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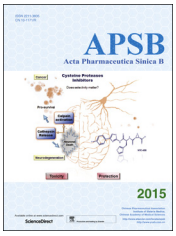

FEATURE

An Odyssey in antiviral drug development—50 years at the Rega Institute: 1964–2014

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KEY WORDS

Erik De Clercq; Antiviral drug; Poly(I)·poly(C); Polyacrylic acid; Interferon; Reverse transcriptase; Suramin; Valaciclovir; Brivudin; Stavudine; Tenofovir disoproxil fumarate (TDF); Truvada®; Atripla®; Complera®/Eviplera®; Stribild®; FV-100; Mozobil®; Tenofovir alafenamide (TAF); Holý's legacy; Sofosbuvir

I. How it started

I entered the Rega Institute for Medical Research in August 1964, as a medical student, to start working under the guidance of Prof. Piet De Somer, then professor of microbiology at the Leuven School of Medicine. When I graduated as medical doctor (MD) in 1966, I hesitated between a clinical career in Internal Medicine or a scientific career in experimental research, the latter under the tutorship of Prof. De Somer who persuaded me to work on interferon (inducers). The discovery of the interferon-inducing capacity of double-stranded RNAs, such as poly(I)·poly(C), by Maurice Hilleman's group at Merck in 1967 would prove of key importance in my decision to engage in interferon research. In 1968 I described the induction of interferon by polyacrylic acid and polymethylacrylic acid; one year after Thomas C. Merigan at Stanford University had described interferon induction by pyran copolymer. As a postdoctoral fellow at Stanford (from 1968 till 1970), I discovered, with T.C. Merigan, several new polynucleotides as inducers of interferon. Upon my return to Leuven at the end of 1970, I picked up a new line of research, that of the reverse transcriptase (RT), which had just been discovered by Temin (and Mizutani) and Baltimore. In 1975 I then discovered suramin as a potent RT inhibitor (published in 1979), and this prompted Mitsuya and his colleagues (including R.C. Gallo and S. Broder) to evaluate suramin as a potential anti-HIV agent.

2014 (August 2014 to be precise) marks the 50th anniversary of my arrival, in 1964, as a 23-year old medical student who had just passed his 5th year medical studies (second doctorate), at the Rega Institute. I do not recall it as "une entrée joyeuse" ("blijde intrede"), but only as a "let us try and see". That my stay at the Rega would finally last for 50 years could hardly be anticipated, at the beginning of an uneventful start of what later could be considered as an equally uneventful career. At the age of 18, right on time, I finished high school ("Oude" Grieks-Latijnse Humaniora) at the Heilige Maagd College (HEMACO) in Dendermonde. As Primus Perpetuus, being the first of my class from the age of 12 till 18th (Fig. 1), I was predestined to become a priest, certainly after having studied the classical humanities (Greco-Latin), but I did not feel like being summoned by any providence or superior force. Instead, I thought of mathematics, physics, chemistry or chemical engineering, algebra being my favored course at high school, but to further enroll at the

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Figure 1 Photograph of class Retorica, 1958.

university in engineering, I would have to follow a preparative year, which for medicine was not necessary, and my mother dreamed of seeing her only son becoming a medical doctor in general practice. She won! Mainly because the heavy emphasis on chemistry in the first undergraduate year of the medical school. And there I went! The first year at the university was partially successful. I passed the first year with "distinction", the second year, I got "great distinction", and the third year, as the only of my class, I climbed up to "greatest distinction", by surprise, I should admit, as I did not feel I deserved such accolade which I rather saw as a discrimination. Meanwhile, I had started to work in the laboratory as a "free" student. This was expected only from the best students, and advised by Prof. Xavier Aubert, professor in physiology (at the future UCL) and son-in-law of Prof. Albert Dalcq (Université Libre de Bruxelles, ULB), also permanent secretary of the Royal Academy of Medicine. I was parachuted in the laboratory of a certain Prof. Raymond Devis (Laboratoire de Chimie Hormonologique). I missed the opportunity to start working in the laboratory of Christian de Duve (who in 1974 would be honored by the Nobel Prize in medicine or physiology, but this was not obvious (yet) around 1960, although de Duve's basic discovery of the lysosomes is going back till 1955). I spent a lot of time in Prof. Devis' laboratory, trying to set up an analytical test for catecholamines through some spectrophotometric techniques, but this work carried out in the period of 1960 till 1963, despite encouragements and flattering comments of the professor concerned, never resulted in any publication. Adding to the disenchantment was that I worked in a French speaking laboratory, which in the wake of the imminent separation of the university in a Flemish and French speaking section, gradually became an untenable situation for Flemish-speaking students of the then called Université Catholique de Louvain (UCL). The fact that I spent my time in a French-speaking laboratory was only a small part of the problem, the major part being it was not an inspiring environment for any significant accomplishment or prospect thereof.

In 1963, at the exam of microbiology (bacteriology), Prof. Piet De Somer, who must have been informed of the fact that I was not tremendously enthralled by my "séjour" in Prof. Devis' laboratory, offered me the opportunity to come to work with him at the Rega Institute, on viruses. My first reaction was "No, thank you. I do not want to work on viruses, just chemistry". When my fellow students and in particular, the preses of the medical students, Olav Leuridan, heard that I had declined an offer of Prof. De Somer, who at that time was already Scientific Adviser to the Rector Magnificus of the university (Monseigneur Descamps), he told me I had to be stupid to refuse such an offer. In 1964, again at the exam of microbiology (virology), Prof. De Somer asked me once more whether I had in the meantime changed my mind, and I gladly told him "I had" and that I would start working in his laboratory on "the chemistry related to viruses", whatever that meant. For De Somer, it meant "interferon". The discovery of interferon by Isaacs and Lindenmann in 1957, had made De Somer very enthusiastic about the prospects of interferon as a broad-spectrum antiviral agent, and he wanted to transmit this enthusiasm to myself. At the time, interferon was still an esoteric principle rather than a molecule, and many chemists I talked to even doubted that this molecule really existed, but De Somer believed in it (in 1976 he would lose his belief in "interferon"), and he could persuade me to start working in his laboratory, originally not on interferon, but on rubella, in setting up an immunofluorescent technique to detect antibodies against rubella virus, and following up on the production of these antibodies in rabbits given the rubella virus vaccine (this was the Cendehill strain vaccine that was later commercialized by RIT, and, is as of today, still part of the GSK vaccines against measles, mumps and rubella). This work gave rise to sort of a master's thesis which I must have completed in 1965. For Prof. De Somer, it was sufficient to drag me into research and start a scientific career. In July 1966 (Fig. 2), I finished my MD studies, graduating as first of the class with the greatest distinction, and Prof. De Somer was there at my graduation, to tell me he had been of some help in securing that I got the greatest honor ("maxima cum laude"). It was not in vain: being confronted with the option of starting a career in internal medicine (with Prof. Jozuë Vandenbroucke) and a career in science (with Prof. Piet De Somer), I first settled for a 50%–50% solution, which later on became 100% De Somer, and so in August 1966 I started to work, now full time, in the laboratory of Prof. De Somer. While in 1964, Prof. De Somer had tried to couple me to an older colleague Prof. Alfons Billiau, I had told him by December 1964 that I wanted to work independently,