



Translational research: the changing landscape of drug discovery

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Drug discovery represents the first step in the creation of new drugs, and takes place in academic institutions, biotech companies, and large pharmaceutical corporations. Until recently, these sectors have each operated independently with little collaboration between those at the forefront of discovery research and those with experience in developing drugs. With the rise of translational research these relationships are shifting and new hubs are emerging, as key players seek to pool the expertise necessary to generate new therapies by linking laboratory discoveries directly to unmet clinical needs. In this article I discuss how the increasing adoption of translational research is leading to novel integrated discovery nexuses that may change the landscape of drug discovery.

Introduction

Historically, the development of new drugs and vaccines was pioneered by physician scientists until the second half of the 20th century when the study of biology expanded, and the field diverged into separate domains of basic scientific research and clinical practice [1]. By the 1990s and early 2000s, four interconnected but distinct players emerged as the drivers of drug discovery and development: pharmaceutical corporations, biotechnology companies, academic institutions, and the National Institutes of Health (NIH). In general, these entities operate separately, each with its own processes, goals, measures of success, and reward systems (Table 1). However, there is increasing recognition by all parties that the traditional system of creating drugs is inefficient and is failing to capitalize on the scientific advances and technological breakthroughs that have transformed other industries. Several recent reviews have analyzed the low productivity of drug development [2–5], reflected in the static drug approval rates of the past decade (showing an average of only 24 new drugs per year [6]) despite the rising investment by the pharmaceutical industry [7].

The sharply contrasting trends of investment and productivity have gained significant attention and have led the key sectors involved to re-examine their practices and their relationships with one another [8,9]. A changing paradigm for the development of

new drugs is emerging, captured by the current buzzword ‘translational research’. This new approach is based on directly matching ideas for new therapies with the needs of patients as observed in the clinic, and represents a more focused strategy for creating new drugs than the traditional model. In this review I will discuss how these different institutions are embracing translational research and are re-organizing their relationships with one another to increase the efficiency of bringing new drugs to market.

Culture differences in the status quo

The efficiency of new drug development in the past two decades has been hampered by the separation that has developed between those performing the discoveries needed for new therapies, and those with the funding and commercial capabilities to bring the drugs to market. In the prevailing system, ideas for new drugs most commonly arise in either academic institutions or biotech companies. Limited funding, however, enables them to perform only early-stage research before needing to raise money from investors, either in the form of private investments, venture capital (VC) funding or by licensing out the drug. In the majority of cases, large pharmaceutical companies are needed to finance the late-stage clinical trials and submissions to the U.S. Food and Drug Administration (FDA), and to perform the sales and marketing activities that ultimately put the drugs in doctors’ and patients’ hands (Figure 1).

Currently, different cultures prevail in academia, biotech companies and the pharmaceutical industry [10,11]. Table 1 highlights

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TABLE 1

Differential goals and practices among the key sectors in drug development in the United States. The table shows the key statistics for the different types of institutions that underly the different organizational cultures between pharmaceutical companies, biotech companies, academic institutions and the NIH

	<i>Pharmaceutical companies^a</i>	<i>Biotechnology companies^b</i>	<i>Academic institutions^c</i>	<i>National Institutes of Health (NIH)</i>	<i>Refs</i>
SIZE:					
No. of organizations	41 (29 in PhRMA)	1715 (215 public, 1500 private)	350	27 (20 institutes, 6 centers, 1 office)	[7,38]
No. of employees in sector^d	650,000	150,000	66,700	17,000	[39,40]
Average no. of employees per company or institution^e	33,104	446	190	630	
History^f	Earliest companies founded in 1850s. Significant growth in 1950s–1960s.	Earliest companies founded mid-1970s. Significant growth in 1990s–2000s.	Research Universities in US started in 1880s. Significant growth in post-WW2 era ^g , and in 1980s. ^h	Formed in 1930. Significant growth in 1960s and 1970s.	[39,40]
Ownership structure	Publicly traded Privately held	Publicly traded Venture Capital-backed Financed by Angel or other private investors	State-owned non-profit (e.g. public Universities) Private non-profit (e.g. private Universities) Government institutions (e.g. NIH)	Government institution; parent agency is Department of Health and Human Services.	
Research funding sources	Profits from drug sales	Partnership deals with Pharma Public market offerings Private investments	University or institutional budget Government (e.g. NIH) grants Grants from charitable organizations Collaborations with Pharma and Biotech companies Licensing of intellectual property	Government-funded. Budget approved by U.S. Congress	
Employee reward systems	Salary and Bonus Promotions Options or shares	Salary and Bonus Promotions Options or shares	Promotion or tenure Recognition, for example, awards Increased funding for future projects	Promotion or tenure Recognition, for example, awards Increased funding for future projects	
Strengths in drug development	Clinical Development NDA submissions Marketing and Sales	Discovery Research Clinical Development (Phase I, II)	Discovery Research	Discovery Research Clinical Research	

^a Pharmaceutical companies are defined in accordance with the Pharmaceutical Researchers and Manufacturers of America (PhRMA) definition [7], as companies engaged in the manufacture and marketing of final dosage pharmaceutical products, who also perform research and development of new molecular entities or therapies. Amgen, Biogen Idec, Cellgene, Cubist and Gilead are included as pharmaceutical companies (Genentech is not included as it is now part of Roche).

^b Biotechnology companies are defined as companies that use biological organisms, systems or processes for the development of new drugs or drug-development platforms, as identified by Huggett *et al.* (2011) [38].

^c Academic organizations are defined according to data from the Carnegie Foundation, listed as doctorate granting universities or special focus institutions (Medical schools and medical centers) (see: <http://classifications.carnegiefoundation.org/descriptions/basic.php>).

^d Data for biotech represents public companies only; private company employment figures not available. Academic numbers represent life science researchers and are from 2006.

^e Calculated from employment statistics of identified organizations.

^f Data on the history of the sectors or employee numbers were obtained from references cited, company websites, Yahoo finance (see: <http://finance.yahoo.com/>) the National Science Foundation (<http://www.nsf.gov/statistics/seind10/tables.htm#c3>) and the NIH (<http://www.nih.gov/>).

^g Following publication of *Science*, *The Endless Frontier*, letter to the President, 1945 written by Vannevar Bush.

^h Following the Bayh-Dole Act, 1980.

the key differences between these sectors in size, organizational structure, and funding sources, and outlines how researchers and employees in the respective types of organization are rewarded and thus motivated. This structure has created an environment in which each sector possesses strengths in different aspects of the drug development process, resulting in a disjointed process for developing drugs that often involves successive hand-offs of responsibility between the parties involved. This frequently includes steep learning curves and re-evaluation of the scientific and commercial data by each new owner of the drug along the way, which in turn contributes to the long timelines for bringing the drug to market.

Several studies in the field of drug development over the past ten years show that large pharmaceutical companies do not serve as fertile grounds for innovation [2,4,10] and are dependent upon academics and biotech companies for fuelling their pipeline [12,13]. On the other hand, discovery scientists in academia or small biotech companies are often not well-trained in clinical considerations or business strategies, and have little access to the necessary funding for generating the proof-of-principle data needed to attract investment. Lack of communication between these parties has resulted in many good ideas lying unexploited, while many drug pipelines become barren.

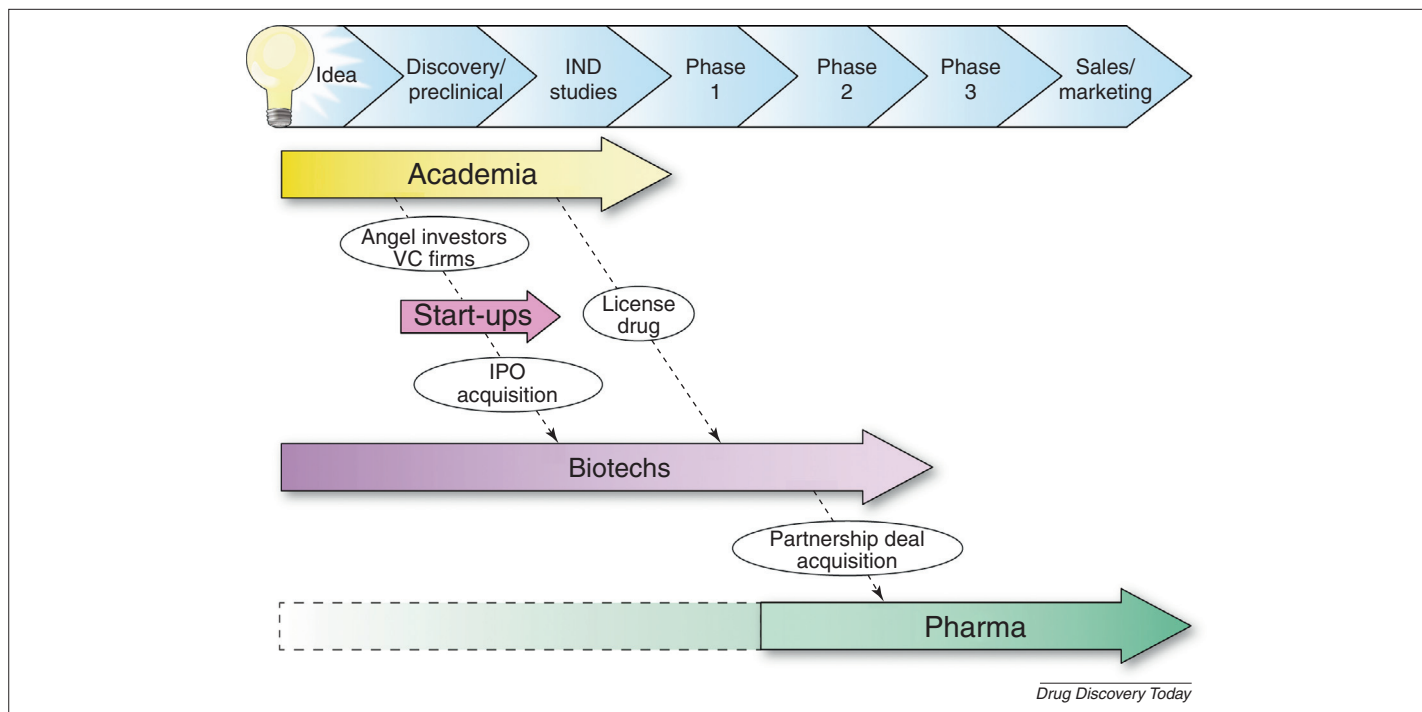


FIGURE 1

The prevailing model of drug development. The current respective roles and strengths of academia, biotech companies and pharmaceutical corporations in the process of drug development, from drug discovery to commercialization. Arrows and shading correlate to the areas of strength for each sector. *Abbreviations.* IND: investigational new drug; IPO: initial public offering; VC: venture capital.

Defining translational research

Increasingly, the field is recognizing the need to enable a closer collaboration of industry and academia to create a more efficient system for developing new drugs [1,14,15]. In parallel with this,

the world of drug discovery has seen the emergence of translational research as an alternative approach to the creation of new drugs, and there is growing support for the claim that this strategy may provide solutions to some of the woes of the pharmaceutical

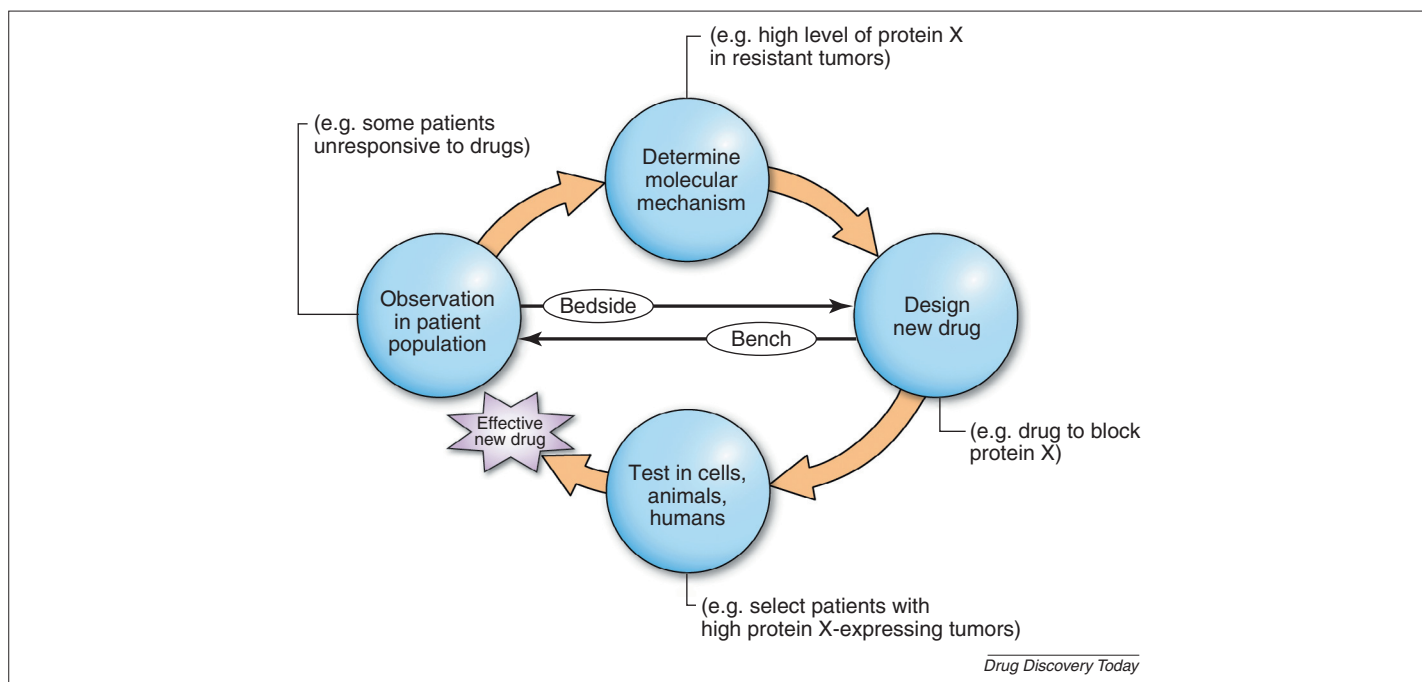


FIGURE 2

Translational research: from bench to bedside and back again. The translational cycle, showing the stages from the genesis of an idea to its translation into a product. An example is given for a translational product in the field of oncology.

TABLE 2

The spread of translational research among different types of institutions

	<i>Institutions with NIH-funded translational projects</i> Number (% non-profit total)	<i>Translational departments</i> Number (% non-profit total)
For-profit:		
Commercial organizations	62	nd
Non-profit:		
Universities	204 (53%)	111 (76%)
Research institutes	41 (11%)	4 (3%)
NIH institutes	19 (5%)	11 (8%)
Hospitals	53 (14%)	17 (12%)
Other organizations	66 (17%)	3 (2%)

Institutions containing translational departments or centers, or performing NIH-funded translational projects, were identified through searches of MEDLINE or the RePORT databases, respectively. MEDLINE was accessed via PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) and a search was performed for articles with the term *translational* in the affiliation field. Information regarding NIH funded projects was obtained by searching the NIH RePORT (Research Portfolio Online Reporting Tools) database (<http://report.nih.gov/>) for active, new projects containing the search terms 'translational research' or 'translational medicine'. Projects in the years 2001–2010 were included, and the search was limited to project terms and project abstracts. All data were exported to Microsoft Excel and duplicate entries were eliminated prior to analysis. Only U.S.-based projects were included.

Abbreviation: nd: not determined.

industry [16,17]. The belief that this approach can improve the pace of drug development is underscored by the creation of the NIH-funded Clinical and Translational Science Awards (CTSAs) in 2006 [18], and the spearheading by Francis Collins, director of the NIH, of the establishment of the National Center for Advancing Translational Sciences (NCATS) in 2012 [19].

Defining translational research, however, remains a source of much debate [20,21]. Adopted by scientists across the spectrum of life sciences, the term has found itself with multiple definitions for its meaning and its use. Translational research, translational medicine, and translational science are often used synonymously, and the term 'translational' has been used to generate a variety of other disciplines such as translational genomics [22], translational psychiatry [23], translational bioinformatics [24], and translational neuroscience [25]. The common element among these is the notion of translating discoveries in the laboratory into new clinical therapies. Often described as research 'from bench to bedside and back again' [26], translational research is based on the concept that the creation of new drugs should relate directly to patient needs and should couple laboratory research with observations made in the clinic (Figure 2).

The hallmark of the translational approach to drug development is that it incorporates the target of a specific unmet clinical need from the outset. Unlike traditional research-based discovery, which seeks to understand basic cellular mechanisms and apply these learnings to design new therapies, translational research targets mechanisms underlying clinically relevant problems and designs drugs to address those issues directly. At its broadest, translational research encompasses three principal components: laboratory research, clinical practice, and population effects in the community. These are often described in a two-stage process, termed T1 and T2, which refer to laboratory-to-clinic and clinic-to-community stages, respectively [21]. By focusing drug design and testing stages on the defined goal, translational research represents a streamlined approach with the potential to yield new drugs faster than the traditional drug development, and with a greater probability of success in the defined patient population.

The increasing spread of translational research

Initially the province of academia, translational research is now being implemented in a wide range of institutions. Insight into the

spread of translational research can be obtained by identifying departments or organizations who define themselves as translational in their name. A MEDLINE search for publications arising from institutions whose name includes the word 'translational' in the affiliation field shows a dramatic shift over the past two decades in the number of translational departments in the USA producing publications, from only five departments in the years 1991–2000 to 146 in the years 2001–2010. The majority (76%) of these departments are affiliated with or belong to universities, as expected for a search based on publications, but hospital-based departments represent a notable proportion (12%) of the total, as do translational departments within the NIH institutes (8%) (Table 2). These departments belong to 107 different organizations, including 80 academic institutions. Interestingly, this convergence of translational research with drug discovery efforts in academia is supported by the similar numbers produced by Frye *et al.* [27], who identified 78 academic institutions housing small molecule drug discovery efforts, and who showed that many of these were established between the years 2004 and 2010.

Further evidence for the increasing spread of the concept of translational research can be found in the use of the term 'translational' in the title of NIH-funded projects, as identified by a search of the NIH RePORT database. Between the years 2001 and 2010, universities and NIH institutes represented the majority of organizations receiving NIH funding for translational studies, as expected, but there were, in addition, a considerable number of projects being performed in hospitals, research institutes or other non-profit organizations such as disease-focused charities or foundations. Significantly, although the vast majority of the funded organizations were non-profit organizations, more than 60 commercial companies or for-profit organizations received NIH funding for translational projects, reflecting the spread of this approach in both the private and the public sectors (Table 2).

Many of the departments, centers, and institutes identified as having translational departments are involved in collaborations between different organizations, frequently including academic institutions and hospitals. These relationships represent the core of translational research in facilitating access between clinicians treating patients and bench scientists exploring mechanisms of drug action. The diverse use of 'translational' in these departments' names or projects reflects a range of different objectives,

which broadly can be categorized into T1 and T2 research. T1 departments reside primarily in universities or other institutes of higher learning, and focus on the laboratory discoveries that relate to specific clinical endpoints. Idea generation for new drugs and the earliest stages of drug discovery occur in these T1-oriented departments, which enable laboratory scientists to team together with practicing physicians who provide input into clinical practices for different diseases, and who can perform early stage clinical trials on new drugs. Similarly, as the clinicians discover significant unmet needs among their patients, these centers allow them to brainstorm directly with laboratory researchers, and to devise potential solutions or plan projects that determine the underlying molecular mechanisms.

T2 departments integrate community outreach programs with clinical practices, with the aim of providing a means for understanding how well treatment strategies are working at a population level. Fewer departments appear dedicated solely to T2 rather than T1 research, although this may reflect a lower tendency to publish in the scientific literature, issues related to patient confidentiality or ability to obtain NIH-funded grants. T2-focused centers can relay medical issues in the community to physicians, leading to the adoption of improved treatment paradigms. For example, St Jude's Children's Hospital in Tennessee contains a translational imaging department that performs research using magnetic resonance technology to characterize how cancer treatment in children affects their brain structures and cognitive performance [28,29]. This information is then incorporated directly into treatment protocols in the relevant cancer prevention and control programs applied in the wider community.

Changing the paradigm of drug development: the integrated drug discovery nexus

In addition to the adoption of translational strategies in academia, hospitals, and commercial organizations, the past few years have seen the emergence of several biotech incubators or hubs aimed at fostering innovation and facilitating access between private and public sector parties involved in drug discovery. This trend is growing among all the players in the field. In addition to the CTSA institutes sponsored by the NIH, there are several centers of innovation created by large pharmaceutical companies, such as Pfizer's Global Centers for Therapeutic Innovation, Merck's California Institute of Biomedical Research (Calibr), and Janssen Labs innovation center created by Johnson & Johnson [30,31]. These are self-contained entities supported by the pharmaceutical industry, which complement several recent significant direct investments by pharmaceutical companies into academic institutions under the umbrella of private-public partnerships [32,33].

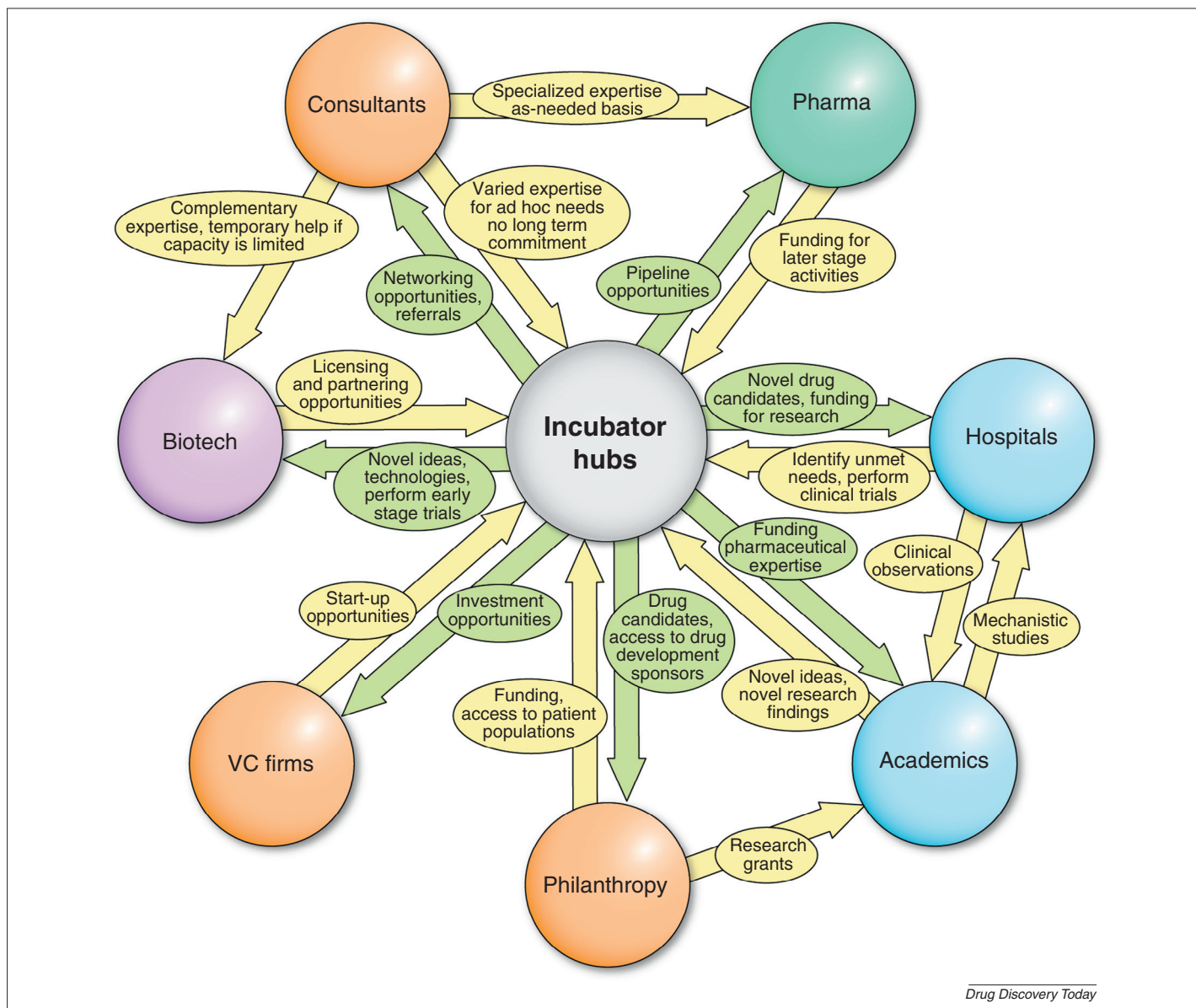
Beyond these high profile investments by government and industry, however, there are several more grass-roots attempts to create networks that will foster innovation. In some cases these are 'research parks,' sponsored by local government or state initiatives, which provide physical proximity between organizations and access to facilities to spur the creation of new businesses connected with the biotech industry. Examples of these are found across the USA, and include the more recently created hubs such as the Hershey Center for Applied Research in Hershey, PA (opened in 2007), the HudsonAlpha Institute in Huntsville, AL (2008), the CSU Research Innovation Center in Fort Collins, CO (2010) and

the New Orleans BioInnovation Center (2011), in addition to the more well-established hubs such as the North Carolina Biotechnology Center in Research Triangle Park, NC (1984) and the Massachusetts Biomedical Initiatives in Worcester, MA (1985).

An alternative model is also developing, which can be described as an integrated discovery nexus between many different organizations or individuals. These nexuses aim to couple innovative researchers with industry representatives from multiple scientific and business disciplines, who advise the scientists on what it takes to convert a breakthrough discovery to a commercial product. One format for this is found in the example of the QB3, the California Institute of Quantitative Biosciences, a nonprofit organization which has research facilities at three University of California campuses (UC Berkeley, UC Santa Cruz and UC San Francisco [UCSF]), and which has a fourth division, the Innolab, that provides assistance to researchers to help them commercialize their innovations [34]. The three scientific arms supply shared facilities and educational programs, and are complemented by the business-oriented division which provides connections with pharmaceutical companies and VC funds, in addition to entrepreneurship training and mentoring. A different form of this nexus can be found inside some universities, such as the Taube-Koret center at the Gladstone Center of UCSF, which is focused on neurodegenerative diseases [35], or the SPARK program at Stanford University, which aims to advance to the clinic promising Stanford-based discoveries in multiple therapeutic areas. The SPARK program brings together graduate or postdoctoral researchers, faculty professors, and a wide range of volunteer industry advisors from the Bay Area's rich supply of biotech companies. These contributors meet in a team setting on a weekly basis to review project progress, provide helpful connections, and mentor the researchers, towards the generation of valuable new therapeutics and diagnostics [36].

The integrated discovery nexus concept may lead to a new architecture for the field of drug development. It has the potential to benefit all parties, providing academic researchers with access to funding and expertise from biotech and pharmaceutical companies, while giving opportunities for the pharmaceutical companies to access novel discoveries. This model for advancing the creation of new drugs is based on the core elements of translational research, and offers the potential to radically transform the industry and the organizations involved. In this evolving model for integrative drug development, the novelty lies not only in the potential funding of new ideas by connecting academia with industry, but in the creation of a network of expertise that includes an array of other contributors, such as VC firms, philanthropic organizations, and independent consultants. For the success of any such integrative nexus, each of the participants must both contribute and receive value, while facilitating the conversion of laboratory discoveries to new drugs (Figure 3), including:

- (i) Academic researchers provide the cornerstone of innovative research to discover new mechanisms underlying diseases and conditions observed in clinical practice. In return, they receive funding in addition to commercial and pharmaceutical expertise for what makes a compound 'druggable,' an essential part of the picture that is often not well taught in academic environments.
- (ii) Hospital-based clinical researchers identify medical problems and trends within the patient population, and



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FIGURE 3

The integrated discovery nexus. The emerging model of an integrated drug discovery nexus, illustrating the roles played by the different participants and their respective contributions and benefits to the collective organization.

collaborate closely with academic scientists to determine the mechanistic bases of these trends, which can drive the ideation process for new drugs. Hospitals thus contribute to the identification of unmet clinical needs, and perform clinical trials where relevant. Their researchers receive novel drug candidates for treating patients who need them, and funding for their studies.

- (iii) Established biotech companies provide licensing and partnering opportunities for novel ideas coming from academia. These companies bring industry know-how for the early stages of drug development, which can include essential components such as how to create an effective target product profile, how to design critical path activities and select go/no-go criteria, and how to evaluate issues that may come up later from a business standpoint, such as reimbursement. The partnering opportunities or access to

novel technologies that they receive from the connection with academia can serve to bolster their own drug portfolios. In addition, they reap benefits for their proprietary compounds by gaining access to hospitals that can perform early stage clinical trials, and closer collaboration with big pharmaceutical companies that can provide strategic input for development programs and pave the way for partnering and other business opportunities.

- (iv) Representatives from pharmaceutical companies contribute by providing key industry expertise in the commercialization of drugs, which can include factors for consideration for late-stage development, regulatory submissions or economic perspectives. These contributions can influence early drug development decisions in both academia and biotech companies, and can shape the selection of the target indication or regulatory strategy. Given the crisis facing

the pharmaceutical industry today, this sector has arguably the most to gain by sponsoring the creation of, and having access to, new pipeline opportunities that are key to their long-term survival. Although pharmaceutical companies do not depend on these types of nexus for access to biotech companies, their current access to academic discoveries is limited. Because their in-house research efforts have declined, pharmaceutical companies can benefit greatly from the closer connection with the innovative core of the drug development field.

- (v) Venture Capital firms can provide advice or funding for the creation of businesses based on promising discoveries from universities or other non-profit research institutes. They may provide opportunities for researchers to start their own companies, and can create avenues of access to small privately-owned companies who could develop these innovations while the researchers continue to pursue their academic careers. In return, VCs find promising investment opportunities which form the core of their businesses, and remain well-informed about cutting-edge advances at the forefront of pharmacology.
- (vi) Philanthropic organizations and advocacy groups contribute by providing funding for drug-related research. Some have access to specific patient populations, in particular for rare and neglected diseases, or diseases that occur only in certain sub-populations of patients. Such organizations are often dedicated to specific diseases or disorders, and can provide ready access to clinical observations and information about the disease to help guide discovery research. They benefit by creating connections with researchers who may direct their efforts to addressing their chosen causes, and thus promote fruitful investment of their philanthropic dollars.
- (vii) Independent consultants and Contract Research Organizations (CROs) have a dynamic but important role in these discovery nexuses. As pharmaceutical and biotech companies control their expenditures by reducing their full-time employee workforce, independent consultants and CROs provide a reservoir of expertise and capability that can be tapped on an as-needed basis. Consultants and CROs with experience in drug development can advise biotech companies, start-ups, and VCs on different aspects of the process, by providing assistance, for example, with temporary needs such as writing regulatory documents, analyzing data or performing preclinical or early clinical experiments, without the costs and management obligations of hiring full-time employees. The drug discovery nexus creates an advantage for them in networking opportunities and referrals which promote their own practices.

Does this model of an integrated drug discovery nexus represent a utopian fantasy and ignore the potential conflicts that will arise?

Although there have been concerns regarding conflicts of interest when pharmaceutical companies sponsor academic research, these appear to be the exception rather than the rule [33]. Inevitably, changes in approach will be needed regarding intellectual property and ownership of data for publication, both from universities and from the private sector, but efforts are under way to create working models that address this [9]. Technology incubators have been highly successful in other industries, and have led to the efficient and profitable conversion of research discoveries into new products [37]. Whether such nexuses can succeed for drug discovery will depend largely on the willingness of the relevant players to solve problems that arise and promote their common interests. Because the alternative is to continue with the status quo, it will benefit all the participants, and most importantly patients, for the field to capitalize on the momentum of translational research and use it to re-energize the process of creating new drugs.

Concluding remarks

Academia, biotech companies and pharmaceutical corporations are embracing translational research for its potential to increase the number of drugs successfully brought to market. Acknowledging the need for greater collaboration between these different sectors, substantial investments have been made by the NIH and the pharmaceutical industry, through the NCATs institute and centers of innovation, respectively. Biotech hubs are budding around the USA to spur business creation based on coupling academic discoveries with industry know-how, and smaller grass-roots translational initiatives are emerging within universities to integrate expertise from multiple aspects of the industry. The evolving picture of an integrated drug discovery nexus is still in its infancy, and it remains to be seen how efficiently such organizations will be run, and whether they will have a significant impact on the efficiency of new drug creation. Nonetheless, translational research clearly represents a dominant new strategy across the field of drug discovery, and the next decade will most probably see significant changes in the relationships between academics, biotech companies, and pharmaceutical corporations.

Disclosure statement

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