

Capitalizing Science

Public Knowledge into Pharmaceutical Assets

I cannot imagine that, had there not been an NIH funding research, that there would have been a biotechnology industry.

—PAUL BERG, 1980 NOBEL PRIZE WINNER IN CHEMISTRY¹

Financial capitalism is dependent on the constant searching out, or the construction of, new asset streams. . . . What we can see now is an impulse to identify almost anything that might provide a stable source of income, on which more speculation might be built, being brought into play.

—LEYSHON AND THRIFT, *THE CAPITALIZATION OF ALMOST EVERYTHING*²

In the mid-1970s, physicians and scientists at the National Institutes of Health (NIH) were stumped. Patients receiving blood transfusions were developing liver inflammation, but the cause was unknown. Scientists suspected a virus, but found that neither hepatitis A nor B, viruses which had been identified in the prior decade, was the culprit.³ Though this mystery virus did its damage slowly and often unbeknown to the patient, clinical studies that tracked these patients showed that it could cause liver failure, and ultimately death, over time.⁴

The virus eluded scientists for another fifteen years, making it difficult to develop diagnostics and know the level of threat it might present to patients and public health. Harvey Alter, a physician and research scientist at NIH involved in the hunt for this pathogen, recalls a poem he wrote back then: “Oh GREAT LIVER in the sky / Show us where and tell us why / Send us thoughts that will inspire us / Let us see this elusive virus / If we don’t publish soon / They’re going to fire us!”⁵ The long wait would end in the late 1980s, when a company called Chiron, in its search for new markets for diagnostic tests, worked with scientists at public agencies to uncover the molecular structure of the virus. In 1989 this group of scientists, including Alter, published a landmark paper describing the virus and its genome.⁶ They called it hepatitis C.

Even after its identification, however, the virus remained furtive in other ways, just beyond the grasp of chemists and the few companies targeting the pathogen. Ten years after the identification of hepatitis C, the hunt for drugs against it had borne little fruit. Epidemiological studies suggested that three to four million people in the US were infected—primarily as a result of injecting drug use, as well as blood transfusions received before the early 1990s.⁷ As many as three-quarters of infected patients remained undiagnosed. Yet at the turn of the millennium, physicians had few options to offer even their diagnosed patients. The existing interferon-based treatments, a toxic regimen requiring a year of weekly injections that offered cure rates of only 30–40%, was often a last resort, used only for the sickest patients.

This chapter traces what transpired next: the capitalization of publicly financed and cumulative knowledge into private assets for financial markets. This process—central to financialized drug development—would shape the trajectory and price of a potential breakthrough for hepatitis C.

In the late 1990s, scientists with public funding would overcome a key obstacle to hepatitis C drug development by discovering a method to test potential compounds in the laboratory. These public investments led drug companies to join the fray of hepatitis C treatment, and within a decade several were in pursuit. One upstart company would emerge in 1999 from a publicly funded lab. The company would go on to raise over \$50 million from venture capital and get traded on the stock market—even as it accumulated \$330 million in deficits, had no sales, and would never bring an approved drug to patients. Yet a compound developed by this company would ultimately become the backbone of a curative treatment for hepatitis C.

With science capitalized into assets, particular future and growth-oriented logics of price and value dominated the speculative markets where these assets were owned, traded, and sold. For investors and traders, these speculative markets offered a high-stakes opportunity to make sizable gains from bets on hepatitis C compounds, in periods far shorter than the time needed to develop those compounds into usable treatments. This opportunity for speculation, in turn, depended on an uncertain and fraught promise: unprecedented drug prices and market valuations.

OVERCOMING A TECHNOLOGICAL HURDLE: THE REPLICON TOOL AND AN ENTREPRENEURIAL STATE

Throughout the 1990s, the deadly hepatitis C virus confounded scientists and chemists in their pursuit of treatments. Viruses are *intracellular parasites*, meaning they work inside human cells and hijack their machinery to reproduce. But unlike most viruses, hepatitis C did not grow in cell cultures generated in laboratories.⁸ The reasons were unknown at the time. A handful of private labs had

identified the structure and function of parts of the virus that are critical for its replication—most importantly the protein “subunits” called NS3 and NS4a proteases, as well as the NS5b polymerase.⁹ But without any ability to grow the virus in cells, scientists could not test whether their compounds actually inhibited viral activity. Scientists remained vexed by this puzzle through much of the 1990s. Trials of different culturing approaches yielded little success.¹⁰ One scientist lamented the “painfully slow process” and the “struggle to establish research tools and cell culture systems for HCV” (that is, hepatitis C virus) as critical factors holding back progress in the field.¹¹ Without a way to test drug compounds against it, drug development for hepatitis C was stalled.

Growing a Stubborn Virus and the Development of the Replicon

In the mid-1990s, government-funded German scientists, led by Ralf Bartenschlager at Heidelberg University, began to tackle this puzzle.¹² After their initial attempts to reproduce the hepatitis C virus failed, they tried another route: instead of growing the entire hepatitis C genome, what if they could reproduce just a part of it—the part that contained the main viral proteins involved in replication? They constructed a line of genetic code with only the internal proteins thought to be critical for hepatitis C replication.

They then inserted this line of code (or “genome”) into cancerous liver cells, which by their very identity replicated very rapidly. This would allow them to see whether copies of the virus could be produced. Bartenschlager’s team found what they had long sought: hepatitis C genetic material (RNA strands) of the anticipated size and correct protein units teeming inside the cancerous liver cells.¹³ In other words, drug companies could finally test whether their compounds worked against the parts of the virus that enabled its replication, such as the NS3/4 proteases and the NS5b polymerase. If that worked, it could mean stopping the virus, and the disease, in its tracks. This research tool, in which strands of genetic material are replicated within cells, is known as a *replicon* (Figure 1).

For veteran science journalist and writer Jon Cohen, who attended an NIH meeting on hepatitis C in June 1999, reports of the replicon were the “show stopper.”¹⁴ The implications for drug discovery appeared to be significant. Discussing Bartenschlager’s work, leading hepatologist Stanley Lemon said, “If these results hold up, they’ll be enormously useful for drug screens.”¹⁵ The group described the replicon in a November 1999 paper in *Science*, completing nearly five years of work.¹⁶

Yet the replicon had limitations. Charlie Rice, a leading hepatitis C scientist in the United States, noted: “Bartenschlager’s replicon was a landmark discovery in its own right, but the frequency with which you could initiate viral RNA replication was low.”¹⁷ That is, the hepatitis C genome in Bartenschlager’s replicon only replicated itself in approximately one out of every million host cells, which added a cumbersome step of selecting the right cells for testing.¹⁸

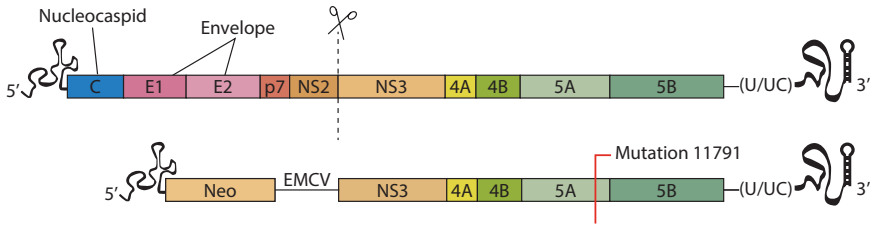


FIGURE 1. The replicon for hepatitis C. While the full hepatitis C genome (*top*) could not be replicated in the lab, the replicon version (*bottom*)—trimmed to include the main proteins needed for viral replication—could. This development set the stage for scaling up the testing of potential antiviral compounds. Source: Marshall (2000).

A virologist at Rockefeller University in New York, Rice had spent nearly a decade studying the virus and the parts and steps required for its replication.¹⁹ As he examined Bartenschlager’s replicon, Rice knew that considerably boosting viral RNA reproduction would be critical to realizing the replicon’s potential for drug development.

To pursue a better replicon, Rice would rely on sources of public support that existed because of a major expansion of investments in scientific research by the US government in the latter half of the twentieth century. Before World War II, US government support for scientific research was modest. But successes in publicly financed wartime mobilization across an array of technologies, including penicillin, drew the interest of leaders like president Franklin Roosevelt, who saw such investments as a potential route to postwar prosperity. In his famed report *Science, The Endless Frontier*, FDR’s chief scientific advisor, Vannevar Bush, mapped out a vision in which “the Government should accept new responsibilities for promoting the flow of new scientific knowledge. . . . These responsibilities are the proper concern of the Government, for they vitally affect our health, our jobs, and our national security.”²⁰

The Public Health Service Act of 1944 inaugurated a more intentional public investment strategy for health, with prior iterations of government laboratories transformed into the National Institutes of Health (NIH). NIH grew rapidly in the postwar years, from a total budget of \$8 million in 1947 to \$1 billion in 1966.²¹ These investments aimed to improve public health, and also to give the US an economic and national-security edge in the Cold War.²² NIH expanded from a handful of centers in 1949 to fifteen institutes by 1970, and twenty-seven by 1998. Scientists at these institutes found their physical home at NIH’s Bethesda, Maryland, campus and formed what is known as the organization’s “intramural” (or internal) research program.

As in many areas of clinical advances, NIH’s Bethesda campus had played a pivotal role in viral hepatitis research. Physician-scientists like Harvey Alter had performed long-term clinical studies to identify the virus’s deleterious health

effects. Their work led to the identification of the other viral hepatitis pathogens, such as A and B, that would sharpen the focus on pursuing hepatitis C. NIH scientists also led the initial tests in the 1980s, even before the virus had been identified, to show that the mystery pathogen could be eliminated from the bloodstream with the use of a treatment known as interferon.²³ Though the early studies demonstrated interferon to be effective in only a small percentage of patients, the finding was still noteworthy: the pathogen's elimination in these patients proved that the virus had some vulnerabilities that scientists could exploit. With the identification of the virus in 1989, much of NIH's focus shifted toward a better understanding of the biology of hepatitis C in hopes of developing treatments that could significantly outperform interferon.

Investments in hepatitis C research stretched far beyond Bethesda, extending to university laboratories across the US that received grants through NIH's Extramural Research Program. This decentralized network represented approximately 80% of NIH's budget, which doubled from \$8.9 billion in 1990 to \$15.6 billion in 1998.²⁴ A primary mechanism for financing extramural research has been the R-01 grant, which provides funding to senior scientists at universities across the US. These renewable grants, historically the longest and most widely used avenue for NIH funding, provide three to five years of funding disbursed annually over the period of the award.²⁵ With R-01 grants as a key vehicle, NIH supported hepatitis C research across the US that elucidated viral replication and pathophysiology, at places like the Scripps Research Institute, Emory University, and the University of Georgia, as well as Charlie Rice's work at Washington University in St. Louis and later the Rockefeller Institute.²⁶ Combined with private philanthropy (most notably from the Greenberg Family Foundation), these NIH grants would enable Charlie Rice and his lab to build on the work of the Bartenschlager lab to make crucial improvements in the replicon tool.²⁷

Rice's team aimed to make the replicon reproduce at far higher rates.²⁸ Their strategy: to hunt for genetic mutations that would make the replicon more productive. Led by a scientist in Rice's lab, Keril Blight, they rebuilt the replicon system using Bartenschlager's data. Support for the research came from NIH grants that amounted to \$3.4 million between 1999 and 2003 (when much of the replicon work was carried out). This was part of an overall NIH investment of \$10.8 million between 1993 to 2005 in Rice's hepatitis C-specific research.

With this financing, Rice's lab identified mutations that produced a more infectious strain of the virus than the one used by Bartenschlager's team.²⁹ The new replicon produced abundant viral proteins in one of out of ten host cells, rather than one in a million. "That really makes a big difference," Rice said at the time. "It is going to allow us to do genetic studies on a much shorter time scale."³⁰ This replicon technology was further refined in the coming years by both Bartenschlager's and Rice's labs, with drug developers eagerly awaiting the technology to use in their hunt for anti-hepatitis C compounds.³¹

To share this new technology with drug companies, Charlie Rice turned to a small biotechnology company he had previously founded, named Apath.³² Rice had envisioned Apath as a vehicle to get the fruits of his discoveries into the hands of other firms and scientists working on therapeutic advances.³³ To make good on this vision for Apath and the replicon technology, state investments would again come into play.

*Sharing the Replicon Widely with the Small Business Innovation
Research Program*

Apath would look to a little-known government funding stream, the Small Business Innovation Research program (SBIR). Begun with a legislative act by the US Congress in 1982, SBIR requires government agencies with a research and development (R&D) aim (such as NIH) to invest part of their budget in domestic small businesses that show a strong potential for technology commercialization.³⁴

SBIR grew out of an emerging policy debate in the 1970s and 1980s about the role of government in incentivizing innovation and private entrepreneurship.³⁵ As part of his broader agenda to promote small business during a period of economic stagnation in the 1970s, Massachusetts senator Ted Kennedy wanted to make it easier for entrepreneurs to commercialize promising technologies and start new businesses.³⁶ After a successful pilot within the National Science Foundation, the SBIR program was replicated across the federal government through the bipartisan passage of the 1982 Small Business Innovation Development Act.³⁷ In 1992, to further bridge the perceived gap between basic sciences and commercialization, Congress funded the Small Business Technology Transfer (STTR) program, in which small businesses must formally collaborate with a research institute (typically at a university or nonprofit) to receive a grant.³⁸

SBIR and STTR are primarily intended to fund precommercial technology development. All agencies (such as NIH or the Department of Energy) with extramural research budgets of over \$100 million are required to set aside a small percentage of their research budgets for these programs. In the decade between 2007 and 2016, NIH's SBIR and STTR programs together provided \$3.53 billion in grants to small businesses advancing products for biomedicine. Across federal agencies, SBIR alone has reported the creation of 700 publicly traded companies due to its program between 1982 and 2016, with those companies attracting approximately \$41 billion in venture capital investments.³⁹

Two decades after its launch, SBIR would help Apath's efforts in hepatitis C. In its first five years of SBIR support, between 1999 and 2004, Apath received \$4.26 million, including a \$750,000 grant in 2002 to further develop the replicon.⁴⁰ The funding gave Apath the capacity to build a business organization capable of manufacturing and distributing the replicon across academic and industrial laboratories.

In a 2000 *Science* article reporting on the discovery, Rice shared Apath's plans for commercializing the replicon.⁴¹ He made his strategic interests clear. Not wanting to do anything that would "impede academic research," Rice assured the interviewer, "I think that sharing material for academic research should be done with as few strings as possible."⁴² Within two years, private and public labs began to acquire the replicon, which was dubbed Blazing Blight 7 (for its co-inventor Keril Blight, one of the scientists in Rice's lab). Apath offered nonexclusive licenses to use the technology.

In the field of hepatitis C, the replicon served as a kind of "general-purpose technology" on which almost all subsequent drug development was based. Examples of other general-purpose technologies are the Internet, semiconductors, and nanotechnology. Though the replicon is not a general-purpose technology on the kind of scale that crosses industries, it had an effect on all subsequent hepatitis C drug development. Marc Collett, then the head of discovery research for a small biotechnology company, ViroPharma, commented, "That's definitely a breakthrough that every group has used."⁴³ One of the many companies to use Apath's replicon around this time would be a small startup in Atlanta called Pharmasset that would be pivotal in making a cure for hepatitis C.⁴⁴

*An Entrepreneurial State, Curative Directions,
and Value Co-creation in Hepatitis C*

Public investments played a pivotal role in the development of the replicon, which in turn shaped the trajectory of all subsequent hepatitis C drug development. As this chapter later presents, government financing was one element of public investment in the science that made sofosbuvir-based medicines possible (Table 1). While I do not provide a total figure for these contributions, a study by Harvard's Program on Regulation, Therapeutics, and Law that examined the underlying patents and linked them to public funding sources found at least \$60.9 million in direct and indirect US public investments in the science that ultimately produced sofosbuvir.⁴⁵ The authors note that this is a striking figure because it approximates the amount of private funding Pharmasset would later report in their development of sofosbuvir. But numbers alone do not tell the story.

Situating this financing and the development of the replicon in the technology-development process disrupts the conventional narrative of government's role in innovation. While public investments in science are often labelled "basic research" as opposed to the more "applied" work carried out by the private sector, the story of the replicon shows us that these categories are often blurry. Programs like SBIR, for example, explicitly finance businesses to develop technologies—as they did for Apath in the creation of the replicon. Of course, the COVID-19 pandemic brings the state's role in the later stages of innovation into sharp relief, with major direct public investment in clinical trials and even the manufacturing of vaccines.

TABLE 1 Important public contributions behind sofosbuvir drug development

Phase of contribution	Description and significance	Public actors
Replicon development (1995–2002)	German and US scientists created a research tool called the replicon that enabled hepatitis C drug development to accelerate.	German government (German Research Society, Ministry for Education and Research); US government (NIH R01 and R37 grants)
Replicon commercialization (2000–2003)	The replicon was manufactured and distributed by Apath, a company supported through multiple major NIH grants, to enable hepatitis C drug development across company labs.	NIH Small Business and Innovation Research Program
Nucleoside science (1991–2007)	Antiviral development by Emory University and University of Georgia researchers formed the basis for Pharmasset's viral hepatitis research.	NIH R01 and R37 grants, Veterans Affairs (VA) Office of R&D
Pharmasset launch (1998–2004)	Sixteen early-stage grants provided important financial support—and market signals to venture capitalists.	Small Business and Innovation Research Program, VA, Emory
Sofosbuvir development (2005–2008)	The prodrug method developed by McGuigan (UK) in the 1990s was used by Pharmasset to develop sofosbuvir.	British Medical Research Council, European Research Council, Belgian government (for McGuigan); NIH grants in 2005 and 2006

SOURCES: NIH RePORTER database; Barenie et al. (2020). See the text for citations of key papers.

In thinking about the replicon and other public investments in hepatitis C technology development detailed later in this chapter, Marianna Mazzucato's conception of the *entrepreneurial state* provides a useful map. Far from crowding out private funding, as often claimed by critics of government, the risk-taking investments by public agencies “dynamize[d] in” private capital, as Mazzucato puts it.⁴⁶ Until the replicon, private capital had largely languished on the sidelines, as the problem of efficiently testing candidate compounds had dissuaded all but a handful of pharmaceutical companies from taking on hepatitis C. Yet with a new tool that dramatically expanded innovation possibilities, the industry began to direct capital toward hepatitis C.

This is an example of what Mazzucato calls the state's role in “co-creating” value in innovation, as public investments in technologies like the replicon enabled a much larger market for hepatitis C drug development.⁴⁷ Yet this process also demonstrates the opportunity for contradictions *within* the state—on the one hand, financing research for the purpose of improving human health, but on the other

spurring private commercialization in ways that can later come to undermine treatment access. This conflict is not a given. Rather, it is shaped by the conditions of financialization, which will come into full view in chapters 2 and 3.

The public investment in overcoming technological uncertainty both accelerated the rate at which drug developers could test compounds, and, as Mazucato points out, shifted the *direction* of the innovation process—in this case, toward therapies that could result in increasing rates of cure for all patients with hepatitis C. Instead of treating only the sickest patients (with toxic interferon-based regimens), the replicon enabled drug developers to find targets that directly halted the replication of the virus. Such “direct-acting” antiviral compounds promised a short, simple, and safe course of treatment for hepatitis C. Further improvements in the replicon also allowed testing of compounds on the multiple genetic variations of the virus.⁴⁸

The significance of this achievement would gain recognition. In 2016, when the prominent Lasker Prize committee chose hepatitis C as a major medical advance to spotlight, they awarded Rice and Bartenschlager’s early-stage scientific and technological work on the replicon, along with Michael Sofia’s later work to eventually develop the curative compound.⁴⁹ The crowning recognition would come in 2020, when Charlie Rice would win the Nobel Prize in Medicine for his team’s replicon research (along with Harvey Alter and Michael Houghton, who discovered the virus).⁵⁰ The replicon would not be the last advance made possible by public investments in the search for hepatitis C treatment.

THE TRIPLE HELIX: PUBLIC AND PRIVATE SCIENCE IN THE LAUNCH OF PHARMASSET

In the spring of 1998, an Emory University scientist, Ray Schinazi, launched a company called Pharmasset. From the very beginning, his intentions were clear. “I coined that name,” Schinazi would tell a reporter later. “It’s actually ‘pharmaceutical assets’ and the idea was to create assets that would be sold to companies. That was the initial business plan.”⁵¹ Rather than build a durable enterprise, Schinazi’s ambitions exemplified what was at the time a relatively new form of pharmaceutical venture: one founded to land the lucrative rewards of being bought by another company. One of the company’s main assets would turn out to be sofosbuvir, the curative backbone of hepatitis C treatments. Pharmasset’s assets, however, did not appear out of thin air. Rather, the company emerged through long-term public investments in science and technology development and also the particular approach of the US government to patents and intellectual property. This approach enabled the conversion of publicly funded science into private financial assets and would shape the pricing and value logics governing the trajectory of sofosbuvir.

*The Development of Nucleoside Chemistry and the Public Science
behind Pharmasset*

Before starting his venture, Schinazi benefited from decades of public support for drug development focused on nucleoside chemistry. Nucleosides are chemical precursors to nucleotides, which are the building blocks for DNA and RNA. Schinazi's research focused on synthesizing "analogues" to these nucleosides, which then get modified by the body and are taken up by viruses. When viruses take up these analogues into their growing DNA or RNA chains, the analogues gum up the chain and block further viral replication.⁵² Nucleosides, then, carried the potential to abort viruses. In the 1980s into the 1990s, many large pharmaceutical companies avoided these compounds, as nucleosides were deemed to have a high risk of toxicity because they also interfered with the production of genetic material by human cells.⁵³ Two institutions would give Schinazi the long-term funding necessary to figure out how to make safe and effective nucleosides: the Department of Veterans Affairs (VA) and NIH.

Schinazi came to Atlanta in the early 1980s, running a laboratory at the Atlanta VA hospital while also joining the faculty of Emory University.⁵⁴ Since the early postwar years, the VA—a publicly funded national health system for military veterans—had expanded a nascent set of research projects into a fully fledged research program whose breakthroughs included the first cardiac pacemaker (1958), concepts that led to the development of the CT scan (1960), and liver transplantation (1968).⁵⁵

Schinazi has credited the VA as important for the successes of his Laboratory of Biochemical Pharmacology. He enjoyed space for a staff of nearly 40, equipped with the latest technologies, as well as a state-of-the-art animal research facility, critical for preclinical testing of potential drugs.⁵⁶ In a nationally broadcast interview, Schinazi shared that in the 1990s and 2000s seven-eighths of his salary came from the VA system. He would translate these resources into research into new nucleoside therapies, most notably for HIV/AIDS and hepatitis C, both of which affect veterans in large numbers. For this work he would later receive the VA's William S. Middleton Award, its highest honor for biomedical research.⁵⁷

NIH was another primary source of financial support for Schinazi. Like Charlie Rice, Schinazi was the beneficiary of NIH's extramural funding; his support included R-01 grants as well as the special R-37 National Merit Award.⁵⁸ The latter goes beyond the R-01 grant by giving exceptional scientists the opportunity to pursue projects that are "more adventurous," that carry "greater risks," and that take time to develop: these awards are given typically for *no less* than five years and can be renewed for a total ten-year window of research. According to a separate analysis performed by the access-to-medicines group Knowledge Ecology International, Schinazi was a principal investigator under 64 NIH grants between 1991 to 2012, involving \$10.5 million in public funding. He filed a total of 49 patents

that disclosed federal funding, with NIH and the VA listed as two of the principal federal agencies.⁵⁹

By the late 1990s, Schinazi had developed multiple compounds that could serve as leading candidates for development. He and his team had iterated on a prior discovery by a Canadian team to produce a nucleoside compound, emtricitabine, that showed particular promise for HIV.⁶⁰ This work expanded their knowledge of nucleoside activity against viruses, a direction that Schinazi and his team hoped to carry forward into antiviral compounds for hepatitis C. In a preview of the approach he would take toward hepatitis C, in 1996 Schinazi launched a small biotechnology company, Triangle Pharmaceuticals, to further develop emtricitabine in clinical trials. In 2004 the compound would be acquired for \$464 million by a company that would also later be central to the hepatitis C tale: Gilead Sciences.⁶¹

Though Triangle would ultimately sell for a lucrative return, in late 1990s the company became embroiled in legal challenges related to its nucleoside compounds.⁶² Seeking a fresh start, Schinazi sought to launch Pharmasset as a vehicle through which a larger array of nucleoside compounds could be developed into valuable “assets” for established pharmaceutical companies to buy. Building on his years of HIV research, Schinazi sought financing for this new venture. One stream (documented in further detail in the next section) would be over \$50 million in venture capital gained through several rounds of financing between 1999 and 2004. But another key stream remained the US state and its SBIR program, the same source that had funded Apath and the development of the replicon.

Between its initial founding in 1999 and the discovery and development of the more efficient replicon by Apath in 2002, Pharmasset’s focus remained on other nucleosides for HIV and hepatitis B virus.⁶³ However, after the development of the replicon accelerated interest in discovering drugs for hepatitis C, NIH granted Pharmasset funding to develop compounds against the virus. Over the course of the company’s first seven years, NIH would support Pharmasset with \$2.46 million in public financing through sixteen SBIR grants. Of these, six grants between 2002 and 2006 specifically supported hepatitis C drug development, an investment of \$1.61 million.⁶⁴

Though Pharmasset’s venture capital funding would far exceed its initial NIH funding, these SBIR grants were important to Pharmasset’s early formation. As Keller and Block describe, the importance of an SBIR grant is not limited to the amount of money. SBIR grants provide a kind of “signaling and certification” to venture capital of the promise of a given technology. Keller and Block traced the relationship between venture capital and SBIR grants in five different years between 1995 and 2009. In the life sciences in particular, roughly 20% of venture capital investment went to firms that had previously received one or more SBIR awards.⁶⁵ Pharmasset was one of these. The company featured each of its sixteen SBIR grants prominently on its website, showcasing them to potential investors as badges of public support.⁶⁶

Alongside his long-standing support from NIH and the VA, Schinazi positioned the company as a nodal point in a network of research universities benefiting from public funding in the Atlanta area. An *Atlanta Business Chronicle* article described the configuration of the cofounders: “Schinazi has a team of 30 researchers at Emory continuing to discover new drugs. [Dennis] Liotta has about 15 researchers and another founder, Chung Chu at the University of Georgia, has about 20. The fourth founder is scientist Jean Pierre Sommadossi of the University of Alabama at Birmingham.”⁶⁷ A journalist covering Pharmasset’s origins highlighted these early-stage employees: “Most of them are top scientists from around the world who bring more than 100 patents and the beginnings of 8 potential drug formulas to the company.”⁶⁸ Indeed, a study by Harvard’s PORTAL research group found that during the mid-to-late 1990s Emory University and the University of Georgia received at least seventeen public grants from NIH that were directly or indirectly related to the later development of sofosbuvir. This configuration—taxpayer-funded university research being used to start a biotechnology company like Pharmasset—was possible in part because of a shift in political and legal arrangements that had begun nearly two decades earlier.

*Patents, the Bayh-Dole Act, and the Conversion of Public Science
into Private Assets*

The early 1980s witnessed a significant shift in the political-legal rules governing science and technology in the US that made it easier for publicly funded knowledge to be turned into financially valuable assets. The dominant narrative behind this shift was that a bipartisan group of policymakers saw a need to respond to the economic slowdown of the 1970s and believed that promoting business through the commercialization of new advances in science and technology—including those developed with public funding—could help. The purported national goals of the shift were to promote American jobs through high-tech industries, and to gain an edge in an increasingly competitive global market. A raft of changes followed in the 1980s, making it easier for the nascent biotechnology sector and the pharmaceutical sector, for example, to commercialize knowledge generated with public funds for new technologies and markets.⁶⁹

One specific change came with the 1980 Bayh-Dole Act, which permitted inventions developed with public funds to be patented by a university or a professor rather than be owned by the government.⁷⁰ This fostered a new environment of commercialization for universities and researchers. As an administrator at Emory University explained, “The theory was that a lot of innovation was coming out of federally funded research, but it was all owned by the government and ‘sitting on the shelf.’”⁷¹ That administrator, Todd Sherer, was the head of Emory’s Technology Transfer Office, a new kind of organization that multiplied across American universities in the 1980s and 1990s. They helped university professors apply for patent protection for their discoveries and supported the commercialization process.⁷²

This new legal setup shifted the stakes of research: for university administrators, any research by faculty might generate valuable intellectual property from which the university could gain royalties; and for university professors like Ray Schinazi, discoveries could be converted to private, licensable products attracting capital rather than staying in the public domain.⁷³

In the mid-1990s Schinazi and Emory took advantage of this change with their compound for HIV/AIDS, emtricitabine.⁷⁴ Emory patented the compound, which Schinazi had developed based on the prior work of Canadian scientists and with public funding. The university then later licensed it to Triangle Pharmaceuticals, Schinazi's spin-off business.⁷⁵ When Gilead subsequently bought Triangle for \$464 million and then began selling emtricitabine as part of a combination HIV therapy in 2004, Emory University made \$540 million in royalties—the largest royalty payment to a university up to that time.⁷⁶ A sizable slice, some \$200 million, was split between Schinazi and his two co-developers at Triangle.⁷⁷

The Bayh-Dole Act, along with the broader regulatory shifts of the early 1980s, signified a break from previous pathways for innovation. Science and technology scholar Sheila Jasanoff writes that Bayh-Dole “changed the long-standing presumption that publicly funded work could not be privately owned and exploited.”⁷⁸ In his work on the emergence of the biotechnology sector, business scholar Gary Pisano detailed the shift in incentives for publicly funded scientists: knowledge assets were now to be monetized by academics with a direct economic interest in research efforts.⁷⁹ This configuration of university labs, public funding, and small enterprises has been dubbed a “triple helix,” with many innovations tracing their genesis to this triad.⁸⁰

The Bayh-Dole Act produced a new political-legal contract that sanctioned the conversion of public science into private financial assets. But it presented a risk: the government would be granting control over knowledge to new owners, who might use it in ways that went against the public interest. To guard against this risk, the act contained a “march in” provision, which enabled the US government to license any intellectual property that emerged from federally funded research in the case of public health need.⁸¹ Though this step has been contemplated on multiple occasions, it has never been taken.

Beyond the Bayh-Dole Act, a broader system of intellectual property protections granted by the US government for pharmaceutical development also applied to the emergence of companies like Pharmasset. The patents granted by the US Patent and Trademark Office give companies twenty years of protection for new drug compounds.⁸² Some of this period is used by companies to further develop and test drug compounds and to seek regulatory approval, so the “effective patent life” can be shorter. Companies typically use multiple maneuvers—such as pursuing patents for minor changes or manufacturing processes—to extend their control, often for much longer than twenty years.⁸³ Alongside this temporal dimension is a geographic one: patent laws have become increasingly globalized, driven

by countries in the “global North” and multinational pharmaceutical companies. For reasons I describe in later chapters, these changes give pharmaceutical companies with patents easier access to global markets in which to sell drugs.

This intellectual property landscape had two important implications for Pharmasset. First, the shifts produced by Bayh-Dole gave Schinazi and his cofounders the organizational and political-legal environment in which to commercialize public science into private financial assets. While sofosbuvir would be developed later in the company’s evolution and development efforts, this environment enabled Schinazi to use his publicly funded nucleoside research at Emory University and the VA as a foundation for the company’s startup phase. Emory University retained stock in the company.⁸⁴ Universities like Emory thus became big financial winners in this legal setup, receiving public investments as well as royalties and capital gains from owning intellectual property made possible by these investments. Notably, no US public-sector organization—such as NIH or the VA—was a shareholder in the company their investments had made possible.

Second, owning patents for compounds with *possible* therapeutic value—even if they were years away from human clinical trials or FDA approval—formed the basis of the company’s value. In other words, Pharmasset’s value in financial markets would come not from the sales or profitability of any medicine but from the forecasts of *potential* global earnings from its ownership of certain assets. This strategy, which Pisano calls “monetizing intellectual property,” would take on heightened importance in an era of financialized drug development.⁸⁵ For the larger companies that would later buy companies like Pharmasset, owning patents—and the potential value of earnings that might come with them—would be a way to meet the growth expectations of financial markets. For small companies like Pharmasset, monetizing patents would be their *raison d’être*—the primary mode and rationale for their existence. Rather than using its own capital from prior sales and earnings—of which it had none—Pharmasset would use patents to attract speculative capital for its continued R&D efforts.

Sofosbuvir as a Hybrid Advance: Public Science Meets Private Asset

While Pharmasset relied on the mobilization of this speculative capital, the company’s later breakthrough would be made possible by the application of publicly funded science. This breakthrough, the development of sofosbuvir, would reveal the critical role of public investment and knowledge production across the stages of technology development. But it would also illustrate a pivotal dynamic underpinning financialized drug development: the enclosure of collectively produced knowledge into privately owned assets.

As Pharmasset pursued its initial set of compounds for hepatitis C in the early 2000s, the company saw promise in PSI-6130, a nucleoside synthesized by one of its chemists, Jeremy Clark, that showed activity against one of the main parts of the virus. By 2004, the company had filed patents on the compound and launched a

partnership with Roche to further test its effectiveness. But Pharmasset's scientists knew the compound had an important limitation: when it entered the blood circulation, it morphed into multiple chemical versions, reducing its overall potency in the liver.⁸⁶ This chemical unraveling limited its effectiveness in eliminating the virus from the liver. While Roche continued its clinical trials for the drug, Pharmasset's own scientists pursued research into other potential hepatitis C compounds.

One of these scientists, Michael Sofia, had come from one of the "Big Pharma" companies, Bristol Myers Squibb, and he was eager to make a mark in a smaller biotechnology business like Pharmasset. He examined the PSI-6130 effort and began searching for an alternative direction based on several crucial questions.⁸⁷ Was it possible to reduce the pill count, lower the dosage, and increase the potency of the compound even further than PSI-6130 could? A more potent compound might eliminate the need for the toxic interferon altogether, which would dramatically increase the number of patients who might benefit from treatment.⁸⁸

To develop a compound that transcended PSI-6130's limitations, Sofia and his team at Pharmasset built on methods pioneered in antiviral and cancer therapeutics. The reason for PSI-6130's limitations was known: once in the bloodstream, the compound was blocked from completing a pivotal step that would optimize its potency in the liver.⁸⁹ Sofia surmised that bypassing this blockage was the key to successfully attacking the part of the virus the compound targeted, the NS5b polymerase.⁹⁰ He needed a "Trojan horse," something that would help him stealthily deliver the compound to the liver in its most potent form. To solve this problem, he drew on the work of scientists who had confronted similar challenges, particularly with the HIV pathogen. One of these scientists was Christopher McGuigan, a British chemist at Cardiff University who had worked with colleagues to develop a particular "prodrug" method. A prodrug is an inactive substance that the body's enzymes can convert into an active drug.

In a prodrug method, an additional chemical structure called a phosphoramidate is added to the base compound and serves as a "mask" until the compound reaches the liver.⁹¹ The idea would leverage existing physiology: because the liver is often the first place a drug is absorbed and modified, Sofia hypothesized that the mask would fall off in the liver, revealing a chemical structure ready to undergo the necessary modification steps to bind to and inhibit the virus's NS5b polymerase.⁹² This way the compound would have its greatest effect in precisely the organ where hepatitis C was wreaking its damage. Sofia figured he had found his Trojan horse.

McGuigan had pioneered this method in collaboration with Belgium scientist Jan Balzarini over the prior fifteen years.⁹³ Based at Cardiff University in the UK, McGuigan's team led the effort to develop this phosphoramidate structure and method, first in the context of HIV and then for other viruses (like hepatitis C) and cancers.⁹⁴ The initial breakthrough came in 1992 when McGuigan was working to improve AZT, a treatment for HIV.⁹⁵ In a seminal 1996 paper describing the approach, McGuigan, Balzarini, and their collaborators cited four public

sources of funding: the British Medical Research Council, two programs of the European Commission, and the Belgian government.⁹⁶ Between 1993 and 2013, the McGuigan team published 85 research papers on their method, creating a large network of citations and possible applications for their prodrug approach. When the UK government later sought to profile impactful public investments in research, McGuigan's work was highlighted as a critical contribution to broader antiviral drug development for hepatitis C, including Pharmasset's eventual compound.⁹⁷

Sofia applied this publicly available knowledge about phosphoramidate prodrugs to Pharmasset's hepatitis C research.⁹⁸ Trying multiple versions of a phosphoramidate "mask" fixed to a base PSI-6130 structure, Sofia ultimately found one that resulted in a profound decline in the virus. The new structure would be named PSI-7977, and later receive the name sofosbuvir (after its lead scientist). In 2008, after three years of preclinical testing by Sofia and his team, PSI-7977 became Pharmasset's lead candidate for a hepatitis C treatment. Documenting this process in chemistry and medical journals after the development of sofosbuvir, Sofia cited McGuigan's prodrug method (and McGuigan's papers) as the pivotal and defining step in arriving at the curative compound.⁹⁹

Thus the sofosbuvir structure and its curative function constituted a hybrid public-private outcome (Figure 2), recombining publicly funded and available knowledge in the context of a private business traded in financial markets. The cumulative and collective nature of the process also reveals one of the hazards of financialized business models that rely on turning socially produced science into private assets: fierce battles over patents.

Such battles not only unfold only between drug companies and the civil society groups that challenge intellectual property claims in courts of law in a bid to expand access to treatment (which I describe briefly in chapter 3)—they also occur between drug companies themselves. For example, Pharmasset's patents generated significant controversy and became the subject of multiple lawsuits eventually levied at Gilead.¹⁰⁰ As Bourgeron and Geiger illuminate in their work on hepatitis C patents, Gilead's claims over sofosbuvir patents were haunted by its "molecular predecessors."¹⁰¹ Roche, for example, claimed in March 2013 that Gilead infringed on Roche's license because *sofosbuvir* was connected to PSI-6130, the compound at the heart of the earlier Pharmasset-Roche business partnership. Merck also challenged Gilead in this period, seeking royalty payments and suing the company for patent infringement. By this time, Merck had bought Idenix, a company founded by one of Ray Schinazi's colleagues, Jean-Pierre Sommadossi, at about the same time as Pharmasset. A legal question central to Idenix's and subsequently Merck's case against Gilead was whether Pharmasset's chemist Jeremy Clark had first synthesized the PSI-6130 compound that would go on to be a precursor to the lucrative sofosbuvir—or if scientists at Idenix had already made a similar development.¹⁰² Idenix would also later closely collaborate with McGuigan's lab.¹⁰³ Merck challenged Gilead for patent infringement and in 2016 won a \$2.54 billion award, but it was overturned on an appeal that was later upheld by the Supreme Court.¹⁰⁴

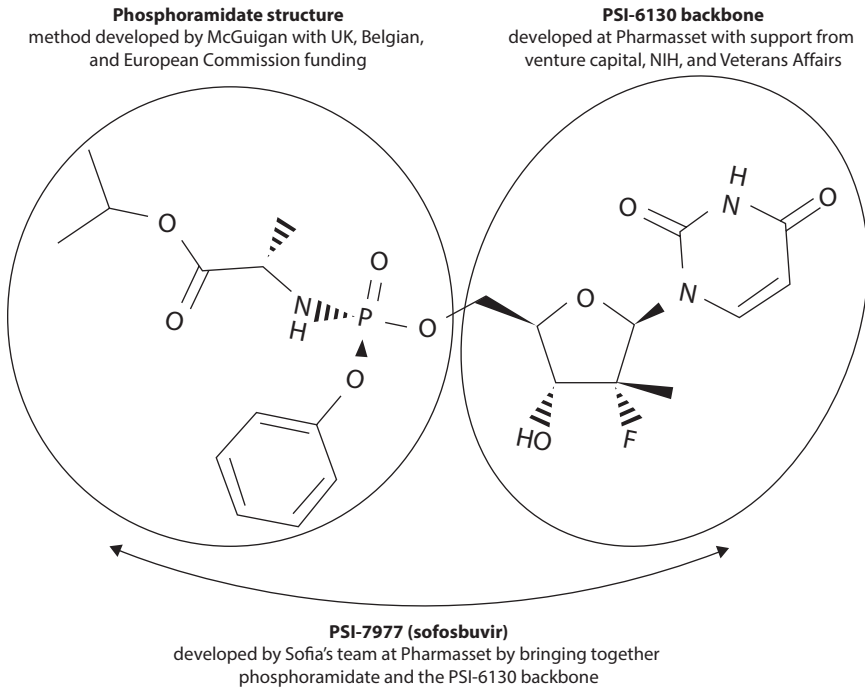


FIGURE 2. Organizational and financial sources of sofosbuvir structure.

As Zeller has noted in his work on intellectual property monopolies, the “socialization” of innovative labor “makes it difficult to assign the elements of an intellectual achievement to specific actors or firms.”¹⁰⁵ In the face of this fraught reality, the US intellectual property system relies on expensive litigation and legal machinations to resolve the specific contours of such claims. Drug companies, in turn, must become specialists in intellectual property battle strategies as they seek to maintain control over socially produced assets.

To lay claim to the sofosbuvir compound as its intellectual property, Pharmasset moved quickly to file applications with the PTO in 2007 and received a patent in 2008. The company then began to prepare for early-stage human trials in 2009 and 2010.¹⁰⁶ Over the course of these two years, Sofia’s application of the prodrug method would be validated in several Pharmasset-led early-stage clinical trials, with each trial showing promising results. Though the numbers of patients were relatively small, the compound showed results heretofore not witnessed in hepatitis C. In the Phase II trials for example, sofosbuvir cured hepatitis C at rates higher than 90% in multiple cohorts among 564 patients.¹⁰⁷ A remarkable advance for patients appeared within reach. Pharmasset used the capital from shareholders to run these trials, at a total cost of \$62.4 million. But the company’s executives also wrestled over what to do next with their prized asset. The answer to this question would be shaped by the financialized trajectory along which the company had already travelled.

SOFOSBUVIR AS AN ASSET AND A RELAY RACE OF FINANCIALIZED CAPITAL

The early 2000s brought an expanding search for hepatitis C therapies, with the advent of the replicon drawing in a growing field of emerging companies and private finance capital. Yet this entry of speculative capital would illustrate key features of financialized drug development.¹⁰⁸ With no internal sources of finance and no products or revenue, Pharmasset would be structurally oriented to meeting the demands of an array of external and speculative forms of capital, from venture capital to stock markets. These finance capitalists were drawn by the economic promise of its hepatitis C assets. At play in these valuations, in turn, would be the future prices investors and traders anticipated for hepatitis C drugs. Defined by specific growth-oriented logics of price and value, these financial markets would let these actors bet on drugs over periods far shorter than it would take to develop any compound into a usable treatment.

Financial Markets and Pharmasset: Venture Capital, Corporate Capital, and an IPO

As Pharmasset embarked on developing its pharmaceutical assets in the early 2000s, it searched for sources of financing to carry forward its research efforts. Neither direct public funding beyond NIH's SBIR program, nor bank financing, would work. Though the state had been a critical source of patient capital in an earlier stage, SBIR grants (highlighted earlier) would not be sufficient for phase I and II trials. According to a US government study using data from that period (2004–2012), the average phase I anti-infective clinical trial cost about \$4.2 million, and a phase II trial, \$14.2 million.

Furthermore, while hepatitis C was a growing public health concern in the late 1990s and 2000s, NIH had not developed a plan to scale up financing of hepatitis C drug development, particularly public funding of clinical trials.¹⁰⁹ This lack of mobilization contrasts with the case of HIV/AIDS, in which political movements had ultimately instigated broad-based public-sector investments in drug development.¹¹⁰ Similar political support had yet to be engendered for hepatitis C at the national level or in the US or abroad. Among the reasons offered by physicians and public health analysts for this relative silence: the chronic and often invisible nature of hepatitis C and the marginalized status of many patients with the virus.¹¹¹

Bank loans were also not an option for Pharmasset. The project's high uncertainty and the lack of collateral of a small biotechnology company without any approved products made it unsuited for bank financing.¹¹²

Instead, Pharmasset would turn to a source that had become more common for biotechnology enterprises since the 1980s: venture capital. Quite unlike the government, venture capital funds typically provide capital to early-stage businesses in exchange for an ownership share.¹¹³ This capital comes in phases, with

companies attracting “rounds” of funding based on the extent of their financial promise. Venture capitalists usually aim to “exit” their ownership after several years and “cash out” their investment when an investee company is acquired by a larger firm or becomes publicly traded on the stock market. Reflecting the typical scale of venture capital investments in biotechnology companies at that time, by 2004 Pharmasset had raised \$55.3 million to finance its nucleoside development work.¹¹⁴

This venture capital financing mechanism did not emerge from spontaneous market activity. It was fostered by two regulatory shifts undertaken by the US government in the 1970s and 1980s and influenced in part by new business interests. First, the Bayh-Dole Act, as described earlier, allowed venture-backed startups to emerge from university research by monetizing publicly funded knowledge.¹¹⁵ Second, in 1979 the government promulgated a regulatory change that let pension funds invest much more of their assets in venture capital, which until then had been deemed to carry too much risk.¹¹⁶

With a new class of university startups in which to invest, as well as new sources of pension-fund financing, venture capital skyrocketed. In 1978, venture capital amounted to only a sliver of economic activity, with a total of \$216 million in commitments.¹¹⁷ And pension funds made up only 15% of that. Ten years later, in 1988, pension funds accounted for nearly half of a total of \$3 *billion* committed to venture capital funds.¹¹⁸ At the height of the dot-com bubble, in 2000, venture capital reached \$120 billion in investment, though this fell to \$23 billion in 2004, the year of Pharmasset’s final major round of venture financing.¹¹⁹ In the 1980s and 1990s, the biotechnology sector emerged as one of the leading destinations for venture capital, with approximately 20% of a total of \$108 billion directed to drug and device development companies.¹²⁰

Yet the scale of these investments in individual research projects would be modest, as it was spread across hundreds of firms. In biotechnology, for example, the median total investment by venture capital funds in the early 2000s was approximately \$50 million.¹²¹ This could not sustain the long and expensive effort typically required to develop initial compounds into approved drugs. The modest and short-term investments of venture capitalists meant that Pharmasset needed more capital. The company turned to two other potential sources: a larger pharmaceutical company, and the stock market.

By the spring of 2004, Pharmasset had what it viewed as a promising pharmaceutical asset in PSI-6130.¹²² Because the compound had shown profound inhibition of the virus via binding to the NS5b polymerase protein both in the replicon and then in rats, Pharmasset decided to pursue early human trials.¹²³ But many questions typical of early-stage drug development remained, including how much of the compound would be needed for the desired effect, and whether it would be safe in humans. With no experience in hepatitis C clinical trials, Pharmasset looked to an approach that had grown in the past two decades in the biotechnology and pharmaceutical sector: the “strategic partnership” between small enterprises and established companies.

These have been pursued in the industry as a way of joining up the supposed comparative advantages of small companies (with few or no approved products) and larger ones (with established revenues). Small biotechnology companies can supply established businesses with compounds from early-stage research often deemed too risky for larger firms, and larger businesses can provide clinical trial expertise to small companies with little background in the development process.¹²⁴ In the past three decades, such alliances have become more common, especially as large companies have outsourced early-stage research.

Several months after closing their final round of venture capital and patenting PSI-6130, Pharmasset struck a partnership deal with Roche, a large Swiss-based pharmaceutical company.¹²⁵ As the manufacturer of the leading hepatitis C treatments at the time (the interferon-based Pegasys and Copegus), Roche saw potential in using PSI-6130 to expand its antiviral strategy. The interferon treatments were toxic, akin to cancer chemotherapy, and many patients avoided taking them until their disease was in its later stages.¹²⁶ The public list price for the regimen was about \$40,000, and the market for hepatitis C, which also included interferon products from Roche's competitor, Schering Plough, had grown to over \$2 billion in sales by 2004.¹²⁷ Roche hoped that by pairing interferon with a compound like PSI-6130, they could make their treatments less toxic and more usable by patients at an earlier stage of the disease.

Leveraging its recent experience in hepatitis C clinical trials (for their interferon regimens), Roche aimed to conduct further investigations of the efficacy and safety of Pharmasset's compound in humans. Roche agreed to provide an upfront payment, further milestone payments of up to \$105 million, and royalties on Pharmasset, in exchange for global rights to any compound and its associated revenue (minus royalty payments);¹²⁸ Roche also gained shares in Pharmasset.¹²⁹

Over the next six years, during which the two companies partnered on clinical trials for PSI-6130 and its modified versions, Roche directed \$44.5 million to Pharmasset.¹³⁰ But this relatively small sum—in the face of the tens of millions necessary for later-stage clinical trials—would be only one part of the relay race of financial actors from which Pharmasset would seek capital. The company would then turn to another source to sustain their R&D efforts: the stock market.

By 2006, Pharmasset was preparing for an initial public offering (IPO): converting itself from a privately held company to one that would be traded on the NASDAQ stock exchange.¹³¹ Two factors shaped this move. An IPO would enable Pharmasset's venture capital investors to exit and "cash out"; it could generate a new round of capital to finance clinical trials. Pharmasset's IPO on NASDAQ, on April 26, 2007, raised \$45 million, with the stock trading at \$9 per share.¹³² Four institutional shareholders—pension funds like Fidelity, and hedge funds like BlackRock—each held more than 5% of these shares. Pharmasset's \$45 million "valuation" was based on its three clinical-trial-stage nucleoside compounds: the PSI-6130 compound being

developed with Roche, as well as one for hepatitis B (clevudine) and one for HIV (racivir).¹³³ For each compound, Pharmasset saw the potential for major revenue, as anticipated improvements in the treatments had the potential to lead to higher prices and more patients being treated. With 15 million people chronically infected with hepatitis C in the major markets of the US, Europe, and Japan, Pharmasset's senior leadership believed its development efforts could produce compounds that would bring it a substantial share of the market for hepatitis treatments.

Financial markets bet on this promise as well. The potential of its drug assets enabled the company to raise further capital in the stock market by issuing new shares, with five separate rounds of follow-on financing bringing \$345.9 million in capital.¹³⁴ Pharmasset spent some of this on clinical trials, in 2010 and 2011, for the compound that would ultimately be sofosbuvir.¹³⁵ These follow-on rounds also allowed new shareholders to trade on Pharmasset's rising stock price, which rose in 2010 and 2011 and reached \$85 per share in October 2011 on the news of clinical trials showing a major breakthrough in hepatitis C treatment.¹³⁶

Such trading on pharmaceutical assets, many of which may never receive regulatory approval or generate earnings, has been facilitated by the specific configuration of NASDAQ. Unlike its older sibling, the New York Stock Exchange, NASDAQ allows companies with no record of profits (like Pharmasset) to execute an IPO.¹³⁷ Like the venture capital system, NASDAQ was a product in part of the US state: the exchange was created in 1971 as the world's first electronic stock market, with the encouragement and guidance of the US Securities and Exchange Commission. NASDAQ would begin to take off in the 1990s with the rise of venture-backed technology companies. The presence of NASDAQ enabled a highly liquid financial market through which venture capitalists could exit their initial investments and subsequent traders could enter and exit based on fluctuations in share price. In Pharmasset's case, these price changes were shaped by development milestones and clinical trial results, which influenced shareholders' perceptions of the company's future value.¹³⁸

By 2011, Pharmasset would be valued at nearly \$5 billion, though it had no approved products, sales, or profitability. This disjuncture was a common feature of small biotechnology companies and was true of Pharmasset from day one. When Pharmasset raised \$40 million from a series D round of venture financing in 2004, the company had run an operating loss in each year since its founding, for a total of \$15.8 million in deficits, and was not expected to be profitable for years into the future.¹³⁹ When Pharmasset raised \$45 million in its IPO and then follow-on financing in equity markets nearing \$350 million, it had an accumulated deficit of \$330 million and no compounds in phase III trials (Table 2). These forms of speculative capital would be fueled, in turn, by specific logics of risk, value, and price that would be entirely tethered to financial markets. We turn to these logics next.

TABLE 2 Pharmasset's sources of financing, 1999–2011 (millions of US dollars)

Period	Financing source	Amount
1999–2004	Venture capital	53.81
2000–2005	Small Business Innovation Research program	2.46
2004–2010	Roche partnership	44.50
2007	Initial public offering	45.00
2008–2011	Follow-on equity financing	345.87
	Total financing, 2000–2011	491.66
	Total operating loss, 2000–2011	(313.9)

SOURCES: Pharmasset SEC filings; S&P Capital IQ database.

Paying Out on Assets:

Speculative Capital and the Logics of Price and Value

Why did this chain of speculative financial actors get behind an unproven business like Pharmasset? The most obvious reason is that each actor, from venture capitalists to shareholders, aimed to make money. But the *way* they aimed to make this money is crucial for our understanding of the financialization of biomedicine and its consequences for drug pricing and value in drug development. These speculative actors make their money on the basis of two political-economic features of financial markets.

First, to mitigate risks and garner rewards, financial markets offered capitalists the opportunity to “exit” Pharmasset in periods far shorter than the time it takes to develop a drug. Lazonick’s analysis of stock markets—less vehicles to provide capital for innovation, and more mechanisms for business transactions and trading on share prices—sheds light on this process. Second, financial markets enabled actors to make these gains by speculating on rising valuations for Pharmasset’s drug assets on the basis that health systems would one day be compelled to pay more for better treatments. Beckert’s description of “imagined futures” in capitalists’ expectations reveals how forecasts of future earnings streams can fuel speculative transactions.¹⁴⁰ Taken together with the analysis of shareholder power in chapter 2, we begin to see how financial-market-driven drug development is intertwined with unprecedented drug prices.

This first dynamic relates to the temporal dimension of speculative capital. These financial actors did not get involved as part of a long and risky “development marathon” seeking to bring a drug all the way from the bench to the bedside. Rather, they were part of a “relay race” in which they aimed to accrue earnings in periods far shorter than it would take to make a new medicine. In other words, from venture capitalists to traders on Wall Street, they enter, as Powell et al. put it, with “the terminal point in mind.”¹⁴¹ Yet the speculative bets enabled by financial markets varied among the actors, with contrasting time horizons and at stages of the drug development process containing differing levels of risk. A venture capitalist might

make a three-year bet on a business in its fledgling, startup phase; a trader on Wall Street might make a two-day bet on the results of a late-stage clinical trial.

Venture capitalists in biotechnology typically seek a 40–75% rate of return on their investments.¹⁴² These returns are said to be warranted because unlike day traders on Wall Street, venture capitalists provide capital at unproven, early stages of a business and must wait for a payout. Venture capitalists also view themselves as “active investors” who use their technical and business expertise and networks to transform nascent businesses into potentially “high-value” enterprises. Partners at venture capital funds with a biotechnology focus typically have a background in biomedical research or medicine, which they use to evaluate potential technologies for investment. They also serve on the boards of the businesses in which they invest, using their technical and financial expertise to shape management decisions over talent, technology, and strategy in the critical early stages.¹⁴³

While venture capitalists take greater risks than other speculative capitalists, they mitigate these risks in several ways. One way is to come in *after* the public sector has financed the most uncertain stages of technology discovery. As one of Pharmasset’s venture capital backers for their series B round, MPM Capital’s Luke Evnin, noted in a 2014 blog post: “Due to NIH funding now also going towards programs that demonstrate commercial potential, our ‘start ups’ are much further along by the time we invest—even though they may still be straight out of academia.”¹⁴⁴ Another way to mitigate risk: venture capitalists use multiple financial-market strategies to “exit” their investments typically after three to five years. Either through the acquisition of their investee firm by a larger business or via an IPO, venture capitalists seek to transfer their ownership to other shareholders while generating a gain based on the valuation of the acquisition or IPO.¹⁴⁵ Evnin shared his venture capital fund’s preference for exiting via acquisitions: “When we approach an investment, we really think about who’s the buyer and what will we have to show that buyer? Is this a team and a product portfolio that will get us there?”¹⁴⁶ Finally, venture capitalists spread their capital across many assets, betting that a few big wins will cover losses in other investments. Yet because venture capital does not provide the scale and duration of capital required to fully develop and approve a drug, companies like Pharmasset continue to depend on other forms of external capital to sustain their research efforts.

At the IPO stage, institutional shareholders (such as mutual funds, hedge funds, and insurance companies) and stock markets enter the picture. Through his historical work, Lazonick shows us that while stock markets *can* provide capital to businesses, as is commonly held in popular discourse, this is not their primary function.¹⁴⁷ To be sure, the IPO is an example where the stock market functions to provide capital to young businesses. Yet the IPO mechanism also creates a market for speculative trading in which ownership is transferred from venture capitalists to other shareholders.¹⁴⁸ This transfer produces a “market price” based on the value that new shareholders forecast for the company at the time of its launch on the

stock market. This price—represented in the company’s stock price—then enables financial market exchange in which traders pursue financial accumulation—sometimes over mere hours, as in the case of day traders. Across the life cycle of a business listed on a stock exchange, Lazonick demonstrates that the stock market serves more as a mechanism for trading, via which shareholders can use their wealth to pursue capital gains, rather than as a vehicle to finance businesses in a durable way.

Indeed, the liquidity of financial markets (the relative ease with which traders can enter and exit) enables large financial rewards. Across biotechnology, stock markets have largely been kind to both venture capitalists and Wall Street traders. An analysis of annualized returns between 2000 and 2010 of 1,400 venture capital funds shows that life sciences venture capitalists made 20% returns (higher than in information technology).¹⁴⁹ Another analysis found that a trader who bought shares in all 340 biotech IPOs from 1979 through 2000 and held on to those shares until January 2001 or until a company was acquired would have realized an average annual return of 15%, almost twice the average gain on the S&P 500 during that time.¹⁵⁰

This leads into the second dynamic of financial markets: how do these actors collect this scale of rewards? The economic sociologist Jens Beckert’s observation that “expectations should be seen as central to the explanation of economic outcomes” provides insight into the motivations of speculative capitalists.¹⁵¹ Financial actors did not seek to make money from Pharmasset’s profits—the company had none—but by speculating on Pharmasset’s future earnings and the company’s resulting “market valuation.” Trading on these valuations, in turn, gave speculative actors the chance to “buy low” and “sell high.” Underlying these valuations, however, are specific expectations regarding drug pricing and pharmaceutical value.

As Beckert explains, the social bases of such expectations are to be found “within the power structures in which market actors find themselves.” Based on its patents and the political power of the pharmaceutical industry, for example, Pharmasset’s leaders and capitalists in financial markets plausibly expected that health systems could be compelled to pay higher prices for a better treatment. Interferon-based treatments for hepatitis C already cost well over \$30,000 per treatment regimen in 2004, yet they produced severe side effects with a curative response in less than half of the patients that took them.¹⁵² Wall Street analysts and Pharmasset’s leaders anticipated that higher prices and market valuations over time would be contingent on therapeutic improvements.

This amounted to a kind of “pricing escalator,” in which the price of current treatments set the pricing floor for future treatments, with each new generation priced incrementally higher based on the “value” it could offer health systems (Figure 3). Indeed, a retrospective study of launch prices for hepatitis C drugs in the US found that a 1% increase in cure rates was associated with a \$1,000 increase in price.¹⁵³ This ability to turn pricing predictions into realized outcomes was due to the political influence that the pharmaceutical industry pursued through lobbying and other strategies I describe in the next two chapters.

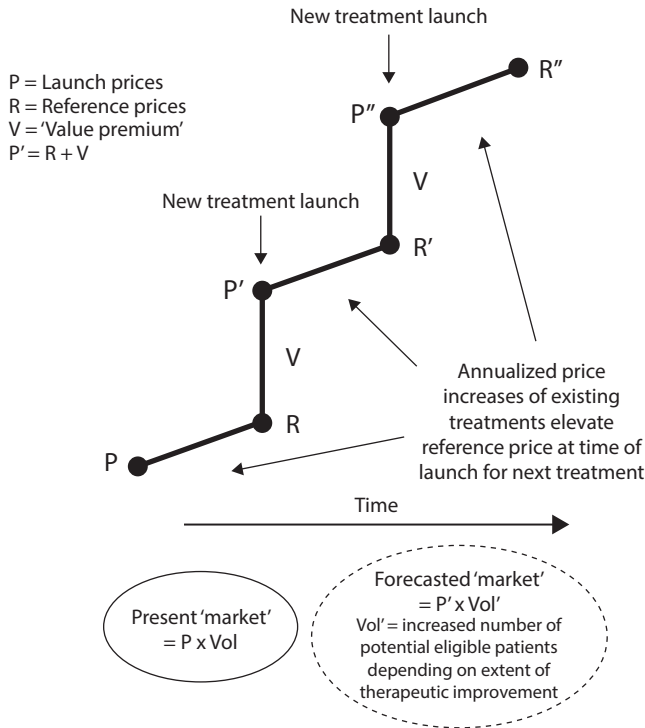


FIGURE 3. The pricing escalator and expansion of market valuation. In this schematic view, the price of the existing standard of care serves as a reference (R), with a next-generation treatment garnering an additional price (D) based on its purported differential value. Higher prices ($R + D$), combined with the larger numbers of patients who stand to benefit from a better medicine, produce forecasts of expanding market valuations. These valuations attract bets from speculative capitalists. See chapter 3 for more on how this pricing comes to be represented as “value pricing” in policy debates.

These higher prices, in turn, would be combined with forecasts of large patient populations that could benefit from a better treatment. While the toxic interferon treatments could only be used on later-stage patients, the industry and Wall Street predicted that improvements could mean that everyone could be treated—even asymptomatic patients. Pharmasset captured these predictions in the SEC filing for its IPO.¹⁵⁴ In documenting a modest improvement in interferon treatments (from 47% to 54% cure rate in clinical trials), for example, Pharmasset’s leadership noted that sales of hepatitis C drugs increased from \$1.3 billion in 2000 to more than \$2 billion in 2002. With further improvements commanding higher prices for more eligible patients, the company predicted that the hepatitis C drug market would grow from \$2.2 billion in 2005 to \$4 billion by 2010 and \$8 billion in 2015.

Even if it was years away, this anticipated earnings stream from financial assets—in this case promising compounds granted patents by the US government—attracted bets from speculative capitalists. Pharmasset would close out the decade with assets valued at nearly \$5 billion. Yet with no revenues, products, or profits, it remained cash hungry. This financialized trajectory, in turn, would shape the options its executives had for the company's next steps. We end the chapter by considering these options.

Potential Pathways for Pharmasset: Durability or Disposability?

As Pharmasset entered 2011 with PSI-7977 looking to be a potent financial asset, the company's senior leadership had a decision to make, one typical of small biotechnology companies with compounds preparing for later-stage trials. Should they aim to grow as a durable, free-standing business, or become what has been called a "disposable" business, with the organization dissolved on the sale of its assets to an established pharmaceutical company?¹⁵⁵ Pharmasset's strategic planning and board meetings, captured by the US Senate investigation, reveal that two major considerations shaped the company's decision: the timing and results of further clinical data on PSI-7977 and competing compounds; and its possibility of growing into a diversified, global enterprise.

If Pharmasset were to find a partner or get acquired, they wanted it to be with the right company for the right price. Early indications from the phase II trials were that PSI-7977 would work most effectively if paired with a second compound, as in the combination therapies for HIV. Using PSI-7977 alone (a "mono-therapy") could lead to high rates of resistance and lower cure rates.¹⁵⁶ Pharmasset and several larger companies, such as Bristol Myers Squibb, Gilead Sciences, and Merck, had developed compounds that might work in tandem with PSI-7977, but the data on those compounds still presented a murky picture, as few had made it into later-stage clinical trials.¹⁵⁷ Pharmasset's executives knew they could gain leverage by waiting.¹⁵⁸ With complete phase II trials for PSI-7977 to be released in late 2011, Pharmasset's compound would likely be in high demand.¹⁵⁹

In the meantime, they also considered whether they could build a free-standing business. But here they saw major barriers. They would have to build marketing, regulatory, and distribution networks, which would require expertise and financial resources they did not have.¹⁶⁰ The larger companies had a major incumbent advantage, with the infrastructural and political power to shepherd drugs through the final stages of regulatory and global distribution. The executives also worried that after the launch of PSI-7977 Pharmasset would need to quickly diversify to other areas of therapeutic development, because a curative therapy for hepatitis C would not support the type of continuous growth their shareholders would want. The company's viability as a single-product business remained a looming question, and the leadership remained wary of the risks in developing other products. "Given the substantial time frame from research program initiation to product

launch,” they observed in a 2011 board meeting update, “it is highly unlikely that any *de novo* research program will provide the necessary revenue in the required timeframe” to deliver growth beyond hepatitis C.¹⁶¹ Sticking to their original vision of the company—making assets to be sold to Big Pharma—appeared to be the most viable strategy.

PHARM(ASSET)

This chapter reveals the dynamics of pricing and value intertwined with sofosbuvir’s financialized trajectory. By tracing how science came to be capitalized, with publicly financed and cumulative knowledge converted into valuable assets controlled by financial markets, three key features of this trajectory come to light.

First, value creation in the drug development process would be contingent on the state. The very possibility of sofosbuvir depended on public investments. All through the development of the replicon, nucleoside science, Pharmasset’s launch, and the prodrug approach, public investments—primarily in the US but also in Europe—co-created value by “crowding in” private capital and setting the direction of the innovation process toward finding curative medicines. This private capital would be mobilized by the state not only through public investments but also through the state-sanctioned political-legal setup that allowed the patenting of collectively developed knowledge. Universities like Emory were big financial winners in the process, receiving public funds and royalties from intellectual property. This process turned knowledge into a financially valuable asset—the kind of asset that Schinazi, as the founder of Pharmasset, one day hoped he could sell to large companies.

Second, as a small biotechnology business with no products or revenue, Pharmasset was structurally tethered to an array of external financial actors. This chain of speculative financial actors—from venture capitalists to traders on Wall Street—bet on the future of Pharmasset’s compounds, over time horizons far shorter than the time it would take to develop sofosbuvir. Of these financial actors, venture capitalists took on the biggest risks by making early investments in unproven compounds, thereby creating value in the evolution of Pharmasset. But the presence of financial markets—whether through acquisition and IPOs or liquid stock markets—provided each of these actors the opportunity to mitigate risks by being able to “exit” long before the fate of sofosbuvir would be determined in clinical trials or FDA regulatory review.

By the end of 2010, Pharmasset would be valued north of \$5 billion, largely on the promise of PSI-7977, the compound that would become sofosbuvir. Yet Pharmasset’s investments in the drug had amounted to only \$62.4 million, and the R&D investments over the life of the firm totaled \$271 million—about 5% of its market valuation.

This disjuncture between Pharmasset's financial market value and its R&D spending reveals the third feature: "value" in this speculative process was not commensurate with R&D investments or profitability. Instead, it reflected predictions—specifically, predictions of *growth* in Pharmasset's earnings potential. In valuing Pharmasset, speculative capitalists anticipated that health systems would one day pay more for a better hepatitis C treatment that could benefit a larger patient population. The high prices of existing treatments—over \$30,000 at the time—made this a potentially wildly lucrative market.

Which path would sofosbuvir take in the hands of Pharmasset? Being acquired gave Pharmasset's shareholders a chance at a major reward, without trying to compete with incumbents that had significant global advantages. Lacking any approved products or the investments to develop the organizational capabilities for a durable business, Pharmasset thus viewed large companies like Gilead as potential suitors rather than as future competitors. To understand the pricing and value logics constituting sofosbuvir's next steps, then, we turn to Gilead—Pharmasset's most interested suitor—and the forces shaping its pursuit of growth.