Cold War Triangle

Loeckx, Renilde

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Brussels. The Brussels team had the know-how to find the particular interferon messenger RNA that would be converted into DNA in Ghent University. The gene could only be identified indirectly through its ability to elicit interferon messenger RNA. To pick out the gene from within ten thousand bacterial clones was a formidable task. Once the gene was isolated and properly identified, interferon could be engineered. It was then sent to Erik De Clercq’s lab to assay the results. The Belgian group confirmed their results in two articles in *Nature* in 1980, their interferon was renamed beta interferon. The race to clone interferon gamma was won by Genentech in October 1981.

Once the genes had been isolated, the chemical structure could be revealed and the way to the mass production of human interferon was wide open. The lack of “pure” interferon in sufficient quantities at a reasonable cost was no longer an obstacle to progress. In less than two years, more insight was gained than in the preceding twenty years since interferon’s discovery. The pharma industry made plans to produce interferon to treat an assortment of malignancies such as hepatitis C, bladder cancer, multiple sclerosis, bird flu and SARS.

In a review entitled “Interferon: A Molecule for All Seasons,” Erik De Clercq summed up the interferon story. What better way to leave the field than to give it an accolade? Now that he had met Walker’s challenge to prove that interferon was not a dream, De Clercq could move on to explore new fields. He was now ready to concentrate on the world of nucleosides.
Chapter VIII
The first antiviral drugs

*Most scientific discoveries belong to a continuous, collective process of exploration of nature rather than a series of individual explosions of imagination.*
— Salvador Luria

**NATO supports a nucleosides network**

Erik De Clercq was introduced to the North Atlantic Treaty Organization and its *Advanced Study Institutes* in the most enjoyable way. He was selected to travel to the idyllic Greek island of Corfu together with about a hundred other investigators. The workshop tackled antiviral mechanisms and attracted a fine group of medical doctors and virologists.¹ De Clercq’s old friend, David Shugar, was one of the stars of the meeting. Nobody paid any attention to the fact that his scientific homestead was based in Poland, not exactly a NATO country at the time. His Canadian passport was all he needed to gain a spot at the speaker’s podium.

Another researcher from the National Institutes of Health, Robert Gallo, then barely forty years old, caught De Clercq’s attention. He had plenty of nervous energy. Erik immediately felt he was a kindred spirit, one of the few people who shared his passion for retroviruses. A retrovirus with its unique enzyme was a hot topic for scientists in the early 1970s, but a few years later no longer seemed interesting. It was considered to be at the periphery of the grand questions of modern biology. Gallo, however, was determined to prove that retroviruses could disrupt not only animals but also humans. He was on a hunt to find at least one retrovirus that caused cancer in humans.²

Gallo was immediately interested in Erik’s discovery of a substance that was active against the Moloney murine leukemia virus, an animal retrovirus. The substance could contain the replication of the retrovirus,
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but unfortunately had no effect on the cancer cells. Its common name was suramin, a compound known since the 1920s and used in treatment of African sleeping sickness, a tropical disease caused by microscopic parasites.

Rather than dismissing De Clercq’s findings, Gallo encouraged Erik to publish this story in his Journal Cancer Letters. Gallo’s suggestion came as a total surprise. So far, no publisher had shown any interest in De Clercq’s findings on polynucleotides and retroviruses. The reviewers claimed that its enzyme, reverse transcriptase, had no biological relevance. De Clercq’s article appeared in one of the Journal’s 1979 issues. Five years later, it would suddenly come to the fore when NIH scientists were desperately seeking a means to combat another retrovirus, the AIDS virus.

After their meeting in Göttingen, Richard Walker and Fritz Eckstein asked Erik De Clercq to join them in developing a nucleosides network. The three men felt it was important for scientists to step out of the laboratory, confront theories and exchange test results with people coming from different backgrounds. Rather than confining scientists to their field of expertise, their platform would bring together virologists, chemists, pharmacologists, clinicians, and representatives of the pharma industry.

Richard Walker brought his experience from the publishing world to the table. Fritz added his prestige and that of the Max Planck Institute, while Erik would take care of all administrative questions. With that, they started working on their common project. All they needed now was to find an attractive place in relaxed and pleasant surroundings for their meetings. And what could be better than the Italian countryside?

Searching for ways to fund these gatherings, De Clercq’s experience in Corfu served as an inspiring model. NATO’s scientific affairs division would be a perfect partner. It provided the funding and means to gather scientists from both sides of the Atlantic. For young scientists, it was truly a blessing to participate in such a forum. In the seventies and eighties, communications were still rudimentary. The personal computer and internet were not yet commonplace. The photocopier and fax machine were the only sophisticated devices available at that time.

The NATO administrators set strict conditions: The Advanced Study Institute (ASI) could only include scientists from NATO member countries; no country, not even the US, could be overrepresented with more than
twenty participants. One truly remarkable rule was that the study courses had to take place over a period of at least ten days. It was believed that a minimum of ten days together was necessary to build the kind of lasting relationships that can serve as a cornerstone for productive science.

Walker, Eckstein and De Clercq worked diligently to select the 100-odd participants for their NATO-ASI. The first course took place in May 1979 in Sogesta, close to Urbino, in central Italy. They abided by the rules of inviting only scientists from NATO member countries, but decided to test the limits. Could they add a scientist from a communist country if they covered the costs? They did not explicitly ask and did not get a formal refusal either. So, they selected Peter Langen from East Germany, financed by FEBS, the Federation of European Biochemical Societies. The workshop carried a promising headline: Nucleoside Analogue Chemistry, Biology and Medical Applications. Richard Walker was going to be the master of ceremonies. He would introduce the speakers and weave a common narrative through their presentations.

Walker was driven by the deep-seated dissatisfaction with the way the work of chemists was treated. He felt that in the past few years many useful and potentially useful nucleoside analogues had been synthesized but little more had been done with them beyond a few perfunctory biological tests. He recognized there was a dearth of adequate knowledge about the available testing procedures.

In the proceedings of the first NATO ASI, Walker did not mince his words. He expressed his irritation over a lack of communication between the chemist, pharmacologist and the clinician. As a result, he believed that few compounds received the testing and evaluation they deserved. Another cause of Richard Walker’s frustration was the fact that so much attention and research money was going to interferon and not enough to nucleosides research. He was pleased to introduce a company that was an exception to the rule: Syntex, the first pharmaceutical company in Silicon Valley. It had made its fortune thanks to some blockbuster products like “the pill,” the first effective oral contraceptive. Very early on its Institute of Molecular Biology explored the effects of nucleoside analogs on nucleic acids biosynthesis and cell growth. Around 1970, the management of Syntex abolished its Institute of Molecular Biology. But John Moffatt, however, as the head of the new research department, kept the
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tradition and skills alive.\textsuperscript{7} Two of his brightest co-workers, John Martin and William (Bill) Lee later used these skills to develop some of the best anti-HIV drugs that came on the market in the twenty-first century.

At Sogesta in May 1979, John Moffatt was one of the most captivating speakers. He was glowingly introduced by Richard Walker. He and Moffatt shared a common connection, a formidable mentor: the charismatic Indian-American chemist, Gobind Khorana who received the Nobel Prize in Medicine in 1968. John Moffatt was among the few graduate students ever trained by Khorana while Richard Walker was one of the many postdoctoral fellows coming from Khorana’s orbit.\textsuperscript{8} Their mentor’s love of nucleoside and nucleotide analogs was infectious and permeated the atmosphere of the first NATO course. The sojourn into this medical frontier was an exciting experience for all participants and had them yearning for more.

\textbf{Bringing antiviral therapy to the clinic}

Now that Erik De Clercq had his boss’s blessing to devote himself entirely to nucleosides research, he also had to suffer the consequences. Even though De Somer was now the rector of the university he still kept a close watch on his institute. Just about every day, Piet De Somer made the rounds in the Rega Institute, relentlessly asking the same question, “And? Did you find anything new, anything that could become a drug?”

A drug in De Somer’s eyes meant something to try out on human beings, if needed, on himself. If the compound from Birmingham, UK was indeed active against one or two types of the herpes family, there was no better way to find out than to test it on his patients. Luck lurked just around the corner. An urgent phone call came from the university clinic begging for “something” to alleviate the pain of a nun. She was suffering with cancer and had also acquired herpes zoster, better known as “shingles.” De Somer thought it was an ideal opportunity to try out the British-Belgian compound, BVDU. “If it works, it’s another milestone in antiviral drug development, if it doesn’t and worse, if the nun succumbs, you should not worry, she will go straight to heaven,” he told De Clercq.

The nun survived and the shingles miraculously disappeared. A few weeks later, a prominent speechwriter of Piet De Somer, then rector of