Cold War Triangle

Loeckx, Renilde

Published by Leuven University Press

Loeckx, Renilde.
Cold War Triangle: How Scientists in East and West Tamed HIV.

For additional information about this book
https://muse.jhu.edu/book/56628

For content related to this chapter
https://muse.jhu.edu/related_content?type=book&id=2042956
intellectual property ownership. It sent shockwaves throughout the Rega Institute in Leuven. Did De Clercq influence Prusoff when he gave a lecture at Yale in May?

As was the case with AZT and the other dideoxynucleosides synthesized by Jerome Horwitz, the chemical substance of d4T was already described in literature, therefore the patent application could not be for its chemical composition but rather for a method of use. Prusoff had filed a patent after discovering that d4T was not toxic to human cells in cell cultures, but he did not possess any viruses in his lab, let alone HIV. How could he prove the antiviral activity of the compound? One of Prusoff’s postdoctoral fellows, Raymond Schinazi, who had just moved to Emory University School of Medicine to study viruses and immunology with his uncle, a well-known herpes researcher, held the key. He proved in 1987 that d4T was indeed active against HIV.10

Yale had filed the patent first, but Leuven felt they were the first to invent. Could the Rega Institute prove this in court? Would De Clercq start a battle with Yale, and what is more, against one of his best friends, Bill Prusoff? Yet, the goal posts were moving. Demonstration of antiviral activity in cell culture was not enough to support a patent. At that time, the patent office required proof of antiviral activity in human clinical studies. That ruling was not taken into consideration in Leuven. All hopes were still vested in the Dutch patent lawyer while Bristol-Myers was already introducing d4T into human clinical trials.

Although there were never any ill feelings between Prusoff and De Clercq, John Martin put an end to the bickering by inviting them both as co-authors in his article that appeared in “Antiviral Research” in 2010.11
Chapter XI
First attempts to halt the epidemic

One person can make a difference and everyone should try.
— John F. Kennedy

Two irons in the fire: Bristol-Myers and Janssen

De Clercq and Holý’s article about the acyclic nucleoside phosphonates appeared in Nature on October 2, 1986. It was a follow-up to one of their first articles. This time it was even more authoritative: a new class of antiviral compounds was born. Their antiviral activity was captured in Sakuma’s assays and a friendly ophthalmologue in Leuven had tested them on eye infections in rabbits.

The authors received praise from all sides and were courted even more intensely by Bristol-Myers. Talks to acquire a license became more pressing. In order to study the compounds, Bristol-Myers had to copy a few samples. Holý provided them with guidance while De Clercq tested and analyzed the copies. They enjoyed all the niceties that were thoughtfully arranged for them on their visits to the new research facilities in Wallingford, Connecticut: limos waiting at the airport and relaxation time to practice his favorite sport, squash. De Clercq nevertheless remained wary after the d4T episode. But John Martin was so enthusiastic and prophesized: “You will develop something much stronger than d4T. You have phosphonates!”.

As for Tony Holý, every time he visited Wallingford, he went on a shopping spree at the hardware stores. He was always on the lookout for the latest gadgets and tools. Bristol-Myers executives knew Holý was fond of playing pool, so a billiard table was reserved for him and his assistant. Law enforcement officials kept circling around John Martin. They wanted to know what Holý was up to in the United States. They were particularly worried about him taking pictures everywhere with his little camera.
Martin’s mundane responses to their questions, “This time he bought a fancy screwdriver,” exasperated them.

Meanwhile the Rega Institute was expanding Rudi’s AIDS lab with the tremendous support of Jan Desmyter who acted as an all-in-one spokesman, broker and promoter. The activity at the Rega Institute sparked the interest of the legendary Belgian drug maker, Paul Janssen. He had been a friend of Piet De Somer. Both had inspired each other with their ever expanding curiosity and an unquenchable thirst for novelties. Both relentlessly pursued their staff with the same question “Is there anything new to report?” They had an unwritten gentleman’s agreement not to approach each other’s collaborators. Now that De Somer had passed away, “Dr. Paul,” as he was affectionately called by his assistants, invited Erik De Clercq to his stronghold not far from Antwerp.

Beerse was the small town that hosted the pharma installations and several of the office buildings where Paul Janssen had started his company in 1956. He merged it five years later with Johnson & Johnson to allow his laboratory potential to grow. In less than twenty years time he had motivated some 1,300 young people to join his company. He hired them not on the basis of their school or academic degrees but on the basis of their ability to memorize. Next he helped his newly hired men and women expand their knowledge in one or another field, sending them to academic courses and asking them to focus on a specific subject until they became expert medicinal researchers. Even though Janssen pharmaceutical belonged to an American group, it was and still is the pride of Belgium.

By the time De Clercq went to visit Paul Janssen on a grey November day in 1986, his company had already invented more than fifty drugs, five of which had been posted on the WHO’s list of essential medicines. Janssen had also acquired world fame with the opening of his plant in China, being the first western pharmaceutical company to set up a factory in the People’s Republic of China.

Janssen was unable to bring HIV inside his facilities, at that time the virus was still considered too dangerous and AIDS was surrounded by all kinds of taboos. The general public placed the blame for the spread of AIDS squarely on the gay community and anger mounted as more people died. However, Janssen, who had travelled in Africa knew better. He was shocked and obsessed by what he had seen there.
Erik De Clercq knew Janssen only superficially at that time. He had met him socially at functions organized by De Somer, where Janssen’s extroverted wife was always the life of the party. People loved to be in Janssen’s presence, his mastery of any subject from history to architecture to science to linguistics was a pleasure for the mind. It was a great experience for De Clercq to sit down with him for lunch at the local restaurant. They must have talked about everything under the sun because eight hours later they were still sitting in the restaurant. By dinner time they had made up their minds: they were going to work together!

Once Janssen and De Clercq decided to join forces, it took the university establishment another six months to formalize their agreement. Janssen would finance fellows and the Rega institute would examine a library of 600 Janssen compounds as a starting point. It was a splendid boost for the brand new laboratory that had been set up by a student, Rudi Pauwels, who had not even started work on a Ph.D. Yet, AIDS research was now firmly established in the Rega Institute.

When Jan Balzarini returned to Leuven, after his sabbatical year at the National Cancer Institute (NCI) in Washington, his mission was not entirely overtaken. He introduced the system he had gained experience with in Washington on a different floor than the basement laboratory Rudi Pauwels had assembled. They worked in totally separate ways, technicians who learned to work with one system did not want to adopt another way of following the protocols. The Rega Institute now effectively possessed two AIDS laboratories: one based on Rudi Pauwels’s system that soon would acquire world fame and another based on the Broder and Mitsuya method of the NCI.

The NCI had grown in stature not in the least because of Sam Broder’s accomplishment. He had successfully steered AZT (azidothymidine) through regulatory procedures from test-tube to patients in a record-breaking 19 months. The drug was given to patients for the first time in July 1985, the phase two clinical trials starting in 1986 as a double blind study had to be aborted. It was almost immediately obvious that many more people died on the placebo than on the drug. The effects were so immediate and protests in the gay community were so violent that trials had to move straight to the final phase.
Taking stock after AZT

The elation following the FDA’s approval of AZT did not last long. It soon became obvious that the drug had plenty of side effects and only allowed life to be prolonged by a year.

It was nevertheless an occasion for President Reagan to give his first (and only) public speech on the subject of AIDS. The day after he and French Prime Minister Chirac announced that French and the American scientists would share credit for the discovery of the virus, he addressed a conference of medical doctors in Philadelphia in April 1987. Reagan remarked on how American scientists were making rapid progress in identifying and fighting the virus, suggesting that a viable vaccine would soon be available and extolled the miracles that their medicine was producing. He had already greatly increased government spending for the National Institutes of Health after Rock Hudson died and would now double it between 1987 and 1989.1

Although some progress was noticeable in the treatment of “opportunistic infections” that afflicted AIDS patients, the disease could still not be treated with the largely ineffective AZT. By this time the bulk of AIDS research funding had shifted to the National Institute for Allergy and Infectious Diseases; the NIAID was better equipped than the National Cancer Institute to create a national system for coordinating, funding, and directing research to find a treatment against AIDS.

Tony Fauci, a determined immunologist, became the public face of the National Institutes of Health. He was not afraid of stepping into the limelight to engage with gay activist organizations. One of the loudest among them, ACT UP, was founded in 1987 by charismatic playwright Larry Kramer. The AIDS Coalition to Unleash Power had but one objective: to get drugs to those who needed it most. In order to shake up the establishment, it angrily took to the streets. The organization became known for its public disturbance, attention-drawing antics and media stunts such as the creation of traffic jams or the disruption of the communion mass at Saint Patrick’s Cathedral. Other gay associations were more subtle and felt that cooperation and persuasion would be more productive. But Kramer was out to attack everybody including the pharmaceutical companies. ACT UP started by placing pressure on Burroughs Wellcome to lower the price of
AZT from $10,000 to $6,400 a year. Following their first successes, they would demand a seat at the table in many corporate boardrooms and a voice in the FDA decision-making. The high levels of media coverage dramatically raised public awareness of the ongoing tragedy.

AIDS had also become the focus of the nucleosides network, Richard Walker and Erik De Clercq had created. Their third NATO conference was held in May 1987 in Il Ciocco, a beautiful resort in the heart of Tuscany overlooking the medieval town of Barga, once Michelangelo’s marble workshop.

It came as no surprise that the keynote speaker would be the fifty year-old Robert Gallo, now at the peak of his fame. He had restored his good name thanks to the joint announcement of President Reagan and Prime Minister Chirac a few weeks earlier. The settlement with his rival Luc Montagnier felt “like a piece of lead came off my shoulder,” Gallo told reporters. Not long before, he had been the guest of honor at Leuven University where he was awarded an honorary doctorate for his discovery of the human retrovirus that caused leukemia. His detailed descriptions of the behavior of a human retrovirus were crucially important in aiding the science community to tackle HIV.

George Galasso was another stirrer of commotion, albeit on a different level: his talk was a pressing call to arms, to find the drugs to combat HIV immediately. Galasso was one of the leading figures at the NIH. He had himself worked with interferon and was an early supporter of recombinant interferon. He supported many clinical studies through NIH funding. Because of the very effective way in which he assisted drug research and development, he was much appreciated in the nucleosides community. When he spoke at the conference in Il Ciocco, the audience listened closely and took his advice to heart. Gallasso expressed what was on everybody’s mind:

AIDS has helped antiviral drug development. We have made giant advances thanks to AIDS. The prevailing skepticism of the past has given way to optimism and determination. This determination is partially due to recent successes in the field, but more likely the results from the AIDS epidemic. We did not realize the severity of AIDS, the causative agent was just being identified as a virus. It is most unfortunate that a
disease such as AIDS proved to be the needed stimulus to advance antiviral research. We now know more about HIV than any other virus or cell thanks to the urgency of AIDS.

He encouraged the scientists to concentrate on one goal: to identify essential components of the virus specific to HIV and develop methods of blocking them.\textsuperscript{7}

It was the first time John Martin was able to attend a NATO-ASI. As a representative of Bristol-Myers, he encountered two of his “drugs-in-the-making” in the room: Bill Prusoff of the Yale University and the Holý-De Clercq tandem. Prusoff had clinched the victory in the race to file the patent for d4T. This aided Bristol-Myers’s neighborly relations. At a 20 minute distance from each other, Wallingford and Yale University, New Haven were geographically very close.

But John Martin was not impressed by the proceedings of the ten day conference. He shared the scepticism of his friend, Richard Whitley, regarding the strict rules of the NATO-ASI’s. Together with George Galasso from NIH they fomented a quiet revolt and laid the groundwork for a new nucleosides network. It brought together the same mix of people, but more frequently, in annual conferences and without a limitation on the number of American participants. So as not to compete with NATO, they simply convinced De Clercq to join their new venture and ignored Walker’s objections. Thus the third NATO ASI on nucleosides gave birth to a much larger organization: the International Society for Antiviral Research (ISAR). With its annual ICAR conferences, it has become a thriving community of scientists.

Not all participants in Il Ciocco were involved in the projects that were taking shape behind the scenes, they very much enjoyed the lighter moments. An outdoor swimming pool was quickly becoming the main attraction. After all, dainty ladies swimming topless was not something these scientists were used to seeing every day. They also looked forward to one of the highlights of the conference, the excursion to the coast. It was a leisurely drive through the magical Italian landscapes and towns disgorging history, artisanship and colorful markets.

But when they reached the beaches of Marina di Pietrasanta, the group was shaken by a drama that unfolded in front of their eyes. The Japanese
fellow of the Rega Institute, Takashi Sakuma, was taken by an undertow and about to drown in the Thyrrenian Sea. Rudi Pauwels jumped in the water and dragged the almost lifeless body to shore and resuscitated him with chest compressions until lifeguards brought him to the hospital. It was not the first time Rudi Pauwels saved someone’s life. He had saved a technician who had fallen out of a kayak on a turbulent river in the South of Belgium. The incident solidified Pauwels “can do” reputation forever. His homecoming to Leuven was nothing short of triumphant.

**Holy’s compound is active against HIV**

Nothing daunted or deterred Rudi Pauwels. His energy was unwavering, his output prodigious. Now that Janssen’s financial support was kicking in, he became even more zealous. The two man-team he formed with his Japanese colleague and friend, Masanori Baba, attracted other talents as well. A young immunologist, Dominique Schols, liked the idea of becoming a “Janssen fellow.” Coopting him would not only result in an inflow of new skills for the virology department, but also meant acquiring equipment that was previously reserved for the immunology department only: the FACS machine, a top of the line fluorescent automated cell sorter, which Schols adapted for their HIV research.

Erik De Clercq could not be more pleased. He felt his dream team was taking shape; Dominique Schols became involved with two HIV laboratories and liaised between them. Both groups always coalesced around De Clercq’s treasure chest—the room where he kept his vast and ever expanding collection of compounds neatly stored in refrigerators and from where he issued instructions to each of his technicians and assistants. The enthusiasm and energy generated by the new team was infectious, and attracted an even wider circle of young scientists. Together, they worked long hours, sometimes through the night.

On one of Rudi’s forays into Erik’s treasure chest, he found the compounds from Prague and started to assay PMEA. Its antiviral activity had already been known, but Rudi discovered it could work against HIV as well! Years later, the compound also became a hepatitis B treatment. Erik De Clercq found another compound from the Holy collection, HPMPC, to be a strong antiviral, albeit not against HIV. A decade later, the FDA
Almost simultaneously a package of compounds from the Showa University in Tokyo arrived, courtesy of the Japanese co-workers in Richard Walker’s lab. The Japanese compounds were named HEPT and resembled acyclovir; the next logical step was to test whether they could be effective against the herpes viruses. But De Clercq’s intuition told him that they would not, which proved indeed to be the case. Masanori Baba then looked at the Japanese compounds in Rudi’s HIV lab, repeatedly testing them. They concluded that HEPT belonged to a new class of antivirals with anti-HIV activity. Similar compounds were discovered at Merck as well and were given the cumbersome name, non-nucleoside reverse transcriptase inhibitors (NNRTI). This new class of antivirals used a different method to thwart HIV’s invasion of human DNA than the Acyclic Nucleoside Phosphonates. Soon, other non-nucleosides were also discovered, but this time from the Janssen library.

All these exciting discoveries raised the curtain for a new generation of drugs. They had unmistakably influenced and quickened the pace of the triangular negotiations with Bristol-Myers and the Czechoslovak Academy of Sciences. Everything was readied for the concluding session in Prague: Erik De Clercq as the representative of the Rega Foundation and Julius Vida representing Bristol-Myers were the two foreigners confronting a gaggle of more than twenty Czech lawyers, Communist party bosses as well as the leadership of IOCB and members of Inventia, the Office for the Protection of Intellectual Property; all were in a combative mood.

They were determined not to repeat the bungling that ensued from the licensing of Otto Wichterle’s soft lens to an American company. The deal was poorly negotiated by the Academy of Sciences, at that time still under the leadership of František Šorm. The most comprehensive technology transfer from East to West in the sixties had developed over the years into a tremendous commercial success. Both the Academy in Prague and the inventor had remained largely unrewarded.

But before tackling Bristol-Myers, the Czech lawyers wanted to review the patents that De Clercq and Holý shared. They proposed that the chemist receive a higher reward than the virologist. After all it is the chemist who synthesizes the compound. Who is the creator, the inventor?