INVESTING IN BIOTECHNOLOGY

INTRODUCTION

The global arms race we live in does not involve weapons but nation states competing to buy vaccines to protect us against coronavirus. The pandemic is a unique moment in history, enlightening the value of science and research. Around the world, governments and individuals are looking to the biotech industry for hope. Hope that lives can be saved, that families can unite, that economies and communities can soon return to normal. Fortunately, we are living in an unprecedented time of innovation. At the centre of this are some of the most important and exciting companies in the world. One of which is Moderna. Never in history has any company been able to develop a vaccine ready for human testing in just 42 days from receiving the genetic blueprint of a virus, a process that usually takes years with traditional technologies.

The pace of innovation in medicine is exploding thanks to the convergence of different technologies and sciences, paired with our growing understanding of disease biology. Developing new drugs has been an arduous process which has historically taken up to 10 years and cost more than $1 billion on average. However, we believe the industry is at the cusp of transformation, as technological innovation combined with new funding and business models will potentially change the economics of the drug-making business, making the whole process faster, cheaper and more predictable with higher success rates. This will form a rich avenue of extraordinary growth businesses for long-term investors.

For us, investing in biotech is identifying those outliers which are at the forefront of innovation and which can bring transformative medicines to patients, while acknowledging that success is not a straight line. Knowing that not all companies will succeed in terms of translating their scientific discoveries into a commercially successful business, how do we at Health Innovation seek to identify the long-term winners in biotech?

IDENTIFY THE LONG-TERM WINNERS

When looking at some of the most successful biotech companies in the world such as Genentech, Amgen, Biogen and Regeneron, they share a commonality that is their ability to bring multiple drugs to market which lead to sustainable and profitable long-term growth. Having one drug approved is already challenging (on average only 1 in 10 drugs tested on humans make it through the approval process), but only the true outliers can hope to repeat that success time and time again. In hunting for extraordinary biotech companies, we look for fundamentals which we believe can increase a company's chance of repeating success over time.

SCIENCE

Biotech is a science-based business and like any other business driven by cutting-edge scientific innovation, there is inherent uncertainty of whether the science works or not. This question can only be answered by lots of experiments, and in the case of biotech, clinical trials. However, instead of trying to outsmart the scientists or shying away from the uncertainty that underlies the upside attraction of equity investment, we focus on three aspects of the science: (1) Is it credible? (2) Is it scalable? and (3) Is it differentiated?

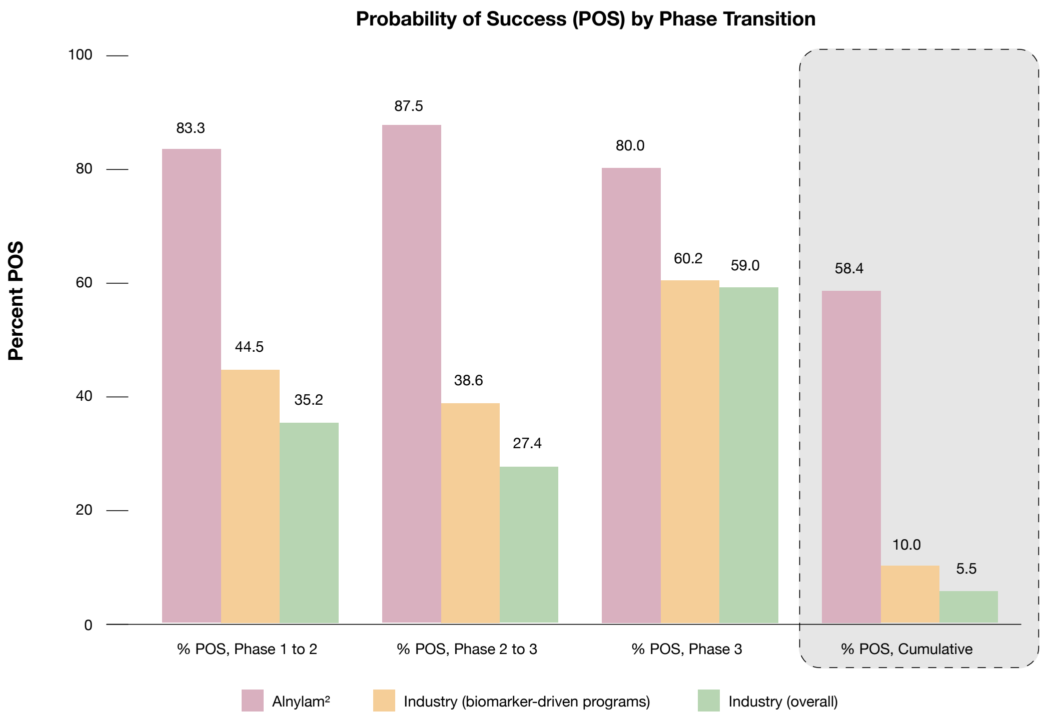
Credibility: From Theranos's revolutionary blood test to Ambrosia's crimson elixir of life, the world of biotech is unfortunately stained with companies with outlandish claims that lack scientific rigour, yet shockingly still capture the minds and pockets of many investors. This only happens when investors overlook the first and foremost step that is examining the credibility of the science and the innovators in charge of developing it. For us, assessing the teams' track records, looking into their peer-reviewed publications and understanding how they are perceived in the scientific community is an indispensable part of our due diligence. We also engage with our industry network of academics and thought leaders around the world to seek their opinions on both the people and the scientific approach of the company that we are interested in. Experts and specialists are often the most critical of novel science and technology in their respective fields; however, they can provide us with insight into how the new science/technology fits into the broader context of the field, why now might be different and what they will need to see to be convinced of the science's feasibility. This also helps us evaluate how early or mature the science is and the extent of de-risking that has taken place.

Scalability: The scalability of the underlying science and technology is key to repeating the success in future programmes. We are focused on identifying companies whose knowledge and technologies can be applicable across multiple indications and diseases. This will lead to improved R&D productivity and lower costs of drug development over time as success in one programme helps de-risk the underlying science and technology, and increases the likelihood of success of other programmes. We tend to avoid investing in single-asset companies or those who pursue a specific disease pathway that we deem too narrow to be scalable.

At Health Innovation, we are particularly excited about companies that can change the economics of drug discovery and treat diseases we couldn't treat effectively in the past. Take Alnylam as an example. It is a US biotech company that has been leading the field of RNA interference (RNAi) and turning the Nobel Prize-winning science into actual medicines for patients. RNAi is a natural biological process that turns off genes by destroying the messenger RNA, which carries the DNA instructions for making proteins without changing the core DNA code. For the past 15 years, we have struggled to turn RNAi into drugs mostly due to the delivery mechanism. Short-interfering RNA strands (siRNA) are easily broken down by enzymes in the blood and cannot pass the cell membranes to get inside the cells. Alnylam first overcame the delivery challenges by using lipid nanoparticles as smart bomb shells that protect and transport siRNA strands to the destination. This was then followed by further innovation which directly modifies the siRNA strands so that they will remain stable without the need for bulky bomb shells. Solving the delivery challenges will essentially allow us to 'industrialise' the production of RNAi drugs to go after many different disease targets. Alnylam's technology platform has been validated and the company has demonstrated its ability to bring multiple drugs to market at a remarkable success rate. Since its first drug approval by the US FDA in 2018, the company has brought another three drugs to market with several others in late-stage clinical trials. Compared to the historical average success rate of 10 per cent in the drug industry, Alnylam has achieved an impressive success rate closer to 60 per cent based on its technology platform. By transforming the drug discovery and development process, we believe companies like Alnylam could deliver significant returns for both society and investors.

Productivity of Alnylam RNAi Therapeutic Platform

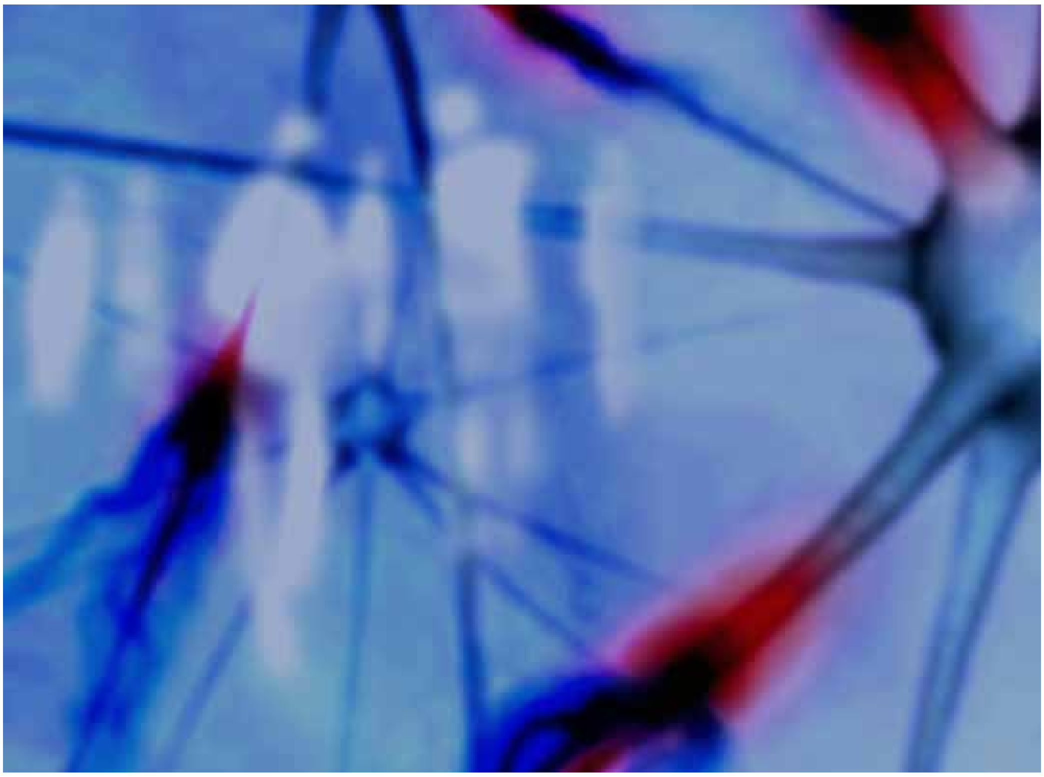
Comparison of Historical Industry Metrics to Alnylam Portfolio[1]



Source: Alnylam Pharmaceuticals, October 2020. Wong et al., Biostatistics 2019.
[1] Past rates of Alnylam and Industry respectively may not be predictive of the future
[2] Alnylam programmes biomarker-driven at all stages of development (100%)

Differentiation: Our investment philosophy is investing in companies that can help transform human health and healthcare systems. We are focused on companies whose differentiated approaches can potentially bring radical benefits to patients' lives rather than just incremental improvement. We are particularly intrigued by companies that are trailblazing new sciences and leveraging genomics and other novel techniques to develop life-changing treatments for those who suffer from chronic illnesses, such as diabetes, depression, heart failure and Alzheimer's. These are some of the most common human diseases but also the most complicated because they are often the results of multiple gene mutations, not one, plus other lifestyle and environmental factors. Understanding these diseases will require a system biology approach that integrates all the different components (genes, proteins, metabolites, diet, exercise data and so on) to figure out how they form functional networks at the organ and patient level, and how dysfunction of these networks underlies diseases. This is no simple task; however, we are looking for companies which are making quantum leaps in the understanding of disease biology, and that we believe have strong scientific rationales that can skew the odds of success in their favour.

For example, California-based Myokardia is a clinical-stage biotech that is pioneering a precision medicine approach to treating heart diseases. Guided by genetics and a wide range of biomarkers, including imaging and wearable data, the company is developing targeted therapies for well-defined patient subgroups within the broader category of heart failure. This is distinguishing in a field that has been typically characterised by one-size-fit-all treatments. This will increase Myokardia's probability of success and learning from one patient subgroup will also enhance the company's knowledge about the disease overall to help them design better drugs in the future.



PEOPLE AND CULTURE

At Baillie Gifford, we have always placed a strong emphasis on management and culture when analysing businesses, but even more so for biotech, which is as much a science-based as a people-based business. Drug discovery and development is an incredibly challenging process which involves a series of experiments and trials. The purpose of each experiment is to help increase or decrease your conviction level to take the next step forward. Sometimes the decision will be easy because the results are clear, but oftentimes the lines will be blurred as to whether it is worth proceeding, redirecting or stopping altogether. The decision-making is likely to involve behavioural biases, and under improper conditions, sub-optimal decisions may be made that will be detrimental to the long-term success of the company. Assessing people and culture is undoubtedly a long-term task that requires close observations and relationship building between us and the management teams. We look for teams whose vision and ambition are aligned with our long-term interests, and whose culture is conducive to innovation, which is the lifeblood of biotech.

Vision: As we get to know management, we want to understand what motivates them as individuals and what their long-term visions are for the business. Even though we believe that most people who go into biotech aspire to make a difference to the health and wellbeing of patients, they may adopt different routes to commercial success. There is quite a distinction between teams who are focused on building an independent long-lasting company to serve patient needs in the long run versus those who are keen on achieving a quick exit through acquisition by a larger entity to then channel the profits into the next idea. Both are necessary for the health of the ecosystem; however, we are attracted by the former because we believe they have higher chances of becoming true outliers and delivering exceptional performances for both patients and shareholders. Management's vision will manifest into strategy. A company that would rather make itself an acquisition target will tend to devote most resources into its leading drug candidate to take it to proof-of-concept as fast as possible, instead of investing in the broader technology platform and the research pipeline.

It was precisely Moderna's bold vision of building a different type of biotech based on an entirely novel technology platform capable of producing dozens of drugs over the years in a highly efficient and automated manner that caught our attention. Despite many challenges of delivering messenger RNA into human cells that caused several big pharmaceutical companies to abandon their efforts, Moderna persevered and invested more than $500 million in the early years to advance and broaden its technology platform. That was a testament to the team's ambition and commitment to patients. This approach requires a lot of capital and patience from both management and shareholders; however, the outcome can be astounding. Not only is Moderna leading the race to develop vaccines against Covid-19, its 20 other drug programmes, spanning across a host of different diseases, also offer potential to bring substantial benefits to patients.

Culture: We have come across a countless number of biotech companies in our conversations which claim that they strive to be "the next Genentech". However, it takes more than just sheer willpower to do so. Besides great science and talent, Genentech was well-known for its unique culture that resembled that of academia rather than corporate, with extremely transparent rigorous open debate, no political correctness, and a lot of individual freedom. It encouraged risk-taking and even celebrated failures in its "Awesome Failure Awards", knowing such efforts will fuel innovation. Achieving and maintaining such innovative culture is incredibly hard, as Professor Pisano pointed out in his paper 'The Hard Truth About Innovative Cultures':

A tolerance for failure requires an intolerance for incompetence. A willingness to experiment requires rigorous discipline. Psychological safety requires comfort with brutal candor. Collaboration must be balanced with individual accountability. And flatness requires strong leadership. Innovative cultures are paradoxical. Unless the tensions created by this paradox are carefully managed, attempts to create an innovative culture will fail.

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A company's culture is not built overnight and does not happen by accident, it takes deliberation and thoughtful craftsmanship to mould the culture to one's desire and balance those conflicting forces. At Denali, a clinical-stage US biotech that is developing treatments for neurodegenerative diseases, such as Alzheimer's and Parkinson's, the management team perhaps understands the importance of culture more than anyone else because they themselves came from Genentech. They brought the best elements of Genentech's culture and implemented them in a fast-moving biotech world. At Denali, there are no committees. Teams and individuals are empowered to make decisions and move fast. The science is executed to very high standards with absolute transparency and integrity. The company has a thorough and extensive hiring process to make sure that not only will it hire the best talent but importantly the talent must fit its culture.

CAPITAL AND FUNDING

Drug development is a capital-intensive and lengthy process, and one of the main problems facing the industry is lack of long-term funding and misalignment of interests and time horizons between companies and investors. Start-ups typically get access to capital through venture capital and/or partnerships with large pharma. However, getting the quantity and quality of capital right at the outset is very important for future success. An insufficient amount of funding can prevent a company from investing in its technology platform and its pipeline, reducing its ability to withstand setbacks and chances of success. It is also easier for management to be behaviourally biased and reluctant to kill bad programmes early when all of their eggs are in one or two baskets.

It's not just the quantity of capital that matters. The quality perhaps matters even more. Early investors and partners can contribute a lot to the company's long-term strategy. A founding venture capitalist (VC) focused on early exits through flipping the company's assets to a large pharma acquirer will be less encouraging of the company spending time and resources to develop its broader technology platform. A VC's time horizon is also typically much shorter compared to the time it takes for a company to develop a drug. This forces companies to go public too early, leaving their fate in the hands of many short-term and impatient public investors. While science is marching ahead at a rapid rate, fixing the funding problem has been a slower and more frustrating process. However, there are new models emerging that we believe will better align the interests of investors, management and patients.

An example is BridgeBio. It has a business model that marries the best of pharma and VC worlds through an unusual parent-subsidiary structure. It partners with academic institutions to seed individual subsidiaries that run their own drug programmes. Like a large pharma, it has a broad portfolio of programs and it aims to retain ownership of these programmes through development and commercialisation. But its VC-like decentralised operation enables incentive alignment and an entrepreneurial start-up culture at the subsidiary level. This model positions BridgeBio well to develop drugs faster and shift the risk-reward profile in its favour.

Having said that, public market investors play a big role in supporting companies like BridgeBio and other biotechs on their journeys to turn promising science into medicines. Investors' time horizons can materially influence a company's chance of success. Here we believe that we have a role to play as long-term investors. Instead of obsessing over quarterly results and fretting at the earliest sign of setback, we focus on what really matters and prepare to support our holdings with primary capital. We feel confident that through providing patient capital, we can contribute to the acceleration of scientific innovation and the discovery of wonderful medicines that will improve many patients' lives around the world.

LUCK

A successful biotech company needs a combination of people to make the right scientific and business decisions, cutting-edge science and technology, access to the right amount of capital from good quality investors and, finally, a dose of luck. As investors, we need to be humble to the fact that even when all the conditions are right – a great talent pool, novel science, and ample capital – things can and will fail because we are still early in our endeavour of unpacking millions of years of evolution in human biology. However, these four elements (science, people, capital, luck) are not independent of each other. Great people with lots of experience tend to make better calls about which areas of science are coming of age and ripe for experiments. This attracts more financing, allowing the company to invest in technology, diversify its pipeline and increase its chances of success or, as others may put it, of being 'lucky'. The more successful a company is seen to be, the easier it is to attract the top talent, which improves your chances of making scientific advances and therefore begetting further success.

CONCLUSION

Investing in biotech is not for those who seek certainty and safe havens, but those who appreciate the asymmetry of investment returns that outliers can bring. As the drug industry evolves, we are very excited that our hunting ground for great ideas is getting larger. We believe that our investment philosophy and process will increase our chances of identifying those long-term winners. Should this belief become a reality, this will not only bring about great returns for our clients but will also contribute to improving lives around the world, including our own and those close to us.

JULIA ANGELES
Portfolio Manager

Julia joined Baillie Gifford in 2008 and is the Portfolio Manager of the Health Innovation Strategy. Prior to Baillie Gifford, Julia worked as a management consultant for McKinsey & Co advising firms in Denmark, Russia and Hungary. Since joining Baillie Gifford Julia has worked on a number of regional and global investment strategies. Julia has a passion for the transformation taking place in healthcare, and it was this passion which led to the establishment of the strategy. She believes that over the next 10 years healthcare systems around the world will experience a monumental change and we will witness a move away from reactive medicine to a world where prevention and cure will become an integral part of healthcare driven by technology. Julia is also a member of the International Growth portfolio construction group. Julia obtained a BSc, MSc and PhD in Economics from the University of Aarhus, Denmark and speaks fluent Russian and Danish.

ROSE NGUYEN
Portfolio Manager

Rose joined Baillie Gifford in 2013 as an investment analyst. Rose worked on various regional and global strategies before joining the Health Innovation team as an Investment Manager. Having observed the innovations in multiple industries, she believes that the great convergence of different technologies and sciences will ultimately transform life science. Biology can move from alchemy and randomness to become a more predictable, deterministic and repeatable science, that will give rise to a plethora of exciting investment opportunities. She joined the Health Innovation team in September 2018 at the inception of the strategy. Rose graduated BA (Hons) in Economics and MPhil in Finance and Economics from the University of Cambridge in 2012 and 2013 respectively.

MARINA RECORD
Portfolio Manager

Marina joined Baillie Gifford in 2008 as an investment analyst. She worked in a number of global teams before joining Long Term Global Growth, where she focused on analysing companies with the potential for sustained rapid growth. It was here that Marina developed an interest in healthcare, intrigued by the accelerating pace of progress in the field. She joined the Health Innovation team in January 2018 as an Investment Manager, to fully focus her attention on exploring the potential consequences of such progress and how Baillie Gifford can help. Marina graduated from the London School of Economics and the Higher School of Economics in Russia with BSc degrees in Banking and Finance and in Economics, having studied on these programmes simultaneously.

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