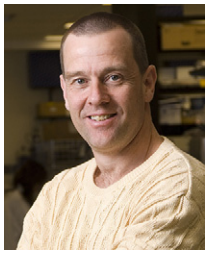
editorial



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Open-source science to enable drug discovery

Productivity and the drug discovery sector

Over the past three decades, the drug discovery enterprise, despite the advent of genomic technologies, structure-guided methods, combinatorial chemistry approaches, knockout animals, and even the entire biotechnology sector, has been producing fewer new chemical entities per dollar invested in research and development. The enterprise, in which I include public and private sector investments in biomedical research, has survived largely because of its ability to increase spending: to get more 'shots on goal'. With the increasing sensitivity of drug payers to the cost of pharmaceuticals and with government funding for health-related science flat-lining, this strategy is probably not sustainable.

The pharmaceutical industry has been responding to its economic situation by consolidating, retrenching from early-stage science to focus on later-stage programs and outsourcing to academia, biotech or to other jurisdictions that have, at least for now, more-favorable economic conditions. Industry is also implementing scientific and marketing strategies that maximize the value of existing drugs, for example, by expanding their indications and extending their patent lives. The public sector is responding by focusing more of its resources on 'translational' science: to make its own contribution within the 'shots on goal' paradigm. These approaches could sustain drug discovery in the short-term, but without an increase in productivity – defined as new medicines per research dollar – the long-term economic prospects for this drug discovery strategy are poor.

Fortunately, it is clear where the greatest productivity gains can be made: over 80% of the costs of bringing a new drug to market are associated with the attrition of compounds in the clinic. The reasons behind the attrition rate are also known: clinical safety, toxicology, and lack of efficacy account for as much as 70% of failures in the clinic. Unfortunately, no biologist, chemist, pharmacologist, or clinician can currently predict which compounds will fail. It is therefore obvious that the economics of small-molecule drug discovery, which is dominated by attrition, would best improve with greater scientific understanding of human pathophysiology, pharmacology, and heterogeneity.

Defining the 'scientific grand challenges' that limit productivity gains

Of course, it is far simpler to state the problem (attrition) than to identify the solutions. It is possible, even likely, that existing technologies cannot provide the solutions; however, there are some features of the general problem that both highlight the challenges and suggest an optimal path forward. First, the most important scientific problems are common to industrial and academic groups focused on early drug discovery: they are not unique to any one sector or organization. Avoiding duplication of effort seems the most efficient way forward. Second, the task of increasing the productivity of the drug discovery process should not be industry's problem alone to solve. The public have an interest in seeing the drug discovery sector succeed, both in terms of providing medicines for unmet needs and as a driver for the economy. Accordingly, industry and the public sector should be motivated to invest resources in this area. Third, neither sector alone has the capability to solve the problems. Industry is unable to tackle the fundamental science because the projects will require resources far

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beyond those any individual company can afford, particularly given the trend in industry to focus on shorter term goals. In turn, industry cannot rely on the public sector to solve these problems because academics lack capabilities that pharmaceutical scientists have; for example, the problem-orientated pragmatism that defines industrial research and experience in preclinical drug development and in the regulatory process. It is therefore apparent that these core scientific/economic problems would be best addressed through collaborative relationships between the public and private sectors.

Funding research into the fundamental science of drug discovery

How then should research in this area be funded? In developing a funding strategy, it is first important to note that the scientific problems can be divided into those that are well defined and can be addressed with current technologies, and those that are either not well defined or that are beyond the reach of current knowledge. As a result, it would seem logical to fund this area of research in unguided and targeted ways. Funding for 'unguided' research, from which transformative discoveries will emerge, would remain the responsibility of the public sector. By contrast, funding for targeted research, which would be focused on the major problems that limit productivity gains, would be performed in collaborations between the public and private sectors. The areas for targeted research would be defined collaboratively, and perhaps codified as the 'scientific grand challenges' of drug discovery. These could include target validation, predictive toxicology, and better models of human disease. Specific subprojects might include, for example, the creation of specific, selective, and bioavailable chemical probes for all human enzymes, the generation of highly selective protein affinity reagents for all human proteins, and the creation of a well-annotated dataset of toxicity profiles for every compound that has been in clinical or preclinical development. The ensuing public–private partnerships would capitalize on the strengths of the two sectors, benefit from risk sharing among the partners and minimize duplication of effort.

Structuring public–private research partnerships

These concepts must resonate: public–private partnerships (PPPs) are highly touted by industry, governments, and philanthropic organizations. However, as attractive as they sound at a high level, they can be difficult to organize, operate, and assess. The challenge facing funders is to develop metrics of success, ensuring that resources are spent wisely. The problem with assessing the success of PPPs stems from the fact that it is often difficult to define and agree upon quantitative metrics. In addition, academic scientists are often reluctant to embrace quantitative goals. The main operational challenges are to foster a sense of openness and collaboration among the scientists, to keep scientists focused on the deliverables while encouraging intellectual freedom and creativity, and to manage expectations about the use of the information that is generated. There are now many examples of PPPs that have succeeded (see Box 1).

Interestingly, the challenges of organizing the science and developing quantifiable metrics, daunting as they may seem, pale in comparison with the problems in organizing the partnership at the outset. Creating the framework for a research-focused PPP requires not only legal expertise but also an intellectual property agreement that is consistent with the needs and expectations of the different sectors and organizations, which often operate in different legal jurisdictions. Indeed, projects often do not get off the ground because differences are insurmountable. Even in the best cases, agreements are so complex they take years to complete. In fact, because no agreement can fully anticipate all scenarios, negotiations never really end.

BOX 1

Successful public–private research partnerships

The single nucleotide polymorphism consortium

Ten large pharmaceutical companies, IBM, Motorola, and the Wellcome Trust formed the single nucleotide polymorphism (SNP) consortium, whose mandate was to find and map 3 00 000 common SNPs and to place the resulting SNP map into the public domain, with no restriction on use. The industrial sector contributed >US$ 30 million, and the Wellcome Trust contributed >US$ 14 million. The experimental work was distributed over four academic institutions – Sanger Centre (now Sanger Institute), Stanford University, Washington University (St. Louis), and Whitehead Institute – and the data were consolidated at the Cold Spring Harbor Laboratory. By the end of the funding period, the SNP Consortium had exceeded its expectations, discovering >1.8 million SNPs, and the project evolved to become the HapMap project, and the results provide the basis for genome-wide association studies.

The Structural Genomics Consortium

The structural genomics consortium (SGC) is another example of a successful public–private partnership. With laboratories at the Karolinska Institute and the Universities of Oxford and Toronto, funded by Merck, Novartis, GSK, the Wellcome Trust, the Wallenberg Foundation, and the governments of Canada, Ontario, and Sweden, the SGC was formed to place 3D structures of proteins of relevance to human health into the public domain, with no restriction on use. With a budget of US$ 25 million per year, the SGC has purified >1500 human proteins and has determined the structures of >500 new human proteins, accounting for ~20% of all the unique human protein structures determined over the past four years. As an example of its relevance to industry, the SGC has contributed about half of the new human protein kinase structures into the public databases over the past three years. The SGC is also meeting its academic mission, having published papers of significant impact.

The success of the SGC as an organization has been attributed to three factors. First, by locating in three premier academic institutions, the SGC has been able to attract outstanding scientists. Second, the non-proprietary philosophy of the organization enables SGC scientists to collaborate freely, and take advantage of the rich scientific environment in academia and the experience of industrial scientists. Finally, the project is managed carefully with oversight from public and private sector funders; the scientists are therefore highly focused on meeting their objectives.

Drug discovery science in a creative commons

Pragmatically, although it is possible to create blanket agreements that enable research-focused PPPs to exploit any intellectual property, the most streamlined way to create them is to agree at the outset that any resulting information is released immediately into the public domain with no restriction on use. This approach not

only simplifies the legal issues but also allows the research output to be exploited by the larger research community.

Disclosing findings without intellectual property protection not only enables the research to occur in the first place but also stimulates drug discovery. This view may counter much of the current thinking in drug discovery enterprise, but a closer examination of the issues provides a clear rationale for this approach. First, when creating intellectual property is an explicit or even an implicit objective of a partnership, the scientists and their managers must constantly examine their work for potential patentable discoveries and be cautious about prior disclosure. This has a dampening effect on open communication among the scientists in the partnership and leads to the second problem: an organization that develops intellectual property inevitably creates a management layer(s) explicitly devoted to technology transfer, leading to the implementation of 'simple' agreements to transfer materials, which in turn continues *in absurdum* to the situation in which materials with no possibility of any commercial value are encumbered. Third, protection of intellectual property, particularly in academia, is a drain on the time of the scientist and the university technology transfer offices, which are not usually resourced adequately to manage complex research portfolios. In the drug discovery sector, it is also very difficult to assess the net present value of any early discovery. Fourth, current patenting strategies do not necessarily aim to disclose the invention completely, which is the intent of the patent system, but rather to make the broadest claims while revealing the least about the invention. This leads to perhaps the most insidious aspect of the strategy to patent early-stage discoveries in the drug discovery setting. In many areas of pharmaceutical development, patents, even ones of questionable strength, serve to keep other scientists away from areas of investigation of great potential value to society.

Conclusion

The drug discovery process is losing productivity to the detriment of the global economy and human health. The greatest productivity gains in the sector can be achieved by solving the fundamental scientific problems limiting the progression of compounds through clinical trials. These problems must be addressed through a combination of 'blue sky' and targeted research on priority issues, perhaps defined within a 'grand challenges' framework. For many reasons, targeted research should be performed in PPPs that release information into the public domain immediately, with no restriction on use.

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