Can Open-Source Drug R&D Repower Pharmaceutical Innovation?

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Open-source R&D initiatives are multiplying across biomedical research. Some of them—such as public–private partnerships—have achieved notable success in bringing new drugs to market economically, whereas others reflect the pharmaceutical industry's efforts to retool its R&D model. Is open innovation the answer to the innovation crisis? This Commentary argues that although it may likely be part of the solution, significant cultural, scientific, and regulatory barriers can prevent it from delivering on its promise.

Open-source drug R&D has become respectable. Some big pharmaceutical companies, including Lilly, Johnson & Johnson, Novartis, and GlaxoSmithKline, have embraced it. New research models such as such as CollabRx, the Pink Army, Open Source Drug Discovery (OSDD), and the African Network for Drug and Diagnostics Innovation are using it to design customized cancer therapies and new treatments for neglected diseases. After 10 years and $315 million in cumulative spending (matched by an equal in-kind contribution from industry), the Medicines for Malaria Venture has launched its first drugs and built a pipeline of over 50 projects. Massive investment in publicly funded research and a growing number of public–private partnerships and consortia have produced an abundance of open-access computational biology and chemistry tools, many of which have become references across the industry.[1–3] Although these advances are impressive and confirm the capacity of virtual R&D models to produce new drugs economically, their impact is in danger of being stifled by some of the same challenges that have precipitated the current innovation crisis. Interestingly, the open-source model can also be used to address those.

Overly narrow translational research

In launching the Critical Path Initiative in 2004, the US Food and Drug Administration (FDA) correctly argued that improving R&D productivity required both faster incorporation of new science and improving R&D predictability. It seems, however, that these seminal insights have often been interpreted too narrowly. Incorporating cutting-edge science into new therapies lies at the heart of translational research. It is a complex undertaking that requires the collaboration of multiple disciplines and relies greatly on ingenuity. Each challenge is different, and so is its solution. This makes it difficult to reduce translational research to processes that lend themselves to optimization. It is inherently messy. As Alfred Whitehead put it, "It is a great mistake to think that the bare scientific idea is the required invention, so that it has only to be picked up and used. An intense period of imaginative design lies between."[4] Many biomedical breakthroughs of the twentieth century came from harnessing sciences that were often tangential, if not alien, to pharmacology. When Lilly licensed insulin in 1924, there was no technology to extract and purify proteins and no supply network to collect large amounts of glands from slaughterhouses. After Alexander Fleming discovered penicillin in 1928, it took 10 years and more than 1,000 scientists in 40 major laboratories to bring it to market.[5] Henry Kaplan's breakthroughs in oncology in the 1950s resulted from the bringing together of disciplines such as particle physics, medicine, and statistics that were seldom found under one roof at that time. In fact, the entire field of molecular biology was born in a physics laboratory at Cambridge University in the United Kingdom.

The ability to marshal unfamiliar sciences toward elusive goals is a prerequisite for translational research. The above examples were driven by vision and passion, not risk assessments and net-present-value calculations. At the root of these breakthroughs was the conviction that disruptive innovations are worth pursuing because they are the raison d'être for what we do and are critical to the industry's future vitality. An industry in which everyone strives to be a "fast follower" is at risk of losing its way. Sadly, much of that vision seems to have been deemphasized in current translational research and replaced by an analytical process—target-based drug discovery—that has considerably narrowed the scope of that research (Figure 1). As a result, breakthroughs that hold vast therapeutic potential, such as stem cells and nanotechnology, are languishing. There is some attempt to correct this through open-innovation initiatives such as Enlight Biosciences, but this is not enough to address the range of opportunities waiting to be translated.

Knowledge gaps

The target-based system used by industry has prevailed because it delivers some output, lends itself to scale-up, and is not disruptive. It assumes that modulating designated targets will cause some good, and it is designed to find and optimize compounds that do so. Unfortunately, the cell being a jumble of intersecting biological pathways, such modulation often initiates a cascade of adjustments as the cell reacts

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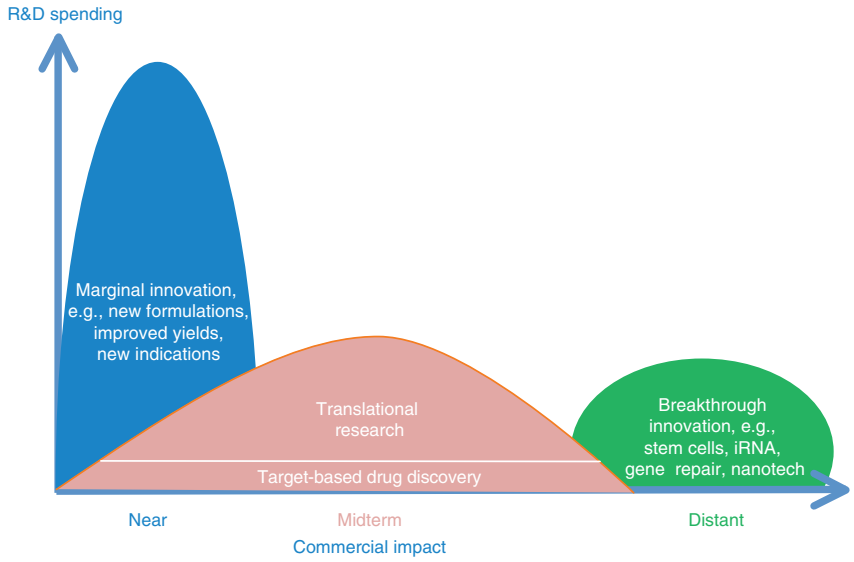

Figure 1 Target-based drug discovery is a small subset of translational research that is not suitable for some promising technologies. iRNA, interfering RNA.

to changes in the concentrations of the biomolecules involved in the targeted pathways. This produces second-, third-, and higher-order effects that are responsible for side effects, including those that derail phase III trials or force the withdrawal of products already launched. Only when these side effects do not matter much—an extremely uncommon occurrence—does a molecule become a potentially viable drug candidate. Unfortunately, predicting side effects is nearly impossible given the large gaps in our knowledge of cell biology. About 40% of human genes (~8,000) are unannotated.[6] Any system that has 40% of its makeup undiscovered can hardly be modeled. Systems biology is often criticized for having delivered little, but until we eliminate knowledge gaps it can hardly do better, and the FDA goal of identifying reliable biomarkers and improving R&D predictability will remain elusive. More than $150 billion is spent on biomedical research annually. Earmarking some of that to complete the annotation of the human genome should be a top priority. This is a task that the open-source model can be drafted to do quickly and cheaply, as suggested by the experience of OSDD with *Mycobacterium tuberculosis*. Although the genome of this pathogen was sequenced 10 years ago, more than 1,000 of its 4,000 genes remain unknown, vastly complicating the search for new treatments. To eliminate this problem, OSDD recently launched the "Connect-to-Decode" open-source initiative. Within weeks, 830 qualified scientists volunteered to reannotate the entire *M. tuberculosis* genome. The work started in December and is expected to be completed by April 2010, packing nearly 300 man-years into 4 months!

Regulatory gaps

Closing knowledge gaps and practicing broad-based translational research cannot help much, however, unless the FDA provides timely regulations for the novel therapies that lie outside the existing regulatory framework. Unsurprisingly, disruptive innovations do not sit well with regulations designed for the therapies being disrupted. To avoid becoming a barrier to innovation, the FDA must be able to offer guidance as innovation takes shape. What, for instance, are the requirements for stem cell–based treatments? How does the FDA regulate customized therapies for which the trial size is one patient? These questions are complex, but they should not have to wait years for an answer. Here again, an open-source process, such as a wiki, could be used to inform and speed rule making. By allowing stakeholders to discuss ideas online, while keeping the FDA responsible for the ultimate regulation, wikis can foster a debate around important issues, thus strengthening consensus and the legitimacy of the resulting policies.

Intellectual property concerns

There have been concerns that open innovation can debase the intellectual property that has been the industry's cornerstone. Sharing, it is feared, might thwart patents and facilitate the misappropriation of intellectual assets. In fact, the opposite is far more likely to happen. Much of the interest in open innovation is directed toward discussing scientific enigmas, not commercial projects. Cutting-edge drug research targets diseases that are poorly understood. Collaborating to better comprehend their etiology serves the interests of both patients and industry. The sooner scientists decipher the mysteries of cancer or Alzheimer's disease, the faster they can

	✓ Managing for operational excellence	✗ Managing for breakthrough innovation
Goal	Defend and grow current business	Replace current business
Focus	Current markets and customers	New technologies and products
Culture	Efficiency, discipline, order Improve, optimize	Intuition, ambiguity, opportunity Disrupt
Organization	Hierarchical, differentiated, complex	Light, flexible, fluid
Processes	Numerous, exacting, formal Focused on planning and execution	Fewer, fuzzy, informal, adaptive Driven by intuition
Thinking	Aligned	Orthogonal
Decision making	Analytical, rule-based, cautious	Intuitive, vision-driven, bold
Working style	Sticks to job description	Crosses boundaries
Personality	Conforms, fits in	Sticks out, frequent outliers
Environment	Risk-averse, change-wary	Risk-taking, change-friendly

Figure 2 Drug companies that fixate on operational excellence risk degrading their capacity for breakthrough innovation.

compete to develop effective treatments. Sharing and precompetitive collaboration are simply ways to increase the value of the pie, leaving companies to compete on how to divide it.[7]

Conflicting goals

The open-source model is a powerful tool to break down "silos" and encourage the formation of networks that promote cross-pollination and breakthrough innovation. But networks alone cannot change innovation dynamics and guarantee that breakthroughs will occur in greater numbers. The movie industry, for example, has operated a networked business model for five decades, but the studios' output of blockbusters is flat and linear, just like the output of new drugs.[8] Interestingly, it seems there is plenty of creativity in Hollywood to support a higher output of blockbusters, as thousands of scripts are constantly worked on by independent writers. Yet, when it comes to funding a movie, the studios, which provide the money, insist on funding the scripts they believe will become the blockbusters that moviegoers crave. They are wrong most of the time—blockbusters are notoriously impossible to forecast—but nonetheless their conservative culture ultimately filters out the innovation that does not fit their stereotypes.

One can perhaps draw a parallel with the drug industry. Corporate lore abounds with stories of breakthroughs that emerged from "skunkworks" because management had dismissed the unorthodox projects as risky or unsound. Thousands of "small pharmas" struggle to explore novel therapeutic avenues. Collectively, they produce more innovation than "big pharmas," at a smaller cost, yet they often find it hard to attract interest from large companies. Research has shown that the competence for breakthrough innovation and the competence for "operational excellence" are at crosscurrents,[9] (Figure 2), and firms that focus on one tend to degrade their capacity for the other. One cannot attain breakthroughs without a readiness to embrace their consequences, which include the forced obsolescence of corporate processes and tears of the organizational fabric. Balancing these conflicting goals used to be a strength of the companies that became big pharmas. But this seems to have been lost as companies grew and focused on managing their complexity. Perhaps the open-source model offers a chance to restore that balance by locating disruptive innovation outside corporate walls, where it can thrive unencumbered.

In the past three years, the acceptance of networked R&D models by the drug industry has grown dramatically. This is encouraging because they bring benefits that address some of the root causes of the current innovation drought. Yet one should be mindful that open-source research by itself is unlikely to repower pharmaceutical innovation unless it is accompanied by concurrent changes in corporate culture and the behavior of other stakeholders.

CONFLICT OF INTEREST

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The Need for Precompetitive Integrative Bionetwork Disease Model Building

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If you doubt that there are enormous gaps in the current drug discovery process, you should probably skip to the next article. Yet even while critiques rightly highlight inefficiencies or operational issues, they often miss a fundamental reality: until we better understand diseases as altered bionetworks and view diseases at an individual patient level, efforts to develop effective biomarkers and therapies will be inefficient at best.

There is a curious communal denial of how little we actually know about the consequence of perturbing the selected targets and pathways that drive drug discovery. Engineers who built the software systems and spaceships that embody our twenty-first-century world smirk when they see the frequently feeble models of disease and the ways drug effects are tracked that are at the heart of current drug discovery. We need to find a better way to generate predictive models of disease if we are going to effectively identify the needed biomarkers and therapies to affect disease.

Two strategies in particular currently frame the debate on the best strategies

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