Editorial Review

Antiviral research at the Rega Institute (KU Leuven), now 50 years old

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Introduction

The Rega Institute has been associated throughout its history with fundamental and applied research in microbiology, virology, immunology and medicinal chemistry. The breadth of research at the Rega Institute is the legacy of its founder, Professor Pieter De Somer. His original research led to the designing and building of a fermentation plant for the production of penicillin – a successful venture which led to the establishment of the pharmaceutical company Recherche et Industrie Thérapeutiques (RIT) in 1950, later to become SmithKline RIT, and now part of GlaxoSmithKline (GSK).

In 1954, De Somer founded the Rega Institute (named after an 18th century rector of the university) to promote research in microbiology. He was joined by H Vanderhaeghe, and later by H Eyssen, M Vandeputte, A Billiau, J Desmyter and E De Clercq. In 1970, the Rega Institute separated from RIT (when RIT was incorporated in the SmithKline and French concern), to become an integral part of the university.

Notable achievements in the Institute's first decade included the discovery of the antibiotics clometocillin and virginiamycin, the upscaled production of the (dead and live) polio vaccine, and the initial steps in the development of the rubella vaccine. From the late 1950s, Professor De Somer's interest turned to interferon, and the Rega Institute soon acquired a high-level reputation in the interferon and antiviral research field, reflected today by the Institute's track record in the discovery of a number of cyto- and chemokines, and antiviral substances for the treatment of a wide variety of virus infections.

Hendrik Jozef Rega (1690–1754)

As patron of the now 50-year-old Institute, founded in the period of the unitary and bilingual (Flemish/French) Catholic University, a famous professor of the Old University of Leuven during the early 18th century, Hendrik Jozef Rega (1690–1754), was chosen (Figure 1). After obtaining a medical degree in Leuven, and further studies in Paris, Rega was first appointed to the Chair of Chemistry in 1716. In 1718 he took a doctorate and, 1 year later, was appointed as *professor primarius* in clinical medicine. In 1719 and 1722 he served as rector of the university, twice for half a year as was then customary. HJ Rega was not only a scientist and a builder (part of the University Hall is still known as the Rega wing), but also a general practitioner, treating the wealthy and the poor, and having the reputation of kindness towards his patients. It is mainly because of the existence of the Rega Institute that the name and fame of this remarkable figure of the early 18th century is still alive. For 50 years his name has provoked among many at first a certain curiosity but then reminds them of the famous past of medical science at the Old University of Leuven.

Rector magnificus Mgr Honoré Van Waeyenbergh (1891–1971)

When in the 1950s the initiative for the creation of the Rega Institute was taken, the university was a completely different institution from as it is today, being still bilingual. Then, the university was led by Mgr Honoré Van Waeyenbergh. Rector Van Waeyenbergh was aware of the growing importance of scientific research as the cornerstone of the University, and had to face a growing diversification and the development of new autonomous institutes. More than in any other faculty, expansion was visible in the Medical School and the University Clinics. In this atmosphere of growth, the rector magnificus Mgr Van Waeyenbergh, in the presence of the founder of the institute, Pieter De Somer, could solemnly lay the first stone of the new Rega building at number 10 of the Minderbroedersstraat, then also known as the Rue des Récollets (Figure 2). He expressed the firm hope that this institute would grow in importance as a centre of research.

Figure 1. Hendrik Jozef Rega (1690–1754)

Figure 2. Commemorative stone Rega Institute anno 1954

Professor Dr Pieter De Somer (1917–1985), founder of the Rega Institute and rector of the KU Leuven

A university student in Leuven since 1936, Pieter De Somer (Figure 3) enrolled in the medical faculty to obtain his medical doctor's degree in 1942. After obtaining his degree, De Somer stayed at the university as an assistant to Professor Richard Bruynoghe, who was a specialist in bacteriology. It was in a cellar of his laboratory and in primitive circumstances that De Somer started his search to develop penicillin. In the late 1940s, with the financial support of Jacques Lannoye, a Walloon industrialist, he created the pharmaceutical industrial company RIT in Genval/Rixensart, which, in turn, made possible the foundation in 1954 of a research institute (called 'Rega') in Leuven. The new institute was to acquire international fame in the field of antibiotics and, later, vaccine and interferon research.

In 1962, the new archbishop LJ Suenens appointed Mgr A Descamps as rector, and decided that the faculties would be split along language lines, so that Flemish- and French-speaking sections of the university were created. At the head of each section were appointed a pro-rector, a vice-rector, an administrator-general and a scientific advisor. On the Flemish side, it was Pieter De Somer who fulfilled the last function. In the following years, the two linguistic communities would drift further apart. The bishops then appointed Pieter De Somer with the title of pro-rector as head of the Flemish section. De Somer immediately started the reorganization of 'his' university. Starting with the academic year 1968–1969, De Somer could preside over the opening ceremony of the academic year as the full rector of the new Flemish 'Katholieke Universiteit Leuven'. Meanwhile, he remained head of the Rega Institute, following the research, depending on the subject, from a close or far distance, but leaving the daily leadership to his direct 'acolytes' Hubert Vanderhaeghe, Hendrik Eyssen, Michel Vandeputte, Alfons Billiau, Jan Desmyter and Erik De Clercq and their collaborators.

Pieter De Somer would remain rector for the rest of his life. He reorganized the university and provided it with new structures. He introduced the participation of scientific personnel and students at different levels, and organized a system of elections for the rector every 5 years. He saw himself re-elected by the academic community in 1971, 1976 and 1981. In that long period, he succeeded in consolidating and expanding the university. He oriented it more towards the Anglo-Saxon academic world, and by doing so he preserved and strengthened its international reputation. He also defended the position of the university on the vanguard of modern Catholicism by maintaining an honest intellectual openness and tolerance. A symbolic

Figure 3. Pieter De Somer (1917–1985)

confirmation of this concern came when Pope John Paul II visited Leuven on 20 May 1985. De Somer pleaded in his speech for space within the church for autonomous research and freedom of action, even freedom of error in searching for the truth; it was his last public address. On 17 June 1985, Rector De Somer passed away, the victim of an illness that had afflicted him for the last 3 years of his life.

The Rega Institute (1954–1971)

It all began in the post-second world war period, when a young assistant in the Laboratory of Microbiology, the later Professor and Rector Pieter De Somer, aimed at the large-scale production of penicillin, which during the second world war had proved of revolutionary importance in the treatment of bacterial infections. After having founded the pharmaceutical company RIT in Genval/Rixensart, Pieter De Somer founded the Rega Institute in 1954 (Figure 4), under the rectorate of the Mgr Honoré Van Wayenbergh and with the support of the industrialist Jacques Lannoye [as reflected in the commemorative stone of the Rega building (Figure 2)].

During the early years, focus at the Rega Institute was on the search for new antibacterial agents (antibiotics), but from 1955 onwards there was a gradual move toward the search for antiviral prophylaxis and therapy. The new building erected on a terrain of the university, close to the Medical Campus, was financed entirely by RIT, which also provided financial support for research. In the agreement with the university, the building became its property, but in return, for a period of 50 years, RIT had the right to bring the Institute's research achievements to commercial exploitation. This led to a close collaboration between the Institute – where fundamental research was done in the field of infectious diseases – and the Research and Development section of RIT, where the products of 'Rega' research would be developed into new medicines. It was a first and unique example of a joint venture between university and industry, and 3 years after the start of this program, RIT, as one of the first companies in Europe, succeeded in the industrial production of penicillin. In the following years, the activities were expanded to include the production of streptomycin, chlortetracycline, tetracycline, virginiamycin and clometocillin. The last two antibiotics were discovered in Leuven.

In the field of virology, the first research activities were concentrated upon polio(myelitis) virus, resulting in the development of a sero-neutralization assay and a potency-test for the killed poliovirus, recognized by the World Health Organization. This work laid the basis for the development of the inactivated (Salk type) polio vaccine, and, later, of the live attenuated (Sabin type) polio vaccine, which was then produced on a large scale by RIT and distributed in Belgium and several other countries. Also, the live attenuated rubella vaccine (Cendehill strain), which is now used worldwide, was pioneered in the early years of the Rega Institute.

The discovery of interferon in 1957 by A Isaacs and J Lindenmann meant a new élan for the virological team of Prof P De Somer, who then used poliovirus as a model to unravel the mechanism of antiviral action of interferon. The work of De Somer's team on interferon would

Figure 4. The Rega Institute for Medical Research

ultimately lead to the unravelling of several aspects of the mechanism of action and induction of interferon as well as the development of procedures for mass production of interferon.

In 1968 – at a time when Pieter De Somer had become the first rector of the autonomous Flemish University of the KU Leuven – the shares of RIT fell into the hands of the Philadelphia-based American pharmaceutical company SmithKline and French (SK&F). SK&F at first chose a continuation of the original agreement between the university and RIT, but gradually internal difficulties within the company led to a reorganization of the research there. Meanwhile, in the Rega Institute divergent opinions developed on the chances and dangers of a joint venture of university with industry, stimulating discussions on the policy concerning priorities in the research projects. Those tensions, also affected by the departure of the French-speaking part of the university from Leuven, resulted in the dissolution of the contract between SK&F and the Rega Institute in 1970.

When in July 1971 a new law on university expansion passed through parliament, it was only just in time. It created a supplementary parallel system of financing, channelled through the National Fund of Scientific Research, contract research and special research programs launched by the government. At Leuven University – largely due to the stimulating policy of De Somer – the portion of research financing increased significantly, so that at that time almost three-quarters of the sum granted to the KU Leuven through the parallel financing program originated from the national government. The Rega Institute also benefited from this new resource.

At that time, the Rega Institute was incorporated in the new Flemish University KU Leuven, as one of the showpieces of its first rector, Pieter De Somer. It remained mainly in its original building, Minderbroedersstraat no. 10 (Figure 4), with an extension *extra muros* to Kapucijnenvoer 35. Eventually it became one of the (now) eleven departments of the Faculty of Medicine, comprised of five divisions: Virology and Chemotherapy (E De Clercq, J Balzarini, D Schols, J Neyts, L Naesens, C Pannecouque, R Snoeck and G Andrei), Bacteriology (J Anné, J Van Eldere and J Verhaegen), Clinical and Epidemiologic Virology (A-M Vandamme, M Van Ranst), Immunobiology (G Opdenakker, H Heremans and P Matthys) and Molecular Immunology (J Van Damme and P Proost), as well as the Division of Medicinal Chemistry (P Herdewijn, R Busson, J Rozenski and A Van Aerschot) belonging to the Faculty of Pharmaceutical Sciences. The research accomplished at the Division of Virology and Chemotherapy, to an appreciable extent resulting from a collaboration with the other divisions, is highlighted in the following pages.

The Rega Institute (from 1971 onwards): Division of Virology and Chemotherapy

From 1971, the main experimental efforts of what later became the Division of Virology and Chemotherapy at the Rega Institute were concentrated on two fields. Firstly, the search for new inducers of interferon and the structural requirements for interferon inducers to be able to induce interferon and, secondly, the search for inhibitors of reverse transcriptase, an enzyme that just had been discovered by H Temin and D Baltimore, and that a few years later would win them the Nobel Prize for physiology and medicine. Following the interferon line, many new interferon inducers, primarily double-stranded polynucleotides were described, and in collaboration with PF Torrence [then at the National Institutes of Health (NIH)] the role of double-stranded RNA as inducer of interferon during viral infections was documented (for a review, see, for example, Carter & De Clercq, 1974). This line of research is still continuing today, as interferon and its inducers (in particular, double-stranded RNA) have been found to be effective in the therapy of Coxsackie B virus-induced myocarditis (Padalko *et al.*, 2004) and flavivirus-induced encephalitis (Leyssen *et al.*, 2003) in mice. These observations point to the potential usefulness of interferon and interferon inducers in the therapy and/or prophylaxis of viral myocarditis and encephalitis in humans.

Also following the 'interferon' line, a major breakthrough in interferon research was accomplished in 1980 through a collaborative effort between the University of Ghent (with Walter Fiers), the Brussels Pasteur Institute (with Jean Content) and the Rega Institute, that led to the cloning and expression of human interferon-β (Derynck *et al.*, 1980a,b). Human interferon-β was originally hailed as a treatment for cancer, but later used as the treatment of multiple sclerosis. A secondary protein, interferon-β2, was discovered (Content *et al.*, 1982) which was later know as interleukin-6, and is still one of the best-known cytokines.

Following the 'reverse transcriptase' line, suramin was discovered (De Clercq, 1979) as a specific inhibitor of this enzyme in retroviruses, such as murine leukaemia and sarcoma viruses. This finding went greatly unnoticed, as at the end of the 1970s retroviruses were still looking for a disease in humans and therefore not taken very seriously. It all changed in 1981 with the advent of AIDS and the identification, two years later, of HIV as the aetiologic agent of AIDS. Suramin, based on our earlier observations (De Clercq, 1979), became the first antiviral drug to be found active against HIV (Mitsuya *et al.*, 1984) and to be used in the treatment of AIDS (Broder *et al.*, 1985). Because suramin was too toxic to be used in HIV patients, it was soon to be replaced by azidothymidine (AZT, zidovudine), which is nowadays still used in the treatment of AIDS.

Suramin, however, made it clear that a chemotherapeutic approach for treating AIDS was not a utopian goal.

Our further work on anti-HIV agents led to the discovery of several AZT-like dideoxynucleoside analogues [such as stavudine (d4T)], described for the first time by our research team as a powerful inhibitor of HIV replication (Baba *et al*., 1987; Balzarini *et al*., 1987). This compound would ultimately be commercialized, as part of different drug combination regimens, for the therapy of AIDS.

In 1976, as a consequence of the *Symposium on Synthetic Nucleosides, Nucleotides & Polynucleotides* in Göttingen, several collaborative projects were initiated, one with the late Richard T Walker (University of Birmingham, UK) and another one with Antonin Holý [from the Institute of Organic Chemistry and Biochemistry at the Czechoslovak (now Czech) Academy of Sciences, Prague]. The collaboration with the chemists of Birmingham led to the identification of an exquisitely potent antiviral agent, BVDU (bromovinyldeoxyuridine) (De Clercq *et al*., 1979) (Figure 5), that after a rough start was eventually commercialized (first in Germany and then in other European countries) for the systemic treatment of herpes zoster infections (shingles) (De Clercq, 2004). The collaboration with Holý quickly led to the identification of a broad-spectrum antiviral agent, DHPA (dihydroxypropyladenine) (De Clercq *et al*., 1978), later to be marketed in the Czechoslovak Republic for the treatment of herpes labialis.

This was only the prelude to the major breakthrough that came in 1986 with the discovery of a totally new class of antiviral agents, the acyclic nucleoside phosphonates (De Clercq *et al*., 1986) (Figure 5), which brought a new dimension to the antiviral therapy discipline. From this class of compounds, three have been licensed for clinical use: cidofovir, for the treatment of cytomegalovirus retinitis (an eye infection that in AIDS patients may lead to severe visual loss and blindness); adefovir dipivoxil, which is now used worldwide in the treatment of chronic hepatitis B virus (HBV) infection (a disease for which more than 300 million people are at risk and that may ultimately lead to cirrhosis and primary liver cancer); and tenofovir disoproxil fumarate, which has become one of the key components in the drug combination regimens ('cocktails') used in the treatment of HIV infections (AIDS), and that, based on experimental findings in monkeys with simian immunodeficiency virus, should also be effective in the prevention of HIV infections. Thus it could well substitute for an AIDS vaccine that after so many years of concentrated efforts still remains further off than ever.

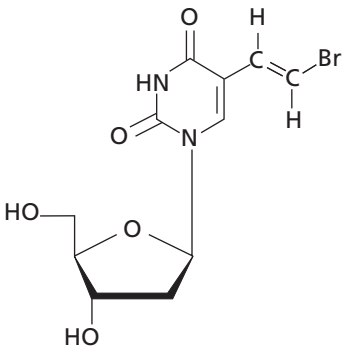
All the aforementioned acyclic nucleoside phosphonates were licensed to, and marketed by, Gilead Sciences. It should be mentioned that John C Martin and his staff at Gilead have played an invaluable role in the industrial development of this class of compounds. Meanwhile, cidofovir has also proved efficacious in the treatment of a number of DNA virus infections, including papilloma-, adeno-, herpes- and also poxvirus infections. In fact, cidofovir is the only drug on the market that has so far been reserved (and stockpiled) for potential use in the prophylaxis and/or therapy of the complications of the vaccination (with vaccinia virus) against smallpox, or of smallpox should the aetiologic agent thereof (variola virus) be inadvertently released through a bioterrorist attack. Also, in collaboration with A Holý we have recently identified a new class of acyclic ('alkoxy') nucleoside phosphonates [Balzarini *et al*., 2002; Holý *et al*., 2002; De Clercq E *et al.,* Antiviral potential of 'new' acyclic nucleoside phosphonates, the 6-[2-(phosphonomethoxy)alkoxy]-2,4-diaminopyrimidines. *16th International Round Table on Nucleosides, Nucleotides & Nucleic Acids*, 2004, Minneapolis, USA] that are again active against a broad range of hepadna-, retro-, herpes-, adeno-, papilloma- and poxviruses and that may ultimately be developed as antiviral drugs.

The efforts of the Rega AIDS research team have not only yielded 'nucleoside' and 'nucleotide' types of reverse transcriptase inhibitors for the treatment of AIDS, but in the years 1988–1990 also led to the identification of an entirely new class of reverse transcriptase inhibitors, the 'non-nucleoside' type (Figure 5). This class interacts with the enzyme at an allosteric, non-catalytic site, distinct from the site of interaction of the deoxynucleoside triphosphate metabolites. This new principle for the therapy of HIV infections, which later became applicable by the clinical use of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine, delavirdine and efavirenz, was originally demonstrated for the so-called HEPT analogues (in collaboration with investigators at Showa University) (Baba *et al*., 1989; Miyasaka *et al*., 1989) and TIBO analogues (in collaboration with the late Dr Paul Janssen and the Janssen Research Foundation) (Pauwels *et al*., 1990). Further work along these lines would lead to the identification of various other classes of NNRTIs, including the α-anilinophenylacetamides (α-APAs) (Pauwels *et al*., 1993), the TSAO-T derivatives (Balzarini *et al*., 1992; Camarasa *et al*., 1992; Pérez-Pérez *et al*., 1992) and the thiocarboxanilides, which are currently being pursued as topical microbicides (Balzarini *et al*., 1996, 1998).

In the early 1990s we discovered, based on an impurity present in a commercially available cyclam preparation, the anti-HIV activity of the bicyclams (De Clercq *et al*., 1992; De Clercq *et al*., 1994) (Figure 5). Although it became rapidly clear, through mode of action studies, that the target of antiviral activity of the bicyclams was a viral entry-associated event, the molecular target for their anti-HIV activity was not resolved until 1997, when it was shown that the bicyclams actually block viral entry through a direct interaction with a cellular membrane protein, CXCR4, the receptor for the chemokine stromal

Figure 5. Antiviral substances discovered (and/or first described) at the Rega Institute

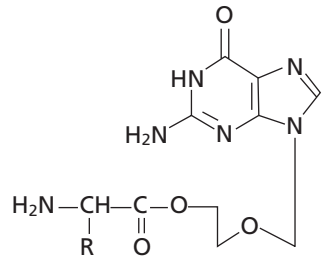
A For the treatment of HSV-1 and VZV infections



BVDU, brivudin, Zostex®, Brivactin®

Key references: De Clercq *et al*. (1979); De Clercq *et al*. (1980).

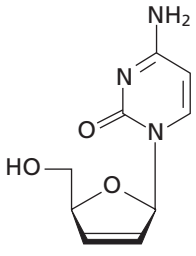
B For the treatment of HSV-1, HSV-2 and VZV infections



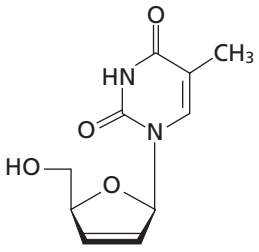
Amino acid esters of acyclovir
R = –CH(CH$_3$)$_2$: VACV, valaciclovir, Valtrex®, Zelitrex®

Key references: Colla *et al*. (1983); Maudgal *et al*. (1984).

C For the treatment of HIV infections



d4C
2′,3′-didehydro-2′,3′-dideoxycytidine

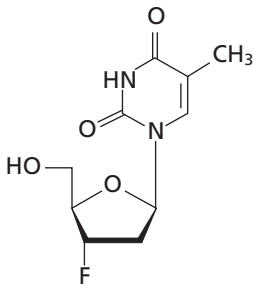


d4T
2′,3′-didehydro-2′,3′-dideoxythymidine
stavudine, Zerit®

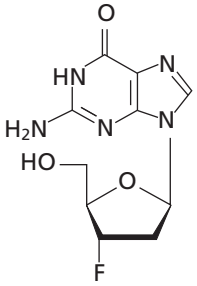
Key references: Balzarini *et al*. (1986); Balzarini *et al*. (1987); Baba *et al*. (1987).

Figure 5. *(continued)*

D For the treatment of HIV infections



FLT
3′-fluoro-2′,3′-dideoxythymidine

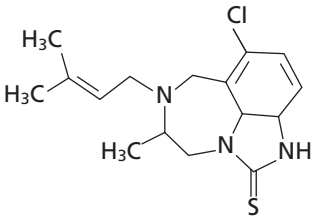


FLG
3′-fluoro-2′,3′-dideoxyguanosine

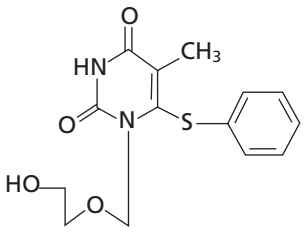
Key references: Herdewijn *et al*. (1987); Balzarini *et al*. (1988).

E For the treatment of HIV-1 infections

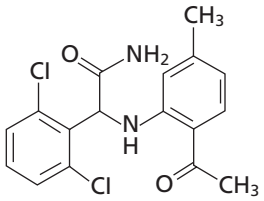
NNRTIs



TIBO



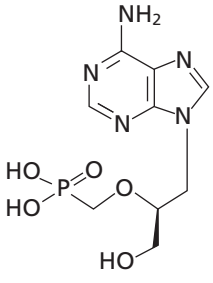
HEPT



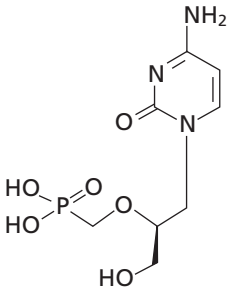
α-APA

Key references: Pauwels *et al*. (1990); Baba *et al*. (1989); Pauwels *et al*. (1993) Debyser *et al*. (1991) Miyasaka *et al*. (1989).

F For the treatment of DNA virus (herpes-, adeno-, polyoma-, papilloma-, poxvirus) infections



(*S*)-HPMPA

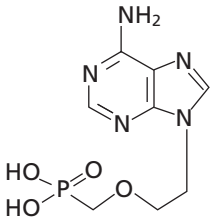


(*S*)-HPMPC, cidofovir, Vistide®

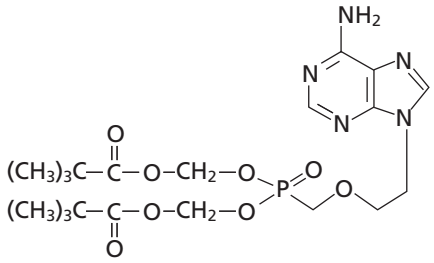
Key references: De Clercq *et al.* (1986); De Clercq *et al.* (1987); Snoeck *et al.* (1988).

Figure 5. *(continued)*

G For the treatment of HIV, and as a spin-off thereof, HBV infections



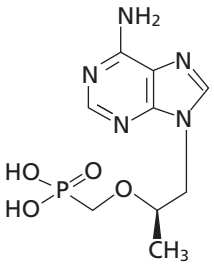
PMEA,
adefovir



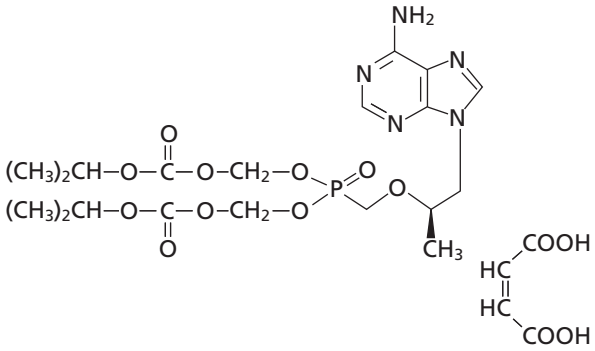
adefovir dipivoxil,
Hepsera®

Key references: De Clercq *et al.* (1986); Pauwels *et al.* (1988); Balzarini *et al.* (1989).

H For the treatment of HIV infections



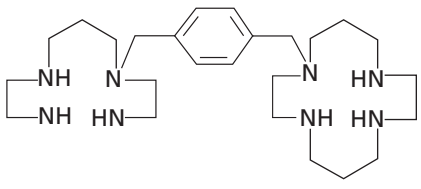
PMPA,
tenofovir



tenofovir disoproxil fumarate,
Viread®

Key references: Balzarini *et al.* (1993); Naesens *et al.* (1998).

I For the treatment of HIV infections, and as a spin-off thereof, CXCR4-mediated processes



AMD3100
(previously named JM3100)

Key references: De Clercq *et al.* (1992); De Clercq *et al.* (1994); Schols *et al.* (1997a,b).

cell-derived factor 1 (SDF-1). CXCR4 is also used as co-receptor for the T-lymphotropic HIV strains to enter the cells. This discovery (Schols *et al.*, 1997a,b) heralded the search for CXCR4 antagonists as inhibitors of HIV infection, and this search (in collaboration with investigators at AnorMED) has yielded a number of CXCR4 antagonists that show great potential for the treatment of either HIV infection or other diseases in which the interaction of SDF-1 with CXCR4 plays a crucial role, such as cancer and rheumatoid arthritis (De Clercq, 2003). SDF-1, through its interaction with CXCR4, is involved in the homing of haematopoietic precursor (stem) cells in the bone marrow, and, hence, CXCR4 antagonists that block this interaction should be useful in mobilizing stem cells from the bone marrow into the blood circulation. In fact, one of the bicyclams, namely AMD3100, has been clinically pursued for the purpose of stem cell transplantation in patients with multiple myeloma or non-Hodgkin's lymphoma.

Our search for new anti-HIV agents has in recent years gone unabated, and in this respect both 'old' targets (such as reverse transcriptase and viral entry-associated events) and 'new' targets such as proviral DNA integration into the host cell genome and expression (that is, transcription) of this proviral DNA are being explored. These investigations have already allowed the identification of a few lead compounds that may evolve into new strategies for the treatment of AIDS, and perhaps other diseases as well. Meanwhile, the scope of our antiviral drug development attempts have been extended to far beyond the initial viruses, that is, vaccinia virus (VV), herpes simplex virus (HSV) and vesicular stomatitis virus (VSV), which we worked with in the 1970s, in addition which were then added HIV and varicella-zoster virus (VZV) and cytomegalovirus (CMV) in the 1980s.

Our antiviral activity assays have now been extended to include polyoma-, papilloma- and adenoviruses, all eight human herpesviruses (HSV-1, HSV-2, VZV, EBV, CMV, HHV-6, -7 and -8), Coxsackie- and echoviruses, alphaviruses (sindbis virus), flaviviruses (yellow fever virus), pestiviruses ([bovine viral diarrhoea virus (BVDV)], arenaviruses (tacaribe virus), bunyaviruses (punta toro virus), orthomyxoviruses (influenza) and paramyxoviruses [parainfluenza and respiratory syncytial virus (RSV)], reoviruses, hepadnaviruses (HBV), hepaciviruses [hepatitis C virus (HCV)] and, last but not least, coronaviruses, including the severe acute respiratory syndrome (SARS)-associated coronavirus.

While most of these viruses are human pathogens in their own right, some of the viruses listed are used as model viruses for human pathogens, which cannot be handled in the Rega facilities for safety reasons. In this respect, sindbis virus is used as a model for the western, eastern and Venezuelan equine encephalitis viruses, tacaribe virus as model for lassa fever virus, punta toro virus as model for haemorrhagic fever viruses, that is, Crimean-Congo, among the bunyaviridae, and vesicular stomatitis virus (VSV) as model for both the rhabdoviridae (rabies) and filoviridae (Ebola and Marburg). BVDV can be considered a model virus for the development of drugs against pestivirus infections in cattle and pigs, as well as a surrogate virus for the development of drugs active against hepaciviruses (that is, HCV).

In recent years, a number of new antiviral strategies have emanated from the Rega Institute that offer great potential for the treatment of VZV and CMV infections (that is, bicyclic nucleoside analogues and derivatives thereof, in collaboration with C McGuigan, Cardiff University, UK), as well as the treatment of BVDV and HCV infections (in collaboration with G Pürstinger, University of Innsbruck, Austria). An effective antiviral strategy for the treatment of hepatitis C is highly warranted, given the high number of HCV-infected people (170 million) worldwide, the risk of cirrhosis and primary liver cancer which may develop in infected people, and the often partial response rate achieved with the current drug regimen used for treating hepatitis C (pegylated interferon in combination with ribavirin). Other virus infections with the highest need of antiviral therapy include HPV (associated with genital, laryngeal and common warts, and cervical cancer), Coxsackie B (associated with, among other manifestations, myocarditis and heart failure), adeno- and coronavirus (that is, SARS virus) infections. Varying antiviral strategies aimed at combating these viral diseases have been, or are currently being, worked out, including attempts to understand and fight development of viral drug resistance.

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