Porter & Co.

BIOTECH FRONTIERS

EXPLORING NEW HORIZONS

INVESTMENT GUIDEBOOK FOR BIOTECH FRONTIERS

Exploring New Horizons

Investment Guidebook for *Porter & Co. Biotech Frontiers*

Bob Duggan was not a typical biotech CEO.

He had no medical degree and no formal education in science… In fact, he was a college dropout who had spent much of his time at the University of California, Santa Barbara, partying and surfing. Duggan proudly belonged to the Church of Scientology, the organization founded by science fiction writer L. Ron Hubbard that many ridiculed as a cult…

Far from reading top scientific journals like *Nature*, Duggan unapologetically enjoyed *National Enquirer* and would sometimes hand out copies of an *Enquirer* article, "24 Qualities of All Geniuses" – lessons Duggan sought to emulate in his own everyday life.

Duggan had no experience running a life-sciences company… advancing a promising new therapy through clinical trials… or navigating the maze of the Food and Drug Administration's ("FDA") drug-approval process.

And yet in 2008, after a successful run building several other businesses unrelated to life sciences, Duggan found himself a shareholder and new CEO of Pharmacyclics – a tiny, fallen-star biotech company. Duggan had accumulated many of Pharmacyclics' shares when they traded below $1 on the "pink sheets" – the pejorative term used to describe over-the-counter trading in stocks that have been delisted from large national exchanges such as the Nasdaq.

In 2008, when Duggan took over, one could be forgiven for describing Pharmacyclics as a total trainwreck. The company had originally been founded by well-pedigreed physician-scientists affiliated with Stanford University and backed by top Silicon Valley venture capitalists ("VCs"). Its original CEO, Dr. Richard Miller, was biotech royalty whose previous company IDEC Pharmaceuticals had been acquired by Biogen for $6.4 billion.

But by 2008, Pharmacyclics lead drug candidate – a novel treatment for brain cancer – had failed three key clinical trials. The FDA had declined to greenlight this lead drug candidate on three separate occasions. The last time, the FDA issued a rare Refusal to File – the agency's version of ejecting a player from the game with instructions not to come back.

With a college-dropout Scientologist at the helm… stock trading below $1… multiple clinical-trial failures and FDA rejections… and its luminary founders having abandoned it… Pharmacyclics did not look like a winner in 2008.

But biotech is full of surprises — scientific surprises… regulatory surprises… and investment surprises too. Indeed, there may be no corner of the economy or the stock market more full of surprises than biotech.

Most observers weren't focused on it, but it turns out that among the undeveloped molecules in its pipeline, Pharmacyclics had in 2008 what would become a first-in-class Bruton's tyrosine kinase ("BTK") inhibitor. BTK inhibitors, of which Pharmacyclics's drug ibrutinib would be the first developed and approved, would revolutionize the treatment of an important category of deadly blood cancers called B-cell lymphomas. This drug would cut the risk of death in B-cell lymphoma patients by 49% – enabling over 75% of them to stay alive more than six years after treatment. For these patients, ibrutinib would prove to be a miracle drug. In 2015 – betting on the promise of ibrutinib – Big Pharma giant AbbVie bought Pharmacyclics for $21 billion… netting Bob Duggan personally over $3.5 billion.

* * *

Welcome to *Biotech Frontiers*.

I'm so excited for you – and for me – as we embark on this journey together.

Life-science and biotech investing will be our focus in *Porter & Co. Biotech Frontiers*… Not all biotech stocks follow the comeback-kid path of Bob Duggan and Pharmacyclics… but many do. Some startups follow a clear, smooth path to success. Others skyrocket, then quickly fall back to Earth. But, generally speaking, as a sector, biotech stocks perform differently than tech stocks, "forever stocks," and certainly the blue chips…

So close your eyes for a moment and remember the best learning experience of your life. Maybe it was your years in college. Maybe it was a high-school or grade-school teacher who made a subject come alive and lit your brain on fire. Maybe it wasn't in school at all, but in a job that made you realize you'd found your calling… or a trip you took somewhere different on the map… or a conversation that changed the way you understand the world.

We're going to aim to match that electric learning experience here… and best of all, we're going to help you make the cash register ring along the way.

I grew up in the San Francisco Bay Area in the 1980s. At that time in the Bay Area – even if you knew nothing about computers – you could sense that something important was happening… something that was likely to change the world. If you were lucky, like me, you had a childhood friend whose dad brought back one of the very first Apple II computers and let you tinker with it. Or maybe you had another friend – as I did – who subscribed to one of the first dial-up internet services while he was still a teenager, and toyed with it so that he could trade stocks online… If you were curious, experiences like these would have helped clue you in earlier than most to the revolutionary impact the internet would have on every aspect of life.

In every human lifetime, we encounter a small handful of *tsunamis* – the proverbial 100-foot-tall waves that change everything… across technology, economics, and culture. I am 51 years old, and in my lifetime so far, I've seen two: the PC-internet revolution and the advent of Bitcoin/Web 3.0.

We are now on the cusp of two more. One is the proliferation of artificial intelligence ("AI") into our everyday lives.

The second, I believe, is the unfolding revolution in life sciences and biotech. It will be at least as important, far reaching, and profound. It's my great privilege to get to explore this with you in *Biotech Frontiers*.

The thing about these tsunamis is… if you are relatively early to them, understand what they're about, and are able to identify the right financial instruments to ride them, you can earn generational wealth. For example, investing $1 million into a basket of Amazon, Google, Microsoft, and Apple in 2003 would have generated $50 million today.

Another thing about these tsunamis is that they're not only about generating wealth, but also about understanding the world we live in as it changes. There aren't many sectors of the stock market where novel developments are going to reshape how humans live. This isn't true, for example, about property-and-casualty (P&C) insurance or financial services.

But it's true about life sciences – it's true about biotech. What's coming down the pike in life sciences holds out the potential to eradicate or dramatically shrink the leading disease-driven causes of death… and to change our sense of what it means to be human – for instance, by giving us the tools to pre-select many traits of our offspring before they're born.

Why Am I Qualified to Explore These Topics With You?

I attended Stanford University, where I double majored in biology and English… then earned a Master's in cell biology and genetics at Oxford University. Next, I got a law degree at Yale, then moved into finance, working at McKinsey & Co., then at a large hedge fund affiliated with Goldman Sachs, and then for Julian H. Robertson at Tiger Management.

In a magnificent commencement address Steve Jobs gave at Stanford before he died, the Apple Computer founder said: "You can only connect the dots backward."

Strangely, the different dots of my work life are almost perfectly suited to help parse the interdisciplinary complexity of life sciences – which melds together science, finance, law, and regulation in an intricate dance.

Having had the good luck to study biology at two of the world's leading research universities, I also met and befriended people who are now among the leading scientists of our generation, and who teach today at places like Stanford, Caltech, Harvard, MIT, and Columbia University Medical School. These friends still let me bother them with "dumb questions" – and I do.

As an investor, I've also met several hundred biotech CEOs and management teams, at every stage of the corporate life cycle – from the pre-seed/venture stage to pre-IPO (initial public offering) and beyond. Collectively, these meetings – over two decades – have provided some powerful pattern recognition of the green flags and red flags that often presage success or failure.

Finally – this introduction would not feel complete without a few words about how I met Porter Stansberry. Back in 2008, while working for Julian Robertson at Tiger Management, I left the office late one night to get a large print job done at Kinko's. I noticed a few stray pages of a newsletter someone had left on a copy machine. Those pages explained why Fannie Mae and Freddie Mac were already insolvent and would inevitably go bust.

Fascinated, I returned to the office and searched online for Stansberry's Investment Advisory and became a subscriber that night… That issue of the Investment Advisory helped me make a tidy sum for Julian. I wrote to Porter to say thanks and to invite him to lunch. We've been friends ever since.

You might conclude from the anecdote above that my favorite issue of Porter's writing is that piece on Fannie Mae and Freddie Mac. But it's my second favorite… not my first.

My all-time favorite piece of Porter's writing is, instead, the September 2009 issue of *Stansberry's Investment Advisory*: "The Seven Real Secrets of the World's Best Investors."

The specific recommendations Porter made in the "Seven Real Secrets" are not what makes that piece stand out. What makes the piece memorable is that it reveals seven methodological tools that are always relevant to any investment. For example, Porter's Secret #1: "You can time the market… You must time the market."

Give a man a fish, and he'll eat for a day. Teach him to fish and he'll eat forever.

Porter's "Seven Real Secrets" piece helped improve my fishing.

So, in this *Introductory Guidebook for Biotech Frontiers*, I'm going to attempt something similar.

The first issue will include recommendations for a basket of 10 stocks, meant to construct a portfolio that will benefit from the mean reversion that I believe the biotech sector will experience throughout 2024. Future issues will often include specific stock recommendations. This *Guidebook* does not include a stock recommendation.

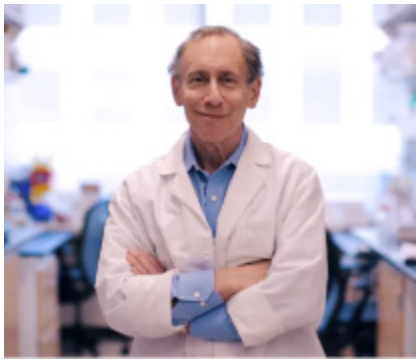
Instead, in this *Guidebook*, I'll lay out the seven-part framework we'll use to identify compelling opportunities in the life-sciences domain… the lenses we'll peer through to find winners. I hope these seven pieces help you improve your fishing, too.

I. The Science

To identify the most promising investments opportunities driven by science, it makes sense for us to start with the science.

We're going to be on the lookout for big, important advances – the kinds of discoveries that have the potential to change the standard of care for a disease or entire category of illnesses… or that can function as entirely new platforms to power drug development.

To find these innovations before they enter the mainstream, we will track down cutting-edge labs at the world's leading research universities. We'll zero in on labs that have a proven track record of spinning out ideas that lead to clinical impact. In other words, we'll rely on the world's best scientists to guide our search for high-impact science.



Let me share an example...

MIT Professor Bob Langer, a chemical engineer by training, is known among life-sciences entrepreneurs as "the Edison of Medicine." A scientist's **h-index score** measures how often other scientists cite his papers. For a scientist who has run a lab for 20 years, an h-score of 20 is good... 40 is great... 60 is remarkable. Bob Langer's h-score is 230 – the highest of any engineer ever. The Langer Lab's discoveries have translated into both clinical and commercial success. His lab has given rise to 40 companies – 39 of them either acquired or still in existence, with a collective market value of over $50 billion.

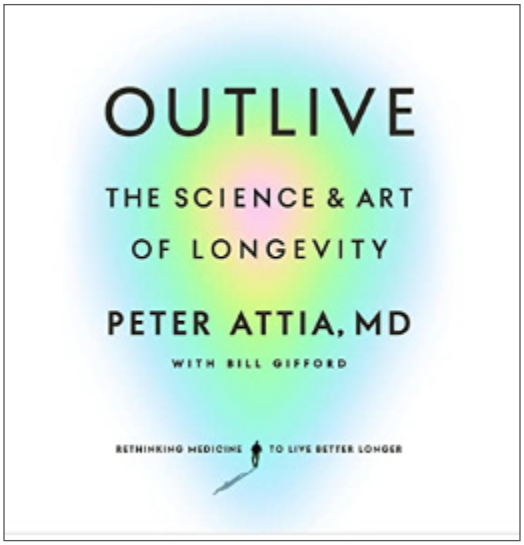
If you've received a COVID vaccine in the U.S., there's a two in five chance you've gotten it from one of Langer's best-known companies – Moderna, the mRNA-medicines platform he co-founded in 2010, which by itself has a market capitalization of $44 billion. An investment in Moderna in the year after its 2018 IPO would have netted somewhere between a 3x to 5x gain through the end of 2023, not bad for a five-year holding period.

We at *Biotech Frontiers* are going to pay attention to Langer's Lab. But we will also find and follow the younger, less-famous labs that are building reputations among their scientific peers as hotbeds of innovation. We'll do this by speaking with leading scientists... top biotech entrepreneurs... and by reading scientific papers.

Because this advisory is not meant to be a variation of *Scientific American* – but instead to focus on where transformative science can propel an investment – we will filter ideas for their commercial promise.

In his superb recent book *Outlive: The Science & Art of Longevity*, Stanford University-trained physician Dr. Peter Attia introduces the concept of the Four Horsemen. The Four Horsemen are the illnesses that will ultimately kill the vast majority of people who live past 40: heart disease, cancer, neurodegenerative

disease (e.g., Alzheimer's and Parkinson's), and Type II diabetes. We will naturally be on the lookout for discoveries that may be game-changing cures for these four diseases.



But we will also be following the orphan-disease space. An orphan disease is a rare ailment that afflicts a small percentage of the population. Some of these are well known, such as ALS (popularly known as Lou Gehrig's disease) and cystic fibrosis. Others you've almost certainly never heard of. One thing orphan diseases have in common is that their treatments tend to be very expensive, as the developers of these treatments must "amortize" their research-and-development (R&D) expense (and risk) over a smaller number of patients. So orphan diseases, despite the small patient numbers, can be big business.

We've talked about following "top gun" scientists… and about sifting out commercial relevance. One other lens that we'll bring to bear on our investigation of science is a focus on important scientific themes. These are the domains in science that have either already achieved or are nearing a critical mass that can propel them forward explosively. These are the domains in science where, if they were stocks, we'd be observing sharp "gap ups" in the price charts. A few examples –

- AI-driven and computational-biology-driven drug discovery and development
- Next-generation, precision medicine-guided immuno-oncology
- Genomic editing technologies and gene therapies
- Advances in tissue engineering and regenerative medicine

- Medicine 2.0 early-detection technologies

I can't wait to explore these and a long list of other brave new world advances in the issues that follow.

II. Sizing the Prize: The Opportunity

From the 49th Floor of 101 Park Avenue in Manhattan, the jet-black skyscraper that served as the headquarters of Tiger Management, legendary hedge fund investor Julian H. Robertson had a saying that he delivered in a booming southern drawl:

"If you're right, you've got to get paid."

Meaning: When an investment works out favorably, you don't want to make 10%, 15%, or even 25%. Instead expect returns of 50%, 100%, or better yet. Earning 2x, 3x, or 5x – that, in Julian's parlance, is "getting paid."

The good news is, earning a multiple on your investment with biotech stocks is probably more achievable than in any other part of the stock market. But that doesn't mean it's easy.

To improve our odds, the second factor we'll look at when we hunt for attractive life-sciences investments is the size of the prize – or what I call **The Opportunity**. With this factor, we'll estimate, in percentage terms, how much we stand to make if our investment works out.

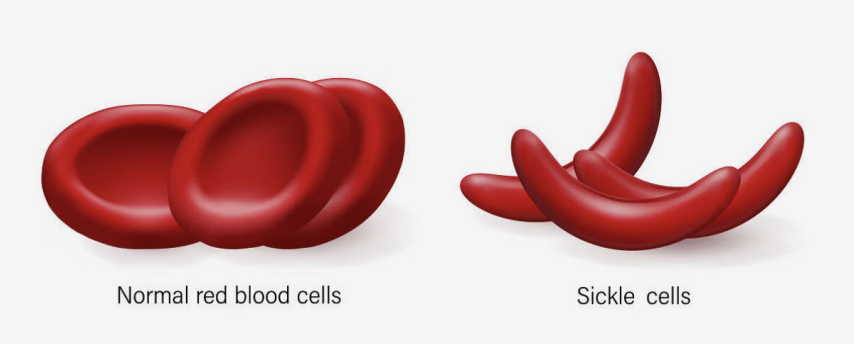
We'll break down The Opportunity into two specific components:

1. The company's **total addressable market** (TAM), which we'll estimate in dollars
2. The company's **market-implied probability of success**, which we'll compare to our own estimate of its probability of success

Let's walk through an example to make these ideas more concrete.

Sickle cell disease ("SCD") is an inherited blood disorder marked by defective hemoglobin, the protein in red blood cells that carries oxygen to tissues of the body. Normal red blood cells are smooth, disc-shaped, and flexible, like doughnuts without holes. In people with SCD – whose hemoglobin is defective – red blood cells come to resemble a sickle, like a letter C. These cells stick together and can't easily pass through blood vessels. People afflicted with SCD live with chronic anemia and pain, but also significantly elevated risk of serious infections and stroke. It's an awful disease and, until recently, one that did not have any good treatment options.

There are about 100,000 people in the U.S. who suffer from SCD. That makes SCD an orphan disease – which, you'll recall, is what the name for diseases that affect a small percentage of the population. The average price of an orphan-disease treatment in the U.S. is $32,000 per year... but fully a third of such drugs cost more than $100,000 annually. It would be reasonable to guess that an effective, novel therapy for SCD could be priced at between $50,000 and $100,000 per year. With 100,000 potential patients paying between $50,000 and $100,000 annually, the TAM for a new SCD drug that captured the entire U.S. patient population is about $5 billion to $10 billion in annual peak sales.



We needn't nail down this number exactly through what I call "false precision math." Our goal here isn't to arrive at a falsely precise estimate, but instead to get the order of magnitude right.

Harvard-trained physician Dr. Ted Love founded Global Blood Therapeutics ("GBT") in 2011 with the goal of developing a cure for SCD. By 2017, GBT had advanced its lead drug, a promising compound called voxelotor, through successful Phase I and Phase II clinical trials. The results of an important, pivotal Phase III clinical trial lay ahead, but the publicly available data from GBT's Phase I and Phase II trials provided a strong basis for some optimism about voxelotor's Phase III results. Even so, during most of 2017, GBT's market capitalization was about $1 billion.

Let's return to our TAM calculation. We concluded that an effective SCD drug that captured 100% of the market could plausibly generate $5 billion to $10 billion in peak sales annually. Of course, few drugs capture all of a market. A therapy that can capture 20% of a disease market is often still a major success. At a 20%

market share of the SCD market, voxelotor would generate about $1 billion to $2 billion in sales annually. A reliable metric in biotech values a drug at between 3x to 5x its annual peak sales. For voxelotor, this would translate to $3 billion to $6 billion – assuming a conservative 20% market share.

In 2017, then, with GBT at a $1 billion capitalization, the market was implying a 15% to 30% probability of success for voxelotor. We arrive at this range by dividing GBT's $1 billion capitalization by $3 billion of estimated value at the low end and $6 billion at the high end.

I concluded that this market-implied probability of success was too low. In my estimation, GBT had closer to a 60% chance of advancing voxelotor to a successful Phase III trial and commercial launch. I estimated that GBT's market capitalization would appreciate to the $3 billion to $6 billion range – i.e., anywhere from 3x to 6x from its value in 2017. Attendees of Stansberry Research's annual conference in Las Vegas may remember my GBT pitch.

There were some twists and turns along the way, but voxelotor did indeed deliver superb Phase III results, and was ultimately approved for SCD treatment by the FDA. Pfizer acquired GBT in 2022 for $5.4 billion, believing that its Big Pharma sales force could drive voxeletor's sales significantly beyond my conservative 20% market share estimate.

Not all of our endings will conclude as happily as the GBT story. But we will always "size the prize" and quantify our opportunity so we can sharpen our assessment of our risk – and our reward.

III. The Cap Table

"Play the players, not the cards" is a familiar insight to anyone who's played much poker. This maxim teaches us that in competitive games who else is playing and what we can deduce about their incentives and their likely behavior can be more important than anything. In many situations, reading the other players well can enable us to win by itself.

That's why in any investment we consider, we are going to study the **Cap Table** closely. The Cap Table – short for Capitalization Table – is the list of who owns shares in the company, how much they own, and whether they've been adding to or reducing their investment.

When we study the Cap Table, we're going to focus on three players in particular: **The Insiders, The Smart Money**, and **The Whales**.

The Insiders

The Insiders are the people who run the company: The management team, board members, and strategic advisers. We call these people insiders because, well,

they have inside information – i.e., what securities lawyers call "material non-public information," which outsiders like us can't know until it's disclosed publicly. Insiders know a company's prospects better than any outsider can. That's why we want to pay careful attention to their ownership stake and whether they're buying, selling, or holding.

When we study insiders, we're looking for two distinct things: **skin in the game** and **signals**. Skin in the game refers to how much insiders own – as expressed in both percentage and dollar terms. For example: Is the CEO of a company we're studying one of the largest shareholders, with a 10% stake that's worth, say, $25 million? That's a CEO with skin in the game. We're looking for situations where insiders are strongly aligned with shareholders and incented to raise the stock price.

Signals refer to what we can infer from insider buying or selling. If a C-level officer or board member makes a seven-figure purchase of shares, that's a powerful signal of his confidence in the company's prospects. Conversely, if we see insider selling – especially consistent, sizable insider selling – that's reason for caution.

Insider signals are especially relevant to life-sciences stocks because the catalysts that cause these stocks to move dramatically up or down often involve clinical trial outcomes, regulatory decisions, or the early results of a new drug's commercial launch. When we see a biotech stock move up 300% in a single trading day… or decline by 70% in a matter of minutes… it's most often because one of these catalysts has played out.

Federal securities laws prohibit insiders from trading based on knowledge about an outcome of one of these catalysts before it's disclosed to the public. But insiders are allowed to buy or sell in advance, based on their business judgment or even just a hunch. And we want to pay attention to these signals because they can help us get paid.

The Smart Money

While insiders are the most important players we'll be following, we will also be tracking **The Smart Money** – the hedge funds, venture capitalists, and private equity firms who focus on life sciences, who manage billions of dollars for large institutions, and who live or die based on their abilities to pick winners consistently in this space over time.

Let's take an example to demonstrate why we care about these guys. Joe Edelman is the founder and CEO of Perceptive Advisors, which manages $8 billion and focuses exclusively on life-sciences investing. The son of Professor Isidore Edelman, a renowned biochemist at Columbia University's College of Physicians and Surgeons, Joe grew up around science. Since founding Perceptive in 1999 with $6 million of capital, he has earned net average annual returns of 30% over 24 years – a better track record than Warren Buffett has.

Today, Perceptive's research team includes 46 life-sciences professionals, including 10 PhDs and MDs from some of the world's leading scientific institutions. So when Perceptive Advisors appears on the Cap Table of a company we're studying, we pay attention. Better yet, we will use the 13F disclosures (required quarterly Securities and Exchange Commission filings revealing an investment manager's holdings) of Perceptive and a small handful of the world's other best life-sciences investors to guide us as we sift through investment ideas.

The Whales

The final players we'll follow in the Cap Table are The Whales. There are two kinds of whales: First are the large pharmaceutical companies like Eli Lilly, Johnson & Johnson, and Merck, which we'll call Big Pharma. The combined market capitalization of those three companies alone is over $1 trillion.

We care about these giants because they grow principally by acquiring smaller, promising rivals. And the pressure on them to ramp up their mergers-and-acquisitions (M&A) activity is likely to become sharper over the coming years. Why? Because between now and 2030, Big Pharma faces a "patent cliff" that threatens over $200 billion in annual revenue. This patent cliff is when Big

Pharma's blockbuster drugs – like AbbVie's anti-inflammatory Humira and Merck's top-selling cancer therapy Keytruda – lose their patent protection. At that point, these blockbusters become vulnerable to competition from generic drug manufacturers that can price bioequivalent drugs around 85% lower.

To replace that lost revenue, we can expect Big Pharma to go on a buying spree over the next three to five years. It's often the case that before a Big Pharma whale acquires a smaller rival, it will strike a strategic investment or partnership with it, as a way of establishing a toehold. We will pay careful attention to these strategic investments and partnerships.

The second kind of whale are the giant financial investors, such as Fidelity Investments, Capital Group, and Wellington Management. Fidelity manages $3.9 trillion in assets... Wellington $1.1 trillion... and Capital Group $2.3 trillion. When they buy, they've got to buy a lot of stock to move the needle on their portfolios. When a hedge fund like Perceptive Advisors invests in a biotech stock, it may deploy as little as $5 million or $10 million at a time. When Fidelity invests for its life-sciences portfolios, it will rarely come in for less than $50 million. Because these giant institutional money managers can single-handedly drive up the stock price of a small- or mid-cap biotech stock significantly, we will pay attention to any signs of their interest in a company, and to their earliest appearance on a Cap Table.

IV. The Catalysts

"Hope is not a strategy" sums up one of the most frustrating things about many investors: they ask us to rely on hope. Take the classic Warren Buffett-style of investing, as taught by Buffett's mentor Benjamin Graham in his iconic book, *The Intelligent Investor*. Graham suggests looking for stocks that trade at a steep discount to intrinsic value, where one can buy shares with a significant margin of safety to their actual worth. Years later, influenced by his partner, the late Charlie Munger, Buffett would add an additional criterion to Graham's advice: Look for high-quality businesses – those that are capital efficient and have strong economic "moats" that protect them from rivals. Porter has put his own spin on this style of investing when he suggests patiently assembling a portfolio of "forever stocks" – a collection of the world's best businesses, which you've ideally purchased at compelling prices by waiting to buy until shares go on sale.

I've got no problem with this approach to investing so long as your time horizon is, well, almost forever. For my 14-year-old daughter Daphne or Porter's 16-year-old son Traveler – both of whom can anticipate decades of runway ahead of them – patiently assembling a "forever portfolio" seems exactly right. It also makes sense for those wealthy enough to carve out a piece of their assets to invest for an indefinite duration, perhaps even intergenerationally – for example, someone in their 60s or 70s putting together a stock portfolio that will be passed on to their kids or grandkids.

But what about those of us with a shorter investment horizon? Or folks who, due to an upcoming milestone in their lives (e.g., a child starting college, or their own retirement), anticipate a need to access their investment dollars at a foreseeable point in the future?

The Problem With the Forever Portfolio

The forever-portfolio strategy is complicated. History has shown that the stock market can go through long periods – over two decades! – during which stock prices remain depressed. Buffett's mentor Ben Graham lived through one of these eras in the aftermath of the Great Depression: From its 1929 peak, the Dow Jones Industrial Average did not reclaim its high again until 1954 – 25 years later. Buffett himself had a similar experience during the 1970s, a decade during which major stock indexes were flat in nominal terms – and declined by almost 50% in real terms (i.e., adjusted for inflation).

"But hold on, Erez!" I can hear some thoughtful readers exclaim. "Haven't we learned that the modern Federal Reserve – starting with Chair Ben Bernanke and continuing today with Chair Jerome Powell – will just print trillions of dollars to re-inflate stocks quickly if there's a stock market crash?" Yes, that has been our recent experience. That's indeed what happened during the Global Financial Crisis in 2008, as well during the COVID crash of 2020.

But for reasons that I may explore in a separate note for Porter & Co. – not for this *Guidebook* – I'm not convinced that this "Fed put" is going to keep working forever. I certainly wouldn't want to bet my life savings that it will. Hope is not a strategy.

An Alternative Approach: Catalyst-Driven Investments

The good news is proven investment strategies exist that are **catalyst driven** – instead of simply hoping that a stock will appreciate in price someday, when Mr. Market comes to recognize its intrinsic value, we can anticipate concrete, specific events that will move the stock price significantly. If these events play out favorably, they will propel a stock's price upward. Of course, if they play out unfavorably, they can result in a stock getting crushed. Either way, we can generally count on them to move the price.

Porter & Co. readers are already familiar with one of the best, time-tested strategies that relies on catalysts: investing in distressed debt. With distressed-debt investing, the most important catalyst is a bond's maturity date. If a company is already in bankruptcy, the approval of its restructuring plan and its eventual emergence from Chapter 11 are meaningful catalysts too.

Key Catalysts for Life Sciences Stocks

Life-sciences investing, like investing in distressed debt, is also catalyst driven. The five most important catalysts for life-science companies are:

1. Clinical trial results
2. Regulatory decisions
3. Commercial launches of new drugs and therapies
4. Refinancings
5. Partnership announcements

Each of these catalysts has potential to move a life-science stock up more than 100%, or down by more than 50%.

5 Key Decision-Making Catalysts				
Clinical Trials	**Regulatory Decisions**	**Commercial Launches**	**Refinancings**	**Partnerships**
Safety and efficacy tests	Government approval… or not	Acceptance by the medical world	Exploring new capital	Milestone event for small firms
Complete Phases I, II, III to advance	U.S. FDA and Europe's EMEA are authorities	Turning a drug into a marketable product	Adding value or diluting shares	New investments or strategic alliances
Good design is critical for approval	Life or death stage for young biotech companies	Reviewing the business plan and rollout strategy	Critical factor in making a "buy" decision	Signals a stock's future value

Clinical trials are the research studies designed to test the safety and efficacy of new drugs and therapies on people. The most important are those designated as the Phase I, Phase II, and Phase III clinical trials that help advance a novel drug or therapy toward regulatory approval. Renowned German architect Ludwig Mies van der Rohe said "God is in the details" – and van der Rohe's dictum is emphatically true of clinical trial design. When a clinical trial result is part of our investment thesis, we will examine the trial's design with care and rigor.

Regulatory decisions are the judgments by specialized arms of the government – the FDA here in the U.S., the European Medicines Evaluation Agency ("EMEA") in Europe – to approve a novel drug or therapy for commercial sale. Moving a new drug or therapy from the "scientific bench" to approval for patients in the clinic has been called "crossing the valley of death" for young life-sciences companies. Obtaining such approval is exceptionally hard: National Institutes of Health ("NIH") data shows that only 7.8% of drugs in Phase 1 clinical trials are ultimately approved by the FDA. Regulatory review by the FDA or EMEA is its own complicated maze. Fortunately, we have a lot of distinctive tools to help us handicap the odds of these catalysts.

Commercial launches happen after a novel drug or therapy has been approved but are also fraught with risk. Will the medical establishment embrace this new drug? How convinced are prescribers that it offers compelling advantages in efficacy, safety, convenience, or cost? For a company launching a new therapy, what is the company's go-to-market strategy and how does its prior track record inform the likelihood of success? Finally: What are market expectations about the new launch, and do they seem too rosy… or too conservative? We will seek to answer some or all of these questions when a commercial launch is part of our investment.

Refinancings happen when a life-sciences company is running low on funds… or sometimes, after it has struck gold with a successful clinical outcome or regulatory approval, and sees a chance to build a cash buffer on its balance sheet when shares are "hot." Whether a refinancing should serve as a prompt to buy or to sell shares depends hugely on the context. In some cases, a successful refinancing can de-risk the balance sheet and help propel shares higher. In others, we may infer that a looming refinancing is likely to be so dilutive that it will crush the share price. Regardless, we'll need to be thoughtful about the upside and downside risks that these balance-sheet events pose to prospective investors.

Partnerships are often positive events for a young life-sciences company shepherding a novel drug, therapy, or platform – as they may include an up-front cash payment or a big-dollar milestone payments downstream. But here too, God is in the details – and we will want to parse the partnership terms carefully, as we seek to disc

Anticipating Catalysts to Improve Our Risk/Reward

One last observation about catalysts in life sciences. Sometimes the market's mere anticipation of an imminent catalyst can drive a life-science stock's price up dramatically, even before an event has actually played out. When this run-up happens, savvy investors have a chance to take money off the table and significantly de-risk an investment.

In 2020, BiondVax was a small-cap, Nasdaq-listed biotech company seeking approval for what would have been the first-ever universal flu vaccine – a vaccine that you could take once and would protect you against all future variants of the flu in years to come. Based on three decades of innovative research in the lab of Dr. Ruth Arnon at the prestigious Weizmann Institute in Israel, BiondVax's universal flu vaccine candidate had already successfully passed half a dozen Phase I and Phase II clinical trials. The last major hurdle left was the pivotal Phase III trial.

As the date for that trial drew closer, BiondVax shares appreciated 5x over six months – before the trial results were made public. An investor who had bought the stock a year before could have taken all of their original investment dollars off the table – realizing double their money – and let the rest ride on the publication of the trial results. Alas, when the trial went public, BiondVax's drug failed to pass the agreed clinical endpoints, and the stock collapsed by 90%. But BiondVax stands as a magnificent lesson in how navigating catalysts wisely can make all the difference between an epic win or a total zero in life-sciences investing. We will heed this lesson well.

V. The Balance Sheet

In his introductory course on entrepreneurship, renowned INSEAD Business School

Professor Phillip Parker has a memorable line: “Companies fail for one reason and one reason only – they run out of cash.”

What Parker says about companies generally seems doubly true for development-stage biotech companies. Creating a novel, effective medicine is both expensive and risky. NIH estimates that the average investment required to bring a new drug from the bench to the clinic is $985 million. And that’s only to cover the R&D and regulatory approvals – marketing isn’t included in the NIH estimate. Little wonder then that so many small- and mid-cap biotechs struggle in their journeys to bring new therapies to life.

The risk is not only that a young biotech company may encounter unexpected setbacks that drive it out of business… though that’s the worst-case scenario. For shareholders, an almost equally bad outcome can be **serial dilution** – where a company has to raise capital so many times on the way to success that early investors are left with almost nothing.

Imagine having the foresight to be among a promising biotech start up’s earliest shareholders… and the company ultimately delivers a blockbuster drug worth billions. But management dilutes early shareholders so significantly, raising fresh capital along the way, that those investments get watered down to 10% or 20% of what they were to start. This is the nightmare scenario my old mentor Julian Robertson warned about – you “got it right,” but you didn’t “get paid.”

To minimize the risk of this nightmare, when we study a company we’re going to pay very careful attention to its balance sheet. Let’s go back to that NIH figure: The average cost to create a new drug and get it approved is almost $1 billion.

In practice, young biotech companies do not raise $1 billion up front. Instead, they usually raise a smaller figure – say, $100 million to $250 million – and promise their early investors that this cash will enable the company to reach a milestone that will justify a much higher valuation. They will then raise cash again at that higher valuation – promising those later investors a similar valuation step-up at the next milestone. If things go right, the process continues this way until the company gets its drug approved, partnered, or bought out.

But things don’t always go right. In fact, they often go wrong. Maybe a company experiences a setback in its clinical trials. Maybe it encounters a CMC (chemistry, manufacturing, and controls) hiccup. Maybe the FDA changes its feedback on what it will require to get a novel therapy approved. These types of obstacles happen routinely in biotech. Well-run biotech companies anticipate them and build in buffers on their balance sheets to protect shareholders. Poorly-run biotechs don’t… and leave shareholders holding the bag. It will be an important part of our job to distinguish between them.

To so do, here are some of the questions we will ask when we consider a prospective investment:

- Where is the company in its capital-raise cycle – e.g., has it recently raised capital or is it approaching the window for another raise?
- How strong is the current balance sheet – e.g., how much net cash does the company have and what is its burn rate?
- How much runway does the balance sheet provide before another raise becomes unavoidable?
- What is the next milestone the company will need to reach to justify a valuation step up, and how achievable is it?
- What is the company's likelihood of achieving this milestone relative to market expectations?
- If the company is likely to raise capital again during our time as shareholders, how dilutive is the next raise likely to be?
- How do the company's likely capital raise needs impact our risk/reward calculus and our expected return?
- Have management demonstrated themselves to be shareholder friendly, good stewards of capital?

VI. The Big-Picture Backdrop

Recently I emailed the CEO of a public biotech company who has been a long-standing friend. A doctor by training, he's been in the world of life-sciences entrepreneurship for five decades now and has made his shareholders billions of dollars over that time. He is one of the biotech leaders I most admire – a brilliant scientist with a nose for making money and a strong ethical spine. Over the past year, his company's stock price, like that of many other public biotech companies, has declined by 80%. He's the company's largest shareholder with an 11% stake, so I know he's felt the financial pain personally. We hadn't connected in months and I was writing simply to check in on him. Here is an excerpt from his reply:

"Dear Erez: Great to hear from you. It has been an unreal, even insane period. The industry has never seen interest rate increases anywhere near this magnitude. It has devastated development-stage biotech."

It's notable that my friend – one of the gray-haired wise men of the life-sciences industry – would begin his note to me by referencing interest rates. If we're going to invest successfully in life-sciences stocks, it's crucial for us to understand why. Let me explain . . .

The Importance of Interest Rates to Biotech Investments

Interest rates are like financial gravity. When interest rates are low, stocks float

upward. When rates are high and gravity is strong, valuation multiples collapse – and stocks fall back to Earth.

But while physical gravity causes all objects to fall at the same constant rate (9.8 m/s2), financial gravity has a stronger effect on some kinds of stocks than others. And life-sciences stocks working to bring novel drugs and therapies to the world tend to be among the hardest hit.

To grasp why, it's helpful to think of development-stage biotech stocks as long-duration equities… or the equity siblings to long-duration bonds – one whose maturity is far off in the future. As most investors know, these bonds are especially sensitive to changes in interest rates.

A long-duration equity is one whose free cash flows ("FCF") are far off in the future. And this describes most development-stage biotechs. In the near future, they have to spend a lot of money up front – performing R&D, running clinical trials, paying lawyers to help them obtain regulatory approvals, and eventually launching their new product. All of this is money out the door – before any money comes in the door.

If they're successful, their FCF tends to lie far out in the future. These FCFs can be astronomical for an effective new drug. But they have to be discounted back to the present. And as anyone who's built a financial model knows, the more periods you have to discount your FCF back, the more sensitive the model is to changes in your discount rate – or in this case, to the U.S. interest rates that are the foundational benchmark for every discount rate in the world.

All of which brings us back to what the billionaire founder of Oak Tree Capital, Howard Marks, has called the sea change in our interest rate environment.

A History of Modern Interest Rates in Five Minutes or Less

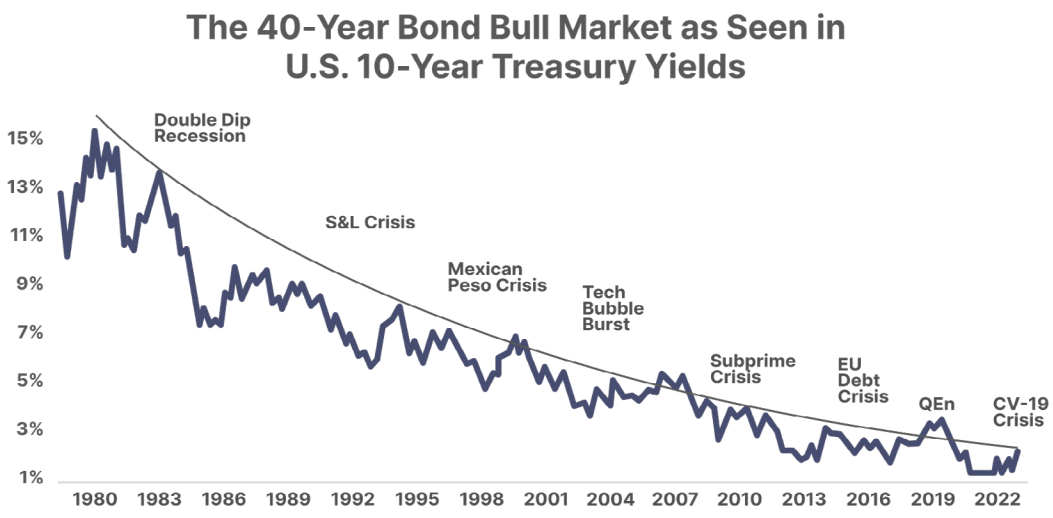
For four decades – from 1982 to 2021 – U.S. interest rates mainly moved in one direction: down. In the early 1980s Fed Chair Paul Volcker raised interest rates dramatically in a bid to slay inflation, which had haunted the U.S. economy for much of the 1970s. The Fed funds rate peaked at 20% in June 1981. And that did the trick: Volcker's draconian interest rate medicine banished inflation.

Starting from the Volcker high of 20%, successive Fed chairs after Volcker… first, Alan Greenspan, then Ben Bernanke, then Janet Yellen, now Jerome Powell… have cut interest rates every time they've perceived the U.S. economy to encounter a problem. Bernanke, of course, cut rates all the way to zero during the Global Financial Crisis.

Believing that the U.S. needed an even more powerful stimulus, he then proceeded to print $4 trillion. But whereas Bernanke's zero-percent rates and trillion-dollar

printing press were advertised as “emergency measures” in response to the Global Financial Crisis, they ended up becoming business as usual for the Fed for the ensuing decade – long after our economy recovered from the mess of 2008.

Fed Chair Powell, faced with the COVID-pandemic shock to our economy in 2020, dusted off Bernanke’s playbook and printed $4 trillion in less than a quarter the time it took the Bernanke Fed to do so. But this time, the Fed’s money printing was accompanied by $2 trillion of the Biden administration’s fiscal stimulus, as well as supply shocks to both the U.S. labor force and global supply chains. The result was a headline consumer price index (“CPI”) inflation rate of 9.1% in June 2022 – the highest rate since 1981.



Source: Federal Reserve Bank of St. Louis FRED database

Chair Powell may be many things, but he does not want to be remembered as the Fed chair on whose watch the inflation bogeyman returned to haunt America as it did during the 1970s. And so, faced with the highest CPI inflation rate in 40 years, Powell borrowed a page from Volcker. Powell has proceeded to raise the Fed funds rate from 0% in March 2022 to 5.25% by the end of 2023, the steepest Fed rate hikes since the Volcker era.

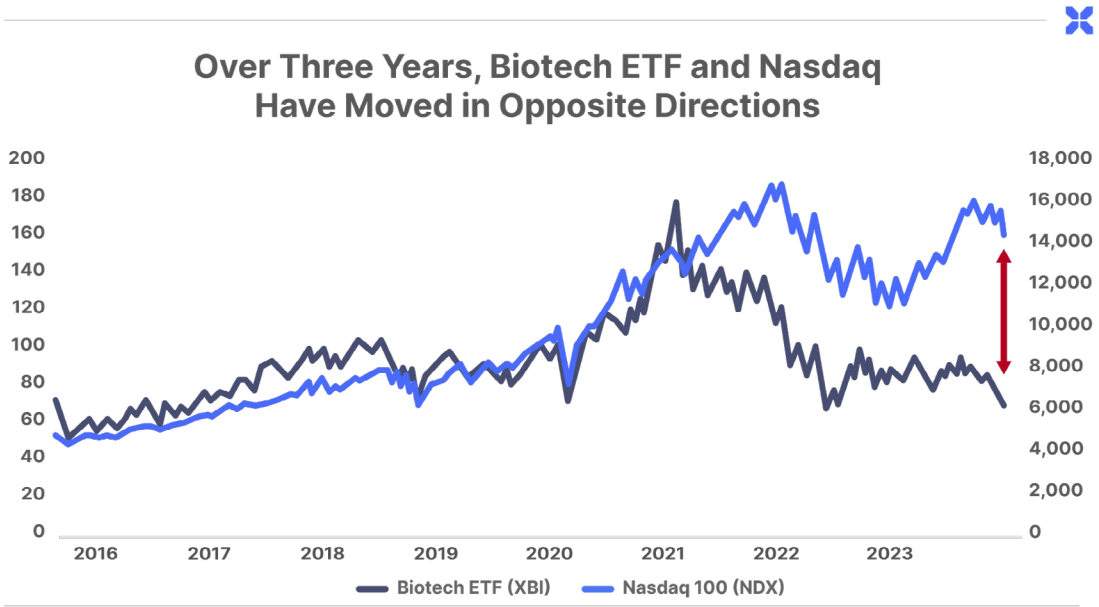
The Biotech Bear Market

Let’s return to my CEO friend’s note with which we began our discussion of interest rates: “It has been an unreal, even insane period. The biotech industry has never seen interest rate increases anywhere near this magnitude.”

My friend is not exaggerating. The biotech industry didn’t exist in the early 1980s.

Genentech, the granddaddy of modern biotechnology companies, IPO'd in October 1980 – and at the time it had no direct competitors. So the severe Fed interest rate hikes of the past 18 months truly are a first for the biotech sector.

And because we've now understood how biotech stocks are long-duration equities – similar to long-duration bonds in their sensitivity to interest rates – we can also appreciate the punchline of my friend's note: these interest rate hikes have "devastated" biotech.



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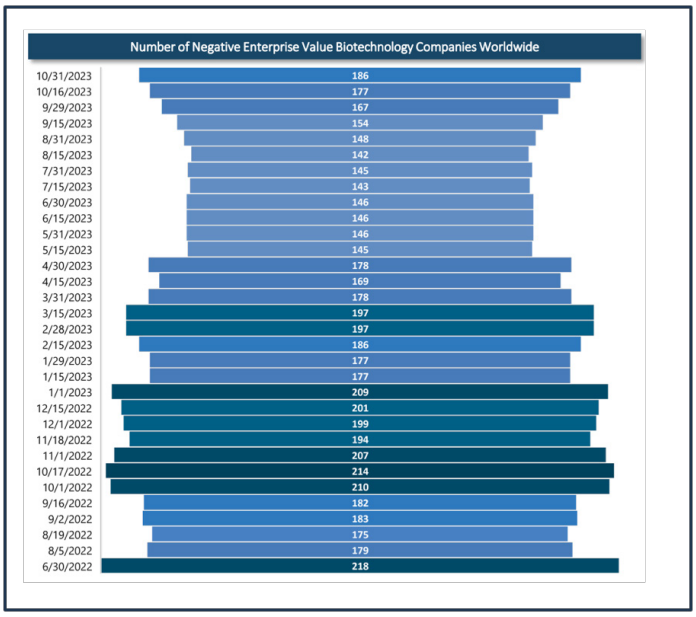
The bear market in biotech that we're in the midst of today is the longest, biggest, and most punishing bear market in the history of biotech. While the Nasdaq Biotech Index is down 20% from its peak in September 2021, small-cap biotech stocks in the Russell 3000 are down 70%, and biotech stocks removed from the Russell 3000 because they no longer meet its inclusion criteria are down over 85%. Large-cap biotech underperformed the S&P 500 by over 30% in 2023.

More than 70% of the global biotech sector now trades with an enterprise value

("EV") of $100 million or less. The number of biotech IPOs, and the amount raised in these IPOs, is down over 90% from their 2021 peaks. Measured in length, the current bear market has stretched over 1,000 days – more than double the average duration of past biotech bears, and the longest biotech bear market on record.

But the most startling statistic may be this: Of 790 biotech companies that trade on the Nasdaq or NYSE, roughly 25% (or over 180 companies) trade with a negative EV.

A company's EV is defined as its market capitalization less net cash. So a negative EV means there's more net cash on the company's balance sheet than the entire market capitalization of the company.



Over my two decades in investing, it's been exceptionally rare to come across any meaningful swath of public companies trading with negative EVs. Why? Because a negative EV implies that if you could buy the whole company at once, you could shut it down, take the cash on its balance sheet, and come out ahead – i.e., you could get paid that net cash for shutting the company down.

Finding a stock market sector with a meaningful number of negative-EV companies can only mean one thing – that sector is the subject of the most extreme fear and loathing by investors. In fact, investors are so repelled by the sector, they're ascribing negative value to many of its companies.

Which is a perfect opportunity for us.

The Opportunity Ahead

Self-made billionaire and legendary investor Shelby Cullom Davis once remarked,

"You make most of your money during a bear market. You just don't realize it at the time." We're going to lean into Davis's maxim while we can.

The great news is that today – amid the fiercest biotech bear market of all time – we can buy some of the most promising life-sciences companies in the world at a fraction of the price they traded at during the last bull market... prices that hold out potential for many multiple returns when the biotech-market tide turns – or when specific companies experience positive catalysts.

As my old boss Julian would have said, these prices offer us a fantastic opportunity to "get paid."

But this fabulous opportunity doesn't mean we can proceed without caution.

Even though the biotech sector has been bottoming for months, the threat of continued inflation in the U.S. economy isn't gone... nor has the interest rate cycle turned yet. In addition, many thoughtful observers believe the ultimate result of the Fed's interest rate hikes will be a hard landing – i.e., a recession. And as students of financial history know, recessions tend to drive almost all stocks sharply lower. All of this means there's a decent chance that financial gravity will continue to exert some downward pressure on the biotech sector in the months ahead.

But through thoughtful asset allocation, portfolio construction, and position sizing we can balance this opportunity and risk.

How to Build a Life-Sciences Portfolio

Risk management for individual investors starts with sound **asset allocation**. A complete discussion of asset allocation is beyond the scope of this guide. Here I will simply say: picture the allocation to life-science investments as one piece of the overall investment portfolio.

Think of it as constructing a **risk barbell**: On one end of the barbell will be more conservative investments – short-term Treasury bills, short-term and medium floating-rate bonds, non-speculative investments in real estate, and perhaps a forever portfolio of blue-chip stocks.

On the other side of the risk barbell are more aggressive investments – investments in start-up companies or a VC fund, in private equity, or hedge funds, and maybe even a small speculative ownership stake in Bitcoin.

The life-sciences investments we pursue together here should be placed on the more aggressive side of the barbell. What percentage of investable assets

allocated to them depends heavily on each investor's specific circumstances. As the opportunity set in biotech changes dynamically, I will offer updated guidance on a range I think is a reasonable allocation for most folks — stay tuned.

My next suggestion is to avoid the temptation to pick the favorite two or three recommendations we make here. Instead, commit to building a more diversified **biotech portfolio** of between 10 and 20 investments over time. This **portfolio approach** mitigates the risk that any single failed investment could cause acute harm to a portfolio.

And I am going to stress repeatedly to size biotech investments equally to start. Think of it as having a punch card for biotech with between 10 and 20 investments, each an equal size punch. There are two reasons to approach it this way:

1. As tempting as it may be to think otherwise, we can't know in advance which of our investments will be a home run, and which a strikeout. So we don't want to warp our portfolio with our own biases about which specific at bat is going to be our biggest winner. Occasionally, we may identify an investment where the risk/reward is so compelling… so unusual… that it makes sense to swing harder – invest more. When that happens, I may suggest using two punches for that investment. But I promise you those situations will be very rare.
2. By following a guideline to size all of our investments equally, we once again mitigate risk that any one failure can cause our portfolio serious harm.

The final step in our approach is to diversify each of our investments across time. So, when we make a recommendation on a stock, we generally will not recommend buying a full allocation to that stock all at once. Instead, we'll suggest that beginning with either a half-size buy or a one-third-size buy. Time diversification will provide the opportunity to double down and occasionally even triple down as more information comes in on our investment thesis.

If a recommendation moves against us for surprising reasons, which we believe are likely to be discredited, we may double down at a lower price than our original buy. Conversely, if a recommendation receives good news, and we think the market has under reacted, we may double down at a higher price than our original buy. Like professional poker players who adjust their bets as new cards appear on the table, we want the flexibility to adapt to new information as it unfolds.

How long should recommendations be held? Some recommendations may have short-term catalysts and may work quickly. In others, we may anticipate our thesis playing out over a few years. But to be prudent, we strongly suggest treating every member of the biotech portfolio we'll be building as having a three-to-five-year lock up – anticipate giving the portfolio three to five years of runway before expecting to harvest it.

Putting It All Together

Let's walk through an example to bring to life how our approach works in practice.

Imagine having a total investable portfolio of $500,000, with a clear sense of what's in the different sides of your risk barbell. After careful reflection of where you are financially – including both your short-term liquidity needs and your longer-term goals – you decide to allocate 10% of your investment portfolio to life sciences. This means investing $50,000 of your total portfolio into biotech.

For simplicity, let's assume making 20 biotech investments over the coming two years, or about 10 per year. This implies allocating $2,500 per investment.

As we've discussed, generally that does not mean putting all of that $2,500 to work at once on a recommendation. Instead, we'll suggest starting with either $1,250 (a half buy) or $830 (a one-third buy) – and we'll update on when we recommend doubling down or tripling down on a specific pick.

VII. Expected Value and Risk/Reward

In the history of Silicon Valley, one venture-capital firm stands above all the rest: Sequoia Capital. The roster of companies Sequoia backed at the start-up stage is a *Who's Who* of American business: Apple, Google, Cisco, LinkedIn, YouTube, Instagram, Nvidia, Airbnb, WhatsApp, and Zoom among them.

Sequoia's partners have been unusually transparent about the firm's investment process. One distinctive Sequoia practice is the **pre-parade** and the **pre-mortem**.

- A **pre-parade** prompts us to imagine what would happen if everything for this company goes exactly right. What does the company become then? How does it change the world?
- A **pre-mortem** invites us to perform an autopsy of an investment in advance: If this investment fails, what went wrong? By asking this question, we seek to learn from our mistakes before committing them. Instead of waiting until we lose money and then asking, what happened?, we perform the analysis up front.

In the final aspect of our due diligence, we'll start with a pre-parade and pre-mortem. We'll then use the results of these analyses to help us create an **expected value tree** – which forces us to **quantify our risk/reward** into a **base case**, **downside case**, and **upside case**, with **probabilities** assigned to each.

As Bob Rubin – the legendary architect of Goldman Sachs' storied arbitrage desk during its heyday – spells out in his book The Yellow Pad: Making Better Decisions in An Uncertain World, the expected-value tree is a simple but incredibly powerful tool that helps drive decisions at every world-class investment firm around the globe. We will use it as well.

In sifting the life-sciences world for investments, we will be looking for **favorably asymmetric risk/rewards** – situations where our upside case offers us at least 3x more in probable gains than our downside case does in probable losses. Our expected-value tree will help us check that this criterion is met (or failed) for any investment we're considering.

Conclusion – What's Next

If you've made it this far, thank you! I expect future issues of *Biotech Frontiers* will be a lot shorter.

Not every issue will follow the seven-part framework I've shared here – although many will. But studying each of these seven components and incorporating them into other research on biotech opportunities, I'm confident they'll help make you a better "fisherman."

Feel free to write to me with questions, feedback, suggestions, or whatever else at erez@porterandcompanyresearch.com. I can't promise I'll reply to every note, but I will read each one. And if a critical mass of readers ask a similar question, I'll do my best to answer it in these pages.

I look forward to taking this journey with you –

Best regards,

Erez