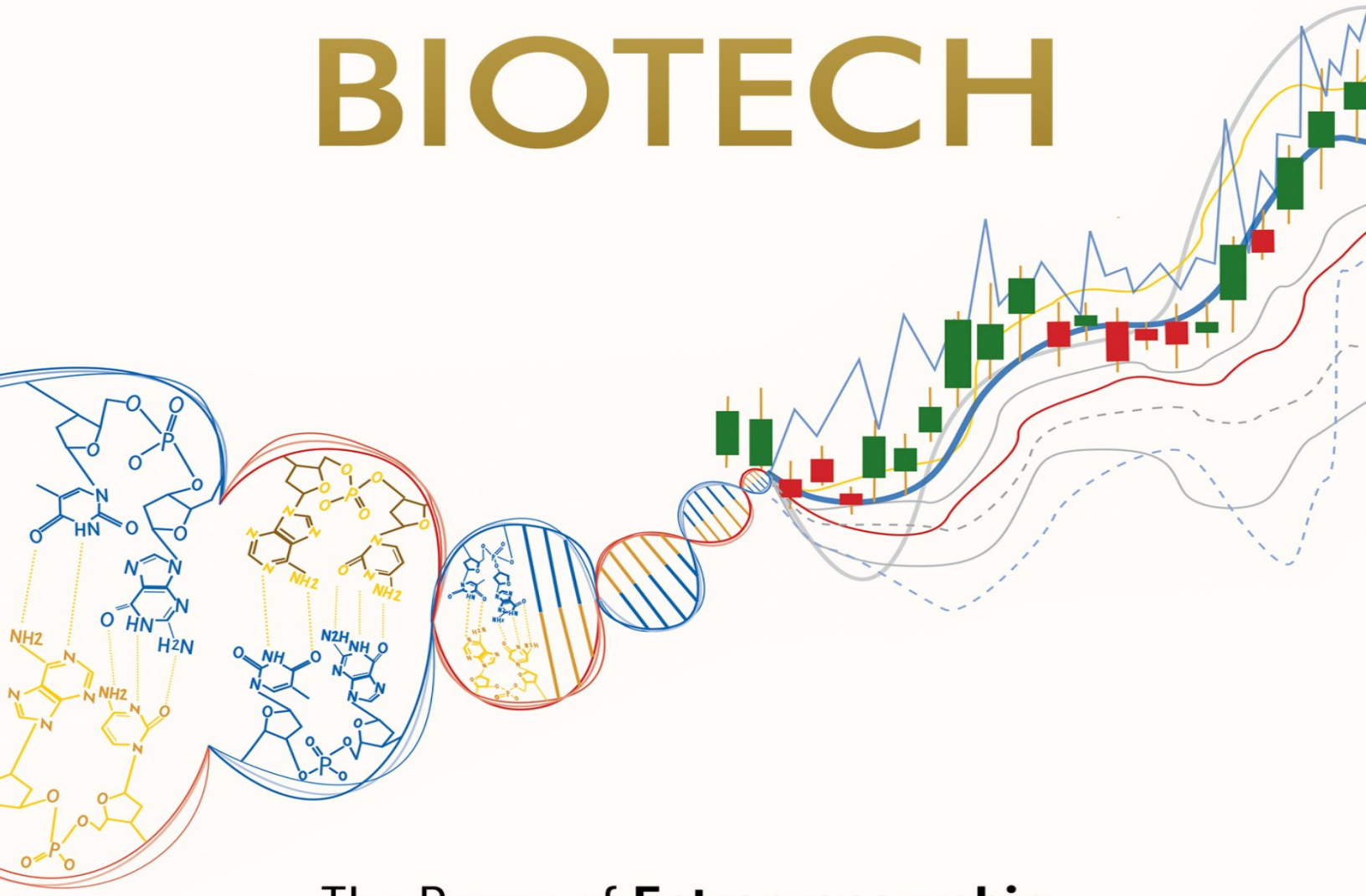
BUILDING BACKWARDS TO BIOTECH



The Power of **Entrepreneurship** to Drive **Cutting-Edge** Science to Market

STEPHANIE A. WISNER

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For my parents, who believed in me before any words of my story were ever written. I love you.

For my mentors, who supported me, invested in me, and took a chance on me. Particularly, Keith Crandell, Jacob Glanville, Martin Sanders, J. David Gangemi, Kristina Burow, Ben Cravatt, and Cheryl Fuller.

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INTRODUCTION: BEGINNINGS

I stood alone in the hospital bathroom, bent over the sink, trying to catch my breath. I replayed the words the doctor had said to me only moments ago after the door had clicked safely shut behind our last patient:

"There's nothing else we can do for her."

When I took this job as a medical scribe in primary care, I was fully aware that there were plenty of diseases for which there were no cures. I just hadn't anticipated the frequency with which I would hear these words, nor my difficulty accepting the reality of them.

This patient was a young woman only a few years older than me. She had inoperable cancer and had undergone the standard chemotherapy and radiation treatments, but neither prevented the cancer from metastasizing. Her oncologist's notes suggested we speak to her about palliative care and other end-of-life options.

This patient did not say much. Instead, she cried big, choking sobs in front of us—the kind I had only ever let out behind closed doors. In response, I did my job—the only thing I could do. "*Patient presents with grief reaction*," I wrote in her chart.

I had, at this point, witnessed many such cases: cases where, at some point, the standard of care protocols we followed had exhausted treatment options. The only remaining guidelines pertained to helping a patient to die comfortably.

One oncologist I worked with specialized in liver cancer, a particularly terrible disease for which existing medicines were largely ineffective. "I've become really good at walking people down the path to death," he told me sadly.

I was shaken by these patients' grief. I was shaken by their lack of options. I wondered, *Isn't there anything else we can try?*[1]

On days I wasn't scribing, I worked in a research lab focused on pancreatic cancer.[2]

Similar to liver cancer, pancreatic cancer is a disease with a dismal survival rate. It has proved so difficult to treat that the way we address pancreatic cancer, known as the "standard of care," has largely remained consistent for the past twenty years.[3,4,5,6,7,8,9,10]

The lab I worked in often tested new potential strategies for attacking pancreatic cancer—usually in a petri dish or a mouse model. Sometimes, we could cure the mouse of its cancer.

In response, the head of the research lab would often say, "Cancer has been cured a million times in mice."

I came to realize this was a common saying in the research world—a saying that expressed not only the difficulty of translating discovery from the bench to the bedside but also the irony of "finding a cure" in this setting.

Academic research labs, such as the one in which I worked, were frequently discovering new pathways, molecules, and mechanisms, some of which might eventually inform standard cancer therapy—but likely not for a few more decades. In the meantime, though, people such as the patients I had encountered in primary care were still suffering. Perhaps current research could lessen this suffering *if*

candidate therapies could reach the clinic sooner.[11] Was there a way to speed up the process while still ensuring patient safety? How did research innovations make it to the marketplace in the first place?

In my clinical and research roles, I had made two observations:

- There is an **innovation gap**: more new medicines are needed. Many patients are suffering from diseases for which we lack great treatment options. Moreover, the paradigm of treatment does not always progress in parallel with the evolving science—sometimes for several decades.
- There is a **translation gap:** innovations from the lab rarely progress beyond the bench. While academic groups frequently discover new approaches for treating disease, there is not a widely used, broadly effective mechanism for allowing these findings to efficiently benefit patients.

At the same time, as a newly minted college graduate, I was thinking about what I wanted to do with my future. I was primarily interested in bridging the gap between the research lab and the medical clinic. I just wasn't sure how.

As I was puzzling through these questions, I received an email from my alma mater. The subject line: "Free entrepreneurship training for scientists—learn how to turn your scientific research into something practical with an I-Corps short course."

I had stumbled upon a free class taught by successful scientists-turned-entrepreneurs. The course focused on translating research into something that could tangibly help people through building a business. Was entrepreneurship the answer to the questions with which I had been struggling?

At this point, I knew little about business. My only previous exposure to entrepreneurship was time I'd spent with a billboard business owner whose passion for entrepreneurship was contagious.[12]

Impulsively, I texted my friend Emily: "What are you doing on September 15? Want to take a trip to New York?"[13]

Over the following two weeks of the course, the instructors demonstrated to our class of young scientists how business approaches could be leveraged to bring cutting-edge science to patients. They shared stories from their own experience as entrepreneurs, including examples of how they were able to translate a new discovery in the lab to a successful start-up and product that could benefit patients.[14]

I left New York convinced that such start-ups (called "biotechs") could be effective solutions to the innovation- and translation-gap problems I had witnessed on both the clinical and research sides. Back at home, I continued with my job in the lab. However, biotech had piqued my interest, and I wanted to continue learning about it.

BIOTECH AS THE "BRIDGE"

Biotech is short for biotechnology. Although the technical meaning of the word "biotechnology" is "technology based on biology," the word "biotech" is commonly used to refer to a *start-up* company that uses science to create new medicines or products. This word can also be used to refer to the industry itself.[15] In this book, we will adhere to these latter two definitions.[16]

People in the biotech industry often say biotech began with Genentech in 1976, one of the first scientific start-ups to

demonstrate the power of combining science with business.[17] Within only a couple of years, the company discovered a way to use recombinant DNA technology, which at the time was used only in the lab, to grow human insulin in bacteria. This was significant because growing insulin in bacteria allows it to be produced in large quantities with consistency in quality. Without insulin, diabetes is a deadly disease. In order for insulin to be an effective medicine for diabetic patients, it must be reliably available in large quantities.

At the time, diabetes was treated by harvesting insulin from pancreases obtained from cows and pigs. This animal form of insulin sometimes caused potentially life-threatening allergic reactions in patients; potency varied up to 25 percent per lot, causing difficulty with dosing, occasional life-threatening side effects, and imperfect control over dangerous secondary conditions (such as diabetic retinopathy, kidney disease, cardiovascular disease, high blood pressure, and high cholesterol).[18]

By 1982, only five years after its founding, Genentech received FDA approval for its human insulin, which it called Humulin.[19] Humulin revolutionized diabetes care. Before Genentech, the lifespan of someone with diabetes was between forty-five and sixty-five years.[20] Now, the life expectancy for someone with well-controlled diabetes approximates that of a healthy non-diabetic individual, thanks in large part to Genentech's innovation.[21,22,23,24]

Since Genentech, biotech has served as a vehicle to bring hundreds of new medicines to the market to the great benefit of patients. The story of Genentech serves to demonstrate the key advantage of biotech, which holds true to this day—a focused and efficient pathway to translate novel research into tangible treatments.[25]

After work one day, I was on the phone with Brad Treat, my I-Corps instructor-turned-mentor, seeking advice on how to gain more experience in biotech. I was calling him from the parking lot outside the University of Michigan lab building where I worked, so I paced the parking lot as we spoke, playing absently with my U of M Hospital badge.

While we were on the call, he was also searching online for local entrepreneurship events.[26] Treat was in the process of recommending such events to me as excellent places to meet representatives from a variety of start-ups, thereby speeding up the process of interning, volunteering, or getting hired.

"The best way to build business experience quickly," he was telling me, "is to do so through hands-on experience with real companies."

"I'm open to that," I said.

There was silence for a minute as he scrolled through his Google results. Then, in an excited voice, he said hurriedly, "I found an event, run by Steve Case, the former CEO of AOL. He's doing a tour through the Midwest and running pitch competitions, but it's happening *right now!* It looks like there's networking afterward, so there would be a chance for you to meet start-up CEOs. Can you make it there?"

I was taken aback. The thought of meeting CEOs was extremely intimidating for me, and I had expected to have more time to mentally prepare. I had just finished at work for the day and glanced down at the outfit I had worn to the lab: my typical jeans and a hoodie. While ideal for comfort underneath a lab coat, it was less ideal for networking with CEOs. Nevertheless, I replied, "Okay, I'll go now."

I drove to downtown Ann Arbor, where the event was already well underway. Since I had come late, I hung to the back of the auditorium. Regardless, I found the enthusiasm and energy of the room to be completely enthralling. As I watched, multiple companies pitched their businesses, hoping to be selected to receive Case's investment dollars.[27]

One company, in particular, stood out to me. Let's call it Company G. This medical software company was tackling the problem of the sheer amount of information on the online medical platform PubMed—specifically, information on genetic mutations in cancer. A lot of useful scientific data about them is available online, but a streamlined way for clinicians to readily utilize this knowledge is lacking.

In response to this problem, Company G was creating software that would codify the existing literature into actionable insights. This software would allow clinicians and drug developers to more readily harness findings from the literature to better treat diseases, such as cancer, that are characterized by a multitude of possible genetic alterations.

As it happened, I had become aware of the difficulty of readily linking new insights from the literature to clinical use during my time as a medical scribe. Thus, I was especially interested in Company G. Excitedly, I decided to wait until the pitch competition ended and the auditorium had cleared.

A cosmetics start-up won the prize money, not Company G, but G was still the most interesting in my opinion. When the competition was over, I hung back until the only people left in the auditorium were the CEOs and me. They were all dressed in suits.

Self-conscious of being young and underdressed, I found the CEO of Company G and approached him, doing my best to hide my nervousness.

"Hi, I'm Stephanie," I said in what I hoped was a confident tone.

He smiled and shook my hand. "Nice to meet you," he said. So far, so good.

"I think your company's focus on making genetic variant information more accessible in oncology is really interesting," I said. "It's a problem that fascinates me too. Is there anything your company needs help with? I'd be happy to work with you for free."

He looked thoughtful, appearing to consider what I said. Then, to my surprise and relief, he replied, "Yes, actually, I think we could use some help although, of course, we would pay you. What did you say your background is in?"

"I have a bachelor's in chemistry and chemical biology," I said.

"Oh, that's great," he replied. "Here." He handed me his business card. "Follow up with your résumé, and let's schedule some time to meet."

A week later, I had my first consulting job working for Company G.[28]

THE BUSINESS OF BIOTECH

Though this was my gateway to work with scientific start-ups, Company G was not a "biotech" company the way we will define it here, i.e., a start-up company developing new medicines called therapeutics.[29]

The CEO of Company G tasked me with writing G's white papers, press releases, and several other materials key to the business. In these documents, I sought to explain the technology and the business's value proposition in a way that would make sense to physicians, scientists, and the general public. I loved the impact of my work. I loved that I was playing a part in helping science reach the market where it could help people more quickly.

It didn't take long, though, for it to become clear to me that I understood very little about how companies and businesses actually worked. Although I was playing an active role in Company G, I knew I could be an even more substantial contributor to future companies if I had more business knowledge and acumen.

I decided to apply to business school. In some ways, this was a terrifying decision for me. I had always expected to be a medical doctor or PhD scientist, and getting an MBA had never been on my radar. In business school, I would surely be the least knowledgeable person in the room, confronted with many topics I knew little to nothing about. More discomforting to me, though, was the prospect of the pivot. Was I leaving behind my love for science by getting an MBA? Nevertheless, I am a big believer that sometimes you have to take chances when something feels right.

Within only two months of the I-Corps program, I was accepted to the University of Chicago Booth School of Business, where I concentrated my degree in entrepreneurship, finance, and accounting. While there, I met Keith Crandell. This introduction led to him generously offering me an opportunity to work under him at ARCH Venture Partners for nearly two years. ARCH is a leading biotech venture capital (VC) firm known in VC for funding as well as *starting* companies.[30,31] Previous ARCH companies include Illumina (whose technology is famously credited with decreasing the cost of

DNA sequencing a full human genome from $1 million to $1,000 in only seven years), Juno Therapeutics (bought by Celgene for $9 billion), and Receptos (bought by Celgene for $7.2 billion and resulting in the recently approved new medicine for multiple sclerosis, ozanimod).[32,33,34] Because ARCH often founds the companies they fund, they have developed multiple "best practices" over the years around how best to create new companies. Working there and learning from the team provided me the great fortune of being trained by some of the most experienced builders of biotech companies in the field.

Seeing an opportunity to help fill the gap between science and business, I started my own biotech consulting company, BioVenture Advising LLC, while in business school. At first, my major contribution was translating science into marketable data for investors. Increasingly, though, I was able to help biotech company clients in developing and executing business strategy, including acquisition and spinout; pitching investors to raise capital; developing market strategy and product positioning for commercialization, among other activities.[35]

In late 2019, as I was finishing my MBA and consulting for him, Jacob Glanville invited me to cofound his new venture, Centivax, Inc.[36] Centivax uses computationally based immunoengineering technology to develop new medicines. This means we use computational algorithms to help us engineer better therapeutics and vaccines. Currently, we are developing therapies for multiple applications, including a broad-spectrum ("universal") flu vaccine that might end the need for a new shot for every flu season, multiple potential treatments for cancer, a potential treatment for COVID-19, a medicine to treat MRSA, and many others. Netflix featured our work on its original series *Pandemic: How to Prevent an Outbreak*. In

2022, we will reach a key milestone in drug development when we begin clinical trials in partnership with the US Navy.

At the end of 2021, I was fortunate to be listed on the Forbes 30 Under 30 List for Healthcare.

I wrote this book because not so long ago, I was a novice in biotech and wanted to learn more but was unsure of where to start. When I first entered the industry, I felt ill-equipped. I didn't understand how drug development in biotech generally worked, let alone what the best practices in the industry were. I also quickly discovered that resources intended to teach scientists about the *business* of biotech are quite scarce.

Over the past five years, I've learned and refined a variety of strategies and skills that have helped me greatly in navigating the biotech industry successfully. In an industry known for the truism that most companies fail, I've also learned multiple best practices to increase the probability of identifying or founding a biotech start-up that is more likely to succeed. Building a biotech company successfully can be accomplished by keeping one process always in mind—Building Backwards. In this book, you will understand the concept of Building Backwards and how it can:

- Increase your chances of starting a "winning" company
- Inform more successful capital raising
- Lead to a strong clinical and scientific strategy
- Mitigate business and scientific risk from the outset

Understanding these topics (and others) is critical to starting a biotech company and will be covered in detail in this book.

My father, who speaks German, sometimes says: "*Aller Anfang ist schwer*," which roughly translates to "every beginning is difficult."

Though I surely have much more to learn about this industry myself, my hope is this book can help you through your own beginning—whether you're just getting started in biotech or are simply curious about the industry. By capturing the stories and takeaways of seasoned biotech entrepreneurs, the lessons encapsulated in this book reflect hundreds of years of cumulative experience among the many interviewees included here. Additionally, I have written this book close enough to my own beginning such that I still vividly recall some of my initial perceptions and uncertainties, as well as which early lessons were the most helpful for me. These stories have been included as well.

I also believe in the power of science to create hope and genuine help for those suffering from diseases currently considered untreatable as well as the ability of scientists to be biotech leaders. Good science combined with innovative business practice has the power to literally save and enrich lives. My hope is this book will make it easier for interested individuals to bring this kind of work to a waiting world.

The purpose of this book, then, is threefold. First, I want to inspire scientists to use their unique training to help create new businesses and new medicines while showing them their potential to do so. Second, I hope to acquaint the reader with concepts common to the business, intellectual property, and clinical trials aspects of biotech that they will need to enter the field, including the structure of the industry itself. Third, I wish to demonstrate to scientists and entrepreneurs the power of "Building Backwards" to maximize the probability of business success. This leads us to the book's title… what is "Building Backwards"?

BUILDING BACKWARDS TO BIOTECH

Over the course of the more than thirty interviews I conducted for this book, I came across a common theme that often seemed to be at work in successful companies and projects—the idea of Building Backwards.

Building Backwards is ***building with the end in mind***—defining your end goal early on such that you can more easily optimize your path toward achieving that end.

This might sound like an oversimplification because science rarely behaves the way we predict. However, this is not a step-by-step protocol to put into practice but rather a method of *thinking*, which is adaptable to any unforeseen scientific complication.

To demonstrate the power of Building Backwards, I would like to point the reader to an example outside the realm of science. In 2002, the Oakland Athletics baseball team essentially applied the principles of Building Backwards when General Manager Billy Beane tasked Paul DePodesta with building a winning team on a low budget. Rather than the traditional way of selecting recruits by relying on the experience and intuition of talent scouts, DePodesta (a Harvard economics graduate) selected players statistically using their on-base percentage from previous seasons.

The theory was simple. To win a baseball game, you need to maximize the number of runs. To increase the number of runs, you must—above all—maximize the number of times players get on base. Therefore, DePodesta assessed the promise of potential players solely by their ability to get on base, measured by their historical "on-base percentage," and ignored players' traditionally perceived weaknesses such as weight, batting style, etc. The Oakland A's selected players who maximized the team's overall "on-base

percentage," and two months later, the team went from ten games behind first to twenty consecutive wins.[37] The results of the Beane-DePodesta approach were so startling that they became the subject of a book and then a film.

Clearly defining an end goal—in this case, maximizing the number of runs—enabled the A's to Build Backwards to uncover a strategy that moved them closer to that end. By focusing on creating a team with a high overall on-base percentage, the A's were able to increase their total runs and succeed at their goal.

Though this is not a biotech example, the takeaway stands. ***To increase the probability of success, Building Backwards from a defined end goal can be a useful tool.*** It can also enable you to clearly and efficiently focus your energy on ***optimizing for the outcome you seek.***

Building Backwards is a simple concept, yet it is so easy to botch. Particularly in biotech, it can become especially challenging not to lose sight of a larger goal as an entrepreneur struggles with the oh-so-challenging immediate goals common to an area as exacting and detail-oriented as science.

In biotech, then, Building Backwards is particularly important to spur constant refocusing on the end goal. In this book, we will analyze multiple examples of the cost of failure to Build Backwards as well as best practices in applying it well.

RATIONALE AND ORGANIZATION OF THIS BOOK

Ultimately, this book seeks to demystify biotech as an industry, leveraging a wide array of collective wisdom to establish Building Backwards best practices that can bridge the gap between research and the clinic.

Some questions we will seek to answer are:

- How does drug development in the context of biotech work, and how can biotech be useful in developing needed medicines?
- Which business principles are most important to learn, and what do you need to know about them?
- How do you increase the probability of launching a "winning" biotech company and/or how do you recognize winning companies?
- What do you need to understand about all-important but biotech-specific topics such as intellectual property and clinical trials?

To address these questions, this book is broken up into three parts.

Part I, Learning, will provide an overview of the drug development industry, examine its characteristics, and demonstrate the need for companies that Build Backwards. It will highlight the power of biotech companies in driving cutting-edge science from bench to marketplace.

Part II, Launching, will describe the essential tenets common to a solid biotech company to allow the reader to recognize or build a good one. It will address how to "de-risk" a company to decrease the likelihood of failure.

Part III, Building, will introduce and examine a number of concepts common to the business, such as intellectual property and clinical trials—aspects of biotech that anyone entering the industry needs to know in order to hold their own in the rapidly moving biotech industry.

This book is written with two primary readerships in mind. The first readership is those who are new to the biotech industry in some

way, whether as a scientist who is interested in starting their own biotech company and looking for guidance or someone contemplating joining the industry in some way. The second is those who might just be curious about biotech in general, perhaps hoping to gain some understanding of how new therapies emerge, gain approval, and ultimately help patients.

To introduce the Building Backwards approach, I explore key questions along with insights from leaders in biotech, academia, pharma, and other fields. Case studies will demonstrate how various companies utilized the principles of Building Backwards to change the face of medicine and impact many people's lives. Some of the people and stories in the book include:

- The commercialization of Gleevec, the famous drug that turned chronic myeloid leukemia (CML) from a death sentence to a treatable disease. Advice on how to increase the probability of success in drug development by Brian Druker, MD, who was a key player in bringing Gleevec to market, where it reached blockbuster status.
- Interviews with two managing directors (Keith Crandell and Kristina Burow) at ARCH Venture Partners, the venture firm responsible for Illumina, Juno Therapeutics, Twist, and other paradigm-changing biotech companies.
- John Crowley's story of saving his children by creating the first medicine for their rare disease. Crowley's work was so successful that his story was portrayed in a film called *Extraordinary Measures*, featuring Harrison Ford and Brendan Fraser.
- Jacob Glanville, PhD, CEO and founder of both Distributed Bio (acquired for $104M) and Centivax, whose work was featured in the Netflix documentary *Pandemic: How to Prevent an Outbreak* as well as on CNN, MSNBC, The New Yorker, Fox News, and others.

The stories of success and failure provided in these pages seek to demonstrate to readers the power of a Building Backwards mindset in driving forward cutting-edge science innovation. By learning to start with the end, my hope is your own beginning in biotech will be made less difficult.[38]

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1 I am sharing this story simply to make the point that many untreatable diseases require new medicines. While many physicians are extremely involved in research and conducting clinical trials, there will always be diseases for which there are no cures as well as diseases for which the standard of care might benefit from improvement.

2 Huge thank you to the Lyssiotis Lab and the many remarkable people I met there who served as scientific mentors. Thank you especially to Costas Lyssiotis, for taking a chance on me, and to Chris Halbrook, for being a consistent and patient teacher. Thank you to Hanna Hong for encouraging me, laughing with me, and sharing the journey with me.

3 "Cancer Stat Facts: Pancreatic Cancer," National Cancer Institute, Accessed June 21, 2021.

4 "Pancreas: Recent Trends in SEER Relative Survival Rates, 2000–2018," National Cancer Institute, 2018.

5 Specifically, Gemcitabine, the current standard of care for pancreatic cancer, has been used since 1997, when it demonstrated slight improvement over bolus 5-FU (fluorinated pyrimidine, also called 5-fluorouracil or 5'FU). 5-FU has been used in the treatment of cancer for more than forty years, often in combination with gemcitabine, although it is no longer a first-line treatment. Both of these are traditional chemotherapeutic agents that work by inhibiting DNA repair and synthesis through incorporating the chemotherapy into the DNA strand, an approach that has been used since the 1940s. Such chemotherapeutic agents cause devastating side effects, including hair loss and immune suppression. The *five*-year survival rates (from moment of diagnosis) over the past twenty years has only improved from 5 percent to 10 percent.

6 "Antimetabolites for Cancer: Effects, Benefits, Risks," Cancer Center, WebMD, May 19, 2020.

7 Ashok Saluja, Vikas Dudeja, and Sulagna Banerjee, "Evolution of Novel Therapeutic Options for Pancreatic Cancer," *Current Opinion in Gastroenterology* 32, no. 5 (2016): 401–407.

8 Amrallah A. Mohammad, "Advanced Pancreatic Cancer: The Standard of Care and New Opportunities," *Oncology Reviews* 12, no 2 (September 2018): 370.

9 Ruediger Goess, "A look at the progress of treating pancreatic cancer over the past 20 years," *Expert Review of Anticancer Therapy* 18, no. 3 (January 2018): 1–10.

10 National Cancer Institute, "Pancreas: Recent Trends in SEER Relative Survival Rates, 2000–2018."

11 I am painting in broad strokes regarding academia versus the potential of biotech. Certainly, some academic labs have mastered the art of translation. However, the majority of academic labs, understandably, focus on publishing papers and winning grants, as this is the major focus in academia by definition. It is also true that increasingly, labs are becoming aware of commercialization. This is an exciting development. My hope is that this book will help prepare academic labs interested in pursuing commercialization.

12 I will always appreciate the encouragement you gave me during this time.

13 This was my friend Emily Trudeau (who ultimately became a medical doctor!), a strong introvert who was not thrilled at the idea of a program that involved a lot of pitching, public speaking, and constructive criticism given publicly. Needless to say, she was a great friend and came along anyway. Without her support, I may not have been brave enough to sign up for the program. Thank you, Emily!

14 Huge thank you to my wonderful I-Corps instructors who are still my mentors to this day: Brad Treat, Ken Rother, Andrea Ippolito, and Eric Young.

15 "What Is Biotechnology?" Biotechnology Innovation Organization, accessed June 21, 2021.

16 In this book, we will also focus on drug discovery specific biotech companies. Although other start-ups that are sometimes included in the biotech definition (e.g., medical device, diagnostics, etc.) will not be specifically addressed here, many of the learnings in this book also apply to these verticals.

17 Sally Smith Hughes, *Genentech: The Beginnings of Biotech* (Chicago: The University of Chicago Press, 2011).

18 "Diabetes Life Expectancy," Diabetes.co.uk, January 15, 2019.

19 "Genentech, Inc.," Company-Histories, accessed April 2018.

20 "Diabetes History," Diabetes.co.uk, January 15, 2019.

21 G. Goodkin, "Mortality Factors in Diabetes. A 20 Year Mortality Study," *Journal of Occupational Medicine* 17, no. 11 (November 1975): 716–21.

22 Diabetes Control and Complications Trial Research Group, et al., "The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus," *New England Journal of Medicine* 329, no. 14 (Sept. 1993): 977–86.

23 R. E. Chance and B. H. Frank, "Research, Development, Production, and Safety of Biosynthetic Human Insulin," *Diabetes Care* 16, no. 3 (Dec 1993): 133–42.

24 Celeste C. Quianzon and Issam Cheikh, MD, "History of Insulin," *Journal of Community Hospital Internal Medicine Perspectives* 2, no. 2 (July 2012).

25 We will talk more about "Big Pharma" and what that is in the next chapter, but for now, know that, for our purposes, when I use the term "biotech," I am not referring to Big Pharma companies such as Merck, Eli Lilly, Pfizer, etc., but rather start-ups as defined above. Also note that while Genentech may now be considered "Big Pharma," it began as a biotech start-up.

26 "Entrepreneurship events" are often pitching events, local business coaching events, or put more generally, events where local start-ups can gather.

27 A pitch is where a company gives a short presentation that covers the basics of the company, focusing on the problem the company exists to solve (such as a new therapy for cancer, etc.) with the goal of achieving funding for the start-up.

28 Huge thank you to the team at Company G for giving me my start in the industry. I love following your successes and am grateful for the part you allowed me to play in your company story.

29 Again, although the definition of "biotech" can sometimes be applied more broadly, such as to larger drug development companies or to companies developing medical devices/diagnostics/scientific tools, for the purposes of this book I will largely focus on drug development-focused start-ups when I use the term "biotech." However, many of the concepts covered in this book apply to other science-based start-ups.

30 Keith, you have become one of the most influential mentors I have ever had. Thank you for allowing me the opportunity to learn lessons of both business and life from you. I am better for it.

31 Thank you to the best team of coworkers I could have asked for. I learned so much from working with you. Especially, Kristina Burow, Mark Mcdonnell, Sean Kendall, David Cruikshank, Ari Nowacek, Corey Ritter, Nilay Thankar, Peter Mintun, Scott Jenkins, Aidan Kahl, Jill Williams, Matt Milligan, Melanie Simms, Honor Crandell, Tracey Pinsoneault, Edward Ho, Julie, Shrader, Edward Ho, Michelle King, and Reetika Bhardwaj.

32 "Illumina's CEO on the Promise of the $1,000 Genome—And the Work That Remains," Vox.com, March 25, 2014

33 Clare McGrane, "Juno Therapeutics acquired by Celgene for $9B in dramatic deal for rising biotech star," GeekWire, January 22, 2018.

34 Bill Berkrot, "Celgene to buy Receptos for $7.2 billion; gains promising drug," Reuters, July 14, 2015.

35 Thank you to every client I have had the privilege of working with. Particularly, Marty Sanders—thank you for believing in me, and especially for giving me my start. This book exists because of you. Sharon Lew, thank you for being a colleague and friend.

36 Jake, thank you for inviting me on the journey that is Centivax. You've become a valued mentor and friend. I'm thankful to know you (see conclusion for a longer note).

37 Michael Lewis, *Moneyball: The Art of Winning an Unfair Game* (New York, NY: W.W. Norton, 2013).

38 This book is not intended to be a commentary on the system nor on the moral status of the system. Nor is biotech meant to be perceived as an all-encompassing solution for untreated disease. Rather, this book seeks to exposit how the industry works and how to achieve success within this framework. Only by understanding a system can we hope to improve it.

PART I

LEARNING

CHAPTER 1

FROM BENCH TO MARKET

"Productivity is meaningless unless you know what your goal is."

—ELIYAHU M. GOLDRATT, AUTHOR OF *THE GOAL*, ORIGINATOR OF THE THEORY OF CONSTRAINTS

Back in my first quarter of business school, I read a book called *The Goal*, which tells the fictional story of a manager at a failing manufacturing plant.[39] Despite producing many machines and a workforce laboring around the clock, the plant is losing money. How is this possible?

Conventional wisdom assumes that many machines produced and many hours worked must equal higher profitability. *The Goal* demonstrates this assumption can be wrong.

In the end, the manager realizes that making too many machines is actually leading to unprofitability. The company is making far more machines than it is selling, leading to expenses being much greater than revenue. Further, he realizes that the employees appearing "busy" and working long hours does not necessarily translate to higher productivity. It would actually be better that they spend fewer hours focused on the specific tasks that lead to higher revenue.

Thus, the true end goal was not to make lots of machines or to maintain a busy workforce. Rather, the *true* end goal of the business was to "make money." Production levels and working hours are *resources* that, when properly harnessed, are means to reach this end

goal. Because the company had not Built Backwards from its end goal, the process itself was inadvertently treated as the purpose.

This may seem somewhat obvious. Yet, *The Goal* is a popular book in business schools for a reason. Losing sight of "The Goal" is a frequent cause of company failure. Building Backwards enables a biotech start-up to avoid this all-too-common outcome.

Building Backwards, as I will use it here, **means defining an end goal from the beginning and then determining a path forward in light of that end.** *The Goal* is a simple example but makes the point nicely: Building Backwards to a specific end goal is helpful to ensure your daily business activities are actually moving you closer to your objectives.

Although Building Backwards may seem a simple concept in theory, it is often not applied in practice. It is simply entirely too easy to miss the forest for the trees, particularly in the day-to-day operations of the company.

I recall one small example of failing to Build Backwards from the ultimate goal of an effort. I was helping prepare one science start-up, Company K, for a pitch to a large pharma company, Pharma F. Company K was a life sciences tools company and wanted to drive uptake of their innovative new tool by pharma companies for use in drug development. If Company K clinched the deal with Pharma F, the resulting contract would be one of the first substantial revenue-generators for the company.

Before meeting with me, the Company K team had put the deck together and practiced their pitch. When they presented it to me during our first practice run, however, the team was often delving into detail that was excessively minute. They were also presenting

the science in a manner that adequately communicated big picture scientific takeaways but did not sufficiently emphasize practical applications, which is what any potential client would most likely want to hear about. I found myself telling Company K repeatedly, "Keep the big picture in mind. Keep what you're saying tailored to the ultimate end goal."

Our pitch to Pharma F needed to be guided by a clear understanding of F's needs and objectives. Pharma F was ultimately only interested in K's tool insofar as the tool would improve F's ability to develop new drugs. Clearly understanding this goal was also the only route to achieve our own goal, which was Pharma F agreeing to give K's technology a try. This meant designing our presentation to precisely address F's likely wants and needs. We needed to Build Backwards from both the goals of the potential client and from our own in order to succeed. This particular case entailed attention to the following points:

- **Focusing on human cell data the company had collected with its instrument.** The goal of any pharma company overall is to create new human medicines. Thus, if Pharma F were to enter a deal, it would be with the intention of applying K's technology to *human* cell samples—as opposed to the mouse cell samples on which K was largely presenting data. Company K had the most data on mouse cells, as these were the easier type of samples for them to study in the lab. However, K needed to largely base its presentation on insights into human cells—even if this meant first collecting more human data.
- **Communicating its expertise.** Company K needed to emphasize it had the best technology in this space by preemptively anticipating the experimental questions Pharma F might want answered and by focusing on the questions that would be difficult

for competing technologies to address. The K team then needed to convey that Company K had the capabilities necessary to conduct the relevant experiments.

In principle, the Company K team understood the approach I was advocating, but in practice, they were initially having a difficult time carrying out these objectives. Building Backwards emerged as a unified way to explain what I really meant when I said, "Keep the end goal in mind."

Ultimately, the team created a pitch that Built Backwards from both Pharma F's goals as well as its own, and Pharma F signed a contract, becoming one of the most important clients for Company K.

Building Backwards can be an especially helpful method for scientists starting out in biotech. This is because it succinctly captures the mindset shift that should occur when transitioning from an academic science to biotech setting. While academic research can sometimes encourage going ever-deeper into a topic, research in the context of a business has a different end goal—and therefore can benefit from a different, more focused mindset—when defining which research questions to ask.

The fundamental "end goal" of academic research is often to improve scientific understanding and disseminate those advances via published papers. In contrast, biotech's end goal is to work toward the creation of a functional end *product*: usually a new drug. Thus, a biotech can benefit greatly from asking research questions with a more practical focus. This is done by Building Backwards from the fundamental queries that must be answered in order to create the end product.

This includes:

- **Defining** where you foresee a company culminating and reverse engineering to achieve that end goal from Day 1.
- **Planning** day-to-day operations such that they work systematically toward your end goal.
- **Weighing factors such as risk,** and de-risking a company early by considering possible pitfalls in light of your end goals. Then, engineering around them before they happen. (We will discuss de-risking in depth in chapter 7.)

To consider the significance of Building Backwards in biotech specifically, we will examine a real example of how detrimental it can be for a company when they fail to Build Backwards effectively.

CASE STUDY ONE: M THERAPEUTICS

M Therapeutics was developing a new therapy for treating stage IV cancer. The technology was relatively far along. The doctor who founded the company, Dr. P, had already used his protocols on human patients through an exception called "compassionate use," which is possible only in desperate cases.[40,41] Dr. P had found the therapy to be very effective at combating stage IV cancer, and he had already used it to bring several terminal cancer patients into remission.

The work involved repurposing several drugs that had been previously approved by the FDA for use in other (i.e., non-cancer) diseases. Dr. P had found the mechanisms of these existing drugs to be synergistic when used in combination for the treatment of late-stage cancer. This meant the drugs upon which the company was based had already been shown to be safe and effective in humans as they had been used and marketed as individual products for many

years prior. (A debate about whether this is a good premise for launching a biotech is beside the point here.)

Dr. P's success sounds impressive. Medically, it is. But to assume that proven medical applications necessarily lead to a successful business is to confuse the process for the goal, much in the same way our manufacturing plant can keep many workers busy making lots of functional, perhaps even highly desirable machines yet fail as a business. The medical benefit of a new cancer therapy does not, in and of itself, guarantee this potential product will successfully anchor a biotech company.

In this case, the drug combination succeeded—it performed as a treatment. What ultimately faltered was the company because it ran out of money without substantially increasing the value of the business, even six years after its founding.

Increasing the value of the business systematically is a key part of pursuing the end goal through day-to-day operations. In biotech, this entails moving toward the end goal of developing a new drug by advancing through the various stages of the drug development process efficiently (more detail on this process in chapter 2). The initiation of clinical trials is one key milestone in the drug development process toward which steady progress is particularly crucial.

Instead of being highly focused and streamlined in data collection in order to expediently initiate clinical trials, however, M Therapeutics' leadership focused on obtaining publication-worthy *in vivo* animal data—over months at first and then years. In academic science, this practice of running many rounds of similar preclinical experiments is both appropriate and typical. Doing so enables the creation of "publishable" data for submission to high-impact journals as well as

increased validation of the results. In contrast, this overinvestment of time and capital into preclinical experiments was likely not as productive as other activities may have been for M Therapeutics as a value-seeking business that already had human validation data.

Specifically, M hired a sizable team of twenty to thirty full-time laboratory employees to conduct preclinical research. While preclinical work certainly has a role, these were previously marketed drugs and known to be safe in humans. Therefore, extensive additional cell and animal data was likely not a requirement. Additionally, hiring such a large team solely for preclinical work demonstrates the extent of M's focus on this single area of the business. Any preclinical experimentation should likely have been highly streamlined, aiming to gather specific data that would facilitate the path to clinic.[42] The capital spent on such a large team to collect this preclinical data could have likely built greater value for the company had it been directed in a more focused way toward generating the preconditions for Phase I (the first phase of clinical trials).

If the company had Built Backwards, it likely would have realized this sooner and invested the majority of its resources into preparing for clinical trials. Instead, the company ran out of capital and struggled to raise more funding due, in large part, to a lack of momentum over the multiple years prior. Additionally, because the value of the company did not substantially increase between each financial raise, M had a difficult time demonstrating to new investors that investing in M would be financially attractive for them.

This anecdote also provides a lesson on why Building Backwards in biotech matters. Considering that M Therapeutics' therapy could put stage IV cancer into remission, society's loss by M's lack of

advancement is far more substantial than simply the failure of another company.

Similar to the manufacturing company from *The Goal*, M Therapeutics became so focused on a step in the process—obtaining preclinical data—that it lost sight of the broader end goal.

- Since it had unique access to human patients early on through compassionate use, M Therapeutics likely had an even more streamlined path through animal data than usual—especially since the drugs in its combo were previously approved and had years of human data each.
- The company did not Build Backwards to define "inflection points" that could ensure the company was increasing its value (we will elaborate on this in chapter 9). Instead, M repeatedly ran out of cash and needed to raise more without substantially increasing the value of the company between raises.

CASE STUDY TWO: SUNOVION

To better understand how one might effectively apply the Building Backwards approach, let's consider a company called Sunovion, a Japanese biotech company that Built Backwards toward the end goal of developing a new schizophrenia medicine. Unlike M Therapeutics, Sunovion started off by determining precisely which experiments to run based on the approval criteria used by the FDA.

Clinical schizophrenia is medically assessed according to both "positive" symptoms (such as hallucinations or movement disorders) as well as "negative" symptoms (such as loss of motivation or pleasure). Several current drugs commonly used to treat schizophrenia work by blocking the dopamine receptor, D2, as their main target in the brain. These existing drugs are somewhat

effective in alleviating the abnormal perceptions and thoughts—the positive symptoms—but oftentimes can be less effective or even exacerbate lack of motivation, dulled emotion, and social withdrawal—the negative symptoms. Blocking D2 receptors can sometimes also cause undesirable side effects, such as weight gain and other metabolic problems.

Diana Perkins, MD, a psychiatrist at the University of North Carolina at Chapel Hill, has previously described the importance of treating the negative symptoms. "Those negative symptoms are often the most devastating," she said. "A person can become, at the most extreme, robot-like."[43]

Therefore, Sunovion sought to create a drug that would alleviate both negative *and* positive symptoms. Sunovion believed the best way to achieve this end was to find a drug that, for the first time, did not treat schizophrenia by binding to D2 receptors. D2 receptor-inhibiting molecules have a high side effect profile because such drugs hit multiple receptors (G-protein coupled receptors, or GPCRs for short). Thus, Sunovion Built Backwards to a clear end goal: FDA approval for a novel drug that did not bind D2 receptors and could treat both the positive and *negative* symptoms of schizophrenia.

To do this most effectively, Sunovion selected its final drug candidate by testing for efficacy against negative symptoms using mice and a special phenotypic assay.

According to the CSO in a *Science* Magazine interview, the Sunovion team "hurtled drug after drug at mice and then analyzed their behavior with algorithms, searching for one that mimicked the effects of a D2 inhibitor—without actually affecting D2."[44,45]

In other words, the scientists used a novel drug screening method that leveraged artificial intelligence technology to analyze the behavior of mice exposed to hundreds of candidate compounds. Then they selected a drug that did not bind to D2 receptors but still seemed to address negative symptoms in mice. In other words, Sunovion relied on animal data to see a reduction in negative symptoms and then used an *in vitro* assay to screen for compounds that did not bind D2 but had already proven efficacy in the mouse model. The mouse model proved efficacy against negative symptoms while the *in vitro* screen selected for drugs less likely to have the host of side effects associated with binding D2—therefore enabling Sunovion to select a drug candidate up front that appeared to meet both criteria of its end goal drug candidate.

Because Sunovion ultimately sought to prove efficacy against negative symptoms in human patients in clinical trials, it was able to Build Backwards from this end goal—finding a way to increase the probability of achieving this outcome by engineering for it early in the drug development process.

The resulting compound, SEP-363856, acts on two dopamine- and serotonin-affecting receptors in the brain called TAAR1 and 5-HT1A (which previous schizophrenia drugs bind) but uniquely does not bind the D2 receptor. In other words, Sunovion found a way to harness the classical therapeutic method of treating schizophrenia by adjusting dopamine signaling. At the same time, it was able to do this by avoiding D2 as a target and thus likely circumventing the host of negative side effects.

By 2019, SEP-363856 had reached the notable milestone of entering Phase III clinical trials. Results from phase trials have demonstrated that treatment with SEP-363856 leads to a significant improvement in negative symptoms compared to a placebo pill. Further, SEP-

363856 had lower rates of side effects compared to currently approved drugs targeting D2.[46,47]

Overall, the findings affirmed what the researchers had set forth as a goal for their new drug: to impact schizophrenia by treating positive *and* negative symptoms and not hitting D2 receptors, minimizing negative side effects. This potential new medicine seemed so compelling that in September 2021, Pharma company Otsuka paid Sunovion $1 billion for the rights to codevelop SEP-363856 (as well as three other less-advanced compounds).[48]

Although the drug has yet to complete its Phase III trial to receive FDA approval, Sunovion is on its way to achieving differentiation in the schizophrenia market and has made significant strides to improve the quality of schizophrenia treatment. How? By Building Backwards from its targeted market positioning (e.g., a schizophrenia drug that also treated negative symptoms with fewer side effects), Sunovion selected a compound early on that was most likely to fit this profile. Screening for an effect on negative symptoms up front also increased the probability that this would also be the case in the clinic.

By creating a distinguished and unique drug profile from the start, Sunovion has paved its way to becoming a market leader and has carved out a market segment for itself up front should it ultimately achieve drug approval. In other words, Sunovion ***built value by Building Backwards.***

At each step, the company proactively Built Backwards by:

- Harnessing the *in vivo* mice data to actively select for the in-human clinical drug profile it hoped to achieve.

- Tying its desired market placement and competitive advantage (e.g., the effect on negative symptoms, in addition to fewer side effects) to its initial data, mouse model, and clinical trial design, which is designed to specifically measure negative symptoms.
- Defining its end goal clearly. It was likely easier to understand where novel technology (e.g., leveraging artificial intelligence to evaluate mouse behavior) could be useful.

Sunovion shows that when both the research and business arms of a company are following the same, clearly defined goals, they can better achieve the larger outcome, bringing novel medicines to patients who desperately need them while building a valuable company.

These case studies help outline how Building Backwards can look in practice. Keep in mind, Building Backwards is a method of *thinking,* not a linear step-by-step process. In the next chapter, we will see how the drug development industry is structured and how this results in limitations Building Backwards is particularly well-suited to overcome.

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39 Eliyahu M. Goldratt, *The Goal: A Process of Ongoing Improvement* (Great Barrington, MA: The North River Press Publishing Corporation, 1984).

40 Scientists can typically only test new medicines on patients after rigorous preclinical safety and efficacy testing, and usually medicines cannot be tested on sick patients until a Phase II trial. The exception is cancer, which allows use in a Phase I trial but still requires years of testing before this is possible. Compassionate use is an expanded access pathway for patients with "an immediately life-threatening condition or serious disease or condition to gain access to an investigational medical product for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available."

41 Office of the Commissioner, "Expanded Access," *US Food and Drug Administration,* FDA, March 23, 2021.

42 We can only speculate about which particular studies potentially should have been prioritized. General examples of "focused" preclinical research work, however, that can serve to progress a company expediently toward the clinic are dosing studies (testing whether lower doses would work, etc.), mechanistic studies (understanding why the combination worked), patient stratification data, and/or pharmacokinetic and synergistic dosing determination studies. M Therapeutics very well may have performed these experiments, but if they did, lingering on them for six years when M already had human data was most likely not the wisest strategy.

43 Kelly Servick, "Experimental Schizophrenia Drug Could Reduce Long-Neglected Symptoms," *Science*, April 15, 2020.

44 Jason Mast, "Sumitomo Subsidiary Flashes New Way of Treating Schizophrenia in PhII Trial," *Endpoints News*, April 16, 2020.

45 Nina Dedic, et al., "SEP-363856, a Novel Psychotropic Agent with a Unique, Non-D2 Receptor Mechanism of Action," *Journal of Pharmacology and Experimental Therapeutics* 371 (October 2019): 1–14.

46 "SEP-363856 is associated with robust improvement in negative symptoms of schizophrenia," *BioWorld*, April 21, 2021.

47 "Sunovion presents data from marketed and late-stage development psychiatric compounds at the American Psychiatric Association (APA) Annual Meeting 2021," Sunovion, May 3, 2021.

48 Nicole DeFeudis, "Otsuka puts nearly $1 billion on the line for four neuropsychiatric candidates from Sunovion," *Endpoints News*, September 30, 2021.

CHAPTER 2

THE LANDSCAPE

"The process [of drug R&D] is highly risky due to profound and persistent uncertainty…the degree to which [this is] present and exaggerated in drug R&D is unique, with important implications for the economics and management of R&D and the pharmaceutical business as a whole."

—GARY PISANO, PROFESSOR AT HARVARD BUSINESS SCHOOL, AUTHOR OF *SCIENCE BUSINESS*

"It was a remarkable compound," Benjamin Cravatt, PhD, told me.

Given his background, Cravatt's assessment of a compound as "remarkable" carried a lot of weight. As a coinventor of activity-based proteomics (i.e., the study of protein activity through the use of small molecules known as "probes"), he is a well-respected leader in the broader field of chemical biology.

Cravatt is currently a professor and Norton B. Gilula Chair of Chemical Biology in the department of chemistry at The Scripps Research Institute. He joined Scripps as a tenure-track faculty member at the age of only twenty-seven. At forty-four, he was elected to the National Academy of Sciences. Three years later, he was also elected to the National Academy of Medicine. National Academy memberships are considered among the highest honors in the scientific field.

He's also a remarkable entrepreneur. The companies he has cofounded include ActivX Biosciences, Abide Therapeutics, and Vividion Therapeutics, among others. The companies were purchased by large pharma companies for $20 million, $400 million, and $2 billion in total deal value, respectively.[49,50,51]

To me, what stands out about Cravatt is his kindness and ability to connect with people on a personal level. When I was an undergraduate, Cravatt gave a seminar at my university, which was well-attended by many professors from various departments. Afterward, I witnessed even the most senior professors crowding around him, hoping for a few minutes of conversation. I had wanted to greet him but assumed he might not have time to talk to an undergraduate when many more important people were in the room.

I waited quietly near the back, not wanting to interrupt. To my surprise, he quickly spotted me and motioned me over. The group of professors stared as he turned toward me with the kind of focus that might suggest I was the only one in the room. "Stephanie," he said, "it's good to see you. How are you?"

Now in conversation with me, Cravatt was referencing his work on fatty acid amide hydrolase (FAAH), one of two enzymes implicated in the termination of signaling in the endocannabinoid pathway. Activated by Δ9-tetrahydrocannabinol (THC), the psychoactive component of marijuana, this pathway has been shown to hold high potential for treating inflammatory pain.[52] Together with Doug Johnson and Kay Ahn at Pfizer, Cravatt worked to target FAAH using a small molecule drug candidate that we will refer to here as "Pfizer-123."

The pharmaceutical giant Pfizer had reached out to him in order to develop this molecule via a collaboration. Pfizer-123 showed

potential for treating disorders characterized by inflammation, such as arthritis and pain.[53]

The collaboration resulted in what Cravatt referred to as "a remarkable compound that was arguably the most selective and potent covalent inhibitor to ever go into humans."

Why did this matter? Because it implied Pfizer-123 had the potential to be a one-of-a-kind medicine. Its high potency (i.e., inhibition of the target FAAH at low concentrations of Pfizer-123) and high selectivity (i.e., no off-target effects, which is often what causes side effects) compared to many other potential medicines suggested that patients with a variety of inflammatory conditions might benefit from Pfizer-123.

The problem? Pfizer had to select *one* disease (i.e., "indication") to test the compound against in clinical trials, but animal models of pain are notoriously poor predictors of human pain syndromes. This made it especially difficult to select an indication for clinical trials based on the animal data.

In making this decision, Pfizer had to factor in *both* the scientific *and* commercial interests of the company. With this, Pfizer understandably preferred indications with larger market size. Ultimately, Pfizer selected osteoarthritis, a large and underserved clinical population that matched its market requirements and commercial interests. Despite clear evidence of strong inhibition of FAAH in humans, the osteoarthritis trial unfortunately failed.

As is often the case with candidate new medicines that fail their first clinical study, Pfizer-123 was considered "tainted" and languished for several years, as the company was understandably hesitant to invest more money into something that had already failed one

clinical trial. This meant that Pfizer-123 was less likely to be expediently tested in other—albeit smaller—indications, where it also had the potential to help patients.

Ultimately, after a period of nearly ten years, Pfizer-123 was out-licensed to Jazz Pharmaceuticals for evaluation in neuropsychiatric disorders, where it is still under development.

Cravatt gained insight into the business model necessitated by large pharma companies—namely, that large pharma companies must factor in commercial requirements of the business alongside the science. "Oftentimes, a pharma company has to make very difficult decisions about which drugs to invest in," Cravatt said. "These decisions include assessing the confidence in the biology as well as market size and commercial interest. Emerging areas of science often suffer from this type of analysis because if an initial hypothesis is proven incorrect, the interest level in a new target or mechanism can dissipate quickly."

He emphasized Pfizer's continued effort to build understanding of the FAAH-endocannabinoid pathway regardless of the failed clinical trial. "In the case of FAAH, that was disappointing but understandable for a large company like Pfizer because the scientific information to match the target to certain clinical indications was still emerging," he said. "To Pfizer's credit, they made Pfizer-123 available to academic clinical researchers, which has allowed several human biology experiments to enrich our understanding of the FAAH-endocannabinoid pathway and pointed to possible other indications, such as post-traumatic stress disorder."

In general, there are certain hallmarks of the way drug development tends to be conducted in the context of Big Pharma. In the case of FAAH, the "unrivaled" chemical matter that resulted from the

project serves as an example of some of big pharma's strengths while its "high risk" profile as a novel target highlighted some of the difficulties big pharma in particular can face when developing drugs for emerging areas of science.

Ultimately, in order to understand the power of biotech as an industry, it's important to first understand where biotech fits with pharma in the drug development landscape. This requires an overview of drug development itself.

OVERALL PROCESS OF DRUG DEVELOPMENT

There are several steps in bringing a new medicine to market. The US Food and Drug Administration (FDA) dictates these steps, which are largely the same for any new medicine—regardless of whether the new medicine is developed by a biotech company or a large pharmaceutical company.

The FDA stipulates the following generalized steps to get a drug to market:

1. **Preclinical efficacy studies.** Although these studies most typically include nonanimal (*in vitro*) studies as well as studies in animal models (*in vivo*), if no adequate animal models exist for a disease, sometimes *in vitro* data providing a rationale for the intended use is sufficient. For biotech "spin out" companies (i.e., when the technology is spun out of a university), the early-stage efficacy studies sometimes are data available from the academic lab and are what first show the promise of the technology. Once a clinical candidate compound is defined, further efficacy data can then be collected for use in an Investigational New Drug Application (IND).

2. **Good laboratory practice (GLP)/good manufacturing practice (GMP) manufacturing.** The terms GLP and GMP simply refer to a certain standard of manufactured drug material, in accordance with specific testing regulations that enable the drug to be used for certain studies, such as in clinical trials. Testing regulations are in place to ensure certain levels of quality and compliance are built into the manufacturing of the drug. In other words, you can't just use the drug you synthesized in the corner of your principal investigator's (PI's) lab in humans during clinical trials.[54,55] This step is accomplished using a contract manufacturing organization (CMO) or a contract development and manufacturing organization (CDMO) that has all the necessary inspections and certifications as well as equipment necessary to adhere to GLP/GMP regulation while completing needed steps such as formulation, analytical services, manufacturing, cell line development, etc.[56]

3. **Toxicology studies.** The main goal of this step is to demonstrate that your new medicine is unlikely to have any widespread safety issues in humans. You do this by testing for several different potential toxicities in both cell lines and animal models. This step is used to define the "margin of safety" for a new drug by characterizing its impact on organ structure and function, dose ranges that result in toxicity (and whether that toxicity is reversible), and to which degree toxicities are dose dependent, related to the route of administration, etc. This information can then be used in defining a clinical dose and guiding parameters for clinical trials to maximize safety.[57]

4. **Investigational new drug (IND) application.** It is essential to understand very early in the drug development process what will be required in the IND so you can build toward this data set from

early on in a company's life. An IND application contains information in three major categories:[58]

a. **Animal pharmacology and toxicology studies**—this preclinical data provide support as to whether the potential drug is reasonably safe and effective in animals. This is the information collected in step 3 above.

b. **Manufacturing information**—this is where information is provided on the drug composition, the manufacturer, stability and controls used for manufacturing, the drug substance (i.e., the active component—your molecule), and the drug product (i.e., the finished dosage form, for example, a tablet, capsule, or solution).[59] This information is used to ensure you can adequately produce consistent batches of the drug, and much of it comes from step 2, the GLP/GMP manufacturing step.

c. **Clinical protocols and investigator information**—this is where you include detailed protocols for the planned clinical studies as well as information about the investigators (scientists) and a commitment to have the study's safety and ethics reviewed and monitored by an Institutional Review Board (IRB) and to obtain informed consent from study participants.

5. **Clinical trials.** This will be discussed in great detail in chapter 11. To give a brief overview, clinical trials are the "in human" testing of the drug and the last step before approval. Clinical trials are broken up into four phases, three of which occur prior to approval:[60]

a. **Phase I.** Twenty to eighty participants (this is considered to be "small"!), usually conducted in healthy individuals (although for some severe diseases such as cancer, the FDA allows for use in patients since these patients often have few therapeutic options). The goal of this phase is primarily to

assess safety of the drug in humans, such as identifying the drug's most frequent side effects. They also seek to characterize various doses of the drug as well as items like drug metabolism.

b. **Phase II**. A few hundred participants, conducted in patients with the disease or condition (i.e., "indication") your drug candidate is aiming to treat. This phase primarily assesses efficacy although safety continues to be monitored.

c. **Phase III**. Often involving thousands of patients. These are expanded studies (i.e., longer and many more participants) and assess both efficacy and safety in addition to studying other factors like dosages and using the drug in combination with other medications.

6. **File for approval (NDA or BLA).** The next step involves filing a Biologics License Application (BLA) if your new drug is a biologic or a New Drug Application (NDA) if the drug is a small molecule. This filing is usually the final step prior to approval by the FDA. After reviewing these data, the FDA determines whether your drug is both safe and effective enough to come to market.

More likely than not, a biotech company is often acquired long before actually reaching approval (for reasons we will discuss in the next chapter). However, in the rare case this stage of development is independently completed, there are two more steps:

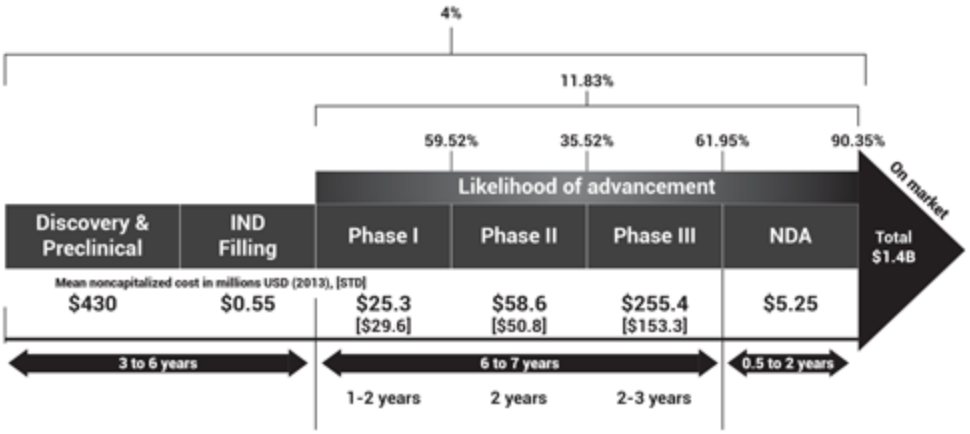
7. **Bring the new medicine to market.** This is often where Big Pharma's capabilities in manufacturing and distribution become particularly noteworthy. Through partnerships or, more often, acquisitions, pharma companies can leverage their resources to assist in scaling up production as well as widely marketing and distributing the drug through their existing channels. If a collaboration with a pharma company has not occurred,

partnerships with other corporations, including manufacturing CDMOs, are likely relevant.

8. **Phase IV trial for post-marketing assessment**. It is never possible to predict *all* of a drug's side effects during clinical trials because of limited time and a limited number of patients in such studies. Correspondingly, a common additional step is to monitor safety issues *after* drugs are on the market. The sponsor is required to submit periodic safety updates to the FDA.

Potential new medicines can fail at any one of these steps. Per the figure below, there is only about a 4 percent chance a new drug will make it all the way from discovery to the market, and the likelihood of failure at each step is substantial. There is roughly only a 12 percent chance a drug that makes it into clinical trials will successfully make it to the market.[61]

Additionally, developing a new medicine is extraordinarily expensive. According to the Tufts Center for the Study of Drug Development, it cost about $2.6 billion to develop *one* new drug and bring it to market (units are 2013 dollars, costs are capitalized; i.e., the cost of failed drugs is included, as are the costs of post-marketing research).[62] Further, the average total time to develop a drug is about ten to fifteen years from start to finish.[63] To give some perspective, the median cost of developing a new phone application is only around $171,000 over three to seven months.[64] Thus, drug development has two crucial hallmarks. It is extraordinarily expensive and the timeline is long. The scale of both time and expense differs greatly from the majority of other industries.



Long, expensive, and uncertain: the process of drug approval. As you can see here, the average noncapitalized cost (i.e., the cost of failures not included) for a single drug is exorbitantly expensive: $1.4 billion, with an average timeline that can be up to fifteen years. This is an average, so keep in mind it can certainly be more. Further, the probability of success overall for a new drug is only 4 percent, while the probability of success of a drug entering the clinic is only 11.83 percent. The mean noncapitalized costs for each phase of development are also listed above, with the standard deviation in brackets below (units are 2013 dollars).[65,66,67,68,69]

Moreover, drug developers face limited market exclusivity. By the time a drug makes it to the market, it typically only has about ten years (at best) remaining in intellectual property (IP) protection rights out of the initial twenty years.[70] This means a pharma company has just those ten years to sell the drug and recoup its $1.4B (or more) investment.[71] When a drug's patent expires, its revenue often plummets by up to 80 percent.[72]

Combined, the high costs, long timeline, substantial failure rate, highly specialized development steps, and limited market exclusivity make any kind of drug development very difficult. This is why potential new medicines sometimes are not developed even when the scientific evidence supports their promise to be an effective treatment. Good science alone does not necessarily bring about the

necessary money, time, resources, or know-how to fully develop a new medicine for patient use.

What has emerged as a possible solution to bring new technologies —often technologies with their origin in university laboratories—to the market efficiently? Biotech companies, of course.

UNDERSTANDING BIG PHARMA

As demonstrated by the FAAH story, Big Pharma has particular strengths in the drug development process as well as certain limitations. In order for biotech to be a powerful tool to create new medicines, a new biotech company must Build Backwards from both. Doing so will enable a biotech venture to take advantage of Big Pharma's unrivaled strengths while focusing its innovative energy on those areas where biotech tends to have an advantage.

We will begin by considering four characteristics of Big Pharma:

1. Financial resources
2. Emphasis on market size
3. Advantage in later-stage drug development
4. Established channels for distribution and marketing

FINANCIAL RESOURCES

Big Pharma has unparalleled financial resources for projects, which also results in its ability to hire highly specialized personnel. These abundant financial resources are largely due to the fact that pharma, unlike biotech, has revenue. A pharma company typically already has multiple drugs on the market generating significant cash flow. Revenue as a source of working capital is, therefore, a key advantage

of pharma over biotech (as well as an advantage of start-ups in other industries over biotech start-ups).

As may be clear, only after full FDA approval can any drug development company—whether pharma or biotech—bring a new medicine to the market, and thus begin to generate revenue.[73] Consequently, biotech start-ups often do not have any revenue simply because they do not have any marketed drugs.

Having significant working capital affords a pharma company the ability to develop a new medicine (such as the FAAH inhibitor) through each step of the drug development process from start to finish (e.g., large pharma companies can often do in-house clinical trials). This is part of the reason Pfizer was so effective in developing a potent, selective, and novel compound to inhibit FAAH. It was able to apply its financial resources (as well as highly specialized personnel, which are supported by their significant financial resources) to enable the development of a molecule with ideal properties. In contrast, refining a compound to this point would have been a very difficult feat for most biotech start-ups.

EMPHASIS ON MARKET SIZE

A large pharmaceutical company has the ability to recoup costs through its revenue stream. Thus, as seen in the case of FAAH, a pharmaceutical company must weigh market size appropriately in its development decisions. Large pharma companies, in particular, need to manage three major considerations:

1. **Direct costs.** Drug development is expensive. As was previously discussed, the average cost of developing a single drug from start to finish is $1.4 billion, with an average timeline of up to fifteen years. Although these costs are certainly applicable to biotech

companies, they rarely develop drugs from start to finish (for reasons we will discuss later in this chapter). Thus, a pharma company must ensure a newly marketed medicine makes a return greater than the roughly $1.4 billion invested in the drug's creation.[74]

2. **Limited marketing monopoly.** Having limited time to recoup costs results in enormous pressure on pharma companies to fill the "revenue gap" created by patent expiry. This results in preference for developing new drugs that will bring in a comparable return: a logical business decision. Although limited patent life is certainly a consideration for biotech companies, since they usually do not market their own products, this precipitous falloff in sales is less common to the small biotech experience.

3. **Cost of failure.** When selling a new drug, Big Pharma companies must recoup their investment for not only that particular drug but also the cost of any failed drugs. Since 96 percent of new drugs fail, when selecting an indication for which to develop a brand-new drug, the pharma company must account for both the cost of development for that particular drug and the costs of roughly nine other failed drugs. Carrying out a calculation of the cost of developing one new drug including failures gives the massive $2.6 billion figure mentioned earlier.[75] Again, because biotech companies typically do not develop drugs from start to finish, these costs are less directly impactful.

Thus, sometimes pharma companies must heavily weigh potential profitability of each disease area when making decisions about the clinical indication for which to develop a drug, as in the case of FAAH.

Rachel Alvarez, executive director for a rare disease nonprofit, emphasizes that market size is often a greater consideration for pharma than for smaller companies like biotechs. “The number one question pharma wants to know about a disease in which a potential treatment has been identified is how many [treatable] patients are there? Basic economics tells us that each identified patient translates into revenue that must return at a higher rate than that invested, or the pharmaceutical company won’t be in business for very long,” said Alvarez. “Depending on the size of the company, there are minimum thresholds of affected and treatable individuals that must be met before pharma will get involved. For smaller, scrappier, specialized companies, that threshold tends to be much lower.”[76]

ADVANTAGE IN LATER-STAGE DRUG DEVELOPMENT

Pharma companies often have many employees with highly specialized roles as well as specialized equipment, specific certifications, and regulatory familiarity. As in the FAAH story, at least in terms of completing the proper steps, Pfizer seamlessly transitioned a preclinical drug, Pfizer-123, from the lab bench to manufacturing to using the drug in human clinical trials.

The ability to develop deep expertise in highly specialized aspects of drug development (e.g., formulation chemistry, clinical trial biostatistics, manufacturing certifications, etc.) means large pharmaceutical companies can often accomplish the vast majority of the nuts-and-bolts work in-house. This is a particular advantage in the later stages of drug development, where specialization can become more crucial because developmental complexity has increased. For example, even writing an IND and filing it with the FDA is a highly specialized process for which most small companies

lack an in-house expert. Magnify this across the many, many specialized roles in later stage drug development, including the immense regulatory requirements and personnel needed to execute a multithousand-person Phase III clinical trial. To conduct such a process correctly under regulatory guidelines requires both many experts in various parts of the process as well as substantial capital. A pharma company has both.

By contrast, a "lean'' start-up often has to outsource various parts of the R&D (research and development) process. This gives Big Pharma a substantial advantage over biotech in this category.

ESTABLISHED CHANNELS FOR DISTRIBUTION AND MARKETING

One of the reasons pharma companies can be so effective at reaching large markets is because they have established sales, marketing, and distribution networks. Thus, large pharma companies can often rapidly and efficiently capitalize on the opportunity a mass-market drug presents.

In a competitive marketplace, it is not enough to simply have a drug that works safely and well. Physicians have to know about the drug in order to prescribe it. Pharmacies have to carry or be able to source the drug. To sell the drugs internationally, a company must have similar sales and distribution channels abroad.

Therefore, pharmaceutical companies spend an exorbitant amount of time and resources building relationships with physicians, which includes attending conferences where they can meet with key opinion leaders.[77] Also, who hasn't seen their fair share of direct-to-consumer marketing from various pharmaceutical companies encouraging you to "talk to your doctor about" a new drug? Their

sales and distribution channels enable them to maximize their market penetration quickly and maximize sales during the patent life of the drug. Generally speaking, few small biotech companies can alone both market and distribute their medicines to the extent that a Big Pharma ceutical company can.

MAKING SPACE FOR BIOTECH

Biotech companies, in comparison to traditional pharmaceutical companies, typically have three primary characteristics:

1. Typically exceling in early-stage drug development
2. Working "nimbly"
3. Being cash conscious

TYPICALLY EXCELING IN EARLY-STAGE DRUG DEVELOPMENT

In contrast to large pharmaceutical companies, which tend to excel the most in later-stage drug development, biotech companies are often particularly adept at early-stage drug development. Biotechs are inherently innovative. This intuitively makes sense as the premise underpinning the founding of any start-up is to develop an innovative idea.

Like the story of Genentech, which revolutionized diabetes treatment through a novel method of producing insulin, biotech is built on ideas that truly shift the paradigm in medicine and patient care. In contrast, it is not as common for Big Pharma to be the originators of a new drug.

For example, a 2019 report from STAT News studied leading products from Pfizer and Johnson & Johnson—two of the largest pharmaceutical companies—to uncover the proportion that had

originated in-house. Out of the forty-four leading products from Pfizer and eighteen leading products from J&J, only ten and two of those products respectively, were discovered in-house.[78] Instead, most of their blockbuster drugs had been acquired from other academic groups or companies, many of which were small biotechs.

As these numbers evidence, large pharma frequently capitalizes on its strength in later-stage drug development by acquiring smaller companies, which tend to excel at the earlier stages. Clive Dix, CEO of C4x Discovery, a biotech company, summarized this for the *Financial Times*, saying that large pharmaceutical companies are "crying out for innovation and are struggling to get enough of it in their own organization to have the best molecules coming through. They're therefore going to… smaller, more innovative companies and licensing products from them."[79]

WORKING "NIMBLY"

A key strength of start-ups in all industries is often described as the ability to be "nimble." Large pharmaceutical companies, like any large company, are more likely to have institutional procedures in place that tend toward doing things "the way they have always been done." This is because trying a novel approach for anything, and particularly in science, is risky. However, though a novel approach is high risk, it's also high reward. For biotech start-ups, the ability to embrace risk provides an opening for them to try such novel approaches and assume the potential rewards of doing so.

In the example of Humulin, Genentech scientists used *E.coli* and recombinant DNA to produce insulin for the first time. The gamble paid off, but significant risk was also involved. At the outset, no one knew for sure if the new technology would be effective or if the new method of making insulin might cause serious side effects.

BEING CASH CONSCIOUS

Because biotech companies have considerably fewer financial resources, they are significantly more cash constrained than a large pharma company.

It intuitively follows that being on a strict budget to complete a project would likely result in greater thriftiness and innovation in completing said project for cheaper than if you had unlimited resources. According to an analysis completed by Matthew Herper of *STAT News* in 2013, companies that had budgets greater than $20 billion in R&D spent an average of $6.3 billion per new drug as compared to $2.8 billion for companies that had budgets between $5 and 10 billion.[80] In other words, companies with larger budgets spent more on average to develop a single new drug. While this analysis pertains to large companies that have budgets in the billions (this is much higher than the average biotech start-up would have), the point is nevertheless clear. Drug development is often more expensive when more resources are available.

For biotech specifically, Herper also discovered in his analysis that small biotech companies had per-drug R&D costs far lower than large pharma company averages. Specifically, BioMarin and Genzyme, two small biotech companies, had average per-drug costs of $195 million and $963 million respectively—far below the average total costs for either budget range as well as below the $1.6 billion cost of developing one new drug on average.[81]

Because biotech companies are spending investor dollars instead of revenue dollars (as in the case of pharma), the cost of capital is considered much more “expensive” (partially because each dollar is purchased by giving away equity in the company). Thus, a biotech company faces significant pressure from investors to make

measurable progress with each dollar. This can result in efficiencies in speed as well as cost.

While traditional drug development can easily take ten to fifteen years or more, biotech companies have the potential—and particular incentive—to be extraordinarily fast. This is in part because biotech companies also experience significant investor pressure to make rapid progress, as most biotech investors expect to see a return within ten years or less. In the case of Humulin, the drug was approved only five years after Genentech was founded.[82] Much of the ten-to-fifteen-year average timeline can be attributed to the fact that drug development is simply innately challenging. Consequently, the distinction is less that Big Pharma is slow and more so that biotech companies have greater ability to work in novel and innovative ways and thus potentially be "fast."

BUILDING BACKWARDS TO BUSINESS MODELS

The drug development process involves complex laws and regulations, making it slow, deliberate, and often eye-wateringly expensive. Further, the inherent complexity of drug development results in a set of constraints that biotech and pharma companies alike must find a way to confront in their respective business models. Thus, biotech and pharma have adapted their own individual sets of business practices that allow each to operate within this environment.

By understanding these broad, generalized characteristics of both large pharma and biotech, biotech entrepreneurs can Build Backwards to understand where their biotech company can fit in the existing drug development landscape. Then, a new biotech company is better prepared to see where it can augment the important

existing work done by Big Pharma, overcome some of biotech's typical limitations, and turn each into an advantage.

Now that we better understand the characteristics of biotech companies as compared to pharma, we will discuss how these qualities result in the typical biotech business model and how you can leverage Building Backwards in this context to succeed.

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49 "Lundbeck to Purchase Abide Therapeutics in $400m Deal," *Pharmaceutical Technology*, May 7, 2019.

50 "ActivX Biosciences Announces Closing of Acquisition by Kyorin," *FDA News*, February 2, 2005.

51 Ryan Cross, "Bayer acquires small molecule startup Vividion Therapeutics for up to $2 billion," *Chemical & Engineering News*, August 5, 2021.

52 Kay Ahn et al., "Discovery and Characterization of a Highly Selective Faah Inhibitor That Reduces Inflammatory Pain," *Chemistry & Biology* 16, no. 4 (April 2009): 411–20.

53 Kay Ahn et al., "Mechanistic and Pharmacological Characterization of PF-04457845: a Highly Potent and Selective Fatty Acid Amide Hydrolase Inhibitor That Reduces Inflammatory and Noninflammatory Pain," *Journal of Pharmacology and Experimental Therapeutics* 338, no. 1 (July 2011): 114–24

54 "What is the Difference between GLP and GMP Laboratory Testing Regulations?" Michrochem Laboratory, accessed October 12, 2021.

55 "GMP vs. GLP in Laboratory Testing & Validation," The FDA Group, LLC., March 15, 2017.

56 "Pharmaceutical CDMOS," Tapemark, accessed October 13, 2021.

57 "Toxicology Studies: Delivering Accurate, Rapid Insights into Safe Dosing Regimens," BioAgilytix, accessed October 13, 2021.

58 "Investigational New Drug (IND) Application," US Food & Drug Administration, updated February 24, 2021.

59 "CFR - Code of Federal Regulations Title 21," US Food & Drug Administration, updated April 1, 2020.

60 "Drug Approval Process Infographic," US Food & Drug Administration, accessed October 13, 2021.

61 Joseph A.DiMasi, Henry G.Grabowski, and Ronald W.Hansen, "Innovation in the pharmaceutical industry: New estimates of R&D costs," *Journal of Health Economics* 47

(May 2016): 20–33.
62 Ibid.

63 "PhRMA Profile 2013," Pharmaceutical Research and Manufacturers of America.

64 Anastasiia Lastovetska, "App Development Cost: Understand Your Budget To Build Powerful Apps," *MLSDev*, September 28, 2021.

65 Aroon D. Hingorani et al., "Improving the odds of drug development success through human genomics: modelling study," *Scientific Reports* 9, no. 18911 (2019).

66 Ibid.

67 Joseph A.DiMasi, Henry G.Grabowski, and Ronald W.Hansen, "Innovation in the pharmaceutical industry: New estimates of R&D costs," *Journal of Health Economics* 47 (May 2016): 20–33.

68 "Standard Costs (in thousands of dollars) for Components of the Process for the Review of Human Drug Applications," US Food & Drug Administration, updated August 13, 2018.

69 Image was created by my Booth Commercializing Innovation teammates—Scott Walbrun, Andrew Hawley, Gerardo Chaquinga, Wenbo Fang—and me. Thank you to my favorite project teammates for being both phenomenal partners and friends.

70 Patents are typically filed immediately upon discovery (i.e., before the step 1 mentioned above even begins, for example shortly after a compound is first synthesized and assayed).

71 Joseph A.DiMasi, Henry G.Grabowski, and Ronald W.Hansen, "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs," *Journal of Health Economics* 47 (May 2016): 20–33.

72 "Drug Patent Expirations: Potential Effects on Pharmaceutical Innovation," Every CRS Report. Accessed October 10, 2021.

73 The exception would be Emergency Use Authorization (EUA).

74 Joseph A.DiMasi, Henry G.Grabowski, and Ronald W.Hansen, "Innovation in the pharmaceutical industry: New estimates of R&D costs," *Journal of Health Economics* 47 (May 2016): 20–33.

75 Ibid.

76 Rachel Alvarez, "Understanding Drug Development—Why It Takes So Long & Costs So Much Money: A Four-Part Series," *Cure CMD*, February 8, 2020.

77 Please note that I am not commenting on the ethics of this practice; rather, I am simply reporting how the system currently works.

78 Emily H. Jung, Alfred Engelberg and Aaron S. Kesselheim, "Do Large Pharma Companies Provide Drug Development Innovation? Our Analysis Says No," *STAT*, December 10, 2019.

79 Sarah Neville, "Nimble Biotechs Become Vital Partners for Large Pharma Groups," *Financial Times*, November 30, 2018.

80 Matthew Herper, "The Cost of Developing Drugs Is Insane. That Paper That Says Otherwise Is Insanely Bad," *Forbes*, October 16, 2017.

81 Ibid.

82 "Genentech, Inc.," Company-Histories, accessed June 21, 2021.

CHAPTER 3

THE BUSINESS OF SCIENCE

"I think in biotech, you oftentimes use a lean business model because you have no other choice…"

—MICHON PINNIX, MBA, VP OF STRATEGIC INITIATIVES AT BEIGENE

My first job in biotech involved working with Seurat Therapeutics, a start-up aiming to develop a new medicine for treating chronic migraines. My job entailed working with the team to develop a business plan as well as slides for pitching Seurat's new migraine drug to investors. At the time, I had very little understanding of how biotech as an industry really worked.

This was partly because my association with Seurat had started almost immediately after I arrived at business school. To be precise, on my second day.

In the middle of class, I'd opened an email message from John Kim, a fellow student I'd met the previous day, i.e., my *first* day of business school. We had been chatting about our professional plans, and I had mentioned I was interested in biotech. John had offered to introduce me to someone he knew who worked in the biotech industry.

I had expected only an initial conversation, so I was surprised to read the first sentence in the email message from my new contact: "Thanks for joining our New Venture Challenge team!" I would later learn this had been a fortuitous miscommunication. A Seurat teammate had dropped out suddenly only the day before.

When I turned to Google to look up what the New Venture Challenge was, I discovered it is one of the oldest and most prestigious business-school-based accelerators, credited with launching several successful start-ups including Grubhub, Braintree, and Simple Mills. The selection process started with two hundred companies, followed by a series of eliminations until the final round consisted only of the top ten. Seurat Therapeutics had already made it into the top thirty semifinals. At this juncture, I was now invited to join their team.[83]

My second Google search was on Seurat Therapeutics itself, the company I would work with during the incubator. It was listed as a Crain's Chicago Business "Start-ups to Watch" and had recently raised $750,000 in seed funding. (I would soon learn this size of a raise, unfortunately, does not go very far in biotech.)

I clicked back to the email. It looked like Seurat thought my chemistry and biology background and experience in authoring key scientific marketing materials communicating product offerings for Company G would be very useful. (More on this later, but this critical function of "translating" the science to high-level business points is sometimes lacking in a biotech and can hamper the success of the venture.)

"I'm in," I typed back, feeling a rush of excitement.

Ten weeks later, Seurat made it to the final round of the New Venture Challenge.[84] I was in charge of pitching the scientific mechanism behind the therapeutic in a way that made sense to a nonscientific audience. My assignment was to communicate key information to potentially interested parties to obtain an investment.

I stepped forward to receive the clicker from my teammate, who had just finished her part of the pitch. The faces of a hundred potential investors and judges stared back at me. I tried not to think of them nor the livestream camera and bright lights in my eyes.

I felt a mix of emotions that had been and would continue to be familiar. I was awed by the good fortune that had brought me to that point. I was exhilarated at the opportunity to do something I loved. And most strongly, I felt the slightly uncomfortable but also wonderful feeling of being stretched in my abilities and pushed to grow in order to acquire new skills and knowledge.

Slowly, I stepped forward to speak.

"Hyperactive electrical signals are the cause of migraine," I said, "but what underlies these hyperactive electrical signals is something known as oxidative stress. The fact that our medicine blocks both the oxidative stress *and* the electrical signaling from occurring is what truly differentiates Seurat and allows us to say that we stop migraines before they start…"

Seurat ended up not placing in the top three (biotech companies rarely do, some of the reasons for which we will discuss below), but we were awarded a $10,000 prize and received helpful feedback to continue to build the business.

After the competition, the angel investor who had cofounded Seurat, Martin Sanders, MD, approached me and mentioned he was CEO and founder of two other biotech companies.

"You did a good job on the pitch," he said. "I could use some extra help on my other companies from someone who can understand

both science and business. Would you want to work with me as a consultant?"

Receiving this invitation from Sanders was especially flattering given his own background. Sanders is an experienced biotech entrepreneur who had previously contributed to the approvals of nine currently marketed drugs, including the blockbusters Tysabri and Remicade. He has also contributed to the conduct of over three hundred clinical trials for sixty drugs and is the co-discoverer of the first two described white blood cell surface molecular interactions (CD2 binding to LFA-3 and LFA-1 binding to ICAM-1) as well as the primary discoverer of the major phenotypic markers for human memory and naive T-cell subsets. Both of these discoveries enable much of modern-day immunology research.

All this to say, in brief, that for Sanders to give me the opportunity to work with him was a kind and generous invitation.

Again, I felt the familiar mixture of terror and exhilaration at a new, unexpected but welcome opportunity.

"I'd love to," I said. And thus began my third and fourth consulting gigs, thanks to Sanders, who ultimately became an important friend and mentor.

In this chapter, we will use Seurat as an extended case study and an illustration of the life cycle and business model of a biotech start-up from early discovery to potential exit. At each stage of the life cycle, I will point out a key tenet of the biotech business model.

In chapter 2, we covered the characteristics of the drug development landscape in terms of both Big Pharma and biotech:

Pharma companies are generally typified by:

- Financial resources
- Emphasis on market size
- Advantage in later-stage drug development
- Established channels for distribution and marketing

In contrast, biotech companies are often characterized by:

- Exceling in early-stage drug development
- Working "nimbly"
- Being cash conscious

By Building Backwards from these characteristics, a general framework of how the biotech business model works emerges. "Business model" is a term for the design and strategy of how a specific business plans to operate: defining its profit outlook, services or products it will sell, target market, and expected costs.

Of course, there are innumerable exceptions to the rule, but the backbone of the business model "lifecycle" employed by most biotech companies often goes something like this (note that the order of steps one to three can be changed or concurrent):

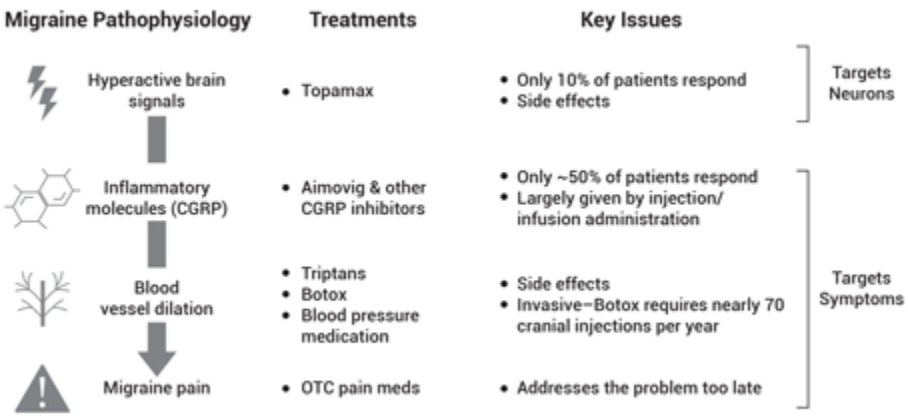
1. Identify prospective spinout assets from a university.
2. Recruit founding team, form the new company, and raise capital.
3. Complete key experiments, often utilizing contract research organizations.
4. Eventually "exit" the company, typically through an acquisition (see chapter 8 for greater detail).

THE BACKGROUND

In 2016, Seurat Therapeutics was founded by Martin Sanders, MD; Richard Kraig, MD, PhD; and Yuan Zhang, PhD, to develop a novel

therapy to treat migraines. According to the American Migraine Foundation, approximately 12 percent of the world's population suffers from this form of severe headache.[85] In the United States alone, 39 million people are currently diagnosed with migraines, and more are certainly suffering from this condition.[86] For some, the migraine is chronic; the typical sufferer experiences somewhere between five and fifteen migraine days per month.[87] During a chronic migraine, which can be triggered suddenly in response to otherwise "normal" stimuli (e.g., lack of sleep, bright lights, or loud noises), many sufferers are largely debilitated and sometimes incapacitated. Many need to go to a dark room and wait for it to pass, which may take hours or even days.

Existing treatments for migraine are often incompletely effective at preventing migraines from occurring in the first place, and they do not work for everyone.



Migraine pathophysiology and currently available treatments. This is one of the slides from the original pitch deck I helped assemble with the Seurat team for the investor pitch deck, outlining the simplified mechanism of migraine and existing treatments. Courtesy of Seurat Therapeutics, Inc.

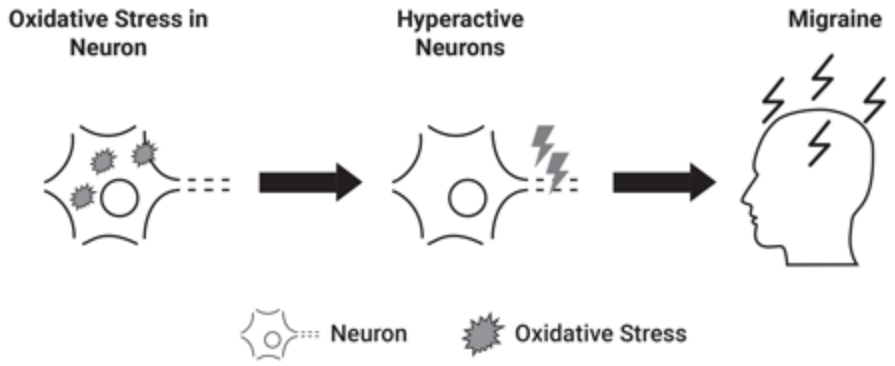
Additionally, many existing treatments are still delivered by injection. This means a typical chronic migraine patient will endure

monthly self-administered injections, in the case of medications such as inhibitors of calcitonin gene-related peptide or its receptor (CGRP/CGRPR) (e.g., Aimovig, Ajovy, and Emgality) or undergo physician-administered injections once every few months (e.g., Botox).[88,89] Often, patients will receive both CGRP/R inhibitors and Botox. Yet, even when combined, these treatments still might not completely alleviate symptoms.

Life cycle step 1: Identify prospective spinout assets from a university.

During Kraig's more than forty years in academia, he made several important discoveries about the naturally occurring protein, insulin-related growth factor 1, often called IGF-1. He found that IGF-1 not only played a key anti-inflammatory role in the brain, but it also appeared to have a role in protecting the brain against "oxidative stress." Thus, reducing oxidative stress in the brain seemed to hold potential for inhibiting the neuronal state that led to chronic migraine as well as decreasing the molecular mediators that were known to lead to migraine pain, such as CGRP and TNF-alpha.[90,91]

Kraig was convinced that IGF-1 could be given as a once-weekly nasal spray that would work upstream of the migraine pathway (i.e., preventing brain oxidative stress), and therefore essentially "stop migraines before they start."[92,93,94]



Simplified model of migraine. By inhibiting oxidative stress, there may be potential to prevent migraine from occurring in the first place. This was also a slide created for the investor pitch deck by the Seurat team for New Venture Challenge. Courtesy of Seurat Therapeutics, Inc.

Kraig's work focused on a rat model of migraine. In short, this model involved measuring rats' hyperactive neurological signals and is called "neocortical spreading depression," which begins with "hyper-exciting" the rat brain. Kraig found that treatment with IGF-1 induced a tenfold reduction in the incidence of migraine in rat brains. The question then was how to translate this exciting discovery from his academic lab, where it was treating migraines in rodents, to the clinic, where it might treat migraines in human patients.[95]

Recognizing this new therapy had immense potential, experienced biotech entrepreneur and investor Sanders (my boss and mentor mentioned earlier) heard about Kraig's new research and quickly joined forces with Kraig, Zhang, and Scott Meadow, MBA, an experienced healthcare investor, to form a new biotech company—Seurat Therapeutics.

Biotech business model principle: Biotech companies often originate from university out-licensing

In order to commercialize a technology discovered in an academic lab (as is often the beginning of many biotech start-ups), typically the intellectual property (IP) owned by the university (i.e., the patents) will be exclusively "out-licensed" to the new company through the university tech transfer office. In other words, the new company obtains the exclusive rights to use the IP described in the patents in exchange for what is typically a mix of upfront cash payment, equity in the company (i.e., stock), and a royalty stream (i.e., the university obtains the right to a percentage of future revenue if the drug makes it to market). In Seurat's case, Kraig and Sanders out-licensed all of the patents for IGF-1 owned by University of Chicago to Seurat. I will discuss out-licensing further in a later chapter.

Out-licensing is part of the reason biotech companies tend to be so good at early innovation. They often work on the most cutting-edge technologies, newly spun out of the academic lab where they were discovered. Recall again the case of Humulin. Genentech took DNA recombination technology directly from the lab and immediately began developing bacteria-produced insulin, something with a more practical application as a drug.

Life cycle step 2: Recruit the founding team, form the new company, and raise capital.

How was Seurat started? What exactly does this mean? First, and most importantly, it entailed the bold decision to bring IGF-1 out of the lab and into commercial development by starting a company in the first place.

Second, it entailed finding cofounders and business partners: namely, Sanders, who then recruited Yuan Zhang, PhD and Scott Meadow, MBA.

It also entailed (among other things):

- Out-licensing the key intellectual property from University of Chicago (discussed in greater depth below)
- Incorporating the company as a Delaware C Corporation[96]
- Opening a business bank account
- Purchasing corporate insurance
- Issuing stock
- Creating company bylaws

Biotech business model principle at work: Biotech companies often have a heavy reliance on outside capital

You have probably heard stories of entrepreneurship in industries other than biotech—whether in tech, food, or a different vertical—where the founder starts a company out of their basement and often is able to "bootstrap" fund it for a while (i.e., cover company expenses through personal savings or from revenue), such that they can delay bringing in investors (and giving away equity) until the company is further advanced. This model, often used by many start-ups outside of biotech, is generally not realizable in biotech. Why?

First, because there is no revenue, this means there is no "cheap" cash source that doesn't "cost" equity. Second, costs in biotech outsize most other industries by a significant amount. This means biotech companies have an especially high "burn rate" and thus, in general, have a much higher reliance on outside capital (i.e., bringing in dollars that are not revenue) in comparison to other types of start-ups. This means they must, on average, raise higher amounts of money from investors sooner and with greater frequency.

For example, compare Gimlet Media, a podcast company that was ultimately acquired by Spotify, to Juno Therapeutics, which was ultimately acquired by Celgene. In the entire life of the company, Gimlet only had to raise money twice, whereas Juno had to raise money five times. Gimlet's largest financing round was only $19.83 million, whereas Juno's was $1 billion. Gimlet only had to raise $26.83 million over the entire life of the company.[97] Juno Therapeutics had to raise $1.56 billion—nearly *sixty* times more![98]

Here is why this is significant. To complete the steps of drug development, a biotech company is only spending money, not making money. Thus, the early life of a biotech company ***consists only of cash burn.*** In other words, the company is making "negative" money. Moreover, recall the long drug development timeline. Many new biotech companies are making negative money for up to ten to fifteen years. This means they are entirely reliant upon outside capital to continue operating.

The other important implication of zero revenue plus high capital requirements is it is much rarer that founders can maintain significant percentages of ownership up to the point that the company reaches maturity. Whereas Mark Zuckerberg still held 28 percent of Facebook at the time of the company's initial public offering, many biotech companies rely upon venture capital (VC) financing to even begin the company.[99] As a result, it is fairly common that a biotech company founder starts out with only a single digit percentage ownership, and that's before dilution, when more investors come in during subsequent raises!

Biotech business model principle at work: **Generally speaking, biotech companies largely have a milestone-**

based valuation (when they are pre-revenue)

At this point, if you're asking why anyone in their right mind would run a company for ten to fifteen years that is literally losing money when their ownership share is also small, that is a good sign you are following this discussion well. The answer to this is that the value of a biotech company does not lie solely in the amount of money it makes.

A company like Gimlet typically has a value (or "valuation") largely based upon revenue, and thus, in general, its value increases somewhat gradually in line with revenue. By contrast, the valuation of a biotech company is largely based upon milestones. Generally speaking, as a biotech company progresses from preclinical, to Phase I, Phase II, and onward, its valuation goes up in a stepwise manner each time it is able to progress to the next phase of development (this will be discussed in greater depth in chapter 9). This pattern prevails because each subsequent phase of development is creating more value in the form of data, even if that value will not be realized as revenue immediately. It also increases the probability of success, increasing the likelihood that value *will* be ultimately realized.

Thus, even though Juno Therapeutics was losing large quantities of money at the time it raised its Series B (we will cover what this means in later chapters), the company was in the middle of its Phase I clinical trials, and thus was valued at $953 million. By contrast, Gimlet was making money, but at the time of its Series B was only valued at $74.83 million (though I note this is probably still quite high for a podcast company).[100]

Life cycle step 3: Complete key experiments, often utilizing contract research organizations.

With these formalities accomplished, the newly established Seurat then needed to find funding to complete key proof-of-concept experiments. I stepped in as part of the New Venture Challenge team approximately at this juncture.

As largely a "virtual" company—i.e., a company that has launched but does not have their own physical and specialized facilities, equipment, or research team—Seurat Therapeutics mostly conducted experiments out of Kraig's academic laboratory at University of Chicago, utilizing contract research organizations (CROs, more on these later) for the bulk of their specialized work. They did not formally set up laboratory facilities, had no full-time employees besides Zhang, and they leased minimal office space and a business address from University of Chicago's Center for Entrepreneurship. This is a typical model for many early-stage biotech start-ups.

Biotech business model principle at work: Biotech companies often heavily rely upon CROs

Recall from the previous chapter that a strength of pharma companies is their highly specialized teams and end-to-end capabilities in drug development. As biotech companies do not have these extensive capabilities and resources, CROs are often the answer as to how these limitations are overcome.

CROs are available to do everything from formulation, to cell line development, to toxicology studies, to *in vivo* efficacy studies, and more. Once a biotech company is in the clinical stages, it is also fairly common to hire a clinical CRO to oversee and conduct the clinical trials. CROs are especially helpful in domains where higher regulation and/or specialized equipment is needed (e.g., manufacturing or clinical trials) because they have the highly specialized in-house expertise and have the

proper regulatory certifications needed. “Virtual companies” by definition lack those resources, but even nonvirtual biotech start-ups heavily rely on CROs.

For example, in order to create drug product for clinical trials, it’s important that the drug product is properly certified and goes through significant testing. This is understandably a highly regulated and specialized process that also requires special bioreactors and other equipment (in the case of biologics). Thus, manufacturing is a frequently outsourced function.

Life cycle step 4: Eventually “exit” the company, typically through an acquisition.

In the case of Seurat, the team knew from the start it would likely get acquired as it advanced through development. It knew it most likely would never have the financial resources, marketing capabilities, and distribution capacity necessary to successfully take a new medicine to market on their own. Knowing this up front, it consistently engaged potential future acquirers early on in order to build relationships.

Biotech business model principle at work: Ultimately, biotech companies are often acquired[101]

Generally speaking, acquisitions are the most common exit strategy.[102] This concept is something biotech has in common with other start-ups. Start-ups are often bought by larger corporations, just as Gimlet was bought by Spotify. While it’s certainly possible (and a wise business practice) to build a company such that it will be independently sustainable over the long term, along the way a start-up will often be purchased by a larger company. In the case of biotech, the purchaser is usually a large pharmaceutical company interested in owning and completing development of the biotech company’s early-stage

medicines itself (recall pharma's advantage in later-stage development) so it can ultimately sell them itself to reap the benefits of a novel revenue stream (recall pharma's advantage in marketing and distribution).

The reason for this pattern in biotech comes directly from the fact that large pharmaceutical companies tend to be better positioned and resourced for the later stages of drug development. Simply put, it is in the interest of both parties—biotech *and* pharma—to allow biotech to do what it does best (early-stage innovation and development) and to allow pharma to do what it does best (later-stage development, marketing, and distribution). Thus, when large pharma companies purchase small biotechs, it is in some ways a "passing of the baton" to the party best equipped to carry the potential new medicine forward.[103] Once again, note the magnitude of difference in biotech acquisitions. Juno Therapeutics was purchased for a massive $9B while Gimlet was purchased for $230M (note that this is still a hugely successful exit and is likely on the high side for its industry).[104]

This is often the path biotech companies take to successfully bring their drug to the market and to the world. One shared success may provide the resources to grow and gain greater independence with future products.

Where is Seurat today? Currently, Seurat is about to initiate its key toxicology studies: intranasal toxicology studies for rodents as well as intranasal toxicology studies in nonrodents. Completing these experiments will allow it to progress into stability studies (i.e., proving that IGF-1 is chemically stable), allowing the company to file an IND and begin a Phase I clinical trial. As does any biotech company, Seurat has a heavy reliance on outside capital and as of

today has raised $510,000 in nondilutive grant financing. As a preclinical company, Seurat is making "negative" money, but it has a positive valuation (although we cannot officially put a number to this until a formal valuation process occurs). Eventually, Seurat will probably be purchased by a large pharmaceutical company looking to diversify its migraine portfolio.

To understand *how* to Build Backwards when launching a biotech company, it's important to first understand how the business of biotech typically works. In Part I, we laid the foundations of how the industry functions, provided an overview of the unique aspects of biotech in the drug development landscape, and introduced how these unique aspects translate to the typical business model. In Part II, we will cover how Building Backwards can leverage this knowledge to create a company that has a higher probability of success from the start.

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83 Thank you to the incredible Seurat Team: Martin Sanders, Scott Meadow, Richard Kraig, Sharon Lew, and Yuan Zhang; as well as my incredible NVC teammates: Scott Walbrun, Catherine Li, and Sreerama Jayanthi.

84 Thank you to everyone who made one of my first entrepreneurial experiences so enriching. Particular thank you to Waverly Deutsch, Mark Tebbe, Star Marcello, Steven Kaplan, Ellen Rudnick, and others.

85 "Migraine Essentials," American Migraine Foundation, accessed October 10, 2021.

86 Ibid.

87 Weatherall, Mark W. "The Diagnosis and Treatment of Chronic Migraine." *Therapeutic Advances in Chronic Disease* 6, no. 3 (May 2015): 115–23.

88 CGRP (calcitonin gene-related peptide) is an inflammatory molecule that is also a vasodilator, which has shown to be released during migraine attacks. It is primarily released from sensory nerves and therefore is implicated in pain pathways. In other words, this molecule is believed to play a role in the pain driving a migraine.

89 Marie Deen et al., "Blocking CGRP in Migraine Patients—a Review of Pros and Cons," *Journal of Headache and Pain* 18, no. 96 (2017).

90 Yelena Y. Grinberg et al., "Intranasally Administered IGF-1 Inhibits Spreading Depression in Vivo," *Brain Research* 1677 (2017): 47–57.

91 Lisa Won and Richard P. Kraig, "Insulin-like growth factor-1 inhibits spreading depression-induced trigeminal calcitonin gene-related peptide, oxidative stress & neuronal activation in rat," *Brain Research* 1732 (April 1, 2020).

92 Treating with anti-CGRP decreases the incidence of migraine, as proven clinically by multiple pharmaceutical companies. Seurat showed in the lab that IGF-1 decreased the level of CGRP, suggesting it would decrease the prevalence of migraine as well.

93 Yelena Y. Grinberg et al., "Intranasally administered IGF-1 inhibits spreading depression in vivo," *Brain Research* 1677 (2017): 47–57.

94 Lisa Won and Richard P. Kraig, "Insulin-like growth factor-1 inhibits spreading depression-induced trigeminal calcitonin gene-related peptide, oxidative stress & neuronal activation in rat," *Brain Research* 1732 (April 1, 2020).

95 See this chapter's references if you're interested in learning more about how migraine is measured in animal models.

96 This is a tax status and is the "gold standard" for most new start-ups.

97 Source: Pitchbook data—Accessed 4/5/21

98 Ibid.

99 Kenrick Cai, "Mark Zuckerberg Has Sold Facebook Stock Almost Every Weekday This Year," *Forbes*, July 13, 2021.

100 Source: Pitchbook data—Accessed 4/5/21

101 There are other types of "exit" as well. This topic will be covered in chapter 8.

102 Rachel Layne, "IPO or M&A? How Venture Capital Shapes a Startup's Future," Harvard Business School, April 27, 2021.

103 Sometimes, pharma companies do not purchase the company outright, instead opting to do a partnership of some sort where both companies develop the drug together. Typically, in this case, the small company contributes its novel technology and expertise, and the pharma company provides monetary resources as well as specialized expertise, manufacturing, distribution, and other capabilities. In return, the pharma company often gets to retain the rights to the majority of future product revenue. The result is both parties get something highly beneficial from the deal by each focusing on their respective key strengths.

104 Source: Pitchbook data—Accessed 4/5/21

PART II

LAUNCHING

CHAPTER 4

START WITH A PROBLEM

"A lot of academics think in terms of the funding they get in NIH grants. They base their success on achieving great publications and as many publications as possible. That's not really the endgame in biotech: we have to make the best medicines. This translates into discipline… You have to build that discipline in."

—JOHN CROWLEY, CEO OF AMICUS THERAPEUTICS

In 1999, Abbott Laboratories, a large pharmaceutical company (in the present day, Abbott's pharmaceutical division operates independently as Abbvie, Inc.), acquired a promising new candidate therapeutic, coined Abbott-ABC. Abbott-ABC was expected to be well-suited for treating high cholesterol. Several of Abbott's large pharmaceutical competitors already had cholesterol-lowering drugs on the market. These competitor drugs, which lowered "bad" LDL, were doing extraordinarily well in terms of annual revenue. Abbott wanted a share of the market.

Abbott-ABC held promise to be a blockbuster drug, with the potential to bring in billions of dollars' worth of sales revenue each year once it was FDA approved. Abbott willingly invested the hundreds of millions of dollars needed to take Abbott-ABC through the clinical trials necessary to demonstrate the potential drug's safety and efficacy in lowering LDL cholesterol.

Abbott-ABC turned out to be very effective in lowering LDL in clinical trials. The drug then successfully made it to the market—a

huge accomplishment in and of itself.

Then came the unwelcome surprise. Because of competition, the drug had sales of less than twenty million dollars in its first year, well short of the lofty expectations set for it.

This was a major disappointment. More importantly, however, this revenue stream was far lower than Abbott needed to recoup the investment of developing Abbott-ABC (recall the average cost of developing one new drug at $1.4 billion). Thus the program was not on track to be well-justified financially within the limited period of the drug's market exclusivity. Translation: Abbott needed to find a way to compete more effectively with the other cholesterol-lowering drugs on the market so it could make back the money it spent developing Abbott-ABC, and it needed to do that fast.

That's where Bob Altman, PhD, MBA, came in. As VP and general manager at Abbott's pharmaceutical products division, his job was to turn the product around.

"My boss told me, 'You'd better figure this out immediately,'" Altman recounted to me.

Altman was tasked with determining what had gone wrong in Abbott's development of the new medicine. The medicine worked. So why were so few people using it?

Could Abbott have Built Backwards earlier to potentially prevent or lessen the probability of this outcome in the first place?

PICKING THE RIGHT PROBLEM

One of the first lessons in business school is that a successful business is ultimately defined by "starting with a good problem to

solve."

The phrase "problem to solve" might seem reminiscent of STEM classes, where solving a problem often entails using a series of steps to work a given question and arrive at a desired answer. In contrast, when this terminology is used in business, the intended meaning is instead **finding a problem that *needs solving*** and then solving that problem ***through*** a business and/or product. In other words, the work of solving the problem through business strategy only comes *after* the problem is identified.

Any business—and therefore start-up—is only successful when it solves a problem for a customer. This ensures the customer keeps coming back and, consequently, that the company earns revenue.

Uber and Lyft are examples of non-biotech start-ups that effectively solved a problem for their customers. The problem they solved was that in many cities, it is impractical and cost prohibitive to own a car, yet taxis and public transit can be undesirable alternatives for transportation because of high cost and low efficiency. The solution, of course, was the creation of ride-sharing. Since customers were willing to pay for this solution, what resulted is known as product-market fit. The product (in this case, ride-sharing) "fits" a specific unmet need in the market.

To further demonstrate the importance of having strong product-market fit, consider an additional example outside the realm of science. Although numerous major airlines were in existence in 1967—including what are now United and Delta—the air travel industry was very much structured around the business traveler. The average business traveler was able and willing to pay the hefty fees charged by the large air travel corporations. However, there was an unmet

need—a problem—in the market. The average person or family who wanted to fly for leisure struggled to afford plane tickets.[105]

Much of the reason for the high ticket prices was because airlines were—and always have been—notoriously costly to run and are therefore among the most unprofitable of business types. Furthermore, the airline industry at the time was extremely highly regulated by the federal government, which impeded price competition.[106] Warren Buffet once remarked on the difficulty of achieving sufficient financial returns from the airline business, saying, "If a far-sighted capitalist had been present at Kitty Hawk, he would have done his successors a huge favor by shooting Orville down."[107] Thus, high ticket prices seemed necessary to airline companies in order for their businesses to be profitable.

Enter Southwest Airlines. Southwest Built Backwards from the problem of unaffordable airfare for personal travel in order to attract a new customer to air travel—the family leisure traveler. To decrease ticket prices, Southwest had to find a way to cut costs but had to find a cost-cutting method that would still enable it to turn a profit. To do so, it rethought the traditional business model for an airline.[108] While large airlines paid huge fees to run many flights at peak times out of major airports, Southwest chose to fly at less popular times and fly shorter routes to smaller cities as well as to secondary airports within major cities (e.g., flying to Chicago Midway instead of Chicago O'Hare).[109] Further, Southwest cut costs by offering few amenities and used (and still uses) only one plane model, the Boeing 737, for all of its flights.

These practices enabled Southwest to cut costs sufficiently enough that it was able to offer the cheapest airline tickets at the time, succeeding in attracting the family leisure customer.[110] To further appeal to this target customer, Southwest also chose to limit other

costs, waiving flight change fees and checked bag fees, and developed a "friendly" corporate culture (i.e., those cheerful Southwest flight attendants) and rewards program.

This approach not only served to solve a "problem" in the marketplace, but it was also such an effective problem-solution fit that, to this day, Southwest has remained one of the most profitable airlines in the world. Specifically, Southwest achieved forty-seven consecutive years of profitability (from 1973 to 2019) out of its approximately fifty-year history—a remarkable feat in the airline industry. Although the pandemic in 2020 temporarily brought Southwest's profitability streak to an end, Southwest was still much stronger on every major financial metric than any of the other three major US airlines (United, Delta, American Airlines) that were deeply unprofitable. During the peak of the pandemic, Southwest delivered the highest returns on capital of the group and was the only airline with an Altman Z-Score (a measure of likelihood of bankruptcy) in the "healthy" range.[111]

This example illustrates the importance of Building Backwards to address ***a problem that needs solving*** and to create a solution that can be implemented profitably. Southwest successfully positioned itself in the market by identifying a problem up front and then solving it through its business model. This resulted in excellent product-market fit and consequently a successful business.

How does product-market fit apply to biotech? A biotech is a business. As in the example of Southwest, businesses succeed when they solve *specific* kinds of problems—i.e., problems that meet the needs, wants, and "pain points" of potential customers**.** Therefore, to start a new biotech company that will succeed in the marketplace, it is important to start with a problem.

This seems like a simple point. Yet, this point is frequently overlooked by us scientists, who often have the tendency to start with an exciting new technology and *then* match it to a problem to solve rather than first understanding which problems exist in the marketplace.

This idea was also emphasized by my I-Corps instructors, during my first-ever science entrepreneurship course in New York.

“Why do most businesses fail?” my instructors had asked the class. “Is it because one, their product doesn’t work, or two because they created a product that people don’t need?”

Most of the people in the room were scientists and engineers—therefore inclined to be technically focused—so almost all attendees (me included) voted for the first option.

“Wrong,” the instructors had replied. “Most start-ups with technical founders have great technology. These start-ups fail because their technology doesn’t have a real need that it’s meeting, which means there’s no real use for it and therefore no customer. If there’s no customer, there’s no successful company.”

This seemingly simple concept is often anything but in practice. Particularly as scientists, we are not trained to *even ask* this question when conducting research. We assume any novel or cutting-edge science will be used because we navigate so much uncertainty to prove that something works in the first place. Moreover, we can be so hyperfocused on understanding the mechanisms underlying *why* something works that we’re much less concerned with whether someone will want to use it if it *does* work. This was Altman’s dilemma. Abbott-ABC worked, yet few were using it.

John Cumbers, PhD, as founder of SynBioBeta, has witnessed and worked with many biotech companies over the years.[112] Cumbers emphasized that scientists often fail because of poor technology-market fit: i.e., failure to start with a problem.

"If you don't have a good technology-market fit, you're just a hammer looking for a nail," he told me. "It's much better to be market driven. Find a problem that people have and then solve that problem with your technology. If you don't have a good technology-market fit, you're likely not effectively coupling your technology with a big problem to solve."

How might starting with a problem look in practice?

CASE STUDY: LUMIZYME, NOVAZYME PHARMACEUTICALS, AND AMICUS THERAPEUTICS

Before John Crowley's life was turned into a movie starring Harrison Ford and Brendan Fraser, he was just a normal dad—who happened to be trying to save his children's lives.

In 1998, Crowley's two youngest children, Megan and Patrick, were diagnosed with a rare disease—neuromuscular disorder glycogen storage disease type II, also called Pompe disease.

Patients with Pompe disease have mutations in the gene that encodes the acid alpha glucosidase (GAA) enzyme, the enzyme responsible for the ability of muscle cells to hydrolyze glycogen. These mutations disable the enzyme, and as a result, the individual is unable to break down stored body sugar. Pompe disease is a type of lysosomal storage disorder, meaning the deficient enzyme is specifically missing in the lysosome—the part of the cell that breaks down complicated substances such as body sugar.[113]

In other words, Megan and Patrick's bodies could store sugar in the form of glycogen, but unlike individuals without the disease, the genetic mutation rendered them unable to break these sugar stores back down again. As a result, glycogen began to build up around their organs and muscles, resulting in progressive muscle weakness, the swelling of vital organs such as the heart, and serious breathing problems. The children were becoming slowly incapacitated.

In the late nineties, there was no cure and no treatment for Pompe—only symptom management. Children with Pompe disease eventually died from organ failure, often at a young age.[114]

Crowley refused to stand by and watch his children deteriorate. Crowley, a JD/MBA, left his job in finance at Bristol Myers Squibb, planning to somehow create a new medicine that would save his children's lives.[115]

He started by looking for the best, existing research on Pompe disease. He soon found that while several academic researchers across the country were studying Pompe, one man's research stood out in particular—the work of William Canfield, MD, PhD.

At least in the movie version of what came next, convincing Canfield to cofound the fledgling biotech start-up was not easy.

In *Extraordinary Measures*, Crowley's character (Brendan Fraser) confronts William Canfield's character (Harrison Ford). He says, "You can work with me to try to cure people in real life, or stay in this lab and only cure them in theory."

Crowley may or may not have said this line in real life, but nonetheless, it nicely illustrates that although academia played a pivotal role in discovering a potential new medicine, business was needed to make that discovery a reality.[116]

The two men launched a biotech company in March 2000 called Novazyme Pharmaceuticals. A year later, the company was acquired by Genzyme (which was the prior name of Sanofi Genzyme, a large pharma company).[117]

The goal of the effort was clear: identify a method to deliver functional acid alpha glucosidase enzyme into the body, where it could begin to break down the dangerously full glycogen stores. Thus, they had a clearly defined problem statement from which to Build Backwards.

Delivering working enzyme into the lysosomes of patients with a genetic deficiency in that enzyme is known as enzyme replacement therapy, or ERT. What makes ERT difficult is delivering working enzyme able to penetrate *into* cells—rather than just circulating through the bloodstream—and *then* into the lysosomes of those cells. Moreover, for ERT to work, sufficient concentration of enzyme must accumulate in skeletal muscle and heart cells, where the majority of the patient's symptoms originate. Delivering sufficient quantities of working GAA enzyme to these cell types turned out to be exceedingly challenging.[118]

In the end, Canfield's research hypothesis and the efforts of many scientists and drug developers at Genzyme did, in fact, lead to a lifesaving medication for Crowley's children. The medicine was called Lumizyme.[119] The key innovation underlying Lumizyme's success was the creation of the correct precursor GAA enzyme through recombinant protein engineering. The patient is treated with the precursor enzyme through an intravenous infusion, which results in the circulation of the enzyme in the bloodstream. The precursor enzyme is able to be taken up by cells, processed and folded properly in the endoplasmic reticulum, and then is sent to the Golgi, where the enzyme receives a chemical addition known as a

mannose 6-phosphate group. The mannose 6-phosphate group then allows the enzyme to bind to the mannose 6-phosphate receptor, enabling it to finally reach the lysosome in its activated GAA form. Once there, it can successfully break down dangerous glycogen stores, leading to disease treatment and symptom relief.[120,121] The data from the pivotal clinical trial that resulted in Lumizyme receiving FDA approval demonstrated that the therapy reduced the risk of death in early-stage Pompe patients by 99 percent.[122]

In January 2003, Megan and Patrick Crowley received enzyme replacement therapy for Pompe disease. Crowley credits the medication with saving the lives of his children.[123] Since then, this medication has also saved the lives of hundreds of other children suffering from Pompe.

At present, Crowley is the CEO of a different biotechnology company, Amicus Therapeutics, where he is working to create new best-in-class therapies for Pompe disease as well as therapies for other rare, otherwise fatal, genetic diseases including Fabry disease and Batten disease. He has successfully brought two other novel rare disease therapies into Phase III clinical trials and one other to the market thus far. In each case, he uses a similarly focused, Building Backwards approach, as he did with Lumizyme.

Although Lumizyme saved his children's lives, the improvement it had on their skeletal muscle was short-lived. This is likely due to Lumizyme's partial instability. For an enzyme to properly function, it needs to maintain its proper shape, or "folding." Lumizyme was not consistently staying properly folded, which led to limited enzymatic activity in the affected tissues.[124]

For the next generation Pompe treatment, called AT-GAA, Crowley is combining ERT with what's called a "chaperone" protein. The chaperone protein helps stabilize the GAA enzyme, which theoretically will increase the efficacy over ERT alone. Further, the Amicus team has improved the GAA ERT itself by adding optimized carbohydrate structures to enhance uptake into cells. As of September 2021, Amicus's AT-GAA successfully completed Phase III clinical trials and the FDA announced acceptance and review of AT-GAA for full FDA approval.[125] This is a huge milestone for the company, which will soon hear whether their new medicine is FDA approved.

When I met Crowley at the Amicus office in Cranbury, New Jersey, I was struck by his warmth and congeniality, which was coupled with a certain quiet intensity. He asked me questions in a manner that suggested he was genuinely interested in the answers, even while in the same breath, he could casually say, "Harrison Ford is a great guy."

While multiple moments in our meeting have stuck with me, one, in particular, stood out. I offhandedly mentioned a family member's prior health condition and Crowley immediately inquired if that person was okay. The look on Crowley's face suggested deep empathy. I was not used to that question being asked so plainly, nor to someone clearly having an intrinsic understanding of the difficulties associated with personal health problems.

When we spoke about business, I asked Crowley what he believed made his drug development efforts successful. In response, he emphasized the importance of creating a clearly defined end goal. In other words, Crowley starts with a problem and then Builds Backwards.

“We have a specific end result we are working toward,” Crowley told me. “Best-in-class—not incrementally improved—new medicines. A substantial part of this is starting with a problem to solve, based upon having a patient-centered perspective and maintaining vision for what we want to accomplish in the future.”

Crowley wants to make a real, impactful difference for patients and their families who are dealing with rare diseases. Part of starting with a problem involves maintaining a patient-centered view—in other words, a specific understanding of which problems matter to patients and their families. Therefore, when selecting the rare diseases for which to develop new treatments, Amicus and Crowley interact closely with patients who actually have those diseases.

“Having a patient-centered view can drive all aspects of business,” he said. “It’s not only the right thing to do. It’s also good business and good strategy.”

Signs of this “patient-centered perspective” were indeed all over the Amicus office. I immediately noticed its unusual decoration. Crowley had chosen to cover the office walls with pictures of rare disease patients and their families—the faces of the individuals whose lives it ultimately hoped to impact with its medicines. Reminders of the “end goal” toward which it was building.

When I asked him how his patient-centered perspective applies to building toward these end goals when he starts a new venture—whether a new company or a new medicine—his answer was to start out focused on a problem rather than a technology. While many founders start new companies wedded to commercializing a particular technology, Crowley begins new projects with just a problem statement to solve. He is intentionally “technology agnostic.”

“We don’t start with the technologies. We start with the diseases,” he told me. “We think about where the greatest unmet need is. We think about what we would want if we were living with these diseases or were a mom or dad or kid caring for someone with this disorder. And then—and only then—do we think about where there are applicable technologies and which one to select for development.”

In other words, rather than starting with a particular technology in mind and thinking about where it might be useful, he starts with a “problem” for a new technology to solve. He then sources a new technology, one that is the best fit for his starting “problem.” Often, this problem statement is heavily informed by the patient perspective.

How does this illustrate the Building Backwards approach?

- By starting Amicus Therapeutics (as well as Novazyme) by defining his **end goal,** Crowley could work **backward**, optimizing and selecting for the outcome he wanted.
- By defining an end goal, Crowley enabled **focused problem-solving**, allowing him to arrive at his “destination” in an expedient manner (e.g., Lumizyme ERT therapy for the treatment of Pompe).
- By selecting a disease with a clear unmet need—Pompe disease patients likely did not have any other therapies in development because rare disease market sizes are limited—Crowley ensured **product-market fit** while also making a substantial difference for patients.
- By starting with a **specific scientific problem**—rather than starting with a technology—Crowley sets himself up to find the best possible technology to solve a particular problem in the marketplace.

While sourcing a technology second to identifying an unmet need is one example of how "starting with a problem" and Building Backwards can look within biotech companies, there are many other ways to do this. One such example is Sunovion, from chapter 1. Recall that Sunovion is developing a new schizophrenia drug. To develop this drug, Sunovion started with a problem. Existing schizophrenia drugs were incompletely effective at alleviating "negative symptoms" and often came with a host of undesirable side effects due to D2 modulation. Then, Sunovion performed focused drug development to discover a specific compound that might impact negative symptoms of the disease without binding D2.

This has resulted in a potential therapy that, should it make it to market, will have a strong, unique value proposition. That is to say: Sunovion specifically chose to develop a drug that it knew from the start would fill a gap in the market. This makes Sunovion's future medicine likely to avoid the initial fate of Abbott-ABC, where the new drug achieved FDA approval but very little market penetration.

Although most biotech companies will never develop a product to the point where they themselves independently bring it to market, operating in such a way as to anticipate the demands of the future market their product may encounter is imperative. In order to increase the likelihood that a new medicine or company will be a potential target for venture investment, pharma partnership, acquisition, or most any business deal, it is crucial that a product fills a gap in the market.

PIVOTING TO A PROBLEM

Let's return to Abbott-ABC and Altman's assignment to increase sales. At this point, it is likely clear what the big-picture task was for

Altman.

In order to increase sales, Altman needed to start with a problem in the marketplace—a need that had yet to be met by existing cholesterol-treating medicines. Then, Altman needed to understand if Abbott-123 could meet that need. If it could, that would result in a problem-solution fit, and sales would likely increase as a result.

Therefore, the first thing Altman did was attempt to understand the existing cholesterol-lowering drug landscape. After performing market research—which largely consists of speaking to patients, physicians, etc. to understand the unmet needs—Altman learned most people did not feel there was a need for Abbott's new medicine. This was because there were already several drugs on the market that effectively lowered LDL cholesterol.

However, he discovered physicians and patients really wanted and needed an LDL-lowering drug that *also* raised "good" HDL cholesterol. Abbott's outstanding regulatory department was able to utilize existing registration study data to garner this approval without running any new trials. Consequently, Abbott pivoted to change the drug's FDA label to *raising HDL, augmenting its performance in lowering LDL and triglycerides.*

In pursuing this new niche product-market fit with very precise execution, Abbott was able to take the drug from its meager launch and set it on a blockbuster trajectory.

Abbott faced several challenges in this situation:

- The predicament was not technical in nature. The issue was *not* that the drug didn't work. The issue was that initially, the drug did not appear to solve an unmet need in the marketplace.

- Abbott was initially not sufficiently distinguishing its drug from competitors. Abbott-ABC appeared to be a "me-too" drug, a latecomer without distinguishing benefits that would sway doctors and patients from existing "tried and true" medications.
- Thus, Abbott initially lacked product-market fit, and revenue suffered as a result. Repositioning the drug in the marketplace under a label that bridged a gap in the market reset the drug's trajectory to blockbuster status.

The Abbott-ABC example illustrates well the importance of knowing where your company fits into the market landscape. Start with a problem early so that you can Build Backwards in regard to the following considerations. Having answers to these questions can inform your decision-making and increase your chances of success:

- The clinical indications considered most valuable by potential acquirers (and therefore which indication should likely be the initial indication, if relevant for the technology).
- The current standard of care, which holds implications for how much better a therapeutic needs to be to actually get adopted by the end users (physicians and patients).

Starting with a problem enables you to Build Backwards to the best technology to meet that need. However, even when you define what you believe is a problem to solve in the marketplace, how do you know that you have the correct perception of the problem? In other words, how do you know the problem you perceive as significant is actually significant? How did Altman conduct market research in order to reposition Abbott-ABC? This is the topic of discussion in the next chapter.

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105 Michael Minnis and Abbie Smith, "Southwest Airlines Co. Credit Analysis and Financial Flexibility in the Era of COVID-19," Booth School of Business at the University of Chicago

for Business 30130, September 2020.

106 The other part of this story, which we will not touch on in depth, is how Southwest effectively navigated the highly regulated airline industry that threatened to impede its business model. This is worth reading about separately if you're interested.

107 Josh Barro, "Warren Buffett Should Have Listened to Warren Buffett About Airlines," *Intelligencer*, May 4, 2020.

108 At first within only Texas—and then with the passing by Congress of the Airline Deregulation Act of 1978—Southwest was poised to become the carrier dominating this niche nationwide. Note: People Express Airlines did aggressively compete in this space until excess debt caused it to cease operating independently and merged into Continental in 1987.

109 Michael Minnis and Abbie Smith, "Southwest Airlines Co. Credit Analysis and Financial Flexibility in the Era of COVID-19," Booth School of Business at the University of Chicago for Business 30130, September 2020.

110 Ibid.

111 Ibid.

112 A leading community of biotech innovators focused on synthetic biology.

113 Giancarlo Parenti, Diego L Medina, and Andrea Ballabio, "The Rapidly Evolving View of Lysosomal Storage Diseases," *EMBO Molecular Medicine* 13, no. 2 (February 5, 2021).

114 "Pompe Disease Information Page," National Institute of Neurological Disorders and Stroke, updated August 9, 2021.

115 Geeta Anand, *The Cure: How a Father Raised $100 Million and Bucked the Medical Establishment in a Quest to Save His Children* (New York: William Morrow, 2009).

116 *Extraordinary Measures*, DVD, (United States: CBS Films, 2010).

117 Emma Yasinski, "Amicus CEO on a Mission to Cure Pompe and Help His Two Children," *Pompe Disease News*, January 30, 2019.

118 Ans T van der Ploeg and Arnold J J Reuser, "Pompe's disease," *The Lancet* 371 (October 11, 2008): 1342–53.

119 Emma Yasinski, "Amicus CEO on a Mission to Cure Pompe and Help His Two Children," *Pompe Disease News*, January 30, 2019.

120 Lara Kohler, Rosa Puertollano, and Nina Raben, "Pompe Disease: From Basic Science to Therapy," *Neurotherapeutics* 15, no. 4 (October 2018): 928–942.

121 Pasqualina Colella and Federico Mingozzi, "Gene Therapy for Pompe Disease: The Time Is now," *Human Gene Therapy* 30, no. 10 (October 2019): 1245–1262.

122 Lara Kohler, Rosa Puertollano, and Nina Raben, "Pompe Disease: From Basic Science to Therapy," *Neurotherapeutics* 15, no. 4 (October 2018): 928–942.

123 Emma Yasinski, "Amicus CEO on a Mission to Cure Pompe and Help His Two Children," *Pompe Disease News*, January 30, 2019.

124 Pasqualina Colella and Federico Mingozzi, "Gene Therapy for Pompe Disease: The Time Is now," *Human Gene Therapy* 30, no. 10 (October 2019): 1245–1262.

125 "US FDA Accepts Filings for Amicus' AT-GAA for the Treatment of Pompe Disease," *Amicus Therapeutics*, September 29, 2021.

CHAPTER 5

CUSTOMER DEVELOPMENT

"Seventy-five percent of all start-ups fail.... Start-ups are not smaller versions of large companies. They do not unfold in accordance with master plans. The ones that ultimately succeed go quickly from failure to failure, all the while adapting, iterating on, and improving their initial ideas as they continually learn from customers."

—STEVE BLANK, AMERICAN ENTREPRENEUR AND ORIGINATOR OF LEAN START-UP AND CUSTOMER DEVELOPMENT METHODOLOGY[126]

Eric Young, MBA, is cofounder and partner at Canaan Partners, a successful information technology and health care venture capital firm. A former engineer, he's a straight shooter, describing himself as possessing "an engineer's logic coupled with a racer's sense of urgency."[127]

I met Young when I was beginning my journey into entrepreneurship. I had sent him a cold email after finding his contact information listed as an alumni reference on Cornell's website. As an entrepreneurship novice, I was seeking his advice. Young kindly agreed to speak with me. Once on the call, he listened patiently as I spouted off my business ideas (the majority of them naive and infeasible).

Thanks to Young, I didn't pursue those ideas. Instead, I was fortunate to gain him as a mentor. Over the years, Young has both invested in and overseen countless technology-based companies.

Therefore, he's especially familiar with why technological companies can fail.

"The great failing of many entrepreneurs is to be extraordinarily influenced by what they are familiar with and assume there's a demand for it," Young told me. "Often entrepreneurs assume there is value customers will place on the invention without having first seen if that's true in the marketplace."

How do you assess what's true in the marketplace? Or, put differently, if Step One from the last chapter is "starting with a problem," how do you determine whether your perceived "problem" is an authentic need? The answer, in short, is talking to people—or, in other terms, customer development.

"Customer development is the notion of not allowing your personal bias to influence your determination of what a new product or service should be without first synthesizing what the marketplace has told you," Young said.

This philosophy and method come from the "Lean Start-up Method," coined by Silicon Valley entrepreneurs Steve Blank and Eric Ries.

Notably, Blank developed the "Customer Development" model himself. He is also one of the founders of the national I-Corps program and teaches entrepreneurship at Stanford University as well as several other prestigious universities.[128] The three key tenets of "lean," as explained by Blank in a 2013 *Harvard Business Review* article, are as follows:[129]

First… entrepreneurs accept that all they have on day one is a ***series of untested hypotheses****—basically, good guesses. So instead of writing an*

intricate business plan, founders ***summarize their hypotheses in a framework.***

This is essentially what we covered in the previous section. The idea of finding a problem-solution fit. The additional idea included is that the problem in need of a solution is really just a *hypothesis* until it is tested in the market. Testing it in the market is what customer development is for.

Second, lean start-ups use a "get out of the building" approach called customer development to test their hypotheses. ***They go out and ask potential users, purchasers, and partners for feedback on all elements of the business model****… New ventures rapidly assemble minimum viable products and immediately elicit customer feedback. Then, using customers' input to revise their assumptions, they start the cycle over again, testing redesigned offerings and making further small adjustments (iterations) or more substantive ones (pivots) to ideas that aren't working.*

Since the lean start-up was initially designed for tech ventures (i.e., ventures that have tangible products early on versus biotech start-ups, which tend to solely have data in the early stages), the above point emphasizes the idea of putting the simplest product possible (i.e., the "minimum viable product") in front of customers and receiving feedback. This idea is still important for biotech but is largely executed in a different way. We will come back to this in greater detail.

Third, lean start-ups practice something called ***agile development****… [which] works hand-in-hand with customer development. Unlike typical yearlong product development cycles that presuppose knowledge of customers' problems and product needs, agile development eliminates*

wasted time and resources by developing the product iteratively and incrementally.

The concept to take away from this is the idea of incremental development: continuously asking for feedback and then readjusting. This is how your customers' ***problem*** informs your building of the ***solution.*** You are consistently looking for feedback from your target customer. That is, development should never be a one-time activity. Lastly, these three tenets are put together in the following manner:

If customer feedback reveals that its business hypotheses are wrong, it either revises them or "pivots" to new hypotheses.

When the hypotheses you devise are inevitably proven wrong to some extent, it's important to engage in this process of amending your hypotheses (in other words, "updating your priors"). To reiterate, a good business always solves a problem. If a customer doesn't have the problem you think they have, they probably won't pay for a solution.

Again, this all might sound straightforward. Yet, failing to follow these principles is an incredibly common reason for failure. In 2019, the business analytics company CB Insights parsed through one hundred essays written by start-up founders after their business had failed in order to determine what had gone wrong. The top reason (cited at 42 percent) was *no market need*.[130]

The point of customer development is to start with hypotheses and then to go out and talk to potential customers in the relevant marketplace. This will allow you to determine whether there is an authentic need as well as help you to understand key opinions, needs, and conceptions of stakeholders in that space. This is

Building Backwards from the end customer in order to inform the specifics of your product.

Before beginning customer development, the first question a company needs to answer is *who* is the customer? Identify the wrong customer, and you'll end up with an inaccurate understanding of the market. You can match products to solve customer "pain points" only so far as you truly understand them *from the target customer's perspective*.

Many biotech start-ups will say their first customer is the patient and, therefore, will focus on patient interviews as the primary customer segment. While understanding the patient perspective is crucial, as any new therapeutic that does not directly benefit patients is ultimately not a useful therapeutic, it's also important for companies to evaluate the perspectives of *all* the key stakeholders, particularly the ones further upstream in the coming to market process than the patients themselves. Here, we will discuss five key stakeholders (although it's certainly possible to have more or less for a specific venture): 1) patients, 2) physicians, 3) investors (e.g., venture capitalists), 4) pharmaceutical companies (potential partners or acquirers), and 5) insurers.

This chapter will touch on customer development through the lens of one particular company, Laurel Therapeutics.

CASE STUDY: LAUREL THERAPEUTICS

The last time I explicitly worked on customer development, I was consulting for a company called Laurel Therapeutics, where Sanders had invited me to serve as VP of Operations and Business Development. Laurel Therapeutics was developing a novel eye drop

treatment for wet age-related macular degeneration (wAMD), which remains the leading cause of vision loss among older adults.[131] In the United States alone, eleven million individuals are currently affected.[132] Left untreated, wAMD leads to blindness.

Although several products exist on the market to treat wAMD, they require frequent visits to the clinic for injections to the eye of something called anti-VEGFs. These drugs are antibody fragments that bind and neutralize the VEGF (vascular endothelial growth factor) protein that underlies many of the symptoms of wAMD.[133]

The injections are not only uncomfortable for patients but they must also be given anywhere from biweekly to once every four months.[134,135] Each injection costs anywhere from $200 to $500 in co-pays to the patient and between $1,500 and $1,800 to insurers (largely Medicare).[136]

While the advent of anti-VEGF therapy has made what was once a previously untreatable disease treatable, the need for it to be administered by specialized physicians has been implicated in what has been called "the makings of an epidemic." As the aging Baby Boomer population correlates with a proportional increase in the number of wAMD patients, expected to reach twenty-two million cases in the United States by 2050, this will likely result in an unsustainable wAMD patient load to the United States health care system.[137,138]

Further, ophthalmologists can often spend greater than 50 percent of their time injecting thirty-five to forty patients per day.[139] This has already resulted in a huge financial burden on the health care system, as injections for wAMD alone accounted for *12 percent* of all of Medicare Part B (the part of Medicare that covers all outpatient procedures) spending in 2018.[140]

Making matters worse, these treatments are not only highly invasive and costly, but they are incompletely or noneffective for at least 10 percent of wAMD patients (i.e., over one million wAMD patients in the United States).[141] Research suggests this lack of efficacy is possibly due to anti-VEGF agents not treating the known inflammatory or neurodegenerative pathologies of wAMD.[142]

Therefore, Laurel Therapeutics started with a problem that clearly needed to be solved. Its challenge seemed to be to develop a treatment for wAMD that was:

- Cost effective
- Able to be self-administered at home
- Treats inflammatory and/or neurodegenerative mechanisms of the disease

Despite the clarity of these expected market needs, Laurel still needed to validate these hypotheses with target customers. This was the best way to ensure the company's posited problem-to-solve was in fact recognized by the five key parties in the pharmaceutical value chain: patient, physician, investor (venture capitalist or other potential investor), pharmaceutical company (partner or potential acquirer), and insurer.

We were considering developing a new Laurel technology that had the potential to meet the above criteria. We called the molecule "EBIN." My mentor and boss, Sanders, had identified the technology at a University of Illinois Chicago lab, where EBIN was discovered. Early preclinical data showed EBIN was likely administrable via an eye drop and looked to have potential anti-inflammatory and neuroprotective properties.

Therefore, Laurel Therapeutics was operating off a multipronged premise that yielded four primary hypotheses:

1. The five key parties felt the current standard of care was insufficient.
2. The five key parties wanted a noninvasive approach to treating wAMD.
3. Patients, insurers, and physicians wanted more affordable solutions.
4. There was a need for new mechanisms of action to treat wAMD.

CUSTOMER DEVELOPMENT: THE PATIENT

How could Laurel test these hypotheses? As suggested by Crowley (chapter 4), Sanders and I started with the patients. Many wAMD patients shared with me how difficult and expensive treatment was for them. They needed to keep up with their regular appointments or they risked irreversibly deteriorating their vision. These conversations were extremely motivating; I felt very passionate about seeing whether this prospective medicine, discovered in an academic lab, might have some promise in helping these patients. From these conversations, I was able to validate the working hypotheses:

- Patients disliked the high out-of-pocket cost of the injections.
- Patients did not want to come into the office for injections and wished they had a different route of administration available.
- While patients overall felt like the injections worked well, they expressed interest in new treatments.

Patient input validated our hypotheses two and three. That is, patients consistently expressed an interest in affordable and more convenient therapies that did not have to be injected.

CUSTOMER DEVELOPMENT: INSURERS

Insurers are also important to understand because, in the United States, the question of who pays for therapies or drugs is complicated, constantly evolving, and greatly affects the incentives to adopt a new medicine or solution. In the United States, private insurance companies (e.g., Blue Cross Blue Shield) or public programs (e.g., Medicare or Medicaid) are typically involved in paying the bill. Understanding what makes companies and the government willing to reimburse a new therapeutic (or not) is important because if physicians and practices are not reimbursed for a new drug or protocol, they are less incentivized to prescribe it.[143]

Through connections, we were able to speak with executives at an insurance company. When I brought up the anti-VEGF drugs, they immediately bemoaned the high cost and spoke of their concern that the growing aging population would make their business model difficult due to the high costs per patient per year across many more people than the system currently has capacity to support. The high cost is due in part to 1) the need for the physician to administer the injection, resulting in the need for the physician to be reimbursed, and 2) the high cost of on-patent new medicines such as the majority of the anti-VEGFs.

This, too, validated hypothesis three, regarding the interest in lower-cost therapies.

CUSTOMER DEVELOPMENT: INVESTORS

When we spoke with venture capitalist groups, they expressed interest in the novel route of administration EBIN offered but also emphasized that they thought anti-VEGFs were really effective and the standard of care would likely not change easily.

This was not exactly what we wanted to hear, but it did validate hypothesis two while drawing into question hypothesis one regarding standard of care.

CUSTOMER DEVELOPMENT: PHYSICIANS AND PHARMACEUTICAL COMPANIES

Next up on the list of key individuals: physicians and pharma. Here, we ran into roadblocks. How were we going to convince multiple retinal physicians to get on the phone with us—complete strangers—and answer our probing questions? Additionally, how could we connect specifically with the ophthalmology business development groups within large pharma?

I learned a large ophthalmology conference was taking place in San Francisco. I was based in Chicago, and the conference was only a few days away. Sanders and I agreed I should attend on behalf of the company, so I booked a flight.

As expected, I seemed to be the only person attending the conference who wasn't an ophthalmologist or in an ophthalmology-specific industry. However, I had a purpose for being there and was determined to gain insights.

Leading up to the conference, I had enlisted the help of two friends interested in biotech, Kevin Lei and Wenbo Fang. Together, we scanned the conference contact information webpage and sent out many emails ahead of the conference in order to schedule meetings with relevant people while I was out there. However, a good number of these meetings would have to be left up to chance and my networking abilities once I arrived.

The most important tenet of conducting customer development interviews is asking questions in such a way as to avoid biasing your

"customer" or giving away your hypotheses. This is done by not mentioning any specifics of your technology (to avoid confirmation bias). You are trying to understand a potential "customer's" organic opinion of *the problem your product is solving*, rather than their opinion of the potential product itself, as people often give less helpful feedback when it comes to theoretical ideas as opposed to lived experiences. Doing this, in addition to allowing "customers" to steer the conversation, such that they respond in an authentic way to the ideas underlying your hypotheses, makes it more likely that the information you gather is honest.

I practiced how I would frame questions to test my hypotheses in such a way as not to bias customers. The list of questions I would ask to validate our working hypotheses (that would vary depending on the "customer") was as follows:

1. *Hypothesis*: The five key parties felt the current standard of care for wAMD was insufficient.
   – ***Question*: What's your opinion on the current standard of care for wAMD? Do you think it works well?**

2. *Hypothesis*: All five key parties wanted a noninvasive approach to treating wAMD.
   – ***Question*: What do you think of the delivery method for anti-VEGF therapy?**

3. *Hypothesis*: Patients, insurers, and physicians wanted more affordable solutions.
   – ***Question*: What do you think of the cost of anti-VEGF therapy?**

4. Hypothesis: There was a need for new mechanisms of action to treat wAMD.

– ***Question*: Do anti-VEGF therapies seem to be a complete solution to wAMD? Are there any gaps in wAMD care or tools for treating patients that you wish you had but do not?**

Physicians

At first, I spent significant time at the conference sitting alone, sipping coffee and attempting to distinguish which physicians were retinal specialists—the relevant ophthalmology specialist to speak with on behalf of Laurel. Convincing busy doctors to agree to speak with me turned out to be no small feat and involved a high tolerance for rejection.

Eventually, a young retinal specialist agreed to speak with me. "I have fifteen minutes to walk from this lecture to my dinner meeting," she said. "If you want to walk with me and do the interview while we walk, I can make that happen."

I smiled, pretended that I hadn't gotten off a red-eye flight mere hours earlier and wasn't tired or jet-lagged in the least, and gratefully agreed.

Of the stakeholder groups to interview, physicians often yield the most actionable information, as they directly interact with patients, hear their concerns, and do the prescribing. Medical professionals tend to be exceptionally familiar with which diseases in their specialty lack sufficient therapeutic options and which needs are not being met. As a result, interviewing physicians can yield insights quickly and efficiently.

A physician prescribes a new medicine when it meets an unmet need of their patients. If a new drug does not meet a need perceived by a physician, it likely will not get prescribed. Not getting prescribed

means the drug will not sell, potentially resulting in a situation similar to that of Abbott-ABC initially, as discussed in the last chapter.

I reminded myself of these facts to focus my thoughts as I walked down the streets of San Francisco next to the ophthalmologist, trying not to lose her in the crowds of nametag-wearing, suit-clad conference attendees we wove through on the sidewalks.

"So," I said, with what I hoped was a winning smile, "tell me a little bit about the standard of care for wet AMD—are you happy with it? How do you feel about it?"

She responded instantly. "I think the standard of care is great. I think anti-VEGF injections are super effective and work really well." Just like that, she'd shot down my top working assumption:

- Physicians felt the current standard of care for wAMD was insufficient

I was jotting down notes on my notepad as we walked, trying not to seem disappointed. I asked a few more questions on this subject, and she continued to emphasize how well she thought the standard of care addressed this disease.

So I reset our conversation, this time focusing on a different hypothesis. "Do you see any gaps in the care for patients with wet AMD? Is there any tool for treating these patients that you wish you had as a doctor that you currently don't have?" Again, I was trying to identify *a problem that needed solving* to determine whether EBIN might match as a potential solution.

"The injections work well," she replied, "but they're really expensive for patients and also to hold in inventory, so it would be great if we

had something that could lengthen the amount of time between injections or could enhance the effect of the injections."

This was interesting. Laurel Therapeutics could run an experiment to test for synergy with existing anti-VEGFs, but developing a company around a new medicine that merely serves as an adjunct for a therapy that is already highly effective was not a great value proposition for a business. Down went my second working assumption about the need for a new treatment:

- Doctors felt that there was a need for a new treatment for wAMD

I tried again. "Anything else?" I asked.

"Well," she said after a brief moment of reflection, "there's an emerging role in the literature regarding neuroprotection and anti-inflammatory effects on this disease. If something worked as a neuroprotective drug, or anti-inflammatory drug, that would be really great."

This, too, was interesting. She was describing novel mechanisms of action, which EBIN happened to show strong scientific potential in. Obtaining additional preclinical data would not be too difficult. So, the conversation had partially confirmed one hypothesis:

- There was a need for new mechanisms of action to treat wAMD.

As we continued to chat, the doctor also emphasized how burdensome it was to treat wAMD through injections.

"I spend probably 85 percent of my time injecting patients over and over again," she told me. "If there was an eye drop or something more convenient, this would not only be cheaper and better for my patients, but it would free up some of my time."

Just like that, she independently affirmed the most fitting of the working hypotheses for EBIN's value proposition:

- Physicians wanted a noninvasive approach to treating wAMD.

Conversations with multiple other physicians at the conference more or less echoed these points. This is another key tenet of customer development. Always have enough "data points" from speaking with people so clear, repetitive themes emerge. This is what happened in this instance, suggesting that two of the working hypotheses—a novel mechanism of action and a noninjectable—seemed to fulfill the criteria of meeting a specific, targeted real-world patient *need*.

Pharmaceutical companies

At this same ophthalmology conference, I also spoke with several business development representatives from pharmaceutical companies. I was chiefly interested in speaking with them in order to understand their perspective as potential "customers." Pharmaceutical companies could be future business partners, future acquirers, or simply sources that know the wAMD pharmaceuticals market well. I wanted to learn the market landscape as they saw it, including the types of wAMD products that would be novel and interesting to them. Understanding this view of the market landscape from pharma's perspective could help inform next directions for Laurel by defining which data would be most interesting to collect in order to obtain potential partnerships.

This involves the concept of the "MVP."

What is an MVP?

The lean start-up method, which we touched on at the beginning of the chapter, focuses on quick product iteration cycles by receiving

rapid, early feedback from customers through the use of a minimum viable product (or MVP). An MVP is a version of the future product that has the minimal number of features required to test a given market hypothesis. This is often used in software, where early "apps" are released and then updated in line with user feedback. This necessitates allowing customers to use the MVP before the product is totally perfect. While this may seem counterintuitive, it prevents a company from falling into the trap of building a product no one wants by receiving feedback while they still have time to adjust.

An MVP in therapeutics, on the other hand, might be thought of as the *target product profile* that then informs the initial data set needed to prove the future product's key attributes.[144]

Nature Biotechnology describes an MVP in biotech like this:[145]

"MVP concepts can and indeed should be applied to fundamental research driven industries like biotech. [This] will lead to more capital efficient commercialization of technologies. One important test is to create the appropriate product profile… [identify] key stakeholders for a given indication and present to them a product profile of the anticipated active drug…Research is often perceived to be a necessarily meandering path. However, as the development effort moves toward the application of the technology in the marketplace, applied research has to be efficiently guided. This requires… a significant amount of discipline from everyone involved to ensure that experiments are designed from the bottom up to really answer the important questions about the MVP product."

Bringing an anticipated product profile (i.e., anticipated features of the drug. In the case of Laurel this might be eye drop delivery, anti-inflammatory and neuroprotective mechanisms) to potential partners (or other key stakeholders) is crucial in order to receive

needed feedback on which *data* a partner might want to see to back up your projected attributes of the drug. Additionally, getting this feedback early enables you as a company to build "discipline" into experiments, ensuring they are "designed from the bottom up to answer the important questions" a potential partner would likely have.

Who better to define such developmental research questions as a large pharmaceutical company, who themselves are operating in the market landscape? Perhaps the data it is interested in is a clinical Phase I study with particular endpoints, or perhaps it's a particular animal model.

Additionally, these conversations are helpful in order to determine *how much* improvement over existing products (if any exist for your indication of interest) is needed for a therapeutic to be relevant in the marketplace. What comprises an exciting new product can differ by indication because the standard of care varies by disease. For example, for some cancers, we have medicines that are extremely effective, and for others, we have almost nothing. If the standard of care for treating a patient with that disease is currently only extending life by one month, increasing life expectancy to three months is likely substantial. However, if the standard of care for treating patients for that disease increases life expectancy by twelve months, maybe a therapeutic that adds one month extra isn't enough to lead to its widespread use. As pharma companies are operating in the context of the market, they often have a good handle on this information.

To the pharma business development representatives, I asked questions such as, "What do you see as gaps in the market?" and "What sorts of technologies are you interested in commercializing?"

Ultimately, I wanted to determine how our target product profile compared to the "résumé" of a new medicine they would be interested in commercializing and understand what type of data set they would want to see. In short, I was testing hypotheses one, two, and four.

I learned *in vivo* distribution experiments would be most desirable (but only in rabbits or primates, as they largely viewed small rodent model data as not highly translatable). I also determined that pharmaceutical companies were generally much more comfortable with an additive product, referring to something patients would use in conjunction with, rather than instead of, their current schedule of injections; this was due to the fact that prescribing physicians tended to highly regard the current standard of care.

Although it became clear from these conversations that pharmaceutical companies seemed to see a market need and foresaw potential market success for an eye drop, the companies I spoke with also generally expressed a certain nervousness about investing in an eye drop because many previous eye drop candidates for wAMD had failed in late-stage clinical trials. The cost of those failures had dissuaded pharmaceutical companies from investing in eye drops further, even in a different product.

WHAT THESE CONVERSATIONS REVEALED

These conversations left Sanders and me with helpful insights and additional key questions.

As far as insights gained, the company now had several potential new directions it could take along with clear market validation from target customers. Specifically, Laurel Therapeutics knew that it

ideally needed a strong efficacy data set around any anti-inflammatory or neuroprotective effects of the EBIN molecule.

The key questions that had emerged were on the subject of what had caused so many previous eye drops for wAMD to fail. Was it something about the distribution of the drugs in the eye? Something about the molecular targets of the drugs? Was it a mechanism of action that did not work sufficiently through eye delivery?

When we conducted initial research into these questions, it seemed that previous eye drops had failed clinically largely due to lack of distribution to the correct part of the eye. This had understandably caused physicians and pharma companies alike to be highly focused on this question and very skeptical of new potential therapeutics unless specific data addressed the issue of distribution.[146]

Thus, collecting this distribution information early on (i.e., information on how the eye drop travels through the eye) was crucial in order to overcome existing skepticism.

We needed to gather data on all of these areas proactively in order to differentiate our approach as well as de-risk it from the perspective of potential future customers. To this end, I had attended the conference with four working hypotheses and had managed to test all of them. We learned how much resistance versus receptivity was out there for an eye drop delivery system, long before anyone had invested a lot of money into the molecule, thus decreasing a great deal of risk (the subject of chapter 7). By conducting customer development, we as a company had gone from our hypothesized problem in need of solving (as outlined in chapter 4), to specific problem statements that our technology was potentially uniquely capable of addressing.

In other words, we Built Backwards from our end customers' problems to understand how we should ultimately position ourselves in the marketplace. This enabled us to build toward that from the beginning, avoiding opportunities for wasted time and money.

The result for Laurel Therapeutics? We hired a CRO to conduct a specialized formulation of EBIN to optimize delivery to the back of the eye, as per our interviews. We conducted distribution studies in rabbits, and we developed data sets on the anti-inflammatory and neuroprotective activities of the molecules. Although Laurel is not yet a clinical-stage company, the company is now well-positioned to receive venture financing or a pharmaceutical partner. By starting with a problem and Building Backwards, Laurel is better positioned for success.

Another important aspect of Building Backwards to success at an early stage of a new company is laying the foundations of the company correctly by anticipating key fundamentals that will set you up for success later on. This is the subject of the next chapter.

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126 Steve Blank, "Why the Lean Start-Up Changes Everything," *Harvard Business Review,* May 2013.

127 Shortly before this manuscript went to publishing, Eric passed away suddenly. I had spoken to him only weeks before and was devastated when I heard the news. Eric was an incredibly generous person. When I first contacted him in 2017, I had no idea how successful he was, how well-known he was, nor even what venture capital was. Although I had researched him and his firm, I didn't recognize "Canaan Partners" nor realize VC is considered "prestigious." Yet Eric took the time to speak with me anyway and never felt the need to point these facts out. It wasn't until I independently learned these things about him that I realized exactly *how* generous Eric had been. His generosity never ceased. He was willing to make time for me often, whether for questions, advice, or anything else. Friends of mine who knew him say this was their experience with him as well. Eric taught me the value of generosity and being willing to invest in others. The lesson I hope this can impart to the reader is this: do not underestimate the impact of investing in someone and expecting nothing in return. Eric, I'll never forget you.

128 Greg Satell, "This Program Uses Lean Startup Techniques to Turn Scientists into Entrepreneurs," *Harvard Business Review,* March 7, 2017.

129 Steve Blank, "Why the Lean Start-Up Changes Everything," *Harvard Business Review,* May 2013.

130 "The Top 12 Reasons Startups Fail," Research Briefs, CB Insights, August 3, 2021.

131 Katie L. Pennington and Margaret M. DeAngelis, "Epidemiology of Age-Related Macular Degeneration (AMD): Associations With Cardiovascular Disease Phenotypes and Lipid Factors," *Eye and Vision* 3, no. 34 (2016).

132 Ibid.

133 Jaclyn L. Kovach et al., "Anti-VEGF Treatment Strategies for Wet AMD," *Journal of Ophthalmology* 2021 (February 2012).

134 According to my customer discovery interviewees, bi-weekly injection regimens are typically scheduled in order to keep from injecting both of a patient's eyes in the same day.

135 Marcia Frellick, "Two Expensive Diabetic Macular Edema Drugs Not Cost-effective," *Medscape*, June 9, 2016.

136 "Where the Newest Anti-VEGF Agent Fits in the Exudative-Disease Toolbox," *Retina Specialist*, November 26, 2019.

137 Katie L. Pennington and Margaret M. DeAngelis, "Epidemiology of Age-Related Macular Degeneration (AMD): Associations With Cardiovascular Disease Phenotypes and Lipid Factors," *Eye and Vision* 3, no. 34 (2016).

138 Michelle Stephenson, "Managing the Retina 'Epidemic,'" *Review of Ophthalmology*, August 9, 2012.

139 Ibid.

140 Shriji Patel, MD, "Medicare Spending on Anti-Vascular Endothelial Growth Factor Medications," *Ophthalmology Retina* 2, no. 8 (January 15, 2018).

141 Paris Tranos et al., "Resistance to antivascular endothelial growth factor treatment in age-related macular degeneration," *Drug Design, Development and Therapy* 7 (June 17, 2013): 485–90.

142 Ibid.

143 Physicians are reimbursed at a certain rate for each drug and procedure they perform during a patient's appointment. In the case of anti-VEGF injections, physicians are paid for the injection procedure needed to administer the therapy. Most every drug you are prescribed by a physician is reimbursed by insurance. This results in it being prescribed

at a higher rate. Thus, for a new drug to succeed on the marketplace, it must obtain reimbursement.

144 This is also an incredibly useful tool for Building Backwards to clinical trials, which we will discuss in depth in chapter 11.

145 James Taylor, "Minimum Viable Products in Biotech," Trade Secrets, *Nature Biotechnology*, December 20, 2011.

146 Shinya Horita et al., "Species differences in ocular pharmacokinetics and pharmacological activities of regorafenib and pazopanib eye drops among rats, rabbits and monkeys," *Pharmacology Research & Perspectives* 7, no. 6 (December 2019).

CHAPTER 6

THE FUNDAMENTALS

"Making sure the founding DNA isn't messed up with mutations at the outset gives a start-up its best shot at success."

—BRUCE BOOTH, PHD, PARTNER AT ATLAS VENTURE

In the last chapter, we established the best ways to determine how to build a company around a problem-solution match and established *why* doing so is important from the perspective of Building Backwards:

1. This approach enables you to start a company that is more appealing from day one to potential investors, partners, government investors, grant agencies, and, down the road, patients, insurers, and physicians.
2. It ensures you have created a company that is most likely superior to its competition because you looked at multiple assets and found one that solved your needed problem in the best way.

Building Backwards also applies to the fundamentals of the business itself. By thinking about your goals early on—and using those goals to inform the foundation of your company—you can optimize for a successful company from day one.

BUILDING A COMPANY: THE KEY INGREDIENTS

During interviews for this book, I asked the same question of key biotech industry leaders. **What's the best way to optimize for a**

terrific outcome up front when you're setting up the fundamentals of a new biotech company? Their insights essentially boil down to six key ingredients:[147]

1. Build a company for the long term, not just to get acquired.
2. Develop an idea that's big enough to support a mega company.
3. Form a strong team.
4. Build a strong intellectual property (IP) portfolio.
5. Capitalize your company appropriately.
6. Develop a *patient-centric* mission that drives you.

KEY INGREDIENT 1: BUILD A COMPANY FOR THE LONG TERM, NOT JUST TO GET ACQUIRED.

Rationale: Many founders are so focused on a singular, shorter-term goal—such as an exit after Phase I—that they neglect to position themselves for long-term success.

Few people know how to execute long-term company building better than Kristina Burow, managing director at ARCH Venture Partners.[148]

"The best way to optimize for a terrific outcome is to build a company for the long term," Burow told me. "It's highly likely that along the way, the company will get acquired because most companies do. But if you build it with the idea that all you're trying to do is get Phase I data so you can flip the company to Big Pharma or go public, and then you're going to liquidate your stock, you will inevitably hire people who are not big thinkers. You will not staff the company to a place where you can actually build a multihundred million or multibillion dollar organization."

It's correct and prudent to plan for a strategic exit (chapter 8). However, founders can sometimes shoot themselves in the foot by

building a company that is only equipped for acquisition rather than expansion and development.

One way this shortsighted mindset may become apparent is in the way companies view partnerships. When building for long-term success, partners such as academic groups, other companies (e.g., large pharma, midsize companies, other biotechs, etc.), government groups (National Institutes of Health, Department of Defense, etc.), or even experienced venture investors can be especially beneficial to companies in validating data, enhancing credibility, and providing additional resources to expediently pursue company goals. Some biotechs are hesitant to bring in partners because, if the biotech ends up succeeding, profits, equity, and/or the "glory of winning" may need to be shared.

This approach is not only shortsighted but "puts the cart before the horse," so to speak, as only a successful company will have resources to share. By placing unnecessary financial and resource limits on the foundational phase of company building, the refusal to bring in complementary partners can hobble the company and leave it in a weaker position overall—a position that leaves it less likely to succeed.

KEY INGREDIENT 2: DEVELOP AN IDEA THAT'S BIG ENOUGH TO SUPPORT A MEGA COMPANY.

Rationale: A company cannot become "big"—and thus garner the necessary funding, partnerships, and attract a talented team—if the technology underlying it isn't innovative or significant enough to make a substantial impact. In Burow's words, "It's got to be a big enough idea to elicit excitement and energy."

A helpful way to think about this might be to start with discussing the type of technology that is *not* ideal to begin a new company around—technology that is an *incremental* improvement over what already exists. An example of an incremental improvement technology is Sumatriptan's novel route of administration. Sumatriptan, an existing drug for migraine, was switched from oral administration to nasal delivery.[149] Although a migraine patient genuinely derives benefit from this innovation—as nasal delivery seems to increase the concentration of drug that reaches the brain—this is not a fundamentally new way of treating the disease. Thus, patients are likely to see only incremental improvement by making the switch to the nasal delivery form of the drug. So, while effective, this innovation would be less likely to generate the "excitement and energy" to which Burow referred.[150]

In contrast, when starting new companies, ARCH searches for technologies that provide a problem-solution fit in a *tenfold* better way along two orthogonal "figures of merit." Figures of merit is a fancy way of saying you can evaluate a technology on multiple dimensions. For example, a technology could be valuable because it is less costly, has a more convenient route of administration, or has less severe side effects than existing therapeutic options. Each of these comparisons is an example of a figure of merit: cost, route of administration, and side effect profile. ARCH looks for a new technology that is *tenfold* better in *two* nonoverlapping figures of merit ("*orthogonal* figures of merit"). This helps ensure the company, if successful, will be an enormous success rather than a marginal one.

An example of an ARCH company founded upon such a technology is Vizgen, whose underlying single-cell imaging technology (known as MERFISH) improved upon current methods across four key figures

of merit. First, single-cell imaging techniques available previously largely struggled with multiplexing. While most prior technologies could analyze less than one hundred genes on the single-cell level, MERFISH enabled the study of tens of thousands at once. Second, many prior technologies were unable to obtain simultaneous spatial information from tissues (i.e., how the gene expression in a single cell compared based on where the cell was located in a tissue). MERFISH provided this information. Third, while prior technologies were unable to detect "rare" genetic transcripts, which were often the most interesting for obtaining novel insight, MERFISH was highly sensitive. Lastly, MERFISH decreased the cost of analysis from about ten to twenty dollars per cell to cents on a dollar.[151] Thus, Vizgen's technology was superior along four orthogonal figures of merit: multiplexing, spatial context, sensitivity, and cost. Thus, Vizgen made an "exciting" new company, allowing it to more easily attract investment and partnership.

Another aspect of selecting a "big idea" around which to start a company is the idea of a "platform" technology. A platform technology enables multiple applications, such as GPCR crystallization at Receptos (more on this later in the chapter). The idea is a platform company has multiple potential applications. Multiple "shots on goal" may mean a higher likelihood of success.

This can enable a higher valuation for a preclinical company. "Sometimes, you can construct a broad enough technology platform that is able to truly transform an enormous number of diseases," Burow explained. "If you can show this in a fashion that gives people confidence it's going to work, that's significant for increasing your valuation."

By contrast, single-asset/single-application companies solve important issues but are generally much more difficult to scale than

those founded upon technology platforms.

This is not to say you should never consider commercializing technologies that are not platform technologies or clearly tenfold or more improved over the existing technology standard. Rather, this is to get you thinking about how a top-tier venture capitalist group typically thinks about selecting new technologies in which to invest.

KEY INGREDIENT 3: FORM A STRONG TEAM.

Rationale: A strong founding team elicits credibility with investors and increases the likelihood of successfully executing on the company's value proposition.

Although a strong team can look different by company, some general principles for consideration on core skill sets for a founding team are as follows:

- Someone able to serve as a **principal investigator (PI)**: often an academic scientist who, ideally, is widely regarded as being at the top of their field.

  An important note here is that the PI and the technology often go together. The PI is often the inventor of the technology. Thus, when you select a technology, you are likely also selecting a PI. Because of this, it is wise to consider the level of involvement a PI is able to commit to your new company, as their background and success can serve in some ways as a proxy for credibility of the technology. Investors often appreciate dedication from the PI, although PIs often do not always join the company full time.

  Having a "well-recognized" PI is helpful for securing funding quickly. In particular, if your PI has already started other successful companies, they are much more likely to be financially backed again. Though raising a financing round can take a year or more to

close, the more reputable and established your PI, the faster the round is likely to fill. For example, Kojin Therapeutics spun out from Harvard in late 2020.[152] By early 2021, the company had already closed its Series A.[153] The company's ability to fundraise this quickly likely had to do with 1) how well-known the scientific founders were, 2) the fact that many had previously successfully run biotech start-ups, and 3) the fact that they had highly experienced drug development experts on the team. Likely all of these factors left investors itching to be a part of their newest venture.

Keith Crandell, cofounder and managing director of ARCH Venture Partners, is also very familiar with this process. He has played a key role in the formation and initial funding of more than fifteen biotech companies, many of which have been acquired or gone public. He describes how to access the background of a potential PI you might work with. "Look at an academic's CV, the awards they've won, their H-index, the impact of their publications," he said. "Those are all helpful tools to understand the background of the person you're potentially going to work with."

- An individual with **industry drug development experience**: It's not always recognized within academia that the expertise needed to discover novel targets and perform groundbreaking basic research is *not* the same skill set required to develop a molecule that can function as a working drug in humans nor the same skill set needed to guide a new drug through the regulatory process. Ideally, this individual will have brought drugs to market already, or if not, they should have experience bringing molecules into the clinical trials process. If it's not possible to bring this person on full time, a consultant is also an option.

- An **operations/finance/business development person:** This person will focus on raising money, maintaining the budget, and ensuring that day-to-day operations of the company align with overall company goals.
- BONUS: The **veteran biotech entrepreneur:** The veteran entrepreneur can double as any or all the above roles. (It's actually much better if they do!) This lends credibility to the group if there is a team member with experience in a past successful venture that has undergone an exit. If it's not possible to have a biotech veteran on the core team, someone on the advisory committee, scientific advisory board, or board of directors is also helpful.
- Additionally, although not part of the core team, it's important to have access to **stellar biotech-specific intellectual property (IP) lawyers**. We'll talk more about IP later (chapter 12).

Notice who I didn't explicitly include: a CEO, laboratory scientists, etc. The needs of every company are different, and it's common for biotech companies to launch without a CEO and plan to recruit someone stellar in a later postfinancing round. It's also common to hire lab technicians, to outsource research almost entirely to CROs, to secure a PhD or postdoc (one who may have helped discover the original invention) to continue on the team, or some combination of these.

Additionally, you will have a **scientific advisory board** whose purpose is to provide scientific guidance to the company as well as a **board of directors**, whose purpose is to ensure the company's management team is acting in the best interests of shareholders (in the case of a new company, this is mostly management and the investors). Practically speaking, the board often serves as guidance for management early on, and it is not uncommon for a member of the board to fill an interim CEO role. For both boards, it is often wise

to keep them small early on, as it is much easier to bring on new board members than to get rid of existing ones.

Overall, your team should communicate to investors that you are *the* team to execute on your value proposition. You should strive to build a team with a track record of previous biotech success, backgrounds that clearly outline your ability to successfully develop new medicines, or ideally, some combination of both.

KEY INGREDIENT 4: BUILD A STRONG IP PORTFOLIO.

Rationale: Your IP is what you own, and without a strong IP position, your ability to make business deals (including acquisitions) or to attract investment is limited.

We will discuss IP in great detail in chapter 12, so we will touch on it only briefly now. Assessing the strength of IP (typically patents) is a key part of the diligence process when ARCH chooses to begin a new company. Weak IP can tank an otherwise promising new idea. Strong IP enables a company to keep competitors from infringing on its idea and is ultimately the tangible "asset(s)" a biotech company owns. You need to think about IP protection from the very beginning of a new company.

KEY INGREDIENT 5: CAPITALIZE YOUR COMPANY APPROPRIATELY (I.E., APPROPRIATE AMOUNT OF EQUITY FINANCING).

Rationale: Raising too little capital can result in unnecessarily lengthened timelines and loss of momentum. Raising too much capital results in decreased focus and typically an inflated valuation that carries through to later rounds, often resulting in a decreased return.[154] As Booth puts it, "Goldilocks financings are just right."[155]

Within the Building Backwards framework, a crucial component of any biotech's founding strategy is forecasting the capital required to reach major value inflection points. We will talk in more detail about reaching major value inflection points in chapter 9, but for now, just know that "raising to reach value inflection points" means raising enough or a little more capital than is needed to reach key milestones that increase the value of the company.

Raising *too much* capital ahead of these milestones can blur the company's focus, which can result in longer timelines. When a company has been around for ten years with little progress to show for it, investors raise their eyebrows. Additionally, the longer development takes, the less attractive the asset becomes because of its constantly shortening patent life. Typically, when a larger financing round is raised (i.e., more money), this means the company valuation is also higher. Founders should keep in mind that carrying forward a high valuation results in "a capitalization burden that carries through [a company's] later rounds."[156]

Likewise, too little capital is also a problem. Sometimes founders fail to raise enough money for fear of dilution or loss of control. As mentioned above, too little funding can result in a company stuck without enough progress, a state that Booth referred to as "an anorexic state that leads to a failure to test the [company's central] hypothesis." He went on to explain, "Raising an initial financing round that has a razor-thin margin of error leads to bad outcomes when research plans hit reality." In other words, planning to raise too little capital with only a thin margin for leeway will be difficult when research plans inevitably do not unfold as planned. Further, de-risking the company (the topic of chapter 7) is crucial, so testing the company's "central hypothesis" (i.e., experiments to de-risk and/or validate a core asset or platform) should occur expediently.

The importance of planning a financial strategy early cannot be overstated. “If you’re doing pharmaceuticals,” Crandell remarked, “it will take multiple hundreds of millions to get through clinical trials. You want to be thinking about how you’re going to slay that dragon from the beginning.”

What does this mean? “Focus on capital efficiency,” he said. “Funding toward the value inflection points. The classic ones in biotech are going to be filing an IND to get your drug in the approval process. Or maybe you’ve got critical animal data or some model that predicts human receptivity to the particular therapeutic. Whatever is in your particular category, you want to make sure that when you go out to raise money, you’ve achieved something that’s demonstrable that you can showcase. That’s the idea of milestones, and you want to have a set of them that are well thought out. This allows you to showcase to people that you have momentum—that you’ve accomplished a lot and are building value.”

Burow agreed, stating, “You need to raise enough money so that you’re not making stupid decisions based on capital needs. You need to have enough capital that you can make the right decision for the company at every step.”

KEY INGREDIENT 6: DEVELOP A *PATIENT-CENTRIC* MISSION THAT DRIVES YOU.

Rationale: Part of Building Backwards is understanding the purpose of the company itself. Why do you exist and what is your overall goal? In biotech, when it comes down to it, your work is about the patients. Developing a patient-centric mission allows you to continue to make the best choices to ultimately benefit patients.

Josh Brumm is CEO of Dyne Therapeutics, which as I write this in the Summer of 2021 is currently worth more than $1 billion. Throughout his career in biotech, Brumm has raised over $1.5 billion through four IPOs and multiple financing rounds. When giving advice on raising capital, Brumm focuses on mission. "There can be a temptation to think of mission and vision as window dressing to be used on the opening slide of a pitch deck and then forgotten," Brumm said. "[Your mission] is the commitment you communicate to patients and their families. You need to live your mission and make sure everyone on your team lives it, too. Mission is also crucial to investors. They need to know that you know where you're headed as a company—and that you have a clear understanding of the value you will create when you've achieved that goal."[157]

John Crowley, CEO of Amicus Therapeutics, mentioned in chapter 4, also emphasized the significance of a patient-centric mission. At Amicus, Crowley and his employees focused their mission in biotech as a "sacred responsibility," where they as a company have a moral obligation to their patients. This means they strive to make medications affordable and involve real patients and their families in their drug development processes to make sure their drug development goals align with patients' actual needs.

"Working with patient organizations and working closely with patient families is the right thing to do, and I think it provides deeper meaning to our work. But it's also going to make Amicus a better company," Crowley said. "I have always believed that to have that patient-centered view, you need to build it into every aspect of your business and decision-making. If you do that, you will be driven to make better medicines."

Crowley shared a story with me of how having a patient-centric mission drives business. Amicus had spent four years and $50

million developing a small molecule drug, a protein chaperone, for Pompe disease. The drug was finally in the clinic, when one month in, his chief scientific officer (CSO) walked into his office carrying several large binders.

The drug was staying in the muscles for too long, the CSO informed him. This was inhibiting the functioning of any working acid alpha-glucosidase enzyme remaining in the muscles. "The drug is making some patients worse," the CSO said.

Not only was the medicine not working, but it actually seemed to be making patients' muscle strength deteriorate. Crowley thought of the company's mission statement. Without hesitating, he called the FDA and ended the trial. The company's stock fell 50 percent in one day.

Crowley took several days off to recoup and to contemplate next steps. As discouraged as he felt, Amicus's mission kept him going. He knew he could not give up trying to bring a new medicine for Pompe disease to market. No one else was doing it, and without Amicus's work, there would be no hope for a more effective medicine for patients suffering from this debilitating condition.

Fast forward seven years and Crowley has now brought a different chaperone molecule successfully through clinical trials and has filed with the FDA for approval. "A massive failure, but combined with a focus on patients, forced us to an even better solution for them," Crowley told me.

COMBINING INGREDIENTS

To recapitulate, the six key ingredients are: 1) building a company for the long term, not just to get acquired; 2) developing an idea

that's big enough to support a mega company; 3) forming a strong team; 4) building a strong IP portfolio; 5) capitalizing the company appropriately; and 6) developing a patient-centric mission that drives you. These ingredients are not mutually exclusive. However, **the more a company Builds Backwards using these key ingredient frameworks, the greater the likelihood the company lays the foundation for success down the road.**

Now that we have gone over the six key ingredients, let's go through an example to demonstrate how these principles can work together to create strong companies.

CASE STUDY: RECEPTOS

In 2007, Raymond Stevens, PhD, a professor from The Scripps Research Institute, pioneered work in G protein-coupled receptor (GPCR) structural biology. Stevens and his group had developed a GPCR technology platform, enabling GPCR crystallization.

GPCRs are the largest family of proteins targeted by approved drugs, but they are very difficult to hit effectively with a small molecule drug and even more difficult to crystallize.[158] Crystallizing them, however, helps to "drug them," as establishing an understanding of the receptor structure helps in creating an effective drug candidate.

Thus, Stevens' work was ultimately credited with opening up the entire field of GPCRs for more immediate drug discovery and small molecule identification. The platform also led Stevens and his group to successfully define the structure of the β2-adrenergic G protein-coupled receptor, which was named a Top 10 Scientific Discovery that year by *Science* magazine.[159]

Stevens had also previously been a cofounder of two other biotechs: Syrrx, a high-throughput structure-based drug discovery platform

acquired in 2005 by Takeda Pharmaceuticals, which ultimately resulted in an approved drug known as Nesina, and MemRx, acquired by Sagres Discovery and later by Novartis (an even larger pharmaceutical company) for its membrane protein expression technologies.[160,161]

Given this promising new technology combined with Stevens' impressive background, when Burow heard about Stevens' GPCR crystallization platform, she, along with Keith Lenden, who was an instrumental cofounder, immediately conceptualized a new company.

"I was incredibly excited," she recalled. "GPCRs are the largest drug class but impossible to crystallize before this came along. I started talking to Stevens about a company built around doing this. But I also wanted to see a small molecule (i.e., a potential drug) that came out of the platform, or something that would allow me to hire some of the best clinical experts early on, to help get feedback and inform decisions on target selection and early screening results."

Lenden found that another professor at Scripps, Hugh Rosen, MD, PhD, a professor of chemical physiology and immunology, was working on a new molecule against a GPCR called sphingosine-1-phosphate receptor 1 (S1P1).

"It looked at that time to be first in class, better than a number of the other competitors," Burow said. "So we folded that asset into the company."

Burow, Lenden, Rosen, and Stevens named the company Receptor. The company launched in 2007 with the goal of developing best-in-class and first-in-class GPCR therapeutic candidates. In other words,

they would aim to generate only new medicines that would be paradigm-changing for patients.

The team targeted a $25 million Series A (this is the terminology used for the first major round of financing raised by a company, more in chapter 9). At the time, however, it was 2008, and the country was in the middle of a recession. To put it lightly, the biotech market was not booming.

“No one wanted to fund early-stage chemistry,” Burow said. “And moreover, no one wanted to fund a discovery platform company. So the ARCH partnership told me, ‘We’re not doing this unless you can underwrite some of the costs by doing something else.’” She needed a different way to raise $25 million.

Burow started thinking. Another ARCH-backed company, called Apoptos, Inc., had just run experiments that invalidated the first three targets they had in-licensed from their academic partners. They had spent a bit of their Series A money but only had negative data to show for it.

“They had proven their technology didn’t work really quickly and really cheaply,” Burow said. “That was good. But they had an incredibly strong team I wanted to work with.”

Several members of the Apoptos team joined the new company, including William Rastetter, Marcus Boehm, and Robert Peach as cofounders. The team decided to put the $7.5 million that Apoptos had left over from its own Series A to work. They named this new company Receptos: a portmanteau of Receptor and Apoptos. Burow put together a Series A that drew from the existing Apoptos shareholders while recruiting new investors, raising a total of $25 million (this being “really small in today’s [2021] numbers,” Burow

noted), but it was enough for the company to move forward. Receptos finally launched in 2009, following this "incredible amount of work" to get it off the ground.

Through the early days, the team funded the company by making multiple partnership deals with pharma companies. The pharma company would pay Receptos to crystallize the pharma company's target of interest using Receptos's GPCR platform. The crystal structure would give the pharma company insight into the binding sites on the target, making it easier to develop a new drug. In return, Receptos gained revenue. The revenue from these partnership deals enabled the company to raise less capital than it ordinarily would have. This was significant because the amount of capital needed by Receptos—$60 million—would not have been possible to raise in that market environment.

"The early revenue allowed us to actually stay alive," Burow said. "And in that environment, the 2009 to 2010 timeframe, there just wasn't a lot of capital for companies. It made us scrappy… what the revenue gave us was an opportunity to prove out the technology platform."

The company discovered the compound it had in-licensed from Scripps—ozanimod, later named Zeposia—was a chemical enantiomer. A chemical enantiomer means there are two versions of the molecule, which are mirror images of each other. Sometimes, each "mirror image" can have a different function, which turned out to be true of ozanimod. Therefore, in order to move the molecule forward, Receptos had to identify the active enantiomer. This was Receptos's first step. As soon as Receptos ran the studies, they officially had a lead development candidate. They began IND enabling studies and were in clinical trials within eighteen months, an impressively fast timeline.

“We started to build out the team. We brought in several individuals as CEO, CFO, chief medical officer, who were all just at the absolute top of their game.[162] And very quickly, we moved the S1P1 compounds through the various stages of development,” Burow recalled. “We identified not only the traditional applications in multiple sclerosis, but given the safety profile of the drug, we identified that we could go into other things like ulcerative colitis and inflammatory bowel disease.” These were other indications in which patients desperately needed options, and the market size was substantial. This made Receptos even more valuable.

In 2015, Celgene acquired Receptos for a massive $7.2 billion amid ozanimod’s Phase III trials, after Receptos reported success in ulcerative colitis from a midstage trial. This is an incredibly large exit and speaks to the value Receptos was able to build. Ozanimod ultimately garnered FDA approval as an oral treatment for relapsing forms of multiple sclerosis in early 2020. Ozanimod was found to decrease the number of brain lesions (the severity of relapsing multiple sclerosis is measured by number of brain lesions) by 63 percent over the existing standard of care as well as significantly reduce the yearly relapse rate.[163]

The medicine also changed the paradigm for patients. The medication works by novel means, sequestering white blood cells in the lymph nodes, which essentially keeps them from attacking the brain and spinal cord and thereby prevents new damage to the neurological system.[164] Further, the medication is logistically easier and cheaper to use; it doesn’t require cardiac monitoring or genetic testing, and unlike other options, patients can just take a pill at home. The drug also has significant additional clinical benefits; for instance, approximately 75 percent of patients were free of relapses during the clinical trial, and nine out of ten patients did not

experience worsening of their functionality during the trial (worsening of functionality is the unfortunate typical trajectory for MS patients).[165]

Receptos is the story of a company that changed the lives of patients suffering from multiple sclerosis through building a foundationally solid company. How did Receptos do it? By Building Backwards to success through establishing the right fundamentals—that is, the right key ingredients—early in the company's life.

Key ingredients at play:

- **Build a company for the long term, not just to get acquired.** Burow built a company for the long term when she combined an outstanding team with powerful scientific assets. When the company was acquired, it was during a late-stage Phase III trial. Had Burow only built the company to last until, say, a Phase I trial, perhaps ozanimod would have never come to market.
- **Develop an idea that's big enough to support a mega company.** Burow solidified a platform technology that had the ability to "change the medical paradigm" if it worked, but she also had the foresight to include a drug candidate to test. This drug candidate had the ability to change the paradigm of treatment for multiple sclerosis patients by preventing new damage from happening in the first place while also being logistically easier to use *and* reducing the relapse rate. In other words, it offered a potential trifecta, exemplifying the desired multiple orthogonal figures of merit that were improved by tenfold.
- **Form a strong team.** As PI, Stevens was not only at the top of his field, but he was also a two-time successful entrepreneur who had led his previous companies to substantial exits. Burow also worked with an extremely strong team that included William Rastetter, PhD (partner at Venrock; former executive chairman

Biogen Idec, and president and CEO of Idec Pharmaceuticals from its founding), Marcus Boehm, PhD (former vice president of chemistry at Conforma Therapeutics prior to the acquisition of Conforma by Biogen Idec), Robert Peach (former senior director of oncology discovery at Biogen Idec), and Keith Lenden.[166]

  – This is a relatively large starting team, but note the adherence to the key skill sets. In addition to academic scientists, Burow included individuals with significant industry drug development experience as well as business and operations people. That balance was also important to the company's success.

- **Build a strong intellectual property portfolio.** Though this ingredient is less explicit in the story, the fact that Burow selected an award-winning, first-of-its-kind technology upon which to build the company implies that the preexisting IP in GPCR crystallization was not very strong before Receptos and its technology came along. These conditions paved the way for them to create a strong IP portfolio. This is further suggested by the fact that customers (pharma companies) paid to access Receptos's technology, and, ultimately, one large pharmaceutical company acquired Receptos itself; in the absence of strong IP, pharma companies would likely have simply replicated the technology themselves.
- **Capitalize your company appropriately.** Burow knew Receptos needed a $25 million Series A to meet the crucial milestones to increase the value of the company. Further, she knew she really would need more than that, but it would be a struggle to meet the initial $25 million target. She could have simply launched the company with less financing, maintaining more equity for the starting investors. However, she remained disciplined and creative and found a way to get the financing needed ($7.5 million from

Apoptos as well as revenue from partnerships) which enabled the company to build to the needed milestones.

- **Develop a *patient-centric* mission that drives you.** Receptos launched with a vision of developing the best GPCR drug candidates possible. By maintaining this mission focus, the company was able to create a medicine that changed the way multiple sclerosis is treated—one that both prevents worsening of the disease and allows patients to avoid constant disruption to their lives by needing to go to the clinic for treatments. In more ways than one, Receptos's medicine changed the lives of multiple sclerosis patients.

In summary, we've seen how Building Backwards principles can be applied to establish strong fundamentals at the beginning of a company's life. These fundamentals may not seem as pressing when you are just getting started, but if a company neglects to build with the end in mind, getting to the end may never happen. Founding a company with the six key ingredients described here will increase the probability of success of a new biotech start-up and ensure founders are building toward the end goal of a successful company that creates value for patients.

Another way to increase the probability of success is to systematically decrease specific risks that could lead to failure. Extremely high risk, after all, is a hallmark both of biotech start-ups and of drug development in general. Is there a way to Build Backwards to decrease the potential impact of risk up front? We'll discuss this next.

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147 You will notice that many of the insights in these key ingredients came from interviews with leaders from ARCH Venture Partners. This is because ARCH is one of the most successful life science venture capital firms in the world, known for founding highly successful biotech companies such as Illumina, Vir Biotechnology, and Juno Therapeutics. ARCH has utilized a less typical business model since its founding, relative

to the traditional VC business model. ARCH often builds the companies themselves from the ground up. This means the ARCH team is familiar with the company building process, as it founds a new company itself almost every time it makes a new investment. As many of its companies have gone on to be highly successful, it has mastered the art of laying the foundations of a company well. Thus, many of the points below are heavily based on advice and experience from its managing directors.

148 Kristina, thank you for providing encouragement when I needed it most, being willing to invest in me, and consistently going out of your way to help me when you didn't have to. I am so grateful for and inspired by you.

149 Stewart J. Tepper and Merrilee R. Johnstone, "Breath-Powered Sumatriptan Dry Nasal Powder: an Intranasal Medication Delivery System for acute Treatment of Migraine," *Medical Devices* 11 (May 2018): 147–156.

150 Note that while this might not be a great innovation for a new start-up, these sorts of incremental improvement innovations are key for large corporations that must constantly improve their existing products, which by definition is "incremental improvement."

151 Stephanie Wisner, "Visualizing the Future: Spatialomics Transforms Study of Gene Expression," Synbiobeta, April 20, 2021. https://synbiobeta.com/visualizing-the-future-spacialomics-transforms-study-of-gene-expression/

152 "Kojin Therapeutics Launches with $60 Million Series A to Develop New Category of Drugs Based on Cell State Biology," *Business Wire*, June 9, 2021.

153 Ibid.

154 Bruce Booth, "Foundings Matter: Thiel's Law Applied to Biotech," *Forbes*, June 11, 2013.

155 Bruce Booth, Twitter thread, April 24, 2018.

156 Bruce Booth, "Foundings Matter: Thiel's Law Applied to Biotech," *Forbes*, June 11, 2013.

157 Joshua Brumm, "Beyond the Balance Sheet: Thinking Broadly about Dilution in Building a Transformative Biotech," Life Sci VC, December 16, 2020.

158 Krishna Sriram and Paul A. Insel, "G Protein-Coupled Receptors as Targets for Approved Drugs: How Many Targets and How Many Drugs?" *Molecular Pharmacology* 93, no. 4 (April 2018): 251–258.

159 Eric Sauter, "Scientists Define Structure of Important Neurological Receptor, Establishing a Platform to Understand G Protein-Coupled Receptors," *News & Views* 8, no. 29 (October 6, 2008).

160 "Sagres Acquires MemRx, Enhances Discovery Programs," *The Pharma Letter*, April 27, 2003.

161 "Syrrx Acquired by Takeda," Crunchbase, accessed October 20, 2021.

162 Faheem Hasnain was CEO; Graham Cooper was CFO; Sheila Gujarthi, MD was CMO

163 Gianna Melillo, "Bristol Myers Squibb Launches Ozanimod (Zeposia) for RMS," *AJMC*, June 2, 2020.

164 Caroline Craven, "Hope in the life of the Covid Pandemic—a New MS treatment, Zeposia, approved by the FDA," Girl with MS, accessed October 20, 2021.

165 "Ozanimod," ScienceDirect, accessed October 20, 2021.

166 "Receptos Completes $25M Series A Financing," Flagship Pioneering, November 23, 2009.

CHAPTER 7

RISK AND DE-RISK

"For companies today in the world we live in, with the amount of human biology information we have, there's really no excuse anymore for a biotech company to take a tremendous amount of biology risk. Innovative start-ups should embrace technical risk and avoid biology risk."

—BENJAMIN F. CRAVATT, PHD, PROFESSOR AND NORTON B. GILULA CHAIR OF CHEMICAL BIOLOGY IN THE DEPARTMENT OF CHEMISTRY AT THE SCRIPPS RESEARCH INSTITUTE

"We're de-risking our drug candidate, see?" the CEO of biotech company A Therapeutics said, lowering his voice as if sharing a secret. I'd been hired by A Therapeutics to develop its investor pitch deck and was in the process of getting briefed on the major selling points of the company over lunch. "Our biggest selling point?" he repeated. "We're de-risked."

Scrawling on the napkin resting on the table between us, he wrote: "Probability of success of a typical new drug: 4 percent." A well-known statistic within drug development, this percentage is frequently quoted because it emphasizes an unfortunate truism. Drug development is difficult, and most efforts fail.

The CEO wasn't done. Underneath this statistic, he wrote: "Probability of success of A Therapeutics: 20 percent." He underlined 20 percent with a flourish and pushed the napkin toward me.

My eyebrows jumped in surprise. He was making a bold claim—namely, that A Therapeutics' drug candidate had a 16 percent higher probability of making it to the market than a typical experimental drug.

I needed to hear more detail to be convinced this was truly the case. However, if the CEO could back up his claim, this could be interesting.

Before we delve deeper into a discussion of potential strategies to de-risk a drug development effort, it's worth first understanding *why* de-risking is important. We will do this by considering a well-known late-stage "failure."

In 1999, multiple scientific groups (including both academic and industry) simultaneously reported the discovery of Beta-secretase (BACE), which soon became an exciting first-in-class target for the treatment of Alzheimer's disease.[167,168,169] While extremely risky—as all first-in-class target drug development is—developing a new drug to inhibit BACE was also extremely promising. If successful, a BACE drug held promise to change the paradigm for Alzheimer's, becoming the first treatment available for the devastating disease.

A first-in-class target is the term used to describe a *newly* defined molecule in the human body, usually a protein, that can potentially be modulated using a new drug. When such a target is identified, this discovery can frequently enable the development of a new prospective medicine.[170] This is because the discovery of a new target relevant to a disease means that there is a newfound angle from which to treat the disease.

When such a target-based drug discovery approach is used, scientists then attempt to identify a drug candidate that can bind

and modulate the novel target with the hope that modulating the target will likewise modulate the disease.[171,172] This is an incredibly complex and difficult process. Drug candidates that survive the gauntlet of preclinical tests may eventually advance to clinical trials, at which point it can finally be determined whether or not hitting that particular molecular target in humans will even actually treat the disease. Oftentimes, it does not.[173]

In the case of the first-in-class target, BACE, its discovery seemed incredibly promising. Scientists found that BACE was an enzyme critically involved in generating the amyloid beta peptides (Aβ) that make up the beta amyloid plaques in Alzheimer's disease. In theory, then, a drug that blocked BACE (i.e., a BACE *inhibitor*) would prevent the buildup of beta amyloid in the brain, thus potentially treating or slowing the progression of Alzheimer's disease.[174]

Over more than a decade, multiple inhibitors were developed by several large pharma companies. During the preclinical and early clinical phases, the inhibitors appeared to work as anticipated. They could bind to BACE, their biological target, and they succeeded in decreasing the production of amyloid-β peptides in the brain.

However, during Phase III clinical trials (the final phase before FDA approval), the five major drug companies developing BACE inhibitors found that the underlying scientific assumption—that blocking BACE would slow Alzheimer's disease—did not seem to hold up.[175,176] Despite the fact that the drug candidates were effectively blocking BACE and decreasing amyloid-β peptides, they seemingly had little effect in slowing disease progression. In some cases, patients with the BACE inhibitor actually experienced greater cognitive decline when compared to a placebo and also had unanticipated negative side effects.[177,178,179]

In the face of this negative data, all five companies chose to halt their clinical trials, effectively killing their own drug candidates. After over a decade of research, this was a disappointing but not uncommon end to the story, particularly for a first-in-class agent.

Early success in drug development is often followed by clinical failure—so much so that clinical failure is viewed as a somewhat inevitable peril. There is validity to this, as the oft-quoted success figure for an agent that has made it to late-stage trials is around 50 percent, according to *Forbes*.[180] However, the success rate for "novel, first-in-class agents is considerably lower," with estimates falling below 25 percent.[181] While a Big Pharma company, such as those in the BACE case, may have the capital to survive a Phase III failure, a late-stage failure can tank a biotech company that relies upon ongoing investor enthusiasm and financial support of its research.

Thus, the BACE story is just one example of a fairly common situation. A promising new medicine ultimately did not come to fruition due to a late-stage clinical failure.[182] Although in the case of BACE there seems to have been nothing the pharmaceutical companies could have done differently, the BACE story highlights just how disappointing, expensive, and time consuming late-stage clinical failures can be, and *why* it's crucial to do everything in our power to avoid such an outcome.

Not only is this sort of failure expensive, but sometimes companies will continue to run further expensive clinical trials in an attempt to get positive results under different trial conditions. Such use of resources can sometimes hold back the advancement of ideas and/or research in areas that may be more fruitful.

Although it's certainly true that the risk of late-stage failure is simply a peril of drug development, to return to the question of de-

risking, is it *actually* possible to Build Backwards in order to mitigate developmental risk and increase the probability of late-stage clinical success?

BUILDING BACKWARDS TO DE-RISK

In drug development, risk is a constant. De-risking is about giving your company the highest possible chance of success by decreasing the probability of failure in any areas you can.

De-risking is exactly what the CEO of A Therapeutics claimed on his napkin. His company *reduced* chances of failure while *increasing* potential for success—even though the biotech business landscape remained just as challenging and variable. This type of development is part of Building Backwards. You are striving to decrease risk down the line by reverse engineering the best development strategy up front.

We will discuss four different "best practice" ways a company might consider Building Backwards to de-risk. Of course, these approaches to risk reduction will not all be relevant for all companies and situations, but they remain a helpful way to think about decreasing risk where you can.

1. LEAVE UNCERTAINTY OUTSIDE THE COMPANY FROM THE OUTSET WHEN POSSIBLE

Generally speaking, it's often preferable to leave as much uncertainty outside of a biotech as possible. Where there is uncertainty, there tends to be higher risk. While academic research can encourage leaning into uncertainty, research within the context of a business has a different end goal, and that goal must weigh heavily when defining which research questions to ask.

Because the ultimate "end goal" of academic research is often to improve scientific understanding and to disseminate those advances via published papers, this process of trial and error allows for significant risk to be taken in the research questions that are explored. This can sometimes mean asking as many questions as possible and following them to whichever potential ends they may lead. While this process of scientific discovery is certainly intellectually thrilling and necessary in the context of academia, it usually does not work as a business strategy for biotech companies.

In contrast, the end goal in biotech is a working end product—a drug. Thus, a business can often benefit from minimizing the number of risky research questions it must answer down the line when failure is more costly. While there is certainly a role for basic research, asking questions, and testing hypotheses, Building Backwards toward the end goal *while also minimizing risk* is crucial.

An example of how this might look in practice is that biotech founders may choose to minimize uncertainty within a new biotech by waiting to launch the company or in-license a new asset until the more fundamental "risky" questions are investigated. In other words, "de-risking" preclinical experiments are run in the context of the academic lab or through a CRO prior to officially launching.

Jake Glanville, PhD, is the primary founder of Centivax (of which I am also a cofounder), where he serves as CEO. He was also a founder and CEO of Distributed Bio, which was sold to Charles River Laboratories in late 2020 for $104 million.[183] He's a brilliant entrepreneur and scientist as well as a highly talented strategic thinker. I have personally witnessed him derive positive outcomes from extremely delicate situations. He has been featured multiple times on media outlets such as CNN, MSNBC, Fox News, The New Yorker, and in Netflix's original series, *Pandemic*. I believe much of

Glanville's success has come from his ability to navigate risk and his foresight in "de-risking" precarious projects.

For example, one asset for an oncology indication that we were considering in-licensing targeted a protein that could potentially create autoimmunity issues in the clinic. Glanville conceptualized a preclinical experiment we could run that would allow us to answer with some degree of confidence whether autoimmunity would be a problem down the line—*before* we decided whether to acquire the asset. This left a certain amount of risk outside of the company, ultimately decreasing the chance of failure down the road.

It's often possible to decrease downstream risk by asking questions that decrease the uncertainty within a new company at the outset. This is the essence of adopting a Building Backwards mindset. Maintaining this mindset when developing new medicines can increase the probability of success.

2. BE WILLING TO FAIL FAST

It began as many legendary start-ups had. Two college students from a top-notch school start a company with an idea that might change the world.[184]

In 2016, undergraduate Nathaniel Brooks Horwitz (now a principal investor at RA Capital, a well-known biotech venture firm in Boston) dropped out of his bachelor's program at Harvard to partner with cofounders Nikita Shah (of the Bob Langer lab) and Marc Kirschner, PhD, (founding chair of the department of systems biology at Harvard Medical School) to start a company: Nivien Therapeutics. The company sought to develop a drug against a target in a well-known pathway, "Hippo-YAP," or "Hippo" for short.

Kirschner had discovered that targeting the Hippo pathway showed potential to annihilate pancreatic cancer tumors. Extremely lethal, pancreatic cancer typically has a 5 percent five-year survival rate. Unlike other cancers, that rate has remained relatively unchanged in decades—in part because of pancreatic cancer's ability to "shield" itself from existing drugs.[185] Kirschner's early research suggested it was possible to deactivate Hippo, thereby *restoring* the efficacy of cancer drugs.[186] When scientists in Kirschner's lab deactivated Hippo in mice using genetic manipulation, the concept held true. Drug-resistant pancreatic tumors were destroyed.[187,188,189]

The key caveat for these results was "*in mice*." Would it work in humans?

Buoyed by these promising results and determined to answer this question, Horwitz and Shah moved to San Francisco and assembled a team. Their first goal was to discover a drug candidate that could bind and inhibit their target in the Hippo pathway.

"We ran a barrage of experiments with partners on three continents to test our approach," Horwitz said. "I pitched Nivien to hundreds of scientists and investors at the IndieBio Accelerator Demo Day."[190] As a result of Horwitz and Shah's efforts, AstraZeneca invited Nivien to join its state-of-the-art BioHub, which provided free rent and equipment as well as an opportunity to work with scientists from one of the best oncology teams in the world.[191,192]

In traditional drug development, it can sometimes take up to a decade or more to develop a drug candidate selective for particular targets. Remarkably, Nivien developed the first potent and selective compounds inhibiting a target in the Hippo pathway within a year of launching the program. Success built on success; excitement and optimism surrounded the development of Nivien's potential therapy.

From the start, Nivien took a bold approach to drug development. First, it launched with a small amount of capital and a drug development hypothesis. This hypothesis was that targeting Hippo would be an effective treatment for pancreatic cancer by simultaneously reactivating the effect of existing chemotherapy and stimulating an innate anticancer immune response. Immediately after launch, it designed and ran a high-bar proof-of-concept experiment. When it ran the experiment, it set specific parameters defining what "failure" would be. That way, if its experiment failed, Nivien could confirm with relative confidence its hypothesis was wrong and halt development before spending too much capital and time. However, if the experiment succeeded, Nivien's risk would be much lower because its key hypothesis would be further validated. The development process, consequently, would be de-risked.

Many companies are afraid to run such experiments because debunking one's own hypotheses is demoralizing at best and can signal failure for the business at worst. Nivien realized there was value in being willing to fail early—or, if the experiments succeeded, moving forward with greater confidence. The team boldly adopted this strategy in the name of de-risking. They would Build Backwards from data that, when obtained, would allow the company to quickly reach a "go/no-go" decision point.

Armed with Kirschner's early research, Nivien's first goal as a company was to design an experiment that would give a clear answer on whether its underlying hypothesis was valid. As per chapter 4, it started with a problem statement their therapy would be solving for pancreatic cancer patients should it make it to the market.

"It's important that you figure out at the beginning whether the drug you're developing is actually going to be meaningful for the

end user," Horwitz told me. "You have a difficult time knowing this unless you've been talking to patients and doctors all the way through the process to make sure you're taking a shot on a goal that people care about in the first place."

In cancer specifically, Horwitz focused on the need for transformative new therapies in lieu of new products that provide marginal benefit at exorbitant costs, which is sometimes the case with new cancer medicines. "When we engaged with patients, their families, and doctors, we found that in general, people do not seem to care about a new drug that doesn't lengthen lifespan but decreases the size of their tumor," Horwitz said. "They care about more time with their family. And they care about how good that additional time is, that there's fewer side effects."[193,194]

Armed with this information, Nivien set the bar for the "go/no-go" experiment extremely high.

"Because we knew what people actually cared about," Horwitz explained, "we tied that back to the initial preclinical experiment we were going to run. If it worked, we would be able to say with some degree of confidence that it would matter to the people who would ultimately use this drug."

The "go/no-go" experiment was designed to test exactly *how much* targeting Hippo would potentially benefit cancer patients?

Although Nivien had demonstrated its compounds could powerfully inhibit Hippo activity, the efficacy of the chemotherapies Nivien sought to enhance was only mildly elevated. The profound effects seen when Hippo was genetically deactivated were not reproducible when the compound was used instead. This common reproducibility issue stymies many promising translational efforts.

Though the founding hypothesis of the company proved correct to an extent, the magnitude of benefit was uninspiring. The team declared the program a failure. Horwitz and Shah, along with input from advisers and investors, decided to shut Nivien down.

"Because of the patient perspective, it was an incredibly easy decision to make in some ways," Horwitz said when we spoke on the phone shortly thereafter. "We knew it was nowhere near the type of data we initially saw in genetic studies that we had based the premise of this company on. After $100 million in clinical trials, years of work, and patients and scientists committing years of their lives—*maybe* we would have seen some marginal benefit in a clinical trial. But marginal benefit was not good enough. Continuing to devote time and money to an idea that was no longer commensurate with the standards we had for a new medicine would have been a waste of time and resources that could be going toward a better idea."

In other words, Nivien Built Backwards from its end goal of a successful drug that made a difference for patients to the type of data set it knew it needed to see to move the company forward—a "de-risking experiment." The data was clear. The answer was "no-go."

Yet, arguably, Nivien is a success story. It is a story of Building Backwards to define key questions and having the courage to make the tough decision. It managed to test an academic scientific idea—Hippo as a new target for pancreatic cancer—and received actionable data quickly. Nivien went from an idea to a drug target to results from a proof-of-concept preclinical study in only two years. That is less than the time it often takes to publish a scientific paper.

Contrast this with BACE, which did not fail until midway through Phase III, nearly two decades after the target was originally described.[195] At that point, failure is exorbitantly expensive with respect to time and money. If the pharmaceutical companies targeting BACE had the opportunity to make the "no-go" decision earlier (which by nature of the target it did not have), it would have saved significant resources and been able to put them toward a different project.

Unlike many leaders, Horwitz is eager to share his company's "failed" data.

"I think it's important to share both 'successful' and 'unsuccessful' experiences," he explained. "Unsuccessful experiences are not talked about, which is a real shame in a similar way to the fact that it's a shame we don't have more high-impact journals publishing negative results."

I asked him why he thought more companies are hesitant to run experiments that might disprove hypotheses.

"I think it's because of the human interest of the people involved. It's their salaries, their favorite project," Horowitz continued. "Also, there are instances of companies getting a drug approved even when the clinical data doesn't look so good… Sometimes companies can theoretically pivot when they fail, but often they would benefit from being recreated from scratch."

Horowitz views this sort of face-saving tactic as a waste of time and money. "The companies that just sort of tick along and are kept alive with more financial and human resources are best described as 'zombie companies.' They distract, they confuse, and they're taking away resources from more valid efforts."

At the end of the day, Nivien's drug didn't work, but Nivien successfully de-risked the company by failing fast.

The take-home lesson from this example is by asking the most high risk questions early—and being willing to fail quickly—biotech companies can decrease the probability of an expensive, time-consuming late-stage failure or of becoming a "zombie company." If the experiment succeeds, it de-risks the company, increasing the probability of late-stage success.

3. SELECT TARGETS WITH AS MUCH HUMAN BIOLOGY DATA AS POSSIBLE. EMBRACE TECHNICAL RISK AND AVOID BIOLOGY RISK

Let's return to the quote at the beginning of the chapter: "Embrace technical risk and avoid biology risk." What does this mean?

Technical Risk can best be phrased as a question: **Is it possible to actually *create a drug candidate that modulates the target*?** In the BACE story, the technical risk involved was the risk of whether it would really be possible to create a drug candidate that successfully inhibited BACE. Ultimately, scientists overcame this risk, and multiple compounds were created that were able to do this.

In contrast, **biology risk** is the risk that **binding the target of interest does not actually treat the disease**. In the BACE story, the biology risk involved was the question of whether modulating BACE would actually result in a viable treatment for Alzheimer's. In this case, it did not. Scientists and companies did not overcome the project's Biology Risk, although they did overcome its Technical Risk.

According to Cravatt, part of decreasing overall risk in a biotech company is about considering which *type* of risk is being undertaken. "For companies today in the world we live in, with the amount of human biology information we have, there's really no excuse anymore for a biotech company to take a tremendous amount of biology risk," he said. "Innovative start-ups should embrace technical risk and avoid biology risk."

Much of the "human biology information" Cravatt references is the human genetic information that has become increasingly available, which can yield clues as to which proteins are most significant in particular diseases long before clinical trials.

To further illustrate embracing technical risk and minimizing biology risk, Cravatt gave me the example of Vividion, an ARCH portfolio company he cofounded. Based on an innovative chemical proteomic platform, this platform enables drugging proteins and pathways that might not necessarily appear druggable according to the framework of classical pharmacology. By focusing such platforms on drugging targets with validated human biology, the intersection of those targets that are difficult to hit yet highly biologically validated can be compelling for new drug development.

"Every protein Vividion is studying [as a potential target] has compelling human biology evidence for being important for physiology of disease," he said. "Here's where the philosophy of embracing technical risk comes in. It might be ten times as difficult to find drugs that work against some of these proteins, but whatever price is paid up front in technical risk will be gained tenfold through increasing the probability of success in the clinic by going after a target with known biological significance instead of creating drugs for a protein that has ill-defined biology."

Vividion is going after targets with well-defined biology. If it is able to find a working drug candidate—thereby overcoming technical risk—the likelihood of succeeding in clinical trials is much higher because its biology risk will have been low to begin with. This de-risks the company because avoiding biology risk up front decreases the probability that the drug fails clinically because of insufficient relevance of the target in the disease.

Bayer certainly seemed to find this logic compelling, as it recently acquired Vividion and its drug discovery platform for $2 billion.[196]

To understand how this philosophy of minimizing biology risk and embracing technical risk might look within other companies, consider the following case studies.

CASE STUDY ONE: GLEEVEC & BLUEPRINT MEDICINES

The story of Gleevec is famous in the biochemistry world. Gleevec is a medicine for chronic myelogenous leukemia (CML). Before the advent of Gleevec, only about 30 percent of patients with CML survived for even five years after diagnosis. After Gleevec, that number rose to almost 90 percent.[197] Today, someone with CML who is in remission after two years of Gleevec treatment has the same life expectancy as someone who doesn't have cancer.[198]

Although Gleevec wasn't discovered by a start-up, the Gleevec story is a great example illustrating the idea of minimizing biology risk by understanding a target up front—even in the face of significant technical risk.

I had the opportunity to speak to Brian Druker, MD, on the phone. Druker was among the first to push for Gleevec's commercialization, and he eventually conducted the pivotal clinical trials that brought Gleevec to market as a medicine. He was soft-spoken and easy to talk

to. Had I simply met him on the street I might not have guessed the caliber of his credentials. Druker's many awards include the Warren Alpert Foundation Prize from Harvard Medical School, the Lasker-DeBakey Clinical Medical Research Award, the Japan Prize in health care and medical technology, and the 2018 Tang Prize in Biopharmaceutical Science. He has been elected to the National Academy of Medicine and the National Academy of Sciences. To put it lightly, he is an extremely accomplished scientist.

What is less well-known is Druker's ongoing participation with translation and commercialization of research.

In the 1960s and '70s, academic researchers at various institutions discovered the existence of the "Philadelphia chromosome" and the fusion gene product known as BCR-ABL in patients with CML.[199] Although some evidence suggested that the BCR-ABL fusion was what is known as the "driver mutation" in CML (i.e., the mutation causing the cancer), this was controversial. Further, the BCR-ABL gene produced a type of protein called a "tyrosine kinase," a family of enzymes believed at the time to be too difficult to target specifically with a small molecule drug because of a high degree of similarity in the active site of the many different kinases in the body.[200,201,202]

By the nineties (yes, it took twenty to thirty years to translate the initial finding!), Druker wanted to find a treatment for CML that would kill cancer cells but leave healthy cells intact. He thought perhaps patients could be treated with a drug that blocks BCR-ABL. Since healthy cells do not have BCR-ABL, they would theoretically be left intact. If BCR-ABL was truly the driver mutation in CML, he reasoned this should essentially cure a patient.[203]

Druker contacted his colleague, Dr. Nicholas Lydon, PhD, an expert in the field of kinase drug development who was working at Ciba-Geigy (now Novartis, a large pharmaceutical company). Lydon's team had generated a number of kinase inhibitors that he believed might be effective against BCR-ABL.

"Within six weeks of arriving in Oregon, I had compounds in my lab; within three months, I had data showing we could kill leukemia cells without harming normal cells," Druker recalled in a recent interview with *The ASCO Post*. "Then, it took me five years to convince Novartis to go into clinical trials. Frankly, I don't fault Novartis for their lack of interest in CML. Their cost was upward of a billion dollars to develop a drug that had a one in ten chance of success, and their estimates were that even if it was successful, the market size was too small to recoup their costs."[204] (Note again the influence of market size in pharma decision-making.)

In 1998, Druker initiated a Phase I clinical trial for a chemical called ST1571, now called Gleevec. To the researchers' delight and shock, a Phase I trial involving thirty-one CML patients resulted in all thirty-one people experiencing complete remission. In other words, their blood counts returned to normal. By 2001, Gleevec was FDA approved.

Because of Gleevec, Druker is considered the father of modern-day targeted therapies. The discovery of Gleevec became a proof of principle, spurring the development of more than fifty similar precision therapies for other cancers.[205]

Gleevec is also an example of successful de-risking. Gleevec used human genetic data up front in order to obtain target validation, thereby minimizing biology risk. By using sequencing info from many, many CML patient tumors, Druker realized the BCR-ABL

genetic mutation was likely driving the cancer. Put simply, he validated the *biological and clinical relevance* of the target ahead of time. This resulted in de-risking the development effort overall, even though Druker embraced high technical risk given the fact that BCR-ABL was initially considered undruggable.

Despite Gleevec's well-known history, some would argue the company lucked into a rare situation that cannot realistically be repeated. Druker disagrees. "I think the reason for the high failure rate in drug discovery is in part because the validation of a target isn't as well-documented as it should be," he said. "When you talk to people in the drug industry, they say only about 3 percent of drugs succeed. But oftentimes, the reason for this is that the model system people are looking at when they pick a target just isn't very good."

In other words, one reason drugs fail is because developers are picking targets that have very high biology risk. "Because of this," Druker concluded, "it's not until you get into the clinical trials that you actually get to test whether a target is a good one or not."

Much of this, of course, is because there are simply not better model systems for certain targets—as in the case of BACE, where scientists tried everything possible but the program still failed. However, we do have a choice in the drugs we choose to develop, Druker told me. We can select which targets we choose to develop drugs for, and we can preferentially develop drugs first that have the highest probability of success.

As if to prove his point, Druker did it again. Working with Gleevec collaborator Nick Lydon, he began a company called Blueprint Medicines, focused on developing precision therapies for rare cancers and other diseases. In only three years, Blueprint was able to

advance two drugs into Phase I clinical trials. Blueprint now has two approved drugs on the market and multiple others in clinical trials.

How did Blueprint accomplish this? Similar to the case of Gleevec, Blueprint found a way to obtain early target validation. Once again, it decreased its biology risk up front.

Druker explained their process to me. First, Blueprint analyzed genetic sequencing on all of the genes expressed in a number of tumor samples (the "whole exome"). In parallel, they screened their library of chemical compounds on the patient tumor samples in order to determine which drugs could successfully kill the cancer cells. By integrating both types of data—linking mutated genes to drugs that were effective in treating them—they vastly accelerated their ability to predict which genetic changes were important in these different cancers. Then, if "knocking out" the gene in an animal model served to kill the cancer, they had further validation that inhibiting that target was probably going to succeed.

Using this method enabled them to quickly identify a specific genetic mutation in patients with Systemic Mastocytosis (SM) who were resistant to Gleevec. The target, KIT tyrosine kinase, had a mutation that many believed was a driver mutation. Several KIT inhibitors had been tried in SM but had shown minimal activity. This led some to believe that KIT was not a good target. Druker, however, was convinced that the issue was not the target but rather the drug's ability to inhibit the specific KIT *mutation* present in SM. Blueprint developed a molecule, avapritinib, that effectively inhibited the SM KIT mutation and was able to show significant responses in clinical trials.

Very quickly, then, Blueprint had a well-validated target in a "small market disease." They had a product that precisely solved a niche

problem in the market.

“We went after well-validated targets but in very small-market diseases,” Druker told me. “We asked ourselves which targets were out there where it looked like a kinase was driving a disease? Other companies weren’t as interested in developing drugs against small-market diseases. We would make sure we were 100 percent convinced that the target we selected was good and that no good drug for that target existed. Then, we felt especially confident that these drugs would work because of the target validation we had done.”

Druker used Building Backwards thinking to decrease biology risk up front through early target validation. In turn, this resulted in a pipeline of medicines that proved to be extremely effective in clinical trials. By de-risking the targets he chose to pursue, Druker increased the probability of both scientific and business success.

CASE STUDY TWO: PCSK9

To drive home the power of decreasing biology risk in the early stages of a development effort by selecting a target with significant genetic information up front, we can also consider the story of PCSK9 inhibitors.

PCSK9 inhibitors were developed by multiple large pharmaceutical companies, and two are currently on the market: Repatha (from Amgen) and Praluent (from Regeneron/Sanofi).

Both of these monoclonal antibody drugs target a protein called PCSK9 to treat high cholesterol. (PCSK9 is notoriously undruggable via small molecules.)

In the early 2000s, the PCSK9 gene was identified in parallel by multiple academic groups that had been studying and collecting DNA samples from individuals and families with very high or very low cholesterol. Researchers identified the gene PCSK9, linking it as relevant to high or low LDL "bad" cholesterol. When individuals carried mutations that made PCSK9 overactive, LDL cholesterol was elevated. When individuals carried mutations that made PCSK9 *nearly nonactive*, however, they had extraordinarily low LDL (e.g., fourteen milligrams per deciliter, versus a normal individual's LDL target of one hundred milligrams per deciliter). Additionally, it was found that these individuals also had greatly reduced chances (up to 90 percent lower) of developing heart disease versus "normal" individuals.[206,207,208]

When researchers tested whether the mutation was what was driving the low cholesterol—which they did by "deleting" the gene in animal models (i.e., "knocking it out")—the knockout animals did, in fact, have low cholesterol.[209] This implied that targeting PCSK9 with a drug would result in low cholesterol. The discovery of the target initiated an arms race among several pharmaceutical companies.[210]

By July 2015, Regeneron and Sanofi received approval for their PCSK9 inhibitor, Praluent, for adults with hereditary high cholesterol and those with atherosclerosis who require additional lowering of LDL when diet and statin treatment have not been sufficient.[211] Only a month later, Amgen received FDA approval for Repatha for the same indication.[212]

PCSK9 inhibitors are highly effective. They have been found to lower LDL by 47 percent on average and by as much as 60 percent in patients on statin therapy.[213,214]

By starting with upfront human biological data that decreased biology risk, Regeneron/Sanofi and Amgen started from a position that strengthened their odds of success. When this result was recapitulated in animal models (note the power of Building Backwards in going from *human* genetic information and *then* to animal models), it suggested the target was a good one.

But you're probably asking, What about the many, many cases in which genetic data on a target isn't available? Let's consider one more case study to see how this may look.

CASE STUDY THREE: ABIDE THERAPEUTICS

One of Cravatt's previous companies, Abide Therapeutics, developed inhibitors for the enzyme target monoacylglycerol lipase (MAGL). Before selecting MAGL as a target, Cravatt thought early on about de-risking. He wanted human data on the company's target—long *before* clinical trials. However, clear genetic validation data on MAGL was lacking. How else could he obtain human pharmacology and safety information early?

To do this, Cravatt looked to previous research on MAGL and its role in what is known as the endocannabinoid system, which is comprised of cannabinoid receptors, endocannabinoids, and the enzymes responsible for the synthesis and degradation of the endocannabinoids and is expressed throughout the central and peripheral nervous systems.[215] (It should also be noted that Cravatt had been extensively involved in research on the endocannabinoid system for years.) The endocannabinoid system is the same system targeted by marijuana's psychoactive component, THC (short for Δ9-tetrahydrocannabinol). THC produces most of its effects in the body through activation of two endocannabinoid receptors: CB1 and CB2.[216] While THC has long been known for its therapeutic effects—

providing pain and anti-inflammatory relief, among other benefits—it also can cause many undesirable neuropsychiatric side effects in part because of off-target effects.

MAGL, however, is responsible for the breakdown of naturally occurring "endogenous" cannabinoid, 2-arachidonoylglycerol (2-AG). These molecules bind and activate the same CB1 and CB2 receptors as THC, providing natural anti-pain and anti-inflammatory benefit.[217]

Cravatt wondered if he could target MAGL to harness the therapeutic benefits of marijuana while mitigating the negative side effects caused by THC. Because MAGL is responsible for 2-AG breakdown, inhibiting MAGL with a drug would theoretically result in increased activation of the THC receptors CB1 and CB2, thus causing similar effects without any off-target side effects.

So, while there was still a question of which disease would be most effectively treated with a MAGL inhibitor, Cravatt could draw upon strong evidence of pharmacological significance at an early stage in humans and strong evidence of safety that came from research on THC use in humans. He had found a way to obtain human data very early.

"For MAGL, there's an absence of human genetic information," said Cravatt. "So without that long history of cannabinoid pharmacology in humans, it would have been more difficult. We were lucky in the sense that that pathway had historically ancient pharmacology associated with it."

Strengthening Cravatt's conviction that MAGL inhibitors would not produce the negative cannabis-like effects that would limit usefulness were comparative studies done in rodents. Among other

experiments, scientists characterized THC side effects in rodents by treating rodents with THC and then compared the effects to those from MAGL inhibition. They found a "lack of cannabis-like behavior" from the MAGL inhibitors, suggesting that the MAGL inhibitors would be less likely to produce negative side effects in humans as well.[218] This is also another example of what it can look like to Build Backwards to animal models from any existing human data (in this case, the well-characterized effects of the use of THC).

"We had quite a bit of confidence that MAGL inhibitors going into humans would have robust CNS activity based on the human activity of THC and the preclinical comparison of THC effects and MAGL inhibitors in rodents," Cravatt said. "The question was just how do you match that activity to the right clinical indication. We also knew the safety wasn't going to be anything like the risks you see with opioids. People can be on high doses of THC and the clinical safety risk is much lower than opioids."

Today, the Abide MAGL inhibitors are owned by large pharma company Lundbeck, which acquired Abide in 2019 in a $400 million deal.[219] The MAGL inhibitors are now in Phase II clinical trials for Tourette syndrome and in Phase I trials for PTSD, fibromyalgia, MS spasticity, neurology, and psychiatry indications.

While Cravatt and the Abide team did not have clear human genetic data validating MAGL as a target, they were able to de-risk it using human pharmacological information and animal models that were Built Backwards, enabling them to get an early sense of how MAGL inhibition might work in humans. This decreased the biology risk taken by the company, ultimately increasing their chance of success down the road.

In summary, de-risking is a way of Building Backwards. By considering how to minimize downstream risk up front, a company can increase its probability of success. Some ways that may be relevant for a biotech company to do this are:

1. Leave uncertainty outside the company from the outset when possible
2. Be willing to fail fast
3. Select targets with as much human biology data as possible. Embrace technical risk and avoid biology risk

In the industry of biotech, the benefit of de-risking companies and projects to increase the probability of success is especially high. Every new medicine that makes it to the clinic provides hope and options for those suffering from difficult or debilitating medical conditions. Part II of this book has described how you can Build Backwards to lay the foundations to increase the likelihood of this outcome. Next, Part III will delve into greater detail regarding specific business, clinical trials, and intellectual property concepts and how Building Backwards can inform their success.

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167 It should be noted that target-based drug discovery has been the dominant method of drug discovery for the past three decades.

168 Chitra Venugopal et al., "Beta-secretase: Structure, Function, and Evolution," *CNS & Neurological Disorders Drug Targets* 7, no. 3 (June 2008): 278–294.

169 Christopher Southan and John M. Hancock, "A tale of two drug targets: the evolutionary history of BACE1 and BACE2," *Frontiers in Genetics*, December 17, 2013.

170 Such first-in-class targets are extremely risky but extraordinarily rewarding if they work.

171 John G. Moffat et al., "Opportunities and challenges in phenotypic drug discovery: an industry perspective," *Nature Reviews Drug Discovery* 16 (2017): 531–43.

172 Jörg Eder et al., "The discovery of first-in-class drugs: origins and evolution," *Nature Reviews Drug Discovery* 13, no. 8 (August 2014): 577–87.

173 I am focusing here on the drug discovery methodology in which first it is determined whether a molecular target is relevant for the disease you are seeking to treat. Second a drug is developed to "hit the target," and then third it is validated that target results were hit in effective treatment of the disease clinically. However, several successful drugs on the market achieve the desired clinical outcome (i.e., disease treatment), but we are still unsure of the precise molecular target. However, much of drug discovery is conducted by the methodology I am commenting on above.

174 Francesco Panza et al., "BACE inhibitors in clinical development for the treatment of Alzheimer's disease," *Expert Review of Neurotherapeutics* 18, no. 11 (November 2018): 847–857.

175 The companies included Merck, Janssen, Novartis, Eli Lilly/AstraZeneca, and Eisai/Biogen.

176 "New Data from Past BACE Inhibitor Trials Shed Light on Side Effects," *ALZFORUM*, December 16, 2020.

177 "Therapeutics: Umibecestat," *ALZFORUM*, updated January 21, 2021.

178 Phil Taylor, "2. Elenbecestat," *Fierce Biotech*, December 16, 2019.

179 "New Data from Past BACE Inhibitor Trials Shed Light on Side Effects," *ALZFORUM*, December 16, 2020.

180 David Grainger, "Why Too Many Clinical Trials Fail—And a Simple Solution That Could Increase Returns on Pharma R&D," *Forbes*, January 29, 2015.

181 If you are thinking a 25 percent success rate is not nearly as dismal as 5 percent success rate and are trying to figure out why those estimations are so different, it's because *Forbes* is looking at solely the probability of failure during the narrow window of Phase II/III trials rather than the probability of failure in the development process from beginning to end. Looking at the probability of failure at the beginning of the development process alone leaves room for more chances to fail, resulting in a higher probability of failure.

182 It should be noted that most likely, nothing any different could have been done to alter the outcome for the BACE inhibitors specifically. Rather, this example serves to highlight just how disappointing late-stage clinical failure can be.

183 "Charles River Laboratories Acquires Distributed Bio," *Distributed Bio*, January 4, 2021.

184 Nathaniel Brooks Horwitz, "Go/No Go," Medium, November 26, 2018.

185 The American Cancer Society medical and editorial content team, "Survival Rates for Pancreatic Cancer," American Cancer Society, updated February 12, 2021.

186 Note that deactivating the pathway at this stage was not done with a drug, as no drug was yet discovered, but with genetic manipulation. This is a common research technique

to study potential drug targets, but for obvious reasons, it is not a viable strategy therapeutically in humans.

187 The Kirschner lab accomplished deactivating the Hippo pathway by using CRISPR knockouts and siRNA knockdowns—not through a pharmacological agent, which did not yet exist.

188 Nathaniel Brooks Horwitz, "Go/No Go," Medium, November 26, 2018.

189 Taranjit S. Gujral and Marc W. Kirschner, "Hippo pathway mediates resistance to cytotoxic drugs," *Proceedings of the National Academy of Sciences* 114, no. 8 (May 2017).

190 Nathaniel Brooks Horwitz, "Here's what happened when I tried to develop a new drug for a deadly cancer," *Washington Post*, January 12, 2019.

191 Ibid.

192 Nathaniel Brooks Horwitz, "Back to Boston," Medium, July 16, 2018.

193 [Homepage], National Cancer Institute.

194 Horwitz is referring to progression free survival (PFS) or overall response rate (ORR), which are endpoints sometimes used in approving new cancer drugs. Progression free survival—or PFS—measures the amount of time a patient lives with the cancer but the cancer does not get worse. However, this metric often doesn't correlate with longer lifespan. Similarly, overall response rate—or ORR—measures the proportion of people who experience a decrease in the size of their tumor, which also might not correlate to longer lifespan. Horwitz caveats this by explaining that patients caring largely about OS and less about PFS/ORR is a more recent phenomenon. Abraxane, for example, improved median overall survival by just five weeks, Horwitz said. At the time, this was significant when median overall survival was only around six or seven months. Nowadays, however, patients are generally much more sensitive to adopting therapies characterized by marginal benefit, often severe side effects, and a cost that can easily reach hundreds of thousands of dollars a year.

195 To be fair, in the case of BACE, it's not at all clear that experiments could have been run earlier to prove that inhibiting BACE would not sufficiently treat Alzheimer's in human patients.

196 Ryan Cross, "Bayer acquires small molecule startup Vividion Therapeutics for up to $2 billion," *Chemical & Engineering News*, August 5, 2021.

197 Leslie A. Pray, "Gleevec: the Breakthrough in Cancer Treatment," *Nature Education* 1, no. 1 (2008): 37.

198 "How Imatinib Transformed Leukemia Treatment and Cancer Research," National Cancer Institute, updated April 11, 2018.

199 Ibid.

200 Oliver Hantschel et al., "Target spectrum of the BCR-ABL inhibitors imatinib, nilotinib and dasatinib," *Leukemia & Lymphoma* 49, no. 4 (2008).

201 Marc Brehme et al., "Charting the molecular network of the drug target Bcr-Abl," *Proceedings of the National Academy of Sciences of the United States of America* 106, no. 18 (May 5, 2009): 7414–7419.

202 "BCR-ABL fusion gene," National Cancer Institute, accessed October 20, 2021.

203 "How Imatinib Transformed Leukemia Treatment and Cancer Research," National Cancer Institute, updated April 11, 2018.

204 Ronald Piana, "Groundbreaking Cancer Researcher Brian J. Druker, MD, Shows No Signs of Slowing Down," *The ASCO Post*, March 25, 2021.

205 Ibid.

206 Stephen S. Hall, "Genetics: A gene of rare effect," *Nature* 496 (April 9, 2013): 152–155.

207 Derek Lowe, "What PCSK9 Is Telling Us about Drug Discovery," *Science*, March 20, 2017.

208 "Landmark deCODE genetics Study Points to a New Mechanism that Affects Cholesterol Levels and The Risk of Heart Disease," Amgen, accessed October 20, 2021.

209 Marianne Abifade et al., "Living the PCSK9 Adventure: from the Identification of a New Gene in Familial Hypercholesterolemia Towards a Potential New Class of Anticholesterol Drugs," *Current Atherosclerosis Reports* 16, no. 9 (September 2014).

210 Nihar R. Desai and Marc S. Sabatine, "PCSK9 inhibition in patients with hypercholesterolemia," *Trends in Cardiovascular Medicine* 25, no. 7 (October 2015): 567–574.

211 "Sanofi and Regeneron Announce FDA Approval of Praluent® (alirocumab) Injection, the First PCSK9 Inhibitor in the US, for the Treatment of High LDL Cholesterol in Adult Patients," Sanofi, July 24, 2015.

212 "FDA Approves Amgen's New Cholesterol-Lowering Medication Repatha™ (evolocumab)," Amgen, accessed October 20, 2021.

213 Erik SG Stroes et al., "PCSK9 inhibitors: Pharmacology, adverse effects, and use," UpToDate, updated September 14, 2021.

214 Sharon Liao, "What You Need to Know about PCSK9 Inhibitors," WebMD Medical Reference, May 27, 2020.

215 C.J. Fowler, "Monoacylglycerol Lipase—a Target for Drug Development?" *British Journal of Pharmacology* 166, no. 5 (July 2012): 1568–1585.

216 Ibid.

217 Giulia Donvito et al., "The Endogenous Cannabinoid System: A Budding Source of Targets for Treating Inflammatory and Neuropathic Pain," *Neuropsychopharmacology* 43 (August 31, 2017): 52–79.

218 C.J. Fowler, "Monoacylglycerol lipase—a target for drug development?" *British Journal of Pharmacology* 166, no. 5 (July 2012): 1568–1585.

219 "Lundbeck to purchase Abide Therapeutics in $400m deal," Pharmaceutical Technology, May 7, 2019.

PART III

BUILDING

CHAPTER 8

BUILDING BACKWARDS TO AN EXIT

"Great is the art of the beginning, but greater is the art of the ending."

—HENRY WADSWORTH LONGFELLOW

Back in my first year of business school, I was finding seats before class one day with my friend, Scott Walbrun (now a venture investor at BMW Ventures).

"Where should we sit?" I asked him.

Scott is always thinking strategically, and I suspected something as simple as finding seats would be no different. He didn't disappoint.

"Here," he said, motioning to some aisle seats positioned close to the door. If you had to get up in the middle of class, these would be the least disruptive seats in the classroom.

I pointed this out to him, inquiring about his logic. With a very serious expression, he turned to me. "Stephanie, lesson number one," he said. "*Always* have an exit."

While classroom seating arrangements serve as a lighthearted example, Scott's words of wisdom nevertheless hold true in business. It's always wise to have an exit strategy.

What's an exit strategy? An exit strategy is a plan for an entrepreneur and/or investors to eventually sell their ownership in the company, whether to another company or on the public

markets.[220],[221] Just as it was important to Build Backwards in *starting* a business, it is equally—if not more—important to Build Backwards in order to get *out* of a business.

Why is an exit so important, and why would you want to get "out" of a business?

An exit is typically part of the start-up "life cycle" because an exit serves as a start-up's "path to liquidity," i.e., your moment to transform your investment of time, blood, sweat, and tears into actual cash.[222] To put it simply: it is often when founders and investors can (more or less) begin to realize the majority of their financial return.

Thus, a simple model of how exit often fits into the start-up "life cycle" is the following:

CAPITAL INVESTED IN COMPANY→ COMPANY GETS BUILT→ EXIT (initial public offering—IPO—or merger and acquisition—M&A)→ CASH RETURNED TO INVESTORS AND ENTREPRENEURS

In start-ups, then, exit strategy is something investors care a lot about. This is because investors usually have their own set of investors, and investors' investors often want to see a return on their capital in less than ten years.[223] The way investors get to realize this return is only if that initially invested capital is no longer tied up within a company and instead has become liquid (i.e., cash). It's much more difficult to reach this point if you do not Build Backwards to an exit from the beginning, understanding that the

exit path appropriate for your company will often change as your company does.

In addition, an exit is also about passing the "baton" to the appropriate party to carry the company to the next stage of growth. As discussed in prior chapters, a large pharma company has multiple developmental advantages in carrying a program forward that can make an acquisition a potentially appealing route. An IPO, on the other hand, can provide both an immediate and potential future source of growth capital if founders are not yet ready to sell.

The last two biotech deals start-up advisor and angel investor Robert Okabe structured for the University of Chicago resulted in the two largest initial funding rounds ($22 million and $10 million) for technology start-ups in the history of the school. One of them completed its October 2021 IPO in less than three years from its start. When I asked him about how biotechs should conceptualize exits, he gave an analogy. "When I'm driving on the freeway, I have a choice to take the often-faster express lanes or the slower but more flexible local lanes. The express lanes do not have access to every exit that is available from the local lanes," he said. "So, I have to plan ahead. Is the higher speed of the express lanes the better choice or can I take advantage of multiple exit options if there's an accident on the freeway? I always have an awareness of which option is appropriate for each trip. If I see an alternative exit that will be a better way to get to my destination, I can make sure I'm in the correct lane."

In other words, Building Backwards to an exit often entails maintaining an awareness of "which exit is appropriate" at every moment in time. This knowledge subsequently informs which "lane" it makes sense to utilize to get there.

In biotech, an exit is usually one of the following:

1. An acquisition (i.e., mergers and acquisitions, or M&A)—your company is bought by another company[224]
2. An initial public offering (IPO), also called "going public"—your company becomes "publicly traded" on a stock exchange (think NASDAQ or the New York Stock Exchange)

We will discuss these two options further below. The key point to understand is both exit types can provide liquidity and high returns to investors and founders when executed well. Therefore, it's important for founders to Build Backwards from potential exit strategy at the start and then continually as the company grows. Even from the very first round of funding, investors usually want to hear that you have a plan to reach exit. Further, the exit strategy that makes the most sense for your company will likely evolve over time.

A IS FOR ACQUISITION

An acquisition is exactly what it sounds like. It's when a corporation—in biotech this is often a large pharmaceutical company—purchases another company.

To quickly review some points from previous chapters, start-up companies—in this case biotechs—tend to be especially good at innovating and being nimble. They tend to be excellent at finding cutting-edge technologies, investigating new ideas, and beginning the process of development. However, small companies, by definition, may have a good idea or core concept, but they often lack the capital and resources (relationships, distribution channels, manufacturing scale up, a designated sales force, etc.) to easily develop that idea to its fullest potential.

The solution? An acquisition by what is often a larger company that has both capital and resources will help *both* companies succeed. It's a good deal for the biotech company, which then doesn't need to build out infrastructure for commercialization activities as well as for the Big Pharma acquirer, which benefits from the addition of a new but somewhat de-risked program to its portfolio. It's also a good deal for the founders of the biotech company, especially as the acquiring company (i.e., the company buying the start-up) often pays a premium, and the founders get to see their technology advance.

As Bruce Booth puts it:

"… A reality in biotech: it's hard to escape the gravity of the balance sheets of larger firms. These big firms need external innovation to feed their pipelines and salesforces. This cycle of life often makes sense: the biotech takes the early stage R&D risk to bring new product candidates forward, and bigger firms take the later stage and commercial risks to get those to patients around the globe… [this] underpins the price behavior of a lot of biotech valuations, as there's an expectation great emerging companies will get acquired (e.g., Loxo, Juno, Kite, etc)."[225]

Thus, an acquisition is usually beneficial to all parties.

SETTING UP A BIDDING WAR

Part of Building Backwards to a potential acquisition is positioning yourself for what Keith Crandell, who has sold multiple companies as an ARCH managing director and cofounder, refers to as a bidding war. When selling a company, much like selling another big-ticket item like a house, you will typically get the best price by having multiple interested buyers bidding against each other.

Therefore, it's wise to ask early in a company's life whether not only one but ideally *several* potential acquirers exist for the technology. If the potential product is too "niche," creating a bidding war becomes much more difficult.

Crandell emphasized Building Backwards from a future bidding war can also inform other developmental business questions. "You need to develop a company that is readily valued by a variety of other potential acquirers," he said. "So, part of what you spend your money on needs to be helping create a desirable product that's easily integrable into other people's businesses and easily understood as additive to their particular businesses."

For a non-biotech example, consider how the Building Backwards strategy came into play early in a company's life. My friend Troy Schrock owned a landscaping business in which his company mostly did one-off projects for families and businesses. Troy was aware from the beginning of the company there were minimal acquisition opportunities for landscaping businesses, even highly profitable ones. Why? Because landscaping is largely a one-off project business, there is no **contract for future work.** In other words, there is no promise of reliable, recurring revenue. Each one-off project Troy's company was hired to do did not guarantee a next one-off project. He had to rely on constantly attracting new customers.

Troy learned potential acquirers were only interested in acquiring landscaping companies that had large contracts because the contracts represented the promise of future revenue—even if the business were to change hands. Thus, he made the decision to expand the business into fertilization, which was known to be a contract-based enterprise. Clients, such as country clubs, would give Troy a contract to do monthly fertilization services for them into the

future rather than the one-off projects Troy had largely been focusing on previously. In bringing on new services, Troy made his customers "stickier" and thus made the business more attractive to a future acquirer. Even though he was not yet ready to sell the business, he Built Backwards to ensure someday he *could*.

How might this look in biotech? Considering which indications are most highly valued by Big Pharma might be a helpful lens through which to consider market selection. This connects to questions you should be asking in customer development.

UNDERSTANDING VALUATION IN M&A[226]

A "valuation" is a way of describing the worth of your company (for more info on this, see chapter 9 next). One of the primary valuation methods in biotech is performed by conducting a precedent transactions analysis (example shown below).[227] Such transactions, which use numbers from previous M&A deals of companies that are economically similar to your company, can act as guideposts for projecting a future valuation from an M&A. In seeking out relevant data points, one ought to consider both (a) similar indications and (b) companies acquired while in similar phases of development.[228]

For example, see the below set of precedent transactions relevant to Seurat, whose flagship drug candidate (a) targeted migraines and (b) was in the preclinical/proof-of-concept stage (although we expected Seurat would more likely be acquired in Phase I or after). These numbers give an approximate idea of what Seurat might be acquired for, at any given phase:

Target	Acquirer	Phase	Value	Drug Type	Market
Oculeve	Allergan	I	$125M	Dry eye	24M patients
Abide Therapeutics		II	$400M	Tourette Syndrone	0.3M patients
Protez Pharmaceutical	NOVARTIS	I	$400M	Recurrent hospital infections	0.1M patients
Catalyst Biosciences	Attenua	I / II	$106M	Alzheimer's and ADHD	15M+ patients
Labrys	teva	II	$825M	Anti-CGRP migraine	14M patients
CoLucid	Lilly	III	$960M	Acute migraines	16M patients

Precedent transactions for proof-of-concept exits. This list of historical deals in similar indications, clinical stages, and market sizes gives an important indication of potential exit value. Courtesy of Seurat Therapeutics, Inc.

While every company and technology is different, this is powerful evidence there is an opportunity for an M&A event for the company. Obviously, the more interest there is in an asset, the greater the potential exit figure, as companies compete for your asset.

Crandell emphasized the importance of strategic partnerships as, in his experience, they can often lead to an acquisition down the road. Particularly for indications that wouldn't typically attract investment from venture, support from strategic partnerships demonstrates buy-in and investment on the part of the investing companies. It is also a valuable relationship for the partner, as they are given a "seat at the table" as the business grows. For example, Distributed Bio, an antibody discovery business, was eventually acquired by Charles River Laboratories—the same company with which they formed a partnership more than two years prior to the acquisition—for $104 million.[229]

GOING PUBLIC: THE IPO ROUTE

An IPO is often considered an exit, even though the act of going public is not, itself, an exit. To understand this statement, it's crucial to first clarify more about how IPOs work.

When a company "goes public," this is typically referred to as a "primary offering." The company sells *new* shares (that are not investor or founder held) to public investors. This is advantageous for the company because the sale of these shares allows the ***company*** to raise capital, which is why IPOs are also often thought of as a financing round, resulting in dilution for existing investors and founders. This dilution is typically on the order of 20 to 25 percent.[230] However, a primary offering does not result in an exit. Founders and investors need to actually *sell* their shares in order to obtain liquidity. This process is referred to as a secondary offering.[231]

After a company becomes publicly listed (i.e., its shares become bought and sold on stock exchanges such as NYSE, NASDAQ, etc.), the founders and investors in the company are then able to begin to slowly exit their positions by selling their shares on the exchanges (or distributing them to their limited partners).[232] These are called secondary sales, as you are not issuing new shares. Thus, secondary sales *return capital to* ***investors and founders***, *not* to the company directly. Typically, investors and founders have to hold on to their shares for at least 180 days following an IPO (known as a lockup period).[233]

Achieving liquidity after an IPO is not without its challenges. Specifically, investors and founders must consider the timing of selling their shares, as the amount of a particular stock that is sold per day can be limited. Further, a single stockholder often does not want to be more than 25 percent of the daily volume of stock traded in order to prevent downward pressure on the stock price.[234] Therefore, when an investor is holding hundreds of millions of

dollars' worth of stock, it can take up to hundreds of days to fully exit.[235]

As of late 2021, the public biotech markets have been rapidly growing over the past decade.[236] With this increase in capital, there has been an increase in biotech companies pursuing an IPO as an exit strategy. According to an analysis by Bruce Booth, the number of public biopharma companies has nearly tripled since 2012 with over 620 biopharma companies listed on the NASDAQ and NYSE as of March 2021. Further, total biotech financing activity for IPOs and public follow-ons (i.e., when more shares are offered in a primary offering after the IPO) grew 86 percent between the first quarter of 2019 versus the fourth quarter of 2020, and the biotech stock market index ($XBI) increased 76 percent over that same period.[237] Thus, the public markets have been becoming increasingly friendly to biotech IPOs.

Crandell estimates a 30 to 40 percent increase in valuation when a company goes from private to public because more investors are in public markets compared to private ones. (In investment banking, this effect is often referred to as the "liquidity premium.") In the latter, only specialized institutional investors can buy in.[238]

IPOs are also seen as prestigious "branding events" for a company. One example of why this is the case is that when a company goes public, they take part in what *The Wall Street Journal* refers to as a "glitzy bell-ringing ceremony." In this ceremony, CEOs, employees, and early investors assemble on a podium at the NASDAQ or NYSE and ring the bell that commences the start of daily trading.[239] This moment is a celebration of the IPO as a major milestone in the company's life and is even broadcast on television. This type of publicity is part of what shapes the perception of going public as a

demonstration of leadership in a particular business segment as well as a sign of endorsement from private and public investors alike.

Combine the increased access to capital with the "prestige" of an IPO, and it can be tempting for companies to want to go this route, said Booth. "Whether warranted or not, taking a company public via an IPO is tantamount to grabbing the proverbial brass ring, a publicly recognized marker of success," he said. "Unfortunately, it's not always the right choice for shareholders."[240]

Keeping the long-term prospects of his company in mind, one pharmaceutical CEO said, "The best reason to go public isn't to exit. It isn't to get the going-public experience. It's because it's the right step in the path on which you're guiding your company."[241,242]

IPO VERSUS M&A:

Both IPOs and M&As come with pros and cons. Booth emphasizes the following as the major differences:[243]

- **Risk/return profiles:** An M&A usually comes with the potential to earn "milestone" payments down the road. Much of the value of the deal could be in these milestone payments, which often have to do with the drug succeeding in various clinical trials and/or sales milestones (e.g., greater than $500 million in revenue). In an M&A, you are sharing downstream risk with the acquirer—which is beneficial—but you are also sharing the reward for that risk. In an IPO, you receive more of the downstream upside, but there are also downsides to being involved in the company for longer (i.e., increase in risk).
- **Time to liquidity:** While an M&A offers liquidity at the time of the deal, an IPO can take years to exit (particularly, Booth notes, for "thinly traded stocks or for insider shareholders").

- **Dilution:** Going public can result in a 20 to 40 percent dilution for existing shareholders, as new securities are often issued for the primary market. This decreases shareholder returns. In contrast, an M&A does not decrease shareholder returns.

Thus, weighing the anticipated respective valuations for each scenario can inform decision-making about which exit plan makes sense at the time of exit.

OVERLAP IN EXIT STRATEGY

In Building Backwards to exit, there is some overlap in preparing for each potential outcome.

For example, the market comparables (such as in the figure above) are also helpful in preparing for an IPO; as for the IPO process, you will need to be able to demonstrate that companies similar to your own were able to achieve particular valuations.

Second, the prospect of an IPO can also lead to M&A interest. Companies that may have been monitoring your progress might, upon learning of IPO plans, make an offer. Specifically, shopping your company around to potential acquirers is sometimes incorporated into the IPO process (where the IPO is the "stalking horse," referred to as a "stalking horse strategy") to give a company a strong second alternative to going public. In other words, part of preparing for an IPO involves meeting with large institutions that could be potential acquirers in order to determine if they would be interested in participating in the IPO. This can sometimes drive up valuation and result in an acquisition offer.

In addition, integral to preparing to go public is obtaining buy-in from institutional investors, which include mutual funds, hedge funds, banks, insurance companies, pension funds, and other

corporate finance intermediaries.[244] Part of securing buy-in from these parties is demonstrating you have thought about the strategic options in the M&A markets and have considered a variety of exit and funding alternatives. Therefore, part of getting IPO-ready involves thinking through all potential acquisition options.

As an example of how initially pursuing one exit strategy can potentially lead to another, Vividion Therapeutics (cofounded by Ben Cravatt, mentioned in chapter 2, and founding investment made by Kristina Burow of ARCH, mentioned in chapter 6) had been planning to go public up until June of 2021 when it was given an acquisition offer by Bayer, a large pharmaceutical company, for $1.5 billion up front and up to $500 million in milestone payments.[245] According to the company, it was "won over" by Bayer's offer.

Cravatt touched on some of the advantages and disadvantages of M&A versus IPO that we have been discussing here in an interview with *Biopharma Dive*. Access to Bayer's substantial resources, Cravatt said, would allow Vividion to make fewer "trade-offs" and develop more medicines than it could have otherwise developed had it gone public and remained an independently operating company. "When a small biotech company has to take a product all the way through deep clinical development and commercialization, it's a huge cost," said Cravatt. "[The acquisition] became a much more preferred path for us, relative to an IPO path, where we would have been successful but would have had to continue to pursue our many opportunities in what I would consider a somewhat arbitrarily defined prioritization."[246]

Vividion considered what was best for the future of the company and its technology as a whole in its choice of exit path. It was driven by the needs of the company rather than by the desire to achieve an exit in and of itself. By doing so, Vividion positioned its technology

to best succeed into the future and therefore allowed both its investors (Burow) and founders (Cravatt) to achieve an exit.

BUILDING FOR THE LONG TERM

This leads into the next important point. Building Backwards to an exit does not trivialize the significance of simultaneously building a company for the long term.

As Kristina Burow stressed in chapter 6, "The best way to optimize for a terrific outcome is actually to build a company for the long term." She explained that while it's important to think about the opportunity to exit, at the same time, it's crucial to ensure that focus on an exit does not lead to shortsighted decision-making.

In other words, the goal of building any business is not *solely* to exit. It is also to establish an organization that is creating *long-term* value. Ironically, these companies, i.e., those with a clear long-term vision, often attract players who can ultimately drive an exit, such as institutional investors (who can participate in an IPO) or potential acquirers.

As Burow emphasizes, if your start-up succeeds at what it sets out to do, "it's highly likely that along the way, the company will get acquired because most [successful] companies are."

Therefore, best practice is to build your company as a solid endeavor capable of lasting beyond its own sale. Yet, it's wise business practice to plan for exit from the start by Building Backwards.

According to Crandell, the best way to Build Backwards to both a future acquisition or IPO is (as discussed in chapter 5), to continue to "interact in the marketplace."

"A key aspect of building toward an exit is trying to be relentless in testing your hypothesis about market receptivity. Gain primary knowledge from potential customers, and that informs your decisions," Crandell said. "For example, if you find from talking to people that you have to build your own distribution network before you can accept one customer's dollar, maybe the time is right to sell. On the other hand, if there is a [lot of excitement] in that market segment, you may be able to continue to access capital to grow, scale, and hold out to sell for a bigger opportunity." In other words, talking to potential customers can provide early clarity around both exit type and timing.

In conclusion, both types of exits can be highly profitable. As in the example of Vividion, the most important aspect of Building Backwards to an exit is to continuously make choices that are in the best interest of the company's longevity while never losing sight of the seats closest to an exit door.

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220 Note that this can be done all or in part.

221 Adam Hayes, "Business Exit Strategy," *Investopedia*, October 31, 2020.

222 Note that I am oversimplifying this a bit, as a variety of structures effectively result in an exit without literally resulting in cash. For example, you can get acquired and receive stock that comes with a two-year lockup period as compensation (i.e., you are not allowed to sell, converting your stock to cash, for two years). Also, founders who do not want to sell can often "rollover" their equity into shares of the acquiring company, or they can choose to continue to hold their shares in the case of an IPO.

223 Investors in the business you built (i.e., general partners) give you money on behalf of their own investors (i.e., limited partners)

224 Within this category, there are both strategic buyers (corporations) and financial buyers (e.g., PE firms). Biotech companies are often acquired by the former, so they will be the focus of this chapter.

225 Bruce Booth, "Five Macro Risks to Biotech Coming Out of Washington," Life Sci VC, April 22, 2021.

226 Note there are multiple other ways to value a company. The way shown in this chapter, using comparables, is often the most appropriate for a pre-revenue biotech company. Other valuation methods are often heavily revenue based and tend to be less helpful for early-stage biotech.

227 This is often the method employed to value biotech companies for two reasons. First, because biotech companies are often acquired before they ever have a revenue stream by which to value. Second (and to get into finance detail a bit more), many biotech companies—if their medicines make it successfully to the market—theoretically have the potential to do hundreds of millions or billions of dollars or more per year in sales. Thus, the relevant term in valuing the company becomes more about the discount rate utilized, which can be difficult to accurately access. Thus, looking at comps is often more reliable.

228 Other comparable characteristics that could be used include therapeutic modality (e.g., small molecule, monoclonal antibody, cell/gene therapy), geography of the company, drug target, disease area (e.g., orphan indication/rare disease, autoimmune, immuno-oncology).

229 "Charles River and Distributed Bio Enter Exclusive Partnership to Create an Integrated Antibody Discovery and Development Platform," Charles River, October 25, 2018.

230 Bruce Booth, "Evolution of the Biotech IPO Markets from Busted to Booming," Life Sci VC, September 21, 2020.

231 Bruce Booth, "Biotech IPOs: The Exit Challenge as Lockups Expire," Life Sci VC, October 31, 2013.

232 Ibid.

233 Ibid.

234 Ibid.

235 Bruce Booth, "Tradeoffs and Timing: IPO vs. M&A Decision Making in Biotech," Life Sci VC, April 2, 2014.

236 Bruce Booth, "Biotech's Relevancy Challenge in an Expanding Universe," Life Sci VC, June 1, 2021.

237 Ibid.

238 This increase in valuation can serve to offset or somewhat offset dilution from the IPO. (Dilution is discussed in further detail in chapter 9.)

239 Corrie Driebusch, "The (Opening) Bell Tolls for Thee—If You're Lucky," *The Wall Street Journal*, August 10, 2021.

240 Bruce Booth, "Tradeoffs and Timing: IPO vs. M&A Decision Making in Biotech," Life Sci VC, April 2, 2014.

241 “Guide to going public: Strategic considerations before, during and post-IPO,” EY, 2018.

242 Note that going public can allow the founder to retain ownership in their company while the earlier institutional investors are able to sell their shares.

243 Bruce Booth, “Tradeoffs and Timing: IPO vs. M&A Decision Making in Biotech,” Life Sci VC, April 2, 2014.

244 “Guide to going public: Strategic considerations before, during and post-IPO,” *EY*, 2018.

245 Ryan Cross, “Bayer Acquires Small Molecule Startup Vividion Therapeutics for up to $2 Billion,” *Chemical & Engineering News,* August 5, 2021.

246 Shoshana Dubnow, “How Bayer lured a biotech away from an IPO and into a buyout,” *BioPharma Dive*, August 5, 2021.

CHAPTER 9

BUILDING BACKWARDS TO AN EFFECTIVE FINANCING PLAN

"You want to be thinking about how you're going to slay the dragon of finding financing from the beginning of the company's life… the question of where the next set of dollars are going to come from should never leave your consciousness…"

—KEITH CRANDELL, COFOUNDER AND MANAGING DIRECTOR OF ARCH VENTURE PARTNERS

I was pitching a biotech company to a prospective investor and had just finished talking through the slide on valuation for comparable companies—in other words, projected exit options. I was about to advance to the next part of the presentation when the investor asked a follow-up question. He wanted to know what our current near-term and long-term milestones were that would move us closer to an exit.

This is a standard question, and I was prepared for it. I advanced to the slide in our deck that showed our financing strategy for the current raise. "This is a full development plan for our lead asset," I said. "Therefore, right now, we are raising $25 million to advance our lead program through a Phase I trial, but ultimately, we believe we will likely be acquired later."

Our financing strategy was intimately related to the company's development plan, including exit strategy. By Building Backwards in

planning our financing strategy, I was able to anticipate and answer the follow-up question.

Building Backwards from the end of the drug development process provides a basis for creating an effective financing strategy.

THE SEARCH FOR FUNDING

The search for funding is often an ongoing process in the life of a biotech company because biotech companies often do not earn revenue, they have high capital costs, and they tend to be acquired long before drug approval (and therefore a potential revenue stream) occurs.

While the primary mission of any biotech start-up is to develop a drug candidate through the steps of the FDA process, this is not possible without a well-thought-out finance plan. Such a finance plan must reflect the costs and timing of this process in addition to the realities of the investor marketplace.

In order to understand the potential stakes involved when thinking through financing strategy, consider the following example story from a previous client.

RAISING THE STAKES

I was on the phone with both a new client, Company B, and a prospective investor. I had just begun working with Company B, and after signing an NDA, it had asked me to join as a silent listener for this meeting.[247] We were talking about raising capital for the next milestones in Company B's development.

"How much money are you looking to raise for your Series A?" the investor asked.

"We want to raise $400 million," Company B said confidently. Company B went on to list the multiple things it would do with $400 million, including all three stages of clinical trials.[248]

I swallowed hard. As this was our first official call after signing the NDA, Company B had not yet told me the amount of money it was planning on raising, though I knew B should likely be asking for a (much) smaller number. Further, it is very uncommon for a company to get more than two phases of funding in a single round, and it had asked for three.[249]

The company was only in the preclinical stage. That combined with what I knew of this particular company meant that the company's total value—called the ***valuation***—was probably only around $1 million. (It was a particularly early-stage spinout company, but this is a low-side estimate, as you will see later on in this chapter.) To raise $400 million would mean Company B was likely giving away 99.8 percent of the value of the company to the investors.

How does this math work? The ***Pre-Money Valuation***, or the value of the company ***before*** investment, is the main factor in determining how much equity is given away. The amount of money being raised from *all* investors participating in the financing round is the second factor that determines how much equity is given away. Calculating the percent of a company the investor is "buying" with his or her investment is calculated as:[250]

$$\%\,of\ company\ sold\ to\ investors = \frac{\$\ raised}{(\$\ raised) + (PreMoneyValuation)} \times 100\%$$

Thus, to calculate the percentage of the company maintained by the founders:

$$\%\ of\ company\ held\ by\ founders = 100\% - (\%\ of\ company\ sold\ to\ investors)$$

(Note that the dollars raised plus the Pre-Money Valuation is known as the ***Post-Money Valuation***, or the value of the company ***after*** investment. This is logical, as the existing value should go up by the added value, i.e., the cash going into the company).

Therefore, Company B's post-investment founder's ownership percentage would be:

$$= 100\% - \left(\frac{\$400,000,000}{(\$400,000,000 + \$1,000,000)} \times 100\% \right) = 0.02\%$$

When raising capital from VC investors, you are often effectively selling some level of ownership in the company (i.e., equity) in exchange for upfront cash. In addition, however, a company gains the ability to pursue value-building, capital-intensive investments only possible with cash on hand that, in turn, raises the value of the company.[251]

The company's value is represented by:

$$Valuation = n \times p$$

$$n = number\ of\ shares\ issued\ and\ outstanding$$

$$p = price\ per\ share\ of\ stock$$

Therefore, owning a certain number of shares of the company also represents owning a certain percentage of the company's total shares. This, in turn, represents owning a certain percentage of the company itself.

In this case, raising $400 million at a $1 million Pre-Money Valuation would mean B would lose "control" of the company by giving the majority of the company away to new investors who would own 99.8 percent while B would own 0.2 percent.[252,253]

In short, this was likely a bad deal. We needed a better financing plan. We needed to Build Backwards.

THE DILUTION DILEMMA

This phenomenon of raising capital by "selling" ownership is called "dilution." Dilution is largely inevitable in biotech, and it's a normal part of growth. However, when carried out as in the example above—which is to say, *without* Building Backwards—dilution can quickly become too much. The company can become so diluted it throws into question the benefit to the founders of building the company at all. Unlike Facebook, for instance—in which founder Mark Zuckerberg maintains a substantial equity stake to this day—biotech companies often require financial raises in the range of hundreds of millions of dollars just to demonstrate an early proof of concept. Developing many tech companies, including companies based on a social media platform or electronic devices, does not require hundreds of millions of dollars simply to reach initial revenue.

Biotech faces the signature hurdle of raising capital to such an extent because scientific research, clinical trials, and manufacturing can cost hundreds of millions of dollars to complete. However, it's important to understand dilution (at a reasonable level) is acceptable. While your percentage ownership goes down, the value of your shares increases because of the increase in valuation. (We will discuss this further below.) Remember you are ultimately raising capital *to create more value* through that capital.

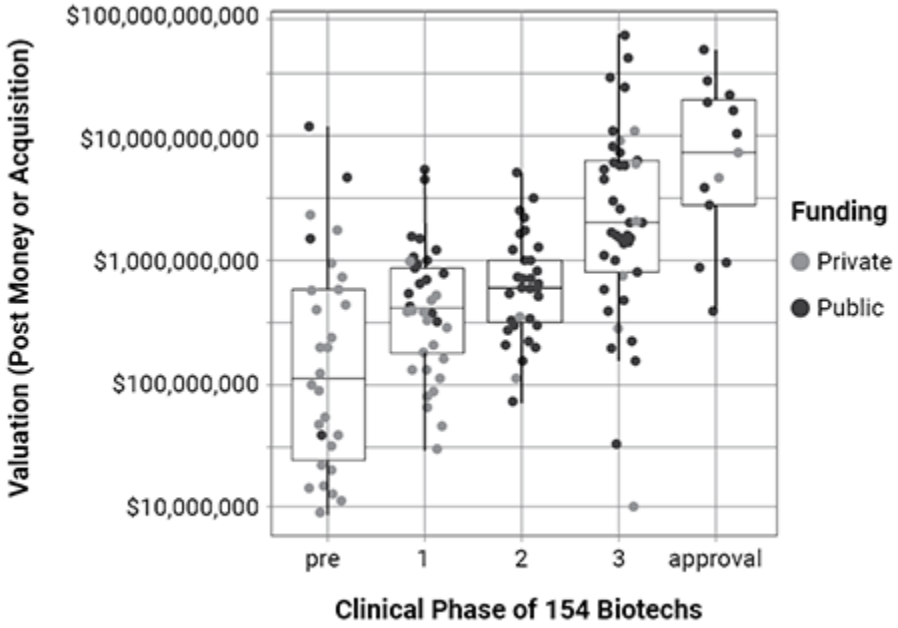
It is also worth noting that despite financial challenges around capital needs, biotech entrepreneurs are often uniquely dedicated to their companies for reasons much greater than profit. These entrepreneurs usually want to make a difference in the lives of

patients, so they might be willing to build a company even when there is little potential for high personal profit.

This altruistic spirit is honorable, but to attract more aspiring entrepreneurs into this sector, it's crucial a potential biotech entrepreneur understands and prepares for both the exciting and foundational realities of how financing works. The Building Backwards approach stresses the importance of thinking through the financing strategy by conceptualizing the development process at the beginning. We will start by learning how valuation fits into this process.

UNDERSTANDING VALUATION[254]

As illustrated by the figure below, another hallmark of biotech is the fact that the valuation increases 1) sharply, not gradually, and 2) the valuation is based on where a company is in a distinct stage of development.



Post-Money valuation of 154 biotech companies by stage. As a biotech company progresses through the various developmental stages, its valuation sharply increases (note the log scale: the valuation increases at each stage are massive!) The x-axis charts the progression of the company from "pre" (preclinical), to "1" (Phase I trials), to "2" (Phase II trials), to "3" (Phase III trials), to "approval" (FDA approval). Image was created by Jacob Glanville and me using data from Crunchbase, Pitchbook, and publicly available market cap information and press releases from 154 biotech companies.

As you can see in "Post-Money valuation of 154 biotech companies by stage," as a company progresses from preclinical to Phase I, then Phase II, Phase III, and eventually FDA approval, its valuation increases in a step function. (Note that all the milestones within the preclinical phase are merged into one group in this graph, and preclinical phase lumps many companies with different levels of preclinical progress under the same label, which explains the large variability of data points there.) Thus, reaching Phase I, for example, is also reaching a ***value inflection point*** because at this point of progress, the value of the company increases to reflect a Phase I level valuation. Reaching each of the following milestones are other value inflection points because the valuation increases sharply again each time.

Overall, the company's ***progress through the scientific/technological/clinical development process*** and the company's ***valuation*** are ***intimately related and bound together.***

Recall another point from chapter 2. The failure rate of a drug is highest earliest in its life. In the early discovery phase, the probability of failure has been cited as being as high as 96 percent.[255] As the drug progresses, its probability of failure overall continues to decrease.[256] Therefore, another key concept is **as a drug progresses and value inflection points are reached, the *valuation* of the company *increases*, and the *risk* of the program *decreases*.** This makes logical sense. Decreasing risk is associated with gathering

more data, and gathering more data also serves to progress the company, increasing its value (or valuation).

To think of this in terms of expected value, at stage X, there may be a 97 percent chance of failure (company is worth zero dollars), and a 3 percent chance of success (company is worth, say, $1 billion). Thus, expected value is $30 million. At stage X+1, there is a lower chance of failure and a higher chance of success—say, a 50 percent chance of failure (company worth zero dollars) and a 50 percent chance of success (company worth $1 billion), thus expected value is $500 million.

Another important point is that increasing valuation is crucial for existing investors to consent to raise the next round of financing. The increase in valuation would then more than offset any dilution they undergo.

DEFINING VALUE INFLECTION POINTS

The way to minimize dilution while still building value is to fundraise in tranches that correlate with value inflection points.[257] Fundraising in tranches means that instead of raising your money all at once, you instead raise the minimum sufficient (or often, slightly greater than the minimum sufficient) amount of money you need to push your company to the next value inflection point.

This is because as discussed before, every time you raise money, you give away a portion of your company in equity. ***The less money you have to raise and the higher the Pre-Money valuation of the company, the less equity you need to give away.*** Thus, if you can choose to *time* a raise for a given amount of money to occur when the valuation is *higher*, you are *giving away less of the company to raise the same amount of money.*

Therefore, it is advantageous to time fundraising rounds to coincide with when the company reaches its next value inflection point.[258] An example of this from the figure "Post–Money Valuation of Biotech Companies by Stage" is waiting until a company has reached Phase II trials to raise money rather than doing so mid-Phase I. By waiting, the company was able to reach a new valuation inflection point and therefore was able to give away less of the company's equity (ownership) for the same amount of investment (assuming the Phase I comes out positive of course).

A true value inflection point increases the valuation of your company. For example, a value inflection point is a Phase I clinical trial. It would be reasonable to estimate that a successful Phase I trial might raise the company valuation from $1 to $15 million or even to something like $300 million (see figure "Post–Money Valuation of Biotech Companies by Stage").

To return to the example of raising capital from earlier with Company B, had the company proceeded with the plan to raise $400 million from investors at an estimated $1 million valuation, it would have given away 99.8 percent of the company (although arguably, it may have increased value in the company sufficiently to offset this, this is less likely).[259]

If Company B had instead followed the strategy suggested here—and waited until *after* a Phase I trial to raise the $400 million (This is assuming, of course, that this is a valid number. In reality this is still very likely too high of a raise for even most Phase I companies.)—the ownership now comes out to be:

$$= 100\% - \left(\left(\frac{\$400,000,000}{(\$400,000,000 + \$300,000,000)} \right) \times 100\% \right) = 42.9\%$$

Thus, even though Company B would be raising the *same amount of money* in either scenario, in the second scenario it times its raise with value inflection points and would be maintaining a *much higher ownership percentage* while still retaining the ability to build further value in the company.

Therefore, Building Backwards to a financing strategy involves roughly determining the major value inflection points in the company's life from early on and projecting the capital needs for the company to reach each value inflection point. Those quantities will give you a good estimate of the size of your raises.

Of course, *underestimating* the amount of capital you need to raise to reach a value inflection point can be a problem, as waiting until you've completely run out of cash to raise money puts you in a desperate position while negotiating terms with potential investors. Drastically overestimating is also an issue. It's dilutive to your ownership and can contribute to lack of discipline and focus in spending those funds while simultaneously building value.

There is a very high likelihood that this financing plan will change with time. It should. At each stage of the business, the financing plan and budget will consistently be reassessed and adjusted.

To Build Backwards effectively, a company should define its value inflection points from Day 1 in the company's life.

This is more of an art than a science. Generally speaking, good value inflection points adhere to three different rules:

1. They *increase* the value of the company.
2. They *decrease* the risk of scientific failure.
3. They demonstrate the *future potential* of the technology.

Taking the example of phases of clinical trials illustrates these criteria, but other inflection points precede this stage of the life cycle of a biotech company. Ideally, milestones should be determined in partnership with investors. In general, though, here are some potential milestones, written in order of early to late-stage. However, do note that these milestones might not be relevant for all new drugs, as these example steps are largely focused on small molecules.

EXAMPLE MILESTONES/VALUE INFLECTION POINTS

1. **Show the potential of a particular target or pathway to treat a disease.** This could involve *in vitro* models or *in vivo* models highlighting the potential of a technology. This data might be the potential of a novel target or the benefit of targeting a novel pathway, for example.

Why this example value inflection point fits into the three key rules for milestones:

a. **Value:** Having solid data proving that a novel target or pathway might be relevant for a disease *increases the value of the company* by demonstrating the "value" of owning IP on said novel target/novel pathway.

b. **Risk:** Such data de-risk the company. Data that validate a pathway's relevance in disease decrease the probability the science fails in actually treating disease down the road.

c. **Potential:** Potential application data demonstrate the prospective value of a company focused on *creating assets* down the road (i.e., therapeutics) that will target this pathway.

2. **Define a "lead" compound.** In the development of a new drug hitting a desired target, thousands of potential compounds and drug candidates are often tested to find a "lead."

Why this example value inflection point fits into the three key rules for milestones:

a. **Value:** Having a "lead" compound is a standard step in bringing a company one step closer to the clinic and, therefore, closer to realizing the value of a successful drug. It also further validates your hypothesis about the relevance of a target/pathway, as it demonstrates that finding a working drug for the target or pathway is probably doable. Completing this step, therefore, increases the value of the company.

b. **Risk:** Success here reduces the risk that the target or pathway will not be druggable (i.e., treatable via a drug).

c. **Potential:** The potential of finding and developing a singular working drug has increased.

3. **Define a clinical candidate.** After the "lead" is defined, typically the chemical structure is used as a starting point to optimize the molecule for desirable drug-like properties, such as bioavailability, pharmacokinetics (e.g., desirable half-life), and so on. Many drug candidates fail here.

Why this example value inflection point fits into the three key rules for milestones:

a. **Value:** This progresses the company to the point of having a drug candidate that is almost ready for clinical trials.

b. **Risk:** Because many potential medicines cannot be made to have drug-like properties, success in this stage substantially decreases risk.

c. **Potential:** A clinical candidate increases the drug's potential by having a clear potential future product for the first time.

4. **Obtain a clean toxicology study.** If you recall from chapter 2, toxicology studies are some of the last preclinical studies that need to be performed before a drug can enter (human) clinical trials. Many compounds fail here because they are found to be toxic at certain doses or to have disabling side effects in animals.

Why this example value inflection point fits into the three key rules for milestones:

a. **Value:** Toxicology data represent a clear step closer toward clinic. A successful toxicology study is needed for an IND (Investigational New Drug Application—i.e., the submission needed to begin clinical trials).

b. **Risk:** Toxicology data de-risk the asset by providing evidence that there will not be future safety issues.

c. **Potential:** Toxicology data increase the potential of the new drug (and perhaps also the entire pathway, which might have multiple targets) of being made into successful new medicines. If you can target the pathway and yield a clean toxicology report, you might be able to target other parts of the pathway as well.

5. **Begin Phase I trials.** This demonstrates the FDA's acceptance of all your prior steps in the form of your IND. This is further strong validation of your technology.[260]

Why this example value inflection point fits into the three key rules for milestones:

a. **Value:** Starting Phase I trials represent a definitive step forward in validating safety, one of the two major criteria FDA uses for approval (the other being efficacy). Entering this stage validates the strength of your preclinical data.

b. **Risk:** Beginning Phase I trials de-risks your program, as the FDA has deemed it safe enough and potentially effective enough for you to enter clinical trials. The overall probability a drug candidate that enters clinical testing will eventually be approved has been estimated to be 11.83 percent.[261] Although this sounds low, compare it to the estimated 4 percent success rate of a brand-new drug candidate. The risk has decreased, and the probability of success has increased.

c. **Potential:** The further validation of your program provided by FDA approval to enter Phase I lends substantial credibility to your company as well as to the whole platform technology/pathway/program.

6. **Complete a successful Phase I trial.** The first instance of proving safety in humans (and sometimes part of the drug's efficacy).

Why this example value inflection point fits into the three key rules for milestones:

a. **Value:** By demonstrating that a compound is safe in humans (and sometimes by also demonstrating some amount of efficacy of the drug), you are one step closer to FDA approval and therefore one step closer to revenue, which makes the company more valuable.

b. **Risk:** A successful Phase I trial de-risks your program because the drug is less likely to fail because of safety issues. As the risk of failing a Phase I trial is 45.9 percent, your

company has *overcome* this risk by succeeding at a Phase I trial.[262]

c. **Potential:** A successful Phase I trial is further validation of your program, company, and technology platform.

7. **Complete a successful Phase II trial.** This represents the first instance of proving some level of efficacy of your drug in real patients with the disease you are hoping to treat with your new drug.

Why this example value inflection point fits into the three key rules for milestones:

a. **Value:** Demonstrating your compound has *efficacy* in humans provides the strongest evidence thus far that your medicine will work to treat human disease (and gives evidence for the second of the two major FDA criteria for approval—efficacy).

b. **Risk:** Phase II data de-risk your program substantially; your drug is no longer as likely to fail because of efficacy issues. The probability that a drug will successfully complete a Phase II trial is only 35.52 percent. Further, if a drug successfully completes this stage, the probability of a successful Phase III trial increases because Phase III—like a Phase II—tests efficacy, except in a larger study population. To be precise, the probability of a successful Phase III trial once a drug candidate has successfully completed Phase II increases to 61.95 percent, therefore de-risking the program further.[263]

c. **Potential:** After Phase II, a company now has both safety and efficacy information on their new drug for the first time. Making it to this point suggests the potential of the drug to pass the larger size studies on safety and efficacy in Phase III.

It also suggests a high potential for the remainder of the drug development platform (if applicable).

8. **Complete a successful Phase III trial.** Phase III data give you more efficacy and safety data—i.e., more scientific support that your drug works and is safe for human patients.

Why this example value inflection point fits into the three key rules for milestones: See the above points regarding Phase I/II, except now value is even higher and risk is even lower.

9. **Obtain FDA approval.** Obtaining FDA approval is the "okay" to go ahead to market. At this point, the risk of scientific failure that could inhibit reaching the market is nearly zero.

Why this example value inflection point fits into the three key rules for milestones:

a. **Value:** After FDA approval, the value of your company substantially rises. Now, the probability that you will realize revenue from your drug is nearly 100 percent.
b. **Risk:** The risk of your drug failing scientifically is very low (pending some serious adverse events that happen once it's in a wider human population).
c. **Potential:** The company now has high revenue and/or exit potential, and any other drugs in development based off of a similar platform are "de-risked" as well.

In summary, these are example value inflection points that one might want to map out at the beginning of a company's life. By starting with defining your milestones, it becomes much easier to Build Backwards to determine how much and when to raise. To determine how much your company needs to accomplish these various value inflection points, you might use a table of cost and

time by Building Backwards from FDA approval (example table shown below):

	Preclinical	IND	Phase I	Phase II	Phase III	NDA
Estimated cost						
Duration (yrs)						

Building Backwards from FDA Approval. Use the table below to Build Backwards to NDA (New Drug Application, or a Biologics License Application, BLA is the final application package submitted to the FDA to receive approval). By calculating expected costs and duration of your program to understand funding needs and how they correlate with value inflection points. Graphic courtesy of Robert Okabe.

For example, you might determine it will take $15 million and two years to complete preclinical studies comfortably. Thus, you will seek to raise at least $15 million (and likely more as a contingency) in order to reach that point and plan to start your next raise about two years in (although you will want to time starting the raise to be about one year earlier to account for the time it takes to find the right investor), with data in hand, to raise the next tranche of financing.

“Rounds” are another critical part of financing to understand. When you hear discussions about Seed, Series A, Series, B, and Series C funding rounds, this refers to the process of raising capital from outside investors. A round is simply the terminology used to describe each individual funding event. As described previously, there are strategic reasons on both the entrepreneur’s and investor’s sides not to raise all investment dollars at once. Thus, each time a financing event is completed, it is called a separate round and each round has its own name.

As the business becomes increasingly advanced and developed, it will proceed through subsequent funding rounds: commonly starting with a "seed" round and advancing to Series A, B, and then C rounds (the letters can go as high as needed).[264]

As we've discussed earlier in this chapter, funding rounds are inextricable from valuation and equity considerations. Before a round of funding begins, both the investor and entrepreneur analyze the company to come up with a fair valuation of the company receiving the investment.[265] Valuations in biotech are largely driven by progress, but they're also driven by market size, exit potential, and risk.

SEED FUNDING

Sometimes, start-ups engage in "seed" funding first, which is often synonymous with angel investor funding (think of a few wealthy individuals investing rather than a formal venture capital—VC—group although seed rounds can sometimes be from VCs as well). A **Seed Round** is typically associated with starting the company. Seed rounds are typically quite small, often somewhere from a couple hundred thousand to single-digit millions (a million sounds like a lot, but as an operating budget for a biotech start-up, it's typically fairly bare bones).

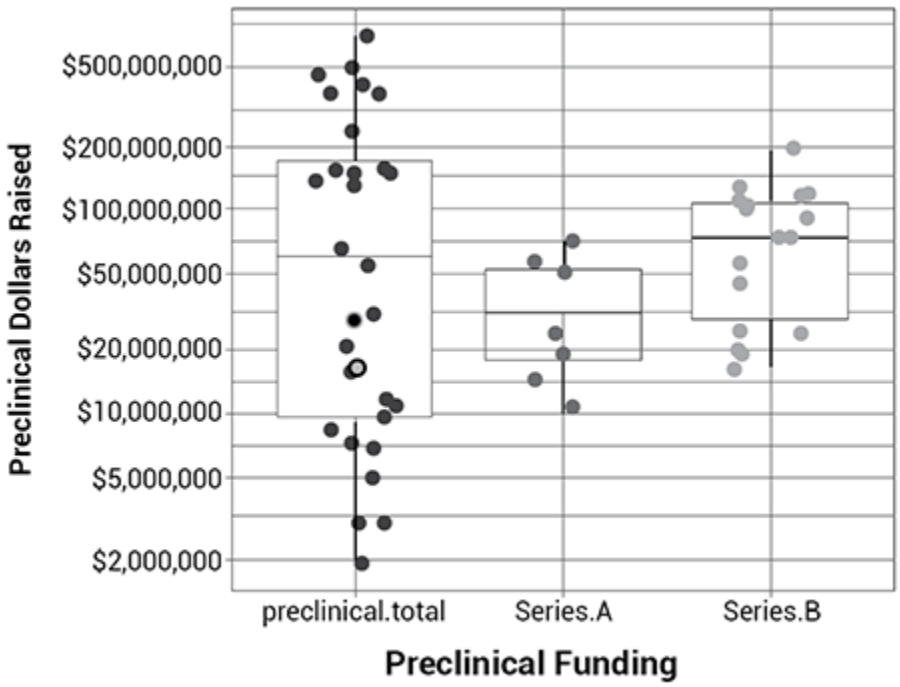
SERIES A AND BEYOND

Next, if a start-up decides it needs to raise further funding—which is usually the case in biotech—it will proceed to Series A, B, C, etc. financing rounds. The investors involved in these rounds often largely come from more traditional VC firms. Each round is typically "led" by one firm, but multiple investment groups can participate,

forming what is called an investment "syndicate." Sometimes, investors who participate in one round, like the Series A, will choose to participate in further rounds, such as the Series B and beyond. These investment rounds can be thought of as stepping-stones on the path of turning a new idea into a big, successful company, sometimes on the path to an IPO.[266] The earlier stages, like Series A, enable the establishment and development of the company, and the later stages finance the various stages of growth that occur across the company's life.[267]

To give an example of the difference between biotechnology companies and non-biotechnology companies, the average Series A funding amount across all types of start-ups (out of the 763 Series A deals in the United States in 2020) was $15.6 million.[268] In this study, the authors note that the size of biotechnology rounds is roughly double the median Series A size. This is supported by the figure "Preclinical biotechnology raising trends," which shows that for preclinical companies, a Series A is roughly $40 million.

As you can see, for preclinical biotech companies, companies mostly raised Series A or Series B rounds, which makes sense as it is early in the company's life. The Series A rounds are typically around $40 million, while Series B rounds are more often around $75 million (for more on financing rounds, see bioventureadvising.com).



Preclinical dollars raised as a function of funding rounds. Here, you can see the range of Series A and B round sizes raised by preclinical companies. The pink data (preclinical total) shows the total amount of funds raised by most preclinical-stage companies. Image was created by Jacob Glanville and me using data from Crunchbase, Pitchbook, and publicly available market cap information and press releases from fifty-six Series A and B preclinical biotech companies.

Building Backwards appropriately when it comes to raising financing is crucial in order to build a company that will survive the long term. While the primary mission of any biotech start-up is to progress a drug candidate through the development process, this is not possible without access to capital and a solid financing plan. Here, we have discussed how to Build Backwards from FDA submission to the start of a new company by planning for key value inflection points. However, part of Building Backwards in capital raising also requires an understanding of how the types of investors appropriate for your company to approach change over the company's life.

Understanding this dynamic and the investor marketplace is the subject of the next chapter.

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247 Non-Disclosure Agreement

248 Generally speaking, $400 million is likely an overly large raise for most preclinical companies.

249 This is due to both high failure rates as well as the fact that an exit may occur well before this amount of cash is used.

250 Note the percent of a company an investor is "buying" is the dollars invested by *only that particular investor*. On the company side, the percentage ownership the company gives away is calculated by the *total dollars raised from all investors*.

251 Of course, there are multiple other ways to raise capital, including debt, through convertibles, etc. For the purposes of this chapter, I am focusing on equity raises.

252 This is an illustrative example to make the point that Building Backwards from an end goal enables you to have a clearer ask in fundraising. It is possible, even in this case, that B could potentially build so much increased value with the $400 million that the 0.2 percent ownership stake is still more valuable than its initial 100 percent ownership stake of $1 million.

253 Note I am talking about direct percentage ownership and am not factoring in "super-voting" shares, where a founder can remain in control of the company even without majority ownership because one share may translate to more than one vote. This is the case at Facebook, for example.

254 To learn more about valuation, visit my website: bioventureadvising.com.

255 Aroon D. Hingorani et al., "Improving the odds of drug development success through human genomics: modelling study," *Scientific Reports* 9, no. 18911 (2019).

256 Although do note, the standalone probability of success of Phase II is actually lower than the probability of success of Phase I.

257 Note that in this context, I use the word "tranche" differently than, for example, some venture capitalists do when they say they "award funding in tranches." Awarding funding in tranches means giving out raised dollars for a single given round based on accomplishments. What I'm talking about here is from the entrepreneur's perspective: raising money when your company is at "peak" value points.

258 Note that from the VC perspective, the timing of the financing needs to be balanced with evidence the company has already achieved certain value inflection points as well as having near-term inflection points or incremental value-generating milestones.

259 Another important point is that few investors can supply $400M to a single investment.

260 If you're looking for information on clinical trials, good news! There's a whole chapter on that. See chapter 11 for more detail.

261 Joseph A.DiMasi, Henry G.Grabowski, and Ronald W.Hansen, "Innovation in the pharmaceutical industry: New estimates of R&D costs," *Journal of Health Economics* 47 (May 2016): 20–33.

262 Joseph A.DiMasi, Henry G.Grabowski, and Ronald W.Hansen, "Innovation in the pharmaceutical industry: New estimates of R&D costs," *Journal of Health Economics* 47 (May 2016): 20–33.

263 Ibid.

264 I will note some companies are capable of growing without any outside investment. However, this is extremely rare in biotech because large amounts of capital are usually needed at the very outset.

265 Nathan Reiff, "Series A, B, C Funding: How It Works," *Investopedia*, May 31, 2021.

266 Ibid.

267 Ibid.

268 John Dukes, "Average Series A Round Reaches Record $15.7 million," Fundz, June 29, 2020.

CHAPTER 10

BUILDING BACKWARDS TO FINANCING SOURCES

"The experience, motivation, and relative power of each participant in a financing can be complex, and the implications are often mysterious…"

—BRAD FELD AND JASON MENDELSON, ENTREPRENEURS AND VENTURE INVESTORS, *VENTURE DEALS*

A critical element of raising capital necessitates understanding the requirements of both your target investor and of your own company. Clearly defining these characteristics up front will likely enable you to improve your pitch "hit rate," saving everyone time and frustration.

When I was an analyst at ARCH Venture Partners, I had the opportunity to sit in on pitches from start-ups and filter some of the pitches that came in over email.

ARCH is a well-known venture capital (VC) firm with an established investment philosophy—meaning the types of companies it chooses to invest in, and the manner in which it invests is typically consistent across deals. To put it simply, ARCH most frequently invests in life science companies (quite often university spin-outs) and almost always invests no later than a Series A.

Therefore, it was always somewhat off-putting to read numerous cold emails that evidenced a total lack of prior understanding of

ARCH's well-established investment philosophy. An example might read:

Hi [insert name of ARCH partner],

Exciting news for you! Our company, Amazing Rental Homes Start-up, is actively taking on investors for our Series C. The round is currently oversubscribed and will be closing soon. We're looking for only $100 million to close the round…

Part of Building Backwards is understanding what type of investor is appropriate at each stage of the company's life. This comes to fruition in the *way* you pitch but also who you pitch *to*. Whether a VC group with an investment strategy that is a match for your company or a different potential funding source, the type of investor appropriate for you to approach changes depending on the stage the company is at.

In the last chapter, we covered the various rounds of financing (e.g., Seed, Series A, etc.). Each round of financing reflects, to some extent, how far along in development a company is. This is significant because depending on the company stage, different potential investors are both available and appropriate to approach for capital. Building Backwards from your capital needs will help to illustrate which investor may be the best fit at each point in your company's life.

You must first understand a couple of key points that generally apply to biotech financings at large:

- Regardless of the type, any investor—including government grant or corporate partner investors—will lend "signaling value" to you and your company. The more experienced and well-established

your investors, the more credibility you will gain by proxy (and likely the easier it will be to obtain follow-on funding in subsequent rounds). Therefore, it is important to be aware of the signaling value of the investors you accept, understanding that their track record could either diminish or enhance your own credibility.

- Generally speaking, the funding capacity of a given investor increases with the sophistication of the investor (e.g., a VC firm is likely to have greater funding capacity than an individual angel investor).
- The amount of money it is reasonable to ask for depends on where you are in the drug development process. According to Okabe (introduced in chapter 8), "The smartest ask is for a bit more than the amount of money needed to reach the next stage in the process for your drug candidate. You can ask for more if your candidate is in a hot sector or if you have multiple molecules to develop."
- Few companies get more than two phases worth of funding in a single round. Okabe explained the reasons for this, saying, "First, why give a company so much money when the failure rate is so high? Second, why throw so much unusable cash at a company if the exit is going to occur well before it gets used?"
- Dilution is often not as concerning as entrepreneurs may initially perceive it to be. While an entrepreneur's percentage ownership goes down when they are diluted, the value of their shares should also rise due to the increase in overall valuation.

R&D, EARLY PRECLINICAL STAGE:

SEED ROUND:

In the earliest stages of development, many companies tend to find small business grants or academic funding (e.g., the PI's current grants, their own lab funds, flexible funds—areas of spending that are allowable) particularly helpful. This is because these funding sources often require less initial data in order to obtain capital. Early-stage venture groups are also an option.

Option 1: Grants

Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) grants encourage US-based small businesses to engage in Research and Development (R&D) that has the potential for commercialization.[269] Much of the funding supporting these grants comes through National Institutes of Health (NIH) or the National Science Foundation (NSF), although it can come from many various other federal agencies as well. Their objectives (as stated on the NIH's website) are to "stimulate technological innovation" and "increase private sector commercialization of innovations developed through federal R&D funding." That is, NIH wants to use this money to help laboratory-based technologies come to the consumer market.

The most important thing to note about SBIR financing is it is "nondilutive." In other words, a company does not give up equity to receive a grant. This gives your company the ability to build value early, which can be helpful in order to obtain key data sets needed to approach other investors.

SBIR/STTR grants are competitive. Precisely because these grants are so competitive, receiving these and similar grant types lends credibility to your project. This is in part because, much like academic grants, small business research grants undergo review. NIH small business grants, for example, have two stages of review: scientific review and council review. The scientific review is

composed of scientists from both academia and industry, some of which have a business background in addition to a scientific background. The top applications are identified by score and then proceed to council review. This is where programmatic decisions are made, and grant applications are funded. This process of rigorous review serves to validate the scientific premise of a new start-up similar to the peer review mechanisms in academic science.

Receiving a grant also demonstrates a certain level of "hustle." When an investor is funding you, it helps to know their contribution will be augmented by grant financing, and it's a positive signal when an entrepreneur is able to secure one.

The money funding SBIR/STTR grants comes from the fact that each year, federal agencies with extramural R&D budgets greater than $100 million are required to put aside 3.2 percent of their funding (since 2017) to fund small businesses through the SBIR program; and 0.45 percent (since 2016) of budgets over $1 billion are required to be put aside for the STTR program. (If you're thinking it sounds like SBIR as a program probably has more funding than STTR, this is correct!) Each agency oversees its own individual program and the funding available in that program within guidelines established by Congress. The agencies select R&D topics to fund within their own solicitations (solicitations are what the announcements for funding are called) and accept proposals from small businesses. (Note STTRs require the small business to formally collaborate with a research institution in Phase I and Phase II; for more information on the differences, see bioventureadvising.com.) Below is an example of some of the participating agencies and examples of previous budgets they have had:

SBIR & STTR	Budget	SBIR only	Budget
Dept. of Defense (DoD)	$1.8 B	Dept. of Agriculture (DoC)	$30 M
Dept. of Health and Human Services (HHS)	$1.15 B	Dept. of Commerce (DoC)	$9.5 M
Dept. of Energy (DOE)	$308 M	Dept. of Education (ED)	$8.4 M
National Science Foundation (NSF)	$212 M	Dept. of Homeland Security (DHS)	$17 M
National Aeronautics and Space Administration (NASA)	$183 M	Dept. of Transportation Security (DOT)	$5.2 M
		Environmental Protection Agency (EPA)	$3.6 M

Budgets of various SBIR/STTR agencies as of 2019.[270]

Similar to typical academic grants, applicants submit SBIR/STTRs to the NIH or NSF. While traditional academic grants (like "R" series grants) are rated based on whether your science is innovative and fits the goals of the funding program, an SBIR/STTR grant requires strong rationale for these aspects in addition to strong rationale for commercial potential and the business overall. SBIR/STTR reviewers want to know whether there is a reasonable likelihood that any awarded funding would eventually result in an actual product coming to market.

Since SBIRs are more common and typically have higher associated budgets with a greater number of awards able to be given out compared to STTRs, we will focus mostly on SBIRs here. SBIRs are broken into phases: Phase I, Phase II, and Phase IIb. Each phase is associated with particular milestones (that you define in your grant), and successful completion of milestones (or scientific progress) will increase your chances of receiving follow-on funding. (Note: a common point of confusion is the resemblance between the

SBIR/STTR phase names and clinical phase names, but there is no connection.) As the grants progress in phase, they are increasingly more competitive to win (i.e., the bar for a Phase II SBIR is much higher than Phase I). Additionally, as the proposed projects become more complex, the timeline given for a company to complete each project gets longer.

Phase of Funding (SBIR)	Description of Activities	Timeline and Funding Amount
Phase I	Feasibility and Prototype	~$250K and 6 months
Phase II	Research and Development	~$1-2M and 24 months
Phase IIb/Commercialization Readiness Pilot	Final activities to be commercialization ready	Situational, work can be up to thirty-six months or greater

SBIR funding phase, description of activities, timeline, and funding amount.

The funding amounts listed above are rough estimates (and note that the funding amounts could very well be different a few years from now, as these numbers were compiled in 2021) because it depends on the specific NIH institute awarding your funding (e.g., the National Cancer Institute might provide more funding than, say, the National Institute of Neurological Disorders and Stroke). In short, you can apply to many institutes for SBIR/STTR funding, and you will need to speak with the relevant program officials to determine which one is the best fit for your company and project. One critical way to determine if your project will be eligible (and to ultimately save time) if you're working on an NIH application is to talk to what's called your "program officer" whose contact information you can easily find on Google under the search terms, "SBIR program officer [agency name]." A program officer is essentially a scientist employed by the NIH who oversees the administration of certain grant funding.

Generally speaking, it's never too early to begin building a relationship with your program officer. It is usually quite common to ask for phone calls to run your draft budget and milestones past the program officer. Staying in communication and obtaining their buy-in on your project is crucial. The program officer is also deeply familiar with the NIH categories of funding as well as their deadlines and eligibility requirements. For example, one company I know of kept a close relationship with its program officer. As a result, the company landed $500,000 from its first Phase I grant (above the average size at this stage of funding) because the program officer informed the company of increased funding available *for certain initiatives,* which ended up being in line with this particular company's capabilities.

Option 2: Angel investors

Angel investors were discussed in the previous chapter, so they will only be briefly touched upon again here. Angel investors differ from VCs (discussed next) because angel investors are often individuals as opposed to a firm. As a result, angel investors are often more flexible on terms (i.e., how much equity they take) than a full-fledged venture group, and they are often capable of responding quicker. Angel investors are often sought after in Seed Rounds, when a start-up is seeking a smaller amount of capital and at an earlier stage in the company's life.

Failing to secure any angel investors that are biotech specific when raising an angel round can be a credibility and signaling problem. If the investors you are working with are not specialists in biotechnology, why should other investors trust that you know what you're doing? Thus, it is advantageous to determine key angel investors in your specific area of biotech and aim to secure funding from them if you choose to raise a Seed Round from angels. However, if angel investment is raised in combination with a grant,

it is perhaps less crucial as validation comes from receiving a grant.[271]

Option 3: Early-stage VC

As a common fallacy, some biotech founders may believe a new company with minimal data is too early to pursue VC funding. On the contrary, many top-tier biotech venture firms (e.g., ARCH Venture Partners) *primarily* invest early, particularly when the PI whose lab the tech was spun out of is at the top of his or her field with recent high-impact publications on the technology.

It is worth considering taking venture financing early on in the company's life, as early-stage VCs often take a long-term partnership approach and are usually able to advise the company on developmental strategy as industry pros. However, it can be difficult to secure a meeting with a VC firm. VCs also usually will not respond to cold outreach, so warm connections are key. You almost always will need some sort of trusted introduction, which signals some level of legitimacy and will help you to stand out from the hundreds of cold emails VCs receive. Note it is often important to build a relationship with VCs over time; VCs often require multiple meetings before investment.

It is also worth noting that VCs prefer varying levels of involvement in their investment ("portfolio") companies. Therefore, this is also a factor for consideration based upon the needs of your company. VCs can add a lot of value through their domain experience, expertise, and network.

Generally speaking, VCs often require larger scale returns, on the order of ten times their initial investment. A difference between angels and VCs is angels invest in lots of deals every year, whereas VCs usually do fewer. This is relevant to you as the entrepreneur

because while it might be slightly "easier" to get angel funding, VC funding is typically higher amounts of financing and comes with a certain "prestige."

LATER-STAGE PRECLINICAL STUDIES

In the later stages of preclinical studies (i.e., toxicology, manufacturing, etc.), costs increase. This generally ranges somewhere from the mid to high single digit millions.

Option 1: More grants

At this point, it's certainly possible to continue to support using a program grant like SBIR, but as folks familiar with academic grants know all too well, federal *grants are "slow"* (relative to private sector financing) *and receiving one is not guaranteed*. You often have to apply multiple times, risking running out of cash and slowing down your company progress if you don't plan adequately (or do not receive the grant at all).

Option 2: More angel investors (see above)

It is always a possibility to obtain more angel investment. However, at this stage of a company's life, it is worth considering the downside to having too many angel investors who are not biotech experts. This could make the company seem less attractive to investors with a specialty in biotech. Too many angel investors can increasingly distort the cap table to give equity to an investor who does not necessarily bring domain expertise. It is also worth noting that even if the angel investor does have some level of domain expertise, that does not mean seasoned biotech VCs will view them that way.

Option 3: Going public (early IPO, SPAC, etc.)

The public markets have been increasingly favorable to biotech IPOs, paving the way for companies to sometimes IPO earlier in

their developmental process.[272], [273], [274] This makes going public to raise capital earlier in a company's life an option.[275] However, proceed on this route with extreme caution. Going public too early can sometimes be shortsighted, as the prospect of a future IPO (recall the 30 to 40 percent valuation jump discussed in chapter 8) can serve as an incentive for certain private investors to invest early.

To successfully go public, you must be able to demonstrate a compelling public capital markets "story" to investors. A pivotal piece of this story is how much capital you will likely need in order to reach subsequent valuation inflection points. Also, going public generally signals you will be raising the remaining capital you need solely from the public markets (through subsequent follow-on primary offerings or "at-the-market" programs).

Additionally, while raising new capital as a public company may be structurally easier than having to raise capital as a private company, you also have much more scrutiny (not to mention regulatory requirements) as a public company. If your company has bad news, public investors can easily sell their shares in your company, which will hurt your stock price and may result in you no longer being able to raise funds at attractive prices. As a public company, you must follow stringent regulations such as highly regulated finance and accounting processes, quarterly and annual reporting, and other cumbersome tasks that may not be the best use of time early in a company's life. In addition, VCs generally do not invest in public companies, so by going public, you often close the door to future investment from VCs.

In summary, going public can be a great route for a company when growth capital is needed, but timing of the IPO (and the implications of being a public company) should be considered carefully.

Option 4: Revenue stream/cash flow

It is not very common for biotech companies to have early revenue, as these start-ups cannot sell pharmaceuticals unless they are approved. However, if the company is able to produce some level of cash flow (even if small), this can be helpful in decreasing its dependence on investors, particularly in the preclinical stages when expenses are lower (e.g., the example of Receptos, chapter 6). Typically, biotech companies that have early-stage revenue make this money by selling services to pharma, like the case of Distributed Bio, who leveraged its antibody discovery platform technology to conduct antibody discovery for Big Pharma, which allowed the company to channel that revenue source back toward internal R&D efforts.

The caveat is that not all VCs are necessarily concerned or impressed with seeing a revenue stream in an early-stage company, as this can sometimes lead founders to argue for a higher valuation beyond what might be typical for a company of similar stage (see figures in chapter 9 for average valuations by phase). Additionally, venture groups are often more interested in the therapeutic assets versus the services business.

Generally, the key distinction for revenue is whether it is "core" to the long-term value of the company. For example, if you are developing a therapeutic, the revenue coming from the chief scientific officer providing consulting services may be worth very little to the VC and may in fact signal that the focus of the company is not solely on creating what the VC will view as the true value proposition of the company.

From the company perspective, however, developing your own revenue stream can enable you to have a "cheap" cash source (it is often considered "cheap" because you do not have to give away

equity in exchange for it). This can sometimes finance the company to reach a key clinical value inflection point, at which point it may be possible to raise capital at a higher valuation.

CLINICAL STAGE: PHASE I, PHASE II, PHASE III

Options 1 to 4: See above

However, phase trials are so incredibly expensive that options 1 to 4 are going to be largely insufficient (though venture groups are still a good option and often the most typical option).

Option 5: Corporate partnerships

Corporate partnerships *as a financing source* are an option for a company at any stage of its life, but I am mentioning them here because large pharma companies are one of the few non-VC funding sources that can be substantial enough to potentially support a clinical trial. Although these partnerships can be nondilutive to ownership equity, they often claim ownership in other ways, such as through revenue sharing, joint IP rights, or exclusive licensing arrangements that indirectly could dilute the value of the company.

In general, pharma companies are often less risk-tolerant than VCs and generally prefer later-stage programs, such as those in the clinical stages, because they have already been significantly de-risked.

Corporate partnerships can take almost any structure. Generally speaking, they take the form of an exchange of upfront cash with the purpose of jointly developing intellectual property, which, if successful, will be jointly owned or commercialized by the two companies. Equity in the start-up may be taken in exchange for this cash, or it may be future revenue shares, joint intellectual property rights, or exclusive licensing arrangements. The best way to

understand how corporate partnerships might be structured is to read press releases when new partnerships are announced. For example, one press release from 2020 by Vividion Therapeutics (note that Vividion is preclinical) was entitled "Roche taps Vividion in $135 million protein degradation deal." In other words, to break this down:[276]

- Roche gave Vividion $135 million.
- In exchange, Vividion performed preclinical work on certain targets and promised Roche the exclusive right to license compounds that came out of the deal.
- Meanwhile, Vividion could opt into sharing developmental costs and profits on certain programs.

Note that, although the deal itself was not focused on running a clinical trial, this level of capital *could* potentially enable a biotech company to conduct clinical trials (depending on the indication and the trial design).

Keith Crandell said of corporate partnerships: "When you have no validation [of your technology] at all, a large corporation that decides to partner with you might be what elevates the level of interest [of investors] because the pharma company represents a super knowledgeable, experienced group that is willing to spend real money on the program."

The downside, he warned, is a partnership structure that limits the upside for investors too much: If you enter partnerships that expropriate all the wealth and potential out of the effort or appear to cap the upside, that would be a bad structure. If you've got a platform technology that has ten different applications, and several of them are very attractive, you can give one away and it's not the end of the world. In many small companies, there's a lot of push to

get that first partnership done. And invariably we [as investors] wind up undoing it because it doesn't work three or four years later. So, whatever partnership you do, you want to make sure you have the prearranged divorce clauses included in the agreement so you can pull yourself back if needed. However, the whole idea of validation is important because most investors do not have the ability to read bottom up all the facts in your company or technology. They're going to reason by analogy. If your technology is validated by "smart people" at a pharma company, investors are going to spend more time on it.

In other words, the most important takeaway is to strive to maintain meaningful financial upside in a codevelopment agreement.

It is somewhat typical to strike at least a few partnership deals over the duration of a biotech's life, but it's not abnormal to do more or less, as each company will be different. Often, initial contacts and relationships can be forged through conferences focused on partnerships, such as the annual BIO International Convention or the J.P. Morgan (JPM) Health Care Conference. To emphasize Crandell's point, in order to exit deals down the road, should they no longer make business sense for the company, it is often possible to build language into the agreement that will enable various contingencies. (Employing a legal firm for this is important and can help you draft language and strategy.)

Option 6: Out-licensing specific programs to pharmaceutical companies

Out-licensing one program (e.g., one target, asset, one indication, etc.) to fund development of other programs is another financing strategy. Out-licensing involves an agreement for certain intellectual property (IP) (in this case, IP owned by the biotech company) to be utilized by a third party (in this case, a large pharma

company) for some consideration in return (such as cash, royalties, equity, or some combination of the three). This enables the biotech company to use these funds to develop its other programs. This is different from the above (option 5) because out-licensing typically involves giving away the rights to one drug entirely.

For example, Agios Pharmaceuticals, a biotech company in the field of cancer metabolism, licensed its first program, AG-221 (an inhibitor of mutant IDH2 protein), to Celgene Corporation, a large pharmaceutical company. At the time, AG-221 had just finished its Phase I trial. Celgene gained worldwide development and commercialization rights for AG-221 (i.e., the ability to finish developing and then sell the drug). This was good for Agios because Celgene took on all further developmental costs for AG-221, Agios became eligible for up to $120 million in milestone payments and would receive a royalty on any revenue Celgene made on sales of AG-221. The deal also enabled Agios to focus its resources—and likely use some resources from the AG-221 deal—to develop its next program, AG-120. Agios then chose to develop AG-120 (an inhibitor of mutant IDH1) internally and was able to bring it to market and benefit from sale revenue of the drug itself (although Celgene had ex-US commercialization rights for the program).[277]

Diagram of how out-licensing AG-221 looked. Courtesy of Christian Lamarco.

Option 7: Later-stage VC

As we touched upon previously, different VCs have different investment philosophies. For example, ARCH is likely not going to

be a fit for the vast majority of companies, because it tends to have a particular investment style (e.g., university spin-out stage) and "thesis" it looks for (e.g., certain indications, cutting edge versus more standard approaches, etc.). Similarly, most VCs also have varying amounts they typically invest in their first and second rounds. The more homework you do, the better you can target the right venture groups for your company. An example of a few VC groups that have been amenable to later-stage investing in the past are RA Capital Management, Foresite Capital, and Casdin Capital.

A good place to start to look up venture groups is called Crunchbase. On Crunchbase, you can search for companies similar to yours and see who funded them, the size of the investment, and at which stage in the company's life. Alongside Crunchbase is Pitchbook (which is similar to Crunchbase but, in my opinion, has an easier user interface) and the respective companies' websites and filings (if they are public). Although Crunchbase and Pitchbook cost money, oftentimes, universities have licenses and make the databases available for students. When considering different VCs, try to determine their investment philosophy by considering these questions:

1. **What types of biotech companies does this VC fund?** (i.e., small companies, companies only in a particular health sector, only medical device companies, etc.)
2. **At which stage does the VC normally invest, and at which stage in development is the company when they receive the investment?** (i.e., Do the investors only invest in Seed Rounds? Only Series A? Only Series C? Is the company preclinical at the time or clinical? Does it invest in public companies, private companies, or a mix? You can usually find the answer with a quick internet search, for instance, by reading multiple press releases of

funding announcements the firm has released. I also recommend looking at investment sizes relative to round and company stage.)

3. **Is the VC already funding a biotech company solving a similar problem to yours?** (If the answer to this is yes, the likelihood of them funding you is typically smaller since you will be competition to their existing investment. The caveat would be if, as per question 1, you realize the investment philosophy for this VC group is funding multiple similar companies.)

You should aim to cultivate relationships with the venture groups that appear to be a good match for you. Again, getting a personal introduction will greatly increase the odds that you will eventually get a meeting. Meeting with VCs at conferences like BIO and JPM is also helpful.

Option 8: Other types of investment securities

You can also finance your company through securities that are not equity only—for example, convertible notes. These may be useful investment instruments at earlier stages in the company's life as well. For more information on convertible notes, multiple resources are listed on bioventureadvising.com. Here, I will just give a brief overview.

Convertible note:

One client company I worked with closed a convertible note round as a way to finance work leading up to Phase I clinical trials.

A convertible note is essentially an investment instrument that is a mix between debt and equity. It starts out as debt, and like debt (think student loan debt or debt on your credit card), it comes with interest payments at a certain percentage. This interest rate is typically between 2 and 10 percent.[278] At a certain point in the future —typically a qualified financing event such as a Series A or an IPO—

the value of the note converts to shares of stock in the company. To put it simply, the investor gives you cash up front in the form of a loan. This cash is available for the company to spend. Later, instead of paying back the debt, the company can instead award the investor with equity in the amount of the total original amount of the debt plus the value of any interest that has accrued. (Rarely these notes allow for prepayment, which enables you to pay off the interest and/or debt before it converts.)

An advantage of a convertible note for the biotech company is it delays the point in time when the company is assigned a valuation. This is beneficial for the reasons discussed earlier in this chapter. If you are doing biotech right, your valuation should increase as your development progresses. However, the value inflection points in the company's life don't always align with the timing of your need for cash. The advantage of convertible notes for investors is also clear. It enables them to invest in your promising new tech but at a discount relative to investors that join the next round of financing, and the debt component of the note makes the investment less risky in some ways (as debt holders are paid out before equity holders in the event of a sale or liquidation).

In the example of my client company, the company wanted to avoid raising cash at a preclinical level valuation. It preferred to instead raise cash after Phase I clinical trials, as this stage would confer a much higher valuation. The problem was that the company had bills to pay: down payments on the clinical trial, personnel expenses, rent, laboratory equipment, etc. The solution we came to was to raise funds using a convertible note, which prices the investor's equity ownership off of the future Series A or IPO valuation, which would occur post-Phase I (and thus confer the higher valuation).

This then gave the power to strategically time our Series A and IPO for after the start of Phase I trials.

The downside to using convertible notes for the company is that the more debt a company has, the riskier the company is considered (as it's more highly "leveraged"). Additionally, the note still converts to equity eventually, enabling investors to get *more shares for less money invested* (relative to the participants in the financing round), in exchange for them investing early. As such, you do not want to overload your company with convertible debt since it does convert to an equity percentage eventually, and the more debt you take up front, the more equity you must give away later.[279] Additionally, significant convertible debt could be a deterrent to future investors.

Simple agreement for future equity (SAFE) Note:

SAFE notes are a kind of convertible note. Originally devised by Y Combinator (a famous start-up incubator), SAFE stands for simple agreement for future equity. As far as functionality and negotiation terms, a SAFE note works almost the same as a typical convertible note. The only difference is that it does not start out as debt. Instead, cash is paid up front, and there is no interest payment. The cash then converts to equity at the time of a subsequent financing round. The advantage of this for the new company is again the ability to delay naming a valuation until a future date, in addition to the added benefit of not having interest that accrues.

Whether a SAFE note or a convertible note is used depends on the specific negotiation.

To Build Backwards effectively in raising capital, it is important to understand the various potential funding sources available to a biotech company. While funding capacity generally increases with

investor sophistication, not every "sophisticated" investor will be appropriate at every stage of the company's life. To set yourself up for success, then, it is crucial to tie your capital raising needs to a strong understanding of the realities of the investor marketplace.

Next, we will review clinical trials in detail to understand how Building Backwards from these key experiments can be conducted effectively to inform market positioning, fundraising, value inflection points, and more.

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269 "About the SBIR and STTR Programs," SBIR.gov, accessed October 20, 2021.

270 "Leveraging America's Seed Fund," US Small Business Administration, March 2020.

271 A separate founding capitalization challenge to consider is when to raise from angels versus institutional investors. Often angels tap out at $10 million or so in a given biotech, which typically leaves a company at an early stage with an above-market valuation but without the deeper pockets required to get to the big inflection. This is a painful place to be for founders and companies, and the trajectory is often set at the outset. Getting institutional engagement on pricing and funding alongside angels is well worth considering.

272 Bruce Booth, "The Incredible Expanding Universe of Biotech Stocks," Life Sci VC, September 21, 2018.

273 Bruce Booth, "Biotech's Relevancy Challenge in an Expanding Universe," Life Sci VC, June 1, 2021.

274 Ben Fidler, "A record number of biotechs are going public. Here's how they're performing.," *BioPharma Dive*, updated October 21, 2021.

275 An IPO, or "going public," is when a company's shares are available for purchase for the first time on a public stock exchange, such as the New York Stock Exchange (NYSE). This gives companies access to more capital (because they can raise capital from the public, and not just specialized VCs) and also provides a pathway for future liquidity, as previously discussed.

276 Amirah Al Idrus, "Roche Taps Vividion in $135M Protein Degradation Deal," *Fierce Biotech*, May 19, 2020.

277 "Agios Pharmaceuticals Announces that Celgene Exercised its Option to License AG-221 Under Global Strategic Collaboration," *Business Wire*, June 13, 2014.

278 “What does the interest rate indicate on a convertible note?” *Education Center, Funders Club*, accessed October 20, 2021.

279 To understand the key terms to negotiate on convertible notes, see bioventureadvising.com. In short, they are discount rate, valuation cap, interest rate, and maturity date.

CHAPTER 11

BUILDING BACKWARDS TO CLINICAL TRIALS

"In biotechnology, what you're selling is the future. You are selling data and hope."

—JOHN CROWLEY, CEO OF AMICUS THERAPEUTICS

Pamela Garzone, PhD, is a force to be reckoned with. As the medical and regulatory consultant for Centivax, I first knew her as the calm, assured voice at the other end of a Zoom call.

As Centivax's chief business officer, I create our company financial projections and often speak to Garzone to understand the regulatory and business implications of new potential programs. Sharp, serene, and wise, Garzone is often able, off the top of her head, to rattle off a potential clinical trial design solely based on her ample experience.

She's also the current chief development officer at Anixa Biosciences and former chief medical officer at Calibr (the drug development arm of The Scripps Research Institute). When I asked her to estimate how many projects she's worked on, she approximated that she has led or co-led on more than twenty-five INDs (Investigational New Drug applications to the FDA) and four approved drugs. She also estimated that she has guided more than one hundred assets through various stages of the drug development process, including toxicology, pharmacology, clinical pharmacology, translational sciences, and clinical research.

In addition, she was a woman in science at a time when there were very few, making her one of the early women to have broken the "glass ceiling," so to speak. As we spoke over tacos, she told me about navigating a male-dominated industry. When she became a mother, she simply continued attending her business trips—baby in tow, hiring any needed assistance upon arrival. She didn't see why she should have to choose between her family and the work she loved.

Garzone emphasized the importance of Building Backwards in clinical trial design, sharing a story with me about the repercussions of failing to do so.

Garzone had been working on a therapeutic for a disease that largely affects women. The large pharmaceutical company developing the drug had run a Phase I trial, but there was a catch. Despite an indication that was 95 percent women, *only four* out of one hundred subjects were women in the trial's study population.

This was a problem. Given most of the subjects tested were male, how could the company apply the Phase I data in a way that would correctly extrapolate dose levels appropriate for women? Additionally, how could it feel confident that issues specific to women's health, such as fertility, would not be adversely impacted?

There was another layer of difficulty with this Phase I study. The wrong design was employed, Garzone said. Instead of using a parallel study design—in which each group is given only one treatment (i.e., one group receives the real drug and a separate, second group receives a placebo pill)—the pharma company used a crossover design. A crossover design has each subject serve as their own control. That is, each subject completes two conditions: one in which they take real doses of the drug and another where they take a

placebo, in a randomized order. For this study design to work, there must be a sufficiently long interval between drug treatment and placebo treatment to separate the effects of each (i.e., a "washout" period). However, the company did not account for the known, lengthy half-life of the potential therapeutic. This confounded the results. The drug was not sufficiently cleared from subjects' bodies during the placebo condition (for the group who received the real drug first). Due to this critical study design flaw, in addition to the fact that the trial was largely conducted in male participants, it "failed miserably," in Garzone's words.

"They spent millions of dollars and the drug was stuck in Phase I for two or three years," Garzone recalled. "And this was likely to be a good drug. It could have helped a lot of patients had they designed the trials correctly so the molecule could progress. I think this is an example where the failed proof-of-concept study could have been prevented."

Unfortunately, because development had taken too long and the potential market size was vastly underestimated, the pharma company sold off the promising new drug to a venture capital group, who then sold to another large pharmaceutical company for multiple hundred million. Today, that drug is on the market and making hundreds of millions of dollars in revenue annually.

The first large pharmaceutical company likely missed this opportunity by not carefully Building Backwards from how it ultimately anticipated the drug might be used—and the gender of the patient population it expected it to be used in—to the execution of its Phase I trial.

BUILDING BACKWARDS TO CLINICAL TRIAL DESIGN

This large pharmaceutical company trial failure is only one example of how failing to Build Backwards to clinical trial design early on can be detrimental to a company's success in phase trials.

However, biotech companies might overlook Building Backwards in planning for the clinic in multiple other ways as well. One way this can occur is through a lack of research focus, resulting in a less efficient path to the clinic. While it is both necessary and appropriate for academic science to pursue many of the interesting research questions that arise, that tendency can sometimes run counter to the objectives of biotech, where the goal is a viable end product that requires focused research questions to be answered first.

How do you do this practically? By conceptualizing what you want your final drug "label" to be at the beginning of the drug development process.

The final drug label is exactly what it sounds like. It's the end label on your drug after it is approved, instructing users how to correctly take your new drug. One of the most important aspects of the label is the indication(s) that received FDA approval (i.e., what the drug can be used for). Other info on the drug label includes:[280]

- Description of the drug
- Clinical pharmacology
- How often the drug should be taken (once a day, once a month, once every three months, etc.)
- Contraindications (i.e., who should not take the drug, hypersensitivity to the drug or excipients in the product)
- Dosage and administration (e.g., intravenous, subcutaneous, intramuscular, oral, etc.)

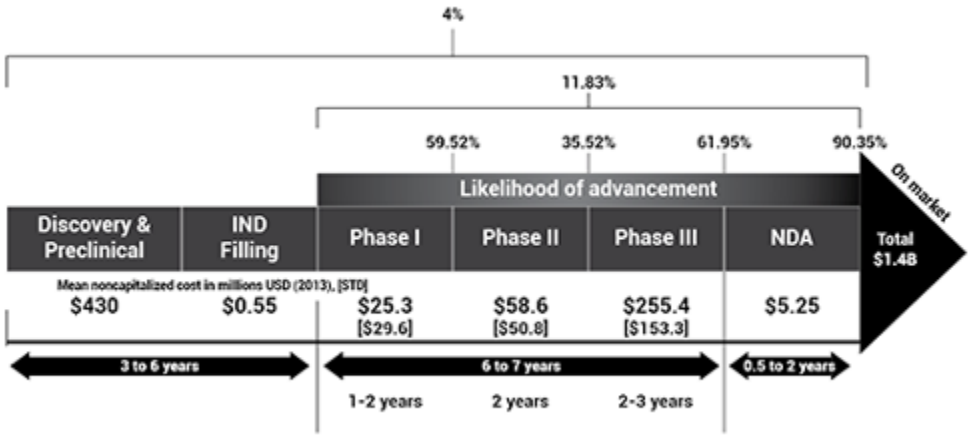
Less relevant for planning purposes (as it's hard to know ahead of time and plan for which potential adverse events might occur) but also included on the drug label are:[281]

- Adverse events (side effects)
- How the drug is supplied
- Safety information for the patient
- Use in pregnancy, nursing mothers, children, and older patients

To develop a new drug for market, then, preclinical and clinical experiments are fundamentally about building toward the end label. In turn, the end label affects how a new medicine is ultimately positioned in the market. This is why understanding the end label is so crucial in Building Backwards early on. It informs not only the science but also early business decisions. You can employ several Building Backwards strategies when setting up and running your clinical trials. First, however, we will cover the details of how clinical trials work.

HOW CLINICAL TRIALS ACTUALLY WORK

As touched upon in earlier chapters, clinical trials are the last sets of experiments you need to run before you can get your drug approved. As noted in chapter 2, clinical trials tend to be the largest cost driver in drug development. The figure from that chapter has been copied here as well to give an idea of cost and timeline per phase, although this varies drastically by indication and study design.



Long, expensive, and uncertain: the process of drug approval. As you can see here, the average noncapitalized cost (i.e., the cost of failures not included) for a single drug is exorbitantly expensive: $1.4 billion, with an average timeline that can be up to fifteen years. (This is an average, so keep in mind it can certainly be more.) Further, the probability of success overall for a new drug is only 4 percent while the probability of success of a drug entering the clinic is only 11.83 percent. The mean noncapitalized costs for each phase of development is also listed above, with the standard deviation in brackets below (units are 2013 dollars). Note that the timeline and number of patients required for each phase can vary drastically by indication. The numbers below represent the average as given by the sources utilized. Image courtesy of Scott Walbrun, Andrew Hawley, Gerardo Chaquinga, Wenbo Fang.[282,283,284,285,286]

To review, clinical trials are conducted in phases, with each phase specifically designed to answer certain questions around efficacy, safety, or both. There are typically three phases of clinical trials before the FDA (and other regulatory agencies) will approve a drug, and one additional phase post-approval: Phase I, Phase II, Phase III, and (post-approval) Phase IV. However, with innovative trial designs and several accelerated regulatory approval pathways, the lines between the phases are often no longer discreet.

PREPARING FOR CLINIC

The clinical team develops a synopsis that includes the core protocol elements developed with biostatisticians who can recommend study

design, how many subjects are needed to assess the statistical significance of various outcomes, and which statistical models will be appropriate for assessing these outcomes. The early trials focus on safety and tolerability, with subsequent studies evaluating efficacy along with safety.

The team then writes the protocol, expanding the synopsis to be very specific. The protocol seeks to outline every relevant detail, including screening criteria, for the types of participants who can take part in the trial. It specifies which tests and procedures will be performed for participant monitoring as well as evaluation(s) of efficacy, laying out guidelines for the dosages of the drug and stipulating the necessary follow ups and length of the study. Most importantly, they also describe the endpoints of the study. An endpoint is the "readout" that will be measured at the end of a trial in order to determine success (e.g., frequency of migraines, for a migraine drug). All this information will then be shared with regulatory authorities to obtain marketing approval and with payers (i.e., insurance companies, Medicare, or Medicaid) to obtain reimbursement.[287]

Typically, clinical trials by small biotech companies are conducted through clinical contract research organizations (clinical CROs) available for hire. It is also fairly common to hire regulatory consultants, biostatisticians, etc. to help with preparing for clinical trials. Often, a clinical CRO will have recommendations and be able to help facilitate the necessary introductions to needed services depending on what they have in-house themselves.

In the case of Centivax, Garzone guided us in the selection of our clinical CRO, helped hire biostatisticians to design the study, scheduled a pre-IND meeting with the FDA to get feedback on our study design, and helped write the clinical protocol and IND.

To summarize, before clinical trials can begin (in addition to the target product profile, or TPP, which will be discussed in depth later and should ideally have been completed before this), a non-exhaustive list of steps to complete include:

- Selecting CROs and other third-party vendors that will facilitate execution of the trials, including subject recruitment
- Hiring biostatisticians to help design the study to determine the number of subjects needed for a typical design to prove the hypothesis and provide the operating characteristics of the study
- Scheduling a pre-IND meeting with the FDA to get feedback on product specifications, the nonclinical studies needed to support the Phase I study, and the study design elements
- Writing the IND that includes the clinical protocol, the investigator brochure, and the general investigative plan

GETTING INTO THE CLINIC

Beginning clinical trials is a noteworthy milestone because it demonstrates a certain level of legitimacy and competency to be able to execute to that point. Additionally, the most powerful data in drug development are human data, and clinical trials are the point at which that data can be generated. Progressing to the point of clinical trials de-risks the potential drug (chapter 7) and serves as a value inflection point for the company (chapter 9).

The phases of clinical trials are generally described as follows:[288,289]

Phase I

Phase I trials typically include a "smaller" number (of human participants, approximately between twenty to eighty "normal, healthy volunteers" (in the context of clinical trials, this is considered small!). The overall goal of Phase I studies is to look at

safety. These studies are designed to allow investigators to see what effects an investigational new drug has in human subjects and to determine whether the potential new drug is safe by evaluating what happens to the compound in the body by monitoring patients for the occurrence and severity of side effects they may experience. Phase I studies also seek to characterize drug metabolism as well as the pharmacological actions of the drug (e.g., the pharmacokinetics and pharmacodynamics). Additionally, these studies are used to detect side effects associated with increasing doses. The investigator can get a further idea of what the correct dose level may be to maintain the needed pharmacologic effects that are desired.

Sometimes, in severe diseases for which there are few options (such as late-stage cancers), the FDA allows the drug to be tested in the patients themselves. In cases such as these, Phase I trials can sometimes also look for early evidence of efficacy of the drug, but in certain indications, such as migraine, early proof-of-concept studies can be run in Phase I as well.

Phase II

If the drug has successfully passed Phase I trials, the drug will proceed to Phase II, where it is tested on a larger group of subjects (generally several hundred subjects, depending on the type of disease; smaller indications often imply a lower numbers of subjects). Phase II studies are intended to evaluate the safety *and* efficacy of a new potential drug in *patients*, and this is often the first time you can study your drug in the patient population. These studies sometimes involve one or more treatment arms, which allow for the safety and efficacy of the new investigational drug to be compared to other available treatments, tested in combination with other therapies, or examined as different formulations of the same treatment (e.g., oral versus subcutaneous versus intramuscular

administration). Phase II studies are also typically designed to determine whether different dosages of the compound have different effects. Various dosages of the compound are given, and patients are monitored to determine side effects so the desirable dosing regimen can be better implemented. (This is similar to Phase I but with greater numbers of participants and in your patient population of interest.)

Phase II is the first time efficacy can be directly studied, which is why small biotech companies will sometimes be acquired after a Phase II trial. The acquirer is able to have some level of assurance that the drug will work in people. The Phase III trial that follows next is also the most expensive, so it can be helpful for the biotech company to be acquired before that point.

Phase III

Phase III trials are the last trials before the final dossier is submitted to the FDA. In most cases, two well-controlled trials are required; however, the specific trials that would be needed are discussed with the FDA at the end-of-Phase II meeting. If it's a small molecule, this final submission is known as a new drug application (NDA), and if it's a biologic, it's known as a Biologics License Application (BLA). Phase III trials are the largest, most expensive studies. They often require between several hundred (on the very conservative side) to several thousand patients, depending on the disease being studied. These trials look at both safety and efficacy (emphasis on the latter). A large number of patients is required to confirm both the purported benefit *and* safety of the drug. As with Phase II studies, Phase III studies can also include multiple arms. This information is ultimately used to verify which claims a sponsor (i.e., the company/ies) can make in final drug labeling.

Phase IV

Phase IV studies take place after FDA approval and are known as post-marketing surveillance trials. These studies are designed to collect more efficacy and safety information about the new medicine in large numbers of patients and/or to compare the drugs' efficacy against other available treatments (or in conjunction with these other treatments). Phase IV studies are intended to evaluate the long-term effects of the new medicine, which means that factors like rare adverse reactions can be studied or detected.

Typically, in Building Backwards, it is important to lay out the entire development program from Phase I through Phase III from the beginning of the company. It's possible to get a rough estimate of these numbers even before formally hiring a clinical consultant or determining the statistics. You can make educated assumptions about trial size, endpoints, time, and investigative sites by reviewing the literature and ClincalTrials.gov. For example, with Centivax, when we were initially conceptualizing the clinical trial for our therapeutic antibody, we could look at other antibody therapeutics (such as those by Regeneron and Eli Lilly) that had already gone through trials. We could see which endpoints the FDA required them to meet for each phase as well as how the studies were designed. This was helpful in informing our expected trial design. For example, during the pandemic, we discovered the FDA was allowing Phase I trials to occur with patients, rather than in healthy volunteers. Sick patients had access to a novel medical option, and companies got speedier access to data that confirmed whether their drug did (or did not) work as intended.

Estimating company costs over time is also an important part of Building Backwards. As clinical trials are a major driver of cost, estimating trial design will also provide a general idea of how much

running each phase of trial will cost. Generally speaking, clinical trial costs are calculated as a cost per patient. Rough estimates for this are available online. Knowing the number of subjects to be studied, the type of assessment to be done, and the timeframe of the study allows the developer to project clinical trial costs on a per-subject basis.

SELECTING INDICATIONS

Thinking back to chapter 2 and the FAAH story, an essential question in the development plan of a new medicine can often come down to which initial patient population to pursue in clinical trials, as different indications have different implications for potential market size and, therefore, revenue. Building Backwards thinking in clinical trials means considering early on which clinical indication makes sense based on *both* the preclinical data as well as eventual market size/returns. In short, simply "following the science" and running an organization with a cost structure such that your eventual market, even if it is smaller, will provide a suitable return on investment is often the most effective strategy. Smaller markets have their advantages too: (for better or worse) higher per-patient pricing can often be charged, the development time and therefore costs are typically lower, usually a smaller number of participants is needed for the clinical trials, and getting one indication approved can often make it easier to get follow-on indications approved.

"To me, if you follow the science, develop your initial indications around the science, and execute efficiently, you can generate revenue quickly, and that's a good starting point," said Garzone. "It can also lead to a potential exit opportunity, or once you get approved in a niche market, it's easier for you to expand to other

indications of varying market size to increase the company's revenue."

As an example, consider again the story of Gleevec (chapter 7), which was approved in 2001 for the treatment of chronic myeloid leukemia (CML), a rare and deadly form of cancer. As Gleevec was such an effective drug, subsequent to its approval for CML, Gleevec was approved for treatment of gastrointestinal tumors (GIST), expanding the market size of Gleevec. Today, Gleevec is approved for four other indications in addition to CML and GIST. As of 2020, Gleevec generated $1.2 billion in sales that year alone, making it a very successful drug.[290]

ORPHAN DESIGNATION AND THE ECONOMICS OF SMALL MARKETS

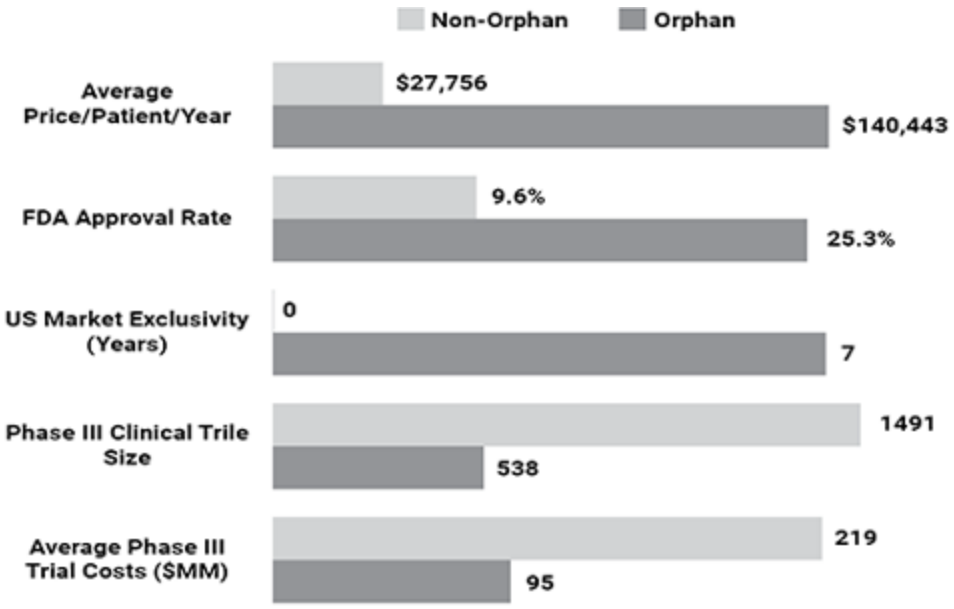
To further drive home the possible potential of smaller indications under certain circumstances, we will discuss developing drugs for what are known as "Orphan Indications." The FDA awards "Orphan Designation" to drugs in development for diseases that have fewer than two hundred thousand US patients. On an economics level, the orphan designation often allows for a development plan affordable by a small company. This has been the strategy pursued by JP Fairbank, CEO and founder of Nymirum Therapeutics.

"Orphan Designation can be an attractive way for a small biotech with limited capital to develop a drug all the way through the clinic," Fairbank told me. "Orphan diseases are also high impact since larger companies typically won't pursue indications with smaller market sizes, leaving orphan disease patients with lower hopes for a treatment."

The number of rare diseases is huge—more than seven thousand.[291] Some orphan diseases can act as a "wedge" in the market, whereby getting an initial indication approved can result in a lower initial financial reward but lead to later label expansion. An example of this is Crestor, which was initially approved for smaller populations of hypercholesterolemia and dyslipidemia.[292,293,294] Though the initial indication was not very profitable, it enabled Crestor to later expand the label to more profitable indications. As Garzone noted, it can be easier to obtain approval in follow-on indications once a new medicine already has approval for one.

"Now, Crestor is one of the biggest selling drugs of all time, making about $6 billion a year," Fairbank said. "If Crestor had tried to go after general high cholesterol first, Lipitor was already on the market, so they would have had to prove superiority to Lipitor. By going after approval for pediatric familial hypercholesterolemia first, there was no standard of care to beat and a high medical need because there was literally no treatment available."

The other possibility regarding orphan disease drug development is related to indications with high pricing power and thus highly favorable economics. To understand why the returns on orphan drugs can be so immense, see the figure below. Not only are trial sizes smaller (e.g., of only ten to twenty participants, leading to lower costs), the FDA approval rate can be higher, and the market exclusivity is longer. These lower costs, decreased risk, and higher prices often translate to much better returns for a small company.



Orphan drug versus non-orphan drug economics. Orphan drugs have favorable economics, particularly for small companies. Image Courtesy of JP Fairbank.[295,296,297,298]

Orphan Designation can be significant for a company because it allows multiple additional advantages:[299]

1. **Marketing exclusivity.** For seven years after product approval, the FDA will not approve a subsequent drug for the same use or indication. This gives additional exclusivity rights on top of any patent protection.[300]
2. **Priority review vouchers.** This gives the drug sponsor the assurance that for its next drug NDA/BLA submission, the FDA will review within six months of submission (compare this to the average one-year timeline). These priority review vouchers can also be sold to another company. The sale or use of such a voucher further rewards a biotech company for developing a drug for an orphan indication. (To a large pharmaceutical company that may purchase a priority review voucher, even paying $70 million for the voucher makes economic sense if the pharmaceutical company expects to earn billions per year in revenue.)[301]

3. **Streamlined approval.** The FDA reviews and responds to NDA/BLA applications expediently. For example, the case of Ivacaftor, which was approved only about three months after submission:

- Oct 26, 2011: Submitted
- Dec 15, 2011: Priority review granted
- Jan 31, 2012: Approved

4. **The sponsor receives additional R&D tax credits**. The sponsor receives a 25 percent federal tax credit, which can be applied to prior year or over as many as twenty years.

5. **Waiver of Prescription Drug User Fee Act (PDUFA) fees for Orphan drugs.** In other words, no NDA/BLA fees—this was valued at approximately $2.9 million in 2021.

6. **Availability of nondilutive government grants to promote/incentivize orphan drug development.** $30 million in funding was set aside for this purpose between 2013 and 2017.[302]

- Research grants from the Office of Orphan Products Development (OOPD) to support clinical studies

7. **The FDA gives regulatory assistance and guidance in developing the overall drug development plan.**

- Fairbank said, "If the FDA itself is helping you write your milestones, they are less likely to object to those milestones later."

In summary, Building Backwards to an orphan indication can be an effective development strategy for a company and, moreover, result in extremely high impact medicines for a patient population in need.

THE IMPORTANCE OF A TPP: A TOOL FOR EARLY SUCCESS

Now that we have established the intricacies of how clinical trials work and the significance of strategically selecting an indication, we can return to our discussion of how to Build Backwards to a drug's end label. A specific tool for doing this is a target product profile (TPP). A TPP should be created early on in the life of the company and is a specific tool used throughout the development process.

A TPP is a planning tool used to outline the desired characteristics (i.e., "profile") of your future product, and includes, but is not limited to:

- Intended indication(s) (i.e., disease(s) the drug can be used for)
- Patient population, including demography (i.e., whether drug can be used on all patients with a certain disease, or only a subset of patients with this disease)
- Dosage form and administration
- Clinical pharmacology: pharmacokinetics (absorption, distribution, metabolism, excretion), use in special populations e.g., liver dysfunction; prolongation of QT interval (a measurement of the heart via electrocardiogram); fed versus fasted states

Creating a detailed TPP that includes "best case" and "base case" possible end labels for each of these categories can be very helpful in planning early experiments as well as designing clinical trials. Garzone recommends the following list, which isn't meant to be exhaustive but will help you think through the details of the possible relevant issues and questions you should consider early on. Understanding every detail of the following list is less important than generally understanding the *type* of questions that a TPP helps you plan to answer:

- Indication

– Best initial patient population?
  - Which demographic factors are important (e.g., evaluate prevalence of disease in a particular gender)?
  - Are genetic driver mutations relevant (this is particularly important in oncology)?
  - Any precedent set for the target. How can my product be differentiated from the drugs that currently exist in the space?

- Molecule type: biologic (e.g., monoclonal antibody), peptide, small molecule.

The questions in this category determine chemical properties/stability of the molecule and how it can be formulated.

– Potency in micromolar or picomolar (or nanomolar)?
– Is there a pro-drug involved?
– What is the delivery? Can it be systemic or local?
– Does the molecule need to be orally administered? Is parenteral administration (infusion or injection) acceptable?

- Pharmacokinetics
  – How long do you want the drug to be circulating (i.e., half-life criterion.)?
  – Is it bioavailable?
  – If it's oral, subcutaneous (SC) or intramuscular (IM), can you reach the target at concentrations of the IC50 (concentration at which there is half of the maximum inhibition) or EC50 (concentration at which there is a half maximum response) for whatever it needs to be to elicit a response?
  – Is it a substrate, inhibitor, or inducer of cytochrome P450 enzymes?
  – Is it a substrate for transporters?
  – How is it eliminated—by metabolism or renal excretion?

- Frequency of dose feeds into the route of administration decision, whether the drug needs to be intravenous (IV), subcutaneous (SC), intramuscular (IM), or oral. This, in turn, affects requirements about chemical properties, concentration, and stability of the molecule, which also help determine how the drug needs to be formulated.
  - Chronic or intermittent dosing
    - Chronic: indicates the route of administration likely needs to be oral and thus very safe in order to justify daily exposure (People often will not take injections shots on a daily basis unless it's a life-threatening illness such as oncology.)
    - Intermittent: one time only, dosing by cycles (e.g., oncology indications)
- First in class or not?
  - If yes, can a drug be created for that target?
  - What is your differentiating factor from competitors going to be? Which data need to be gathered to demonstrate this preclinically?
  - Understanding the competitive landscape. To be better, are we going to focus on being first in class or best in class? Differentiation is important.

Each of these factors will align with the final end label that would likely be desirable to label the final product. All this information feeds into which preclinical *and* clinical data will be necessary to achieve the desired label.

Here's an example of a very simple TPP, below, for a potential drug for ischemic stroke patients:

Product Targets	Base Case Scenario	Best Case Scenario
Primary Product Indication	Emergency medicine for acute stroke patients immediately on hospital arrival.	Emergency medicine for acute stroke patients in the community even before arrival to hospital.
Patient Population	Adults of all ages with moderate to severe stroke, with potential concurrent use with tPA (treatment used for blood clots)	Adults of all ages with moderate to severe stroke, with potential concurrent use with tPA or replacement of tPA (treatment used for blood clots)
Treatment Duration	Acute	Acute
Delivery Mode	IV	SC
Dosage Form	Solution in *pre-filled syringes*	Solution in *autoinjectors*
Regimen	Infusion or bolus	Bolus
Efficancy	20% or more favorable in comparison to standard of care on minimal or no disability 30 days after treatment in patients using: Modified Rankin Scale (score≤1)and NIHSS (score≤1). Exporatory endpoint: imaging evidence of revascularization.	30% or more favorable in comparison to standard -of-care on minimal or no disability 30 days after treatment in patients using: Modified Rankin Scale (score≤1) and NIHSS (score≤1). Exporatory endpoint: imaging evidence of revascularization. Functional outcome in addition to Rankin: overall survival increased and reduction in symptomatic intracerebral hemorrhage (sICH)
Risk/SIde Effect	Devoid of symptomatic intracranial hemorrhage and significant mechanism related adverse effects.	Devoid of any symptomatic hemorrhage and any mechanism related adverse effects.
Therapeutic modality	Protein	Protein

Example TPP. Data courtesy of National Institute of Neurological Disorders and Stroke, input by Pam Garzone.[303]

Referring to the chart above, you can note that the major differences between the base-case and best-case scenario are largely around:

1. Timing of drug administration
   – The base case is hospital administration whereas the best case is outpatient basis if SC
2. Indication: ischemic stroke
3. Patient population

– Used concurrently with the standard of care versus replacement of the standard of care (tPA, or tissue plasminogen activator, which is an IV medication that dissolves the stroke-causing blood clot)[304]

4. Dosage form
   – Prefilled syringes versus autoinjectors (prefilled syringes often require hospital administration, while autoinjectors can be used at home or in an outpatient setting)
5. Efficacy
   – Twenty percent improvement over standard of care versus 30 percent; but both have the exploratory endpoint of revascularization. The best-case scenario also has functional outcome endpoints of overall survival. The significance of this is that to obtain approval and/or reimbursement, the FDA and insurance companies want to know the 10 percent improvement in revascularization in the best-case scenario *actually* translates to practical benefit. Thus, measuring revascularization has to be tied to improvement in quality of life. This can be helpful as this can also be studied preclinically through animal experiments.

As you can see, creating a TPP does not have to be a difficult or cumbersome process. It's a short document you can create yourself early on in the drug's development. This document becomes helpful for conversations with the FDA to determine whether your clinical trials endpoints are properly worded and adequate to support your ultimate end label.[305] In early stages, a TPP is most useful to guide preclinical R&D work by ensuring that the preclinical data you collect *actually* supports the promotional claims you plan to make, as in the example above in which functional endpoints are likely needed in order to obtain reimbursement. For example, since the "best case" label indication for *pre*-hospital administration simply implies a higher efficacy bar in revascularization (i.e., 30 percent

versus 20 percent), the way you would Build Backwards to get early evidence for this is by conducting certain preclinical experiments. Specifically, you might evaluate efficacy in an acute model of stroke in animals. The brains of the animals can then be removed and evaluated for revascularization, giving you a sense of whether the drug seems to be working more like your base-case or best-case scenario.

In the clinic, you could then collect data to justify this labeling by designing your clinical trial in a certain way. Specifically, you would identify the time of the stroke relative to hospitalization to confirm the "acute" setting (i.e., to confirm the treatment duration category from the TPP). Then, the endpoints would be an imaging endpoint to confirm revascularization, along with safety assessments such as lab values, vital signs, questioning symptoms, and patient-reported outcomes (e.g., resumption of daily activities, improvement in speech, walking, cognitive function, and so on).

In sum, as Garzone stated: "Scientists need to know that they don't need to pursue every interesting developmental research problem. Pursue the questions that arise that will specifically help you set up your clinical program. This looks like Building Backwards from your final drug label using a TPP."

In short, TPPs can be used for the following:

- To guide R&D (such as molecular characteristics or formulation work) to reach desired characteristics of the drug.
- To facilitate identifying characteristics to differentiate your drug from competitors.
- To frame submission of product filings to understand the desired end product and see how the data measures up. In terms of regulatory planning (such as IND/NDA/BLA submission), product

> fillings contain a plethora of information about the drug, including pharmacokinetics and pharmacodynamics. Both the originating company and the FDA now often use TPPs in this fashion.[306]

To further highlight the importance of a TPP, here's a real story from FDA documentation about what happened when a company ***didn't*** use a TPP to inform their early/preclinical development:[307]

A company, Company Z, developed a new drug that hit a target similar to other, already-approved molecules within that drug class. Although the new potential drug had a novel mechanism of action and Z wanted to claim this new mechanism of action on its final drug label, it did not clearly define this as a goal early on through use of a TPP.

What this meant in practice is that Company Z did not discuss with the FDA which endpoints would be needed in a clinical trial to ultimately make this claim for a novel mechanism of action. Because it did not do this, it inadvertently failed to conduct the necessary preclinical and clinical studies to provide adequate evidence supporting the desired claims. Thus, it could not ultimately make these claims on its drug label.

Although we can only speculate about the impact this ultimately had on Company Z, this very likely might have resulted in a failed product on the market or the need to rerun trials—costing time and money—to be able to make the claim about a novel mechanism. As in the example of Abbott-ABC from chapter 4, the specific claims made on the end label are often so highly tied to a drug's market research and positioning, they can make the difference between success and failure. Without differentiated claims—such as a novel

mechanism of action—it's difficult to carve out a corner of the market among competitors.

Had Company Z created a TPP early on in development, it could have potentially avoided this outcome. Use of a TPP would have aided Company Z in communicating its desired label claims, and the FDA thus might have been more helpful in identifying the type of data and trial design needed to support these claims. Company Z then could have integrated this information into its existing development program *before* it reached the point of having its drug approved through a trial that didn't validate the claims they desired to make.[308] It also would have allowed for labeling negotiations with the FDA about the relationship between the endpoints and the end label to occur much earlier in the process, saving Company Z substantial money and time.[309]

In summary, it's well worth it to plan your desired end label very early on in the process and *then* Build Backwards to design experiments and protocols that will support the claims you wish to make on the market.

Centivax presents another example of Building Backwards through a TPP. In developing an antibody therapeutic against SARS-CoV-2, we knew we wanted a versatile drug. We knew, for example, that if we wanted to treat subjects postexposure, i.e., persons exposed to (confirmed) SARS-CoV-2 in COVID-19 outbreak situations as well pre-exposure prophylaxis and individuals with confirmed SARS-CoV-2 infection but who are asymptomatic or experiencing mild symptoms, convenient administration would be imperative. Existing antibody therapeutics at the time were only available through IV administration although other routes were being evaluated in clinical trials. IV administration is a procedure that must be

conducted by trained health care professionals, typically in a hospital setting, over the course of several hours. Thus, we wanted to do something different to make our antibody for COVID-19 broadly accessible for varied patient populations.

Specifically, we wanted our end product label to allow for intramuscular and/or subcutaneous administration. However, delivering the drug intravenously also requires large volumes of fluid, especially compared to SC and IM methods, where only a limited volume of liquid can be delivered. This told us—long before we ever actually started a human clinical trial—that we needed to gather certain data around concentration and stability (i.e., the molecule needed to be stable at high enough concentrations to allow for IM/SC formulation). Gathering these data extremely early on allowed us to start Building Backwards to our end label from the beginning.

After formulating the concentrated version, the next consideration was whether or not to provide the drug in prefilled syringes, as development and approval of prefilled syringes can sometimes take significant additional time. Awareness of this potential obstacle from the beginning and being able to plan for this early made the process more seamless down the road.

On a different note, at the outset, we also made other plans for our antibody. We knew that developing an IV formulation as well would make sense for mild to moderate COVID-19 cases who are hospitalized, as patients who are ill may have reduced peripheral circulation, reducing the effectiveness of an IM or SC drug by prolonging its absorption resulting in delayed response compared to an IV, which is much better suited for this application. Thus, we also planned for an IV formulation and trial early on. We knew this wouldn’t require the same amount of formulation and stability

testing as SC or IM, and it would greatly improve the versatility and marketability of our drug.

Building Backwards is fundamental to efficient linking of preclinical drug development with clinical trials and your goals for the market. Understanding the three phases of clinical trials and how to Build Backwards to an end label through use of a TPP can help you plan effectively for clinical trials early in the company's life. Doing so is key in planning experiments and economic projections early on and will ultimately ensure your new medicine is able to reach the patients who need it most.

Next, we will discuss how Building Backwards informs intellectual property strategy.

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280 "Drugs@FDA: What's in a Drug Product Label?" US Food & Drug Administration, updated May 6, 2016.

281 "Drugs@FDA: What's in a Drug Product Label?" US Food & Drug Administration, updated May 6, 2016.

282 Aroon D. Hingorani et al., "Improving the odds of drug development success through human genomics: modelling study," *Scientific Reports* 9, no. 18911 (2019).

283 Ibid.

284 Joseph A. DiMasi, Henry G. Grabowski, and Ronald W. Hansen, "Innovation in the pharmaceutical industry: New estimates of R&D costs," *Journal of Health Economics* 47 (May 2016): 20–33.

285 "Standard Costs (in thousands of dollars) for Components of the Process for the Review of Human Drug Applications," US Food & Drug Administration, updated August 13, 2018.

286 Ibid.

287 "What is a clinical trial and how does a trial work?" Roche, accessed October 20, 2021.

288 "Step 3: Clinical Research," US Food & Drug Administration, updated January 4, 2018.

289 Note that the timeline and number of patients required for each phase can vary drastically by indication. The numbers below represent the average as given by the

sources utilized.

290 "Full Year 2020 Product Sales," Novartis, accessed October 20, 2021.

291 "FAQs About Rare Diseases," National Center for Advancing Translational Sciences, accessed October 10, 2020.

292 "Dyslipidemia," Merck Manual, accessed October 10, 2020.

293 Pediatric familial hypercholesterolemia (FH) is a genetic cause of premature coronary heart disease. If treated and diagnosed early in childhood, children with FH can have normal life expectancy. Dyslipidemia is elevation of plasma cholesterol, triglycerides, or both.

294 Albert Wiegman et al., "Familial hypercholesterolemia in children and adolescents: gaining decades of life by optimizing detection and treatment," *European Heart Journal* 36, no. 36 (September 2015): 2425–2437.

295 "Orphan Drug Report 2017," EvaluatePharma®, February 2017.

296 OECD, *New Health Technologies: Managing Access, Value and Sustainability* (OECD Publishing, 2017), 87

297 "Frequently Asked Questions on Patents and Exclusivity," US Food & Drug Administration, updated February 5, 2020.

298 Earl Gillespie et al., "Orphan Drug Development—What are the Real Costs?" Health Advances Blog, April 10, 2019.

299 Scientific Writing Team, "FDA Orphan Drug Designation for Rare Diseases," Nuventra, April 21, 2021.

300 "The Enduring Role of Orphan Drug Exclusivity for Biologics," Pharmaceutical Law Group, October 2, 2021.

301 "The Food and Drug Administration's Orphan Drug Program," Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation. Breakthrough Business Models: Drug Development for Rare and Neglected Diseases and Individualized Therapies: Workshop Summary. (Washington, DC: National Academies Press, 2009).

302 "Orphan Drug Act—Relevant Excerpts," US Food & Drug Administration, updated March 9, 2019.

303 "CREATE Bio Example: Target Product Profile (TPP)," The National Institute of Neurological Disorders and Stroke, updated January 19, 2020.

304 Peter O'Donnell Jr., "Tissue Plasminogen Activator," UT Southwestern Medical Center, accessed October 20, 2021.

305 Multiple examples of TPPs and templates can also be found online. See FDA document "Guidance for Industry and Review Staff: Target Product Profile—A Strategic

Development Process Tool" for more info.

306 "Target product profiles," World Health Organization, accessed October 20, 2021.

307 "Guidance for Industry and Review Staff Target Product Profile—A Strategic Development Process Tool," US Department of Health and Human Services, Food and Drug Administration, and Center for Drug Evaluation and Research (CDER), March 2007.

308 Sponsors (i.e., drug developers such as biotech companies) often hold formal meetings with the FDA. These meetings are formally requested in writing, and there are various types of meetings. A common early meeting is a "pre-IND meeting" (also known as a "Type B meeting"), which is often conducted to receive early feedback from the FDA on clinical study design as well as on data collected thus far before the sponsor submits the IND. Type B meetings are typically scheduled within 60 days of request, so they should be requested around two months before the desired meeting time. For more info, see book resources at my website, bioventureadvising.com.

309 Note that creating the drug label is a collaborative process and "negotiation" between the FDA and the sponsor. The sponsor has goals for the label and the FDA has certain standards for agreeing with particular labeling. This is part of the benefit of the TPP.

CHAPTER 12

BUILDING BACKWARDS TO INTELLECTUAL PROPERTY

"As with any game, you should play the patent game with the end in mind. If you don't know what you want, or why you want it, then it will prove impossible to devise an optimal strategy."

—VANCE V. VANDRAKE, *THE PATENT GAME*

"We can get a new composition of matter patent!" my boss and CEO of Laurel Therapeutics, Martin ("Marty") Sanders, MD, exclaimed. As a seasoned biotech entrepreneur, Sanders did not often get so excited.[310]

We were on the phone discussing our company, Laurel Therapeutics. We had just received exciting new data back on our eye drop, EBIN, for treating wet age-related macular degeneration (wAMD; see chapter 5 for the background on this project).

The data came from a CRO (Contract Research Organization, i.e., outsourced research) that we had hired to optimize EBIN's delivery to the back of the eye by creating a novel formulation.[311,312] This experiment was informed, in large part, by my customer development work at the ophthalmology conference (chapter 5). The data showed the new formulation the CRO had created increased the amount of drug delivered to the back of the eye by more than tenfold. The bonus? This new formulation meant we could file an application for a composition of matter patent, which is typically

considered one of the stronger types of patent protection. It also, very significantly, would "reset" our intellectual property (IP) clock back to zero.[313]

On the other end of the phone call, I smiled. "This is big for us," I said.

TICKING CLOCKS AND PATENTS: AN OVERVIEW

Why would an IP clock reset be so impactful for Laurel Therapeutics? It had to do with patent life.

Though patents are important in many businesses, in biotech, patents are paramount. Why? Unlike non-biotech companies, where assets are largely tangible (e.g., real estate, equipment, inventory such as clothing for a clothing store, etc.), for a biotech company, patents are what you "own" in terms of novel science.[314]

However, a patent does not *give you rights* to your invention. It gives you the right to *exclude others* from using your invention over a certain period, typically twenty years.[315] This enables a company to develop novel science theoretically without worry of someone else infringing upon its original work.

Marty, who has become very adept at biotech IP as CEO of several biotech companies, often emphasizes the importance of patents to me by saying: "Stephanie, patents are the most important thing to get right… patents are what you own as a company. Without patents, you have nothing."

Vance VanDrake, JD, a patent attorney and start-up cofounder, highlighted how crucial patents also are for future M&A or valuation calculations. "When you are trying to sell your company, your intellectual property portfolio and patent strategy can play a major

role in defining the purchase price," he said. "An early stage company's revenue and profits can lag well behind a reasonable valuation.... Intellectual property can be used to boost the purchase price to an acceptable amount by attributing value to this intangible asset. Without intellectual property or a patent strategy, it can be more challenging for you to negotiate a high sale price.... Being able to articulate your intellectual property position can also dissuade the potential acquirer from passing on your offer and developing a competing technology themselves."[316]

Thus, part of Building Backwards requires you to consider IP, and consider it early—often before the company even formally begins to operate.[317] This allows you to build company value from the start and helps in preparation for a future M&A, financing round, or other partnership. They're also essential for getting investment, as any VC will conduct diligence on your IP; that is, they'll investigate how strong your patents are. VCs will often pass on deals where the IP coverage is not strong enough because this dampens both the potential of the invention on the market and thus the potential for a sizeable exit.

While a patent awards you the right to exclude others from using your invention, at least one exception to this rule is known as the "safe harbor" provision (also known as the Hatch-Waxman Act)."[318] Under this provision, it is legally allowable to use another party's patented invention for *research purposes*, so long as the research activity is "reasonably related" to the "development and submission of any information" under the federal laws governing FDA approval.[319] Therefore, testing another company's patented compound in preclinical experiments or clinical trials, for example, is not patent infringement.

Another concept central to the discussion of IP protection is Freedom to Operate (FTO). FTO is the ability of your company to operate in a space without infringing upon other groups' IP. While a patent gives you the right to exclude others from using your particular invention, this does not necessarily mean you are able to make a full product or build your technology without infringing on *someone else's IP*. FTO means that it is "commercially safe" for you to make or sell your own product without infringing on a third party's IP. On the other hand, having your *own* patent makes it more difficult for *someone else* to infringe on *your* IP.[320] Thus, FTO is separately determined from patent rights, and it is important to have a strategy around FTO when building and working with IP portfolios. We will return to the concept of FTO.

UNDERSTANDING PATENTS AND HOW TO OBTAIN A PATENT

A patent differs from other types of IP protection, such as copyrights, trade secrets, and "know-how" where protection arises automatically.[321] A patent in the United States requires a formal process of filing and eventually receiving approval for your claims via the United States Patent and Trademark Office (USPTO).

Specifying "United States" here is important because there is no such thing as an international patent. Patent laws vary from country to country, meaning the patentee will need to secure separate national patents in each country of interest. However, an international patent mechanism, called the Patent Cooperation Treaty (PCT), allows a single patent filing to be processed and then converted into individual regional or national applications. In this chapter, we'll focus mostly on patenting in the United States, but take note of this nuance and plan to talk to your patent attorney about international filing, if applicable. While filing an initial

provisional application is relatively easy, the bureaucracy of handling multiple national applications is substantial, and best practice requires the use of a specialized IP attorney.[322,323]

What can be patented? To obtain a patent, one's invention must satisfy all five of the following criteria: 1) not excluded from patentability, 2) sufficiently disclosed (i.e., "enabled"), 3) novel, 4) nonobvious, and 5) useful.[324]

1. Not excluded from patentability: patent inventions, not discoveries

A patent cannot fall into any categories excluded from patentability, such as laws of nature (e.g., you cannot patent gravity) or naturally occurring beings, objects, or phenomena (e.g., you cannot patent a human gene in the United States).

In the United States, 1) laws of nature, 2) natural phenomena, and 3) abstract ideas cannot be patented.[325] This means that a certain gene cannot be patented; neither can sunlight, nor can a new scientific formula.[326] This is because these are *discoveries*, not inventions.[327,328,329]

In the United States, you can patent any *applications* that result from scientific discoveries, such as new antibodies you develop or engineer. For instance, at Centivax, we cannot patent SARS-CoV-2, the virus that causes COVID-19. However, we can (and have) patented the antibody treatment for COVID-19 that we are developing.[330]

You *can* also patent transgenic animals, modified nucleic acids, tagged molecules, novel chemical reactions, new molecules you create, and methods of treatment. A famous example of a patented transgenic animal, for example, is "the Harvard mouse," which

obtained the first issued patent for a genetically modified animal. The mouse contained a recombinant oncogene sequence that increased its susceptibility to breast cancer and thus made the model suitable for cancer research. This paved the way for patenting other transgenic animals.[331,332]

2. Sufficiently disclosed: enough detail is provided (also known as "enablement").

When you patent something, you obtain the right to exclude others from using your invention in exchange for publicly sharing your knowledge. This is the fundamental logic underlying the awarding of patents by governments and is sometimes referred to as the "grand bargain." Thus, the intent of the patent system is not only to incentivize innovation but, significantly, to also incentivize *sharing the details* of innovation to improve the world's knowledge as a whole.

The result of this "grand bargain," in terms of patent requirements, is a patent filer must provide enough information to warrant a patent. A patent examiner will decide whether you have sufficiently adhered to these criteria. In biotech, **enablement** does not often require human data or animal models, or even necessarily *in vitro* data. In Marty's words: "Provided you have a believable rationale and a written description of what the invention is and how to use it, such that one skilled in the art could use the invention, you need minimal data. Occasionally you have a patent examiner who will say, 'I need an animal model,' or 'I need an *in vitro* assay,' and you either have to do it or negotiate with the examiner."

3. Novel: patent first, publish later

The invention must be new and not in the public domain before filing. In practice, this means that the USPTO patent examiner will search for what's known as "**prior art**." Prior art is a fancy way of

saying *any evidence that your invention was already known or available, even in part, before the date of filing of your patent application*.[333] The USPTO will search through all existing patents and publications, everywhere in the world, that were available before your filing date. If a single existing patent or publication discloses all the elements for your claimed invention, your application will be rejected.[334]

What's most important for scientists to understand is prior art also includes *any information that is shared prior to filing* in the public domain. This includes presenting at conferences, publishing your data in an academic journal, or even winning a grant, as your grant abstract (and sometimes further details of your work) are typically published online.[335] Prior art can also include participating in business incubators or accelerators, or even public use of your new invention. For instance, if you used your novel mutation screening device to analyze blood samples in a hospital lab, this could provide grounds for the USPTO to reject your patent. Moreover, striking a deal with a corporation prior to patenting could also count as prior art. Even informal communications can count as prior art: talking about your data in a hotel lobby, giving a department seminar, or even tweeting about your new discovery.

"Patent first, publish later" can be a shocking rule for some academic scientists, as it might seem to run counter to the scientific practice of open disclosure.

To clarify, this patenting rule does not mean you *cannot* publish or present your data or findings relevant to your patent. It simply means you should keep secret any key elements of your research *until* you have filed a patent (often a **provisional patent application**, defined below). You do not actually need the patent to be issued, so long as the presentation or publication date of your

research comes *after* the date of patent filing.[336] In the United States, you have a one-year grace period from the time you make a public disclosure of your invention to file a patent before you are barred from filing a patent forever due to lack of novelty. Outside of the United States, however, there is no such grace period. Public disclosure even a *day* before your patent filing could eliminate your ability to obtain a foreign patent.[337] This can be catastrophic for a biotech company, as foreign patent coverage will almost always be desirable. (Eventually, you or a future acquirer will want to be able to sell your medicine abroad without fear of others infringing upon your invention.)

As stated by Vid Mohan-Ram, an acclaimed scientist and IP lawyer: "In the understandable rush to get published and funded, scientists tend to spill the beans too early and in too much detail for them to ever win a patent. Keep in mind that a patent does not give you the right to make your invention—it gives you the right to stop others from making your invention. Therefore, if you don't file a patent application within a year of disclosing it to the public, you may lose the right to stop others from exploiting your invention for their own gain."[338]

Additionally, if you can make your public presentation or abstract less detailed, such that someone cannot copy your work, that information may not impact the difficulty of obtaining a patent. For example, as written by Mohan-Ram, "[I]nstead of spelling out each and every detail of your research when giving presentations, broadly outline the events that led to your invention. Consider using codes to describe your data or the conditions you used. Talk with your in-house legal agents and lawyers about how best to organize your presentation. It may go against everything that you've been taught about enlightening the scientific community, but at the outset,

being vague and general will be more beneficial patent-wise than being precise, explicit, and momentarily famous."

Also, note patenting need not be an overly cumbersome process. This is especially true if you are at a university; it is the full-time job of the university tech transfer or intellectual property office to facilitate patenting (and licensing). It can be as simple as running a potential new manuscript, new data, etc., past your institution's IP department. They can use this information to file a patent application, or a **provisional patent application,** on your behalf.

A provisional patent application is another crucial concept to understand. This "pared-down" type of application allows you to file without formally writing claims, which can be a difficult process (more on claims later in the chapter). By filing a provisional application, you are able to set a priority date using something as simple as, for example, a PowerPoint presentation, without having to commit to claims. However, the provisional also must be sufficiently enabled if you want the provisional to support later filings, as a priority date is only set for what is disclosed. After filing a provisional, you have twelve months from the date of filing to decide to file a subsequent nonprovisional patent application (or PCT application or foreign national stage application for international filings). These twelve months are *in addition to* the twenty years of protection that begins at the time of filing a nonprovisional, PCT, or national stage application. The benefit of filing a provisional patent application for a scientist is it's easy and provides additional time to collect data without compromising on the priority date. Also worth noting, provisional applications are 100 percent confidential, so they do not set prior art if you choose not to pursue a subsequent nonprovisional application. Once an inventor has filed a provisional,

he or she is able to legally say they have a "patent pending," which can be helpful for signaling the intent to pursue IP protection.[339]

The "too long didn't read" version of this patenting rule? File a patent application *before* broadly sharing your work, and work with your institution's IP office to determine how to balance filing while continuing to advance and disseminate your scientific work. Do note, of course, there are pros and cons to filing through your university, as this means you will likely require a license to use the technology in a future start-up, which means sharing future potential upside (such as equity, royalties, etc.) with the university.

Remember what we said at the beginning of the chapter. Your IP is what you own and represents much of your business's value. Eliminating your ability to obtain a patent can mean eliminating your ability to ever start a business around your invention.

4. Nonobvious: there must be a demonstrable aspect of innovation.

This must be the kind of innovation that is not clearly obvious to someone "skilled in the art" based on innovation that already exists.

For this requirement, the patent examiner will usually combine two or more prior art references to reject the application claim because the invention is "obvious." For example, adding an extra die to the Monopoly game would likely be considered an obvious innovation and could probably not be patented. Although the original Monopoly game patent has long expired (it was issued in 1935) and did not include an extra die, a USPTO examiner would likely still reject this patent idea as being obvious. By contrast, a special kind of game board that, for example, was magnetic and resistant to spills, could likely be a patentable invention.[340] An important nuance that is particularly relevant in biotech is the "bar" for obviousness is not

obviousness to just anyone, it must not be obvious to someone who is *skilled in the art*: i.e., to someone in your field with roughly comparable skills.

5. Useful: your invention must be capable of industrial application (i.e., it has to have some sort of use.)

Traditionally, this is an easy qualification to overcome. If you're looking to patent something, you're probably confident that it has a use. However, more recently, this part of the patent law has been applied to render some inventions in the field—including medical diagnostics—as *patent ineligible*.[341] Therefore, it's important to work with a patent attorney experienced in the subject field as they can help you put together a strong initial application.

An example of patent applications that were previously first rejected on the basis of utility were hair regrowth treatments and the associated compounds. These treatments and compounds were not believed to be "useful" because it was believed regrowing hair was not possible. Once it was scientifically proven that in some cases it is, however, this proved that the inventions had sufficient utility.[342]

If your invention fulfills the five criteria specified above, there are at least two and up to three additional steps to obtaining a patent:

1. Writing claims

Patent claims—namely the way in which these claims are written—are one of the major factors in assessing the strength of a patent. Claims are the "legal instrument" from which patent infringement is determined. While a patent typically also contains drawings and specifications (e.g., scientific paper-like figures), the claims legally define your invention. The claims thus determine how easy or

difficult it is for someone to copy your invention without technically infringing on your patent.[343]

Claims range somewhere from "narrow" (highly specific) to "broad" (very general). The first claim in a patent is the **"primary claim,"** which defines the *broadest scope of coverage* in the patent claim set. Claims that follow are often **"dependent"** on the primary claim and serve to further narrow the claim set. For there to be infringement on a claim, someone must perform or include every element listed in a claim. For example, if a claim requires elements A, B, and C, but someone can create the apparatus or complete the method by only doing B and C, there is no infringement.[344] Thus, you ideally want "broad" claims because broad claims have fewer elements. For example, if your claim only includes A and B as opposed to all three, it is much harder for potential competitors to create the apparatus or complete the method without using all elements. A narrow claim (for example, A, B, C, D, E, and F) requires many more elements to infringe, which can make that claim easier to "engineer around."

Vance VanDrake puts it like this: "If your patent claims are too narrow or require more elements than were necessary to be patentable, then a competitor might not have to pay you the 'rent' you might otherwise be owed. If [your claims] are too [broad], your attempted monopoly may be rejected by the USPTO or invalidated after it has been granted. Striking the perfect balance between what is narrow enough to be patentable but broad enough to have business value can be like bending a soccer ball through a small window on a free kick."

Another important point is understanding the difference between **specifications** and claims. Specifications describe an invention and provide support for the claims.[345] In a scientific patent, this is often the data similar to scientific publication at the beginning of the

patent, which is not what is awarded patent protection. Only the *claims* are afforded patent protection. However, anything put in the specifications *is* considered prior art. Therefore, specifications can become an important element in Building Backwards to your patent strategy.

Rishi Bedi, cofounder of Y-Trap, Inc.—who has built a substantial IP portfolio while leading Y-Trap—distilled the relationship between the claims and the specifications by focusing on establishing broad claims while writing detailed specifications. "In your claims, your top claim should be as broad a description of the invention as possible while still skirting all prior art," he said. "In your specifications, on the other hand, it's helpful to lay out not only the principal invention, but also all possible ways that you conceive that the invention could be actualized. This makes it harder for another party to claim comparable ideas as their own."

If IP is licensed from a university tech transfer office, at least for the initial patents, filing (and therefore claims and specifications writing) is often already completed. Once the IP is owned by the company, you will often hire a patent attorney to help you manage your IP.

This brings us to another crucial question. When should an IP attorney get involved? It depends on your desired involvement as a founder. Imagine a continuum of possible involvement. On one end of the continuum, you as a founder are minimally involved; on the other end, you are extremely involved.

For the former scenario, this likely takes the form of handing an IP attorney a scientific document, and the attorney leading the drafting of the claims and specifications.

- **Pros:** Time saved for you up front.
- **Cons:** Likely no one understands the key scientific innovation as well as you and/or the scientific inventor, yet you are relying on the *IP attorney* to capture the key ideas effectively. Additionally, this option will be the most time consuming for the attorney and, therefore, likely the most expensive.

For the latter scenario, where you might be extremely involved, you may want to author the claims yourself:

- **Pros:** The legal fees will be lower, as the attorney is largely just handling filing the IP and managing the bureaucratic process. You can personally ensure that the key innovative concepts of the scientific invention are included in the claims.
- **Cons:** Writing claims is an art. It's extremely difficult to learn to do this well, as writing strong claims involves capturing the specifics of your unique invention while still being as broad as possible. While it's theoretically possible to do this entirely without an IP attorney, your claims are likely to be weaker or less likely to be accepted since they will probably be less well crafted.

While either extreme is certainly a possibility, best practice is likely somewhere in the middle. It's beneficial to be involved enough in the IP process that you can ensure that the specifications and claims reflect the key tenets of your invention, yet it's difficult to do this entirely by yourself. Thus, in order to maximize IP value and scope, it's valuable to get an IP specialist counsel at least somewhat involved in claim writing strategy. Additionally, it's very difficult for someone new to IP to effectively navigate the inner workings of the patent office, particularly if you are simultaneously navigating multiple jurisdictions. Therefore, it is also highly beneficial to, at the minimum, involve IP counsel in managing your filings.

Even if you are simply licensing existing IP and never plan to go through the patenting process yourself, understanding these steps is crucial in order to Build Backwards to a strong IP position. In order to create a strong IP position, you need to understand the strength (or weakness) of what you're starting with. Checking to see if your claims are "broad" or "narrow" is an excellent starting point.

2. Patent prosecution

Patent prosecution is the "office action" that you take to see if your claims will issue. While many applicants might assume there are only two outcomes to filing a patent—either receiving the patent or not—in reality, the patent process often becomes an ongoing negotiation with the patent office. In general, the USPTO examiner will conduct a prior art search after you file your patent. They'll determine whether your application meets the novelty and obviousness claims, as discussed earlier. It's common for all your claims to be rejected on your first filing attempt. In response to the examiner, you will typically have to revise (usually, *narrow*) your claims. In your response, you can also make arguments about why you disagree with your examiner's conclusions. It's typical to speak directly with your patent examiner in order to reach an understanding about acceptable claims. Typically, after one or more rounds of this back-and-forth, the examiner will finally agree, and your patent will be issued. Initial patent applications usually contain about twenty claims, as twenty claims are free with the cost of filing fees. You'll need to get at least one claim "approved" by the examiner for your patent to issue, though the more approved claims, the stronger your patent likely will be.[346,347]

In Vance's words, "Negotiating patent claims requires more interpersonal skills than most people realize…if you anger your USPTO examiner with arrogance, lack of preparation, or with sloppy

play, it's going to be a lot easier for them to block your shots and to want to block those shots."[348]

TYPES OF UTILITY PATENTS

In general, biotech companies and start-ups will seek what are known as **utility patents**. Within that category, two types of patents are especially relevant to biotech companies: **composition of matter patents** and **method of use patents**.

Composition of Matter Patent

A composition of matter patent applies to novel mixtures and chemical compounds. Often, these patents are for a chemical structure, such as the chemical structure for a new molecule. These patents are typically both the most straightforward to get issued (there's much less likely to be existing prior "art," which is to say it tends to be binary: people have either produced exactly your same molecule or they have not) and also the easiest to defend from intellectual infringement (a chemical structure cannot be stolen, and it's very difficult for a competitor to engineer around a new molecule).[349] Thus, composition of matter patents are considered one of the strongest types of patents.

For example, one small biotech company I know of (let's call them Company T) created a new protein by combining known molecules in an innovative manner. They then filed and obtained a composition of matter patent on their combination invention. Later, a large pharmaceutical company created the same combination. Unable to develop this combination drug candidate any further without owning the IP, the large pharma company was forced to negotiate a license to Company T's IP, creating future royalty revenue for Company T should the large pharmaceutical company

successfully bring the new drug to market. This is the power of strong IP, particularly of a composition of matter patent.

METHOD OF USE PATENT

A method of use patent, also known as a "methods" patent, protects a series of steps for performing a function or accomplishing a result.[350] In biotech, this is typically a synthesis procedure, a way to apply a molecule (e.g., Method of use for treating HER2 negative breast cancers), or something similar. These patents are typically considered easier to "engineer around." That is, it is often perceived to be easier for a competitor to do something similar to you without actually infringing upon your patent. Although one method's patent in and of itself is often not the strongest IP position, holding many methods patents at once can often be effective. This is because the more IP "space" your company occupies, the more difficult it is for potential competitors to create their own IP in the space because you hold so much of it.

Bedi said holding multiple patents is fundamentally about safeguarding the company. "Every patent carries a certain risk of getting challenged or invalidated," he said. "If you have multiple patents, including methods patents, if your composition of matter patent gets invalidated, you have a thicker moat. The key is that by holding multiple patents, you free yourself from relying too much on any one patent or set of claims."

UNDERSTANDING THE DIFFERENCE: METHODS VERSUS COMPOSITION PATENTS

Sean Kendall, principal at ARCH Venture Partners, elaborated on the distinction between these two types of patents: "Methods patents are more prone to people being able to find workarounds or

alternative ways to achieve an end, whereas with composition of matter, you can look up a chemical structure and know exactly what infringement would look like."

Let's see how this applies to a project we have already discussed. EBIN currently holds both composition of matter as well as method of use patents. Laurel Therapeutics licenses these patents from the University of Illinois Chicago (UIC), where EBIN was discovered. Specifically, Laurel holds a patent for compositions and methods of use for using EBIN to treat vascular hyperpermeability syndromes. It also holds a follow-on patent with claims for methods of use of the peptides for treating angiogenic diseases. These patents are issued in the United States and issued or pending in more than twenty-five countries worldwide.

First, let's discuss the composition patent (which also contains methods claims).

Here is a picture of the first page of the issued patent, entitled "Peptide compositions and methods for treating lung injury, asthma, anaphylaxis, angioedema, systemic vascular permeability syndromes, and nasal congestion:"[351]


US008912139B2

(12) **United States Patent**
Komarova et al.

(10) **Patent No.: US 8,912,139 B2**
(45) **Date of Patent: *Dec. 16, 2014**

(54) **PEPTIDE COMPOSITIONS AND METHODS FOR TREATING LUNG INJURY, ASTHMA, ANAPHYLAXIS, ANGIOEDEMA, SYSTEMIC VASCULAR PERMEABILITY SYNDROMES, AND NASAL CONGESTION**

(71) Applicant: **The Board of Trustees of the University of Illinois**, Urbana, IL (US)

(72) Inventors: **Yulia A. Komarova**, Chicago, IL (US); **Uzma Saqib**, Chicago, IL (US); **Stephen M. Vogel**, Chicago, IL (US); **Asrar B. Malik**, Chicago, IL (US)

(73) Assignee: **The Board of Trustees of the University of Illinois**, Urbana, IL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/230,642**

(22) Filed: **Mar. 31, 2014**

(65) **Prior Publication Data**

US 2014/0213505 A1 Jul. 31, 2014

Related U.S. Application Data

(63) Continuation of application No. 14/105,385, filed as application No. PCT/US2012/042118 on Jun. 13, 2012.

(60) Provisional application No. 61/496,409, filed on Jun. 13, 2011.

(51) **Int. Cl.**

A61K 38/17	(2006.01)
C07K 7/08	(2006.01)
C07K 7/06	(2006.01)
C07K 14/705	(2006.01)
A61K 47/48	(2006.01)
A61K 38/00	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 47/48276*** (2013.01); ***A61K 38/1709*** (2013.01); *A61K 38/00* (2013.01); ***C07K 7/08*** (2013.01); ***C07K 7/06*** (2013.01); *C07K 2319/033* (2013.01); ***C07K 14/705*** (2013.01); *C07K 2319/10* (2013.01)

USPC **514/1.7**; 530/324; 514/21.3

(58) **Field of Classification Search**

CPC A61K 38/00; A61K 38/08; A61K 38/03; A61K 38/04; C07K 14/705; C07K 2319/10

USPC 514/1.7

See application file for complete search history.

(56) **References Cited**

PUBLICATIONS

Q7UPK4 (UniProt, integrated Oct. 1, 2003).*
A6H8K3 (UniProt, integrated Jul. 24, 2007).*

* cited by examiner

Primary Examiner — James H Alstrum Acevedo
Assistant Examiner — Tara Martinez
(74) *Attorney, Agent, or Firm* — Polsinelli PC; Teddy C. Scott, Jr.; Ron Galant

(57) **ABSTRACT**

Provided herein are peptide inhibitors of the interaction between End Binding Protein 3 (EB3) and Inositol 1,4,5-Trisphosphate Receptor Type 3 (IP3R3). Also provided are methods and materials for treating lung injury, including acute lung injury, which may include hyperpermeability of lung vessels, vascular leakage, the development of edema, asthma, anaphylaxis, angioedema, systemic vascular permeability syndromes, and nasal congestion.

13 Claims, 21 Drawing Sheets

Compositions and methods patent for Laurel. This is a copy of the first page of the patent for the major compositions patent licensed by Laurel from UIC.

You can look up this patent yourself on Google Patents or on the USPTO website to read about it in more detail and view the data attached. All you need for these search engines is either the title or the patent number. The last page of the patent lists the claims, with claim one always being the primary claim.

Claim: *A conjugated peptide comprising an amino acid sequence selected from the group consisting of KFARLWTEIPTAIT (SEQ ID NO:*

1) and FTEIPTI (SEQ ID NO: 3), wherein the conjugated peptide is linked to a carrier peptide or myristoyl group.[352]

This is a composition of matter claim. It describes the composition of EBIN. Because the peptide is a naturally occurring sequence in nature, it is only possible to patent the peptide *bound to a* "carrier peptide or myristoyl group." So, instead of only giving the sequence (as it would if it were not a naturally occurring peptide), the claim also specifies the group that might be conjugated. Thus, in order to infringe, a third party would need to create a peptide composed of both sequences (which are the key binding sequences for EBIN to maintain its function) *and* bind it to a carrier peptide or myristoyl group (these are elements A and B, in the terminology we used earlier).[353]

Next, we'll look at Laurel Therapeutics' methods patent, entitled "Peptides for Inhibiting Angiogenesis:"[354]

US009675660B2

(12) **United States Patent**
Komarova et al.

(10) **Patent No.: US 9,675,660 B2**
(45) **Date of Patent: Jun. 13, 2017**

(54) **PEPTIDES FOR INHIBITING ANGIOGENESIS**

(71) Applicant: **THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ILLINOIS**, Urbana, IL (US)

(72) Inventors: **Yulia A. Komarova**, Chicago, IL (US); **Mark Rosenblatt**, Chicago, IL (US); **Asrar B. Malik**, Hinsdale, IL (US)

(73) Assignee: **THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ILLINOIS**, Urbana, IL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **15/058,938**

(22) Filed: **Mar. 2, 2016**

(65) **Prior Publication Data**

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Related U.S. Application Data

(60) Provisional application No. 62/126,968, filed on Mar. 2, 2015.

(51) **Int. Cl.**

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A61K 38/08	(2006.01)
A61K 38/10	(2006.01)
C07K 14/515	(2006.01)
A61B 3/10	(2006.01)
A61F 9/008	(2006.01)
A61K 45/06	(2006.01)
A61B 3/12	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 38/10*** (2013.01); ***A61B 3/102*** (2013.01); ***A61F 9/00821*** (2013.01); ***A61K 38/08*** (2013.01); ***A61K 45/06*** (2013.01); *A61B 3/1241* (2013.01); *A61F 2009/00851* (2013.01); *A61F 2009/00863* (2013.01); *A61F 2009/00865* (2013.01); *A61F 2009/00872* (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,554,101	A	11/1985	Hopp
8,912,139	B2	12/2014	Komarova et al.
2008/0317773	A1	12/2008	Crisanti
2009/0111754	A1	4/2009	Aggarwal et al.
2010/0190691	A1	7/2010	Epenetos et al.

FOREIGN PATENT DOCUMENTS

WO	WO-2010/072943 A1	7/2010
WO	WO-2012/042118 A2	6/2011

OTHER PUBLICATIONS

Wells, J.A. (1990). Additivity of mutational effects in proteins. Biochemistry. 29(37):8509-8517.*

Ngo et al. (1994). Computational complexity, protein structure prediction, and the Levinthal paradox. In Merz and Le Grand (Eds.) The Protein Folding Problem and Tertiary Structure Prediction. Birkhauser:Boston, pp. 491-495.*

Geyer et al., Microtubule-Associated Protein EB3 Regulates IP3 Receptor Clustering and Ca(2+) Signaling in Endothelial Cells, *Cell Rep*, 12(1):79-89 (2015).

Gong et al., Optimization of an Image-Guided Laser-Induced Choroidal Neovascularization Model in Mice, *PLoS One*, 10(7):e0132643 (2015).

Komarova et al., VE-cadherin signaling induces EB3 phosphorylation to suppress microtubule growth and assemble adherens junctions, *Molecular Cell*, 48(6):914-25 (2012).

Kyte et al., A simple method for displaying the hydropathic character of a protein, *J. Mol. Biol.*, 157:105-132 (1982).

Saqib et al., Structure-based design of inhibitory peptide for end binding proteins, *FASEB J.*, 26:1122.6 (2012).

The Merck Manual, Angioedema, (http://www.merckmanuals.com/professional/immunology-allergic-disorders/allergic,-autoimmune,-and-other-hypersensitivity-disorders/angioedema), copyright 2010-2014, accessed Aug. 20, 2014.

The Merck Manual, Anaphalaxis, (https://www.merckmanuals.com/professional/immunology-allergic-disorders/allergic,-autoimmune,-and-other-hypersensitivity-disorders/anaphylaxis ; accessed Jun. 9, 2015).

Uniprot Accession No. F2AQ33, LolC/E family liprotein releasing system, transmembrane protein (2011).

Uniprot Accession No. A6H8K3, ITPR3 protein (2007).

UniProt sequence Q7UPK4, Probable lipoprotein releasing system transmembrane protein LolC (2003).

WebMD (lung injury http://www.webmd.com/lung/lung-injuries, copyright 2005-2014, accessed Aug. 20, 2014).

International Search Report and Written Opinion of the International Searching Authority issued in connection with International Application No. PCT/US2012/042118, dated Dec. 14, 2012.

International Preliminary Report on Patentability, PCT/US2012/042118, dated Dec. 17, 2013.

* cited by examiner

Primary Examiner — Christine J Saoud
Assistant Examiner — Jon M Lockard
(74) *Attorney, Agent, or Firm* — Marshall, Gerstein & Borun LLP

(57) **ABSTRACT**

The present invention relates to peptides for inhibiting angiogenesis. The present invention also relates to methods of inhibiting angiogenesis and methods of treating disorders associated with VEGF-induced vascular permeability using the peptides of the invention.

18 Claims, 12 Drawing Sheets

Methods patent for Laurel. This is a copy of the first page of the method of use patent licensed by Laurel from UIC.

Claim: *A method of inhibiting angiogenesis comprising administering to a patient in need thereof an isolated peptide comprising the amino acid sequence of KFARLWTEIPTAIT (SEQ ID NO: 1) or FTEIPTI (SEQ ID NO: 3), wherein the patient is suffering from cancer, visual impairment, vision loss (blindness), macular degeneration, central retinal vein occlusion, branch retinal vein occlusion proliferative diabetic retinopathy, neovascular age-related macular degeneration (AMD), retinopathy of prematurity, ischemic retinopathy, intraocular neovascularization, corneal neovascularization, retinal neovascularization, choroidal neovascularization, diabetic macular edema, diabetic retina ischemia, diabetic retinal edema, and proliferative diabetic retinopathy, rubeosis iridis, neovascular glaucoma, retinoblastoma, uveitis, or corneal graft neovascularization.*

This is a method of use claim, although a broad one. This patent claims the application of EBIN to any of the listed diseases. Therefore, someone would be infringing by using EBIN for treating any *one* of these diseases. This also helps us understand why method of use patents might be considered easier to skirt. If there were no composition of matter patent and only this one method of use patent for EBIN (neither of these things is true), someone could apply EBIN to a disease *not* on this list and it would not be infringing.[355] However, as the carrier peptide is not mentioned, this is in some senses a *broader* claim as if someone were to apply just the EBIN peptide without the carrier to any of these diseases, they would be infringing. In contrast, the composition of matter patent would *not* impede someone from using *just* the peptide itself. (However, this is unlikely to be feasible due to lack of permeability of EBIN without a carrier peptide.)

This is why patent portfolios are important. Each patent provides protection in a slightly different way. Together, they are stronger

than any one patent alone.

BUILDING BACKWARDS FROM IP BASICS

As mentioned, filing for a patent and/or licensing patent(s) is one of the first things to do when starting a company.

In an ideal world, Keith Crandell observed (Crandell, once again, is well versed in IP after years of funding, founding, and working with companies), you would "start out with the IP for the seminal work in a new area, and your claims would be crafted beautifully such that you have an effective monopoly in that area, and that those patents would go on to issue, and then that all the newcomers in the area would recognize the value of that intellectual property and immediately register you with tremendous amount of respect and credit that you rightly deserve."

He raised his eyebrows and smiled. "It would also be nice if I was third baseman for the Cubs," he said. "But that's not going to happen."

Since it's not a realistic expectation to start with perfect IP, at least *some* level of IP strategy almost always comes into play. However, it's impossible to Build Backwards to a strong IP position without first understanding the IP basics we just covered. By assessing the strength of your starting IP, you are better positioned to know how to augment it.

As Crandell put it: "Think really hard and objectively about where you are in terms of your IP. Because if you don't know where you are, it's kind of hard to figure out how you're going to get to where you want to be."

BUILDING BACKWARDS TO IP: FORMULATING A STRATEGY

Among other advantages, Building Backwards can prevent IP problems before they even emerge. How do you Build Backwards to a solid IP position up front? Ideally, there are two especially common ways to do this.

1. Augmenting existing IP from the start to Build Backwards to future potential applications of the technology:

To discuss this, we will consider a case study from Company J, a company Sanders previously worked with. Company J began when the founders purchased expiring composition of matter patents from a large pharmaceutical company. (Let's call it Pharma Q.) The patents had only five to six years remaining on them. Picture the timeline of drug development (i.e., in which it can take twenty years or more to get a drug to market) and compare that to the remaining patent life. The bottom line: not a great position for Pharma Q. Thus, Company J was able to buy the patents for cheap. One of the Company J founders had previously developed this compound when he was an employee at Pharma Q. Hence, he believed the molecules might have efficacy in a variety of neurodegenerative diseases although Pharma Q had been developing them primarily for other indications.

"The first thing we did was turn the IP position around," Sanders recalled. "Otherwise, there would have been no future for [Company J]."

The company ran several rounds of exploratory experiments. The experiments confirmed the molecule's promise for treating various neurological diseases. The company filed and received several methods patents broadly, including in the United States, but also in

Canada, Mexico, Australia, New Zealand, South Korea, Japan, South Africa, Israel, and other countries.

“If we hadn’t done that, we wouldn’t have had any patent positions,” Sanders said.

Further, Company J devised sophisticated methods for synthesizing the active compound and patented those methods. This provided Company J with strong IP protection because this particular compound was especially difficult to synthesize and had poor yields. There are multiple stereoisomers of the compound (i.e., different spatial configurations of the same chemical formula), but each has different activity in the human body. Only one stereoisomer has the desired efficacy. Thus, it would be highly difficult for a potential competitor to achieve the same grade and quality of material without infringing upon Company J’s patents.

“If they can’t match our quality standards, a competitor can’t prove efficacy to the FDA without running their own Phase trials using their own money and time,” Sanders said. “This protects [Company J] immensely.”

In practice, how might it look to augment existing IP when you start a company that inevitably does not have an ideal IP position? One way to develop ideas for filing for new or additional IP might be to help your PI or lead inventor think about potential applications through a whiteboarding exercise. On a whiteboard, your team can go through potential new applications that could stem from the original invention.

After a few hours of whiteboard discussions, you may have ideas for other IP to file for, which may require running additional experiments to gather data for the patent application. However, after

one of these whiteboarding exercises, your path to a more substantial IP portfolio might seem less difficult than initially expected.

This is a practice Crandell recommended from personal experience.

“Sometimes, a PI is particularly adept at the basic science and understands the strength of the platform,” Crandell said. “But they might not be able to think of other specific applications.”

You can also hire a patent attorney, agent, or consultant to consider new applications of your existing IP. A patent attorney or patent agent is required to have a strong background in STEM and often holds a science PhD but may be more expensive than a consultant.

2. Obtaining FTO and eliminating competition from the start:

One strategy worth mentioning is combining IP from *multiple sources* into one company. Doing so enables a new company to Build Backwards to a strong IP position by *eliminating competition up front.* By combining IP, you gain three key advantages:

1) Minimizing the risk of competition.

You can make it more difficult for other competitors to enter the space by “owning” more of it. Especially in a particularly hot area, there will likely be a crowd of potential competitors interested in starting companies in the same field. One way you might be able to preclude this is by strengthening your own position by gaining licenses to the major underlying technologies in the field.

Oftentimes, multiple innovators in a space are reading each other’s papers and can tend to come to realizations around the same time. This can lead to the creation of two schools of IP that are reliant on each other; or that are simply improving on each other’s methods.

By "pooling" all this related IP into the same company, future IP disagreements might be prevented, and complementary teams can become aligned.

Kendall shared a story of in-licensing (discussed in depth in chapter 6) a piece of IP that was not needed for the core technology but was potentially enabling for a strong, established competitor. "I advocated we pull it in because, while we didn't need it to practice our tech, it was an elegant technique that could be powerful in other workflows. I felt it could be potentially pretty enabling to a competitor if it were left out there and that maybe in the future, we'd want it," Kendall said. "Sure enough, we discovered that the company's competitor was trying to get an exclusive license to that technology. Their attaining that license wouldn't have prevented us from creating our product, but having it as a nonexclusive license weakened our competitor's long-term position and ability to block us should we decide to go into that direction. So even if there's some IP you're thinking about leaving on the table, think about where else it might live if you pass on it, and if that would be a problem." This prevents a new company from potentially getting blocked by a stronger, more established third party.[356]

2) Enabling the best technology to win within the company.

Often, competing academics within a field of study will have similar inventions that come at a problem in slightly different ways. It can be an effective strategy to license the IP from *both* labs and put it into one company, allowing the best technology to emerge within the company with time.

"Academics often see others working in their area as competitors," said Kendall. "If they can collaborate and let their respective IP compete within the company, you are distributing your risk and increasing your chances of success as well as simultaneously

eliminating potential competition. Innovators have to keep in mind that the real competition is the incumbent. Infighting only dilutes your strength. Taking on the entrenched competitor is the bigger challenge."

3) More efficiently achieving Freedom to Operate (FTO).

Recall that having a patent does not necessarily grant a company FTO. FTO is your ability to operate in a space without infringing on the IP owned by other groups. It is good practice, when contemplating what IP to use to start a new company, to perform diligence to determine FTO. This will inform you of which IP does or does not exist. If there is competing IP you might be infringing upon to operate the way you desire, it might be worth *acquiring rights to that IP as well*.

The broader the IP of other groups in your space, the more likely it is that you cannot operate without infringing. With that said, the patent office can sometimes issue claims to competitors that are overly broad—thereby overly limiting your FTO—which is very difficult and expensive to try to invalidate once the IP has issued. In such an instance, that broad IP owned by a competitor can represent a nearly insurmountable barrier to your company. In order to obtain FTO, it is much easier to obtain access to those patents rather than to go out and invalidate that work.

Ideally, you want to identify the seminal work (i.e., the original concept, upon which other inventions are built—this work becomes the prior art for follow on inventions) in your space of interest. If you can get access to this "central" IP, this not only gives you FTO, but it can also result in effectively excluding competitors.

Sometimes this seminal work is the key enabling invention. Crandell gave the example of the lightbulb and Thomas Edison. "We all hear

about Thomas Edison as the inventor of the lightbulb," Crandell says. "But a zillion other people did work on lightbulbs, too. Edison was just the one that invented the tungsten filament, which ultimately enabled lightbulbs to be practical. But others probably have claims in that area too. The key is not only finding a high-class problem you're trying to solve but pairing it with the key enabling work in the field."

For example, in conducting diligence on a potential investment, Kendall said that at first, it seemed the investment was a no-go because of prior art. Upon examining claims more closely, however, they found that "others had used some of the key innovations in this company, but only in other applications. This company was the first to use it for this particular application, which allowed us to get FTO by having access to the seminal IP in this field. The other companies would not be able to improve in this one area past a certain level because they needed this technique that company held IP on."

Crandell told me that, on average, an ARCH portfolio company licenses four pieces of IP from the start. In other words, it's an intentional strategy when ARCH starts companies to acquire licenses to patents from multiple institutions.

One portfolio company that Crandell and ARCH helped to establish was 908 Devices. To start the company, Crandell performed an analysis of the IP landscape and decided to combine a license from Oak Ridge National Labs with a license from the University of North Carolina at Chapel Hill. "A lot of innovation is basically assembling components of innovation from other areas and then integrating them for a specific application," Crandell told me. "There's another type of innovation where you have a wholly new idea and create the whole thing, but that's pretty rare. A lot of innovation is just being

the first one to realize the potential applications of new technologies."

For example, David Walt, PhD, the key inventor of Illumina DNA sequencing (a company whose technology played a key role in making DNA sequencing affordable), did not invent beads or wells. However, he was the first to integrate these concepts and realize they could be used advantageously for array-based DNA sequencing.

How do you begin the process of ascertaining what other IP might be relevant to your new company?

First, do a careful search through the scientific literature (e.g., on PubMed, Google Scholar, or Google Patents) to find out who else is publishing in your area of interest. The impact of the science and the scientists is relevant for this. Common metrics to check include the scientist's H-index or the prestige of the journals they're publishing in. [357]

This has the added benefit of serving as a prior art search, which also gives you an idea of what is defensible and what is novel.

"Think of it as a conversation," said Kendall. "You're also speaking with the team—the inventors themselves—to get their perspective on some of the other filings and publications in the space. Then, you want to check in with an IP attorney to see if your assumptions of what else is out there are really correct. They will often catch things that you're blind to or missing at this step." Additionally, the inventors can sometimes help you find "nice to have" IP—IP that isn't necessary but that the inventor believes might augment their work.

In short, IP is complicated yet fundamental to the value of a biotech company. Accordingly, it's important to Build Backwards to a solid position and think through your strategy early in the company's life. This can both increase the potential acquisition price as well as save you a lot of trouble down the road; that is, strong IP can fend off competition before it can even start.

This begins by understanding how strong your initial IP is from the beginning, as this informs which strategies you should utilize to achieve a strong IP position. Concepts we covered you might use to assess your starting position might be whether your claims are broad or narrow and whether your patent is a composition of matter or a method of use. If your starting IP is weak and the space is crowded, implementing Building Backwards thinking might lead you to determine this is not the best IP upon which to launch a new enterprise after all. Understanding what can and cannot be patented will help you Build Backwards to understand which future IP positions might be both possible and valuable in a particular domain, and augmenting or acquiring existing IP can enable you to create a stronger IP position that will increase the chances a biotech company will achieve success.

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310 Sanders is an experienced biotech entrepreneur who had previously contributed to the approvals of nine currently marketed drugs, including the blockbusters Tysabri and Remicade. He has also contributed to the conduct of over three hundred clinical trials for sixty drugs and is the codiscoverer of the first two discovered white blood cell molecular interactions (CD2 binding to LFA-3 and LFA-1 binding to ICAM-1) as well as the primary discoverer of the major phenotypic markers for human memory and naive T-cell subsets. Both discoveries enable much of modern-day immunology research.

311 Note the difference between *inventorship* and *ownership*. CROs often have an agreement with their biotech company client (in this case, with Laurel Therapeutics) that any inventions created—such as the formulation IP—would be *solely owned* by the biotech company client. This is regardless of the fact that the CRO scientists are the actual *inventors* of the new IP.

312 Virtually all drugs go through "formulation" before they go into clinical trials. This just means finding an optimal solution (whether by tweaking pH, viscosity, solvent, etc.) in which to solubilize and deliver your drug. In Laurel's case, we had hired an organization to formulate EBIN to *increase the drug's concentration at the back of the eye*, if you recall from chapter 5.

313 We will discuss this more below, but typically, you maintain rights for a period of twenty years after filing.

314 Additionally, in biotech, part of the importance of patents is it is much more difficult to maintain trade secrets given regulatory disclosure requirements.

315 Vance V. VanDrake, III, *The Patent Game: Basics & Strategies for Innovators, Entrepreneurs, and Business Leaders* (Cincinnati, OH: Legal Technology Press, 2019).

316 Ibid.

317 Do note, however, that actually *developing* new IP before your new company is started means that you need to be very cognizant of ownership. For example, if you develop a new technology while working for another company, often employment agreements specify that any new IP generated is owned by your employer. If you work for a research university, the IP will be owned by the university. In the latter case, you can often license the IP from the university, but this then might entail sharing equity ownership, royalties, or other upside from the business.

318 Alicia Russo, Jason Johnson, "Research Use Exemptions to Patent Infringement for Drug Discovery and Development in the United States," *Cold Spring Harbor* Perspectives in Medicine 5(2) (February 2015): a020933.

319 Ibid.

320 Lexology, "What is Freedom to Operate (FTO) in relation to patents and IP?" Accessed October 10, 2020.

321 In other words, you do not need to apply to obtain a copyright or a trade secret. They exist by default, simply due to the fact that you created something.

322 Also note IP costs tend to rise considerably as you enter more jurisdictions, particularly non-English-speaking jurisdictions (as you must pay for translating patents into the relevant language). Minimum common jurisdictions for filing in addition to the United States include the European Union, Japan, and, lately, China.

323 Bedi notes that items to consider when deciding whether to file in a particular jurisdiction include assessing the following items as they relate to the specific jurisdiction: market size, ability for a health care system to pay for the technology, and strength and enforcement of the patent system.

324 Gene Quinn, "Patentability Overview: When can an Invention be Patented?" IP Watchdog, June 3, 2017.

325 Ibid.

326 This controversy has come to light in recent years because of the 2013 case in the SCOTUS in which it was established in *Association for Molecular Pathology v. Myriad Genetics* that genes cannot be patented. In Europe, however, the Directive on the legal protection of biotechnological inventions and the European Patent Convention allows genetic sequences to be patented so long as the industrial application is clear.

327 Vance V. VanDrake, III, *The Patent Game: Basics & Strategies for Innovators, Entrepreneurs, and Business Leaders* (Cincinnati, OH: Legal Technology Press, 2019), 70.

328 Jessica C. Lai, "*Myriad Genetics* and the BRCA Patents in Europe: The Implications of the US Supreme Court Decision," *UC Irvine Law Review* 5 (2015).

329 Lara Cartwright-Smith, "Patenting Genes: What Does Association for Molecular Pathology v. Myriad Genetics Mean for Genetic Testing and Research?" *Public Health Reports* 129, no. 3 (2014): 289–92.

330 Vance V. VanDrake, III, *The Patent Game: Basics & Strategies for Innovators, Entrepreneurs, and Business Leaders* (Cincinnati, OH: Legal Technology Press, 2019), 70.

331 Jerzy Koopman, "The Patentability of Transgenic Animals in the United States of America and the European Union: A Proposal for Harmonization," *Fordham Intellectual Property, Media and Entertainment Law Journal* 13, no. 13 (2002), 28.

332 Jerry Adler, "The First Patented Animal Is Still Leading the Way on Cancer Research," *Smithsonian Magazine*, December 2016.

333 Michael K. Henry, "What Is Prior Art?" Henry Patent Law Firm, September 7, 2017.

334 Vance V. VanDrake, III, *The Patent Game: Basics & Strategies for Innovators, Entrepreneurs, and Business Leaders* (Cincinnati, OH: Legal Technology Press, 2019), 77.

335 Vid Mohan-Ram, "Patent First, Publish Later: How Not to Ruin Your Chances of Winning a Patent," *Science*, October 26, 2001.

336 Ibid.

337 Vance V. VanDrake, III, *The Patent Game: Basics & Strategies for Innovators, Entrepreneurs, and Business Leaders* (Cincinnati, OH: Legal Technology Press, 2019), 77.

338 Vid Mohan-Ram, "Patent First, Publish Later: How Not to Ruin Your Chances of Winning a Patent," *Science*, October 26, 2001.

339 Vance V. VanDrake, III, *The Patent Game: Basics & Strategies for Innovators, Entrepreneurs, and Business Leaders* (Cincinnati, OH: Legal Technology Press, 2019), 88–90.

340 Ibid.

341 Ibid.

342 Gene Quinn, "Understanding the Patent Law Utility Requirement," IP Watchdog, November 7, 2015.

343 Vance V. VanDrake, III, *The Patent Game: Basics & Strategies for Innovators, Entrepreneurs, and Business Leaders* (Cincinnati, OH: Legal Technology Press, 2019), 112.

344 Ibid.

345 Vic Lin, "What is a patent specification?" Patent Trademark Blog, accessed October 21, 2021.

346 Ibid.

347 Gene Quinn, "Patent Drafting for Beginners: The anatomy of a patent claim," IP Watchdog, December 10, 2016.

348 Vance V. VanDrake, III, *The Patent Game: Basics & Strategies for Innovators, Entrepreneurs, and Business Leaders* (Cincinnati, OH: Legal Technology Press, 2019), 113.

349 John Bouvier, *A Law Dictionary, Adapted to the Constitution and Laws of the United States*, "Composition of Matter," Accessed October 20, 2021.

350 Gottschalk v. Benson, 409 US 63, 70 (1972). ("A process is a mode of treatment of certain materials to produce a given result. It is an act, or a series of acts, performed upon the subject-matter to be transformed and reduced to a different state or thing.")

351 Yulia A. Komarova, Uzma Saqib, Stephen M. Vogel, Asrar B. Malik, 2014, "US8912139B2: Peptide compositions and methods for treating lung injury, asthma, anaphylaxis, angioedema, systemic vascular permeability syndromes, and nasal congestion."

352 Ibid.

353 Note many of the later claims in the patent are methods claims.

354 Yulia A. Komarova, Mark Rosenblatt, Asrar B. Malik, 2017, "US9675660B2: Peptides for inhibiting angiogenesis."

355 You might be asking why you wouldn't list all diseases you could think of on this list. If you're asking this question, congratulations, you're using Building Backwards thinking for IP! The answer is that you can't make claims for which you have no data. You can only make claims for diseases based on the data you have. The diseases listed are diseases that have angiogenesis mechanisms. Thus, providing anti-angiogenesis data allowed us to make claims for multiple diseases at once. If we wanted to file for, say, multiple sclerosis, we would need either data or strong scientific rationale to make that case.

356 With that said, licenses can sometimes ultimately revert to the licensor if left unused.

357 For any non-scientist readers, a scientist's H-index is based on their number of publications and number of citations; you can typically find this on Google Scholar.

CONCLUSION: BEGINNING AT THE ENDING

"Wherever the art of medicine is loved, there is also a love of humanity."

—HIPPOCRATES

I'd been working in biotech for several years when Adam, a family friend, called to tell me that his wife, Jen, was dying of stage IV kidney cancer. Stunned, I offered up the heartfelt yet frustratingly cliche line of "so sorry" and proceeded to mumble my way through a list of clinical trial ideas which really cumulated in one thing: I didn't know how to help them.

"Could I get my wife back?" Adam asked me.

I knew Jen's chances as a stage IV cancer patient were slim. I was reminded of the words I had translated into medical jargon as a twenty-two-year-old medical scribe: *There's nothing else we can do for her*.

In this instance, Adam had directly asked the question I had only wondered at the time: *Isn't there anything else we can try?*

A few months later, Jen passed away. I traveled to New Hampshire for a week, staying with a friend nearby in the evenings and helping to look after Adam's three daughters during the daytime. The family's grief was heavy, thick, and covered everything. I was struck by the fact that—regardless of any background in biotech I had—the family simply needed to feel supported and seen.

On the one hand, it was a positive lesson. Helping people through difficult seasons involving untreatable disease extends beyond what I could offer through biotech itself.

But it also reinforced a simple truth. Whether a doctor, husband, or friend, the ability to offer or suggest anything beyond emotional support alone was limited by the medicines available.

As Dr. Nadia Chaudhri, a scientist and terminal cancer patient once wrote, "I'm not afraid to die. Because, ultimately, what choice do I have? I want no one to say that I lost my battle with cancer. The treatments have not worked."[358]

Patients don't truly "lose" their fight with cancer or any other life-threatening disease. Rather, existing medicines—or lack thereof—fail them.

My time with Adam's family reminded me of this truth—reminded me that creating more needed medicines was why I had entered the biotech industry in the first place. Patients and their families—and their very real loss and grief in the face of limited treatment options—was my "*why.*" In the day-to-day of a biotech company, amid the exciting data and new business strategy, it's sometimes easy to lose sight of that.

BUILDING BACKWARDS TO HUMILITY

And so I want to leave you with one more lesson in Building Backwards—humility. When we remember that biotech is truly about fighting for scientific progress on behalf of patients, it becomes easier to maintain an attitude of humility. Build Backwards to success by cultivating humility in yourself early on, and it will likely pay dividends down the road.

Humility is a lesson I frequently encountered interviewing some of the most accomplished biotech entrepreneurs in the country, a theme that doesn't always get enough attention in the scientific world where soft skills are sometimes not discussed.

I can't prove a statistical correlation between the success of a company and the attitude of its founders. Humility isn't simply a strategy like the others I've mentioned, and its impact on company success isn't easily quantified. Regardless, I find humility critical because it underpins many of the strategies we have discussed. Without humility, it's hard to admit it or accept it if your data are wrong, your clinical trial results are inconclusive, or the market doesn't end up wanting what you thought it would. Without humility, you can't build the best teams or do the gritty, boring work that's critical to a company's success. Entrepreneurship—unlike corporate life, where job descriptions can often be neatly packaged into boxes—involves a willingness to be scrappy, to do the "unglamorous" work simply because it's what needs to be done, and to take colleagues' input even when you think you might know better.

One of my mentors, Keith Crandell, is one of three founders of ARCH Venture Partners, which is widely recognized as one of the world's most successful life science venture funds. He's been a part of countless deals worth millions or billions of dollars, and I've personally witnessed people who are well-known and respected in their own right become nervous in speaking with him, seeking to gain his approval.

Nonetheless, one of the most interesting things to me about Keith has always been his humility. He becomes visibly awkward whenever someone directly references his career success. He is not afraid to

make a self-deprecating joke. But when I ask him why he thinks he is able to stay humble, he gives me a practical answer. He tells me he works part time for the government as a ranger at Yellowstone National Park (among other national parks) where he actively counteracts poaching and human trafficking—evidently common issues within US national parks. He told me, excitedly, that he had just gotten upgraded to a level seven. (In the world of park rangers, apparently, this is a big deal.)

"Out in the field," he tells me, "you don't have this overemphasis on credentials or sense of celebrity. What matters is the mission and what you can do to move it forward that day. Things can come down to life and death, whether or not you have each other's backs. Life is simpler out there."

He laughs and references that, out in Yellowstone, very few know or care what he does for his day job. No one knows the latest "biotech wonder" nor keeps track of the latest deal he has executed. He spends many weeks a year patrolling miles in the remote mountains, through the snow, camping in subfreezing weather for days on end—things I had imagined someone with the type of success Keith enjoys would never even consider. He's been part of a team that rescues and carries out climbers after rock climbing disasters. He's tracked poachers, putting himself in life-threatening situations. Anyone in this job encounters death and works alongside it.

"When you see injured people in their worst states or victims in very difficult positions, it changes your sense of proportion and gives you perspective on just how fortunate you have been to arrive at your current station," he said.

Jake Glanville is similar. When I first cold-contacted him in 2017 and asked for an interview, he immediately responded: “Sure, how about now?”

I’ve known him for several years now and was fortunate that he invited me to cofound Centivax with him, where he is also CEO. In the time since that interview, he’s transformed from virtually unknown outside of his scientific field to a Netflix star with a substantial social media following, regularly appearing on media outlets like CNN, Fox News, the New Yorker and CNBC. He also sold his first company, Distributed Bio, where he was founding partner and CEO, for $104 million. (This is especially significant because the company never took on venture investment, which by now you probably understand is very uncommon in biotech.)

This newfound fame and success, however, hasn’t changed Jake’s humility. [359]

To me, one of the ways Jake’s humility is seen most evidently is through his commitment to his principles. I’ve watched him navigate extreme pressure to compromise on seemingly small things that would go against his word or affect an employee. He always refuses, even when no one would know about his decision.

Much of his humility comes from his childhood, he says. “I grew up in the Tzutujil village of Santiago Atitlan on the edge of Lake Atitlan in the Mayan highlands of Guatemala. There was no hospital, and resources were limited due to the ongoing thirty-six-year civil war as well as centuries of oppression. Santiago didn’t have the fundamental civil sanitation systems or medical support that my American friends take for granted,” he explained. “Growing up, I was infected with amoebas, and giardia, and worms, and other common pathogens so many times I have lost count. Comparatively, I was

lucky. I could afford the medicine. Many of the children in the village weren't so lucky. Many had bloated bellies, a red tinge to their hair, and stunted growth—the hallmarks of chronic pathogen burden and malnutrition."

For Jake, his familiarity with illness and death made it difficult to maintain an inflated perspective. This perspective carries forward into the gravity of his work.

When I was growing up, my mother, an experienced scientist with approximately thirty years of experience in drug development and now chief scientific officer of Kojin Therapeutics, used to tell me, "Stephanie, the very top scientists are often the most humble. Why? Because there's always something more to learn in science, something else you don't know or don't understand. The best scientists know that the more they learn, the more they realize they'll never know."

In context, my mother meant there is always one deeper level to go in science. Although she had become an enzyme expert over the course of her career, for each new enzyme she would seek to understand she would realize there was so much more about it that defied characterization. Although she was an expert, the more she specialized, the more she realized there would always be limits to her knowledge.

Humility is not merely about refusing to think too highly of ourselves. It's also about maintaining a keen awareness of the things we do not know.

Sheila Jasanoff, JD, PhD, professor of science and technology studies at Harvard University studies this idea, referring to it as the "technologies of humility." "Real problems in the real world are

infinitely complex, and for any given problem, science offers only part of the picture," she wrote in *Nature*. "Science fixes our attention on the knowable, leading to an over-dependence on fact-finding.... We need disciplined methods to accommodate the partiality of scientific knowledge and to act under irredeemable uncertainty. Let us call these the technologies of humility.... Humility instructs us to think harder about how to reframe problems so that their ethical dimensions are brought to light, which new facts to seek and when to resist asking science for clarification."[360]

In other words, humility is not solely a character trait. It's also a tool that empowers one to operate effectively within a field like biotech that is rife with incorrigible uncertainty. Accordingly, I invite you to enter this industry from a position of humility, accepting the inevitability of limits to our knowledge while at the same time not allowing the fear of what we do not know prevent us from acting in the first place. Change depends on action, but recognizing and embracing uncertainty depends on humility. Successful scientific innovation requires both.

I wrote this book because I saw a substantial discrepancy as a twenty-two-year-old, where I witnessed terminally ill patients with no further medical options as well as medical innovations with no path to real-world application. I hope that by sharing my knowledge —somewhat limited as it is—you may be more empowered to contribute to filling in the gap. If you have made it this far in reading this book, from the bottom of my heart, thank you.

HOPE

I sat in the audience of Adam's daughter's gymnastics class. Emily's red hair—the same color her mother's had been—was tied in a

ponytail. She was learning cartwheels, glancing back at me to see if I was watching as she attempted one again and again, tipping backward as she tried to balance on her hands. I smiled back in encouragement but couldn't shake the thought that I was not the one she wished for in the audience.

I remembered again what the oncologist I worked for had said to me years before: "I've gotten really good at walking patients down the road to death."

But there had been another part of the conversation because of the recent approval of PD-1/PD-L1 inhibitors: "Before, nearly all of my patients would die," he had said. "Now, *some* of them live. That means I can offer patients more than my guidance en route to death. I can offer them hope. That has changed everything."

I thought of what was, at that time, a loose idea for a book and a collection of interviews. I thought of Gleevec, of how, within a few short years, it had transformed a disease that killed nearly all CML patients to a disease that killed few. Was it possible such a medicine was around the corner for stage IV kidney cancer? Might it have been different for Jen had she survived only a few more years?

There was no way to say, of course, but it was a reminder that there is a reason to push—to drive promising new science from the lab and into the clinic as efficiently as possible, to invite more people like you into biotech, and to bring new discoveries from the lab to patients, even one year earlier. There will always be people like Adam's wife, Jen, who might be saved by that "one year earlier."

I glanced across the gymnasium at Emily. As I watched, she once again attempted a cartwheel, her brow furrowed in concentration. She placed her hands on the mat and fell to the side again, unable to

execute the full arc a cartwheel required. Nevertheless, she immediately skipped toward the window where I was sitting, a big smile on her face.

"Did you see me? Did you see me?" she asked gleefully, her voice audible through the glass.

I clapped my hands and smiled back at her. "Yes," I said. "You did great!"

With that, Emily turned, happily running back to try again. What struck me was her child-like joy at the possibility of achieving something new. In Emily's smile, I saw more than grief, or frustration, or disappointment. I saw hope.

On the surface, biotech is a profoundly technical industry. This book is also a profoundly technical book, merging business and science—two industries that are extraordinarily technical independently, let alone together. Yet, at its heart, biotech is deeply personal. At its best, it's driven by a love for people, and for those people fighting for that extra year.

So to Build Backwards to success, beginning with the end—this end—will be the most powerful for your beginning.[361]

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358 Dr. Nadia Chaudhri, Twitter thread, September 17, 2021.

359 So many people have written about Jake's scientific and entrepreneurial brilliance. These traits are very much true of him. He is incredibly intelligent and gifted. But fewer people have written about Jake's character, which has both affected and taught me even more than learning technical skills from him. Jake has taught me so much about humility and meeting people where they are in our years of working together. So much of this is subtle: readily admitting when he doesn't know the answer to something, apologizing openly, and being willing to lift up others even when he could easily claim credit himself. He is a remarkable person and mentor in this way among many others.

360 Sheila Jasanoff, "Technologies of Humility," *Nature*, October 31, 2007.

361 Thank you so much for reading this book. For more resources and information (and to connect with me), visit bioventureadvising.com.

ACKNOWLEDGMENTS

It's a bit of a cliche to say that when I first set out to write this book three years ago, I had no idea what I was in for. It's difficult to quantify the journey that writing this book has been.

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Amrallah A. Mohammad. "Advanced Pancreatic Cancer: The Standard of Care and New Opportunities." *Oncology Reviews* 12, no 2 (September 2018): 370. https://doi.org/10.4081/oncol.2018.370.

Berkrot, Bill. "Celgene to Buy Receptos for $7.2 Billion; Gains Promising Drug." Reuters, July 14, 2015. https://www.reuters.com/article/us-receptos-m-a-celgene/celgene-to-buy-receptos-for-7-2-billion-gains-promising-drug-idUSKCN0PO2OB20150714

Biotechnology Innovation Organization. "What Is Biotechnology?" accessed June 21, 2021. https://www.bio.org/what-biotechnology.

Chance, RE and B H Frank. "Research, Development, Production, and Safety of Biosynthetic Human Insulin." Diabetes Care 16, no. 3 (Dec 1993): 133–42. https://doi.org/10.2337/diacare.16.3.133.

Company-Histories. "Genentech, Inc." Accessed June 21, 2021. https://company-histories.com/Genentech-Inc-Company-History.html.

Diabetes Control and Complications Trial Research Group; D M Nathan, S Genuth, J Lachin, P Cleary, O Crofford, M Davis, L Rand, C Siebert. "The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus." The New England Journal of Medicine 329, no. 14 (Sept. 1993): 977-86. https://doi.org/10.1056/NEJM199309303291401.

Diabetes.co.uk. "Diabetes History." January 15, 2019. https://www.diabetes.co.uk/diabetes-history.html.

Diabetes.co.uk. "Diabetes Life Expectancy." January 15, 2019. https://www.diabetes.co.uk/diabetes-life-expectancy.html.

Goess, Ruediger. "A Look at the Progress of Treating Pancreatic Cancer over the Past 20 Years," *Expert Review of Anticancer Therapy* 18, no. 3 (January 2018): 1–10, https://doi.org/10.1080/14737140.2018.1428093.

Goodkin, G. "Mortality Factors in Diabetes. A 20 Year Mortality Study." *Journal of Occupational Medicine* 17, no. 11 (November 1975): 716–21.

https://pubmed.ncbi.nlm.nih.gov/1195031/.

Hughes, Sally Smith. *Genentech: The Beginnings of Biotech.* Chicago: The University of Chicago Press, 2011.

Lewis, Michael. *Moneyball: The Art of Winning an Unfair Game.* New York, NY: W.W. Norton, 2013.

McGrane, Clare. "Juno Therapeutics acquired by Celgene for $9B in dramatic deal for rising biotech star." GeekWire. January 22, 2018. https://www.geekwire.com/2018/juno-therapeutics-acquired-celgene-9b-dramatic-deal-rising-biotech-star/

National Cancer Institute. "Cancer Stat Facts: Pancreatic Cancer." Accessed June 21, 2021. https://seer.cancer.gov/statfacts/html/pancreas.html.

National Cancer Institute. "Pancreas: Recent Trends in SEER Relative Survival Rates, 2000–2018." 2018. https://seer.cancer.gov/explorer/application.html?site=40&data_type=4&graph_type=2&compareBy=sex&chk_sex_1=1&chk_sex_3=3&chk_sex_2=2&race=1&age_range=1&stage=101&survival_interval=5&advopt_precision=1&advopt_display=1.

Quianzon, Celeste C. and Issam Cheikh, MD "History of Insulin." *Journal of Community Hospital Internal Medicine Perspectives* 2, no. 2 (July 2012). https://doi.org/10.3402/jchimp.v2i2.18701.

Saluja, Ashok, Vikas Dudeja, and Sulagna Banerjee. "Evolution of Novel Therapeutic Options for Pancreatic Cancer." *Current Opinion in Gastroenterology* 32, no. 5 (2016): 401–407. https://doi.org/10.1097/MOG.0000000000000298.

Vox. "Illumina's CEO on the Promise of the $1,000 Genome—And the Work That Remains." March 25, 2014. https://www.vox.com/2014/3/25/11624902/illuminas-ceo-on-the-promise-of-the-1000-genome-and-the-work-that

WebMD. "Antimetabolites for Cancer: Effects, Benefits, Risks," Cancer Center. May 19, 2020. https://www.webmd.com/cancer/antimetabolite-medications-overview#1.

CHAPTER 1

Dedic, Nina, Philip G. Jones, Seth C. Hopkins, Robert Lew, Liming Shao, John E. Campbell, Kerry L. Spear, Thomas H. Large, Una C. Campbell, Taleen Hanania, Emer Leahy and Kenneth S. Koblan. "SEP-363856, a Novel Psychotropic Agent with a Unique, Non-D2 Receptor Mechanism of Action." *The Journal of Pharmacology and Experimental Therapeutics* 371 (October 2019): 1–14. https://doi.org/10.1124/jpet.119.260281.

DeFeudis, Nicole. "Otsuka puts nearly $1 billion on the line for four neuropsychiatric candidates from Sunovion." Endpoints News. September 30, 2021. https://endpts.com/otsuka-puts-nearly-1-billion-on-the-line-for-four-neuropsychiatric-candidates-from-sunovion/.

Goldratt, Eliyahu M. *The Goal: A Process of Ongoing Improvement*. Great Barrington, MA: The North River Press Publishing Corporation, 1984.

Mast, Jason. "Sumitomo Subsidiary Flashes New Way of Treating Schizophrenia in PhII Trial." Endpoints News. April 16, 2020. https://endpts.com/sumitomo-subsidiary-flashes-new-way-of-treating-schizophrenia-in-phase-ii-trial/.

Office of the Commissioner. "Expanded Access." *US Food and Drug Administration,* FDA, March 23, 2021. https://www.fda.gov/news-events/public-health-focus/expanded-access.

"SEP-363856 is associated with robust improvement in negative symptoms of schizophrenia," *BioWorld*. April 21, 2021.

Servick, Kelly. "Experimental Schizophrenia Drug Could Reduce Long-Neglected Symptoms." *Science*. April 15, 2020. https://www.sciencemag.org/news/2020/04/experimental-schizophrenia-drug-could-reduce-long-neglected-symptoms.

"Sunovion Presents Data From Marketed And Late-Stage Development Psychiatric Compounds At The American Psychiatric Association (APA) Annual Meeting 2021," Sunovion, May 3, 2021.

CHAPTER 2

"ActivX Biosciences Announces Closing of Acquisition by Kyorin." FDA News. February 2, 2005. https://www.fdanews.com/articles/68293-activx-biosciences-announces-closing-of-acquisition-by-kyorin

Ahn, Kay et al. "Mechanistic and pharmacological characterization of PF-04457845: a highly potent and selective fatty acid amide hydrolase inhibitor that reduces inflammatory and noninflammatory pain." *The Journal of Pharmacology and Experimental Therapeutics* vol. 338,1 (2011): 114–24. https://doi.org/10.1124/jpet.111.180257

Ahn, Kay, Douglas S Johnson, Mauro Mileni, David Beidler, Jonathan Z Long, Michele K McKinney, Eranthie Weerapana, Nalini Sadagopan, Marya Liimatta, Sarah E Smith, et al. "Discovery and Characterization of a Highly Selective Faah Inhibitor That Reduces Inflammatory Pain." *Chemistry & Biology* 16, no. 4 (April 2009): 411–20. https://doi.org/10.1016/j.chembiol.2009.02.013.

Alvarez, Rachel. "Understanding Drug Development—Why it Takes So Long & Costs So Much Money: A Four-Part Series." Cure CMD. February 8, 2020. https://www.curecmd.org/post/2020/02/09/understanding-drug-development-why-it-takes-so-long-costs-so-much-money-a-four-part-ser.

"CFR—Code of Federal Regulations Title 21." US Food & Drug Administration. Updated April 1, 2020. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=210.3#:~:text=(4)%20Drug%20product%20means%20a,in%20association%20with%20inactive%20ingredients.

Company-Histories. "Genentech, Inc." Accessed June 21, 2021. https://company-histories.com/Genentech-Inc-Company-History.html.

Cross, Ryan. "Bayer Acquires Small Molecule Startup Vividion Therapeutics for up to $2 Billion." *Chemical & Engineering News*. August 5, 2021. https://cen.acs.org/pharmaceuticals/drug-discovery/Bayer-acquires-small-molecule-startup-Vividion-Therapeutics/99/web/2021/08.

DiMasi, Joseph A., Henry G.Grabowski, and Ronald W.Hansen. "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs." *Journal of Health Economics* 47 (May 2016): 20-33. https://doi.org/10.1016/j.jhealeco.2016.01.012.

"Drug Approval Process Infographic." US Food & Drug Administration. Accessed October 13, 2021. https://www.fda.gov/media/82381/download.

"Drug Patent Expirations: Potential Effects on Pharmaceutical Innovation," Every CRS Report. Accessed October 10, 2021. https://www.everycrsreport.com/reports/R42399.html.

"GMP vs. GLP in Laboratory Testing & Validation." The FDA Group, LLC. March 15, 2017. https://www.thefdagroup.com/blog/gmp-vs.-glp-in-lab-testing-validation.

Herper, Matthew. "The Cost of Developing Drugs Is Insane. That Paper That Says Otherwise Is Insanely Bad." *Forbes*. October 16, 2017. https://www.forbes.com/sites/matthewherper/2017/10/16/the-cost-of-developing-drugs-is-insane-a-paper-that-argued-otherwise-was-insanely-bad/?sh=35582eae2d45.

Hingorani, Aroon D., Valerie Kuan, Chris Finan, Felix A. Kruger, Anna Gaulton, Sandesh Chopade, Reecha Sofat, Raymond J. MacAllister, John P. Overington, Harry Hemingway, et al. "Improving the Odds of Drug Development Success through Human Genomics: Modelling Study." *Scientific Reports* 9, no. 18911 (2019). https://doi.org/10.1038/s41598-019-54849-w.

"Investigational New Drug (IND) Application." US Food & Drug Administration. Updated February 24, 2021. https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application.

Jung, Emily H., Alfred Engelberg and Aaron S. Kesselheim. "Do Large Pharma Companies Provide Drug Development Innovation? Our Analysis Says No." *STAT*, December 10, 2019. https://www.statnews.com/2019/12/10/large-pharma-companies-provide-little-new-drug-development-innovation/.

Lastovetska, Anastasiia. "App Development Cost: Understand Your Budget to Build Powerful Apps." MLSDev. September 28, 2021. https://mlsdev.com/blog/app-development-cost.

"Lundbeck to Purchase Abide Therapeutics in $400m Deal." *Pharmaceutical Technology*. May 7, 2019. https://www.pharmaceutical-technology.com/news/lundbeck-acquires-abide-therapeutics/.

Neville, Sarah. "Nimble Biotechs Become Vital Partners for Large Pharma Groups." *Financial Times*. November 30, 2018. https://www.ft.com/content/e199a93a-f3cc-11e8-9623-d7f9881e729f.

"Pharmaceutical CDMOS." Tapemark. Accessed October 13, 2021. https://www.tapemark.com/pharmaceutical-cdmos.

Pharmaceutical Research and Manufacturers of America. *2013 Profile: Biopharmaceutical Research Industry.* 2013.

"Standard Costs (in thousands of dollars) for Components of the Process for the Review of Human Drug Applications." US Food & Drug Administration. Updated August 13, 2018. http://www.fda.gov/forindustry/userfees/prescriptionDrugUserFee/ucm093484.htm.

"Toxicology Studies: Delivering Accurate, Rapid Insights into Safe Dosing Regimens." BioAgilytix. Accessed October 13, 2021. https://www.bioagilytix.com/services/assay-focus/toxicology-studies/.

"What Is the Difference between GLP and GMP Laboratory Testing Regulations?" Michrochem Laboratory. Accessed October 12, 2021. https://microchemlab.com/information/what-difference-between-glp-and-gmp-laboratory-testing-regulations.

CHAPTER 3

Cai, Kenrick. "Mark Zuckerberg Has Sold Facebook Stock Almost Every Weekday This Year." Forbes. Accessed October 10, 2021.

https://www.forbes.com/sites/kenrickcai/2021/07/13/mark-zuckerberg-has-sold-facebook-stock-almost-every-weekday-this-year/?sh=766c606069d4

Deen, Marie, Edvige Correnti, Katharina Kamm, Tim Kelderman, Laura Papetti, Eloisa Rubio-Beltrán, Simone Vigneri, Lars Edvinsson, and Antoinette Maassen Van Den Brink. "Blocking CGRP in Migraine Patients—A Review of Pros and Cons." *The Journal of Headache and Pain* 18, no. 96 (2017). https://doi.org/10.1186/s10194-017-0807-1.

Grinberg, Yelena Y, Lois A. Zitzow, and Richard P. Kraig. "Intranasally Administered IGF-1 Inhibits Spreading Depression in vivo." *Brain Research* 1677 (2017): 47–57. https://doi.org/10.1016/j.brainres.2017.09.022.

Layne, Rachel, "IPO or M&A? How Venture Capital Shapes a Startup's Future." *Harvard Business School*. April 27, 2021. https://hbswk.hbs.edu/item/ipo-or-ma-how-venture-capital-shapes-a-startups-future

"Migraine Essentials." American Migraine Foundation. Accessed October 10, 2021. https://americanmigrainefoundation.org/living-with-migraine/migraine-essentials/.

Weatherall, Mark W. "The Diagnosis and Treatment of Chronic Migraine." *Therapeutic Advances in Chronic Disease* 6, no. 3 (May 2015): 115-23. https://doi.org/10.1177/2040622315579627.

Won, Lisa and Richard P. Kraig. "Insulin-like Growth Factor-1 Inhibits Spreading Depression-Induced Trigeminal Calcitonin Gene Related Peptide, Oxidative Stress & Neuronal Activation in Rat." *Brain Research* 1732 (April 1, 2020). https://doi.org/10.1016/j.brainres.2020.146673.

CHAPTER 4

Anand, Geeta. *The Cure: How a Father Raised $100 Million and Bucked the Medical Establishment in a Quest to Save His Children.* New York: William Morrow, 2009.

Barro, Josh. "Warren Buffett Should Have Listened to Warren Buffett about Airlines." *Intelligencer*. May 4, 2020. https://nymag.com/intelligencer/2020/05/warren-buffett-should-have-listened-to-himself-on-airlines.html.

Colella, Pasqualina and Federico Mingozzi. "Gene Therapy for Pompe Disease: The Time Is Now." *Human Gene Therapy* 30, no. 10 (October 2019): 1245–1262. https://doi.org/10.1089/hum.2019.109.

Kohler, Lara, Rosa Puertollano, and Nina Raben. "Pompe Disease: From Basic Science to Therapy." *Neurotherapeutics* 15, no. 4 (October 2018): 928–942. https://doi.org/10.1007/s13311-018-0655-y.

Minnis, Michael and Abbie Smith. "Southwest Airlines Co. Credit Analysis and Financial Flexibility in the Era of COVID-19." Booth School of Business at the University of Chicago for Business 30130. September 2020.

Parenti, Giancarlo, Diego L Medina, and Andrea Ballabio. "The Rapidly Evolving View of Lysosomal Storage Diseases." *EMBO Molecular Medicine* 13, no. 2 (February 5, 2021). https://doi.org/10.15252/emmm.202012836.

"Pompe Disease Information Page." National Institute of Neurological Disorders and Stroke. Updated August 9, 2021. https://www.ninds.nih.gov/Disorders/All-Disorders/Pompe-Disease-Information-Page.

"US FDA Accepts Filings for Amicus' AT-GAA for the Treatment of Pompe Disease." Amicus Therapeutics. September 29, 2021. https://ir.amicusrx.com/news-releases/news-release-details/us-fda-accepts-filings-amicus-gaa-treatment-pompe-disease

Van der Ploeg, Ans T and Arnold J J Reuser. "Pompe's Disease." *The Lancet* 371 (October 11, 2008): 1342–53. https://doi.org/10.1016/S0140-6736(08)61555-X.

Vaughn, Tom. *Extraordinary Measures*. 2010; Brentwood CA: CBS Films. DVD.

Yasinski, Emma. "Amicus CEO on a Mission to Cure Pompe and Help His Two Children." Pompe Disease News. January 30, 2019. https://pompediseasenews.com/2019/01/30/amicus-ceo-mission-cure-pompe-help-children/.

CHAPTER 5

Blank, Steve. "Why the Lean Start-Up Changes Everything." *Harvard Business Review*. May 2013. https://hbr.org/2013/05/why-the-lean-start-up-changes-everything.

Frellick, Marcia. "Two Expensive Diabetic Macular Edema Drugs Not Cost-Effective." Medscape. June 9, 2016. https://www.medscape.com/viewarticle/864580.

Horita, Shinya, Miwa Watanabe, Mai Katagiri, Hiroaki Nakamura, Hiroki Haniuda, Tomoyuki Nakazato, Yoshiyuki Kagawa. "Species Differences in Ocular Pharmacokinetics and Pharmacological Activities of Regorafenib and Pazopanib Eye drops among Rats, Rabbits and Monkeys." *Pharmacology Research & Perspectives* 7, no. 6 (December 2019). https://doi.org/10.1002/prp2.545.

Kovach, Jaclyn L., Stephen G. Schwartz, Harry W. Flynn, Jr., and Ingrid U. Scott. "Anti-VEGF Treatment Strategies for Wet AMD." *Journal of Ophthalmology* 2021 (February 2012). https://doi.org/10.1155/2012/786870.

Patel, Shrij. "Medicare Spending on Anti-Vascular Endothelial Growth Factor Medications." *Ophthalmology Retina* 2, no. 8 (January 15, 2018). https://doi.org/10.1016/j.oret.2017.12.006.

Pennington, Katie L. and Margaret M. DeAngelis. "Epidemiology of Age-Related Macular Degeneration (AMD): Associations with Cardiovascular Disease Phenotypes and Lipid Factors." *Eye and Vision* 3, no. 34 (2016). https://doi.org/10.1186/s40662-016-0063-5.

Satell, Greg. "This Program Uses Lean Startup Techniques to Turn Scientists into Entrepreneurs." *Harvard Business Review*. March 7, 2017. https://hbr.org/2017/03/this-program-uses-lean-startup-techniques-to-turn-scientists-into-entrepreneurs.

Stephenson, Michelle. "Managing the Retina 'Epidemic.'" *Review of Ophthalmology*. August 9, 2012. https://www.reviewofophthalmology.com/article/managing-the-retina-epidemic.

Taylor, James. "Minimum Viable Products in Biotech." Trade Secrets. *Nature Biotechnology*. December 20, 2011. https://blogs.nature.com/tradesecrets/2011/12/20/minimum_viable_products_in_biotech.

"The Top 12 Reasons Startups Fail." Research Briefs. CB Insights. August 3, 2021. https://www.cbinsights.com/research/startup-failure-reasons-top/.

Tranos, Paris, Athanasios Vacalis, Solon Asteriadis, Stavrenia Koukoula, Athanasios Vachtsevanos, Georgia Perganta, and Ilias Georgalas. "Resistance to Antivascular Endothelial Growth Factor Treatment in Age-Related Macular Degeneration." *Drug Design, Development and Therapy* 7 (June 17, 2013): 485–90. http://doi.org/10.2147/DDDT.S43470.

"Where the Newest Anti-VEGF Agent Fits in the Exudative-Disease Toolbox." Retina Specialist. November 26, 2019. https://www.retina-specialist.com/article/where-the-newest-antivegf-agent-fits-in-the-exudativedisease-toolbox.

CHAPTER 6

Booth, Bruce. "Foundings Matter: Thiel's Law Applied to Biotech." *Forbes.* June 11, 2013. https://www.forbes.com/sites/brucebooth/2013/06/11/foundings-matter-thiels-law-applied-to-biotech/?sh=1e9541ff717b.

Booth, Bruce(@LifeSciVC). "Goodwin legal advice: six great mistakes founders make. #Science2Startup" Twitter thread. April 24, 2018. 12:39 p.m. https://twitter.com/LifeSciVC/status/988819755078422530.

Brumm, Joshua. "Beyond The Balance Sheet: Thinking Broadly about Dilution in Building a Transformative Biotech." Life Sci VC. December 16, 2020. https://lifescivc.com/2020/12/beyond-the-balance-sheet-thinking-broadly-about-dilution-in-building-a-transformative-biotech/.

Craven, Caroline. "Hope in the Life of the COVID Pandemic—A New MS Treatment, Zeposia, Approved by the FDA." Girl with MS. Accessed October 20, 2021. http://www.girlwithms.com/2020/07/hope-in-life-of-covid-pandemic-new-ms.html.

"Kojin Therapeutics Launches with $60 Million Series A to Develop New Category of Drugs Based on Cell State Biology." *Business Wire*. June 9, 2021. https://www.businesswire.com/news/home/20210609005295/en/Kojin-Therapeutics-Launches-with-60-Million-Series-A-to-Develop-New-Category-of-Drugs-Based-on-Cell-State-Biology

Melillo, Gianna. "Bristol Myers Squibb Launches Ozanimod (Zeposia) for RMS." AJMC. June 2, 2020. https://www.ajmc.com/view/bristol-myers-squibb-launches-zeposia-ozanimod-for-rms.

"Ozanimod." ScienceDirect. Accessed October 20, 2021. https://www.sciencedirect.com/topics/medicine-and-dentistry/ozanimod.

"Receptos Completes $25M Series A Financing." Flagship Pioneering. November 23, 2009. https://www.flagshippioneering.com/press/receptos-completes-25m-series-financing.

"Sagres Acquires MemRx, Enhances Discovery Programs." The Pharma Letter. April 27, 2003. https://www.thepharmaletter.com/article/sagres-acquires-memrx-enhances-discovery-programs.

Sauter, Eric. "Scientists Define Structure of Important Neurological Receptor, Establishing a Platform to Understand G Protein-Coupled Receptors." *News & Views* 8, no. 29 (October 6, 2008). https://www.scripps.edu/newsandviews/e_20081006/stevens.html.

Sriram, Krishna and Paul A. Insel. "G Protein-Coupled Receptors as Targets for Approved Drugs: How Many Targets and How Many Drugs?" *Molecular Pharmacology* 93, no. 4 (April 2018): 251-258. https://doi.org/10.1124/mol.117.111062.

"Syrrx Acquired by Takeda." Crunchbase. Accessed October 20, 2021. https://www.crunchbase.com/acquisition/takeda-pharmaceutical-acquires-syrrx--cf3c9f96.

Tepper, Stewart J and Merrilee R Johnstone. "Breath-Powered Sumatriptan Dry Nasal Powder: An Intranasal Medication Delivery System for Acute Treatment of Migraine." *Medical Devices* 11 (May 2018): 147–156. https://doi.org/10.2147/MDER.S130900.

Wisner, Stephanie. “Visualizing the Future: Spatialomics Transforms Study of Gene Expression.” Synbiobeta. April 20, 2021. https://synbiobeta.com/visualizing-the-future-spacialomics-transforms-study-of-gene-expression/.

CHAPTER 7

Abifade, Marianne, Sandy Elbitar, Petra El Khoury, Youmna Ghaleb, Mélody Chémaly, Marie-Line Moussalli, Jean-Pierre Rabès, Mathilde Varret, and Catherine Boileau. “Living the PCSK9 Adventure: From the Identification of a New Gene in Familial Hypercholesterolemia Towards a Potential New Class of Anticholesterol Drugs.” *Current Atherosclerosis Reports* 16, no. 9 (September 2014). https://doi.org/10.1007/s11883-014-0439-8.

“BCR-ABL Fusion Gene.” National Cancer Institute. Accessed October 20, 2021. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/bcr-abl-fusion-gene.

Brehme, Marc, Oliver Hantschel, Jacques Colinge, Ines Kaupe, Melanie Planyavsky, Thomas Köcher, Karl Mechtler, Keiryn L. Bennett, and Giulio Superti-Furga. “Charting the Molecular Network of the Drug Target Bcr-Abl.” *Proceedings of the National Academy of Sciences of the United States of America* 106, no. 18 (May 5, 2009): 7414–7419. https://doi.org/10.1073/pnas.0900653106.

“Charles River Laboratories Acquires Distributed Bio.” Distributed Bio. January 4, 2021. https://www.distributedbio.com/single-post/charles-river-acquires-distributed-bio.

Cross, Ryan. “Bayer Acquires Small Molecule Startup Vividion Therapeutics for up to $2 Billion.” *Chemical & Engineering News*. August 5, 2021. https://cen.acs.org/pharmaceuticals/drug-discovery/Bayer-acquires-small-molecule-startup-Vividion-Therapeutics/99/web/2021/08.

Desai, Nihar R. and Marc S.Sabatine. “PCSK9 Inhibition in Patients with Hypercholesterolemia.” *Trends in Cardiovascular Medicine* 25, no. 7 (October 2015): 567–574. https://doi.org/10.1016/j.tcm.2015.01.009.

Donvito, Giulia, Sara R Nass, Jenny L Wilkerson, Zachary A Curry, Lesley D Schurman, Steven G Kinsey, and Aron H Lichtman. “The Endogenous Cannabinoid System: A Budding Source of Targets for Treating Inflammatory and Neuropathic Pain.” *Neuropsychopharmacology* 43 (August 31, 2017): 52–79. https://doi.org/10.1038/npp.2017.204.

Eder, Jörg, Richard Sedrani, Christian Wiesmann. “The Discovery of First-In-Class Drugs: Origins and Evolution.” *Nature Reviews Drug Discovery* 13, no. 8 (August 2014): 577–87. https://doi.org/10.1038/nrd4336.

"FDA Approves Amgen's New Cholesterol-Lowering Medication Repatha™ (evolocumab)." Amgen. Accessed October 20, 2021. https://www.amgen.com/newsroom/press-releases/2015/08/fda-approves-amgens-new-cholesterollowering-medication-repatha-evolocumab.

Fowler, CJ. "Monoacylglycerol Lipase—A Target for Drug Development?" *British Journal of Pharmacology* 166, no. 5 (July 2012): 1568–1585. https://doi.org/10.1111/j.1476-5381.2012.01950.

Grainger, David. "Why Too Many Clinical Trials Fail—And a Simple Solution That Could Increase Returns on Pharma R&D." *Forbes*. January 29, 2015. https://www.forbes.com/sites/davidgrainger/2015/01/29/why-too-many-clinical-trials-fail-and-a-simple-solution-that-could-increase-returns-on-pharma-rd/?sh=7909b57edb8b.

Gujral, Taranjit S. and Marc W. Kirschner. "Hippo Pathway Mediates Resistance to Cytotoxic Drugs." *Proceedings of the National Academy of Sciences* 114, no. 8 (May 2017). https://doi.org/10.1073/pnas.1703096114.

Hall, Stephen S. "Genetics: A Gene of Rare Effect." *Nature* 496 (April 9, 2013): 152–155. https://doi.org/10.1038/496152a.

Hantschel, Oliver, Uwe Rix, and Giulio Superti-Furga. "Target Spectrum of the BCR-ABL Inhibitors Imatinib, Nilotinib and Dasatinib," *Leukemia & Lymphoma* 49, no. 4 (2008). https://doi.org/10.1080/10428190801896103.

"Homepage." National Cancer Institute. https://www.cancer.gov/.

Horwitz, Nathaniel Brooks. "Back to Boston." Medium. July 16, 2018. https://nbhorwitz.medium.com/back-to-boston-8f32c34e8dac.

Horwitz, Nathaniel Brooks. "Go/No Go." Medium. November 26, 2018. https://nbhorwitz.medium.com/no-go-2f996ef3d17a.

Horwitz, Nathaniel Brooks. "Here's What Happened When I Tried to Develop a New Drug for a Deadly Cancer." *The Washington Post*, January 12, 2019. https://www.washingtonpost.com/national/health-science/heres-what-happened-when-i-tried-to-develop-a-new-drug-for-a-deadly-cancer/2019/01/11/697cf9f6-039f-11e9-9122-82e98f91ee6f_story.html.

"How Imatinib Transformed Leukemia Treatment and Cancer Research." National Cancer Institute. Updated April 11, 2018. https://www.cancer.gov/research/progress/discovery/gleevec.

"Landmark deCODE Genetics Study Points to a New Mechanism That Affects Cholesterol Levels and the Risk of Heart Disease." Amgen. Accessed October 20, 2021. https://www.amgen.com/newsroom/press-releases/2016/05/landmark-decode-genetics-study-points-to-a-new-mechanism-that-affects-cholesterol-levels-and-the-risk-of-heart-disease.

Liao, Sharon. "What You Need to Know About PCSK9 Inhibitors." WebMD Medical Reference. May 27, 2020. https://www.webmd.com/cholesterol-management/pcsk9-inhibitors-treatment.

Lowe, Derek. "What PCSK9 Is Telling Us About Drug Discovery." *Science*. March 20, 2017. https://www.science.org/content/blog-post/pcsk9-telling-us-drug-discovery.

"Lundbeck to Purchase Abide Therapeutics in $400m Deal." Pharmaceutical Technology. May 7, 2019. https://www.pharmaceutical-technology.com/news/lundbeck-acquires-abide-therapeutics/.

Moffat, John G., Fabien Vincent, Jonathan A. Lee, Jörg Eder, and Marco Prunotto. "Opportunities and Challenges in Phenotypic Drug Discovery: An Industry Perspective." *Nature Reviews Drug Discovery* 16 (2017): 531–43. https://doi.org/10.1038/nrd.2017.111.

"New Data from Past BACE Inhibitor Trials Shed Light on Side Effects." ALZFORUM. December 16, 2020. https://www.alzforum.org/news/research-news/new-data-past-bace-inhibitor-trials-shed-light-side-effects.

Panza, Francesco Madia Lozupone, Vincenzo Solfrizzi, Rodolfo Sardone, Carla Piccininni, Vittorio Dibello, Roberta Stallone, et al., "BACE Inhibitors in Clinical Development for the Treatment of Alzheimer's Disease," *Expert Review of Neurotherapeutics* 18, no. 11 (November 2018): 847–857. https://doi.org/10.1080/14737175.2018.1531706.

Piana, Ronald. "Groundbreaking Cancer Researcher Brian J. Druker, MD, Shows No Signs of Slowing Down." *The ASCO Post*. March 25, 2021. https://ascopost.com/issues/march-25-2021/brian-druker-shows-no-signs-of-slowing-down//

Pray, Leslie A. "Gleevec: The Breakthrough in Cancer Treatment." *Nature Education* 1, no. 1 (2008): 37. https://www.nature.com/scitable/topicpage/gleevec-the-breakthrough-in-cancer-treatment-565/.

"Sanofi and Regeneron Announce FDA Approval of Praluent® (alirocumab) Injection, the First PCSK9 Inhibitor in the US, for the Treatment of High LDL Cholesterol in Adult Patients." Sanofi. July 24, 2015. https://www.news.sanofi.us/2015-07-24-Sanofi-and-Regeneron-Announce-FDA-Approval-of-Praluent-alirocumab-Injection-the-First-PCSK9-Inhibitor-in-the-U-S-for-the-Treatment-of-High-LDL-Cholesterol-in-Adult-Patients.

Southan, Christopher and John M. Hancock. "A Tale of Two Drug Targets: The Evolutionary History of BACE1 and BACE2," *Frontiers in Genetics*, December 17, 2013. https://doi.org/10.3389/fgene.2013.00293.

Stroes, Erik SG, Lotte CA Stiekema, Robert S Rosenson. "PCSK9 Inhibitors: Pharmacology, Adverse Effects, and Use." UpToDate. Updated September 14, 2021. https://www.uptodate.com/contents/pcsk9-inhibitors-pharmacology-adverse-effects-and-use.

Taylor, Phil. "2. Elenbecestat." Fierce Biotech. December 16, 2019. https://www.fiercebiotech.com/special-report/2-elenbecestat.

The American Cancer Society Medical and Editorial Content Team. "Survival Rates for Pancreatic Cancer." American Cancer Society. Updated February 12, 2021. https://www.cancer.org/cancer/pancreatic-cancer/detection-diagnosis-staging/survival-rates.html.

"Therapeutics: Umibecestat." ALZFORUM. Updated January 21, 2021. https://www.alzforum.org/therapeutics/umibecestat.

Venugopal, Chitra, Christina M. Demos, K. S. Jagannatha Rao, Miguel A. Pappolla, and Kumar Sambamurti. "Beta-secretase: Structure, Function, and Evolution." *CNS & Neurological Disorders Drug Targets* 7, no. 3 (June 2008): 278-294. https://doi.org/10.2174/187152708784936626.

CHAPTER 8

Booth, Bruce. "Biotech IPOs: The Exit Challenge as Lockups Expire." Life Sci VC. October 31, 2013. https://lifescivc.com/2013/10/biotech-ipos-the-exit-challenge-as-lockups-expire/.

Booth, Bruce. "Biotech's Relevancy Challenge in an Expanding Universe." Life Sci VC. June 1, 2021. https://lifescivc.com/2021/06/biotechs-relevancy-challenge-in-an-expanding-universe/.

Booth, Bruce. "Evolution of The Biotech IPO Markets from Busted to Booming." Life Sci VC. September 21, 2020. https://lifescivc.com/2020/09/evolution-of-the-biotech-ipo-markets-from-busted-to-booming/.

Booth, Bruce. "Five Macro Risks to Biotech Coming Out of Washington." Life Sci VC. April 22, 2021. https://lifescivc.com/2021/04/five-macro-risks-to-biotech-coming-out-of-washington/.

Booth, Bruce. "Tradeoffs and Timing: IPO vs. M&A Decision Making in Biotech." Life Sci VC. April 2, 2014. https://lifescivc.com/2014/04/tradeoffs-and-timing-ipo-vs-ma-decision-making-in-biotech/.

"Charles River and Distributed Bio Enter Exclusive Partnership to Create an Integrated Antibody

Cross, Ryan. "Bayer Acquires Small Molecule Startup Vividion Therapeutics for up to $2 Billion." Chemical & Engineering News. August 5, 2021. https://cen.acs.org/pharmaceuticals/drug-discovery/Bayer-acquires-small-molecule-startup-Vividion-Therapeutics/99/web/2021/08.

Discovery and Development Platform." Charles River. October 25, 2018. https://ir.criver.com/node/19981/pdf.

Driebusch, Corrie. "The (Opening) Bell Tolls for Thee—If You're Lucky." *The Wall Street Journal*. August 10, 2021. https://www.wsj.com/articles/the-opening-bell-tolls-nasdaq-nyse-stock-market-robinhood-mark-wahlberg-krispy-kreme-11628621253.

Dubnow, Shoshana. "How Bayer Lured a Biotech Away from an IPO and into a Buyout." BioPharma Dive. August 5, 2021. https://www.biopharmadive.com/news/bayer-vividion-acquisition-cancer-immune/604485/.

"Guide to Going Public: Strategic Considerations Before, During and Post-IPO." EY. 2018. https://assets.ey.com/content/dam/ey-sites/ey-com/en_gl/topics/growth/ey-guide-to-going-public-strategic-considerations-before-during-and-post-ipo.pdf.

Hayes, Adam. "Business Exit Strategy." *Investopedia*. October 31, 2020. https://www.investopedia.com/terms/b/business-exit-strategy.asp.

CHAPTER 9

DiMasi, Joseph A., Henry G.Grabowski, and Ronald W.Hansen. "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs." *Journal of Health Economics* 47 (May 2016): 20–33. https://doi.org/10.1016/j.jhealeco.2016.01.012.

Hingorani, Aroon D., Valerie Kuan, Chris Finan, Felix A. Kruger, Anna Gaulton, Sandesh Chopade, Reecha Sofat, Raymond J. MacAllister, John P. Overington, Harry Hemingway, et al. "Improving the Odds of Drug Development Success through Human Genomics: Modelling Study." *Scientific Reports* 9, no. 18911 (2019). https://doi.org/10.1038/s41598-019-54849-w.

Reiff, Nathan. "Series A, B, C Funding: How It Works." *Investopedia*. May 31, 2021. https://www.investopedia.com/articles/personal-finance/102015/series-b-c-funding-

what-it-all-means-and-how-it-works.asp.

CHAPTER 10

"About the SBIR and STTR Programs." SBIR.gov. Accessed October 20, 2021. https://www.sbir.gov/about.

"Agios Pharmaceuticals Announces That Celgene Exercised Its Option to License AG-221 Under Global Strategic Collaboration." Business Wire. June 13, 2014. https://www.businesswire.com/news/home/20140613005268/en/Agios-Pharmaceuticals-Announces-that-Celgene-Exercised-its-Option-to-License-AG-221-Under-Global-Strategic-Collaboration.

Al Idrus, Amirah. "Roche Taps Vividion in $135M Protein Degradation Deal." Fierce Biotech, May 19, 2020. https://www.fiercebiotech.com/biotech/roche-tapes-vividion-135m-protein-degradation-deal.

Booth, Bruce. "Biotech's Relevancy Challenge in an Expanding Universe." Life Sci VC. June 1, 2021. https://lifescivc.com/2021/06/biotechs-relevancy-challenge-in-an-expanding-universe/.

Booth, Bruce. "The Incredible Expanding Universe of Biotech Stocks." Life Sci VC. September 21, 2018. https://lifescivc.com/2018/09/the-incredible-expanding-universe-of-biotech-stocks/.

Fidler, Ben. "A Record Number of Biotechs Are Going Public. Here's How They're Performing." BioPharma Dive. Updated October 21, 2021. https://www.biopharmadive.com/news/biotech-ipo-performance-tracker/587604/.

"Leveraging America's Seed Fund." US Small Business Administration. March 2020. https://www.sbir.gov/sites/default/files/SBA_SBIR_Overview_March2020.pdf.

"What Does the Interest Rate Indicate on a Convertible Note?" Education Center. Funders Club. Accessed October 20, 2021. https://fundersclub.com/learn/convertible-notes/convertible-notes-overview/interest-rate-convertible-note/.

CHAPTER 11

Cahn, Pedro, Valeria Fink, and Patricia Patterson. "Fostemsavir: A New CD4 Attachment Inhibitor." *Current Opinion in HIV and AIDS* 13, no. 4 (July 2018): 341–345. https://doi.org/10.1097/COH.0000000000000469.

"CREATE Bio Example: Target Product Profile (TPP)." The National Institute of Neurological Disorders and Stroke. Updated January 19, 2020. https://www.ninds.nih.gov/Funding/Apply-Funding/Application-Support-Library/CREATE-Bio-Example-Target-Product-Profile-TPP.

DiMasi, Joseph A., Henry G.Grabowski, and Ronald W.Hansen. "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs." *Journal of Health Economics* 47 (May 2016): 20–33. https://doi.org/10.1016/j.jhealeco.2016.01.012.

"Drugs@FDA: What's in a Drug Product Label?" US Food & Drug Administration. Updated May 6, 2016. https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-whats-drug-product-label.

"Dyslipidemia," Merck Manual. Accessed October 10, 2020. https://www.merckmanuals.com/professional/endocrine-and-metabolic-disorders/lipid-disorders/dyslipidemia.

"FAQs About Rare Diseases," National Center for Advancing Translational Sciences. Accessed October 10, 2020. https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases.

"Frequently Asked Questions on Patents and Exclusivity." US Food & Drug Administration. Updated February 5, 2020. https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity#howlongexclusivity.

"Full Year 2020 Product Sales." Novartis. Accessed October 20, 2021. https://www.novartis.com/investors/financial-data/product-sales.

Gillespie, Earl, Laura Hatton, Carrie Jones, and Andrew Funderburk. "Orphan Drug Development—What are the Real Costs?" Health Advances Blog. April 10, 2019. https://healthadvancesblog.com/2019/04/10/orphan-drug-development-what-are-the-real-costs/.

"Guidance for Industry and Review Staff Target Product Profile—A Strategic Development Process Tool." US Department of Health and Human Services, Food and Drug Administration, and Center for Drug Evaluation and Research (CDER). March 2007. http://www.ncai-cc.ccf.org/skills/documents/U.S.%20FDA%20Target%20Product%20Profile%20Guidance%20Document%20(2007).pdf.

Hingorani, Aroon D., Valerie Kuan, Chris Finan, Felix A. Kruger, Anna Gaulton, Sandesh Chopade, Reecha Sofat, Raymond J. MacAllister, John P. Overington, Harry Hemingway, et al. "Improving the Odds of Drug Development Success through Human Genomics:

Modelling Study." *Scientific Reports* 9, no. 18911 (2019). https://doi.org/10.1038/s41598-019-54849-w.

"Impact Innovation Predictability Access: FDA's Center for Drug Evaluation and Research January 2021." US Food & Drug Administration. Updated January 8, 2021. https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/new-drug-therapy-approvals-2020.

Langley, David R., S. Roy Kimura, Prasanna Sivaprakasam, Nannan Zhou, Ira Dicker, Brian McAuliffe, Tao Wang, John F. Kadow, Nicholas A. Meanwell, and Mark Krystal. "Homology Models of the HIV-1 Attachment Inhibitor BMS-626529 Bound to gp120 Suggest a Unique Mechanism of Action." *Proteins* 83, no. 2 (February 2015): 331–350. https://doi.org/10.1002/prot.24726.

"Mechanism of Action." Rukobia. Updated 2021. https://www.rukobiahcp.com/.

O'Donnell Jr., Peter. "Tissue Plasminogen Activator." UT Southwestern Medical Center. Accessed October 20, 2021. https://utswmed.org/conditions-treatments/tissue-plasminogen-activator/.

OECD. *New Health Technologies: Managing Access, Value and Sustainability.* OECD Publishing, 2017.

"Orphan Drug Act—Relevant Excerpts." US Food & Drug Administration. Updated March 9, 2019. https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-act-relevant-excerpts.

"Orphan Drug Report 2017." EvaluatePharma®. February 2017. http://info.evaluategroup.com/rs/607-YGS-364/images/EPOD17.pdf.

Scientific Writing Team. "FDA Orphan Drug Designation for Rare Diseases." Nuventra. April 21, 2021. https://www.nuventra.com/resources/blog/orphan-drug-products/.

"Standard Costs (in thousands of dollars) for Components of the Process for the Review of Human Drug Applications." US Food & Drug Administration. Updated August 13, 2018. http://www.fda.gov/forindustry/userfees/prescriptionDrugUserFee/ucm093484.htm.

"Step 3: Clinical Research." US Food & Drug Administration. Updated January 4, 2018. https://www.fda.gov/patients/drug-development-process/step-3-clinical-research.

"Target Product Profiles." World Health Organization. Accessed October 20, 2021. https://www.who.int/observatories/global-observatory-on-health-research-and-development/analyses-and-syntheses/target-product-profile/who-target-product-profiles.

"The Enduring Role of Orphan Drug Exclusivity for Biologics." Pharmaceutical Law Group. October 2, 2021. https://www.pharmalawgrp.com/blog/13/the-enduring-role-of-orphan-drug-exclusivity-for-biologics/.

"The Food and Drug Administration's Orphan Drug Program." Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation. Breakthrough Business Models: Drug Development for Rare and Neglected Diseases and Individualized Therapies: Workshop Summary. Washington, DC: National Academies Press, 2009. https://www.ncbi.nlm.nih.gov/books/NBK50974/.

Thompson, Melanie, Jacob P Lalezari, Richard Kaplan, Yvett Pinedo, Otto A Sussmann Pena, Pedro Cahn, David A Stock, Samit R Joshi, George J Hanna, and Max Lataillade. "Safety and Efficacy of the HIV-1 Attachment Inhibitor Prodrug Fostemsavir in Antiretroviral-Experienced Subjects: Week 48 Analysis of AI438011, a Phase Iib, Randomized Controlled Trial." *Antiviral Therapy* 22, no. 3 (2017): 215–233. https://doi.org/10.3851/IMP3112.

ViiV Healthcare. "Attachment Inhibitor Comparison in Heavily Treatment Experienced Patients." Updated March 22, 2021. https://clinicaltrials.gov/ct2/show/NCT02362503.

"What Is a Clinical Trial and How Does a Trial Work?" Roche. Accessed October 20, 2021. https://www.roche.com/research_and_development/who_we_are_how_we_work/research_and_clinical_trials/what_is_a_clinical_trial.htm?tab_id=tab1.

Wiegman, Albert, Samuel S. Gidding, Gerald F. Watts, M. John Chapman, Henry N. Ginsberg, Marina Cuchel, Leiv Ose et al., "Familial Hypercholesterolaemia in Children and Adolescents: Gaining Decades of Life by Optimizing Detection and Treatment." *European Heart Journal* 36, no. 36 (September 2015): 2425–2437. https://doi.org/10.1093/eurheartj/ehv157.

CHAPTER 12

Adler, Jerry. "The First Patented Animal Is Still Leading the Way on Cancer Research." *Smithsonian Magazine*. December 2016. https://www.smithsonianmag.com/smithsonian-institution/first-patented-animal-still-leading-way-cancer-research-180961149/.

Bouvier, John. *A Law Dictionary, Adapted to the Constitution and Laws of the United States.* "Composition of Matter." Accessed October 20, 2021. https://legal-dictionary.thefreedictionary.com/Composition+of+matter.

Cartwright-Smith, Lara. "Patenting Genes: What Does Association for Molecular Pathology v. Myriad Genetics Mean for Genetic Testing and Research?" *Public Health Reports* 129, no. 3 (2014): 289-92. https://doi.org/10.1177/003335491412900311.

Gottschalk v. Benson, 409 US 63, 70 (1972).

Henry, Michael K. “What Is Prior Art?” Henry Patent Law Firm. September 7, 2017. https://henry.law/blog/what-is-prior-art/.

Komarova, Yulia A., Mark Rosenblatt, Asrar B. Malik. 2017. “US9675660B2: Peptides for Inhibiting Angiogenesis.”

Komarova, Yulia A., Uzma Saqib, Stephen M. Vogel, Asrar B. Malik. 2014. “US8912139B2: Peptide Compositions and Methods for Treating Lung Injury, Asthma, Anaphylaxis, Angioedema, Systemic Vascular Permeability Syndromes, and Nasal Congestion.”

Koopman, Jerzy. “The Patentability of Transgenic Animals in the United States of America and the European Union: A Proposal for Harmonization.” *Fordham Intellectual Property, Media and Entertainment Law Journal* 13, no. 13 (2002): 28. https://ir.lawnet.fordham.edu/cgi/viewcontent.cgi?article=1252&context=iplj.

Lai, Jessica C. “Myriad Genetics and the BRCA Patents in Europe: The Implications of the US Supreme Court Decision.” *UC Irvine Law Review* 5 (2015). https://scholarship.law.uci.edu/ucilr/vol5/iss5/5.

Lin, Vic. “What Is a Patent Specification?” Patent Trademark Blog. Accessed October 21, 2021. https://www.patenttrademarkblog.com/specification-claim-amendments/.

Mohan-Ram, Vid. “Patent First, Publish Later: How Not to Ruin Your Chances of Winning a Patent.” *Science.* October 26, 2001. https://www.science.org/content/article/patent-first-publish-later-how-not-ruin-your-chances-winning-patent-rev2.

Quinn, Gene. “Patent Drafting for Beginners: The Anatomy of a Patent Claim.” IP Watchdog. December 10, 2016. https://www.ipwatchdog.com/2016/12/10/patent-drafting-anatomy-patent-claim/id=75575/.

Quinn, Gene. “Patentability Overview: When Can an Invention Be Patented?” IP Watchdog. June 3, 2017. https://www.ipwatchdog.com/2017/06/03/patentability-invention-patented/id=84071/.

Quinn, Gene. “Understanding the Patent Law Utility Requirement.” IP Watchdog. November 7, 2015. https://www.ipwatchdog.com/2015/11/07/understanding-the-patent-law-utility-requirement/id=63007/.

Russo, Alicia, Johnson, Jason. “Research Use Exemptions to Patent Infringement for Drug Discovery and Development in the United States.” *Cold Spring Harbor Perspectives in Medicine, 5(2), a020933.* https://doi.org/10.1101/cshperspect.a020933.

"Section 2106.03 Eligibility Step 1: The Four Categories of Statutory Subject Matter." USPTO.

VanDrake, III, Vance V. *The Patent Game: Basics & Strategies for Innovators, Entrepreneurs, and Business Leaders*. Cincinnati, OH: Legal Technology Press, 2019.

"What is Freedom to Operate (FTO) in relation to patents and IP?" Lexology. Assessed October 10, 2020. https://www.lexology.com/library/detail.aspx?g=38c0d68a-6a95-4769-bcf1-adc805e19c58.

CONCLUSION

Chaudhri, Nadia. (@DrNadiaChaudhri). "Thank you @Huda_Akil1 for your sensitive translation of the article @RimaElkouri wrote for LaPresse" Twitter thread. September 17, 2021. 9:52 p.m. https://mobile.twitter.com/DrNadiaChaudhri/status/1439059663736168448.

Jasanoff, Sheila. "Technologies of humility." *Nature* 450, 33 (2007). https://doi.org/10.1038/450033a.

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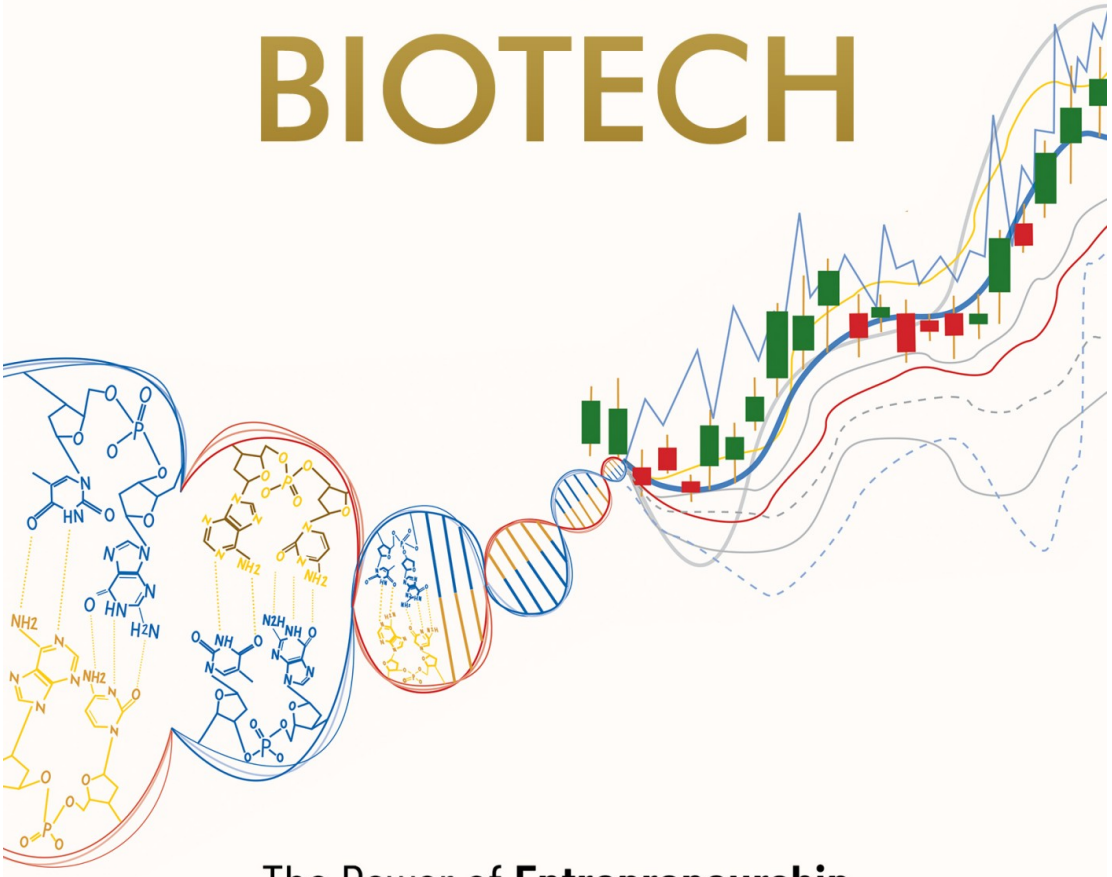

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