Applications of Portfolio Theory to Accelerating Biomedical Innovation

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KEY FINDINGS

- The principles of portfolio theory and financial engineering are applicable to many settings and industries, and this article describes the example of BridgeBio Pharma, a portfolio company focused on developing therapeutics for diseases that have traditionally been overlooked by the biopharma industry.
- Diversification, low pairwise correlation between development programs, and faster, more efficient clinical trials are key drivers in lowering the cost of capital, making early-stage drug development more financially viable, which attracts a broader range of investors.
- Rare and genetic diseases are particularly well-suited for a portfolio approach to therapeutic development, but other areas where there are an insufficient number of programs or too high a level of pairwise correlation to yield meaningful risk reduction may not be appropriate for such an approach.

ABSTRACT

Biomedicine is experiencing an inflection point in which the origins of many human diseases have been decoded, leading to new treatments and, in some cases, complete cures. Many domain experts acknowledge that the gating factor to innovation is not knowledge, but rather a lack of financial resources to translate theory into practice, the so-called "valley of death" between scientific discovery and the clinical testing that must be done with human subjects before regulators will approve a new drug or medical device. This process of translational medicine is largely an exercise in risk management—organized as a carefully planned sequence of experiments, each one involving a progressively larger number of subjects that may or may not be allowed to continue, depending on the results of the prior experiment. It is, therefore, a natural setting in which to apply modern portfolio theory. The authors describe one such application involving a biotechnology company focused on genetic diseases and the lessons learned from that experience.

Editor's Note: This article, which I invited for the Journal some time ago, is unusual given its focus on the development of a specific company, written by its cofounders and senior management. One of the most compelling aspects of this article is its exploration into the practical applications of portfolio theory beyond traditional financial settings, specifically its use in securing funding to support research aimed at combating rare diseases. This is a pivotal extension of portfolio theory that could potentially revolutionize how funding is allocated in the biomedical sector, addressing one of the most

pressing challenges: the scarcity of resources for rare disease research. The significance of this application cannot be overstated. Rare diseases, often overlooked due to their lower prevalence, struggle to attract the necessary investment for research and development compared to more common ailments. By applying portfolio theory, this article illustrates a viable strategy to attract and secure essential funding by distributing risk and demonstrating potential returns across a diversified portfolio of research projects. This approach not only mitigates the financial risk associated with high-stakes biomedical research, but also maximizes the potential to achieve groundbreaking medical breakthroughs. The editor of the journal has recognized this contribution as one of the most critical advancements in the application of portfolio theory. It goes beyond academic interest, offering a tangible method to support a sector that can transform lives, but is frequently constrained by economic considerations. What could be more vital than enabling research that could lead to treatments or cures for conditions that currently have few or no options? By highlighting this novel application, the article contributes profoundly to the ongoing discussion about the role of finance in advancing medical science, particularly in areas that are critically underfunded. This exploration into using financial tools for social good represents a significant shift in how economic theories can be harnessed to address real-world problems, making it a landmark discussion in the literature on portfolio theory and biomedical funding. This article, therefore, stands out not only for its academic and practical contributions, but also for its unique origin and insightful perspectives from those who are directly shaping the field.

The occasion of *The Journal of Portfolio Management*'s 50th anniversary—an extraordinary milestone in the Information Age, where print and online publications come and go like the seasons—is a testament to the durable legacy of Harry M. Markowitz's (1952) breakthrough idea of portfolio theory. It is no exaggeration that this theory has become the basis of most financial products and services, from index funds and ETFs to hedge funds, venture capital, and private equity to personal financial advisory services. In this article, we demonstrate the legacy's breadth by illustrating Markowitz's impact on the field of biomedicine, both in theory and in practice. This far-flung application may seem surprising and forced at first blush, perhaps another instance of someone with a hammer seeing nails everywhere. However, we hope to show that not only is the application genuine, but it has also been repeated in multiple biomedical contexts, achieving results like those in more traditional financial portfolio management settings.

The specific application we focus on in this article is the case of BridgeBio Pharma, a biotechnology company founded in 2015. The company was, and is, an experiment—a new approach to funding and developing medicines based on the principles of modern portfolio theory that was novel for the industry at the time. The company was launched with the mission of developing a portfolio of therapeutics for genetic diseases, many of which are treatments for rare conditions that are not priorities for larger pharmaceutical companies.

It is unusual for company cofounders to describe the origins and evolution of their business in a peer-reviewed journal, and it is even rarer when they are still actively engaged in that business. We have done so for three reasons.

First, we believe that one of the most significant impediments to biomedical innovation is the outsized financial risk involved in the binary nature of clinical-trial outcomes. Portfolio theory can help reduce such risks, allowing more capital to enter this important industry which will lead to more and better treatments for patients.

Second, the idea of applying portfolio theory to drug development was first proposed over a decade ago (Fernandez, Stein, and Lo 2012) and a substantial academic literature has now arisen around the theme of financial innovation to accelerate

biomedical innovation.[1] A persistent question is whether this hypothetical "megafund" proposal is truly practical—we provide an affirmative answer in this article, but in a specific context that also highlights some important limitations and risks. By making our approach more transparent, we hope to support the efforts of those seeking to apply BridgeBio's business model to their own contexts, while not giving false hope to others for whom our approach is ineffective.

Third, by telling BridgeBio's story, we hope to motivate our biotech colleagues to share their experiences as well so that those seeking to develop treatments for diseases they care most about can be properly prepared to do so with the most effective commercialization strategies. In particular, other examples of biotech companies founded explicitly to develop portfolios of drugs now exist, including Biohaven Pharma, ElevateBio, Gossamer Bio, Nimbus Therapeutics, PureTech Health, and Roivant Sciences. According to the McKinsey report by Bleys et al. (2021), "As of August 2020, these companies have raised approximately $6 billion in capital and had an estimated public- and private-market valuation of approximately $20 billion." These examples, and several others under development, all serve to highlight the importance of aligning business and financing structures with the scientific and medical goals of biotechnology at the outset of the company's launch, not just at the point of an initial public offering (IPO), or on the eve of a favorable regulatory decision.

Teaching cases with discussion questions are provided to further aid in exploring the practical applications of the theories and principles discussed in this article. These can be found in the online supplement, offering a hands-on approach to understanding the material covered in this article.

MOTIVATION

There is a phenomenon in the biopharma sector known as the "valley of death." It is where good biomedical research goes, if not to die, then to languish for years for want of funding. Other industries have their version of this valley—for example, Hollywood has its infamous "development hell"—but in the biopharma sector, this valley can have a direct and negative impact on the health and well-being of millions of people. Strong biomedical research that lacks the capital to advance will never turn into medicine for patients.

A lack of investment in primary drug discovery and early-stage translational research causes this valley. Basic research might lead to the discovery of a promising candidate for development into a treatment, but it cannot attract the investment required to bring it from the academic setting through the clinical trial process to approval by national and international regulatory agencies.

At the same time, large pharmaceutical companies have cut research and development funding for entire classes of therapeutics (see Tollman et al. 2016, Knowles and Higgins 2010, and Morgan Stanley Research Europe 2010). Some common conditions, such as Parkinson's, appear too high risk to most companies based on current scientific understanding, while many less-common diseases have limited markets for profitable drug development. These companies see little way to recoup an investment in either of these areas.

Some have speculated that the rate of general technological innovation is slowing.[2] Yet the valley of death is not the result of a slowing pace of biomedical research, but instead of insufficient financial incentives to overcome the risk of successful commercialization. Many large pharmaceutical companies have substantial

[1] See, for example, the literature reviews by Lo and Thakor (2022, 2023).

[2] Scannell et al. (2012). However, more-recent evidence seems to suggest that this trend may be reversing (Ringel et al., 2020).

funds, but choose not to deploy them in pursuit of clinical long shots—even if success would be highly profitable—simply because the risk is considered too high.

There is a clear need for new business models in translational research that align financial incentives with medical imperatives and societal needs. In this era of financial engineering, it is a natural question to ask whether it is possible to use those techniques to create the appropriate incentives to attract investment in these underfunded preclinical areas.

From a purely economic perspective, combining several independently risky assets into a single portfolio will cause the overall risk of the portfolio to drop, provided that these assets are not perfectly pairwise correlated, the first principle of modern portfolio theory formulated by Nobel-prize-winning financial economist Harry Markowitz (1952) over half a century ago. The related cash flows can then be pooled together, repackaged, and sold according to their lower computed level of risk. These assets might be any sequence of well-defined receivables.

A case in point is the US housing boom of the first decade of this century: The securitization of home mortgages uses precisely this form of portfolio risk reduction. In this case, the receivables were mortgages, and the sale of mortgage-backed securities funded the housing boom. This process was able to draw tremendous amounts of investor interest, even in very high-risk mortgages. For better or for worse, this boom and the ensuing financial crisis of 2008 showed the world the raw power of this previously obscure set of financing techniques.

What if it were possible to harness this immense financial power for an underserved social good by investing in the high risk of a preclinical or early-stage clinical biomedical asset?

THE ORIGIN OF BRIDGEBIO

In 2012, Fernandez, Stein, and Lo (2012) took Markowitz's concept of portfolio risk reduction in the ebb tide after the financial crisis and expanded it to propose the establishment of a "megafund" for cancer drug development. As initially proposed, this megafund would pool many oncology drug development programs into a single, very large financial entity, requiring several billion dollars of capital, hence the term "megafund."[3] Historically, any individual oncology program has an extremely low probability of success, enough to make a subprime mortgage look almost risk-free in comparison, but with enough "shots on goal," the economics improve considerably.

While the necessary size of an oncology megafund would take up a significant share of available venture capital, the fund was intentionally designed to tap into the much larger bond market.[4] The multiple shots-on-goal approach of the megafund would use Markowitz's discovery to lower the aggregate risk of the fund and raise the probability of overall drug development success to near-certainty, not merely of one cancer drug, but of several. This would de-risk the drug development process enough for its managers to issue long-term bonds backed by the research itself, dubbed "research-backed obligations" (RBOs) by Fernandez, Stein, and Lo (2012), analogous to collateralized debt obligations (CDOs) such as mortgage-backed securities and other forms of structured financing. These, in turn, would provide a much more attractive risk–return profile for institutional investors than their preclinical components. At the same time, the fund would also issue equity for other, less-risk-averse investors.

[3] Fernandez, Stein, and Lo (2012); Fagnan et al. (2013).

[4] At the end of 2023, the total assets under management by all US venture capitalists was $1.2 trillion (NVCA 2024), whereas the total US corporate debt outstanding was $10.7 trillion (https://www.sifma.org/resources/research/us-fixed-income-securities-statistics/ accessed 13 August 2024).

Extensive Monte Carlo simulations to test the feasibility of a megafund were promising. At the same time, the urgent social need for increased funding for translational research appeared self-explanatory to Fernandez, Stein, and Lo. Open-source software for simulating the megafund and its underlying assumptions was made public,[5] so that others could check the robustness of the analysis, test their own ideas with an entirely different set of assumptions and parameters, and form a working intuition about the advantages and limitations of the megafund concept in other contexts.

The concept captured the imagination of a former student of Lo's, Dr. Neil Kumar, who had enrolled in Lo's introductory finance class years earlier, while completing his PhD in chemical engineering at MIT. While a consultant at McKinsey & Company, Kumar investigated the possible use of portfolio theory by large pharmaceutical companies with BridgeBio's future chief financial officer, Dr. Brian Stephenson. However, these large companies were profitable, had access to debt capital markets, and were not an obvious starting point to apply the original megafund concept.

Any successful research-backed fund, Kumar realized, needed to deploy capital where the system was currently inefficient. In the existing drug development environment, this meant primarily early-stage research and drug discovery programs advanced by prerevenue, still-unprofitable biotech companies. The high risk and long development timelines had historically discouraged most categories of investors from putting capital into this arena, at a significant social cost. However, if a new approach could be established, the combination of diversification, operational synergies, and cost savings would lead to a lower cost of capital for additional programs. This would move existing projects on the bubble from a negative net present value (NPV) to a positive NPV.

Lo began having conversations with Kumar regarding the practical implementation of a megafund in the spring of 2013,[6] soon looping Stephenson into the discussions.[7] The CanceRx conference at MIT,[8] organized by Lo in June 2013, brought together a group of over 100 stakeholders from the biomedical and investor communities to engage in concrete discussions and debate about new business and financing models for drug development, with a particular focus on cancer therapeutics and the explicit intention to spark new business models and collaborations to address the valley of death. This conference—and the various conversations between Kumar, Lo, and Stephenson around it—became the basis for the original BridgeBio proposal.

RARE DISEASES

One of the first questions that needed to be addressed was the amount of financing required. The original megafund model of Fernandez, Stein, and Lo (2012) called for $5 billion to $15 billion to create an oncology-focused portfolio. Given that, at the time, the largest biotech VC funds did not have assets approaching these figures, this seemed unrealistic to most biopharma industry insiders.

By 2013, Lo had already been exploring a range of alternatives to the oncology focus that required a more modest level of funding than the initial megafund model, including portfolios consisting only of therapeutics for rare or "orphan" diseases.[9] The term "orphan" indicates the historical lack of interest in these diseases on the part of the biopharma industry. The US Food and Drug Administration (FDA) formally defines

[5] See https://projectalpha.mit.edu/resources/ for all related software and documentation.
[6] Email from NK to AWL, April 29, 2013.
[7] Email from NK to AWL, June 27, 2013.
[8] https://lfe.mit.edu/events/cancerx-2013/.
[9] See Fagnan et al. (2014, 2015).

EXHIBIT 1

Total Orphan Drug Designations

Time Period	Orphan Drug Designations	Initial Orphan Drug Approvals
1983–1992	531	80
1993–2002	649	151
2003–2012	1,527	181
2013–2022	3,633	470

NOTE: Total orphan drug designations (n = 6,340) and initial orphan drug approvals (n = 882) by decade, 1983–2022.

SOURCE: Fermaglich and Miller (2023, Figure 1).

a rare or orphan disease as a disease that affects fewer than 200,000 people in the United States, corresponding to a prevalence of less than one in 1,600. Specific examples include hemophilia, cystic fibrosis, amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), Duchenne muscular dystrophy, pediatric cancers, and many other genetic and inherited disorders. Although any single rare disease affects only a relatively small number of patients, it is estimated that there are over 8,000 rare diseases,[10] affecting as many as 30 million Americans in total, more than the estimated number of Americans with cancer.

Rare diseases possess several essential characteristics that make them ideal for a portfolio approach. First, in many cases, the scientific underpinnings of rare diseases are more easily identified than those of cancer. For example, many of these diseases are caused by mutations in a single gene, and therapeutic interventions for these "Mendelian" diseases can consequently be more strongly hypothesized, tested, and confirmed. It is believed that more than 80% of rare diseases are genetic in origin.[11] As a result, the historical probability of success has been higher for developing rare disease therapeutics than cancer therapeutics.

The focus on rare diseases for a megafund also made financial sense. Orphan drugs were once thought to have little commercial potential due to their small market size, but they have become an unusually bright spot in the biopharmaceutical industry. Today, this category has an estimated $45 billion of sales annually in the United States, representing 10% of all current US drug sales. This evolution in drug development was both scientific and technological in origin, as well as legislative and economic. Much of the scientific and technological origin of the advancement in rare diseases stems from the Human Genome Project undertaken by the US government in the 1990s. On the legislative front, rare diseases were almost entirely neglected by the biopharma sector prior to the passage of the Orphan Drug Act of 1983 in the United States. This legislation created several economic incentives to accelerate the development of orphan drugs, including tax credits, research grants, a fast-tracked regulatory review for orphan drug candidates, and a seven-year period of market exclusivity in addition to existing patent protection. Before the passage of the Orphan Drug Act, the FDA had approved fewer than 10 orphan drugs. By 2018, it had approved over 500 orphan therapies to treat more than 700 orphan indications (see Exhibit 1).

Two additional aspects of rare diseases made them especially suitable for inclusion in a megafund: their lower overall costs of development and the low theoretical statistical correlation between development programs.

By definition, a rare disease involves a small patient population. As a result, clinical trials will necessarily consist of fewer patients, and all else being equal, these trials will be less expensive to conduct in aggregate (although the cost per patient may be high because of the complexity of the disease). This implies that less capital would be required per drug development program in a megafund, and the total amount of funding needed to achieve a suitable level of diversification would be similarly low.

[10] https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases.
[11] Sharma et al. (2010).

However, the most important aspect of rare diseases for a megafund is the low level of pairwise correlation between the successes and failures of a collection of rare disease candidate therapies. Mathematically, the total risk of return of a portfolio of drug development and discovery programs (as measured by its variance) is the weighted sum of the variances of the returns of each program, plus the weighted sum of all the weighted pairwise return covariances between programs. For example, the formula for risk of a portfolio with 10 programs would include 10 variances, one for each program, weighted by the percentage contribution of that program to the portfolio. But the formula also contains 45 covariances, one for each unique pair of programs (weighted by the product of the two programs' percentage contributions). Since there are many more covariances than variances, the majority of the risk of any given portfolio will be due to the covariances, a key insight from Markowitz (1952). Too much correlation between program outcomes will keep the risk high. However, if those covariances are generally small or zero, then the amount of risk reduction will be tremendous.

NUMERICAL EXAMPLE

To understand the relevance of this property, consider the following simple example of a portfolio of n biomedical assets, each with a 25% probability of success p, development cost of \$75 million, and net earnings of \$150 million per year upon approval. If it requires 7 years of clinical testing to reach an approval decision, each asset has a 20-year patent life, and the cost of capital for these programs is 10%, then, at the time of approval in year 7, the NPV of an approved drug is

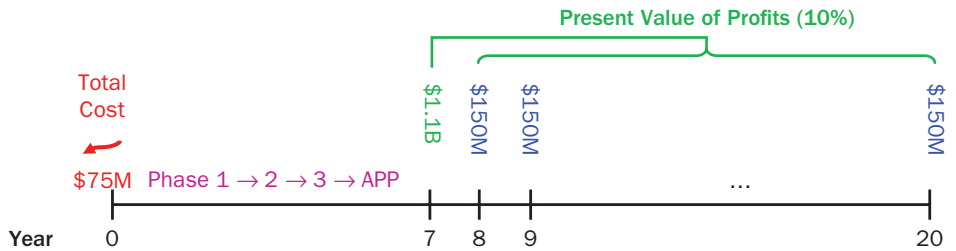
$$\frac{\$150 \text{ million}}{10\%}\left[1-\frac{1}{(1+10\%)^{20-7}}\right]=\$1.1 \text{ billion} \tag{1}$$

This timeline is summarized in Exhibit 2, and the parameters chosen are meant to represent the economics of a typical rare-disease therapeutic program.

The expected return and variance of a portfolio of n such programs that are assumed to be pairwise statistically independent can be computed by introducing binary indicator variables I_k for $k = 1, \ldots, n$, where $I_k = 1$ if program k receives regulatory

EXHIBIT 2

Timeline of Hypothetical Drug Development Process



NOTES: Timeline of hypothetical drug development process requiring 7 years of clinical testing at a date-0 cost of \$75 million, which yields a net profit stream of \$150 million per year from years 8 to 20 if approved. At a cost of capital of 10%, this cash flow has a year-7 present value of \$1.1 billion.

approval and is 0 otherwise. The expected return and variance of the portfolio of programs over the 7-year development period are then given by[12]

$$\begin{aligned}
\mathrm{E}[R_p] &= \mathrm{E}\left[\frac{\$1.1\text{ billion}\times(I_1+I_2+\cdots+I_n)}{n\times\$75\text{ million}}\right]-1\\
&= \frac{\$1.1\text{ billion}}{\$75\text{ million}}\times 25\%-1\\
\mathrm{SD}[R_p] \equiv \sqrt{\mathrm{Var}[R_p]} &= \frac{\$1.1\text{ billion}}{n\times\$75\text{ million}}\times\sqrt{\mathrm{Var}[I_1+I_2+\cdots+I_n]}\\
&= \frac{\$1.1\text{ billion}}{\$75\text{ million}}\times\sqrt{\frac{25\%\times 75\%}{n}}
\end{aligned} \tag{2}$$

Finally, to render these 7-year return statistics comparable to those of typical investment opportunities quoted in the financial industry, we must annualize them:[13]

$$\begin{aligned}
\text{Ann. Expected Return} \equiv (1+\mathrm{E}[R_p])^{1/7} &= \left(\frac{\$1.1\text{ billion}}{\$75\text{ million}}\times 25\%\right)^{1/7}-1\\
\text{Ann. SD} \equiv \frac{SD[R_p]}{\sqrt{7}} &= \frac{\$1.1\text{ billion}}{\$75\text{ million}}\times\sqrt{\frac{25\%\times 75\%}{n\times 7}}\\
\text{Sharpe Ratio} &\equiv \frac{\text{Ann. Expected Return}-5\%}{\text{Ann. SD}}\\
&= \frac{\sqrt{n}((1+\mathrm{E}[R_p]^{1/7}-5\%)}{\sqrt{25\%\times 75\%/7}}
\end{aligned} \tag{3}$$

where we have assumed a risk-free rate of 5% in the Sharpe ratio calculation in (3).

Equations (1)–(3) summarize the key features of this portfolio; numerical values of the key statistics in (3) are computed in Exhibit 3 for n = 1, 5, 10, …, 100 programs. Note from (2) that the expected return does not depend on the number of programs because all programs are assumed to have identical expected return, hence a portfolio of them will also have this same expected return. However, the standard deviation does depend on n, and declines as the square root of the number of programs. This is precisely the diversification effect underlying Markowitz portfolio theory. The Sharpe ratio—a common metric of risk-adjusted return used by investment professionals—is defined as the ratio of an investment's annualized expected return minus the risk-free rate, R_f, to its annualized return standard deviation.[14] Based on the last line of (3), we see that the Sharpe ratio of a portfolio of uncorrelated assets will increase at the rate of $\sqrt{n}$, which can lead to a very attractive risk-adjusted return with a sufficiently large number of assets. For example, even though the Sharpe ratio

[12] For details, see Lo et al. (2014, Supplement, Section 2 "Computing Expected Returns and Variances").

[13] There are two distinct approaches to computing annualized expected returns and standard deviations of multiyear investments: (1) compute the return statistics of the multiyear investment and then annualize the statistics; (2) annualize the multiyear return first and then compute the statistics. These two methods yield different values—the first method yields higher expected returns and typically higher standard deviations than the second method—and there are advantages and disadvantages to both. For expositional and computational simplicity, we adopt the first approach. See Lo et al. (2014, Supplement, Section 2) for details.

[14] See Lo and Chaudhuri (2022, Chapter 7) for further discussion.

EXHIBIT 3

Expected Returns, Standard Deviations, and Sharpe Ratios for a Portfolio of *n* Projects

	7-Year Value		Annualized		
n	E[R_p]	SD[R_p]	E[R_p]	SD[R_p]	Sharpe
1	255.2%	615.2%	19.8%	232.5%	0.06
5	255.2%	275.1%	19.8%	104.0%	0.14
10	255.2%	194.5%	19.8%	73.5%	0.20
25	255.2%	123.0%	19.8%	46.5%	0.32
50	255.2%	87.0%	19.8%	32.9%	0.45
75	255.2%	71.0%	19.8%	26.8%	0.55
100	255.2%	61.5%	19.8%	23.3%	0.64

NOTES: Expected returns, standard deviations, and Sharpe ratios of a portfolio of *n* independently and identically distributed drug development projects, each with the following parameters: $75 million development cost at date 0, 7-year clinical development time, $1.1 billion in net present value at year 7 if approved (corresponding to $150 million per year in profits in years 8 through 20, the remaining patent life), 25% probability of approval, 10% cost of capital, and 5% risk-free rate.

of one program is only 0.06, a portfolio of 25 programs has a Sharpe ratio five times larger, 0.32. For comparison, the Sharpe ratio of the S&P 500—a highly diversified market-capitalization-weighted index of the largest US companies—using five years of monthly returns from September 2019 to August 2024 and a risk-free rate of 5%, is 0.50.

Of course, this extreme case of zero pairwise correlation among all assets is a theoretical ideal that is never realized in practice; there are always sources of correlation that arise, if not from scientific and medical factors, then from macroeconomic and idiosyncratic business factors. Nevertheless, in the case of a portfolio of rare disease programs, the success or failure of a therapeutic for one rare disease is theoretically unlikely to affect the success of another. Each of the many thousands of rare diseases has a unique mechanism of action, and treatments for rare diseases have the potential to be pursued through several different modalities: for example, small molecules, large molecule biologics, or one of a variety of possible gene and cell therapies. In principle, it should not be difficult to reduce the correlation between drug development programs to almost zero. As a result, a rare disease megafund could, in principle, achieve the same level of risk and reward as an oncology megafund requiring many dozens of projects and multiple billions of dollars in capital at a much lower scale of funding.

Fagnan et al. (2014, 2015) have simulated the possible outcomes of a rare disease drug megafund using published drug development statistics. A portfolio of eight preclinical and eight phase 1 orphan drug development compounds would, on average, result in five developed phase 3 candidates that could be sold for further development, using only $575 million in capital.[15] RBOs had a greater simulated return on equity than a pure equity structure, but even the pure equity structure showed considerable success (13.4% versus 11.8%). Follow-up research in collaboration with the National Center for Advancing Translational Sciences using actual drug development data gave even more attractive results.[16] For these reasons, Lo concluded that a portfolio of rare disease therapeutics would be the ideal proof-of-concept for the megafund model.

PARALLEL TRACKS

Kumar and Stephenson were already thinking along similar lines. Their goal was to create a fund that would increase the annual rate of new innovative drug approvals using a much smaller amount of capital than the original megafund proposal—$1 billion instead of the $5 billion to $15 billion described in Fernandez, Stein, and Lo (2012). Instead of oncology, they were interested in rare diseases, specifically in rare genetic disorders. Both Kumar and Stephenson were familiar with several success stories in which small biotechnology startups could develop life-saving drugs for patients with

[15] Fagnan et al. (2014).
[16] Fagnan et al. (2015).

Mendelian diseases, creating attractive returns for investors in the process. The case for rare genetic diseases was clear from the scientific and ethical perspectives, and from a purely financial perspective, such a focus was almost ideal.

There were drawbacks to this emphasis, however. Kumar and Stephenson knew that focusing on rare genetic disorders and orphan diseases might preclude other approaches toward a megafund. For example, large pharmaceutical companies had shifted away from cardiovascular and central nervous system (CNS) therapeutics, which Kumar and Stephenson thought was a large inefficiency in the clinical asset market that a megafund could exploit. By focusing on a megafund in the rare genetic disease space, they might be missing an even larger opportunity to prove the financial and social benefits of the megafund model. Alternatively, investors might view a rare genetic disease fund as too narrowly focused, despite the cumulative size of the patient population.

Several other practical questions about the fundamentals of a genetic disease megafund also needed to be answered. Who would be the market for the equity tranche of the megafund? How would its cost of capital compare to the large pharmaceutical companies? What additional roles could the public markets play in the operational aspects of the megafund (e.g., shorting stocks to hedge risk)? Kumar and Stephenson's first question, however, was the most important: was a focus on rare genetic diseases financially appropriate for a megafund?

Several thousand genetic disorders have been biologically characterized well enough to begin research into therapeutic measures. As of August 14, 2024, the authoritative Online Mendelian Inheritance in Man database recorded 6,882 distinct phenotypes whose molecular basis is known to science.[17] This database and the set of known Mendelian disorders served as the starting point for a new set of simulations conducted by Lo and his colleagues, using parameters and additional considerations proposed by Kumar and Stephenson. These new simulations incorporated features about the practical operation of a megafund, such as the fact that well-run drug development programs would be able to benefit from the assistance and expertise of rare-disease patient organizations committed to supporting research and clinical work on the scientific understanding of a given rare disease and the development of therapies. Another operational feature incorporated into the simulation was the interest pharmaceutical companies maintained in late-stage assets. A megafund might expect a relatively frictionless sale of a developed candidate, or options to partner candidates' mid-development.

Over the course of several months, each of Kumar and Stephenson's questions was addressed. Not only was the focus on rare diseases appropriate, it was also efficient. There would be more than enough "substrate" to provide ideas for further clinical development in a rare disease megafund. Moreover, the megafund could adapt to the specific orphan drug regulatory environment, for instance, deliberately acquiring drug candidates whose phase 2 trials were designed to move directly to FDA approval as a result of the agency's fast-tracking program. This would require close managerial attention to detail in the clinical trial process, but it would significantly benefit the megafund's performance.

However, after further scientific and financial investigation, including discussions with several colleagues who would eventually join BridgeBio's founding team, Kumar and Stephenson concluded that the megafund's focus should be on the broader universe of genetic disorders, not only rare conditions. Many common conditions such as Alzheimer's disease, heart disease, diabetes, and most forms of cancer have some degree of genetic component as well. A seemingly minor shift in focus in

[17] https://omim.org/statistics/entry (accessed 14 August 2024).

a genetic disease megafund could have a significant potential impact on patient lives and improved economics that would attract a broader set of investors.[18]

A CHANGE IN STRUCTURE

By late 2014, Kumar had assembled the basic framework for BridgeBio's structure. He had also left his job at Third Rock Ventures and begun to gather the people he wanted on his advisory team, including Lo and several subject-matter experts in the genetic-disease drug development space.[19]

Several large investors expressed early interest in the BridgeBio megafund. However, Kumar soon realized that the megafund concept was gaining less traction than the individual drugs it intended to develop. BridgeBio the potential *company* gained greater attention than BridgeBio the potential *fund*. One frequent question was, "Why not select the most promising candidate, and create a company around it?"

Kumar was strongly opposed to this approach, since it removed the portfolio basis of the megafund, the key driver in lowering overall risk and thus the cost of capital. Brainstorming over email, Kumar proposed a more traditional holding company structure, one that would manage several drug development and discovery programs simultaneously.[20] It would require much less initial capital, and once established, it could quickly go through an IPO. Over time, it could issue debt according to the original megafund concept, "from the bottom up." This structure would also allow the implementation of core decentralized operating concepts relating to minimum viable teams that Kumar believed would make its R&D more capitally efficient and productive. Stephenson agreed with the approach.

One theme remained constant: Kumar continued to stress the diversification of programs and the resulting reduction in risk and the cost of capital as key to BridgeBio's potential success. The ideal BridgeBio program was one that targeted a well-characterized genetic disease with a large unmet medical need at its source and a strong clinical response. The following year saw BridgeBio make rapid-fire investments in two biotech companies with previous ties to Kumar. MyoKardia, a company launched by Third Rock Ventures with which Kumar had worked closely, was developing a small-molecule treatment for hypertrophic cardiomyopathy. The other was PellePharm, which was developing a topical treatment for basal cell carcinomas and Gorlin syndrome.

On May 12, 2015, BridgeBio closed its Series A financing. Behind the scenes, however, further investor interest was lagging. Kumar had a near-term investment target for BridgeBio of $40 million and a four-year vision of $200 million.[21] Assembling the funding proved difficult. Large investors preferred established biopharma companies, while family offices tended to be too risk-averse to feel comfortable with a new company managing early-stage assets. Hedge funds could tolerate the risk, but many thought BridgeBio's structure was too much like a fund and had no desire to become a "fund of funds."[22] Finally, some investors at the time believed that the BridgeBio team did not have an established enough track record, despite the expertise among its advisors.

[18] See Teaching Case #1: Addressing the First "Valley of Death" in the online supplement. "Teaching Cases" provide more-detailed exposition of aspects of BridgeBio's evolution that are relevant for classroom use, including questions for case-study discussion.

[19] Specifically, Drs. Charles Homcy, Hoyoung Huh, Frank McCormick, Philip Reilly, and Richard Scheller.

[20] Email from NK to a potential investor, January 20, 2014.

[21] Email from NK to founders, November 9, 2015.

[22] Email from NK to founders, September 8, 2015.

The solution, Kumar felt, was to simplify the BridgeBio story for investors. Unmet patient needs, the systematic analysis of drug candidates, the concept of "many shots on goal," and BridgeBio's speed and skill with early-stage programs resonated with investors, even if the megafund concept did not. "We can't be everything to all parties, but our model and the way we tell the story [has] many degrees of freedom, and we should use that to our advantage," Kumar wrote.[23]

After meetings in November 2015, the investment bank of Kohlberg Kravis Roberts (KKR) became BridgeBio's first large investor. KKR's strategists had recently developed an interest in early-stage life science product companies. The New York–based Perceptive Life Sciences fund soon followed, and Kumar's initial goal of $40 million was reached.

EIDOS: A SPOKE FROM THE BRIDGEBIO HUB

In late 2015, Kumar wrote down his visualization of the objective function for BridgeBio, considering its mission as a sustainable, long-term, patients-first company (see Exhibit 4). The first factor in this function is mathematical shorthand for BridgeBio's objective to increase patient impact by maximizing the number of quality-adjusted life years (QALY) from each new medicine. The second factor describes BridgeBio's strategy to be financially sustainable over a long period of time by ensuring that each of its programs would have a positive NPV and that each program would be amenable to an engineering approach to drug development. For a genetic disease, this approach meant that one could connect the dots from genotype to mechanism all the way to the symptom phenotype, something BridgeBio called a "blueprint disease." Over the next several years, these two factors would guide all decision making at BridgeBio.

In early 2016, BridgeBio acquired the biotech startup Eidos and its treatment for transthyretin amyloid cardiomyopathy (ATTR-CM), a hereditary disease leading to an eventually fatal buildup of amyloid plaque in the heart. In April 2017, BridgeBio relaunched Eidos Therapeutics as a subsidiary to bring its small-molecule investigational medicine for ATTR-CM, acoramidis (AG10), toward FDA approval. ATTR-CM closely fit BridgeBio's targeted investment profile: a rare, genetically defined disease with fewer than 200,000 diagnosed patients in the United States and no earlier FDA-approved therapy, but with extensive research toward a disease-modifying compound with clear markers of therapeutic effect, something Kumar emphasized in the preclinical program selection process.[24]

Eidos was originally incorporated in 2013 as a C-corporation. Its scientific cofounders, Isabella Graef and Mamoun Alhamadsheh, discovered and initially developed

EXHIBIT 4

BridgeBio's Objective Function

NOTE: BridgeBio's objective function for achieving its mission of becoming a sustainable, long-term, patients-first company.

[23] Ibid.
[24] Personal communication.

acoramidis with support from Stanford Medicine's Translational Research and Applied Medicine (TRAM) and SPARK programs. In 2016, it was converted into a standard S corporation, obtaining worldwide exclusive licenses from Stanford to make, use, and sell acoramidis until the expiration of its patents.

Clinical trials for acoramidis could, in principle, be designed for rapid clinical investigation and potential FDA approval. Under Eidos's new president and chief medical officer, Jonathan Fox, chief scientific officer Uma Sinha, and chief financial officer Christine Siu, and with Kumar as its chief executive officer, BridgeBio committed $27 million to Eidos.

BridgeBio derived its hub-and-spoke organization model from the original mega-fund concept, where simulations showed a key factor of fund performance was the speed in the phases of drug development. In September 2017, Eidos began its first clinical study for acoramidis, designed not only to determine its safety but also to provide evidence of a dose-dependent physiological effect in humans. Eidos presented its positive preclinical results to the American Heart Association in November 2017 and hosted a symposium to announce its successful phase 1 clinical trials in healthy humans in March 2018. These results supported Eidos's Series B financing in April 2018, raising an additional $64 million to help finance acoramidis's phase 2 and phase 3 clinical trials in patients with ATTR-CM.

In early May 2018, Eidos began its phase 2 clinical trials for acoramidis, which it projected to conclude by the end of the year. In anticipation of a successful result of these trials, Eidos announced its IPO in June at $17 per share, grossing $122 million; BridgeBio retained approximately 65% of the shares. The FDA granted an orphan drug designation to Eidos in October 2018, following the public release of the molecular structure of acoramidis and the clinical data of its earlier trials, which, among other benefits, allowed it to have an additional seven years of market exclusivity upon approval. By November 2018, six months after initiating the study, Eidos announced positive results for its phase 2 clinical trial of acoramidis in patients with ATTR-CM.[25]

BRIDGEBIO REVEALED

In the midst of the Eidos acquisition and relaunch, in January 2017, BridgeBio Pharma uncloaked itself from stealth mode to the public. An investor unaware of the portfolio model would have seen an atomized pipeline of seven high-potential preclinical assets, with few synergies between its tightly focused potential products. They would conclude there was an expert asset-selection team working in the background to bring preclinical research into clinical trials, taking advantage of the sector's inattention to these early-stage programs, but the value proposition might still elude them.

Diversification was still key to Kumar's approach. No matter how excellent an eye the BridgeBio team might have for preclinical science, the modal return of these programs would still be negative—but if large and diversified enough, the mean return of these programs would be positive.[26]

Further diversification, however, would require more capital. In September 2017, now with a pipeline of 10 candidates, BridgeBio raised an additional $135 million, with KKR and new investor Viking Global Investors leading the round, joined by Perceptive Advisors and new investors AIG, Aisling Capital, Cormorant Capital, and Janus Funds. It was important to Kumar's approach that BridgeBio be perceived as a company that could engage in early-stage discovery, early-stage licensing, or later-stage acquisition. For example, BridgeBio acquired global rights to infigratinib from Novartis, which

[25] See Teaching Case #2: BridgeBio's Strategic Carve-Out of Eidos in the online supplement.
[26] Personal communication.

showed potential in oncology, where Novartis had run multiple clinical trials, and in achondroplasia, a genetic condition that is the most common cause of dwarfism. It also acquired global rights to fosdenopterin from Alexion to treat the ultra-rare disease molybdenum cofactor deficiency (MoCD) type A.

This approach proved to be successful. By mid-2018, BridgeBio had already neared the $200 million vision goal Kumar had proposed in 2015. In January 2019, a still small BridgeBio, with only 200 employees, but by this time 16 programs in its portfolio, would close an additional $299.2 million of financing. New investors included Sequoia Capital and an unnamed long-term blue-chip investor.

By 2019, BridgeBio was ready to go public, implementing the equity financing phase of the megafund structure. Although Kumar and Stephenson contemplated using a Special-Purpose Acquisition Company, or SPAC, for this task, BridgeBio ultimately chose the tried-and-true path of a traditional IPO. On June 26, 2019, BridgeBio announced an offering of 20.5 million shares priced at $17 per share, raising $401 million in gross proceeds after thoroughly exercising the IPO underwriting syndicate's 15% green shoe. At its debut, BridgeBio's IPO was the largest biotech IPO of 2019 and one of the largest biotech IPOs in history. Starting from a market capitalization of $2.1 billion at the IPO, BridgeBio ended 2019 with a market capitalization of over $4 billion (see Exhibit 5).

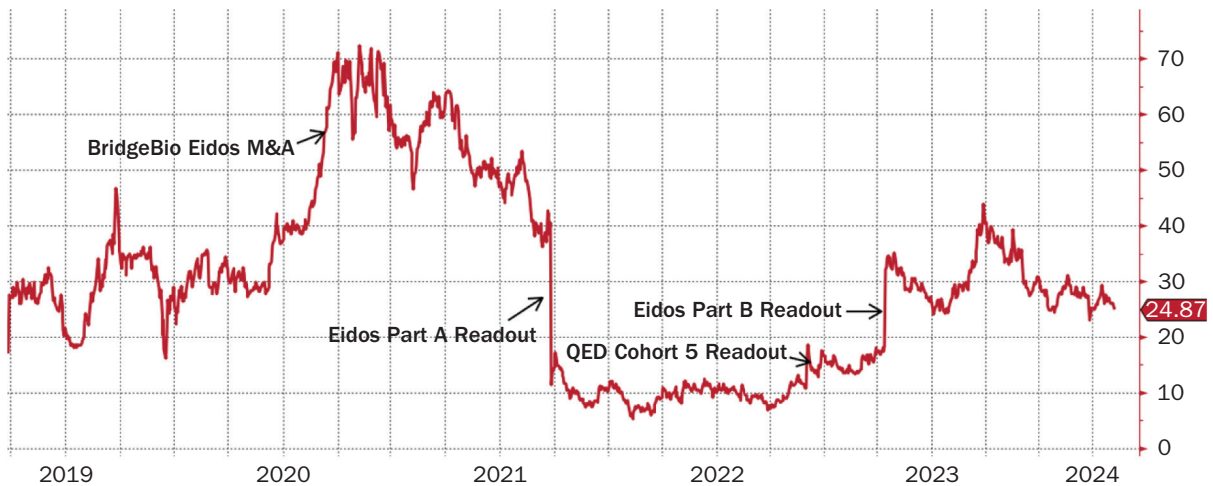
TAPPING INTO DEBT

Up to the IPO, BridgeBio closely approximated the pure-equity model in Fagnan et al.'s (2014, 2015) original simulations of an orphan drug megafund. However, Kumar and Stephenson had begun taking initial steps to expand capital sources beyond private equity and venture capital. On June 19, 2018, BridgeBio secured a $35 million senior secured term loan from Hercules Capital with an interest rate priced at the greater of the *The Wall Street Journal* prime rate WSJ + 4.35% and 9.35% per annum. By May 17, 2019, the amended facility was expanded to $75 million. BridgeBio also took a small amount of debt isolated to its affiliate PellePharm guaranteed by their development partner, Leo Pharma.

Debt has an inherent risk, making raising additional equity more difficult and expensive, particularly as repayment approaches. Within this framework, however,

EXHIBIT 5

BridgeBio's Stock Price from IPO to August 6, 2024



raising debt had helped BridgeBio grow quickly, enabling it to execute more programs in parallel and reducing the cost of capital. Further, Kumar and Stephenson reasoned that by adding some debt, they could add more "runway" to their existing solvency to bridge the company through more clinical data readouts, raising equity later at a higher valuation that would more than cover the cost of the debt through the next equity round.

Drawing on his experience as a former banker and lender, Stephenson asked his team at the outset of each debt financing round to rank-order BridgeBio's financing priorities to zero in on which parts of the structure and terms to prioritize through a competitive debt auction to manage risk and accomplish the company's objectives. The time to repay, a limited scope of financial and operating covenants, and size typically ranked higher as priorities than the cost of debt.

Following the IPO, BridgeBio made the argument to convertible debt investors that a prerevenue biotech company with its broad, uncorrelated portfolio, now financed through multiple clinical readouts, could fall within their risk envelope. Using the Monte Carlo simulation described in Fernandez, Stein, and Lo (2012), investors estimated the odds that the BridgeBio portfolio, given the historical probabilities of success for drug development in its development categories, might deliver clinical readouts generating sufficient value to return their invested capital in a downside and through conversion into equity at a prenegotiated premium in an upside.

On March 9, 2020, immediately ahead of pandemic-driven market declines, BridgeBio raised an additional $550 million via a convertible note offering at 2.50% to qualified institutional buyers. Its team secured a seven-year term, two years longer than the five years typical for new convertible issuers, under the logic that the additional time would bridge the company through additional readouts that would increase its ability to repay the investors or, more favorably, the odds of conversion into equity at a premium. This was followed by another raise of nearly $750 million through a convertible note offering on January 25, 2021, at 2.25%, this time with an unprecedented eight-year term. Because convertible notes are equity-linked capital, BridgeBio also purchased derivatives known as "capped calls" that synthetically increased the conversion price of the notes to a 100% premium to the stock on the issuance date, thus reducing their potential dilutive impact on ownership in the future.

By February 2021, approximately 60% of BridgeBio's funding since its inception came through some form of debt, namely $75 million of senior secured debt in a facility with Hercules Capital, Inc., and nearly $1.3 billion of convertible notes.

EIDOS TUCK IN

In early 2021, the BridgeBio affiliate Eidos appeared to be advancing rapidly in its goal of delivering its acoramidis therapy for ATTR-CM patients to FDA approval. Following feedback from global regulatory agencies, Eidos began a phase 3 study of acoramidis in February 2019 with two primary endpoints deliberately incorporated into the trial design. The first primary endpoint ("Part A") was the change in the distance a patient could walk in six minutes, to be measured 12 months after initiating the study. The trial would then continue 18 more months, with a second primary endpoint of combined mortality and cardiovascular hospitalizations measured at month 30 ("Part B").

This two-part phase 3 trial was not a standard design in the clinical trial world and instead reflected BridgeBio's philosophy of accelerating through the complexities of the drug discovery and development process as quickly and as safely as possible, returning to the megafund simulation findings that showed trial duration was a key element to overall performance.

However, if acoramidis did not meet its primary endpoint, it was intended that such a failure would not be fatal for BridgeBio. Like the original megafund proposal, the hub-and-spoke structure of the BridgeBio model was deliberately designed to absorb this sort of shock—via diversification and low pairwise correlation—unlike a traditional biotechnology firm that might have to fold after a phase 3 failure and lose the knowledge gained in the development process. This lower level of risk is the main driver of BridgeBio's lower cost of capital.

In light of this progress, Kumar and Stephenson believed there was a growing discount between Eidos' intrinsic value and its trading value in the equity market. Furthermore, following the earlier spinout of Eidos, they had learned that investors placed a premium on fully-owned recurring revenue and did not fairly value the net asset value of a firm based on the holding of minority equity stubs where revenue was not booked. To capitalize on this inefficiency, Kumar and Stephenson implemented a share buyback program using capital at BridgeBio to buy incremental Eidos shares in the open market.

In early 2021, perceiving that Eidos' shares were undervalued by the market relative to BridgeBio's assessment of acoramidis' potential, BridgeBio moved to reacquire the outstanding shares of Eidos, funded in part by its earlier convertible debt financing of March 2020 and January 2021.[27]

DEBT AS INSURANCE

In November 2021, a month before the 12-month readout of Eidos' acoramidis trial, Stephenson recognized that the largest downside financing risk BridgeBio faced was a setback on the Part A trial at the same time as successful portfolio readouts elsewhere required capital to move forward. To hedge against the risk, Kumar and Stephenson considered adding incremental capital to the balance sheet, even though they were bullish on the portfolio's long-term prospects.

It is sometimes said that biotech companies fail if their trials or science fails. However, Kumar and Stephenson knew that a lack of available capital to prosecute strong science was a far more common reason for biotech bankruptcies. On a risk-adjusted basis, given BridgeBio's internal assessments of the probability of success on the acoramidis Part A readout, issuing equity ahead of those results would destroy value for insiders through dilution. At the same time, the debt markets were at a peak, given the low interest rates of 2021 and the resulting search for yield among asset managers. Kumar and Stephenson felt that adding incremental long-dated debt to BridgeBio at favorable economic terms and with no financial covenants could deploy equity returns at an acceptable level of risk.

BridgeBio's diversified portfolio allowed it to take an additional $450 million of senior secured debt from lenders, as well as to gain access up to $300 million in delayed draws that were linked to achieving proof-of-concept readouts in its portfolio. Stephenson's team negotiated terms such that success for either Part A of the acoramidis trial, or any three of five proof-of-concept readouts could unlock $300 million at a 9% fixed rate (another instance where diversification and low correlation yield a direct benefit to BridgeBio's access to capital).[28]

This was the largest facility of its type at the time. For the first time, a syndicate of six senior secured lenders—the winning bidders emerging through a competitive auction process—were willing to underwrite large incremental draws of debt,

[27] See Teaching Case #3: BridgeBio Pharma's Portfolio Rebalancing in the online supplement.

[28] Under these terms, success for any two of the five upcoming readouts secured $200 million and for any single upcoming readout secured $100 million.

predicated on midstage clinical outcomes for a prerevenue biotech company still burning through substantial cash. Unlike BridgeBio's earlier and smaller debt facility with Hercules, underwritten primarily to ensure ongoing support from equity investors to repay the loan, this new facility acknowledged the underlying value of proof-of-concept assets in unlocking additional debt capital.

Biotechnology companies trade inversely with interest rates and are therefore poorly positioned to take interest rate risk. In recognition of this fact, Kumar and Stephenson had locked in fixed-rate debt facilities at what in retrospect was a multidecade low point in interest rates.[29] Shortly thereafter, rates and credit spreads surged by 500 basis points to 600 basis points, as the Federal Reserve began its tightening cycle in March 2022.[30]

THE DESERT AND THE ROAD BACK

On December 27, 2021, BridgeBio announced that acoramidis had failed to meet its Part A endpoint, the 12-month improvement in patient six-minute walk distance. The reaction from the market was immediate, with share prices falling from $40.62 at close on December 23 to $13.43 at close on the 27th, a 67% drop (see Exhibit 5). In subsequent months, shares in BridgeBio would fall to as low as $5.21. Meanwhile, BridgeBio realized three positive proof-of-concept readouts,[31] unlocking the $300 million debt facility, but each requiring substantial capital to move into the next phase.

This sort of systemic shock highlights one of the primary differences in perception between the initial concept of the megafund and the biotechnology company structure that was ultimately taken forward by BridgeBio: path dependency.

The initial "frictionless" megafund proposal in Fernandez, Stein, and Lo (2012) involved a bolus of startup financing and a lengthy time horizon (15 years or more), across which it would be deployed in a minimally correlated portfolio. At the end of that horizon, having successfully turned some of its portfolio assets into saleable drugs, an aggregate rate of return would be repaid to investors, and the success of the megafund would be judged based on its ability to deliver that return.

A biotechnology company, however—particularly one financed by the public markets—is not able to simply raise an initial fund, deploy it, and then point to a reasonable rate of return after running its experiment. Instead, it raises funds incrementally over that horizon, with each raise denoting the market sentiment about the company at an instant in time. It is judged over that horizon according to the most recent news about its performance, and according to whichever assets are weighted most heavily by external forces.

The drop in BridgeBio's stock price following its Part A announcement indicated that the company's public valuation was heavily weighted toward acoramidis' potential value, implying there was a real conglomerate discount versus the company's internal valuation modeling at the time. The drop also coincided with a drop in the XBI, the Standard and Poor's biotechnology index, by roughly 50% from its February 2021 peak of $166.78 to $83.00 by the end of 2022 due to a macroeconomic cycle marked by rapidly increasing interest rates.

[29] With $450 million of 9% fixed-rate debt, $550 million of 2027 converts at 2.5%, and $747 million of 2029 converts at 2.25%, the blended rate across BridgeBio's debt stack reached 4% fixed by the end of 2023.

[30] See Teaching Case #4: BridgeBio's Capitalization Strategy in the online supplement.

[31] BridgeBio delivered positive proof-of-concept data for its rDEB program (in its PTR subsidiary), ADH1 program (in its Calcilytix subsidiary), and achondroplasia program (in its QED subsidiary).

Consequently, BridgeBio was doubly punished, both for its trial failure and for being in a sector out of favor for macroeconomic reasons. This dramatically increased the cost of equity for the company at a time when debt markets were already unavailable due to the company's existing leverage, resulting in a great amount of financial stress.

However, this moment of path-dependent pain was ultimately a display of the power of diversification. Kumar declared 2022 a year of focused execution, and the company was able to continue advancing its pipeline with the knowledge that none of the other medicines had become less likely to succeed due to the acoramidis readout and that acoramidis itself would have a fuller data set against more apparent endpoints in 2023. The more than $2 billion in debt capital raised in the 19-month period between March 2020 and November 2021 allowed Kumar and Stephenson to focus on letting the science speak through their various clinical trials.

The company also faced significant challenges on the human capital front. First, Kumar and Stephenson knew that a reduction-in-force was required, and they moved swiftly, cutting 30% of the workforce in the quarter following the Part A readout, while offering the affected employees generous severance and placement opportunities. Second, Kumar and Stephenson granted a one-time special equity award to critical employees, while cutting their own bonuses and equity awards. Third, and perhaps most important, they reinforced nonfinancial incentives and focused on building a patient-oriented community. Kumar increased the frequency of company town halls to once a month, supplemented by patient days once per quarter, which provided BridgeBio's employees a chance to see first-hand the larger impact of their work.

The ability to finance a year of focused execution amid a backdrop of financial stress came down to several factors. Kumar and Stephenson decided to reduce spending and allow BridgeBio the time to reach a series of critical clinical readouts. In some cases, this meant pausing programs whose NPVs were not supported by the cost of capital now available to the firm. In other cases, it meant finding external partners for expensive early-stage trials or for approved drugs that allowed BridgeBio to save on the costs of commercial infrastructure. BridgeBio also took advantage of the priority review voucher (PRV) the company had received with FDA approval in 2021, which was sold to another pharmaceutical company for $110 million.

The primary source of funding for 2022, however, was the money BridgeBio raised before the Part A readouts on the strength of its diversified portfolio. If it had not been able to tap the debt markets in 2021, the pain of 2022 would have been greatly intensified, and BridgeBio would have been forced to stop work on all but its latest-stage programs.[32]

The continued advance of a late-stage asset in the clinical pipeline is one of the most prized assets in biotechnology because of its proximity to revenue. On March 6, 2023, BridgeBio announced strong positive data from its phase 2 trial of infigratinib in children with achondroplasia, propelling its share price from $10.87 to $18.55. BridgeBio released a $150 million public offering that week, acquiring additional cash to prepare for a year when three new phase 3 trials were projected to start.

The primary event of BridgeBio's return from the desert happened on July 17, 2023, when the company announced consistently positive results from its Part B readout of the acoramidis phase 3 trial on the endpoints of mortality and cardiovascular hospitalization. With the benefit of an additional 18 months, the six-minute walk distance and other endpoints also showed improvements. This data validated the scientific thesis of acoramidis, giving BridgeBio a potential "blockbuster" product (usually defined as over $1 billion in annual sales), pending review and approval by the regulatory health authorities. Accordingly, the stock moved from $18.22 to $32.52 (Exhibit 5).

[32] See Teaching Case #5: Stress Test in the online supplement.

One possible reason the stock price did not make up all of the earlier ground it lost at its Part A readout was the high-interest-rate macroeconomic environment.

RECAPITALIZING THE COMPANY

BridgeBio spent much of the second half of 2023 presenting the details of its acoramidis phase 3 study at medical meetings, preparing the acoramidis New Drug Application for the FDA, and simultaneously operating three phase 3 trials in achondroplasia, limb-girdle muscular dystrophy Type 2i, and autosomal dominant hypocalcemia Type I. Despite the successful Part B readout, the delay in regaining access to capital on lower terms left BridgeBio low on cash and short on time to secure the substantial capital needed for multiple late-stage programs and an upcoming launch.

In September 2023, the company announced a $250 million private placement equity financing anchored by a sovereign wealth fund, bringing in another tranche of cash, while also securing long-term investors. Coming into 2024, however, it was clear that additional financing would be required to run BridgeBio's late-stage trials and prepare to launch acoramidis in a manner appropriate to its patient community, while also allowing it to fulfill its blockbuster potential.

Nine months away from a potential FDA approval, BridgeBio found itself in the middle of what is sometimes called the "second valley of death" in drug development. This valley arises when existing shareholders in biotechnology companies are looking to cycle out of their investment after the clinical product that catalyzed their initial interest has been developed, while new investors who reward product revenues are not yet buying the stock.

To capitalize BridgeBio through this second valley of death, Kumar and Stephenson tapped various markets. In January 2024, BridgeBio secured a $500 million funding agreement from Blue Owl and CPPIB in exchange for a 5% royalty on acoramidis sales, capped at an investor cash-on-cash return of 1.9x or $950 million. At the same time, Kumar and Stephenson refinanced their $450 million senior secured debt with Blue Owl.[33]

These royalty and debt refinancing transactions were soon followed by a pair of business development deals that allowed BridgeBio to realize value from its existing programs, while simplifying its commercial task. In the first deal, BridgeBio licensed the Japanese rights to infigratinib to Kyowa Kirin Corporation in exchange for $100 million upfront, as well as sales milestones and royalties in the range of 20% to 30%. In the second deal, BridgeBio licensed the European rights to acoramidis to Bayer in exchange for $310 million in the near term, as well as royalties starting at 30% to 35% and sales milestones. The company also completed a $250 million public stock offering. The combination of these transactions, paired with the ongoing simplification of its portfolio, pushed BridgeBio's projected solvency runway into the second half of 2026.

Finally, BridgeBio had observed for some time that asset-level equity appeared less expensive than equity taken centrally, perhaps a behavioral bias among equity investors, a surge in the AUM of private funds, or a rational consequence of the impact of greater complexity on the price discovery process. On May 2, 2024, BridgeBio successfully launched BridgeBio Oncology Therapeutics to secure financing from external investors for their oncology unit, with an initial $200 million in private financing co-led by Cormorant Asset Management and Omega Funds. By allowing investors

[33] BridgeBio had been fortunate to lock in fixed-rate debt as rates hit historic lows. During the refinance and royalty sale process, the off-market debt was a significant asset to BridgeBio in negotiations, even though interest rates and broader macroeconomic conditions provided significant head winds.

greater choice in the BridgeBio ecosystem, the company sought to unlock greater shareholder value.[34]

FUTURE PROSPECTS

BridgeBio Pharma has provided a proof-of-concept for the portfolio component of the original conception of a pharmaceutical megafund. It is a decentralized company with a relatively "weightless" corporate model, although one at an apparent inflection point in its growth. With Dr. Neil Kumar as its chief executive officer, diversification is still one of the principal goals of its portfolio strategy.

Although BridgeBio began with only a simple small-molecule capacity for clinical development, it now has capabilities in a much broader array of modalities, including gene therapy, protein replacement therapy, and antisense oligonucleotides. This diversification of modalities was made possible by its decreased cost of capital due to the financial diversification of its overall portfolio.

BridgeBio has consolidated its capabilities at scale, with over 20 clinical trials, more than 15 Investigational New Drug applications, and a pipeline of more than 30 drug discovery and development programs since its founding. It received its first FDA approval in February 2021 for NULIBRY™ (fosdenopterin), the first (and so far, only) approved therapy to reduce the risk of mortality in patients with MoCD type A, an ultra-rare and life-threatening genetic disorder, and its second for TRUSELTIQ (infigratinib) for the second-line treatment of cholangiocarcinoma shortly thereafter.[35]

One hypothesis for BridgeBio's ability to survive despite the challenges it faced is its adoption of the corporate objective function in Exhibit 4. BridgeBio's initial diversified portfolio of blueprint diseases was quickly used as leverage to increase the breadth of its pipeline. The breadth of this portfolio allowed the company to raise over $2 billion in a 19-month period between March 2020 and November 2021, mostly through the debt markets. Ultimately, when mean reversion occurred and a key clinical trial was unsuccessful, wiping out 80% of BridgeBio's market capitalization, this ability to raise funds allowed BridgeBio to sustain its operations and survive long enough to finish its most promising clinical trials, reaping the benefits of diversification.

Two key elements can be abstracted from BridgeBio's experience for all megafund-like structures. First, working closely within the regulatory framework is necessary to success. Innovative trial design allowed Eidos's candidate acoramidis to accelerate through the early stages of the clinical trial process. The FDA's orphan drug designation made a drug development desert bloom with possible candidate treatments for rare diseases. Second, the importance of greater access to inexpensive pools of capital cannot be overestimated. Diversification is important as a means to this end, not merely in itself. There is also the case of the "dog that did not bark," hidden correlation in outcomes among portfolio assets. Rare-disease therapeutics have a strong theoretical basis for having uncorrelated clinical trial outcomes, and BridgeBio based its strategy on this strong assumption. It is possible, however, that common modalities or presently unknown science might correlate assets thought to be uncorrelated, eliminating the gains of diversification.

With the benefit of hindsight, the nature of BridgeBio's journey can be viewed as a natural progression of a biotechnology company developing a portfolio of binary

[34] See Teaching Case #6: Navigating the Second Valley of Death in the online supplement.

[35] TRUSELTIQ was withdrawn by the FDA in May 2024, driven by BridgeBio's partner, Helsinn Group, deciding that there was not enough of a commercial market to support studies required by the FDA to support the drug's accelerated approval.

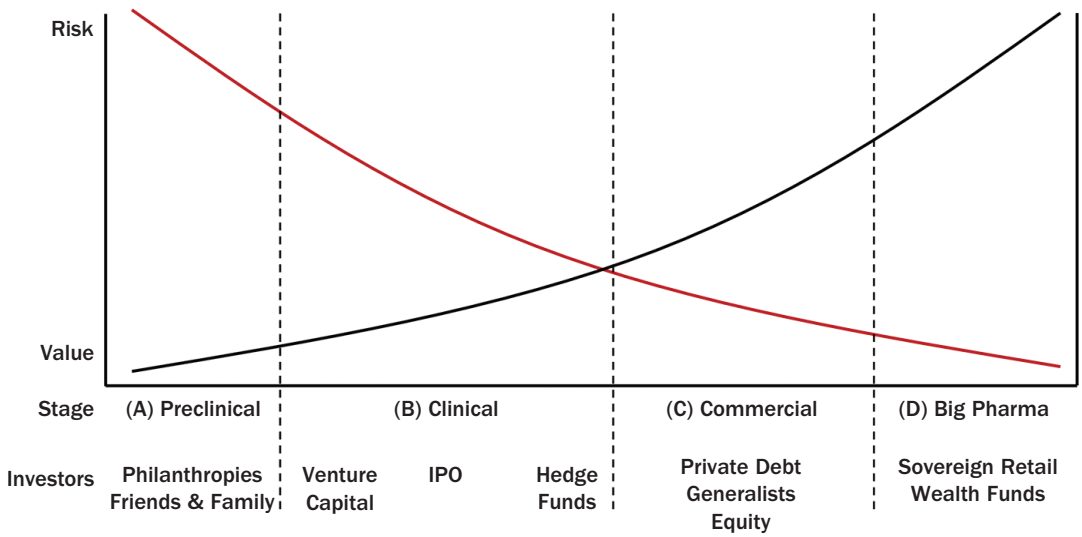
risks subject to resource constraints dictated by those risks. This evolutionary process is depicted in the highly stylized time-series graph in Exhibit 6. At the outset (Stage A), the risk of a biotechnology startup is at its highest point and its value is at its lowest, hence the investor pool is limited both in number and type of potential funders—typically, friends and family, philanthropies, and "angel" investors—and the amount of capital they are willing to deploy. As the startup matures and moves preclinical assets into the clinic, its value increases as it derisks its programs (Stage B). The pool of investors broadens to include venture capitalists, hedge funds, and eventually, public markets, hence the amount of capital available also increases. However, at this point the company's ownership structure has changed, with the original investors being replaced or dominated by larger institutional investors. While this "investor rotation" occurs in virtually every industry and is to be expected, especially those involving complex technologies that require long gestation lags before profitability, the need for management to adapt to the new owners is not a trivial one. As the company reaches Stages C and D in commercialization and profitability, another investor rotation may occur, with private equity and debt investors playing a bigger role in providing capital to the company.

Although the nature of complex technology companies like those in the biopharma industry means that scientific or engineering failure is always possible, a more common source of difficulty is the potential misalignment between the expectations and objectives of company management and their current investors. The importance of properly adapting corporate policy to investor rotation is one of the most important lessons from BridgeBio's journey.

Finally, it should be noted that as of the time of this writing, no biotech company has been able to implement a securitization structure involving the issuance of publicly rated debt collateralized by therapeutic programs as outlined in Fernandez, Stein, and Lo (2012). We conjecture that the gating factor is the absence of a set of widely accepted portfolio analytics that can give generalist investors an accurate summary of the risks and rewards of a biomedical portfolio (and the default probabilities of debt collateralized by such a portfolio). Therefore, there is still considerably more room for financial innovation to help accelerate progress in biomedicine.

EXHIBIT 6

The Four Stages of Evolution of a Typical Biotech Company over Time



CONCLUSION

Under Dr. Neil Kumar's leadership, in the space of a decade BridgeBio Pharma has gone from a concept discussed in email conversations to a biopharma company with a $5 billion market capitalization, two drug approvals, a third major approval expected in November 2024, and several other drug candidates in late-stage clinical trials. BridgeBio is a proof-of-concept of portfolio theory as applied to early-stage programs in drug development. As theorized, the genetic disease space has proved to be an ideal environment for this strategy, but it also required strong analysis of the preclinical science and a managerial emphasis on speed, which BridgeBio provided.

Despite BridgeBio's experience, its hub-and-spoke structure may not be appropriate for all therapeutic contexts. For example, a portfolio of Alzheimer's disease or immunotherapy therapeutics is quite a different proposition (Lo et al. 2014), given the higher pairwise correlations between typical projects in these fields. The megafund structure also faces challenges in the case of vaccines and anti-infectives,[36] not so much because of pairwise correlation, but because this therapeutic area involves public health policy questions that governments must adjudicate. Despite the various successes in the global response to the COVID-19 pandemic, the waning interest in—and declining government funding for—pandemic preparedness is a troubling if predictable trend as the global economy continues its recovery and policymakers move on to more immediately pressing issues.

As important as financial engineering has been to BridgeBio's development, there is unanimous agreement among BridgeBio's senior leadership and its board that the science and medicine should drive the financing, and not the other way around. As Lo and Chaudhuri (2022) remind us:

> The fast-paced intense environment of most financial institutions often leads to tunnel vision for those of us in the financial industry, so it's worth reminding ourselves from time to time that for most people, finance is a means to an end, not an end unto itself. Even the most sophisticated financial tools and business models can't turn a bad drug into a good one. But using the wrong financial tools and business models can easily turn a good drug into a failed asset that will never reach patients.

For those with a focus on bringing more therapeutics to patients suffering from diseases that have traditionally been overlooked by the biopharma industry, BridgeBio's example may serve as a useful template. Given that only 5% of all genetic diseases have approved treatment options, there is still a great deal of work to be done on behalf of patients. For the investors and philanthropists who wish to join in, new business and financing structures may provide a sustainable path for doing so.

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[36] See, for example, Berry et al. (2020), Lo, Siah, and Wong (2020), Vu et al. (2020, 2022), Chaouch, Lo, and Wong (2022), Lo and Sharma (2022), and Barberio et al. (2023).

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