Tony Holý veered up as if stung by a hornet’s nest. He was genuinely angry. He would not tolerate that either the chemist or the biologist take priority over the other. “Both are due equal shares!” he emphatically said and the debate was closed.

Then the lawyers confronted Julius Vida. Royalties were due not only on the basis of drugs developed but also on the basis of all prodrugs that would be derived from the compounds. If Bristol-Myers would not develop these compounds, the whole class of Holý’s compounds had to be returned including all results and calculations of all the tests performed within the company. In order to close the deal, Bristol-Myers had to finance the trips of two communist party executives to the United States.

Vida found this rather amusing but did not object; Czechoslovakia under the Husák regime remained the most hardline country in the socialist sphere, defying Moscow’s recent turnabout. Since Mikhail Gorbachev had come to power in 1985, the Soviet Union had been steadily progressing towards restructuring (Perestroika) and opening (Glasnost) communist society. Gorbachev adopted a laissez-faire approach in dealing with the rest of the Warsaw Pact countries. The changing tide of Soviet priorities placed the Husák party in an awkward position, but the regime shrewdly ensured that Czechoslovakia remained hardline without having to resort to all-out political terror. In the Academy of Sciences, the winds of change were starting to blow and Julius Vida was happy to oblige.

The license to Bristol-Myers meant that the Holý compounds were now going to be intensely scrutinized. Cooperation between the pharma giant and academic institutions became redundant. Holý and De Clercq had to wait more than two years before Bristol-Myers informed them about the future of these compounds; it was a nail-biting time.

When Nobel prizes were announced in the fall of 1988, the field of Nucleosides research finally earned its share in the limelight. A Nobel Prize was awarded to Gertrude Elion and her boss George Hitchings at Burroughs Wellcome for the innovative ways in which they had developed a series of drugs. The Nucleosides community believed that her Nobel Prize was triggered by her discovery of the mechanism of the antiviral activity in acyclovir. Although much attention was not paid to Elion before, the Nobel Prize changed everything. She was now the figurehead of Nucleosides research. Before she retired in 1983, Elion was
the head of the Department of Experimental Therapy and had a hard time convincing her colleagues at Burroughs Wellcome to actually develop the drug.11 Richard Whitley who conducted clinical trials with acyclovir was her closest ally. De Clercq and his friends at Rega helped her drug to become even more popular. They found that the amino acyl esters of acyclovir had better aqueous solubility and could be developed as a better alternative. They received a worldwide-minus-the US-patent for their findings. De Clercq was able to license these to Wellcome, the British parent company of Burroughs Wellcome. Their discovery was superseded in the U.S. by the patent for one of the amino acyl esters, the valine ester, that facilitated oral absorption. In De Clercq’s eyes, these were merely “me-too” drugs and he never touted Rega’s contribution to the acyclovir story very much. Patent rights were nevertheless granted from 1995 to 2002 before valacyclovir turned generic.
Chapter XII
Finding the best therapy: the one-a-day-pill

_The creative act is not an act of creation in the sense of the Old Testament. It does not create something out of nothing; it uncovers, selects, re-shuffles, combines, synthesizes already existing facts, ideas, faculties, skills. The more familiar the parts, the more striking the new whole._

— Arthur Koestler

A new start-up: Gilead Sciences

The biotech gold rush on Wall Street had been unleashed. Companies like Biogen and Genentech had captured the imagination of investment bankers even before a single product was made. Recombinant DNA technologies required to produce interferon synthetically were adapted for use in other proteins. Anything seemed possible.

The excitement had captivated Michael Riordan, a young student at the Johns Hopkins Medical School. Born and raised in Kansas, son of a physician and a mother who wrote textbooks about breastfeeding for medical professionals, he was immensely curious about nucleic acids research. He gravitated very naturally to the world of interferons and gene expression. His favorite place to research was in the Johns Hopkins laboratory of Paula Pitha, a Czech virologist who had fled communism in the late 1960’s.¹

When Riordan graduated from Johns Hopkins with high honors, he toyed with ways of combining theoretical science from the academic world with the product development of the pharmaceutical industry. His next step, an MBA at Harvard, launched him on a different path, the world of venture capital. He was hired by Menlo Ventures in Silicon Valley. The hub of technology and innovation brought him closer to where the action
Cold War Triangle was. He spent a whole year traveling the country, visiting pharma companies and academic institutions, and learning who the players were in the field of DNA chemistry.

In 1987, with $2 million of seed capital from his friends at the venture capital firm, he made the jump to start his own company. He named it Gilead Sciences, after the ancient site of a willow tree that produced a curative balm. The company began as a small lab outside San Francisco with just six employees. Very early on Michael Riordan managed to coax Gordon Moore, the co-founder of Intel, to join his business advisory board.2

Soon, it was time to install a directors’ board. Undaunted, he went straight to the top, and chased the former Secretary of Defense, Donald Rumsfeld. “How many people work in your company?” Rumsfeld asked. “Just six including the founder” answered the twenty-nine year old Riordan. Rumsfeld who had just stepped down as CEO of Searle was impressed by his youth and determination and happy to impart his pharma experience to a start-up in Silicon Valley.

At the start, none of Gilead’s experimental drugs worked outside the laboratory, but the biotech craze was in full swing and his ideas caught the interest of the venture capital world. Riordan remained focused, unperturbed and continued to entice more investors for his search to find drugs to control disease-causing genes.3 One of them was Benno Schmidt, a partner of J.H. Whitney & Company. He had been an influential powerbroker in New York City when President Nixon appointed him to the chairmanship of the President’s Cancer Panel, which initiated the federal government’s “War on Cancer.” Benno Schmidt pushed his firm to invest in biotechnology ventures. As a leader in both the private and public sector, he was considered the “senior gatekeeper of biomedical innovation in the United States.”4 Once Benno Schmidt was on board, Riordan was able to attract capital infusions from Venrock, the Rockefeller investment firm and Glaxo, the pharmaceutical company.

Next, Riordan felt they needed to add a person of stature in Europe to enhance the board of directors’ international prominence. Rumsfeld thought of his Belgian friend, Stevie Davignon, whom he had met during his time at NATO and later became a Vice President of the European Commission.5 Rumsfeld attracted a few other big names and later also George Schultz, the Secretary of State under President Reagan.
Capital was no longer a problem, but now Riordan desperately needed a group of first-rate scientists. 1990 became a “golden year” when the main players of his team would fall into place. Riordan plucked Norbert Bischofberger away from Genentech, and scooped up John Milligan right after he finished his postdoc at UCSF. He spent many months, but eventually pried Bill Lee away from Syntex.

He was still on the hunt for a Head of Research, the thirtieth employee. Riordan was looking for someone who could bring Gilead to the next level, and support the development of innovative drugs. He focused on a charismatic person, steeped in science and with a passion for entrepreneurship. He interviewed all the potential hires personally over dinner paired with fine wines. After many dinners and plenty of wine, he still could not find the right person. At least not until a headhunter drew his attention to the newly merged Bristol-Myers and Squibb and raised the possibility of hiring the director of infective chemistry, John Martin.

One of Riordan’s scientific advisors, Richard Whitley, made it happen. He prepared the terrain and sweettalked John Martin before he would sit down with Riordan over dinner in the Smith & Wollensky restaurant, a popular steakhouse in Manhattan. Perhaps not the most ideal venue for a person like Riordan who had only just become a vegetarian.

However, three hours later everything clicked. They had concocted a plan for John Martin’s smooth transition from Bristol-Myers to Gilead. Martin pointed Riordan to his co-workers, Swami Swaminathan and Mick Hitchcock, both at Bristol-Myers. Both were hired that same year.

Another part of Riordan’s strategy was to visit Erik De Clercq and Tony Holý. Things had to be kept confidential. When Riordan arrived in Prague and Leuven, his stopovers seemed like simple courtesy visits at the time. In fact, they turned out to be reconnaissance for future collaboration.

Just a few months later, De Clercq and Holý felt the ground shift beneath them. They were invited to Wallingford where they were informed that Bristol-Myers Squibb no longer wanted to develop the Acyclic Nucleosides Phosphonates. The news hit them like a ton of bricks! One week after the announcement by Bristol-Myers-Squibb on 20 May 1991, John Martin was on the phone with Holý and De Clercq trying to convince them to transfer their license to Gilead. Allotting their license to a start-up in California seemed like a particularly risky affair—most of these new
Silicon Valley companies went belly-up and could not be trusted. But something told them this adventure could be different. Their positive experience working with John Martin convinced them to consider the offer.

A few weeks later, they agreed to meet in Paris in a restaurant not far from the Tuileries on July 2, 1991. The negotiations were very straightforward, they would stick to the exact same licensing agreement they had concluded a few years earlier with Bristol-Myers.

Riordan, Martin, De Clercq and Holý sealed the deal by signing on a table napkin. The formalities of officially transferring the license followed soon after.

In Wallingford, Julius Vida was distraught over the way Squibb handled the merger and imposed their will on Bristol-Myers. He bemoaned their killing of the goose that laid the golden egg. It was with a heavy heart that he saw the phosphonates leave the company. Nevertheless, Julius Vida was relieved they could be developed under John Martin’s stewardship. Vida played a crucial role in facilitating the transfer of the license and making sure it involved every test, every calculation, and that every single piece of information acquired under Bristol-Myers’s watch was handed over.

Michael Riordan did not want anything to go awry. He traveled to Wallingford to take hold of the dossiers in person and send them by Express mail to California. Only at that moment did he feel assured of the company’s new beginning. Gilead was off to a flying start! Though it had not yet developed any products or posted any profit, the thirty-odd employee company basked in the confidence and promise of the newly acquired intellectual property: the acyclic nucleoside phosphonates stemming from the collaboration between the Rega Institute and the IOCB in Prague.

At the end of that same year, 1991, Riordan began the filing process for an initial public offering with the Securities and Exchange Commission. It was completed three months later, heavily oversubscribed and signaled the public market’s unofficial stamp of approval.⁶

**The birth of Cidofovir, Tenofovir and Adefovir**

Acquiring the license from Bristol-Myers meant John Martin and his colleagues could simply pick up from where they left off in Connecticut. It saved them years of research and bolstered their confidence immensely.
But when Martin was introduced to Paul Janssen at a Gordon conference in March 1992, the famous Belgian drug maker poured cold water all over it. He tempered his enthusiasm about the new company Gilead and gave him only one in a hundred chances to succeed.7

Riordan and Martin used their resources in a savvy way. They did not spend their time building up their internal capacities but made judicial use of outsourcing. In the early years, this philosophy involved intensive cooperation with their academic partners, IOCB in Prague and the Rega Institute in Leuven. The young company needed all the optimism and energy it could muster in order to withstand the roller coaster that was to follow.

There was no abating the AIDS epidemic. By 1991, more than 100,000 Americans had died from the disease, nearly twice as many as had perished in the Vietnam War. People were dying more from the “opportunistic” infections rather than the disease itself. Gilead’s first priority was to tackle HPMP in the hopes that it could be effective against the cytomegalovirus (CMV), a virus of the herpes family. CMV did not cause disease in healthy people but was life threatening to the immunosuppressed. It caused blindness, pneumonia, severe diarrhoea and encephalitis. John Martin knew the disease well since he had synthesized gancyclovir while at Syntex.8

Just as HPMP was on its way to becoming cidofovir, it almost tanked the company: cidofovir was causing cancer in rats! It was one of those all hands on deck situations. Erik De Clercq had to travel urgently to Foster City and finetune the dosage to reduce its toxicity. He was greatly helped by his co-workers in Leuven.9 John Martin had to use all his persuasive powers to keep the FDA engaged.

At the Rega Institute, more compounds kept arriving. Non-nucleosides from Janssen were screened and scrutinized in Rudi Pauwels’s lab.10 The nucleotides from Prague were screened and analyzed in Jan Balzarini’s lab. One day, a new compound from Prague, named PMPA, was thrown in the mix. Holý always gave De Clercq the privilege of naming his compounds, since he usually oversaw all the operations and documented them in publications. When the article about PMPA appeared in 1993, it was already obvious that the compound had a high capacity to fight HIV—100 times greater than AZT—and a very low toxicity.
With an amendment to the original license, PMPA was added to Gilead’s basket of more than 500 Holy-De Clercq compounds. It became the focus of the PMEA-team led by Mick Hitchcock. The former co-worker of John Martin’s at Bristol-Myers had a special intuition for testing and screening, dating back to his days with interferon and later with d4T. PMPA arrived at a critical time in Gilead when it evolved into tenofovir. PMEA was not the anti-HIV agent that it was extolled to be and its toxicity caused concern at the FDA. Before it could endanger the reputation of the company, PMEA was quietly moved to the backburner and re-examined several years later. At a much lower dosage, the compound evolved into adefovir and was ideal for treating the hepatitis B virus. In 10% of the cases it could actually kill the virus.

In the midst of all the activity of readying Gilead’s cidofovir for its approval by the FDA, news of a new anti-HIV treatment shook the scientific community. Three drugs appeared almost simultaneously on the market in 1994, capable of attacking the human immune deficiency virus from another angle, through its protease enzyme.11

After AZT which inhibits the reverse transcriptase enzyme of HIV, these new drugs were another reprieve for people with AIDS. Though short-lived, it kept the hope alive until a miracle breakthrough was announced in 1996 during the International AIDS conference in Vancouver. HAART, the highly active anti-retroviral treatment, was the result of hundreds of researchers toiling in university and pharmaceutical labs. The groundbreaking combination therapy was spearheaded by David Ho, the Director of the Aaron Diamond AIDS Research Center in New York.12 His insights into the reproduction of the virus turned the tide of AIDS.

Until then it was thought that the virus remained in a long, almost dormant, state before it attacked the body’s immune system in full force. Instead, David Ho found that the virus started replicating and mutating itself furiously as soon as it had entered the body. HAART’s success was due to its ability to block two of the virus’s crucial enzymes through the combination of nucleoside and non-nucleoside reverse transcriptase as well as protease inhibitors.

It involved a daunting regimen—requiring some 30 pills per day to be taken at specific times; some with milk and others without, some before a meal and others after. The results were immediate, people who had