OUTLOOK

Success in translational research: lessons from the development of bortezomib

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Abstract | The high price of many innovative drugs, which is in part due to the considerable expense and risk involved in drug development, underlines the need for more efficient approaches to bring drugs to the market, with more effective translational research in particular identified as an important part of such strategies. Here, the development of the cancer drug bortezomib (Velcade; Millennium Pharmaceuticals) by a biotechnology company — Myogenics/ProScript — started by academics from Harvard University is discussed to dissect the key academia–industry/public sector–private sector interactions that made the development of this drug a success despite many barriers. A model to explain how and why bortezomib was approved in record time is presented, and areas for public-policy initiatives to improve translational research in general are highlighted.

> "Be like the cliff against which the waves continually break, but which stands firm and tames the fury of the water around it."
>
> *Emperor Marcus Aurelius – Meditationes, Book Four, circa 170 A.D.*

The success of translational research is not only a function of the quality of the science, but also of the collaboration between academia and industry, the organization and management of research and development (R&D), the public policies that regulate scientific research and the connections among the key people involved. With the aim of understanding the key factors underlying success in translational research, this article focuses on the development of bortezomib (Velcade; Millennium Pharmaceuticals), an innovative anticancer drug created by Myogenics — a company started by academics from Harvard University — for the treatment of multiple myeloma. Myogenics was renamed ProScript and subsequently acquired by LeukoSite, which in turn was acquired by Millennium.

Cancer is the second-leading cause of death in the United States after heart disease, and the amount of funding for cancer research — public and private — is higher than for any other disease[1–3]. However, despite private and public efforts, the process of bringing effective cancer drugs to the market still faces many challenges. So, anticancer research and drug development provides an excellent illustration of the relationships and interactions between: basic, applied and translational research (BOX 1); academia and industry; and public and private funding. The analysis here focuses on the route leading to the proof-of-principle of the therapeutic potential of bortezomib in humans to probe the key interactions between early-stage academic biotechnology spin-off companies, academia, industry, government agencies, public and private investors, and advocacy groups.

Translational research

Translational research is particularly interesting because it gains from and provides valuable information to both basic and applied research (BOX 1). In addition, translational research has the potential to promote the creation of potential therapeutics that are riper for commercialization, thereby decreasing subsequent economic risks (due to possible failure) and development costs.

Although a great deal of federal funding is provided for basic research, there is a funding gap, at least in academia, for translational research, and especially for clinical trials. So there could be a significant number of projects and potential drugs that have shown promise in preclinical studies that are languishing in academic settings because of the lack of adequate funding to take them into the clinic. (For a more thorough listing of project areas that might inform about a gap in funding for translational research, see the Rapid Access to Intervention Development (RAID) website in Further information, and for discussion of the Developmental Therapeutics Program at the National Cancer Institute (NCI), see REF. 4.) In many cases, these drugs might not be taken up by pharmaceutical or biotechnology companies because they are not economically or strategically viable, or simply because they neither target large markets nor promise high returns. However, initial approval for smaller markets, while providing benefits to patients, could open the doors for later approvals in larger, and therefore more profitable, markets and provide the necessary validation for 'first-in-class' drugs that can be used in several other medical applications. Moreover, trials funded by smaller biotechnology companies could potentially be carried out more effectively if additional funding for translational studies were available. Realistically, small biotechnology companies can barely afford to develop one or two products at the same time, and additional basic or translational research cannot be carried out without the risk of running out of funds before subsequent rounds of funding (BOX 2, note 1). It is therefore important to understand the obstacles encountered in translational research today, and whether there are adequate incentives to invest or participate in it.

The Bayh–Dole Act of 1980 entitles US universities to the intellectual property rights of discoveries made using federal funding. The rationale behind this act was to increase patenting of discoveries and the acceleration of economic growth through the creation of 'high-tech' firms that license these technologies from the university.

Box 1 | **Basic, translational and applied research**

The definitions used to describe the biological research that is carried out in the domains of universities and companies vary widely. In this article, basic research is defined as the activity concerned primarily with the elucidation of the biological mechanisms and physico-chemical processes of living organisms, irrespective of whether the findings of this research may eventually have potential therapeutic applications. The term translational research is used to refer to the translation of findings from the 'bench to the bedside'; that is, translational research takes basic and preclinical findings and moves them into humans. Applied research is used to illustrate the development of commercial therapeutic applications, as related to health-care interventions, with the objective of creating health, financial and social benefits.

However, licensing these technologies does not necessarily mean that more funding has been channelled into their translation into commercial products (see REF. 5 for a description of the impact of the Bayh–Dole Act). In addition, although the involvement of academic scientists in translational research and entrepreneurial activities might be more evident, even fostered, in areas such as biotechnology and high-tech 'clusters', these clusters are exceptions; their formation is a complex, expensive and lengthy process and their impact on economic acceleration and growth is unknown, or, at least, not easily measurable. In many respects, the participation of academic scientists in the United States and Europe in commercial activities could still be seen as a distraction or deviation from their academic duties, and many academic scientists prefer not to leave university circles to pursue opportunities as entrepreneurs because of the risks involved, economic and otherwise.

Intellectual property rights, although doubtless necessary, can also be an impediment to the process of translating basic science into commercial products. Of course, most companies and investors will not finance translational science and develop drugs without a strong intellectual property position to protect their investment. But after collaboration conversations have started, the terms and conditions of the licensing and technology transfer agreements can often reach absurd levels for either or both parties, and interesting and highly viable projects can reach an impasse, slowing down the translational process. Indeed, there is a perception among people working in academic biotechnology spin-off companies that a significant number of the obstacles that they encounter come from the universities themselves, especially when dealing with issues related to ownership and economic dividends.

So, how did bortezomib, a first-in-class drug that originated from an academic biotechnology spin-off, make it to market so rapidly? This is a particularly interesting question considering the fragile funding base of its originator, the considerable obstacles (internal and external) encountered and the risks involved in pursuing a new molecular target — the proteasome — with a new and ill-famed class of inhibitor (boronates; BOX 2, note 2).

Properties of bortezomib

Bortezomib (also known as MG-341/PS-341/LDP-341/ML-341) is a first-in-class proteasome inhibitor for the treatment of multiple myeloma, an incurable cancer of the blood (BOX 2, note 3). The proteasome is a hollow and cylindrical enzymatic complex that is present in both the cytoplasm and the nucleus of all eukaryotic cells and is necessary for the degradation of >80% of the cell's proteins. This is an important step in the regulation of other cellular functions, including signal transduction pathways that regulate cell growth and proliferation (see REFS 6,7 for reviews on the proteasome and REF. 8 for a review on its potential as an anticancer target).

In blocking the proteasome's catalytic active site, bortezomib inhibits an important cellular mechanism that regulates the cell cycle through the activation of nuclear factor-κB (NF-κB)[8–10] (FIG. 1). Preventing NF-κB activation leads to apoptosis and renders malignant cells more vulnerable to chemotherapy and radiation[8]. Although not a cure for multiple myeloma, bortezomib has had significant effects in prolonging the life of patients who had received at least two prior therapies and demonstrated disease progression on the last therapy[11,12] (see Multiple Myeloma Research Foundation website in Further information). Below is a short and simplified account of how this drug came to the market.

> How did bortezomib, a first-in-class drug that originated from an academic biotechnology spin-off, make it to market so rapidly?

Discovery and development of bortezomib

In 1992, Alfred Goldberg decided to use the growing basic knowledge on the proteasome to create a biotechnology company focused on one goal: using inhibitors to block the proteasome, with the aims of investigating the physiological roles of the proteasome and translating basic proteasome research into a therapeutic application (the history of proteasome research is far too extensive for this article; see REF. 13 for a description of the history and key players). The company, Myogenics, was founded in 1993, and its initial objective was to target the ubiquitin–proteasome pathway to slow down the process of muscle wasting (cachexia) associated with fast protein degradation.

To create the company, Goldberg formed partnerships with two scientists at Harvard: Kenneth Rock, an immunologist and pathologist who had collaborated with Goldberg on studies of proteasome and antigen presentation; and Michael Rosenblatt, who brought a wealth of experience in drug development. Tom Maniatis, co-discoverer of the NF-κB pathway, who collaborated with Goldberg on gene transcription linked to the proteasome[9], subsequently also joined.

In 1993, the company hired its first Chief Executive Officer (CEO), Frans Stassen, who came from Ciba-Geigy and had significant experience in drug development. A team of enzymologists (led by Ross Stein, who came from Merck) was also employed, and created the first inhibitors of the proteasome, which would eventually lead to bortezomib: peptide aldehyde analogues of the favoured substrates of the proteasome's chymotrypsin-like active site[14]. These inhibitors (such as MG-132, which is still widely used in basic research) were distributed freely to many academic researchers. Next, Julian Adams (who was hired from Boehringer as Head Chemist, and who later became Executive Vice President of R&D) and the team of chemists that he led used, between 1994 and 1995, a straightforward medicinal chemistry approach to create a dipeptide boronate named MG-341, later known as bortezomib (REF. 15), and other inhibitors (for example, MG-519/PS-519).

An important characteristic of Myogenics was its extremely close collaboration with academia, in which important scientific knowledge on the proteasome and the pathways involved in inflammation and apoptosis was quickly created through productive partnerships between several of the founders at Harvard and the scientists within the company. For example, the first

Box 2 | **Additional notes**

- Note 1: the example of bortezomib clearly indicates the value of a company's 'translational' investment in assays relevant to clinical development. The scientists working for Peter Elliott and Julian Adams validated an assay for peripheral blood mononuclear cell proteasome activity and its modulation by bortezomib that crucially influenced the selection of the clinical schedule and allowed a tight dose-escalation scheme, leading to a highly efficient Phase I programme. This should be highlighted as evidence favouring investment by drug companies in this type of assay, particularly for 'first-in-class' agents such as bortezomib.
- Note 2: the history of boronates as pharmaceutical agents is interesting. They were initially developed as serine-protease inhibitors by Dupont/Merck. However, the original compound failed in Phase II clinical trials as a treatment for emphysema, and so boronates acquired a bad reputation among medicinal chemists. Adams's team linked a boronate group to Myogenics lead compounds, which showed considerably increased efficacy against the proteasome, and so created a novel chemotype.
- Note 3: multiple myeloma is predominantly a disease of the bone marrow and is the second most common cancer of the blood (representing 1% of all cancers and 2% of all cancer deaths). It is estimated that in the United States alone there are 40,000–50,000 people with multiple myeloma, and 14,000 patients develop the disease annually. The average life expectancy of these patients is ~4.3 years (see the Multiple Myeloma Research Foundation website in Further information).
- Note 4: agreement reached for up to US$38 million from Hoechst Marion Roussel, plus royalties paid to ProScript on sales of products deriving from this partnership; http://www.archive.hoechst.com/deutsch/news/95/019_95.html.
- Note 5: US$20 million in equity investment from Roche Group to ProScript, plus royalties on sales of products resulting from this collaboration; http://www.prwire.com/cgi-bin/stories.pl?ACCT=105&STORY=/www/story/38582.
- Note 6: from a business point of view, it must be stressed that although the conclusion to focus on cancer was influenced by these results, bortezomib was first developed as an anti-inflammatory agent and was licensed to Hoechst Marion Roussel (HMR) for that purpose (arthritis). The decision to pursue cancer as a business model was a fall-back position because HMR chose to focus upstream of the proteasome in inflammation. Ultimately, HMR dropped proteasome inhibitors for inflammation and cancer, and returned its license rights on the drug to ProScript.

inhibitors created by the company were immediately tested on cells in the laboratories of Goldberg and Rock, and this research afforded insights into the effect of proteasome inhibition on inflammation.

One of the initial key findings from the laboratories of Rock and Goldberg was that blocking the proteasome *in vivo* did not immediately alter the normal life cycle of the cell[13]. Ensuing studies carried out in collaboration between Goldberg and Maniatis's laboratory at Harvard — such as the discovery by Vito Palombella and colleagues that the proteasome is very important in the activation of NF-κB[9], which is in turn involved in the inflammatory response (reviewed in REF. 16) — led to a change of focus in the company: from muscle wasting to inflammation (and a corresponding change in company name, from Myogenics to ProScript). In August 1994, Avram Hershko suggested to Adams that the company investigate cancer as a potential disease target (J. Adams, personal communication), and investigations carried out by the company scientists showed that the proteasome inhibitors blocked the proliferation of cancer cells *in vitro* (bearing in mind the role of NF-κB in gene regulation). This strongly increased the interest of the company in cancer, although it continued to focus on inflammation.

At this time, there was considerable tension between the founders, the company scientists and the Scientific Advisory Board (SAB) owing to differences in opinion on the direction and strategies that the company should pursue — muscle wasting, inflammation or cancer. A step forward in the cancer direction was the establishment of a collaboration between ProScript and Beverly Teicher from the Dana–Farber Cancer Institute (DFCI). Teicher was introduced to the company by Bruce Zetter (Harvard), who had been, in turn, introduced by Goldberg to the company as an SAB member. The group at ProScript then initiated their first proof-of-concept study in cancer in collaboration with Teicher in 1995. At this time, Teicher was studying angiogenesis and the role of toxic agents (such as alkylating agents) in cancer cells and provided ProScript with the first tumour mice models. By 1997, the group had shown that bortezomib (known as PS-341 at the time) inhibits tumour growth and metastasis in a mouse model of lung cancer; the results were published in 1999 (REF. 17). However, there was considerable scepticism about the drug based on what was considered its potential toxicity in humans.

In addition, Adams, through Maniatis, met David Livingston, a leading figure in the mechanistic field of oncology, and subsequently asked him to join ProScript's SAB. Livingston's role was crucial in steering the company to thought leaders in the cancer field, such as Kenneth Anderson from DFCI. At the end of 1995, ProScript established a collaboration agreement with Hoechst Marion Roussel (HMR) to develop orally active anti-inflammatory and anticancer agents based on ProScript's ubiquitin–proteasome inhibition technology (BOX 2, note 4). One year later the company signed a drug discovery/development collaboration with Hoffmann-La Roche (Nippon Roche) on compounds to treat cachexia (BOX 2, note 5). These important collaborations were secured by ProScript's second CEO, Richard Bagley, who was crucial not only in establishing these collaborations but also in further negotiations between ProScript and these companies, including the recovery of rights related to proteasome inhibitors from HMR.

Between 1996 and 1997, ProScript approached the NCI with a view to collaborating. The NCI was interested in looking for new chemotherapeutic agents and had a large collection of cell lines in which bortezomib could be tested. This was a direct collaboration with Edward Sausville, Head of the Developmental Therapeutics Program (DTP) at NCI and Chair of the NCI Decision Network (the body that makes decisions on the commitment of NCI funds to new drug development initiatives arising either from NCI or from outside) and his team. After this collaboration and the initial data that resulted from it, the company started to focus increasingly on cancer, although it also continued to pursue inflammation (BOX 2, note 6).

Through 1997, ProScript continued to collect animal data and established collaborations with several academic researchers (for example, see REF. 18), among them Christopher Logothetis, Chairman of Genitourinary Oncology at the MD Anderson Cancer Center (MDACC). Logothetis was introduced to ProScript by David McConkey (MDACC) and was invaluable early on in the progression of ProScript's clinical trials in cancer (P. Elliott, personal communication). Through Logothetis, ProScript met Howard Soule, Chief of Science Officer at CaP Cure (now the Prostate Cancer Foundation).

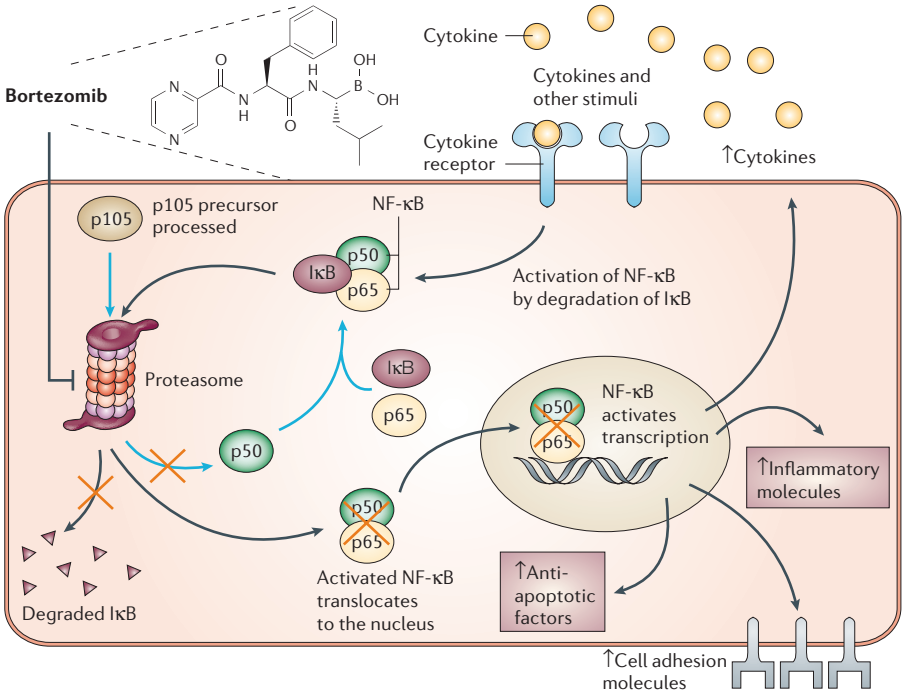

Figure 1 | **The proteasome, nuclear factor-κB and bortezomib.** The proteasome is a barrel-shaped multiprotein particle that destroys proteins that have been marked for degradation by conjugation to ubiquitin. Binding of the transcription factor nuclear factor-κB (NF-κB) to the inhibitor protein IκB in the cytoplasm renders NF-κB inactive. Cellular stimuli, such as cytokines, antigens, oxidants, viruses and other agents, trigger a cascade of signal transduction events that phosphorylate and ubiquitinate IκB, leading to its degradation by the proteasome, which in turn liberates NF-κB for translocation into the nucleus. Once in the nucleus, NF-κB binds to the promoter regions of genes coding for proteins that are involved in the activation of transcription, growth, angiogenesis, anti-apoptotic factors and cell-adhesion molecules. By inhibiting the proteasome, bortezomib inhibits the activation of NF-κB (orange crosses) and subsequent events that can promote tumour cell survival and proliferation.

After encouraging results from the NCI and animal studies carried out by the pharmacology group led by Elliott at ProScript[19], the company won unanimous approval and funding from the NCI, CaP Cure and two academic institutions, the Memorial Sloan Kettering Cancer Center (MSKCC) and the University of North Carolina (UNC), to conduct Phase I clinical trials with bortezomib. After successful initiation of the Phase I trial at MDACC, two additional trials were started. The first was at MSKCC with David Spriggs and the second was with Robert Orlowski at UNC, who was introduced to the company by James Cusack (UNC) and Albert Baldwin (UNC). Both trials were funded by the individual institutions, which shows that it is possible to find external funding for trials of promising drugs and thereby avoid rapid depletion of the limited resources of a small biotechnology company. The trial at UNC focused on haematological malignancies and it was this trial that showed (in 2000) that bortezomib was active in multiple myeloma[20] (BOX 3, note 1).

Although bortezomib worked exceptionally well in animal models of inflammation, especially rheumatoid arthritis, ProScript realized that the therapeutic index was not large enough for chronic administration. Moreover, despite promising progress in cancer, such as the initiation of Phase I trials, ProScript's funds were almost depleted by June 1999. The company had received its initial funding from HealthCare Investment Corporation, which was the leading investor (Dillon Read Venture Capital acted as co-investor). ProScript was unable to secure subsequent funding for several reasons, including the pioneering nature of their technology, and because targeting the proteasomal apparatus with a drug that was considered to be too toxic was viewed as too risky, especially when taking into account the cost of the ensuing clinical trials. In addition, from a venture capital point of view, there were no suitable comparable drugs whose success could be used to provide support for taking further risks. The fact that HMR, during restructuring to form Aventis, dropped proteasome inhibitors exacerbated the negative feeling about further investment in the company.

So, ProScript, like many other small biotechnology firms, fell victim to the financial market psychology of the moment and, faced by a funding shortage, reduced its staff and SAB. Adams, who had become bortezomib's champion, and the ProScript team made many efforts to promote the drug and establish collaborations with more than 50 companies, all of which declined the drug. Eventually, HealthCare Ventures decided to incorporate ProScript into another of their portfolio firms, Cambridge-based LeukoSite. The company team, together with some private investors, tried to buy the drug from HealthCare Ventures for US$2.4 million in cash (J. Adams, personal communication). But, in July 1999, ProScript was sold to LeukoSite for US$2.7 million (~187,000 newly issued shares of LeukoSite's common stock valued at US$2.3 million and US$430,000 in cash)[21].

Three months later, Millennium bought LeukoSite for US$635 million because it was interested in LeukoSite's pipeline, especially CamPath (which also made it to the market), but had no interest in bortezomib[22]. Unsurprisingly, passing from company to company created a major disruption to the bortezomib project. However, the ProScript team did not give up. Adams had regular meetings with Mark Levin, CEO at Millennium, to persuade him to keep the project alive and provide the necessary funding. In August 2000, the UNC clinical trial (that started in 1999 (REF. 20)) demonstrated that bortezomib erased all signs of cancer from a 47-year-old woman, who months before was in the advanced stages of multiple myeloma. Given this data, Millennium decided to make bortezomib Millennium's most funded drug (ML-341), and Adams and others from ProScript quickly assumed leadership roles at Millennium.

Adams's group decided to team up with Anderson, a multiple myeloma expert, and his group at the DFCI (specifically Paul Richardson and Teru Hideshima) to conduct Phase II clinical trials at the institute. Consequently, there was an exchange of results and ideas back and forth between Millennium and Anderson and colleagues to discover more about the molecular mechanisms that made multiple myeloma more susceptible to bortezomib. At Millennium, David Schenkein, Dixie Esseltine, Barry Greene, Michael Kauffman and others, had important roles in this process. This translational process was accomplished through the

following stages: basic research → clinical settings → patients' feedback → return to basic research to gain further understanding of the molecular mechanisms involved (BOX 3, note 2). In addition, through Anderson, Adams established contact with the Multiple Myeloma Research Foundation and the International Myeloma Fund (two advocacy groups that provide information and support to multiple myeloma patients and their relatives) that strongly supported the cause of bortezomib.

After the conclusion of Phase II clinical trials[11], bortezomib was approved in record time on May 13 2003 by the US FDA under a Fast-Track Application (BOX 2, note 3) as an injectable small molecule for the treatment of multiple myeloma. Millennium continued Phase III clinical trials and carried out the marketing of the drug.

Lessons learned: the 'core model'

The way in which Myogenics/ProScript established several important collaborations with outside academics and agency/advocacy groups to move bortezomib forward was unusual. Although some companies form such kinds of collaborations in their programmes, Myogenics/ProScript did this exceptionally well and systematically, and so particularly benefited from these collaborations at crucial points, both when the company needed scientific knowledge to move forward and when it lacked the necessary economic resources. The example of bortezomib emphasizes the potential power of maximizing such collaborative approaches and is useful in providing insights to policy makers, scientists, investors and the public on how the process of drug development can be optimized.

Bortezomib, despite being a first-in-class drug that could have been shelved many times, managed not only to reach the market but also to do so extremely quickly, which is in contrast to many well-funded efforts in industry. Here, I propose that this can be explained using a 'Core Model' (FIG. 2), which defines and structures the roles and bi-directional interactions of the parties involved in the process of drug development.

In the development of bortezomib, the core model could be described as follows (BOX 3, note 4). The 'core' is represented by internal people and resources such as Goldberg, Maniatis, Rock, Rosenblatt, Adams, Elliott, Palombella, managers, other internal scientists and private investors. The 'bridge' is represented by immediate collaborators, such as Teicher, Sausville, Logothetis, Soule, Spriggs, Orlowski, Anderson, members of the various SABs, Millennium and so on, and other private companies (via the simultaneous non-exclusive collaboration with external scientists or via non-exclusive SAB members that work simultaneously with these types of company; BOX 3, note 5). The 'periphery' is represented by CaP Cure, the Multiple Myeloma Research Foundation, the International Myeloma Fund, MSKCC, DFCI, NCI, MDACC, UNC, FDA and so on (see Supplementary information S1 (table)).

Communications with the periphery were established through individual people involved. These players traded assets (that is, materials, animal models, knowledge, connections), and in doing so advanced each other's research. Examination of their publications before, during and after the use of the first-generation inhibitors (such as MG-132 or lactacystin) and bortezomib reveals that the study of these drugs led to a better understanding of their mechanisms of action. The fact that the company decided to distribute bortezomib to outside researchers (BOX 3, note 6), especially when it reached a high level of economic distress, was not risk free. For example, the company took the risk that outside collaborators would have patented discoveries that, even if not valid or dominated by company patents, could have hindered the company. Although sharing the drug with outside

Box 3 | **Additional notes**

- Note 1: the actual timetable of events is as follows: National Cancer Institute (NCI) clinical candidate (Decision Network stage III; DN III) NCI approves funding for clinical trials on 8 June 1998. MD Anderson Cancer Center starts first trial on 7 October 1998. Memorial Sloan Kettering Cancer Center starts a second trial on 15 February 1999. New York University starts a third trial (using NCI funding) on 26 July 1999. The University of North Carolina starts fourth trial on 8 November 1999 (P. Elliott, personal communication).
- Note 2: Adams in an interview in *Myeloma Today* (Autumn 2002, UK; http://www.myeloma.org/myeloma/newsletter.jsp?type=detail&id=1029). Besides the Dana–Farber Cancer Institute, there were collaborations with other hospitals and academic institutions at the same time.
- Note 3: Millennium was granted 'Fast Track Status' by the FDA in June 2002. Millennium filed a New Drug Application for bortezomib (Velcade; Millennium Pharmaceuticals) on 21 January 2003 under the provisions of Subpart H Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses. On 10 March 2003, the FDA accepted the application and granted Priority Review Status. On 13 May 2003, bortezomib was approved under Fast-Track Status (http://investor.millennium.com/phoenix.zhtml?c=80159&p=irol-newsArticle&ID=411937&highlight=). Bortezomib generated revenues for Millennium of US$59.6 million in 2003, *Millenium Annual Report 2003*, Form 10-K, p1 (http://media.corporate-ir.net/media_files/irol/80/80159/reports/ar03.pdf). In 2004, bortezomib had net product sales of US$143 million, *Millenium Annual Report 2004*, Form 10-K, p1 (http://library.corporate-ir.net/library/80/801/80159/items/144438/MLNM_80159_AR_033105.pdf).
- Note 4: key people that interacted before and after the LeukoSite/Millennium acquisitions are included because the 'core' never disintegrated, although legally ProScript had become part of LeukoSite and then Millennium and several of its original members were no longer present. By the time ProScript was sold out, the company had already gained so much influence and momentum with its science and the establishment of a tight network interaction with the 'bridge' and the 'periphery', that even within Millennium it continued to exercise powerful 'centripetal' influence. For example, the key Phase I clinical trial at the University of North Carolina, which showed safety and efficacy of bortezomib in humans, was planned and coordinated before the acquisitions took place. In addition, Phase II key people, such as Kenneth Anderson — who helped attract the Multiple Myeloma Research Foundation and the International Myeloma Fund — had already been contacted years before by Adams and colleagues, as suggested by David Livingston.
- Note 5: when collaborating with people in a non-exclusive way, parties may have a deep knowledge of what is happening in a specific field, but this is not intended to imply that there will be 'leakage of information'. By contrast, these collaborations could be extremely fruitful because they could help avoid unproductive paths and suggest new perspectives.
- Note 6: the company distributed bortezomib from early on, and the group has continued to do so, because the company did not have the resources to carry out all the studies, and high-profile academic groups gave the drug more credibility. (P. Elliott, personal communication).
- Note 7: From a broader perspective, the 'Core Model' also has important implications for economic growth. It has been proposed that it is the state of technology that drives economic development[25]. However, the present study on biomedical research is rooted in my firm conviction that it is trade (in this case of assets — knowledge and technology) and not the state of technology itself that drives economic growth. The 'Core Model' explains how and why, and it could be generalized and used in other fields.

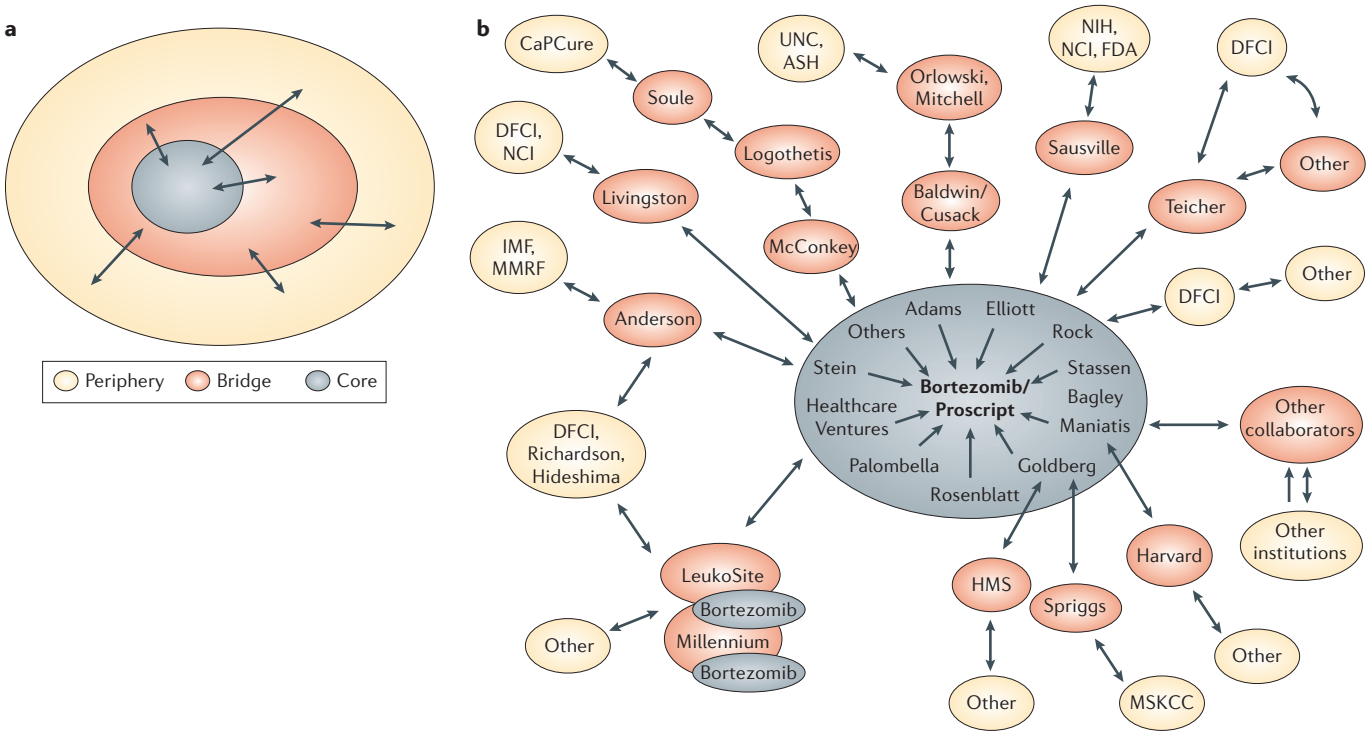

Figure 2 | **The 'Core Model'. a** | This model has three major elements: the 'core', the 'bridge' and the 'periphery'. In a biotechnology startup company, the core represents the company's internal resources and people, who are hired because they have assets that are directly related to the core's objective — making drugs. The core needs a strong leader who is capable of keeping the enterprise focused and is able to secure collaboration with external people. The ideas of the core are protected by patenting and secrecy. The bridge represents the immediate collaborators of the core and the private institutions to which the core has indirect access through the external collaborators. The bridge contains external scientists interested in similar problems or whose research would be enriched as a result of the collaboration. It also includes consultants and Scientific Advisory Board (SAB) members (non-founders) working in exclusive and non-exclusive ways. The periphery contains the institutions/agencies interested in what the core has to offer for the benefit of society, as well as the funding and regulatory structures that support the core and the bridge. The periphery is an open, public and cooperative system. The goal of the core is to absorb efficiently and legally as much relevant knowledge and information as possible from its surroundings in three ways: via the leverage of the assets, professional backgrounds and connections of the people within the core; via the assets, connections and expertise of the external collaborators within the bridge; and via the support, relevant public knowledge and know-how within the periphery. **b** | Illustration of the roles of selected people involved in the development of bortezomib using the core model.

scientists could have led to a tremendous loss of potential revenues for the company, it opened crucial doors that eventually led to bortezomib reaching the market. FIGURE 2b shows how the key people involved interacted within the 'Core Model' framework.

Although the science behind the development of bortezomib 'worked', many people (including well-established companies) did not believe in bortezomib's commercial potential and rejected it, considering the drug to be too toxic, or the market too small. However, bortezomib is marketed today for several reasons. First, the Myogenics/ProScript 'core' had an outstanding, although small, scientific staff that made a number of highly influential basic discoveries, and the initial inhibitors discovered were distributed for free to academic investigators, which led to rapid acquisition of knowledge on their effect in the cell. Second, the collaborations established through the 'bridge' accelerated the generation of knowledge necessary for speedy approval. Third, once at Millennium, ProScript's team rapidly secured valuable resources from Millennium for additional clinical trials and marketing. Fourth, ProScript's core used public resources within the 'periphery' very efficiently (for example, NCI, cancer advocacy groups and the hospitals carrying out the clinical trials). In summary, ProScript developed bortezomib through a 'Core' *modus operandi* using knowledge transfer (collaboration established with external people to exchange assets), knowledge integration (incorporation and assimilation of external assets) and knowledge translation (the conversion of all, internal and external, assets into a commercial therapeutic product).

Bortezomib would not have been successful in a large pharmaceutical company, as ProScript used a strategy that differed considerably from that taken by most such companies, which generally keep assets within the company. Proscript engaged and used the biology at every turn and made a convincing case for the drug, and so obtained support from the public sector at a crucial juncture. The interest in bortezomib from the NCI was unusual: the NCI was going to pursue the molecule even if private funding was not forthcoming because of the drug's unique biological effects. Unlike many biotechnology startups or middle- or late-stage companies, ProScript was not solely focused on economic profits — it initially concentrated on a small and narrowly focused indication, rather than 'holding out' for a more lucrative but scientifically less supportable indication. The company prominently engaged the patient advocacy community (CaP Cure) when starting the first Phase I clinical trials, and when the time came to recruit patients for definitive clinical trials ProScript's 'core' was key in involving the Multiple Myeloma Research Foundation and the International Myeloma Fund.

New academia–industry perspectives

The relationship between academia and industry is generally perceived as being unidirectional, with basic science being translated into applied science. There is also the perception that in the academia–industry relationship, academia is exploited without receiving adequate benefits. However, on close examination, it becomes clear that many scientists see translational research as a legitimate academic activity and that the academia–industry relationship is bidirectional. For example, academic research is stimulated by the questions that industry generates, which usually fall outside the scope, capabilities and economic interests of the companies. Indeed, it could be suggested that the process of academia producing ideas that are translated into commercial products is cyclical; academia provides answers to the questions created by new commercial products that, in turn, could lead to more commercial products. Although there is secrecy and proprietary knowledge in the process of developing a drug, once the drug is marketed, the mechanisms involved in targeting the disease become public knowledge, resulting in more questions that could be investigated by academia.

Considerations related to conflicts of interest and the pharmaceutical industry benefiting from public investment in research have generated debate about the nature of the interactions between industry and academic/public institutions and researchers and the propriety of such interactions. One of the important points emphasized by the 'Core Model' is that these interactions are bidirectional in ways that benefit all parties and science in general, as well as providing society with new medicines. Such benefits are often missing from the debate.

In the case of bortezomib, scientists worked back and forth between academia and industry. The problems in the clinic gave rise to more research in the private sector and vice-versa. This type of interaction allowed the science to be integrally linked to the clinical studies, and, in turn, the clinical studies to drive the science. It was a synergistic interaction that has the potential, as illustrated here, to correct directions that will not be productive. The transfer of knowledge between academia and industry enabled a better understanding of multiple myeloma, of bortezomib's mode of action and the mechanism by which the proteasome is related to other key pathways that regulate the cell cycle. Indeed, there has been an explosive interest in the proteasome and its role not only in cancer but also in other diseases. Many investigators are seeing bortezomib's antitumour effects in other types of cancer and other agents created by Myogenics/ProScript are currently in clinical trials (such as PS-519, which is now known as ML-519). Second-generation drugs have been developed in different laboratories and are awaiting funding to enter clinical trials.

In summary, academia has one characteristic that is particularly important to industry: it creates 'full-stories' in terms of how living organisms work. Academia is a dynamic and open system that allows for the rapid interchange of information among people from all over the world. This constant flow of people and ideas enriches scientific research and promotes progress. In other words, economic and social progress is achieved through a trade of assets and knowledge (BOX 3, note 7).

Improving translational research

In a recent book[13], Goldberg reached, among others, the following conclusion: "The paths to scientific progress are often unpredictable. I certainly never anticipated in studying the mechanisms of muscle wasting or the selective degradation of abnormal proteins in *E. coli* that this work might somehow lead to the discovery of the proteasomal apparatus, or that this finding would, in turn, lead to insights about immune surveillance or even indirectly to novel therapies for cancer. In fact, had we ever suggested in a grant proposal that this research program might have such benefits, every granting agency or study selection would have rejected such statements as fantasy, nonsense, or pure hogwash. It would be good if the lessons clearly illustrated by the development of proteasome inhibitors were appreciated by governmental, private, and industrial offices that decide on research policies." This conclusion is in complete synchrony with the scope and purpose of this article on translational research.

At the centre of a discussion on translational research is the crucial question: if more funding is to be allocated to the research that will bring drugs from academic labs to the bedside, who is going to provide it? One relevant issue to the cost and difficulties of drug development in general is the frequency and risk of failure of drug candidates, not to mention the cost of carrying out the clinical trials. The majority of potential drugs fail at varying points along the development path, often after major investments. Failures are costly to the pharmaceutical and biotechnology industry, and, in the 'Core Model', to the core as well as the periphery (for example, advocacy groups have limited resources). The amount of funding that is allocated annually by the government is not enough to sustain progress in translational research, let alone to create the appropriate economic incentives to attract students, technicians, post-docs and professors[23]. Moreover, the private sector sees no incentives to invest in research that is not necessarily related to their drug portfolio or that does not promise significant returns. So, the burden has fallen on private investors and venture capitalists, whose disillusion about the biotechnology business is well known.

> "The establishment of more academia-based translational research centres would have a major impact on bringing drugs to the market more efficiently."

Overall, the bortezomib story and the Core Model highlight the type of public and private interactions that accelerate the process of translational research. On the basis of this, there are several areas of focus for public policy initiatives that could contribute to bringing drugs to the market more rapidly.

First, the amount of federal and industrial funding that goes into translational research in academia (including clinical trials) could be increased. Companies might then spin-off from universities at a point at which the technologies would be more ready for commercialization, hence increasing chances of success and reducing the risk of subsequent investment. Indeed, the establishment of more academia-based translational research centres would have a major impact on bringing drugs to the market more efficiently. This approach would make better use of the basic research carried out in academia as well as other resources available at university settings, including a diverse and highly qualified personnel, animal facilities and expensive instrumentation. This would save both time, especially in terms of intellectual property rights and other legal issues, and money, in terms of materials, equipment and salaries in non-necessary personnel, including SAB members and consultants[24].

Second, encouraging better collaboration between academia and pharmaceutical and biotechnology companies could help to bring drugs to market more rapidly.

This should be done in such a way that the research from one partner, although self-interested, complements that of the other(s), especially in areas involving 'first-in-class' agents for which no 'validation' exists. The technology transfer/intellectual property issues within and across these sectors need to be optimized so that they do not become a hindrance to collaboration. Internal institutional IP legal paperwork (even for Material Transfer Agreements; MTAs) could be seriously delaying research collaborations. The establishment of partnerships with smaller biotechnology companies that cannot afford the costs of clinical trials, marketing and manufacture should encompass those areas that fill a gap in the pharmaceutical company's portfolio, as well as in areas that promise a new therapeutic agent, even if applied to smaller markets.

Third, the relationship between the NIH, FDA and start-ups should be improved. For spin-off companies in the cancer field, working closely with the NIH and NCI could help them considerably in designing better clinical trials, potentially enhancing the probability of FDA approval. In addition, reducing heavy regulation and paperwork that at times become an obstacle in translational research in oncology could be of benefit, as could increasing the speed of implementation of new NIH, NCI and FDA initiatives at these agencies.

Finally, more involvement of the public, advocacy groups and private foundations in the drug development process should be promoted through educational programmes. Advocacy groups can be important when recruiting patient populations for clinical trials and can have a considerable impact on the drug-approval process at the FDA level. The public needs to consider that it is part of the drug development process and not simply a passive consumer of prescribed medicines. So it is important that the public better understand the complexities, potential, limitations and purposes of each step in drug development and the role of the institutions and agencies involved in this process. The implementation of educational programmes by the government for the general population regarding all aspects of the process of drug development, as well as more information and transparency by the biotechnology and pharmaceutical industries, will have a positive effect on society's understanding and cooperation. Failed clinical trials, drugs withdrawn from the market due to harmful effects, the high price of prescription drugs and the lack of adequate drugs to treat (even mild) maladies in the developing world create public resentment and scepticism, and this situation needs to be urgently addressed.

Summary

The development of bortezomib is an interesting case because, despite ProScript starting without a drug, changing its business model, shifting in focus from muscle wasting to cancer, and running out of money, the company managed to access the right people and resources in a systematic way, leveraging cooperation with other, mostly public, institutions. Although there was intellectual property protection, the parties involved collaborated in a complementary, rather than competitive, way. ProScript's science was strong and pioneering, which is a standard requirement for any spin-off company, but 'good science' is not enough to ensure success. The success of bortezomib was ultimately due to the tenacity of the people involved and the close collaboration, as explained in the 'Core Model' (BOX 3, note 6), between academia, the private sector, private investors, public institutions and advocacy groups. How many potential drugs like bortezomib have been silently buried already or are currently languishing? Policy initiatives in the areas highlighted above should help to ensure that successes such as bortezomib become normal rather than exceptional examples of translational research.

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Competing interests statement

The author declares no competing financial interests.

Disclaimer

Despite several attempts to speak with representatives from Millennium Pharmaceuticals regarding the marketing of bortezomib, no one was available for comment. This history of the development of bortezomib is not intended to include all the people involved in this process, because doing so is well beyond the scope of and space available for this analysis.

FURTHER INFORMATION

Rapid Access to Intervention Development: http://dtp.nci.nih.gov
Multiple Myeloma Research Foundation: http://www.multiplemyeloma.org

SUPPLEMENTARY INFORMATION

See online article: S1 (table)
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Biography
Ibis Sánchez-Serrano was born in Panamá and received his B.S in genetics and Art History from Iowa State University, USA, in 1996. He conducted research on learning and memory at Cold Spring Harbour Laboratory, New York, in 1994; carried out doctoral studies in cancer genetics at the University of Pavia, Italy, and the Pasteur Institute, France, from 1996–1997; and performed research at Boston University on genetic switches in bacteria 1999–2001. In 2004 he received an International Business/Technology management and Momentary Theory/ Policy degree from The Fletcher School of Law and Diplomacy (Tuft's University) in collaboration with Harvard's Business School/Kennedy School of Government and the Massachusetts Institute of Technology's Sloan School of Management. His current interests include his book on cancer and translation research; the creation of a foundation for translational research; the establishment of collaborations with private/public sector investors and early-stage biotech enterprises; and the implementation of effective education and healthcare reforms in the developing world, especially Latin-America.

TOC blurb
Sánchez-Serrano discusses the story of the innovative anticancer drug bortezomib to dissect the key public-sector-private sector interactions that made the development of this drug successful despite many barriers, and considers the implications for improving translational research in general.