeline				
			Number of projects	Discovery	PK	Clinical	Cumulative spending through 2005 (US$ million)
Medicines for Malaria Venture	Malaria	13	19	12	1	6	103
TB Alliance	Tuberculosis	18	12	8	1	3	20
Drugs for Neglected Disease Initiative	Trypanosomiasis, visceral leishmaniasis, Chagas disease	36	20	9	4	7	20
OneWorld Health	Leishmaniasis, malaria, Chagas disease, diarrhoeal diseases	40	5	1	3	1	?
International AIDS Vaccine Initiative	HIV/AIDS	169	6	–	1	5	120
Malaria Vaccines Initiative	Malaria	32	10	4	2	4	?

Source: Annual reports. PK, pharmacokinetics.

and what will be outsourced. The project leader is accountable for generating the data used to decide whether to fund the next step. Commitment to a project is limited to the current step, until the data warrants committing funds for the next one. Open-sourced tasks are posted on the project's website, each on its own page, and outsourced ones are posted on a companion matchmaking website such as Innocentive, or Scienteur. Outsourcing bids are reviewed by the Project Team, which issues recommendations to the SAC.

Intellectual property ownership. There is often a misperception that open-source initiatives are hostile to patents and bent on putting discoveries in the public domain. The reality is more nuanced. Most open-source activities occur at a pre-commercial R&D stage, when the ideas and hypotheses debated fall short of the legal standards that define inventions in patent law. They are an on-going scientific conversation that can be likened to a global instant-messaging system linking scientists interested in a topic. In that sense, open-source is no more threatening to patents than other forms of scientific publishing. A scientist who engages in that conversation and comes up with an idea that can lead to a patentable invention will need to exercise caution with disclosures until the invention has been reduced to practice and patent applications have been filed, just as would be necessary in a traditional research setting. It is generally accepted that open communication promotes advancement of science, but needs to be balanced by the need to protect the rights of inventors. The same applies to open-source activities.

Template features: tools

The discovery toolbox. As of February 2006, 349 genomes have been published and another 1,575 are being sequenced. A new generation of smart, computerized tools is becoming available to mine data, comb the literature, map metabolic networks, perform *in silico* modelling, visualize binding sites, identify chemical leads, design molecules and predict toxicity. These tools should be packaged into a convenient toolbox, together with access to major databases, and offered to volunteers willing to contribute their expertise.

Outsourcing software. Several programs already exist to match projects with talent and capacity. Two examples are Scienteur, a free e-marketplace that allows companies to post tasks, and experts to register their skills, and Innocentive, an online problem-solving tool that lets a company post a challenge with a reward: whoever finds the solution gets the money.

Table 4 | **R&D costs for public–private partnerships (US$ million)**

Stage	MMV	TB Alliance	DNDi	IAVI	Big Pharma
Discovery and PK	8.3	18.6	16.2	20.0	26.0
Phase I	1.6	0.6	Unpublished	2.0	15.2
Phase II	1.2	3.4	Unpublished	5.0	23.5
Phase III	9.5	22.6	Unpublished	30.0	86.3
Total clinical	12.2	26.6	24.2	37.0	125.0

Source: REF. 19. DNDi, Drugs for Neglected Diseases Initiative; IAVI, International AIDS Vaccine Initiative; MMV, Medicines for Malaria Venture.

Template features: costs

PPPs have been able to function on very low budgets for several reasons (TABLE 4). First, they have few people, low overhead costs and no fixed assets. They rely on someone else's unused capacity, and the market seems to price such capacity at marginal instead of full cost. Second, they outsource much of their work where it is cheaper to do so and do most of their trials in developing countries. Third, they concentrate on infectious diseases for which costs are lower. Fourth, they receive in-kind donations.

Will it work?

Despite the promise of open-source drug R&D, both its pioneers, and the veterans of open-source software, point to several potentially troublesome issues that could affect the success of the open-source model.

Availability of talent. Typical open-source projects do not require a large number of contributors. Data from the software industry suggests that the ideal number ranges from 6 to 20 people. Yet much of the drug R&D expertise resides in an industry that has a strong proprietary culture. Employees are routinely asked to assign their intellectual output, including that created on their own time, to their employers[17]. This could stifle talent supply in key areas. Two developments, however, might give open-source drug R&D the permanent talent pool it needs. First, thousands of highly trained pharmaceutical scientists are nearing retirement and might

welcome the opportunity to put their skills to good use. Second, drug companies might be persuaded to ease restrictions on their employee's involvement. There is indeed little conflict of interest in being a cancer scientist by day and an anthrax researcher at night, and firms might gain valuable goodwill from letting employees seek cures for diseases in which they have no interest.

Availability of data and standards. Open-source scientists cannot accomplish much unless they can access data. Biological data is plentiful and getting richer, with terabytes of genomic and metabolic data continuously being added to the pool. Chemical and structural data, on the other hand, are more scarce. In addition, the formats used to handle these data are still evolving. Biologists use a reasonably small number of them, but chemists are further from such consensus. Both the lack of standards and the scarcity of data in certain areas can cause problematic choke points in an open-source R&D effort.

Availability of tools. Open-source scientists need open-source tools to practice their craft. Until recently, such tools were plentiful in bioinformatics, but less so in chemistry, which has long been dominated by commercial software. This is changing. The 2004 launch of PubChem has brought online a powerful suite of tools that allows scientists to connect chemical information with biomedical research and clinical information in an unprecedented way. Non-profit scientists can now access small-molecule high-throughput screening, chemistry and informatics on a scale previously available only to industry. They can even get grants to turn their online discoveries into assays for high-throughput screening[18]. Other tools such as eMolecules, Jmol or the Chemistry Development Kit are adding powerful chemical search and visualization capabilities to the open-source scientist's toolbox.

Intellectual leadership. Just as putting ingredients into a vat does not necessarily cause them to react, connecting smart people online does not guarantee they will produce anything valuable. In both cases, a catalyst is needed. For open-source drug R&D, the presence of a subgroup of highly innovative contributors who can tune in the on-going conversation and fuel it with their own creative insights acts as such a catalyst. Without it, the conversation could remain shallow and fizzle out.

Momentum. Enticing people to join is a challenge. A good website helps, but it's not enough. As Darren Carroll, former CEO of Innocentive, puts it, "If you build it, they will not come!". It takes a sustained effort to get the word out and build trust with stakeholders. It also takes a leader who can connect with people, understand their motivation and foster trust. Linux attracts thousands of contributors because they identify with Torvalds' ideals and trust him to do the right thing. Open-source drug R&D must build such leaders.

Web interface. The design of the project's website is crucial. It must be engaging and appeal to visitors' curiosity. They must be able to quickly find the pages that match their interests, download the toolbox, and be 'up-and-playing' in minutes.

Quality assurance/quality control. When something as complex as drug R&D gets parceled out around the world, quality assurance can become an issue. Oversight, due-diligence, audits, good practices and prior experience can be used to ensure quality. International Organization for Standardization standards could also help in the future.

Selectivity. Not all projects will be equally suitable. Cancer might draw contributors, but hair loss might not.

Conclusion: a new ecology of drug R&D?

Is there still room for big pharma in open-source R&D? One must stress that 'virtual' does not mean 'leaderless'. To succeed, open-source R&D will need deep expertise in the minutia of drug R&D, which today resides overwhelmingly in the pharmaceutical industry. There might be many volunteers, but they must be shepherded towards a goal. Such stewardship is a core competency of pharmaceutical companies. Our model is not a substitute for them, but a way to leverage their capabilities to tackle unmet medical needs, such as the diseases of poverty, orphan diseases and niche markets. Pharmaceutical companies stand to gain from co-opting the open-source model and allowing it to flourish in 'coopetition' with traditional R&D, to handle the diseases or R&D steps for which it is best suited.

Bernard Munos is at Eli Lilly & Co., Lilly Corporate Center, 1085, Indianapolis, Indiana 46285, USA.
e-mail: bhmunos@stanfordalumni.org

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