UCSF TRACS™ Translational Case Studies

CASE ONE

Kyprolis®

Summary

Kyprolis® (carfilzomib) is a multiple myeloma drug that was developed by a biotech startup, Proteolix, from the stage of basic academic research through Phase II clinical trials. Proteolix went through three rounds of funding before being acquired by Onyx Pharmaceuticals for $851 million in 2009. Kyprolis® ultimately received FDA approval in 2012 and since then has been used to treat thousands of patients. The case study of Kyprolis® highlights some of the challenges and opportunities involved in translating basic research into a commercially viable product. Some key lessons offered by Kyprolis® include strategies for forming a team that maximizes the likelihood of commercial success, the need to pivot in response to investors' demands, the importance of developing an appropriate target product profile in order to attract investors, and the role of intellectual property (IP) considerations in determining the trajectory of commercialization.

Discovering the mechanism: from Epoxomicin to YU-101

The FDA approval of Kyprolis® in 2012 was the culmination of over two decades of research and drug development. The origins of Kyprolis® can be traced to the 1980s, when a natural compound known as epoxomicin was discovered by a team of Bristol-Myers Squibb (BMS) researchers in Japan. BMS was granted a patent describing a method of producing epoxomicin and its antitumor activity in 1991.[1] In the following year, BMS scientists published a paper characterizing the anti-tumoral effects of epoxomicin against B16 melanoma cells,[2] but did not further pursue research on epoxomicin. It later became clear that BMS abandoned work on epoxomicin because they were unable to ascertain its mechanism of action, leading to concerns about eventual regulatory obstacles.

DISCUSSION POINTS

- ***Team formation and pivoting***
- ***Intellectual property***
- ***Target validation***
- ***Target product profile***

Almost a decade later, Craig Crews turned his attention to epoxomicin. As a junior faculty member at Yale, his research agenda was focused on elucidating the molecular mechanisms of action of pharmacologically active natural compounds. In 1999, the Crews lab published papers describing the total synthesis of epoxomicin and its mechanism of activity, as well as a 2000 paper detailing the crystal structure of proteasome complexed with epoxomicin.[3,4] They found that epoxomicin is a selective and powerful proteasome inhibitor. However, epoxomicin was not patentable because it is a naturally occurring compound. With this in mind, Crews set out to study analogs of epoxomicin to identify potentially patentable compounds with similar or greater efficacy. Ultimately, one of these analogs, YU-101, was identified as the most promising candidate, and Yale filed a provisional patent application for YU-101 in 1999.

At this point, YU-101 was not considered to be a candidate for a clinical drug, because the proteasome had not been validated as a target for cancer treatment. Proteasomes are protease complexes responsible for degrading proteins tagged with a small protein known as ubiquitin and are key players in the regulation of numerous cellular processes (Fig. 1).[5]

More than 80% of cellular proteins are degraded through the ubiquitin-proteasome pathway. Preventing the proteasome from degrading those proteins leads to an undesired accumulation of proteins and cell apoptosis. This finding led to interest in utilizing proteasome inhibitors to treat cancer, since it was hypothesized that tumor cells are more vulnerable to proteasome inhibitors because they are highly proliferative and have higher levels of protein synthesis than a normal cell. [6] However, a major concern was that a drug able to prevent the breakdown of proteins through inhibiting the proteasome would be too cytotoxic for practical clinical applications.

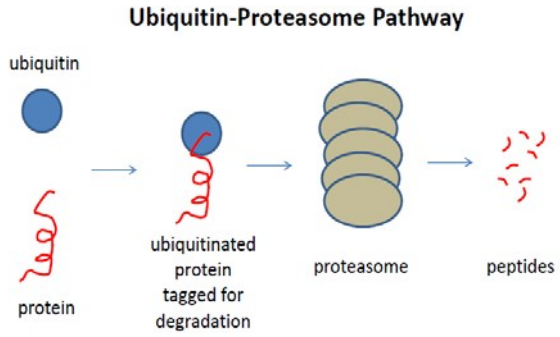


Figure 1. Ubiquitin-Proteasome pathway.

Therefore, when YU-101 was developed, it was thought to be a promising research reagent to study the effect of proteasome inhibition in basic research. Yale filed a patent application in the US but did not file for global IP protection for YU-101; although the explanation may be that they missed the deadline, it is likely that they did not do so because they simply did not see the long-term potential of YU-101.

Pivoting in response to investor demands: the funding of Proteolix

After Yale filed the US patent application for YU-101, the epoxomicin analog, research on YU-101 faded into the background. At approximately the same time, from 1999 to 2000, Crews began to collaborate with Ray Deshaies of Caltech on a project, eventually known as PROTAC (Proteolysis-Targeting Chimeras), which aimed to develop a platform capable of targeting specific proteins for degradation via the proteasome. The possibility of a platform enabling selective protein degradation was particularly compelling before the emergence of relatively cheap gene knockout platforms. In 2000, Caltech, Yale, and the University of California filed a patent for PROTAC, and in the following year, Crews and Deshaies published a paper describing the PROTAC platform.[7]

Crews and Deshaies started to seek funding from investors, primarily based on the prospect of commercializing the PROTAC platform as a research tool. Their pitch also included two other projects: YU-101 and a project to develop isopeptidase inhibitors At this point, YU-101 played the role of a supplemental project to flesh out the portfolio of proteasome-related technology that they were pitching.

Despite pitching several venture capital firms, Crews and Deshaies were not successful in obtaining funding for the original vision of their company. They were eventually put in touch with Phil Whitcome, who had both a PhD in molecular biology from UCLA and an MBA from the Wharton School of Business, as well as extensive executive experience in the biotechnology industry. Through Deshaies, Crews and Whitcome were introduced to Susan Molineaux, a PhD molecular biologist with extensive corporate experience in drug development. In 2003, Proteolix was founded by Crews, Deshaies, Whitcome, and Molineaux, with Whitcome and Molineaux serving as the CEO and CSO, respectively (Table 1).

Table 1. Backgrounds of the Proteolix co-founders when the company was founded

Craig Crews, PhD PhD in Biochemistry from Harvard University Assistant Professor of Chemistry and Pharmacology at Yale University Inventor of YU-101 Co-founder of Proteolix
Ray Deshaies, PhD PhD in Biochemistry from UC Berkeley Associate Professor of Biochemistry at Caltech Recognized expert on the ubiquitin-proteasome pathway Co-founder of Proteolix
Susan Molineaux, PhD PhD in Molecular Biology from John Hopkins University Former Senior Scientist and Manager at Rigel Pharmaceuticals Co-founder and CSO of Proteolix
Phil Whitcome, PhD, MBA PhD in Molecular Biology from UCLA MBA from Wharton School of Business Former Director at Amgen and CEO of Neurogen Co-founder and CEO of Proteolix

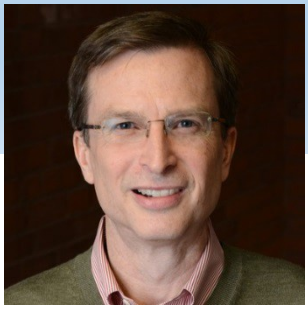
PhD - Doctor of Philosophy; CEO - Chief Executive Officer; CSO- Chief Scientific Officer; MBA -Master of Business Administration

The development of proteasome inhibitors as clinical drugs became much more promising in May 2003, when Millennium Pharmaceuticals received FDA approval for the use of the proteasome inhibitor bortezomib (Velcade®) for multiple myeloma. Multiple myeloma is a cancer of plasma cells, and it is the second most common type of blood cancer in the United States, with an estimated prevalence of 90,000 cases and an incidence of 27,000 new diagnosed cases per year.[8] Velcade® was the first proteasome inhibitor to receive FDA approval, proving that targeting the ubiquitin-proteasome pathway is a viable route for the treatment of multiple myeloma. Knowing the pharmaceutical landscape and seeing a great opportunity for a second-in-class drug targeting the proteasome, Whitcome and Molineaux convinced Crews and Deshaies to restructure their business proposal by placing the primary emphasis on YU-101. Despite the exciting scientific novelty behind PROTAC, venture capitalists were looking for ways of maximizing and accelerating their return on investment, and the development of small, close-to-clinic molecules was considered much more attractive than investing in a platform like PROTAC.

"The venture capital mantra was 'small molecule, close to clinic'–we'd hear it over and over again. We recognized we had what they were looking for and I had to adapt. We pivoted very nicely and that's how we become a proteasome inhibitor company." – Craig Crews

The pitch for YU-101 as a competitor ("me-too drug") for Velcade® drew on certain biochemical features of YU-101 that Proteolix was confident would translate into superior clinical applicability. YU-101 was predicted to be more selective and, most notably, as opposed to Velcade®'s reversible inhibition of the proteasome, YU-101 irreversibly inhibited it, requiring new protein synthesis for recovery of the proteasome activity, therefore making YU-101 more potent than Velcade®.[4] It was also hypothesized—and later proven—that some of the severe and dose-limiting side effects of Velcade®, such as peripheral neuropathy, were due to cross-inhibition with other proteins caused by Velcade®'s relatively unselective mechanism of proteasome inhibition.

"We had the crystal structure, I had some *in vivo* results so I knew it was antitumor, we made analogs that put us into a new patentable chemical space, and moreover, we improved on Mother Nature — YU-101 was more specific and more potent." – Craig Crews



With this new pitch, Proteolix received $18.3 million of funding in December 2003.

The creation of Kyprolis®: from YU-101 to carfilzomib

A major obstacle in obtaining funding for YU-101 was the fact that Yale had filed for IP protection of YU-101 in the United States, but not worldwide. The US pharmaceutical market represents about 50% of the worldwide market, with Europe and Japan making up most of the other 50%. The cost of developing and approving a drug is very high, and only targeting the US market may not be enough to recoup the investment. Since the deadline for filing internationally had been missed, it was necessary to develop a new compound that could receive IP protection. Proteolix had to provide the investors with a detailed technical plan of how they would innovate outside of the YU-101 patent.

Luckily, it was possible to combine outside-the-patent innovation with research designed to solve a clinical problem faced by YU-101: namely, its lack of solubility. Since YU-101 was originally designed as a reagent for basic research purposes, its lack of solubility was not considered especially problematic. However, increasing its solubility was imperative for making it a viable clinical drug. The therapeutic dose of YU-101 would have to be dissolved in a large amount of solution, meaning that hundreds of milliliters would need to be infused into the patient. In contrast, the administration of Velcade® required an injection of a few milliliters. The solubility issue was therefore a major disadvantage for YU-101 compared to Velcade®. This problem was compounded by the fact that the Proteolix team had learned that a respected researcher was not able to reproduce their results, which they believed was due to mishandling of the solubility problem and precipitation of the compound. The lack of pre-clinical reproducibility is a major problem for pharmaceutical companies,[9] and if those negative results had been published, Proteolix would possibly have experienced more difficulties obtaining funding.

The addition of a morpholine ring to the N-terminus of YU-101 made it more soluble by several orders of magnitude, both solving the clinical and experimental problems posed by the insolubility of YU-101 and allowing the new compound to be patented as carfilzomib (Figure 2).

"We had a good clinical candidate which we worked on and then we found carfilzomib, which put us outside the patent and we took a leap of faith and focused on that." – Susan Molineaux

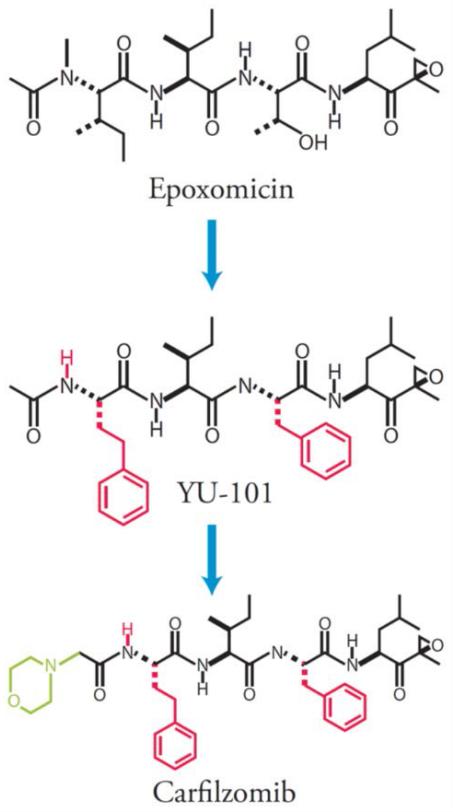


Figure 2. The path of development from epoxomicin to carfilzomib.

Carfilzomib immediately replaced YU-101 in the preclinical research, and as a result, Proteolix was able to file an investigational new drug (IND) application for carfilzomib and to enter Phase I clinical studies within 18 to 19 months of obtaining their first round of funding, which was an unusually quick turnaround.

Phase I clinical trials began in August 2005, the first patient response was observed in March 2006, and in May 2006, Proteolix received a second round of funding of $45 million. In August 2007, carfilzomib entered phase II clinical trials. During the phase II trials, two patients unexpectedly died of tumor lysis syndrome. Tumor lysis syndrome occurs when large numbers of neoplastic cells are lysed quickly, leading to a buildup of intracellular ions and metabolic products in the bloodstream, which in turn can lead to shock and kidney failure. Proteolix put the trials on a voluntary hold and developed a treatment protocol to minimize the likelihood of these complications. After a three-month clinical hold, the Phase II clinical trials continued, and in September 2008, Proteolix received a third round of funding of $79 million.

Shortly afterward, Proteolix was acquired by Onyx in an $851 million deal. In June 2012, carfilzomib was approved by the FDA for use in multiple myeloma patients who had already received at least two therapies. Marketed under the trade name Kyprolis®, carfilzomib became Onyx's most valuable asset. In 2013, Amgen acquired Onyx in a $10.4 billion deal.

Kyprolis® netted $331 million in sales in 2014 and Amgen is currently working to expand the approved indications for Kyprolis®. In 2015, the FDA granted approval for Kyprolis® in combination with Revlimid® and dexamethasone for the treatment of relapsed multiple myeloma. Moreover, recent studies have suggested that Kyprolis® is clinically superior to Velcade® in treating patients with relapsed multiple myeloma (18.7 vs. 9.4 months of progression-free survival).[10] The global market for multiple myeloma drugs is forecast to reach more than $7 billion by 2021, and Kyprolis® is estimated to bring in more than $3 billion in revenue by 2021.[11, 12]

Discussion

Team Formation and Pivoting

The founding of Proteolix involved both a collaboration between two academics (Crews and Deshaies) and the eventual incorporation of co-founders with deep industry experience (Whitcome and Molineaux).

The collaboration between Crews and Deshaies is particularly noteworthy in light of the 2003 restructuring of the Proteolix business proposal—instead of a company in which the primary focus of research was a joint project between the Crews and Deshaies labs, Proteolix eventually focused on a project based on work done in the Crews lab. However, the partnership remained equal, allowing the team to move forward smoothly and draw on the strengths of both research teams, especially Deshaies' deep expertise on the ubiquitin-proteasome pathway.

"For Proteolix, PROTAC was the exact example of a catalyst: something that is not changed during the reaction and not incorporated into the product!" – Ray Deshaies

Only after Whitcome and Molineaux were brought on board was Proteolix able to obtain funding, after restructuring the business plan. This change was specifically informed by Molineaux's perspectives on the biotechnology industry, including both the general move away from funding platform-based technologies to funding close-to-clinic small molecule therapies and the specific fact that Velcade® was moving towards FDA approval as a first-in-class proteasome inhibitor. In contrast, the PROTAC project did not attract the interest of venture capital investors, although it was an intriguing project with the potential to eventually inform a wide variety of basic research. In order to successfully attract funding from venture capitalists, a clear path to commercialization is essential. A well-understood, narrowly targeted product with a definite market niche is more likely to be funded than a more speculative technology with uncertain but possibly wide-ranging long-term potential.

Conflicts between academic and business culture can arise during the initial stages of forming a company, especially during the funding process. The concept of market value crucially differs from the ways in which the value of scientific research is discussed in grant applications. In this particular case, the pre-money valuation of $4 million (with roughly half of that going to founders and half to the company option

pool) was considered low by the academic founders. Molineaux argued that academics often have difficulty dealing with the concept of market value as what investors are willing to pay. Commercial innovations do frequently draw on the results of basic research, but successfully commercializing a product requires building a team that includes members who are familiar with how venture capitalists approach the concept of value.

Interestingly, in 2013 Crews was finally able to found Arvinas Inc., a company based on an improvement of the original PROTAC technology. In 2015, Merck signed a $434 million deal to gain access to Arvinas' PROTAC-based platform. As a result of this and other successful platform companies, many venture firms now consider it an attractive business model.

> "The value of the company is not rational – there is not an equation – the value is what investors are willing to pay. That can be hard for scientists to accept because they are very data driven." – Susan Molineaux

Intellectual Property

Well before the eventual establishment of Proteolix as a company, one of the challenges the Crews lab faced with epoxomicin was the fact that isolated natural products as such are not patentable in the United States. However, variations of a naturally occurring compound can be patented (e.g., YU-101). Additionally, processes for the extraction or synthesis of a naturally occurring compound can be patented. Therefore, when seeking to develop a patentable product, researchers should focus on the modification, formulation, manufacture, and application of natural products.

The fact that Yale did not obtain global protection for YU-101 was a major issue in the early stages of Proteolix, and was one reason why the outside-the-patient innovation that led to carfilzomib was necessary. Filing and maintaining patent protection in multiple countries can be very expensive. After filing one international patent application under the Patent Cooperation Treaty (PCT), applicants can simultaneously seek protection for an invention in 148 countries throughout the world. A university's technology transfer office will usually only seek international protection if a product has attracted commercial interest leading to the reimbursement of those costs. A crucial take-away point is that the clock starts ticking as soon as the provisional patent application is filed—in order to obtain IP protection for an innovation, interest and/or funding must be raised in time to meet the deadlines that follow the filing of a provisional patent application (Fig. 3). This is especially important for pharmaceutical companies. In most countries, drug patents provide 20 years of protection from

the filing date, but since the filing usually happens many years before clinical trials begin, the effective period of protection after the drug is in the market is often less than ten years. After the patent expires, any pharmaceutical company can manufacture and sell the drug. Generic drugs cost less because the manufacturers do not incur the cost of drug discovery, clinical trials, or the initial marketing efforts.

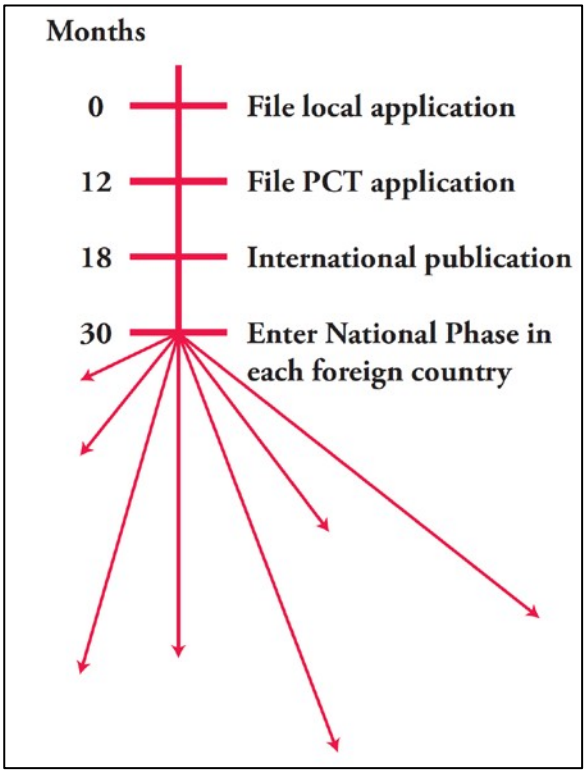


Figure 3. Intellectual property timeline.

Target Validation

One of the reasons that the BMS team that discovered epoxomicin did not pursue further development was that they were not able to establish its mechanism of action. This decision may initially seem puzzling, since the FDA does not require investigators to establish the mechanism of action in order to move a drug into clinical trials. Moreover, many drugs are frequently prescribed although their mechanisms have not been precisely characterized, such as lithium in the treatment of bipolar disorder and several disease-modifying anti-rheumatic drugs used to treat rheumatic disease.[13]

However, moving a drug with an unknown mechanism into trials can be highly risky. In the early 2000's, a San Diego-based company, Medivation, Inc., sponsored a phase II trial of Dimebon® (laterpridine) to treat patients with Alzheimer disease in Russia, where the drug was already approved for use as an antihistamine. The results in this trial were very promising, but the mechanism of action was not well understood, and the effects were attributed to a combination of mechanistic effects—blocking calcium currents in intestinal cells, inhibiting acetylcholinesterase, and acting as a glutamate receptor blocker. Medivation decided to move the drug forward and sponsored a large a phase III trial in the US, at which point a tremendous amount of resources had been invested into the drug development process, and it failed to outperform a sugar pill. It is hard to determine a single specific reason for the failure, but without knowing the mechanism of action, it is challenging to establish the best dose to elicit a desired effect and to define the subset of patients who would benefit most from the treatment. For example, the optimal dose of a statin can be

determined based on the change in blood cholesterol levels; and women can be screened to identify the presence of the known target receptor for Herceptin, thereby selecting the patients with the highest chance of benefiting from the treatment. Therefore, understanding a drug's mechanism of action can help improve the design of clinical trials by enabling the researchers to monitor the effect of the drug more closely, leading to more sensitive dosing, and allowing the investigators to stratify the patients who are most likely to benefit from the drug.

Novel unvalidated targets are unlikely to be attractive to venture capitalists in the pharmaceutical industry. It has been estimated that the probability of reaching preclinical development is only 3% for a drug with a novel target, compared to 17% for a drug with an established target.[14] This discrepancy has major implications due to the immense costs of drug development. It has been estimated that approximately 12 years and $2.6 billion are necessary to develop and receive market approval for a new drug. .[15,16]

A valid target is a target that, when manipulated pharmacologically, provides significant efficacy with acceptable safety for a specific disease process in long-term clinical usage.[17] Target verification proceeds in the following steps:

- Target identification: the generation of scientific evidence that a manipulable target is involved in a disease process.
- Target qualification: preclinical or limited clinical studies that establish the scientific validity and safety of a drug target.
- Target validation: the process of demonstrating in a clinical trial that engaging the target provides a statistically meaningful therapeutic benefit with acceptable safety for a given indication.

Target Product Profile (TPP)

Proteolix was ultimately funded to develop YU-101. Once Velcade® emerged as a first-in-class proteasome inhibitor, a clear path emerged for YU-101 (eventually carfilzomib) to be developed as a second-in-class, "me-too drug," which is a viable, less risky, commercial strategy with well-understood market dynamics. The objective of Proteolix was to develop a more selective inhibitor, leading to a more effective treatment for multiple myeloma patients with fewer side effects than Velcade®.

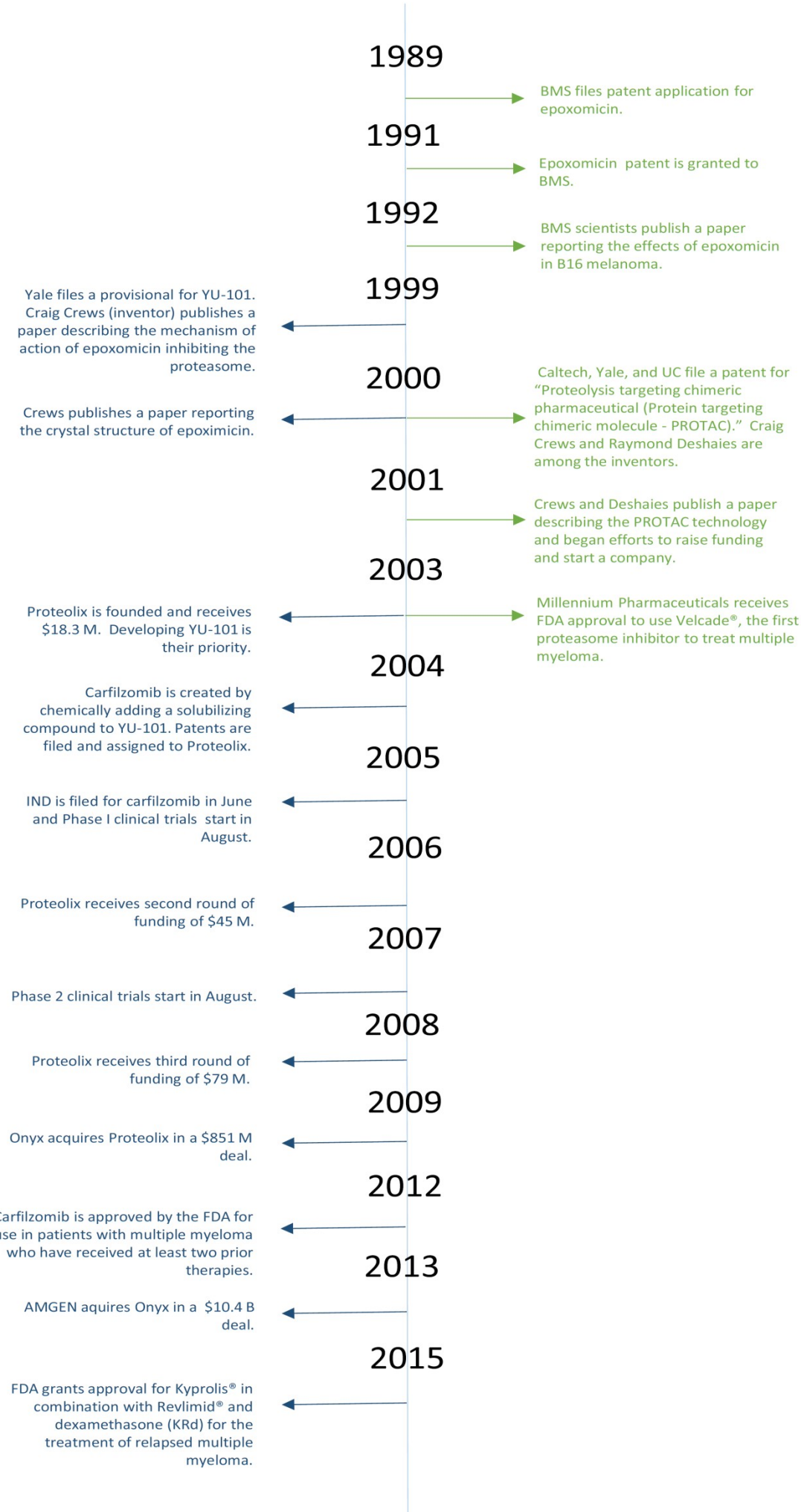
The TPP should provide a clear statement of the desired outcomes of the drug development program. It summarizes the intended labeling content, claims, dosing, administration, contraindications, unmet needs, competitive assessment, and pricing. The TPP is updated as clinical and pharmacological findings emerge, and in response to guidance from regulatory authorities or major market events. Therefore, the TPP is a dynamic strategic document, embodying the notion of

beginning with the goal in mind. A well-defined TPP facilitates discussion with investors and regulatory agencies.

References

1. United States Patent 5,071,957 - Konishi , et al. December 10, 1991
2. Hanada, M.; Sugawara, K.; Kaneta, K.; Toda, S., Nishiyama, Y.; Tomita, K.; Yamamoto, H.; Konishi, M.; Oki, T. Epoxomicin, a new antitumor agent of microbial origin. *J. Antibiot.* 1992. Nov;45(11):1746-52.
3. Sin, Ny, et al. "Total synthesis of the-potent proteasome inhibitor epoxomicin: a useful tool for understanding proteasome biology." *Bioorganic & Medicinal Chemistry Letters* 9.15 (1999): 2283-2288.
4. Groll, M.; K. B.; Kairies, N.; Huber, R.; Crews, C. M. Crystal Structure of Epoxomicin:20S Proteasome Reveals a Molecular Basis for Selectivity of α‘,β‘-Epoxyketone Proteasome Inhibitors. *J. Am. Chem.* Soc. 2000, 122 (6), pp 1237–1238.
5. Bogyo, M., and E. W. Wang. "Proteasome inhibitors: complex tools for a complex enzyme." *The Proteasome—Ubiquitin Protein Degradation Pathway*. Springer Berlin Heidelberg, 2002. 185-208.
6. Crawford, Lisa J., Brian Walker, and Alexandra E. Irvine. "Proteasome inhibitors in cancer therapy." *Journal of cell communication and signaling* 5.2 (2011): 101-110.
7. Sakamoto, Kathleen M., et al. "Protacs: Chimeric molecules that target proteins to the Skp1–Cullin–F box complex for ubiquitination and degradation."*Proceedings of the National Academy of Sciences* 98.15 (2001): 8554-8559.
8. Myeloma: Surveillance, Epidemiology and End Results Program. National Cancer Institute. Available at http://seer.cancer.gov/statfacts/html/mulmy.html. Accessed September 9, 2015
9. Freedman, Leonard P., Iain M. Cockburn, and Timothy S. Simcoe. "The economics of reproducibility in preclinical research." PLoS Biol 13.6 (2015): e1002165
10. “Amgen Submits Supplemental NDA for Carfilzomib in Relapsed Multiple Myeloma.” Drug Discovery and Development. http://www.dddmag.com/news/2015/07/amgen-submits-supplemental-nda-carfilzomib-relapsed-multiple-myeloma. Accessed September 29, 2015.
11. McCaffrey, Kevin. “Kyprolis growth prospects at center of Amgen-Onyx deal.” Medical Marketing and Media. http://www.mmm-online.com/channel/kyprolis-growth-prospects-at-center-of-amgen-onyx-deal/article/308935/. Accessed September 29, 2015.”
12. Palmer, Eric. “New Celgene drug packs punch for multiple myeloma market.” FiercePharma. http://www.fiercepharma.com/story/new-celegene-drug-packs-punch-multiple-melanoma-market/2013-02-10. Accessed September 29, 2015.
13. Editorial. Mechanism matters. Nat Med. 2010 Apr;16(4):347.
14. Baker, Ann, and Jasween Gill. "Rethinking innovation in pharmaceutical R&D."*Journal of Commercial Biotechnology* 12.1 (2005): 45-49.
15. Smith, Caitlin. "Drug target validation: Hitting the target." *Nature* 422.6929 (2003): 341-347.
16. Cost to Develop and Win Marketing Approval for a New Drug Is $2.6 Billion -

Tufts CSDD, November 18, 2014. http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study Accessed November 19, 2015.
17. Joint NIH-Industry Target Validation Workstreams Workshop, 2012, May 31, Cambridge, MA


1989
BMS files patent application for epoxomicin.
1991
Epoxomicin patent is granted to BMS.
1992
BMS scientists publish a paper reporting the effects of epoxomicin in B16 melanoma.
1999
Yale files a provisional for YU-101. Craig Crews (inventor) publishes a paper describing the mechanism of action of epoxomicin inhibiting the proteasome.
2000
Caltech, Yale, and UC file a patent for "Proteolysis targeting chimeric pharmaceutical (Protein targeting chimeric molecule - PROTAC)." Craig Crews and Raymond Deshaies are among the inventors.
Crews publishes a paper reporting the crystal structure of epoximicin.
2001
Crews and Deshaies publish a paper describing the PROTAC technology and began efforts to raise funding and start a company.
2003
Proteolix is founded and receives $18.3 M. Developing YU-101 is their priority.
Millennium Pharmaceuticals receives FDA approval to use Velcade®, the first proteasome inhibitor to treat multiple myeloma.
2004
Carfilzomib is created by chemically adding a solubilizing compound to YU-101. Patents are filed and assigned to Proteolix.
2005
IND is filed for carfilzomib in June and Phase I clinical trials start in August.
2006
Proteolix receives second round of funding of $45 M.
2007
Phase 2 clinical trials start in August.
2008
Proteolix receives third round of funding of $79 M.
2009
Onyx acquires Proteolix in a $851 M deal.
2012
Carfilzomib is approved by the FDA for use in patients with multiple myeloma who have received at least two prior therapies.
2013
AMGEN aquires Onyx in a $10.4 B deal.
2015
FDA grants approval for Kyprolis® in combination with Revlimid® and dexamethasone (KRd) for the treatment of relapsed multiple myeloma.

Supplementary Reading

Team Formation:

- De Rubertis F, Roman F, Werner L. "Six secrets to success—how to build a sustainable biotech business." *Nature Biotechnology*27.7 (2009): 595-597. http://www.nature.com/bioent/2009/090501/full/bioe.2009.5.html
- Steen M, Englis PD, Englis BG. "Scientific team effectiveness and the external CEO: A study of biotechnology university spin-offs." *Industry and Higher Education* 27 (2013): 15-25. http://www.researchgate.net/publication/233884062_Scientific_team_effectiveness_and_the_external_CEO_A_study_of_biotechnology_university_spin-offs._Industry_and_Higher_Education
- York A, McCarthy KA, Darnold TC. "Building biotechnology teams: Personality does matter." *Journal of Commercial Biotechnology* 15.4 (2009): 335-346. http://www.palgrave-journals.com/jcb/journal/v15/n4/full/jcb200919a.html

Intellectual Property:

- Harrison, C. "US Patent Office issues guidelines on natural product patent eligibility." *Nature Reviews Drug Discovery* 13.4 (2014): 250-250. http://www.nature.com/nrd/journal/v13/n4/full/nrd4303.html
- Wong A, Chan A. "Myriad and its implications for patent protection of isolated natural products in the United States." *Chinese Medicine* 9.1 (2014): 1-5. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4086272/
- USPTO – Patent Basics: provisional application for a patent http://www.uspto.gov/patents-getting-started/patent-basics/types-patent-applications/provisional-application-patent

Target Validation:

- Smith, C. Drug target validation: Hitting the target - *Nature* 422.6929 (2003): 341-347. http://www.nature.com/nature/journal/v422/n6929/full/422341a.html
- Baker A, Gill J. "Rethinking innovation in pharmaceutical R&D."*Journal of Commercial Biotechnology* 12.1 (2005): 45-49. http://www.palgrave-journals.com/jcb/journal/v12/n1/pdf/3040147a.pdf

Target Product Profile:

- UCSF Launchpad - Target Product Profile Example for Drug Development http://launchpad.ucsf.edu/target-product-profile-therapeutics-part-1/
- Target Product Profile – A strategic development process tool. FDA Guide www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm080593.pdf
- Lambert, WJ. "Considerations in developing a target product profile for parenteral pharmaceutical products." *AAPS PharmSciTech* 11.3 (2010): 1476-1481. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2974137/