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Breakthroughs at Blueprint Medicines

In June 2019, the excitement was palpable at Blueprint Medicines in Cambridge, Massachusetts, as CEO Jeff Albers and COO Kate Haviland (MBA '05) prepared for an all-staff party to celebrate the submission of the company's first New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA). The NDA was for avapritinib, an investigational precision medicine that showed tumor reductions in 86% of clinical trial participants with a genetically-defined form of gastrointestinal stromal tumor (GIST), a rare cancer affecting the digestive tract.[1] An NDA was the last step in the FDA's review before a drug could be marketed to the public. FDA drug approval took an average of 12 years from discovery to final approval, and only 11% of drug applications made it through the entire process (see **Exhibit 1** for the average timeline).[2]

Blueprint was founded in 2011 by biotech entrepreneur and venture capitalist Alexis Borisy and by 2013, the company had identified the compound that would ultimately become avapritinib. Albers and Haviland felt optimistic they would receive final approval from the FDA in the first quarter of 2020—paving the way for the company to bring to market a lifesaving drug in nearly half the average time.

The company had more to celebrate than just avapritinib. Blueprint expected that its second drug candidate, pralsetinib, used to treat non-small cell lung and medullary thyroid cancers, would be ready for an NDA filing in the first half of 2020. (See **Exhibit 2** for Blueprint timeline).

Blueprint was moving at breakneck speed, juggling the upcoming debut of its first commercial product, avapritinib, with pralsetinib close behind. The company had approximately 240 employees, and planned to double its staff in connection with the planned commercial launches.[3] Albers and Haviland wondered how to prioritize programs and manage growth as Blueprint expanded from a startup to a full-fledged company that encompassed all aspects of drug development, from research to clinical to commercialization. But for now, they would take a deep breath and enjoy the party.

The Early Years

In 2009, Borisy was building the company that would become Foundation Medicine (Foundation) when he started thinking about what it would mean to the biopharmaceutical industry if Foundation was successful. Foundation was a precision diagnostics company that provided patient DNA sequencing to help identify the mutations that were driving a patient's cancer with the goal of informing treatment with medicines targeting those mutations. Once Foundation built up a database

Professor Richard G. Hamermesh, Senior Fellow Kathy E. Giusti, and Case Researcher Susie L. Ma (Case Research & Writing Group) prepared this case. It was reviewed and approved before publication by a company designate. Funding for the development of this case was provided by Harvard Business School and not by the company. HBS cases are developed solely as the basis for class discussion. Cases are not intended to serve as endorsements, sources of primary data, or illustrations of effective or ineffective management.

of information gleaned from sequencing, Borisy hoped that it could provide a layout of mutations across all cancers. He explained what this would mean in the long term:

> Within some period of time—a few years or a decade—we were going to have the roadmap of the genetic aberrations across all cancers. We could create THE precision medicine oncology company because if you know what is driving that cancer, you can create a super selective molecule for it.

Borisy realized this implied a different kind of business model for drug discovery since, if he could make a drug that could precisely hit a specific target, the chances that the drug would be highly effective should substantially increase. If this were the case, he thought:

> The number of patients needed for clinical trials should go down, so you should get proof of concept more definitively earlier and more quickly, so the allocation of resources should decrease and the time to develop should decrease. If your resource allocation and time are decreasing, and trial effect size and probability of success are increasing, and if you can do this again and again, that is a compelling business proposition—for patients and for medicine.

Borisy sketched some ideas on a lab notebook and stashed it away in his desk drawer. But not for long. Early in 2010, he started discussing the idea with oncologist Brian Druker and biochemist Nicholas Lydon, who led the team that created Gleevec, one of the first successful genomically-targeted drugs developed at Novartis to treat chronic myeloid leukemia.[4] In the fall of 2010, Borisy brought on two experienced biotech executives from Third Rock Ventures, where Borisy had recently become a partner, to lead the fledgling company.[5] Chris Varma became Blueprint's first CEO, and David Armistead served as chief scientific officer.

As they incubated Blueprint, the founders decided to focus on a promising but understudied drug target—kinases. Kinases were enzymes that helped control the growth activities of a cell—such as signaling and division—and were associated with cancer. There were 518 kinases in the human genome, but only around 30 FDA-approved kinase medicines that targeted less than 5% of kinases.[6] Gleevec was a kinase inhibitor, and Borisy felt there was an opportunity for Blueprint to create drugs like Gleevec that could block cancer-causing mutations in kinases.

Building a Different Kind of Library

Pharmaceutical companies amassed libraries with millions of compounds, seeking to build as many chances for successful drugs as possible. In 2011, Blueprint began developing its library of compounds that might inhibit kinases. The team knew this would be challenging because outside of Gleevec, the biopharmaceutical industry had been largely unsuccessful in developing highly selective kinase inhibitors. As the leadership team investigated why this was, they realized that there were few compound libraries built specifically for kinases, and the ones that did target kinases focused largely on variants of just a few kinase inhibitors. This led to large libraries of similar compounds.

Blueprint took an agnostic approach to its compound library by casting a wide net, looking to create a diversity of compounds not directed at any particular kinase target, but seeking to cover the entire kinome[a] tree (see **Exhibit 3** for the kinome tree). Borisy remembered that this was a radical idea at the time, and he recalled advocating: "Let's make different shaped libraries and test them without an idea

[a] The kinome is the complete set of kinases encoded in the human genome.

of specific target. Let's explore chemical shape without having a particular program. Let's get chemical matter that lights up different parts of the kinome tree."

Albers compared the creation of Blueprint's library to compound libraries at most biopharmaceutical companies:

> The classic model is that you make all these molecules, you pick one, you find out where it's potent, and then you try to deconstruct what else is it doing. That's really hard to do. What Blueprint did was sort of turn that on its head by saying, "We're just going to start making molecules, even if we don't know what they do." It's like a 1,000-piece puzzle, and if you put 20 pieces in the right spot you still have no idea what it is. But as you get 500 pieces in, you start to see a couple of the shapes and you can tell that there's going to be a lake over here, or a little house over here, or it's blue sky and all your blue pieces should go over there.

This was a risky approach because it required a significant upfront investment. Borisy, however, felt strongly that the idea would work. Blueprint raised $40 million in its series A round in April 2011, led by Third Rock Ventures.[7] (See **Exhibit 4** for the press release). Borisy said, "We were going to spend $40 million and two years to build the library and would have no idea if it was any good until it was done."

Identifying a Winning Compound

In mid-2011, Blueprint recruited a handful of scientists with experience in kinases, and the team scoured academic literature on kinases, looking for any information that could help direct their compound creation. The team slowly began to create molecules and by the end of 2011, they had a library of 1700 compounds; by 2012 it grew to 7000 compounds and ultimately, the library contained 20,000 compounds that reacted to different parts of the kinome tree.

But as time wore on, anxiety mounted at the company. In the spring of 2013, management issues forced Borisy to let Varma go, and Borisy jumped into the CEO role. The programs were not working in conventional ways, the library was behind schedule, and the company was running out of money. Borisy recalled partners at Third Rock asking, "Are we going to hit the wall?"

Although investors were concerned, Borisy told the team to proceed with business as usual. "I kept telling people don't worry about the money, the idea is so good, we are so right, and we are going to get this done. I said, 'I will bring the money, we will get this done,' and we did."

In November 2013, researchers identified a compound that showed promise against diseases driven by mutations in the KIT and PDGFRA genes, in this case GIST (see **Exhibit 5** for KIT and PDGFRA). This compound would eventually become avapritinib. Borisy was ecstatic: "We had something incredibly potent and specific, and it happened just in the nick of time."[8] At the end of 2013, Blueprint had $100,000 in the bank.

On the basis of this early compound, Blueprint was able to raise a $25 million B round, led by Nextech Invest in January 2014 (see **Exhibit 6** for the press release).[9] According to Borisy, it was still early for proof of concept: "We were still selling hopes and aspirations."

In July 2014, Blueprint hired Albers as CEO. By November 2014, when the company raised a $50 million C round, Blueprint synthesized the compound that became known as avapritinib.[10] (See **Exhibit 7** for press release). Albers hired Andy Boral in February 2015 as senior vice president and Boral later became chief medical officer.

In April 2015, Blueprint went public, raising $147 million, at a valuation of nearly $400 million.[11] Boral said, "We raised a lot of money with our IPO, just on the basis of the promise of the platform and really interesting pre-clinical data."

In mid-2015 that promise was realized when the company filed an Investigational New Drug (IND) application with the FDA to request approval to test avapritinib on human patients.

Ultimately Blueprint made several key decisions about the structure of the compound library that impacted its success (see **Exhibit 8** for Blueprint approach). The first was not to target any subset of kinases, but to try to cover as many kinases as possible. The second was to iterate on the compounds it developed. The third was to annotate the library with information based on testing each compound against almost every kinase. Klaus Hoeflich, Blueprint's vice president of biology, said, "This gives us something very unique. For every compound, we not only have the potency, but we have the selectivity data across the kinome and it's available on everyone's desktop computer."

Avapritinib

Blueprint was granted the green light to proceed with clinical trials in July 2015. The company made the decision to be extremely selective about trial enrollment, meaning participating patients had to have genetic mutations in the KIT and PDGFRA genes targeted by the drug candidate. Boral explained:

> From our first phase 1 in-human study, we limited this to GIST patients who either had this particular mutation that we knew was highly sensitive in the PDGFRA gene, or other forms of KIT-driven GIST that had had multiple prior therapies, which causes mutations to arise that we know are sensitive to avapritinib.

Haviland called this "getting more precise on our precision medicine approach." She recalled the questions raised by the investor community about this approach especially since many clinical trials were open to all individuals who met basic eligibility: "Are you going to be slowing yourselves down? Are you going to put a hurdle in front of your development by requiring [genetic] testing so that you make sure you get the right patients for the trials? Why wouldn't you just do all comers and hope to get enough of a response rate?'"

This was especially concerning since PGFRA-driven GIST accounted for only 5% to 6% of an already rare disease. Boral said, "We really had very little idea how we were going to find the PGFRA-driven GIST patients. When we started out, we found a few patients, but there was a high level of anxiety. How would we get the 50 people we thought we needed?" The first patients were treated in October 2015 and in December 2015, the team received word that a patient was showing substantial tumor shrinkage.

Boral explained that it was unusual to see a response to a new drug so soon because patients were treated with a very low dose of the drug at first. The purpose of a phase 1 study was to discover the appropriate dosage of the drug while weighing any side effects. Many companies were not able to determine if their drug was effective until a phase 2 study (see **Exhibit 9** for the clinical trial process). A positive response in phase 1 enabled Blueprint to transition seamlessly into a phase 2 by enrolling additional patients throughout 2016. Albers said:

> In essence, what we've done here is we've turned phase 1 safety studies into multi-registration broad-based trials. So, a study that started with 30 patients gets amended to go to 50 patients, and then gets amended to go to 100 patients. And now we have studies that have 300 to 500 patients.

Boral added this was not surprising given how the company developed its drug candidates:

> If you understand the genetic driver your drug is targeting and you can find the patients with that genetic driver, then we would expect to see tumor shrinkage in the dose escalation part of our first in-human studies. I would say that with our current approach of designing selective targeted drugs, if we don't see responses before we've even chosen the dose, it may mean the drug doesn't do what we think it should do.

Blueprint went from being worried about recruiting patients for its clinical trials to being almost overwhelmed by interest from patients and doctors in the GIST community. Boral remembered, "Once we saw a few responses, and then word got out, then suddenly we were like, 'Oh my God, where are all of these people coming from?'"

These early results led to the FDA granting avapritinib Breakthrough Therapy Designation (BTD) in June 2017 for a specific type of GIST. BTD gave the Blueprint team access to the FDA for faster feedback to expedite the development of avapritinib. Since the BTD was created in 2012, 37% of drug applications received the designation[12] (see **Exhibit 10** for more information on BTD).

As news of the BTD rippled out, it created an additional buzz around avapritbnib. BTD also had a positive impact on the investor community. Boral continued:

> The investors put a lot of value in it, and I was really scratching my head to figure out why, and realized quickly that it's a credible and independent validation of our data and program. Until then, we had been telling the investor community what we thought of avapritinib, and showing them the data, but this was the first indication that a completely independent entity had reviewed clinical data and agreed that it was good.

Blueprint submitted the NDA for avapritinib in June 2019, and it was granted priority review by the FDA in August 2019. Priority review reduced the final approval process from a maximum of 12 months to eight months from the filing date, giving a target of first quarter 2020 to release avapritinib to the public, if approved.

Pralsetinib

As avapritinib moved into clinical trials in 2015, scientists at Blueprint were busy refining another compound that would eventually become pralsetinib, which targeted a mutation in the RET gene that was a known genetic driver of sub-sets of non-small cell lung and medullary thyroid cancers (see **Exhibit 11** for information on RET). By November 2016, Blueprint filed an IND for pralsetinib. The trajectory of pralsetinib closely mirrored avapritinib with an even more condensed timeline.

Pralsetinib was created with one key addition to its development process that increased its appeal. Boral explained:

> We made it so it would do three things: it hit the wild-type[b] version of RET, it hit the mutant version with the driver mutation, but it also hit versions where we predicted resistant mutations would occur. So essentially it was a first and second generation inhibitor combined into one that was made to not only address where the tumor is but where we think the tumor was going to go next.

[b] A wild-type gene was a non-mutated gene that occurred naturally in nature.

Similar to avapritinib, patients were only enrolled in the pralsetinib trial if they had the targeted mutation. The first patient was dosed in March 2017. The first response came in June 2017 from a patient with lung cancer who enrolled in the trial through a thyroid cancer specialist. Boral said, "We opened that clinical trial site with the goal of finding thyroid cancer patients, but actually the first response was in a lung cancer patient who one of the specialist's colleagues sent to him because the patient had an RET-driven lung cancer."

Pralsetinib was granted BTD status in February 2019.

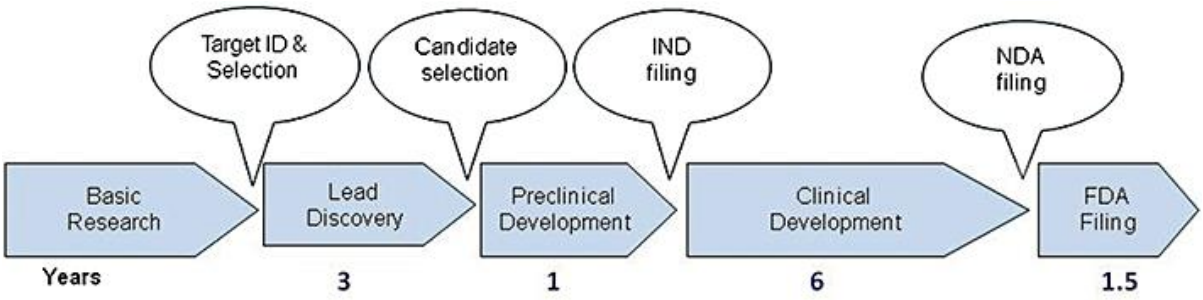
Looking Ahead

As it prepared for avapritinib and pralsetinib's potential commercial debuts, Blueprint continued to develop new drug candidates, including one for advanced hepatocellular carcinoma, a type of liver cancer, and one for fibrodysplasia ossificans progressiva, a disorder where muscle and tissue gradually turned to bone. The company was also running clinical trials testing avapritinib on systemic mastocytosis, a rare disease that caused a host of debilitating symptoms. Boral explained that once a drug had been proven effective against one disease, it was likely to be effective against others: "There's a lot of redundancy in biology and it is incredibly unlikely, I think, to find a target that's very active in some disease that is not relevant somewhere else."

Discussion Questions

1. How do you explain the rapid development of avapritinib and pralsetinib compared to average drug development timeline show in Exhibit 1? List as many factors as possible.
2. Which three factors were the most important?
3. How do platform companies differ from other biotech startups? What are the advantages and disadvantages of the platform model?

Exhibit 1 Average Drug Development Timeline (2011)



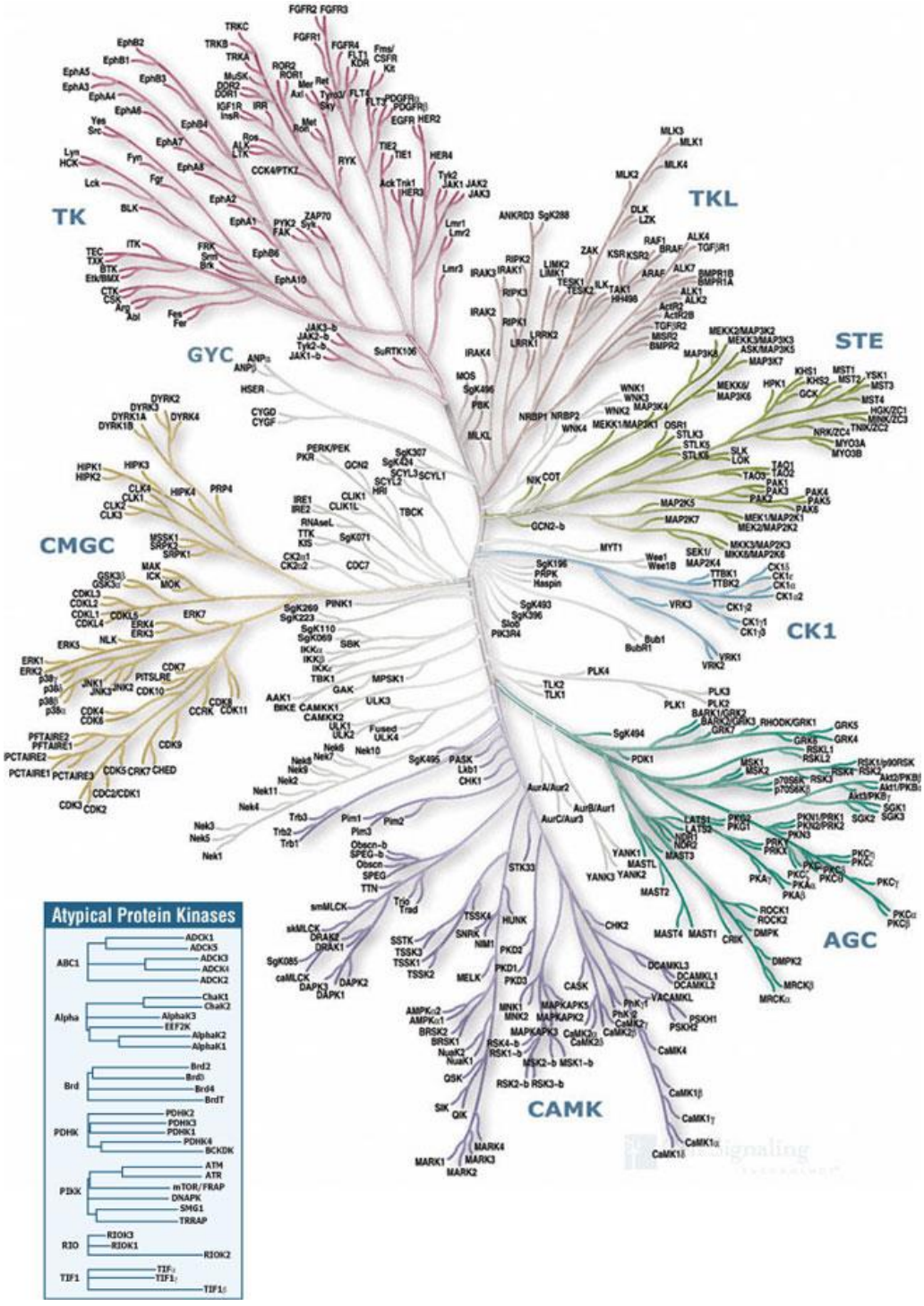
Source: JP Hughes, S Rees, SG Kalindjian, and KL Philpott, "Principles of Early Drug Discovery," *British Journal of Pharmacology*, March 2011, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3058157/, accessed October 2019.

Exhibit 2 Blueprint Drug Development Timeline (2013-2020)

November 2013	Lead compound that would become avapritinib synthesized
April 2014	Avapritinib becomes a development candidate
May 2015	Lead compound that would become pralsetinib synthesized
June 2015	Avapritinib IND filed
October 2015	Avapritinib clinical trials begin
December 2015	Avapritinib first patient response
December 2015	Pralsetinib becomes a development candidate
November 2016	Pralsetinib IND filed
March 2017	Pralsetinib clinical trials begin
June 2017	Pralsetinib first patient response
June 2017	Avapritinib Breakthrough Therapy Designation
February 2019	Pralsetinib Breakthrough Therapy Designation
June 2019	Avapritinib NDA filed
Q1 2020	Avapritinib NDA approval decision expected
Q1 2020	Pralsetinib NDA filing planned

Source: Casewriter compiled from company interviews and documents.

Exhibit 3 Kinome Tree



Source: "Protein Kinases: Human Protein Kinases Overview," Cell Signaling Technology, https://www.cellsignal.com/contents/science-protein-kinases/protein-kinases-human-protein-kinases-overview/kinases-human-protein, accessed October 2019.

Exhibit 4 Blueprint Medicines Series A Press Release

Blueprint Medicines Secures $40 Million Series A Financing to Translate New Molecular Data into Personalized Cancer Treatments

Company Founded by Pioneering Scientists Behind Gleevec®, Leading Entrepreneurs and Third Rock Ventures

April 11, 2011 08:00 AM Eastern Daylight Time

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Blueprint Medicines, a company harnessing the understanding of the molecular blueprint of cancer to develop personalized, highly-selective cancer therapies, today announced the closing of a $40 million Series A financing led by Third Rock Ventures. Nicholas Lydon, Ph.D., and Brian Druker, M.D., co-founded the company along with biotech entrepreneurs Chris Varma, Ph.D., and David Armistead, Ph.D., and Third Rock Ventures. Drs. Lydon and Druker are recipients of the 2009 Lasker-DeBakey Award for Clinical Medical Research for their role in the development of Gleevec® (imatinib mesylate), a targeted kinase inhibitor that transformed chronic myeloid leukemia (CML) from a fatal cancer into a manageable disease. Proceeds from the financing will be used to develop new cancer therapies - using the company's proprietary compound library and Insights-to-Validation™ Platform - that target the driver molecular aberrations of cancer and emerging resistance mechanisms unique to certain cancer patients. Dr. Varma is Blueprint Medicines' founding president and chief executive officer, and Dr. Armistead is the founding chief scientific officer.

"Over the past decade, targeted kinase inhibitors have been successfully designed, advanced into clinical trials and delivered to patients, forever changing the way cancer is treated," said Dr. Lydon. "We are now at a crossroads where innovative drug discovery and development could again enable a transformative shift in cancer treatment. By leveraging the growing body of molecular and cancer genome data and focusing on patients with clearly defined molecular aberrations, Blueprint Medicines is positioned to develop the selective cancer treatments that will make this transformation possible."

Blueprint Medicines' founding advisors are world-renowned experts in cancer genomics, clinical oncology, biochemistry and rational drug development and bring proven ability to translate cancer research breakthroughs into meaningful treatments for patients. These scientific leaders are working collaboratively with Blueprint Medicines' management team and include Dr. Lydon; Dr. Druker, director of the Oregon Health & Science University Knight Cancer Institute; and Scott Lowe, Ph.D., an investigator at the Howard Hughes Medical Institute and deputy director of the Cold Spring Harbor Laboratory (CSHL) Cancer Center.

The company's management team and board of directors include proven biotechnology industry veterans. Joining Dr. Varma and Dr. Lydon on the board of directors is Mark Levin, a long-time personalized medicine visionary, partner at Third Rock Ventures and former chief executive officer of Millennium Pharmaceuticals, and Alexis Borisy, partner at Third Rock Ventures and founding chief executive officer of Foundation Medicine and CombinatoRx.

Dr. Varma stated, "For the first time, Blueprint Medicines brings together expert understanding of the molecular blueprint of cancer with a proprietary chemical library for the development of personalized cancer therapies to improve patient outcomes and shift cancer to a manageable condition." Dr. Armistead added, "Blueprint Medicines' library of novel and highly-selective compounds serve as both invaluable chemistry tools as well as starting points for pharmaceutical

drugs. Our world-class scientific team is using this library as part of our scientific strategy to develop programs powered by the understanding of cancer's aberrant mechanisms."

Mr. Levin said, "The promise and potential of personalized cancer treatments has been anticipated for decades, and many have been working diligently to make them a reality. Today, with a veritable 'revolution' underway in our understanding of the molecular drivers of cancer, we are better positioned than ever to fully realize that promise. We are extremely excited to bring together this group of pioneers and leaders to form Blueprint Medicines to do just that."

About Blueprint Medicines

Blueprint Medicines is driving the development of personalized, highly-selective cancer therapies that harness the growing understanding of the molecular blueprint of cancer. Using its powerful Insights-to-Validation™ Platform and proprietary chemical library, Blueprint Medicines is working to develop new therapeutic compounds and combination therapies that target the molecular aberrations that cause cancer and the emerging resistance mechanisms that make it increasingly difficult to treat. Founded in 2011 by a proven team of scientists and entrepreneurs with world-renowned expertise in the development of targeted cancer therapies, cancer genomics, and rational drug development, Blueprint Medicines is poised to realize the promise of the cancer data "revolution": truly personalized therapies that improve outcomes and shift cancer to a manageable condition. For more information on Blueprint Medicines, please visit the company's website at www.blueprintmedicines.com.

About Third Rock Ventures

Third Rock Ventures is a venture capital firm founded in 2007 with the mission to launch transformative life sciences companies. With more than $800 million and two funds under management, the firm is focused on working with passionate entrepreneurs to build exceptional companies working in areas of disruptive science that will make a difference in the lives of patients. The firm has assembled a team with deep expertise and a proven track record of building respected and successful life sciences companies. With decades of complementary, cross-functional operational and leadership experience, the Third Rock team actively engages with its portfolio companies to provide hands-on strategy and experience to successfully launch companies with the best vision, science, operations, people and culture. With offices in Boston, MA and San Francisco, CA, Third Rock is well positioned geographically to closely collaborate with its portfolio companies to achieve their goals. To learn more about Third Rock and its portfolio companies, please visit www.thirdrockventures.com.

Gleevec® is a registered trademark of Novartis Pharmaceuticals Corporation.

Source: "Blueprint Medicines Secures $40 Million Series A Financing to Translate New Molecular Data into Personalized Cancer Treatments," press release, April 11, 2011, Business Wire, https://www.businesswire.com/news/home/20110411005289/en/Blueprint-Medicines-Secures-40-Million-Series-Financing, accessed October 2019.

Exhibit 5 KIT and PDGFRA

KIT and PDGFRA are homologous tyrosine kinase receptors. In patients with gastrointestinal stromal tumors (GIST) and certain other malignancies, a spectrum of clinically relevant mutations force the KIT or PDGFRA protein kinase into an increasingly active state, resulting in tumor formation and growth. Additionally, in patients with KIT-driven GIST who are heavily pretreated, resistance mutations accumulate more frequently.

Source: Blueprint Medicines, "Research Areas of Focus," https://www.blueprintmedicines.com/science/research-areas-of-focus/, accessed October 2019.

Exhibit 6 Blueprint Medicines Series B Press Release

Blueprint Medicines Announces $25 Million Series B Financing

Product engine delivering a pipeline of selective, genomically defined product candidates

January 07, 2014 04:00 PM Eastern Standard Time

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Blueprint Medicines today announced the completion of a $25 million Series B financing. The oncology-focused investor, Nextech Invest Ltd., led the round, which also included founding investors Third Rock Ventures and Fidelity Biosciences as well as public investors Biotech Value Fund, L.P., Casdin Capital, LLC and other undisclosed investors.

"The strong team of leaders and scientific founders behind Blueprint Medicines have successfully built a product engine and resulting product-candidate pipeline that brings to life the vision of treating patients based on specific genomic drivers of cancer. We believe this approach is core to the future of oncology therapy with the promise of significantly improving survival while minimizing toxicities for patients," said Thilo Schroeder, Ph.D. of Nextech Invest Ltd. "Blueprint Medicines stands out for its high quality science and early track record for successful execution."

Blueprint's lead programs include the first known selective inhibitors of the KIT D816V mutation, which is the genomic driver of the underserved systemic mastocystosis patient population, as well as a key genomically defined subset of patients with gastrointestinal stromal tumors (GIST). The Company's pipeline also includes the first known isoform-selective FGFR4 inhibitors for patients with hepatocellular carcinoma with FGF19 amplification, the first clear genomic driver in liver cancer, and other tumors. Blueprint expects to initiate clinical trials for these programs in 2015.

"The Blueprint team is aggressively advancing our pipeline of selective, genomically defined product candidates," said Alexis Borisy, president and interim chief executive officer of Blueprint Medicines. "Given our approach of selective compounds to clear genomic drivers, with the resources provided to us through this financing, we will be able to move forward into the clinic and rapidly establish clinical proof-of-concept in well-defined patient populations. These product candidates will be developed as single agents in late-stage and resistant patient populations, and in combinations with other targeted agents and modalities in earlier lines of therapy."

About Blueprint Medicines

Blueprint Medicines is a patient-driven oncology company developing highly selective kinase inhibitors for genomically-defined cancer subsets. Led by a management team and advisors with world-renowned expertise in cancer genomics, drug discovery and clinical oncology, Blueprint has

developed a platform that combines genomics with a novel library of kinase inhibitors, enabling Blueprint to rapidly develop potent highly selective compounds against clear genomic driver targets. Founded in 2011, Blueprint is privately held and was initially financed by Third Rock Ventures and Fidelity BioSciences. For more information, please visit www.BlueprintMedicines.com.

About Nextech Invest Ltd.

Nextech Invest is a global investment manager founded 1998 and located in Zurich, Switzerland. With its unique oncology-focused funds, Nextech Invest is a dedicated investor in leading oncology companies developing cancer drugs and diagnostics. Nextech Invest benefits from the support of an active 7-member Scientific Advisory Board of highly influential oncology advisors, chaired by David Livingston, MD, deputy director at the Dana-Farber Cancer Institute/Harvard Cancer Center. For more information, please visit www.nextechinvest.com.

About Third Rock Ventures

Third Rock Ventures is a leading healthcare venture firm focused on investing and launching companies that make a difference in people's lives. The Third Rock team has a unique vision for ideating and building transformative healthcare companies. Working closely with our strategic partners and entrepreneurs, Third Rock has an extensive track record for managing the value creation path to deliver exceptional performance. For more information, please visit the firm's website at www.thirdrockventures.com.

About Fidelity Biosciences

Fidelity Biosciences is a subsidiary of FMR LLC, the parent company of Fidelity Investments, one of the world's leading providers of financial services. For more than 40 years, Fidelity has been a significant presence in the venture capital and private equity industry, investing the firm's own capital since 1969. Learn more at www.fidelitybiosciences.com.

Source: "Blueprint Medicines Announces $25 Million Series B Financing," press release, January 7, 2014, Business Wire, https://www.businesswire.com/news/home/20140107006754/en/Blueprint-Medicines-Announces-25-Million-Series-Financing, accessed October 2019.

Exhibit 7 Blueprint Medicines Series C Press Release

Blueprint Medicines Secures $50 Million in Series C Financing

-Proceeds to support continued advancement of highly selective kinase inhibitors to genomically defined cancers, including first-in-class FGFR4 and KIT Exon 17 inhibitors-

-Investor syndicate includes leading public healthcare funds-

NEWS PROVIDED BY

Blueprint Medicines

Nov 12, 2014, 08:05 ET

CAMBRIDGE, Mass., Nov. 12, 2014 /PRNewswire/ -- Blueprint Medicines, a leader in discovering and developing highly selective kinase inhibitors for genomically defined cancers, today announced the completion of a $50 million Series C financing. Proceeds from the financing will be used to advance Blueprint Medicines' two lead product candidates through clinical trials in 2015 and fund the continued development of Blueprint Medicines' kinase discovery platform and pipeline.

"The proceeds from this financing provide us with the financial strength to initiate clinical trials for our FGFR4 and KIT Exon 17 inhibitors in 2015 with the goal of establishing proof of concept rapidly and ultimately improving the lives of patients," said Jeffrey Albers, chief executive officer of Blueprint Medicines. "We are incredibly pleased to welcome such highly respected public investors to our shareholder base. Their investment provides strong endorsement for the quality of the platform, pipeline and team we've built at Blueprint Medicines over the past three years."

Blueprint Medicines' Series C financing was led by Partner Fund Management and included additional new investors, Wellington Management Company, RA Capital, Tavistock Life Sciences, Perceptive Advisors, Sabby Capital, Cowen Investments and Redmile Group. The Company's existing shareholders – Biotechnology Value Fund, Casdin Capital, Fidelity Biosciences, Nextech Invest and Third Rock Ventures – also participated in the financing.

"Blueprint Medicines' proprietary kinase platform, which combines a first-of-its-kind chemical library and a novel genomics-based target discovery engine, holds significant value creation potential," said Alex Virgilio, Ph.D. of Partner Fund Management. "The team has achieved impressive results to date by rapidly discovering and advancing two first-in-class product candidates toward clinical development. We believe the team can sustainably replicate this success based on the strength of the platform in producing exquisitely selective inhibitors to novel genomically defined kinase targets."

Blueprint Medicines expects to initiate clinical trials in 2015 with its two lead product candidates:

BLU-285 is the first known selective inhibitor of KIT Exon 17 mutants. The Company intends to initiate two clinical studies, including one for the underserved systemic mastocytosis patient population and another for genomically defined subsets of patients with gastrointestinal stromal tumors (GIST).

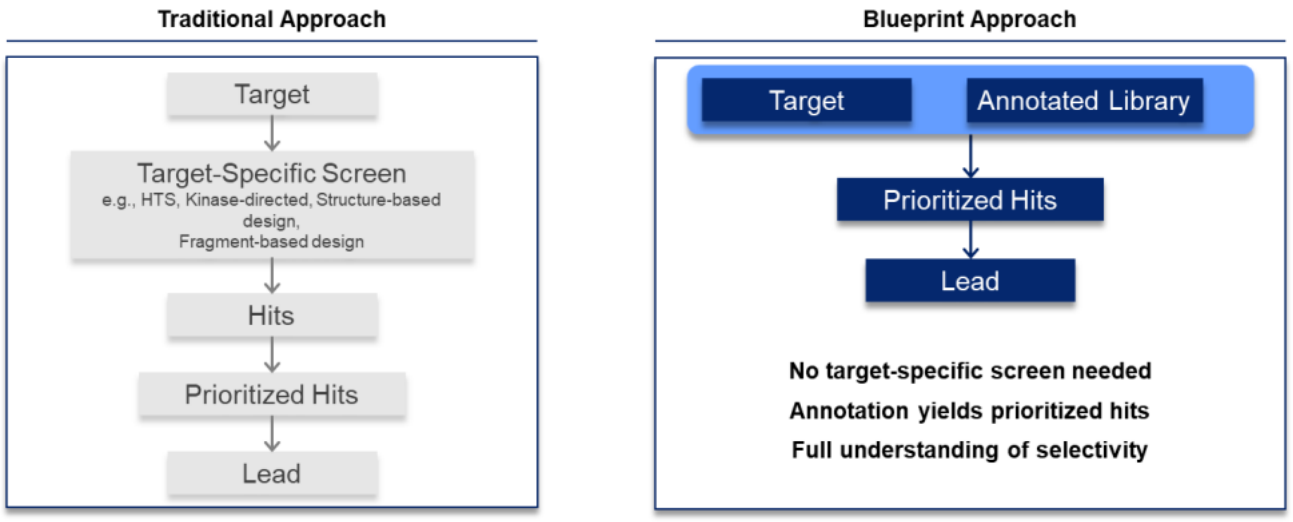
BLU-554 is the first known selective FGFR4 inhibitor. Blueprint Medicines anticipates initiating a clinical study for patients suffering from hepatocellular carcinoma with aberrant FGFR4 pathway activation.

About Blueprint Medicines

Blueprint Medicines is a patient-driven oncology company discovering and developing highly selective kinase inhibitors for genomically defined cancers. Led by a management team and advisors with world renowned expertise in cancer genomics, drug discovery and clinical oncology, Blueprint Medicines has developed a platform that combines genomics with a novel small molecule library of kinase inhibitors, enabling Blueprint Medicines to rapidly discover potent and highly selective drugs against clear drivers of diseases. Founded in 2011, Blueprint Medicines is privately held and initially backed by Third Rock Ventures and Fidelity BioSciences. For more information, please visit www.blueprintmedicines.com.

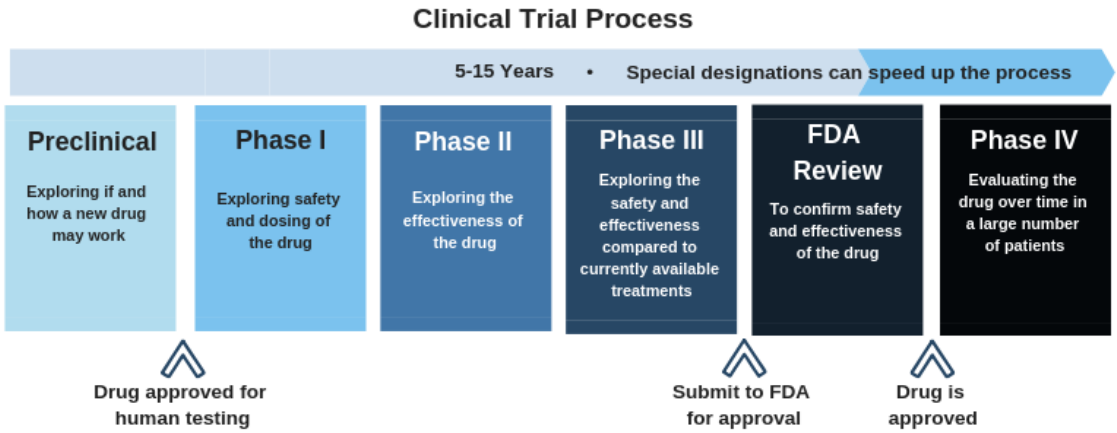
Source: "Blueprint Medicines Secures $50 Million in Series C Financing," press release, April 11, 2011, PR Newswire, https://www.prnewswire.com/news-releases/blueprint-medicines-secures-50-million-in-series-c-financing-282396331.html, accessed October 2019.

Exhibit 8 Blueprint Medicines' Approach to Building its Library Compared to Traditional Approach



Source: Company documents.

Exhibit 9 Clinical Trial Process Based on FDA Requirements



Source: Hepatitis B Foundation, "Phase 3 Clinical Trials Opening for Hepatitis Delta Patients," March 21, 2019, https://www.hepb.org/blog/phase-3-clinical-trials-opening-hepatitis-delta-patients/, accessed October 2019.

Exhibit 10 FDA Description of Breakthrough Therapy Designation (BTD)

Breakthrough Therapy designation is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).

To determine whether the improvement over available therapy is substantial is a matter of judgment and depends on both the magnitude of the treatment effect, which could include duration of the effect, and the importance of the observed clinical outcome. In general, the preliminary clinical evidence should show a clear advantage over available therapy.

For purposes of Breakthrough Therapy designation, clinically significant endpoint generally refers to an endpoint that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease. A clinically significant endpoint can also refer to findings that suggest an effect on IMM or serious symptoms, including:

- An effect on an established surrogate endpoint
- An effect on a surrogate endpoint or intermediate clinical endpoint considered reasonably likely to predict a clinical benefit (i.e., the accelerated approval standard)
- An effect on a pharmacodynamic biomarker(s) that does not meet criteria for an acceptable surrogate endpoint, but strongly suggests the potential for a clinically meaningful effect on the underlying disease
- A significantly improved safety profile compared to available therapy (e.g., less dose-limiting toxicity for an oncology agent), with evidence of similar efficacy

Exhibit 10 (continued) FDA Description of Breakthrough Therapy Designation (BTD)

A drug that receives Breakthrough Therapy designation is eligible for the following:

- All Fast Track designation features
- Intensive guidance on an efficient drug development program, beginning as early as Phase 1
- Organizational commitment involving senior managers

Breakthrough Therapy designation is requested by the drug company. If a sponsor has not requested breakthrough therapy designation, FDA may suggest that the sponsor consider submitting a request if: (1) after reviewing submitted data and information (including preliminary clinical evidence), the Agency thinks the drug development program may meet the criteria for Breakthrough Therapy designation and (2) the remaining drug development program can benefit from the designation.

Ideally, a Breakthrough Therapy designation request should be received by FDA no later than the end-of-phase-2 meetings if any of the features of the designation are to be obtained. Because the primary intent of Breakthrough Therapy designation is to develop evidence needed to support approval as efficiently as possible, FDA does not anticipate that Breakthrough Therapy designation requests will be made after the submission of an original BLA or NDA or a supplement. FDA will respond to Breakthrough Therapy designation requests within sixty days of receipt of the request.

Source: "Breakthrough Therapy," U.S. Food and Drug Administration, https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy, accessed October 2019.

Exhibit 11 RET

Across a range of cancers, including non-small cell lung cancer, medullary thyroid cancer and papillary thyroid cancer, oncogenic alterations in RET, a tyrosine kinase receptor, cause ligand-independent kinase activation, driving tumor formation and growth. The two primary mechanisms of oncogenic RET activation are fusions and activating mutations. In addition, acquired RET resistance mutations have been observed with currently approved multi-kinase inhibitors.

Source: Blueprint Medicines, "Research Areas of Focus," https://www.blueprintmedicines.com/science/research-areas-of-focus/, accessed October 2019.

Endnotes

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[4] Ben Fidler, "Blueprint Medicines Bags $147M in Upsized IPO," Xconomy, April 29, 2015, https://xconomy.com/boston/2015/04/29/blueprint-medicines-bags-147m-in-upsized-ipo/, accessed September 2019.

[5] Robert Weisman, "Third Rock's biggest bet ever is on cancer drugs," *Boston Globe*, April 22, 2011, http://archive.boston.com/business/healthcare/articles/2011/04/11/third_rocks_biggest_bet_ever_is_on_cancer_drugs/, accessed September 2019.

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[7] Gregory T. Huang, "Blueprint Medicines Brings In $40M, Led by Third Rock, for Targeted Cancer Therapies," Xconomy, April 22, 2011, https://xconomy.com/boston/2011/04/11/blueprint-medicines-brings-in-40m-led-by-third-rock-for-targeted-cancer-therapies/, accessed September 2019.

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[9] "Blueprint Medicines Announces $25 Million Series B Financing," press release, January 7, 2014, Business Wire, https://www.businesswire.com/news/home/20140107006754/en/Blueprint-Medicines-Announces-25-Million-Series-Financing, accessed September 2019.

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[11] BPMC, Crunchbase, https://www.crunchbase.com/ipo/blueprint-medicines-ipo--328beb76, accessed September 2019.