

Article

Putting Theory into Practice at BridgeBio

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MANY DRUG COMPANIES spring from scientific discoveries made in a laboratory. BridgeBio Pharma, though, owes its genesis to the musings of a financial theorist.

MIT Sloan School of Management Professor Andrew Lo began educating himself about the world of cancer therapies when in a four-year period of time he lost six friends and his mother to cancer. As Lo searched for information about potential new treatments for people he cared about, he started to learn about the drug development process, and soon came to view the translational science challenge of moving a potential therapy from discovery to proof of concept—a gulf that’s come to be known as the “valley of death”—as being a financial, rather than a scientific, problem. “It occurred to me that finance ends up playing a big role in drug development—often too big a role in my view,” said Lo. “That’s when I started to think about applying the tools that I was familiar with to this area and to see whether or not it can make a difference.”

In a paper Lo coauthored in *Nature Biotechnology* in 2012, he argued that the solution rested in applying portfolio theory to biomedical innovation. The approach to drug development where a so-called “megafund”—a fund of between \$5 billion to \$15 billion—could invest in a large and diversified range of assets at different stages where the success or failure of any single asset was largely independent from the success or failure of another.¹ Doing so could reduce risk and increase the odds of success. At the same time, he argued for a mix of equity and securitized debt to tap into larger sources of capital to fund a multi-billion portfolio of projects.

Even though the approach might reduce the potential for venture capital-sized returns sought by classic biotech investors, it would open access to nontraditional

biotech investors such as pension funds, insurance companies, and large institutions that have a lower appetite for risk but are satisfied with a lower level of return. A simulation for the paper based on new molecular entities to treat cancer from 1990 to 2011 yielded average investment returns of 8.9 to 11.4 percent for equity holders and 5 to 8 percent for research-backed obligation holders.²

The paper came at a time when the expiration on patents from blockbuster drugs were delivering a wallop to Big Pharma revenue and R&D productivity was falling as the industry in 2010 found itself spending nearly twice what it spent in 2002 for R&D investment, but yielding roughly the same number of new drugs year after year.

The paper struck a nerve with Neil Kumar, a principal in the venture capital firm Third Rock Ventures. Kumar had taken a finance class with Lo while he was earning his Ph.D. in chemical engineering at MIT. He later attended a conference Lo organized around the themes of the paper and approached his former professor about an idea he had. He wanted to apply the approach Lo advocated to the world of rare disease. As it turned out, Lo had a preprint of another paper he had been working on that applied the model to rare diseases, which he believed was even better suited for such an approach because of a more streamlined development path and incentives established through the Orphan Drug Act.

In 2015, Kumar and a number of other co-founders including Lo, launched BridgeBio, to develop therapies for rare genetic diseases and genetically-defined cancers. The company’s name is meant to suggest a bridge across the valley of death. BridgeBio licenses therapeutic candidates from universities and research institutes that are good at innovation but lack the capital and expertise to advance these candidates through clinical development. It may also license an asset from a biopharmaceutical company that abandoned it in development because of a change in strategy, or because it has failed in one indication but BridgeBio sees potential for its use in another.

1 Fernandez, J. M., Stein, R. & Lo, A. Commercializing biomedical research through securitization techniques. *Nature Biotechnology* 30, 964–975 (2012). <https://doi.org/10.1038/nbt.2374>

2 *ibid*

LEAN AND FOCUSED

Biotech companies have long liked to boast about big pipelines that provide them with multiple shots on goal, but the financial reality of the substantial capital needed to move a therapeutic candidate through development to market means the fortunes of smaller companies with multiple product candidates often rise and fall with the success or failure of a lead program. “There’s a lot more capital in the world that is scared of taking biotech-like binary risk than there is that wants to take that type of risk,” said Kumar.

BridgeBio puts Lo’s portfolio theory model into practice. When the company finds an asset it wants to develop, it forms a subsidiary company around that asset and charges the subsidiary with advancing the candidate through the development process. These subsidiary companies operate as lean as possible with specialized scientific talent who are incentivized around the subsidiary’s success and provided with enough capital to advance the asset to the next decision point.

The company contends it has among the lowest ratios of headcount to development candidate programs in the industry. As of the end of 2020, the company had 385 full-time employees and 11 part-time employees, 268 of whom are focused on driving research and development programs through its affiliates and 128 of whom work across the company to provide strategic business development, finance, and executive leadership. The company assembles teams of fewer than five people around early-stage assets. That number will increase to about ten people as it finishes preclinical development. Once a program is in the clinic, it will size a team as needed with a focus on the minimum viable number of people needed.

Kumar estimates it takes BridgeBio less than \$10 million on average through preclinical development and about \$30 million for a gene therapy. Part of the ability to run lean comes from minimizing overhead and fixed costs. The parent company’s central team provides certain shared support services and workspaces that limit the fixed infrastructure subsidiaries need. For instance, finance functions reside at the parent level.

And to ensure a scientist’s or executives’ self-interest or commitment to a program doesn’t cloud thinking about whether to advance or kill a program, that decision is left to members of a committee at the parent company whose compensation is not tied to any single program, but rather the success of the total enterprise. They are charged with making dispassionate decisions to maximize the value of the company.

“I disagree with the concept that a group of scientists would kill their own project. If they would, I question their passion for it because there’s always some parameter that’s available to you—there’s always some hope

for a program, particularly preclinically,” said Kumar. “You need to divorce the people who are working in a very focused way to make a program successful from the people who ultimately are going to shut it down or keep it going. That is a key aspect of BridgeBio.”

Today, the company boasts 20 subsidiaries, more than 30 programs in development, with 19 ongoing clinical trials.³ It got additional validation for the model at the end of February 2021 when the U.S. Food and Drug Administration approved Nulibry for its affiliate Origin Biosciences. Nulibry is the first treatment for the ultra-rare, genetic, metabolic disorder molybdenum cofactor deficiency type A, the first drug approval for the company. BridgeBio acquired Nulibry as a late-stage asset from Alexion Pharmaceuticals in 2018 for undisclosed terms.

BridgeBio raised \$348.5 million in an upsized initial public offering in 2019 to help fund its growing pipeline. It was the largest biotech IPO of that year. Part of the argument for the portfolio approach is that by mitigating the risk typically associated with biotech development, a company could access a much broader range of investors and financing instruments, such as convertible debt, to fund translational research. BridgeBio has done that. Most recently it raised nearly \$750 million through an offering of convertible notes in February 2021 that pay 2.25 percent interest.

THE CASE FOR RARE GENETIC DISEASES

BridgeBio focuses on rare genetic diseases because these conditions have clear targets for drug development. The indications it pursues can be tied to a specific genetic mutation and pathway that allows it to develop candidates with mechanisms of action that treat the underlying cause of a disease.

“This is a space where innovation has been incredible in terms of understanding the true causal drivers of disease and being able to map from a genetic aberrant to protein dysfunction, to cell signaling, and ultimately to symptomatology. And that is all happening on the back of cheaper and cheaper exome and genome sequencing and better and better availability of data that marries molecular data like genetic data and symptomatic or phenotypic data,” said Kumar. “There’s a constellation of technologies that allow us to understand these diseases better than we understand diabetes or a common form of heart failure.”

Kumar said working from a clear understanding of the mechanism of a disease is an “elegant” type problem that is more akin to engineering than biology. If there is a link between an underlying mutation to a gene and its relation to the symptom and progression of a disease, a drug developer has more information to work with than is typical for larger, less defined syndromes. That, he said, increases the probability for success. In fact, the company noted in its registration statement with the U.S. Securities and Exchange Commission that from 2006 to 2015, drug programs for orphan indications had a 2.5 times higher likelihood of successful development from phase 1 to approval than drugs across all indications.⁴

At the same time, Mendelian diseases—those caused by a mutation to a single gene—represent a large unmet medical need. There are more than 7,400 rare Mendelian phenotypes that have been identified. Nevertheless, since the passage of the Orphan Drug Act in 1983, there are approved therapies for only about 5 percent of these conditions.⁵ While rare disease drug development has long been encumbered by a lack of understanding of these conditions, advances in sequencing, progress in understanding the molecular basis of diseases, and the availability of long-term retrospective studies that elucidate the connection between genotype to phenotype is changing that.

A BRIDGE PLATFORM

While BridgeBio is agnostic about the modalities of the medicines it develops—its pipeline runs the gamut from small molecules to gene therapy—there are several critical elements the company looks for when it identifies new programs to pursue. In fact, BridgeBio has mapped the known universe of Mendelian diseases and applied a set of 14 criteria to those conditions to identify potential opportunities of interest. From a scientific perspective, those criteria are intended to determine how well described a disease is, the opportunity to target it at its source, and whether there is a clear genotype/phenotype relationship that could enable the design of a drug. It also takes into account business considerations, such as potential commercial viability of a product, intellectual property positions, prospects for favorable pricing and reimbursement, and the potential impact of competition.

4 BridgeBio Pharma Form S-1 Registration Statement, United States Securities and Exchange Commission, May 24, 2019, Page 120. <https://investor.bridgebio.com/node/6571/html>, accessed May 8, 2021

5 *ibid*

To find new opportunities, BridgeBio has a team of scientists who scour public genetic databases to identify potential new targets while a business development team spends its time on the road engaging with technology licensing offices and academics in search of promising programs and new relationships with research centers.

As a reflection of these efforts, the company in April 2021 announced seven separate collaborations with top academic and research institutions around genetic disease and cancers with clear genetic drivers. That increased the total number of such collaborations to 20 for the company. Though the term and focus of each partnership varies, they involve BridgeBio working closely with outside scientists to identify and fund programs that they may choose to license. Among its partnerships include ones with Boston Children’s Hospital, Cincinnati Children’s Hospital Medical Center, MD Anderson Cancer Center, the University of California San Francisco, and St. Jude Children’s Research.

And while the low R&D productivity of the pharmaceutical industry set off a trend many years ago to externalize innovation, Kumar said that for preclinical assets targeting genetic diseases, there is still a lack of capital and interest, particularly in preclinical small molecule programs focused on rare diseases.

“The premise that we started with was that there’s a lot of just great innovation that was going untapped. That was something we were living. I didn’t need a data set to tell me that there was no one who really wanted to start with stuff that was three years before the clinic,” he said.

While there are aspects of the business that have become increasingly competitive, there are broad swaths of therapeutics that BridgeBio pursues where there are few biopharmaceutical players or venture capital interest. That leaves plenty of opportunity particularly at a time when academia has become adept at identifying interesting starting points for drugs.

A NEW PHASE BEGINS

As BridgeBio begins life as a commercial biotech, it has been thinking how to best extend its model from a development company to a commercial company. That in part is complicated by the nature of markets for rare disease therapies and the need to understand the unique characteristics of patient populations and the physicians who serve them.

While its drug Nulibry has been approved to treat MOCD type A, other programs are in late-stage development. In March, BridgeBio subsidiary QED Therapeutics announced a global collaboration and licensing agreement with Helsinn Group to develop and commercialized QED Therapeutics’ FGFR1-3 inhibitor infigratinib in oncology and all other indications except for skeletal

dysplasias including achondroplasia, a rare genetic condition and the leading cause of dwarfism. The deal provided QED with more than \$100 million in upfront payments and the potential to receive a total of more than \$2 billion in milestone payments. The FDA is reviewing an application to approve infigratinib as a treatment for cholangiocarcinoma, a bile duct cancer, in patients with an FGFR2 gene fusion rearrangement.

Under the terms of that agreement, QED and Helsinn will co-commercialize infigratinib in oncology indications in the United States and will share profits and losses equally. Helsinn will have exclusive commercialization rights and lead commercialization for infigratinib in non-skeletal dysplasia indications outside of the

U.S., excluding China, Hong Kong and Macau, which are covered by BridgeBio's strategic development and commercialization collaboration with LianBio.

"We've thought a great deal about it. It needs to continue to be focused on the level of the disease so that we can market these drugs in a way that is consistent with who we are as a company, which is a rigorous science company," said Kumar. "But that needs to be centralized, so that we can build capabilities in things like patient outreach services, market access, or distribution, so that we can be the best owner of these compounds as they are ultimately commercialized. Scale there is useful, but it's not going to be the traditional call-point scale."