ELSEVIER

Racing to define pharmaceutical R&D external innovation models

Liangsu Wang[1], Andrew Plump[2] and Michael Ringel[3]

[1] Merck Research Laboratories, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA
[2] Sanofi, 54, Rue de la Boetie, Paris 75008, France
[3] The Boston Consulting Group, Exchange Place, Boston, MA 02109, USA

The pharmaceutical industry continues to face fundamental challenges because of issues with research and development (R&D) productivity and rising customer expectations. To lower R&D costs, move beyond me-too therapies, and create more transformative portfolios, pharmaceutical companies are actively capitalizing on external innovation through precompetitive collaboration with academia, cultivation of biotech start-ups, and proactive licensing and acquisitions. Here, we review the varying innovation strategies used by pharmaceutical companies, compare and contrast these models, and identify the trends in external innovation. We also discuss factors that influence these external innovation models and propose a preliminary set of metrics that could be used as leading indicators of success.

Introduction

The pharmaceutical industry has been facing decreasing R&D productivity for over several decades driven by many factors, including low success rates in clinical development [1,2]. The return on R&D investment in biopharmaceutical companies has arguably dropped at or below the cost of capital [3]. To address this decline, identify better-understood targets, and develop differentiated therapies, many pharmaceutical companies are designing creative approaches to access external scientific innovation [4–6]. What are these models? Which will bear fruit? And, perhaps most importantly, how will we know that they are any more productive than the approaches used to date?

The external R&D innovation models used by the pharmaceutical industry are wide ranging (Table 1). These models include traditional industry–academic partnerships supporting discovery, open crowdsourcing, academic centers of excellence, company co-creation with venture capital, innovation centers, and shared risk partnerships between companies. Although these creative approaches have by no means made traditional licensing, mergers, and acquisitions obsolete, they act to expand rather than consolidate the industry. Furthermore, whereas traditional approaches are in many cases focused on cost synergies, these new types of interaction are usually focused on improving innovation. This trend toward using open models and early risk sharing is perhaps intuitive and has been something that other industries have embraced for many years.

Traditional pharma–academia early discovery collaboration

The boundary between academia and the pharmaceutical industry is becoming more permeable as the two converge on common goals for the improvement of human health. Most basic research occurs outside the walls of pharmaceutical laboratories; indeed, the initial fundamental discoveries that ultimately lead to new therapies often emerge from academia. Perhaps the greatest contributions to drug discovery from academia are the deep mechanistic knowledge of disease biology and big data techniques, such as seen in the area of human genetics. For example, although attempts have been made to harness the promise of human genetics within the walls of pharmaceutical companies, the expertise, access to cohorts and patient samples that are crucial to these studies, and the breakthrough findings that have driven drug discovery efforts often arise within academia. In addition to, or perhaps because of, the obvious synergy with academia in crucial

Corresponding author: Wang, L. (liangsu_wang@merck.com)

1359-6446/06/$ - see front matter http://dx.doi.org/10.1016/j.drudis.2014.10.008

TABLE 1

Comparison of various external R&D models[a].

Model	Description	Advantage	Disadvantage	Selected examples
Traditional pharma–academic partnership: one company–one investigator	A pharmaceutical company forms a collaboration with an academic investigator by providing funding or other resources in exchange for the investigator's knowledge and contribution to research	Simple relationship; quick start; focused	Ad-hoc and piecemeal manner; communication with other investigators can be limited; limited opportunity to synergize with other investigators	Numerous
Open crowdsourcing	A pharmaceutical company creates a contest to encourage external scientists to submit proposals or ideas. Awards are given in the form of grants or access to drug discovery expertise, tools and reagents with potential for longer-term follow-up collaborations	Unbiased and broad outreach; scale and diversity of solutions in early discovery; potential to lead to unexpected findings; low-cost structure	The problem statements presented in crowdsourcing tend to be less proprietary to avoid revealing company-specific details, which could limit the repertoire of opportunity requests	Lilly PD^2, TD^2; Bayer Grants4Targets, Grants4Leads, Grants4Apps; GSK Discovery Fast Track Competition; AstraZeneca open innovation web portal; third-party platforms such as Innocentive
Academic centers of excellence	A pharmaceutical company builds master agreements with one or more universities; in some cases, scientists from pharmaceutical laboratories are co-localized to the academic institutions to facilitate collaboration	Master agreements that streamline the new collaboration initiation process; potential synergy among multiple investigators within the institution; co-localization of experienced drug discovery scientists making the collaboration more aligned with drug discovery needs	Typically limited to premier institutions; alignment of pharmaceutical scientists in the centers of excellent with internal research units may be challenging; academic investigators sometimes naïve in dealing with the complexities of drug discovery and development; vulnerable to market forces such as strategic changes within and mergers and acquisitions among pharma companies	Numerous, for example, Pfizer CTIs; AstraZeneca – Karolinska Institute; MedImmune – INSERM; Janssen – KU Leuven – Wellcome Trust; Sanofi – UCSF; Boehringer Ingelheim – Harvard University
Biotech co-creation	A pharmaceutical company invests capital funds and/or contributes assets to the biotech start-ups	Combination of nimbleness of start-ups with the deep drug discovery and development expertise of pharmaceutical companies; early access to the products from the new company; opportunity for pharma to influence the direction of the start-ups toward the pharmaceutical company needs	High risk; often long-term investment and potential impatience of involved parties; might need to avoid being controlled by pharma too early so as not to regress thinking to a traditional mean	Numerous, for example, Sanofi – Third Rock Ventures for Warp Drive Bio; GSK – Avalon Ventures for multiple start-ups; Lilly – Atlas Ventures – OrbiMed for Arteaus; Celgene – Versant Ventures for Quanticel; Astellas – MPM Capital for Mitokyne
Pharmaceutical peers risk sharing	Two (or more) pharmaceutical companies co-develop clinical candidates to share development cost	Risk sharing to ameliorate potential financial damages from clinical development failures, especially late stage	Cost synergy rather than novel innovation in most cases	Many examples; for example, development of SGLT2 inhibitors: BMS – AstraZeneca on Dapagliflozin, Lilly – Boehringer Ingelheim on Empagliflozin, Pfizer – Merck on Ertugliflozin
Innovation centers	A pharmaceutical company creates a regional center in a biomedical hub to facilitate collaborations with academia and biotechs, biotech start-up creation, in-licensing and merger activities. Details may vary by each company	One-stop shop for a variety of deals with external partners; efficiency in deal making; first-mover advantage	Alignment and integration with internal research units are yet to be seen	Bayer, J&J, GSK, and Merck

[a] External R&D innovation models of the pharmaceutical industry are wide ranging, with a common goal to identify the best deals, simplify the deal-making process, and improve external R&D productivity. Licensing, mergers, and acquisitions are not listed here.

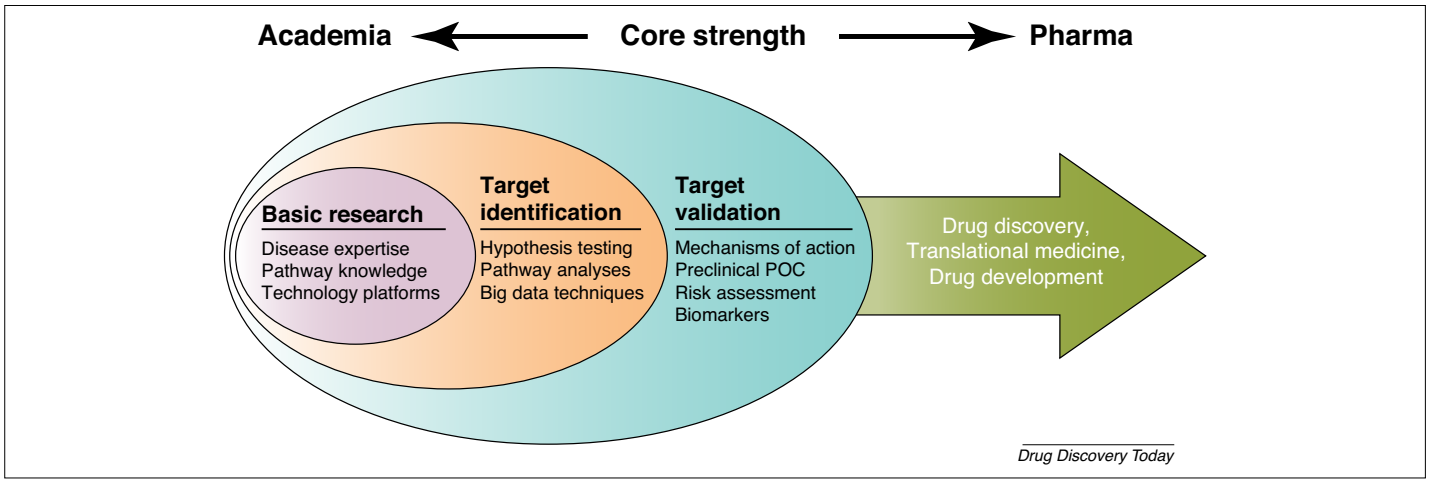

FIGURE 1

Complementary strengths between academia and pharmaceutical companies. *Abbreviation*: POC, proof of concept.

areas such as human genetics, most pharmaceutical companies have been reducing internal investment in early discovery. Pharmaceutical companies need academia.

Likewise, as granting agencies look for translational science with more relevance to human health, the link to pharmaceutical scientists becomes more important for academic researchers, as both a mechanism for justifying the relevance of their work to human health and a conduit for expanding discoveries beyond academia to patients. Demonstration of interest from a pharmaceutical collaborator at the front end of a research project can enhance its competitiveness with funding agencies. Ultimately, access to drug discovery expertise, development prowess, and the commercial engine in large pharmaceutical companies has at least historically been a near-necessity for any biomedical entrepreneur interested in creating new therapies for patients. Academia needs pharmaceutical companies, and the core strengths of academia and pharmaceutical companies are complementary (Fig. 1).

With this common interest, academic and pharmaceutical scientists have been striving to improve collaboration efficiency by confronting cultural barriers as well as issues of confidentiality, publication, and intellectual property (IP) rights [5,7]. Nowadays, industry–academia collaboration has become a norm.

To build a platform to nurture external collaboration in a broad and open manner, many pharmaceutical companies have been experimenting with new external innovation models beyond traditional academic collaboration, such as company-wide

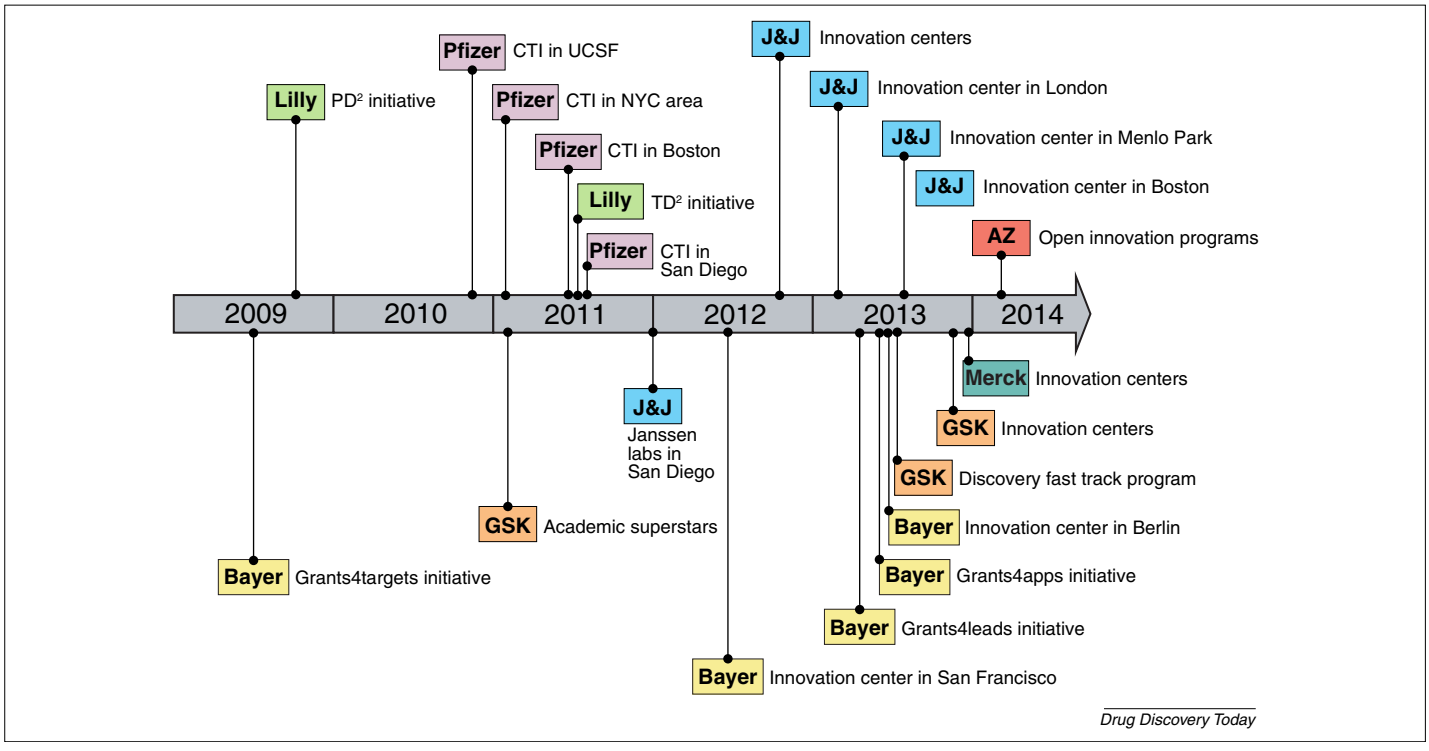

FIGURE 2

Timetable of selected pharmaceutical company-wide external research and development (R&D) initiatives with academia and/or biotech start-ups. *Abbreviations*: CTI, center for therapeutic innovation; PD2, phenotypic drug discovery; TD2, target drug discovery.

initiatives, institutional-level alliances, or regional external R&D hubs, as shown in Fig. 2. A common feature of these collaboration models is simplification to expedite the deal-making process.

Open crowdsourcing

One precompetitive innovation model used by multiple pharmaceutical companies is crowdsourcing, where monetary grants or access to drug discovery expertise and tools are made available to academic scientists to support ideas of mutual interest. Crowdsourcing brings the benefit of scale and diversity of solutions to early discovery. A particularly attractive aspect of this type of relation is the potential to prototype and nurture early ideas at low cost. Once an idea emerges as exciting, in many cases the trust and relations developed between the innovator of the sourced idea and the larger company enable natural evolution into longer-term follow-up collaborations.

As a pioneer in this regard, Eli Lilly launched the Phenotypic Drug Discovery Initiative (PD^2) in June 2009 by introducing an online open innovation platform for researchers to submit new chemical molecules to screen in its collection of cellular to identify compounds acting on mechanisms of interest (https://openinnovation.lilly.com/dd/). Lilly expanded this open innovation drug discovery platform in 2011 to include target-based screening of molecules submitted by academic investigators (an initiative termed 'TD^2'). Although we do not yet know whether PD^2 and TD^2 will prove successful, the cost structure and, thus, the risk are low. From the scientific perspective, this approach expands chemical space for therapeutic molecules [8].

Other pharmaceutical companies using crowdsourcing approaches include Bayer and GlaxoSmithKline (GSK). The Grants4Targets initiative of Bayer (http://www.grants4targets.com/scripts/pages/en/index.php) was launched around the same time as the PD^2 program of Lilly. The initiative encourages academic investigators to submit novel target ideas in areas of mutual interest, and Bayer provides grants to support target validation. Successful projects supported by the grant can lead to further collaboration. From May 2009 to the end of 2013, nine calls for applications were conducted, over 900 applications were received, and approximately 120 grant applications were accepted. Bayer has expanded this open innovation model with the addition of Grants4Leads and Grants4Apps initiatives.

The Discovery Fast Track competition of GSK leverages life-science expertise in the academic community by inviting investigators to share novel drug development proposals, including therapeutic hypothesis, target, assay protocols, and reagents (http://openinnovation.gsk.com/). In return for successful proposals, GSK configures a high-throughput assay to screen the target against its compound library. Launched in mid-2013, eight Discovery Fast Track projects were selected as finalists from 142 proposals received from 70 universities in its inaugural competition (http://www.gsk.com/media/press-releases/2013/gsk-names-inaugural-winners-in-unique-competition-for-academic-d.html).

Earlier this year, AstraZeneca launched its own Open Innovation web portal listing several programs spanning all stages of drug discovery and development (http://openinnovation.astrazeneca.com). To facilitate the expansion of clinical programs through partnerships, the portal provides interested partners with access to the Clinical Compound Bank of discontinued drugs from the company that have demonstrated target coverage and a favorable safety profile in humans, and that could provide a treatment option for a new indication. The portal also includes a route for interested parties to submit proposals to AstraZeneca for grants for target validation partnerships as well as an 'R&D Challenges' section, where the company plans to crowdsource solutions to problems.

Open crowdsourcing is deemed a low-risk approach to expose complex drug discovery problems to a decentralized crowd with varied skills, experience, and perspectives. The major limitation of these approaches is that the problems being crowdsourced are typically general ones or need to be abstracted to avoid revealing proprietary details, which can diminish the likelihood of company-specific solutions [9].

Academic centers of excellence

Pharmaceutical companies have also focused on targeting premier academic institutions to strengthen ties and build sustained relations. To cast a wider net for accessing the best science and technologies in world-class institutions and to expedite transactions for multiple deals, pharmaceutical companies have been striking long-term master agreements with academia at an institution level. For an example, attracted by the large network of labs and hospitals of the French INSERM, MedImmune formed a strategic collaboration with a network of investigators in INSERM to explore translational biology and novel disease mechanisms by pursuing over ten projects covering multiple disease areas [10]. Meanwhile, universities have been revamping and streamlining their approaches to industry partnerships aiming to facilitate the translation from bench to bedside, as exemplified by the University of California at San Francisco (UCSF), which has been successful in attracting multiple industry partnerships. Facilitated by the UCSF Innovation, Technology & Alliances (http://ita.ucsf.edu/) plus parallel efforts at the California Institute for Quantitative Biosciences (QB3) headquartered on the UCSF Mission Bay campus (http://www.qb3.org/), UCSF has formed many broad-scale strategic alliances with industry. As a result of push-and-pull, pharmaceutical–academic alliances at this level have become common. A few selected examples include: Bayer – UCSF for a 10-year master R&D agreement (January 2011); Sanofi – UCSF on brain trauma and oncology research (January 2011) and diabetes research (January 2012); Boehringer Ingelheim – Harvard University on a translational research collaboration to sponsor a variety of research projects (July 2012); Novartis – University of Pennsylvania for cellular therapy (August 2012); Roche – Broad Institute for compound repurposing (November 2012); Johnson & Johnson (J&J) – Mount Sinai in the area of inflammatory bowel disease (June 2013); AstraZeneca – Karolinska Institute on cardiometabolic research (July 2013), Janssen – KU Leuven – Welcome Trust joining forces to combat dengue disease (August 2013), MedImmune – John Hopkins for a 5-year broad-scale medical research partnership in multiple disease areas (December 2013), and many others.

The Center for Therapeutic Innovation (CTI) of Pfizer is one of the most extensive examples of this model (http://www.pfizer.com/research/rd_partnering/centers_for_therapeutic_innovation). A key aspect of CTI, which departs from a traditional collaboration model, is to blend the translational research

expertise and resources of the company with the discovery research expertise of local academic institutions, which essentially become entrepreneurial research units. The goal is to discover and develop therapeutic candidates from early research through proof-of-mechanism in humans across multiple disease areas. Since its launch in late 2010, four CTIs have been formed in biomedical research hubs in the USA in San Francisco, San Diego, Boston, and New York. As of December 2013, CTI had over 20 institutions in its network, with a portfolio of approximately 25 programs selected from >300 proposals spanning a range of therapeutic areas.

Although academic centers of excellence benefit the pharmaceutical companies in accessing a network of investigators in premier institutions, such hybrid academic–industrial partnership arrangements also benefit academia in ramping up its ability to translate fundamental scientific discoveries to therapies for patients. The benefits to academia include not only the funding, but also accessing the resources and drug discovery expertise of pharmaceutical companies [11,12]. The latter is especially important given the relative dearth of drug discovery expertise within the academic community. However, a potential risk of this model is its vulnerability to market forces, such as strategic changes within, and mergers and acquisitions between, pharmaceutical companies [12].

Besides these pharma-driven models, many universities in the USA and UK are also rising to the challenge and have developed new funding systems in recent years to transform breakthrough discovery research into marketable therapies on their own. Examples include the preclinical program of Harvard University and the development fund of Oxford University [12–14]. Although such academic-funded drug discovery efforts have the advantage of flexibility and hold the promise of shaping the development of new discoveries, there are often knowledge and expertise gaps within the academic community in drug discovery and development that might limit their effectiveness. The lack of sustainable funding to support the lengthy drug discovery process will also need to be addressed.

Company co-creation with venture capital

An innovative industry–academic partnership that moves away from traditional inlicensing is the investor–partner model. Many pharmaceutical companies have or are building venture capital funds to invest in early biotechnology to support and create equity in groundbreaking science. These activities range from limited investments in existing venture funds as syndicate partners to independent funds with their own profit and loss (P&L) that have varying degrees of interaction with pharmaceutical management and scientists, including company co-creation.

A tweak of the traditional venture capital model is that pharmaceutical companies contribute in-kind assets to the start-ups as well as capital funds, whereas start-ups trade acquisition options for early funding, resources, and guidance [15]. Under this emerging model, start-ups can gain access to the technical platforms, drug discovery and development expertise, and even clinical candidates of large pharmaceutical companies and, thus, save years in terms of time in building capabilities or generating molecules, while pharmaceutical companies get the benefits of efficiency and flexibility from the start-ups. An example of this is the Mirror Portfolio Program of Lilly, under which Lilly establishes investments with other venture capitalist partners and invests up to 20% in capital or a total commitment of up to US$150 million. In addition to capital funds, Lilly offers development candidates from their own portfolio to these start-ups. These virtual start-ups then have access to the Lilly Chorus group, a lean virtual development organization designed to provide efficient and low-cost approaches for early development. Another creative example of company co-creation is a model built at Sanofi called 'Sunrise', which aims to co-invest with venture companies [16]. The first Sanofi Sunrise investment was Warp Drive Bio, which leverages novel genomic approaches to mine natural product libraries for new therapies. Another recent example is Myokardia, a company targeting novel therapies for cardiomyopathy founded on a growing understanding of this disease based on human genetics. An important aspect of Sunrise is that not only does Sanofi invest with capital, but it also offers in-kind contributions. Warp Drive Bio, for example, has access to the unique Sanofi natural product library, which contains over 100,000 microbial strains. Other pharmaceutical companies, such as Celgene, Roche, Bayer, GSK, and The Medicines Company, are experimenting with variations of this start-up creation model [15].

A driver for some pharmaceutical companies is to be in close proximity to big ideas that have the potential to transform into new therapies, without having to pay large fixed costs to fund the projects internally. This offers a unique path for pharmaceutical companies to tap into innovation, limiting the control and bureaucracy often found inside the walls of pharmaceutical laboratories. For venture capitalists, it provides an opportunity to share risk early on. For example, GSK and J&J were both early adopters, together building a US$200 million fund with Index Ventures to invest in early-stage biotech start-ups, as a move to entice venture capitalists back to the biotech industry (http://www.fiercebiotech.com/story/gsk-jj-back-indexs-new-200m-fund-early-stage-deals/2012-03-21). GSK and Avalon Ventures also forged a US$495 million biotech start-up fund and plan to create around ten companies within the next 3 years (http://www.fiercebiotech.com/story/report-glaxosmithkline-and-avalon-ventures-forge-495m-biotech-startup-allia/2013-04-22). Within the first 18 months, this venture alliance launched three new companies: Sitari, Silarus, and Thyritope.

The investor–partner model is a powerful model for incentivizing and ultimately translating breakthrough biomedical innovation arising in academia. The emerging built-to-buy model for company creation combines the nimbleness of start-ups and the deep drug discovery and development expertise of pharmaceutical companies for risk-sharing and more cost-effective innovation. It also promotes the type of disruptive innovation, such as new modalities, that rarely emerge from pharmaceutical laboratories, which tend to focus on more traditional targets, platforms, and approaches. Although attractive, this model has challenges. Will there be sufficient patience on both the venture and pharma sides to allow disruptive ideas to emerge at a measured pace that is often necessary, without forcing premature ideas or molecules into development just to show progress? Will pharmaceutical companies avoid the need to control and direct these innovative small companies, regressing thinking to a traditional mean? Will venture companies share a vision driven of long-term success rather than focus on a short-term exit?

Pharmaceutical peer-shared risk partnerships

Most disease targets are pursued by multiple companies in parallel, with failures usually resulting in multiple losses across the industry and success resulting in the largest returns accruing to companies that are either first- or best-in-class [17]. The costs to develop follow-on and second-generation therapies for a successful mechanism are significant, yet the benefits to patients are often small and the investment necessary to develop these therapies creates an opportunity cost for the development of novel therapies.

One mechanism to avoid redundant costs is pharmaceutical company partnerships. Profit-sharing collaboration models between pharmaceutical peers are complex because of the competitive nature of the industry. Hence, a more common model for pharma–pharma collaboration is public–private partnership to address research gaps in the precompetitive space [2,18–20]. Two examples are the Innovative Medicines Initiative (IMI) and the Accelerating Medicines Partnership (AMP). A second and very successful type of model is one-to-one collaboration on late development projects. This has become most common in phase III clinical development, where many recent programs have been partnered in an effort to share cost and risk. Recent examples include the sodium glucose co-transporter 2 (SGLT2) inhibitors [e.g., Bristol–Meyers–Squibb (BMS)/AstraZeneca on dapagliflozin, Lilly/Boehringer Ingelheim on empagliflozin, and Pfizer/Merck on ertugliflozin) and the Factor Xa inhibitors (e.g., Bayer/J&J on rivaroxaban and Pfizer/BMS on apixaban]. Another area where pharmaceutical competitors form partnerships is the co-development of investigational drugs for combination use, such as the cytotoxic T-lymphocyte-associated protein 4 (CTLA4) inhibitor ipilimumab from BMS; the BRAF inhibitor vemurafenib combo for melanoma from Roche (June 2011); the Gilead and Tibotec protease inhibitor-based regimen for HIV (July 2009 and November 2011); the nonstructural protein 5A (NS5A) replication complex inhibitor daclatasvir from BMS; and the investigational NS3/4A protease inhibitor MK-5172 for chronic hepatitis C virus (HCV) infection from Merck (April 2013); and pembrolizumab from Merck in combination with crizotinib and axitinib from Pfizer to explore and expand the therapeutic potential of pembrolizumab (August 2014).

Such pharma–pharma partnerships are less common in the preproof of concept and discovery stages. However, there are emerging examples where large companies are recognizing the value of sharing expertise and capacity as well as risk during early development and even discovery. One example is the Amgen – AstraZeneca collaboration on five clinical monoclonal antibodies for inflammation, four of which are still in phase I, while one is in phase III. This risk-sharing collaboration concomitantly liberates resources and boosts pipelines for both partners (http://www.biocentury.com/biotech-pharma-news/strategy/2012-04-09/inflammation-deal-frees-resources-at-amgen-gives-astrazeneca-phase-iii-asset-a8). The recently announced Union Chimique Belgique (UCB) – Sanofi collaboration on anti-inflammatory small molecules in the area of immunomodulation is an example of pharma–pharma peer collaboration in discovery, where the partners plan to use an approach developed by UCB to identify and develop modulators of the pathway (http://en.sanofi.com/Images/35841_20141103_Sanofi_UCB_en.pdf).

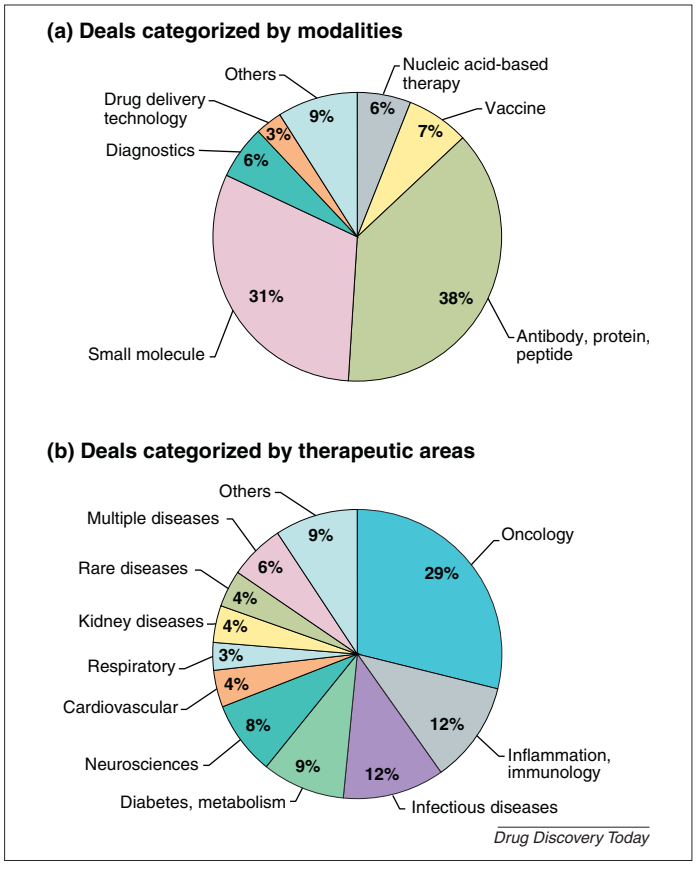

FIGURE 3

Selected list of licensing, merger, and acquisition deals of major pharmaceutical companies in 2012–2013, showing an increased concentration on deals related to biologic products and oncology. Deals categorized by **(a)** modality and **(b)** therapeutic area.

Pharma licensing, acquisition, and mergers remain

Without doubt, the pharmaceutical industry will continue to use more traditional external models, such as licensing, acquisitions, and mergers. These activities are indeed on the rise in recent years, with interesting trends.

First, licensing and acquisition deals in biologics (antibody, protein, and peptide) and related technologies have grown dramatically over the past 2 years, even surpassing that of small molecules, especially in the area of oncology (Fig. 3; Table S1 in the supplementary material online). This is in line with a shift of R&D strategies of many major pharmaceutical companies to focus more on biologic-based portfolios. This common trend is driven by several factors, including the proliferation of enabling technologies for biologics, the lower attrition profile of certain biologics often because of a generally more direct biological hypothesis and fewer safety issues than small molecules, faster speed to market, and pricing and post-patent sales profiles that remain robust [21].

Second, unlike the mega-mergers that occurred in 2009 [i.e., Pfizer–Wyeth (US$68 billion), Roche–Genetech (US$46.8 billion), and Merck–Schering Plough (US$41.1 billion)], transactions over the past couple of years have been mostly in the hundred million to a few billion-dollar range, and frequently with a more targeted focus (Table 2). A good example is the sequential licensing and acquisition approach of AstraZeneca to boost its pipeline. AstraZeneca topped all other pharmaceutical companies in the number

TABLE 2

Selected list of merger and acquisitions by major pharmaceutical companies in 2012–2013, showing mini-mergers in the most recent years, with a few previous mega-mergers are also listed for comparison.

Pharma company	Other party	Value (US$M)[a]	Year	Major collaboration areas
Pfizer	Wyeth	US$68,000	2009	Previous mega-mergers
Roche	Genetech	US$46,000	2009	
Merck	Schering-Plough	US$41,100	2009	
Sanofi	Genzyme	US$20,100	2011	
AstraZeneca, BMS	Amylin	US$5300	2012	Diabetes
GSK	Human Genome Sciences	US$3600	2012	Several pipeline products across multiple indications
BMS	Inhibitex	US$2500	2012	HCV
AstraZeneca	Ardea Biosciences	US$1260	2012	Lesinurad (Ph3) for treatment of hyperuricemia in gout
Amgen	Micromet	US$1160	2012	Acquired treatment for hematologic malignancies (Ph2) and proprietary BiTE antibody technology
Pfizer	NextWave	US$650	2012	Neurosciences
Amgen	deCode Genetics	US$415	2012	Human genetics capability to identify and validation targets for multiple diseases
	KAI Pharmaceuticals	US$315	2012	KAI-4169 program for secondary hyperparathyroidism in chronic kidney disease (phase IIa)
GSK	Cellzome	US$99	2012	Chemoproteomics platform
J&J	CorImmun	ND**	2012	Early development of cyclic peptide for heart failure
Amgen	Onyx	US$10,400	2013	Oncology portfolio and pipeline
Bayer	Algeta	US$2900	2013	Radiopharmaceuticals for cancers
AstraZeneca	Pearl Therapeutics	US$1150	2013	Treatment for chronic obstructive pulmonary disease (phase III)
Bayer	Conceptus	US$1100	2013	Women's health
J&J	Aragon	US$650	2013	Oncology: androgen receptor antagonist in phase II for castration-resistant prostate cancer
AstraZeneca	Amplimmune	US$500	2013	Cancer immunotherapy
	Omthera	US$443	2013	Cardiovascular disease: Epanova
	Spirogen	US$440	2013	Antibody–drug conjugate technology for cancers
GSK	Okairos	US$325	2013	Novel vaccine platform
AstraZeneca	AlphaCore	ND[b]	2013	Cardiovascular disease: lecithin-cholesterol acyltransferase enzyme

[a] Value includes milestones.
[b] ND: Not disclosed.

of licensing and acquisition deals over the past 2 years, with several minimergers in 2012–2013 plus a series of licensing deals of varied sizes in multiple therapeutic areas at all R&D stages, including diabetes asset purchase from BMS for US$4.1 billion. Such an approach to licensing and mergers is not new in the pharmaceutical industry. BMS has been using this strategy, known as 'String of Pearls' since 2007, including its 2009 purchase of Medarex, which came with the experimental immune-oncology drug ipilimumab, now known as the marketed therapy Yervoy for melanoma. Compared with full-on large-scale acquisitions of fully integrated large companies, a major advantage of small-to-mid size mergers and licensing deals is quick absorption and integration, thus avoiding the infrastructural and personnel disruptions that accompany mega-mergers.

The purchase of Onyx by Amgen for US$10.4 billion was one of the largest pharmaceutical R&D sector acquisitions in 2012–2013. This acquisition solidified the position of Amgen in oncology with its marketed cancer drugs increasing from two to five through the addition of Nexavar (sorafenib) for hepatocellular carcinoma, Stivarga (regorafenib) for metastatic carcinoma, and Kyprolis (carfilzomib) for multiple myeloma, and also strengthened its late-stage pipeline through the addition of palbociclib for metastatic colorectal cancer to its existing five phase II or III programs.

Given that pipeline gaps and payer pressures remain, mega-mergers and large deals will continue to be an important part of the landscape. It is not clear that any company over time will be able to sustain growth solely through its internal pipeline, given the inevitability and consequences of patent expiry on sales and the challenge of any single organization consistently driving the necessary breakthrough innovation through its own laboratories. The discussions between Pfizer and AstraZeneca, Valeant and Allergan, and Abbvie and Shire, are a sign of a potential new wave of large mergers.

Beyond the next wave of large mergers, we believe that the diversification of external innovation and targeted acquisitions will be a necessary component of the future of the pharmaceutical industry. Another trend in the industry that is likely to continue is focus. Recent activities in the pharmaceutical industry have revealed a common theme that pharmaceutical companies are choosing to compete in businesses where they believe they can be

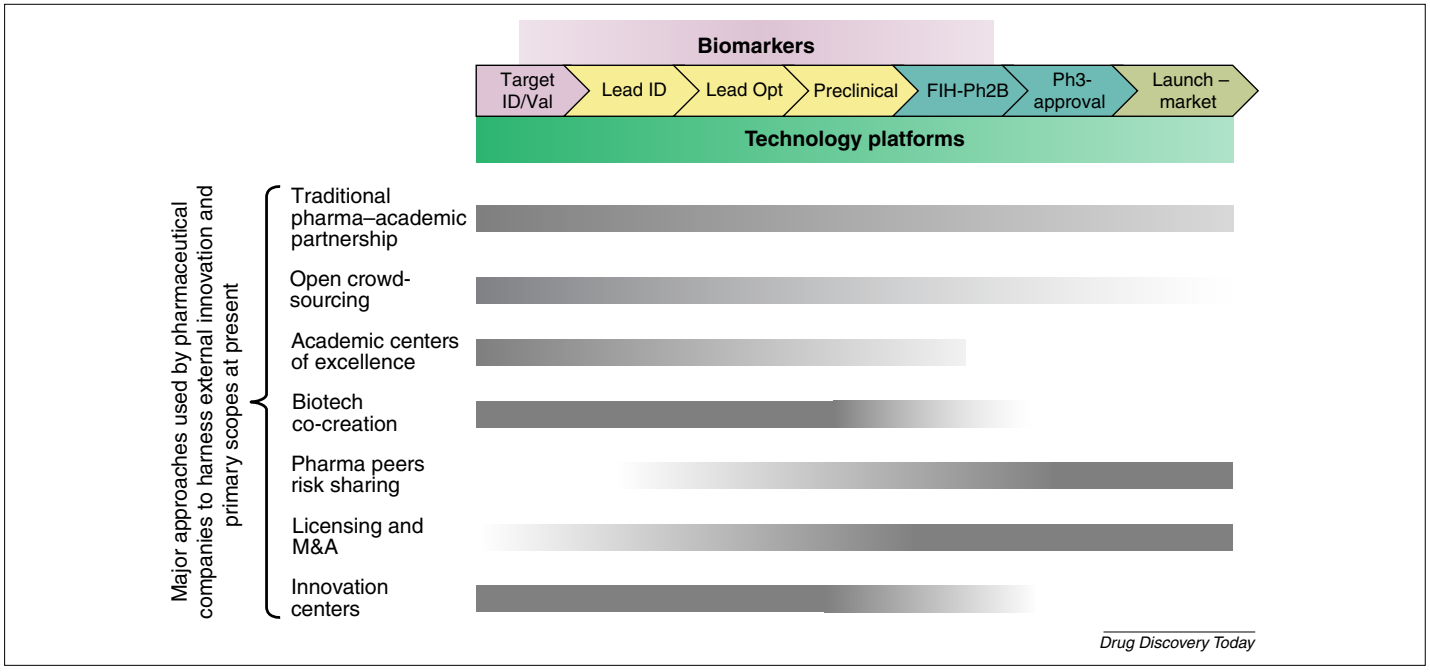

FIGURE 4

Primary scopes of the varied external innovation models. Innovation spanning the entire research and development (R&D) process is required to improve R&D productivity. Multiple models are necessary to harness external innovation at different levels. *Abbreviations*: FIH, first in human; ID, identification; M&A, mergers and acquisitions; Ph2b, phase IIb; Ph3, phase III; Val, validation.

global leaders by refocusing their business. One example is the three-way asset swap among Novartis, GSK and Lilly, in which Novartis divested animal health to Lilly and vaccines (excluding flu) to GSK, acquired GSK oncology assets, and combined Novartis OTC with the consumer business of GSK in a joint venture [22]. Likewise, Merck sees long-term growth drivers in its own pipeline and embraces deals in priority disease areas, such as immune-oncology, while continuing to shed non-core business units, such as its OTC business to Bayer AG. As pharmaceutical companies strive to become integrated healthcare providers, we might also observe future mergers and acquisitions across industry domains.

Innovation centers as a one-stop shop

One new addition to the panoply of external R&D models is the introduction of innovation centers at major life-sciences hotspots. The concept of these centers is to provide a one-stop shop for any potential partner, regardless of origin: academic, biotech, or otherwise, with presumed first-mover advantage by having local representatives in close proximity to scientists on-site to build rapport and promote synergies. Several pharmaceutical companies, including Bayer HealthCare, Johnson & Johnson (J&J), GSK, and Merck, are piloting this model.

In May 2012, Bayer HealthCare launched the CoLaborator Program and opened its first Innovation Center in San Francisco to enable Bayer scientists to reach out to academic institutions and biotech researchers to forge new drug discovery collaborations (http://www.colaborator.bayer.com). The Innovation Center also supports start-up life science companies by providing incubator space and basic research equipment, with the potential for preferred partner access. In May 2013, the creation of the second Innovation Center in Berlin was announced, which is expected to house up to ten small companies.

As a precursor to its own innovation centers, J&J opened its Janssen Labs in San Diego in January 2012, which offers entrepreneurs the Concept Lab space with 'no strings attached' to perform early-stage research before committing additional capital. In quest for more early-stage deals, J&J announced its plan to establish four regional innovation centers in California, Boston, London, and Shanghai in September 2012 (http://www.jnjinnovation.com). The innovation centers are staffed with J&J scientific leaders in areas of strategic focus, together with a business development team involved in venture capital, licensing, and acquisitions. The concept is to foster and expedite a range of collaborations with academics and entrepreneurs, including the seeding of emerging and early-stage biotech companies, research alliances, and licensing deals. Despite having existed for only a short period of time, there has been a flurry of deals from the innovation centers, with over 30 announced by June 2014.

The presence of innovation centers facilitates access to external innovation in the heart of the most-thriving life-science hubs in the world through integration with the local academics, biotech, and venture ecosystems. A common feature of the innovation centers is that they are sufficiently autonomous to simplify and expedite the decision and deal-making process.

Metrics for success

There is a range of external innovation models being explored, covering the full R&D value chain (Fig. 4). The question that we pose is not how we judge the success of these varied models, but how will pharmaceutical companies continue to evolve their

research models to increase productivity and which of these models will offer the greatest value. The future of the industry is unquestionably externally facing. The ultimate test of success is whether the return on R&D investment improves (as measured by sales created or human health improvement per dollar of R&D invested). However, it will take years for results to be seen in this lagging measure. There are intuitive reasons to be optimistic: the industry as a whole has clearly relaxed its 'not invented here' mentality and awakened to the concept that most innovation occurs outside any one company; at the same time, there are reasons for skepticism, including the possibility that the desire to look good on paper as measured by deal activity will drive deals that do not add true value. Given the history of biomedical research and the contribution of value from academia and biotech, it is clear that most true breakthrough innovation and medical value originates outside of pharma. There is also a vast amount of mediocre science and naïveté regarding drug discovery outside of pharma. As a result, external innovation makes sense; the largest barrier facing pharma might be the ability to make a cultural shift and to free up resources to do more externally. Thus, our proposal for metrics of success focuses predominantly on the level of external activity. We are conscious that such a metric can lead to perverse incentives if managers are evaluated solely on this ground: they might be incented to pursue spurious deals to reach activity goals. However, we believe that this risk can be mitigated by the application of complementary qualitative metrics that assess the quality of deals pursued.

In proposing quantitative metrics to measure success we must make certain assumptions: (i) external innovation can be as productive or more than internal innovation in pharmaceutical companies; (ii) the value of me-too or follow-on therapies is dwarfed by that of breakthrough innovative therapies; (iii) human behavior around autonomy and incentive is a major driver of success and has been underappreciated in pharmaceutical companies; (iv) there needs to be a move away from advocacy mode to regularly question the value of all activities, with a willingness to make no-go decisions even if there are significant sunk costs; and (v) companies must engage independent scientific input on their overall research strategies and external investments. This peer review can no longer be a box check to make internal executives in large companies feel better about what they have, but must be a truly independent and diverse set of expert input that is embraced and used to drive decision-making.

If we accept these assumptions, which embrace learnings derived from past failures in the pharmaceutical industry, then surrogate measures may serve as 'pipeline value' leading indicators: (i) percentage of research spending used to fund external innovation through any of the above models. (ii) number of IP-generating external collaborations. This will need to be individualized based on the opportunities. For example, a collaboration with a promising platform-based organization versus one on an individual drug target might have different long-term value. (iii) percentage of research funds used for sourcing to enhance agility; (iv) percentage of research spend or number of investments made with venture or other equity partners. What better indicator of success is there than a shared investment? (v) number of pharma–pharma partnerships. (vi) quality measures, which include: (a) shift in pipelines toward innovative and differentiated mechanisms, exploiting new pathways and targets, rather than 'me too's'; (b) pipeline shifts toward compounds with clearer mechanistic hypotheses based on targets supported by human data (genetics, etc.); (c) decision-making as defined by No-Go experiments in early development based on quality hypothesis-driven experiments or predictive biomarker data and with the right questions being asked upfront (i.e., the 'fast-to-fail' approach).

These are only a few of the proxies that we believe can be leading indicators of value. As with any leading metric, there is the danger of 'managing the metric' rather than focusing on the fundamental long-term aim. As such, we also believe it is important to couple these metrics with additional assessments [23]: is our science materially improving? Are we making materially better decisions? Is our pipeline more robust on a per-unit basis than it was before? It can be easy to get lost in the plethora of deal constructs. Although there is value in exploring these different permutations, company management should always return to the guiding star: are we getting more bang (in human health or dollar return on investment terms) per dollar of R&D investment? To answer these questions honestly, objectivity and independent peer review are crucial.

Concluding remarks and future perspective

The pharmaceutical industry must and is undergoing sea change. A current and future driver of this change is external innovation. In recent years, the boundaries between pharmaceutical laboratories and those in academia and biotech have become more permeable. Numerous models are being developed to optimize the synergies and interface between these symbiotic groups. As pharmaceutical companies try to figure out how to tap external innovation, it is foreseeable that these new models will continue to evolve. Certainly, not all external R&D models will work. To be successful, these external innovation models will require fundamental modifications within industry: integration of external and internal R&D, cultural change, adjusted management behavior, financial restructuring, and more.

Diversified external innovation is the foundation of the future of healthcare. To ensure realization of the potential of external innovation and maximization of synergies, pharmaceutical companies will need to learn from past failures, become more adept at distinguishing hype from true promise, and adopt a more self-critical position. Significant care must be taken in designing the right internal metrics and incentives to drive the right behaviors regarding these partnerships. Clearly, harnessing innovation will be a major determinant of success in the pharmaceutical industry and for future healthcare. The question for the industry is not whether to embrace external innovation, but how.

Conflict of interest

L.W. is an employee of Merck & Co., Inc., and holds company equity; A.P. is an employee of Sanofi and holds company equity; M.R. is an employee of The Boston Consulting Group (BCG), a management consultancy that works with the world's leading biopharmaceutical companies on R&D productivity and external innovation.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drudis.2014.10.008.

References

1 Cuatrecasas, P. (2006) Drug discovery in jeopardy. *J. Clin. Invest.* 116, 2837–2842
2 Khanna, I. (2012) Drug discovery in pharmaceutical industry: productivity challenges and trends. *Drug Discov. Today* 17, 1088–1102
3 Scannell, J.W. *et al.* (2012) Diagnosing the decline in pharmaceutical R&D efficiency. *Nat. Rev. Drug Discov.* 11, 191–200
4 Sheridan, C. (2011) Industry continues dabbling with open innovation models. *Nat. Biotechnol.* 29, 1063–1065
5 Melese, T. *et al.* (2009) Open innovation networks between academia and industry: an imperative for breakthrough therapies. *Nat. Med.* 15, 502–507
6 Schuhmacher, A. *et al.* (2013) Models for open innovation in the pharmaceutical industry. *Drug Discov. Today* 18, 1133–1137
7 Perkmann, M. and Salter, A. (2012) How to create productive partnerships with universities. *MIT Sloan Manag. Rev.* http://sloanreview.mit.edu/article/how-to-create-productive-partnerships-with-universities/?use_credit=262f3d665f3ebe0bb7af2a1044ea9d23 Magazine: Summer 2012. Research Feature. June 18, 2012
8 Alvim-Gaston, M. *et al.* (2014) Open Innovation Drug Discovery (OIDD): a potential path to novel therapeutic chemical space. *Curr. Top. Med. Chem.* 14, 294–303
9 Boudreau, K.J. and Lakhani, K.R. (2013) Using the crowd as an innovation partner. *Harv. Bus. Rev.* 91, 60–69
10 Lou, K-J. (2011) Translational biology with a clinical mindset. SciBX http://dx.doi.org/10.1038/scibx.2011.475
11 Workman, P. (2014) Academia and industry: successes for UK cancer partnership. *Nature* 510, 218
12 Hayden, E.C. (2014) Universities seek to boost industry partnerships. *Nature* 509, 146
13 Frye, S. *et al.* (2011) US academic drug discovery. *Nat. Rev. Drug Discov.* 10, 409–410
14 Tralau-Stewart, C. *et al.* (2014) UK academic drug discovery. *Nat. Rev. Drug Discov.* 13, 15–16
15 Mullard, A. (2014) Built-to-buy start-ups begin to bloom. *Nat. Rev. Drug Discov.* 13, 161–162
16 Zerhouni, E.A. (2014) Turning the Titanic. *Sci. Translat. Med.* 6 221ed2
17 Schulze, U. and Ringel, M. (2013) What matters most in commercial success: first-in-class or best-in-class? *Nat. Rev. Drug Discov.* 12, 419–420
18 Mullard, A. (2011) Partnering between pharma peers on the rise. *Nat. Rev. Drug Discov.* 10, 561–562
19 Mullard, A. (2014) Drug makers and NIH team up to find and validate targets. *Nat. Rev. Drug Discov.* 13, 241–243
20 de Vrueh, R.L. *et al.* (2014) Deal watch: roles and strategies for health foundations in public–private partnerships. *Nat. Rev. Drug Discov.* 13, 406
21 Tufts CSDD Impact Report (2013) Biotech products in Big Pharma clinical pipelines have grown dramatically. Tufts Center for the Study of Drug Development Impact Report, Vol. 15.
22 Anon (2014) Big thinkers diverge. *BioCentury* 22, 1–7
23 Ringel, M. *et al.* (2013) Does size matter in R&D productivity? If not, what does?. *Nat. Rev. Drug Discov.* 12, 901–902