Prof M. Götte
1 November 2022
Filed on behalf of the Claimants
Exhibit MG-1
Claim No. HP-2021-000007

IN THE HIGH COURT OF JUSTICE
BUSINESS AND PROPERTY COURTS OF ENGLAND AND WALES
INTELLECTUAL PROPERTY LIST (ChD)
PATENTS COURT

B E T W E E N:

(1) GILEAD SCIENCES INC.
(a company registered in the US State of Delaware)

(2) GILEAD SCIENCES LTD

Claimants

- and -

NUCANA PLC

Defendant

EXPERT REPORT OF PROFESSOR MATTHIAS GÖTTE

I, MATTHIAS GÖTTE of 6-020K Katz Group Centre for Health Research, University of Alberta, Edmonton, Alberta, T6G 2E1, Canada **WILL SAY** as follows:

A. PERSONAL BACKGROUND

1. I am currently Professor and Chair of the Department of Medical Microbiology & Immunology at the University of Alberta in Edmonton, Canada.

2. A copy of my complete curriculum vitae including a list of publications is attached at **Exhibit MG-1**.

C2 tab. 7

3. I studied chemistry at undergraduate level at the University of Kiel and then the Technical University of Munich from 1984-1991, and obtained the equivalent of a MSc

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degree in 1991. I obtained my PhD in 1997 from the Ludwig Maximilian University of Munich. My PhD studies on the reverse transcriptase (RT) enzyme of HIV-1 were conducted at the Max Planck Institute for Biochemistry in Martinsried, Germany. HIV-1 RT is a multifunctional enzyme that possesses DNA polymerase and ribonuclease H (Rnase H) activities. It is critical for the replication of HIV.

4. My postdoctoral training, between 1997 and 2000, took place in Dr Mark Wainberg's laboratory at the Lady Davis Institute for Medical Research, at the Jewish General Hospital, Montreal, Canada. During this time, I turned my attention to the mechanisms of action and resistance associated with nucleoside/nucleotide[1] analogue RT inhibitors.

5. I started my own lab at the Lady Davis Institute for Medical Research in 2000. While we were still working on HIV, we included HCV and related viruses in our research program. From the beginning, major emphasis was placed on structure-function analyses of viral RNA-dependent RNA polymerase, an enzyme which is critical for replication of RNA viruses such as HCV. We were interested in the development of novel strategies to inhibit these enzymes, including the use of nucleotide analogues. We studied RNA-dependent RNA polymerases in HCV and a virus in the same family as HCV, bovine viral diarrhea virus (BVDV). Unlike HCV, BVDV had the advantage of being able to be grown in cell culture at this time. Hence we were interested in comparing the structure and function of HCV and BVDV RNA-dependent RNA polymerases. Both enzymes are also referred to as Non Structural Protein 5B (NS5B). We initially worked with commercially available nucleotide analogues that lacked the 3'-hydroxyl group. We observed in cell-free biochemical assays that chain termination with these compounds could be reversible in the BVDV model. We presented these findings at the 10th International Meeting of HCV and Related Viruses in Japan, which took place between 2-6 December 2003. The work on nucleotide analogue inhibitors continues today and has been expanded to many other viruses.

6. My lab relocated in May 2005 to the Department of Microbiology and Immunology at McGill University, Montreal, Canada. In 2007, I was promoted to the rank of Associate Professor, and in 2011 to full Professor. In these years, my interests covered a broad

[1] By "nucleoside" I mean "nucleobase plus sugar". A "nucleotide" is a nucleobase plus sugar and at least one phosphate. In my lab, we typically work with the active tri-phosphate form of the nucleoside analogue. Hence, I refer in this context to nucleotide analogues.

range of viruses, including HIV, HCV, BVDV, and human herpes viruses. Findings from my laboratory have contributed to the development of novel classes of viral polymerase inhibitors.

7. My lab made other contributions that help to better understand the layers of complexity associated with the mechanism of action of nucleotide analogue inhibitors of NS5B and HIV-1 RT. We developed high-resolution footprinting experiments to demonstrate that the bound HIV-1 RT can move on its nucleic acid substrate. The corresponding complexes exist predominantly in two conformations, referred to as pre- and post-translocational states.

8. I have collaborated with several pharmaceutical companies, including Merck, Gilead, and Tibotec to study the role of the translocational equilibrium in relation to the mechanisms of action of both approved and investigational viral polymerase inhibitors. We have demonstrated, predominantly with our footprinting experiments, that pre- and post-translocated complexes, respectively, can be targeted by distinct classes of compounds.

9. I have published my work on viral polymerases in approximately 120 peer reviewed papers. Many of my studies are published in The Journal of Biological Chemistry which is a leading scientific journal in the field of biochemical mechanisms of biological processes. I have also published in high impact journals that target a broader audience. My work on the efficiency and fidelity of RNA synthesis by HCV NS5B was published in *The Proceedings of the National Academy of Sciences* (PNAS) in 2011. I am co-editor/co-author of a number of books and book chapters including:

   (a) "Nucleoside Inhibitors of HIV Reverse Transcriptase and the Problem of Drug Resistance" in *The Human Immunodeficiency Virus: Biology, Immunology and Therapy*" (Princeton University Press, 2002);

   (b) "Non-Nucleoside Inhibitors of HIV Reverse Transcriptase" in *Viral Infections and Treatment* (CRC Press, 2003);

   (c) *Viral Genome Replication* (Springer, 2009);

   (d) "Nucleoside analogue inhibitors of HIV-1 Reverse Transcriptase" in *Antiviral Research* (ASM Press, 2009);

   (e) *Human Immunodeficiency Virus Reverse Transcriptase* (Springer,

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2013); and

(f) *Handbook of Antimicrobial Resistance* (Springer, 2017).

10. In 2013, I received the prestigious Career award Chercheur-boursier (senior level) from the Fonds de Recherche du Quebec - Santé, which is a non-profit funding agency which implements government strategy in relation to human health research.

11. My research program is currently funded through grants from the Canadian Institutes of Health Research (CIHR), the National Institutes of Health (NIH), the Government of Alberta and contracts from the pharmaceutical industry. Since 2002, I have been serving on a number of review committees of funding organizations that include NIH and CIHR. My role as a reviewer is to evaluate the scientific merit of research proposals for the purpose of deciding which research proposals to grant funding to. As part of this role, I have also been invited to participate on site visits to assess entire research programs. These visits allow the reviewers to assess the soundness of the proposed program of research by examining the research facilities and considering the competence and productivity of the investigators. During these visits the applicants describe their proposed experimental approach, present data and indicate proposed future directions of their work in terms of immediate strategies and long-term goals. The research proposals I review concern studies aimed at a better basic understanding of biological processes in the fields of virology and biochemistry and also include drug discovery and development programs.

12. I have served as a reviewer for a number of journals including: Science, Nature, PNAS, Antimicrobial Agents and Chemotherapy, Journal of Biological Chemistry, Nature Structural and Molecular Biology, Journal of Molecular Biology, Journal of Virology, Retrovirology, Nucleic Acids Research, Virology, PLoS Pathogens, Journal of Medicinal Chemistry, Journal of the American Chemical Society, Structure, Journal of Infectious Diseases, and Journal of General Virology.

13. I have acted as a mentor in several federal and provincial training programs, including the National CIHR Research Training Program in Hepatitis C. This program provides funding and training for students and postdocs in the field of HCV research. This multidisciplinary program brings together scientists and stakeholders across the country with the ultimate goal of supporting excellence in HCV research.

14. Since moving to Edmonton, Alberta, I have changed directions in my laboratory and my research program is now focused on the study of emerging viruses with high epidemic potential such as SARS-CoV-2, Ebola virus, Zika virus and Lassa virus, among many others.

15. I have served on several scientific and organizing committees of national and international conferences.

B. MY ROLE AS AN EXPERT WITNESS

16. I have been asked by Bird & Bird LLP **("B&B")**, solicitors for Gilead, to act as an independent expert witness in these proceedings.

17. B&B have brought my attention to Part 35 of the Civil Procedure Rules 1998, the Practice Direction which supplements Part 35 and the Guidance for the instruction of experts to give evidence in civil claims 2014. I confirm that I have read these documents and understand my duty is to assist the Court. I understand that this duty overrides any obligation to Gilead or B&B. I confirm that I have complied (and will continue to comply) with my duty, which encompasses the following:

    (a) the evidence and opinion that I present to the Court must be independent and unbiased;

    (b) I must state the facts or assumptions on which my opinion is based, and I should not omit to consider material facts which could detract from my concluded opinion;

    (c) I must make it clear when a particular question or issue falls outside my expertise;

    (d) I must state if my opinion is provisional or requires qualification; and

    (e) if, after exchange of reports, I change my view on a material matter, I must communicate such change of view to B&B without delay so that it can be communicated to the other parties in these proceedings and when appropriate to the Court.

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18. Except where I state otherwise, the facts and matters set out in this report are within my own knowledge and are true. Where appropriate, I have indicated the source of any facts or relevant information and in each case I believe the facts and information to be true.

19. This is not my first time acting as an independent expert witness in UK court proceedings. I have previously acted as an independent expert (for Gilead) in the case of *Idenix Pharmaceuticals Inc v Gilead Sciences Inc* [2014] EWHC 3916 (Pat). I also acted as an expert in the case of *Merck Sharpe & Dohme Ltd v Shionogi & Co Ltd* [2016] EWHC 2989 (Pat).

20. I confirm that I have no conflict of interest of any kind and that I will advise B&B if, between the date of this report and trial, there is any change in circumstances in this regard.

21. I have worked with research companies since the beginning of my career as an independent scientist in 2000. Collaborators include AstraZeneca, Gilead, GSK, Medivir, Merck, Pfizer, Tibotec, ViroChem Pharma, Tonix, Chimerix and Rome Therapeutics. These collaborations involved work on the mechanism of action of viral polymerase inhibitors. In particular, many collaborations focused on nucleotide analogues or nucleotide competitors, i.e. compounds which are structurally distinct from naturally occurring nucleotides but bind the active site of viral polymerases and compete with the natural enzyme-nucleotide substrate interactions. I have also been invited to speak at most of the above companies, for which I was personally remunerated, to give talks about the mechanisms of action of and resistance to antiviral compounds, with a focus on polymerase inhibitors. I have visited Gilead several times as a speaker.

22. My collaborations with the various pharmaceutical companies (listed in paragraph 21 above), including Gilead (since 2003), commonly involve funded contracts in relation to research into human immunodeficiency virus type 1 (HIV-1) and hepatitis C virus (HCV). In 2016, I was the senior author on a paper that focused on the study of the resistance of sofosbuvir. This work was a collaborative effort with scientists at Gilead, McGill University and Emory University.

23. My current research contract with Gilead is focused on emerging pathogens such as SARS-CoV-2 and the mechanism of action of remdesivir and other compounds.

24. I confirm that my funding by Gilead, or any other company, has not affected and will not

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affect my opinions and that I do not have a financial interest in the outcome of these proceedings.

C. MATERIAL INSTRUCTIONS

25. I have been provided with the following documents by B&B:[2]

(a) European Patent EP 2955190 B1 (which I refer to as the "Patent") and European Patent EP 3904365 B1 (which I refer to as the "Divisional");

(b) I have also been provided with the documents entitled "Annex A – Unconditional Amendments" and "Annex B - Conditional amendments" which I understand are proposed amended forms of the Patent (and which I refer to together as the "Amendments");

L tab.148 vol 3 (c) Quintiliani et al (2011) Bioorg. Med. Chem. 19, 4338-4345 ("Quintiliani").

26. Because the Patent and the Divisional are similar documents I shall refer in my report below to the Patent but I intend my comments to cover both documents (unless it is necessary to distinguish between them).

27. I was asked by B&B to consider the following issues:

(a) To whom is the Patent addressed? Who is the person (or team of persons) who would be likely to have had a practical interest in the subject matter of the invention in July 2003?

(b) What was the common general knowledge of the addressee in July 2003 with respect to the treatment of viral infections and research concerning the use of nucleoside analogues for the treatment of viral infections?

(c) Based on the teaching of the Patent would the addressee have understood the Patent to be making any technical contribution in the

[2] I was also (before I was shown the Patent) provided with US 2003/0109697 ("Shepard") and asked to comment on its disclosure, but I have not been asked to address Shepard in this report.

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field of antiviral therapy?

(d) Based on the teaching of the Patent, would the addressee have considered it plausible that the claimed compounds would be effective to treat viral infections?

D. THE SKILLED PERSON

28. I have been told that the Patent is to be read through the eyes of the person skilled in the art. I have been told this person is someone who would have a practical interest in the subject matter of the invention and that such a person considers the relevant literature carefully but is incapable of inventive activity. I have also been told that the skilled person can be a team.

29. Although the Patent on its face is clearly directed to the anti-cancer/oncology field, I understand from B&B that the Defendant previously asserted that one of the technical contributions of the Patent related to the use of the claimed compounds as antivirals and that they now assert that a technical contribution is that the claimed compounds have "cytotoxic activity".

30. The compounds discussed and claimed by the Patent are nucleoside analogues. Nucleoside analogues had two well-described potential uses in July 2003, as anti-cancer drugs and as antiviral drugs. I note that the introductory paragraphs in the Patent discuss both antiviral and anti-cancer activity of certain compounds. On that basis, in my view it would be reasonable for a team interested in developing antiviral drugs to read the Patent and consider whether there is any potential application of the compounds described as antiviral agents. As part of that exercise, they would be interested in the antiviral effects of the compounds (for reasons I explain below) and in the cytotoxic effects of the compounds (because cytotoxicity is an unwanted effect in an antiviral, as I also explain below).

31. In my opinion, a team interested in developing antiviral drugs would include a person with expertise in the antiviral field, with a focus on virology. They would likely have an undergraduate degree, perhaps in biochemistry, chemistry, molecular biology, immunology and/or microbiology and would likely have a MSc or PhD degree in the area of virology, potentially with additional experience as a post-doctoral fellow. They could be working in either academia or industry and/or could be clinicians with a research

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interest in infectious diseases. I shall call such an individual the "skilled virologist" in the rest of my report.

32. The skilled virologist would also have been interested in nucleoside analogues as potential therapies for viral infections. As nucleoside analogues would need to be synthesized before they could be tested, the skilled virologist would need to rely upon a skilled medicinal chemist for this purpose. The skilled virologist would have deferred to the skilled medicinal chemist when it came to matters of synthetic chemistry.

33. The Patent is to some extent directed to prodrugs. While the skilled virologist would have been broadly familiar with the concepts underlying the use of prodrugs, they would not have been familiar with the nuances of the various chemistries. As a result, the skilled virologist would also have deferred to the skilled medicinal chemist when it came to prodrugs. I understand from B&B that Professor Jason Micklefield is the medicinal chemistry expert who will address prodrug issues. I have had an opportunity to review Prof Micklefield's report in draft and agree that his comments about prodrugs (in paragraphs 61 to 70 of his report) accord with my high level understanding of the state of the prodrug field as at July 2003.

34. In summary, the skilled team investigating new nucleoside analogues for use as antivirals in July 2003 would have included a skilled virologist and a skilled medicinal chemist. The chemist would synthesize nucleoside analogues (including prodrug versions) and the skilled virologist would test them for antiviral activity and selectivity.

E. THE COMMON GENERAL KNOWLEDGE

35. Bird & Bird have requested that I outline the information which formed part of the common general knowledge as at 21 July 2003 for the skilled virologist, as I have defined this individual above. I have been told that the term common general knowledge means information which was generally known by the bulk of those individuals working in the relevant field and which was generally accepted by them as a sound basis for further action. I understand that the term common general knowledge is a legal expression, which I have been told is typically represented by information found in textbooks and review articles which were widely available and read or generally consulted at the time.

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36. It has been explained to me that scientific publications will only form part of the common general knowledge of the skilled virologist when such publications are widely known and generally accepted without contention by the majority of those individuals working in the field of the invention of the Patent. It has been further explained to me that the common general knowledge includes material which the skilled virologist knows exists and which they could refer to as a matter of course and is therefore not limited to material which they have memorized.

37. In the following section, I set out information which in my view was part of the skilled virologist 's common general knowledge in July 2003.

What is a virus?

38. Viruses are infectious agents that replicate inside the cells of living organisms. They consist of a piece of genetic material, either DNA or RNA, that is commonly protected by a protein coat or capsid. Some viruses also have additional lipid-protein envelopes as part of their viral outer shell.

39. A taxonomic system is used to classify viruses. At the highest-level viruses are differentiated by the type of genetic material they carry. Viruses can therefore either be DNA or RNA viruses or retroviruses like HIV that transcribe their RNA genome into double-stranded DNA.

40. Taxonomic classification then divides viruses into families with members of each family sharing similarities in genomic organisation, including the nature of the genetic material, DNA or RNA. Genetic sequence similarities will then further divide viruses into different genera and then species. Criteria such as routes of viral transmission, host species and the nature and symptoms of the disease caused by the virus are not criteria used to classify viruses.

41. Selected viral families are:

- ***Coronaviridae***: Viruses in this family typically have very large single stranded genomes of positive sense RNA. An example of a virus within the *Coronaviridae* family is SARS coronavirus (SARS-CoV), which causes severe acute respiratory syndrome.

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- ***Flaviviridae***: Viruses in this family have single-stranded, positive-sense RNA. Examples of *Flaviviridae* include the Hepatitis C virus (HCV), Dengue virus, West Nile virus and the Yellow fever virus.

- ***Herpesviridae***: Viruses in this family have a genome of double-stranded DNA. Examples of *Herpesviridae* include Human herpes virus 1, HHV-1 or HSV-1[3] (which causes common cold sores), HHV-2 or HSV-2 (which causes genital herpes), HHV-3 or VZV[4] (which causes chicken pox and shingles), and other HHVs.

- ***Hepadnaviridae***: Viruses in this family contain small genomes which are partially double-stranded, and which are replicated via an RNA intermediate. Hepatitis B virus is an example of a type of *Hepadnaviridae*.

- ***Retroviridae***: Viruses in this family have a genome which is a dimer of positive-sense single-stranded RNA. The genome is reverse transcribed into DNA which is then integrated into the host chromosomal DNA. Examples of *Retroviridae* include HIV-1 and HIV-2 that cause AIDS in humans.

- ***Paramyxoviridae*:** Viruses in this family have negative-sense, single-stranded RNA. Examples of this virus include the Measles and Mumps viruses.

Viral genome transcription and replication

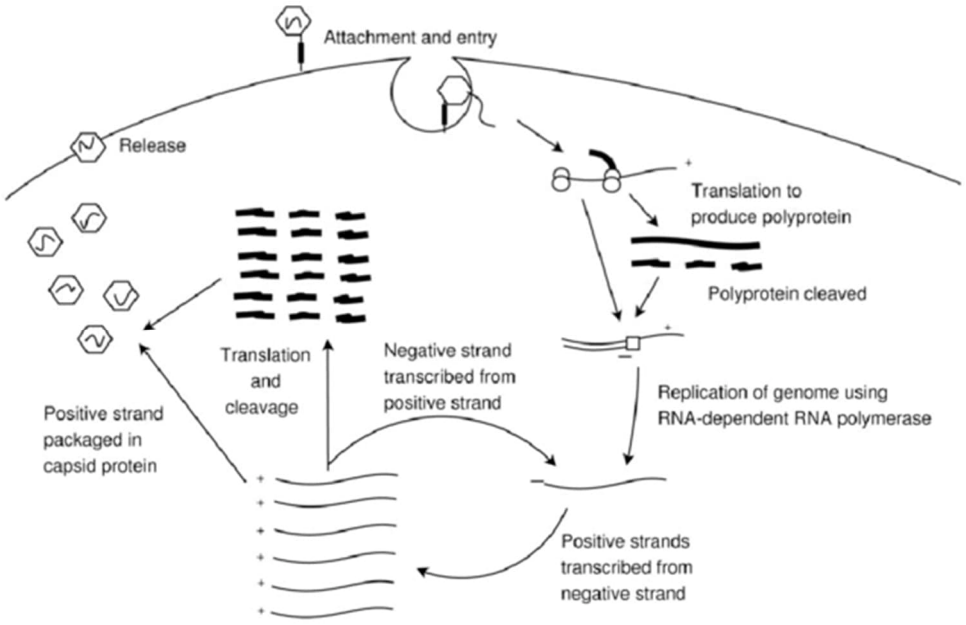
42. The purpose of replicating the viral genome is to allow the virus to generate copies of itself thereby permitting the further infection of other host cells and ensuring its survival. Transcription generates messenger RNAs that can be translated into proteins. These transcripts can be shorter than the genome length. Both replication and transcription require polymerase enzymes.[5]

43. Understanding the process of viral replication is important for the development of antiviral therapies since the mechanism of antiviral compounds is to interfere or disrupt

[3] Herpes simplex virus Type 1
[4] Varicella zoster virus
[5] Transcription can sometimes depend on human polymerases, like human RNA polymerase II in HIV.

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one of the steps of the viral life cycle. The mechanisms, pathways, and location (either nucleus or cytoplasm of the cell) of viral genomic replication will be entirely dependent on the type of genomic material used by the virus. Viral replication depends on viral polymerases that can be DNA polymerases, reverse transcriptases or RNA-dependent RNA polymerases. For illustrative purposes, the typical steps in an RNA virus life cycle are below, showing Polio virus[6]:



(a) **Attachment and entry** – The virus will begin its life cycle by attaching to its target cell's membrane. The virus then fuses its viral envelope with the host cell membrane.

(b) **Cytoplasmic release** – The virus releases viral RNA into the cellular cytoplasm.[7]

(c) **Translation and polyprotein processing** – The polyprotein is then created by translating the RNA genome. The polyprotein is then cut up by both viral and host cell enzymes called proteases into structural and non-structural

[6] Diagram found via internet image search. Source paper: Rogers et al (2005) "Optimal Replication of Poliovirus within cells" *The American Naturalist* 165(3): 364-73

[7] Other viruses such as HCV enter into the cell following fusion, the viral capsid is broken down and the RNA is released.

proteins with the latter being required for replication.

(d) **Viral RNA replication** – A negative strand copy of the positive stranded RNA genome is then generated. The negative strand RNA will serve as a template for producing multiple copies of the positive strand RNA. RNA-dependent RNA polymerase will then replicate viral RNA by adding nucleoside triphosphates which are available in the host cell to the RNA chain.[8]

(e) **Packaging and assembly** – The synthesized positive stranded viral RNA genome along with the envelope and other structural proteins are assembled into new virus particles.

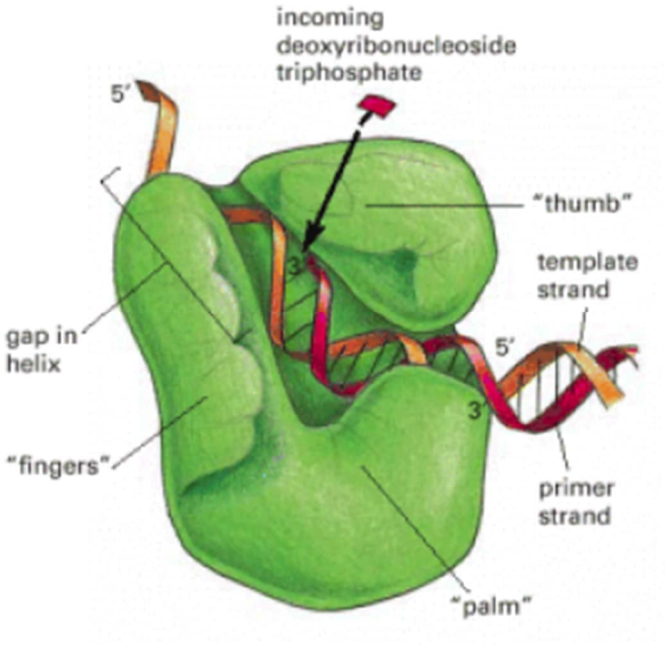
(f) **Virion maturation and release** – The viral particles are then released from the host cell and go on to infect further cells.

44. Viral genome replication as described above is a key target for developing antiviral therapies. The disruption of polymerase activity can be a successful strategy for preventing the replication of the viral genome and therefore the replication of the virus itself. Because of the viral polymerase enzyme's essential function in viral replication, it had been identified as a target for the development of antiviral therapies.

45. DNA or RNA replication require polymerase enzymes to catalyse DNA or RNA synthesis. To function, polymerases must interact with their nucleic acid and nucleotide substrates at the active site of the enzyme. The diagram below illustrates a simplified view of a polymerase[9], which is usually shaped like a human right hand, with the thumb and fingers wrapped around the nucleic acid substrate, with an incoming nucleotide accommodated by an active site in the palm:

[8] Indeed Polio virus was a popular model system to study positive-strand RNA viruses by July 2003, in particular the viral RNA-dependent RNA polymerase enzyme and its inhibition via antiviral drugs.
[9] The diagram (from *"Molecular Biology of the Cell"* (4th Ed.) Alberts et al (2002)) shows a E coli DNA polymerase but the principle is the same.

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46. The genomes of different viruses can vary in length between approximately 3 to 30 kilobases, and in nature (DNA or RNA) as noted above.

47. The genome of RNA viruses commonly encodes for structural proteins that form the viral viral capsid or envelope.

48. On the other hand, viral non-structural (NS) proteins are commonly associated with enzymatic functions such as polymerase, protease or helicase activities.

Antiviral Therapies

49. By 2003, antiviral therapies fell into two types. First, broad spectrum antivirals such as interferon which did not target specific viruses but rather interfered with cellular immune responses. Second, other compounds that could specifically target the virus, such as viral polymerase or viral protease inhibitors. These latter types of inhibitors were available before 2003 for the treatment of HIV, for example.

50. All viruses encode for a polymerase that is essential for replication and which therefore represents a logical target in antiviral research. In the HIV example mentioned above, although the virus uses host cell DNA polymerase at the viral replication stage, the virus also uses its own polymerase - reverse transcriptase – at an earlier stage in its lifecycle. It was this viral reverse transcriptase enzyme which was therefore a key target of antiviral

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therapy for HIV.

Nucleoside Analogues - Virus Infections

51. By July 2003, the skilled virologist would have been aware of the use of nucleoside analogues in the treatment of HBV, HIV and herpesviruses. Outside the field of virology, cytotoxic nucleoside analogues have been used clinically for over 50 years in the treatment of cancer.

52. From the perspective of the skilled virologist, cytotoxic effects of nucleoside analogues are an unwanted side effect and should be avoided as far as possible in the development and use of these compounds as antivirals where the aim is to kill the virus. The use of nucleoside analogues as antivirals therefore requires selectivity towards the viral target (see below). This is in contrast to the treatment of cancer, where the nucleoside analogues target host factors as opposed to viral proteins or components. I understand from B&B that issues relating to cancer will be dealt with by Dr Carlos Galmarini.

53. It was well known and appreciated by 2003 that putative therapeutic nucleoside analogues that target the viral polymerase should have the following properties:

(a) effectively enter the target cell that has been infected;

(b) undergo phosphorylation within the host cell to the triphosphate form (or structural equivalent);

(c) be able to compete with the pool of natural nucleoside triphosphates within the cell;

(d) effectively bind to the active site of the polymerase;

(e) effectively be incorporated into the viral genome and have efficacy in preventing the synthesis of viral DNA or RNA, which in turn inhibits viral genome replication[10]; and

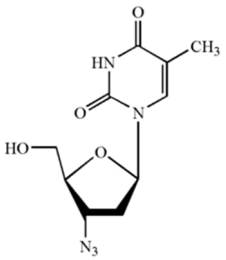
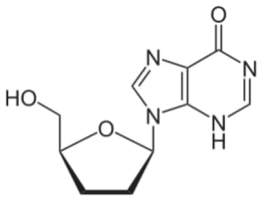
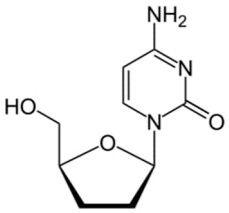
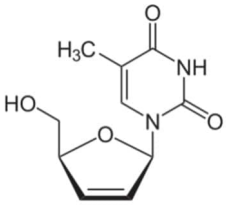
(f) should not be effectively incorporated by human

[10] It is also conceivable that the nucleotide analogue competes with its natural counterpart, binds to the active site of the viral polymerase and inhibits the enzyme but without being incorporated into the growing DNA or RNA chain.

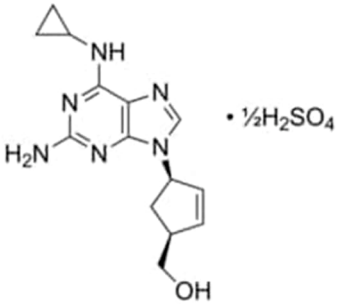
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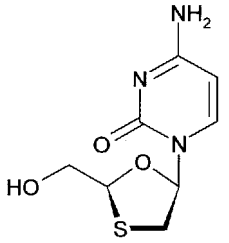
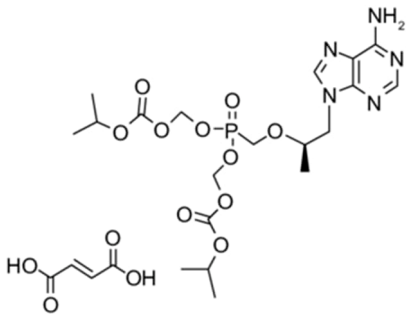
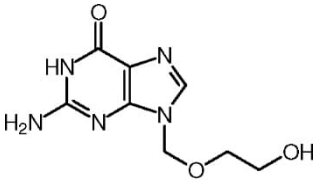
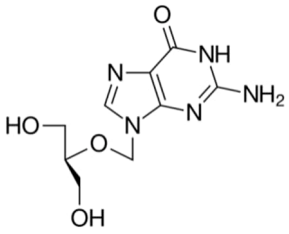
polymerases such as human mitochondrial DNA polymerase gamma to avoid other potential toxicities.

54. The skilled virologist would have been aware of the mechanism of action and antiviral activity of well described nucleoside analogues, including the action of drugs such as 3TC and AZT used in HIV therapy. The below structures are examples of nucleoside analogues which had been approved in the US by July 2003.

Name, approval date and indication	**Structure**
HIV	
Zidovudine (**AZT**) FDA approved 1987	
Didanosine (**DDI**) FDA approved 1991	
Zalcitabine (**ddC**) FDA approved 1992	
Stavudine (**d4T**) FDA approved 1994	

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Abacavir sulphate (**ABC**) FDA approved 1998	

HIV and HBV	
Lamivudine (**3TC**) FDA approved 1995 for HIV, 1999 for HBV	
Tenofovir disoproxil fumarate (**TDF**) [11] FDA approved for HIV and HBV 2001	
Other viruses	
Acyclovir FDA approved 1982 for Herpes virus infections.	
Ganciclovir FDA approved 1989 for Cytomegalovirus (CMV) and herpes virus.	

55. The replacement of the 3'-hydroxyl with a non-natural substituent is a structural feature

[11] Technically, the presence of a 5' phosphonate on the sugar makes Tenofovir a nucleotide rather than a nucleoside.

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in some of the nucleosides in the above table. This 3'-hydroxyl is relevant in the development of antiviral nucleoside analogues. The incorporated monophosphate of the nucleoside analogue, lacking this 3'-hydroxyl, is unable to mount a nucleophilic attack on an incoming nucleoside triphosphate, thereby preventing the addition of further nucleotides to the chain resulting in chain termination and stopping viral genome replication.

56. Ganciclovir (illustrated in the table above) is an example of a non-obligate chain-terminator. It contains the equivalent of a 3'-hydroxyl group, but inhibits DNA synthesis through a different mechanism.

Virus specificity and selectivity of nucleoside analogues

57. The skilled virologist would have known that although cross-reactivity of nucleoside analogues had been demonstrated in some cases, the efficacy of nucleoside analogues against one species of virus would not mean that they would be active against any other viral species. An example of cross reactivity is the nucleoside analogue 3TC and also TDF that work against HIV and HBV. However, more commonly nucleoside analogues only had therapeutic activity against one particular species of virus. For example, the nucleoside analogue AZT only worked against HIV and not against HBV.

58. In order to be identified as a candidate for the treatment of viral infection, nucleoside analogues should show antiviral activity and no significant toxicity in appropriate *in vitro* cell-based assays before animal models would be considered. There must be a sufficient difference between the concentration of a drug that causes an antiviral effect versus the concentration of the drug that causes toxicities. In other words, there has to be a viable "selectivity index " (as I set out below). A compound's antiviral activity is expressed in the following ways:

    (a) The effective concentration (EC) is a measure of the ability of the test compound to show an effect on viral replication. It is usually expressed as EC_{50} or EC_{90} and is the concentration of test compound that reduces viral replication by 50% or 90% respectively. EC_{50} is measured in cell-based assays by measuring the number of plaques in a plaque assay (see below), or amount of viral RNA as measured by PCR. A compound with potent

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antiviral activity will have a low EC_{50} value; the lower the EC_{50}, the higher the potency.

(b) The inhibitory concentration (IC) is a measure of the ability of the test compound to inhibit a target enzyme. It is usually expressed as IC_{50} or IC_{90}, which is the concentration of test compound that inhibits the target enzyme activity by 50% or 90% respectively. The IC_{50} is commonly measured in cell-free, biochemical assays that involve the target enzyme. A compound with potent inhibitory effects will have a low IC_{50} value; the lower the IC_{50}, the higher the inhibitory effect.

(c) The cytotoxic concentration (CC) is a measure of the concentration of test compound needed to kill cells in the assay. Again, it is measured in terms of the concentration of compound that kills 50% or 90% of the cells (expressed as CC_{50} or CC_{90} values respectively). A compound with high cytotoxicity will have a low CC value; the lower the CC_{50} value, the higher the cytotoxicity.

(d) The ratio of CC:EC provides a measure for the "selectivity index". A ratio of at least 10:1 (and ideally much greater than this) is indicative of an agent that preferentially targets the virus. The goal is to identify selective compounds with antiviral activity and no significant toxicity against the host.

Development of nucleoside analogues was empirical

59. By July 2003, assays were available for many viruses to establish whether a nucleoside analogue candidate shows (i) antiviral activity and a good selectivity index in cell-based model systems, (ii) inhibits the viral polymerase, and (iii) is converted into its triphosphate form. Following these initial assays, subsequent steps would have included assessing the pharmacological properties of the candidate nucleoside analogue. If a nucleoside analogue does not show an antiviral effect in a cell-based assay, this does not necessarily mean that the active triphosphate form is inactive against the viral polymerase. If there was such discordance between the biochemical assay (see further below, paragraphs 72 to 77) and an antiviral assay, then prodrug approaches might be

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considered.

60. While knowing the structure of a given viral polymerase (with nucleic acid and nucleotide substrate) could have potentially helped in the design and development of nucleoside analogues, in July 2003 these structures of ternary complexes were only available for a few select enzymes. In addition, polymerases are highly mobile biological molecules whose activity depends on multiple conformational changes, which is hard to infer from static structural models. Therefore, the development of nucleoside analogues to inhibit viral polymerases was largely empirical in nature.

Search for nucleoside analogues with activity

61. The general approach to the discovery of novel nucleoside analogues involved the synthesis and subsequent testing of multiple different compounds to uncover which compounds had activity. Nucleoside analogues can, in theory, be modified at most positions on the base or sugar ring of the molecule by adding a range of different substituents. However, the antiviral activity of the molecule is dependent on its ability to be recognized by cellular enzymes in order for it to be phosphorylated to the active triphosphate form and be recognized by the target viral polymerase and thereby be incorporated into the viral nucleotide chain. The skilled virologist would have appreciated that even the slightest modification in the nucleoside analogue structure could lead to significant changes in activity, selectivity and therapeutic potential. Once a promising candidate had been identified, further studies would have been carried out to understand how its structure dictates its activity.

62. In July 2003, when commencing a nucleoside analogue antiviral drug discovery program, one would have started with the simplest form of the candidate drug – i.e., the bare nucleoside version. If a novel nucleoside or nucleoside analogue were to be studied, it would obviously need to be synthesized.

63. The general concept at that time was that a nucleoside analogue of interest had to be converted into its triphosphate form because this was the form in which it would interact with its target viral polymerase and thus inhibit the virus. Therefore, in order to have a viable antiviral nucleoside, the skilled virologist needed to see that the nucleoside triphosphate inhibits the target. This is assessed via biochemical studies which would

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have included a phosphorylation assay and a polymerase assay. Cell-based assays might have been carried out in parallel. However, biochemical studies give the definitive assessment as to whether a particular nucleoside triphosphate is capable of binding to and inhibiting the target.

64. If a cell-based assay was negative for antiviral effect but the polymerase assay was positive, this might suggest that the nucleoside analogue is not located inside the cell to meet its viral target, or the triphosphate form of the nucleoside analogue is not being made in sufficient quantities. In such a case, the skilled team would have to convene and discuss potential strategies to mitigate this. This would include modifying the nucleoside or considering potential prodrug strategies. I do not consider myself to be an expert on the use of prodrugs per se. Nevertheless, I am broadly familiar with the concept of prodrugs and the skilled virologist would likewise have been broadly familiar with those concepts in July 2003.

65. In 2003, the skilled virologist would have used (i) cell-based assays in which cell-based viral models were incubated with the nucleoside of interest and its ability to inhibit viral replication in a biological setting would be investigated, and (ii) biochemical assays in order to obtain information about mechanism of action at the molecular level.

Assays to test antiviral/inhibitory activity

Cell Based assays

Plaque assay

66. If cells in an agar petri dish are infected with a virus, new viruses resulting from the initial infection can infect and kill surrounding cells. Over a period of days, and multiple rounds of infection, the initial infection results in an area of clearance in the cell 'lawn' which is known as a plaque, and which can be visualized with appropriate staining of the cell monolayer. The plaque assay may be used to quantify virus in a sample via serial dilution. Plaques are counted and the concentration of infectious virus in the original sample can be calculated by factoring in the serial dilution. The resulting value is known as a titer and is expressed in plaque-forming units per milliliter (pfu/ml).

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The replicon assay

67. Assays were available to study specific aspects of virus replication rather than the entire life cycle. These assays were known as replicon systems. Replicon systems were in use in the years before 2003 for a number of viruses. Following the publication of a high impact *Science* paper in 1999, the replicon assay was established as a significant breakthrough in the study of HCV[12]. It enabled the study of inhibitors of virus replication in a biologically relevant system. The assay quickly became the gold standard for assessing antiviral activity and it would have been well known to the skilled virologist by July 2003.

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68. Replicons are engineered self-amplifying recombinant viral genomes that are able to replicate in cells and closely mimic replication of a virus' genome. Using the replicon system, it is possible to measure directly whether a test compound has any antiviral activity. After adding a test compound to cells in which the replicon is replicating, the amount of replicon RNA in the cells can then be measured by polymerase chain reaction, a technique used to amplify and quantify nucleic acids.

69. The antiviral activity of test compounds can be determined by comparing the amount of replicon RNA in the cells incubated with the test compound with the amount of replicon RNA in cells that were not incubated with the test compound.

70. Researchers interested in identifying antiviral compounds adopted the replicon assay and worked on ways of modifying and optimising the assay to make it easier to quantify the replicon RNA.

71. Prior to the development of the replicon assay, viruses which were difficult to culture were studied using a surrogate non-human viral model, if one was available.

Biochemical Assays

Polymerase assay

72. A cell-free biochemical assay involving purified polymerase from the virus in question is used to assess the ability of the nucleotide analog to bind and inhibit that enzyme

[12] Lohmann et al (1999) Science 285(5424), 101-113

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73. To perform this assay, the viral polymerase being studied would first be purified in sufficient amounts.

74. For a newly discovered virus, the viral genome had to be sequenced and even this initial step was more complex in 2003. Then, engineered constructs for expression of the polymerase would be created. For biochemical assays with the purified polymerase, the candidate nucleoside analogue had to be synthesized and purified as well in its triphosphate form (the job of the skilled chemist).

75. If the nucleoside analogue of interest (in its triphosphate form) was shown to inhibit the viral polymerase in the polymerase assay then the skilled virologist would be encouraged that in principle this was a good candidate for an antiviral compound.

Phosphorylation

76. Phosphorylation is necessary for antiviral activity, but a phosphorylation assay is not an assay of antiviral activity. As explained above, for nucleoside analogues to function they need to be phosphorylated inside the cell through the addition of three phosphate groups, in order to be recognized and accepted by the active site of the polymerase. Chromatography can be used to separate different species of molecules, which can be un-phosphorylated, mono-, di- or tri-phosphorylated.

77. Although it is not possible to conclude that a phosphorylated compound will have antiviral properties, it is necessary that the compound have the ability to be phosphorylated. This is a necessary prerequisite for antiviral activity but is not sufficient.

Prodrugs

78. One strategy for improving properties of a drug is to create a prodrug version of it. Put simply, this process involves synthesising a modified molecule in the laboratory which will be reversed *in vivo* and which liberates the parent molecule at a later time following its administration. A prodrug may improve uptake of the molecule into the target cells. Importantly, any modifications made to create a prodrug must be designed in such a way that it can be metabolized back to the parent molecule in the cytoplasm of the target cells. A number of prodrug approaches were known in 2003.

79. As stated previously, I do not consider myself to be an expert on prodrugs although I am (and was in 2003) broadly familiar with the concepts underlying their use. An important point for the skilled virologist in 2003 is that a prodrug approach would only have been contemplated when one wanted to improve the properties of an existing antiviral nucleoside. The prodrug approach per se is therefore not an antiviral issue; it is more of a pharmacological one. A skilled virologist who encountered a core nucleoside analogue which had no demonstrated antiviral efficacy would not see a good reason to take it forward into prodrug assessments. On the other hand, a nucleoside analogue which demonstrated antiviral activity provides a rationale for a prodrug approach with the goal to improve the overall properties of the compound. But the skilled virologist is primarily interested in whether he or she has an antiviral nucleoside in the first place.

The Patent and the Divisional

80. I have been asked to review the teaching of the Patent and the Divisional and to comment on aspects of their technical teaching when read through the eyes of a skilled virologist as at July 2003. I note that the Divisional has claims which are different from those of the Patent, in that the class of relevant compounds is smaller through limitations in the number of substitutions permitted at various positions in the generic compound structures. Although the Divisional is a much shorter document than the Patent, most of its paragraphs are also found in the Patent and so I shall refer in my discussion below to the Patent but I intend my comments to cover both documents. Alongside the Divisional, B&B also provided me with the Amendments. I have considered all of these different versions of the claims and my conclusions apply equally to all of them.

81. I have been asked to address two issues:

(a) Would the skilled virologist have understood the Patent to be making any technical contribution in the field of antiviral therapy?

(b) Is it plausible that substantially all of the compounds claimed in the Patent will be useful in treating viral infections?

General Discussion

82. Overall, the skilled virologist would not find very much of interest in the Patent but would

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recognize that the Patent was presenting a phosphoramidate prodrug approach in order to try to bypass the rate limiting step of phosphorylation of a nucleoside analogue into the monophosphate. The skilled virologist would see that the approach is based on publications cited in the Patent in paragraph [0007]. The skilled virologist would recognize from the cited literature that the phosphoramidate prodrug approach could be useful to improve compounds with an established antiviral activity.

83. Antiviral activity is a property that the skilled virologist examines through biochemical assays, cell culture assays and possibly in animal models. Biochemical studies provide information on the potential mechanism of action against the target. It is important to realize however that any antiviral effect is mediated by the action of a given nucleoside analogue (actually its triphosphate metabolite) on the target polymerase enzyme. Antiviral effects are not per se mediated by the prodrug moiety. A prodrug would not be considered in biochemical studies designed to characterize drug-target interactions. The prodrug could be viewed as having a sort of pharmacological effect; the purpose of introducing the prodrug moiety is to try to increase intracellular availability of the active form of a nucleoside.

Papers cited within the Patent

84. The Patent at paragraphs [0007] to [0010] set out a list of publications which the authors of the Patent say describe their phosphoramidate prodrug approach. The skilled virologist would have considered the references cited to see if they contained useful background information. I therefore reviewed the titles/authors/abstracts of the 12 articles referred to in paragraph [0007] to [0009] and in my view there was only one of these papers which I consider would have been of interest to the skilled virologist in July 2003. This was the Balzarini (1996) paper[13] which is referred to in paragraph [0008] of the Patent.

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85. The Balzarini paper would have been of interest to the skilled virologist in 2003 for a number of reasons. First, it is published in a top-tier journal – Proceedings of the National Academy of Sciences (PNAS). Second, the list of authors includes some very well-known researchers in the antiviral field, several of whom were associated with the Rega institute in Leuven, Belgium which is (and was in 2003) a world-renowned centre of excellence in the field of antiviral drugs including nucleoside analogues. Third, the paper deals with d4T, a well-known antiviral drug which was known at the time to have some toxicity issues

[13] Balzarini et al (1996) PNAS, vol 93, pp.7295-99

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associated with it. This would have been regarded as undesirable by the skilled virologist. Finally, the paper discusses a matter of general interest; it describes making a phosphoramidate prodrug of d4T and the comparison of the prodrug with the parent nucleoside and the demonstration of delivery of the d4T monophosphate as a prodrug.

86. The skilled virologist would have understood the results shown in Table 1 of Balzarini (below).

Table 1. Inhibitory effects of d4T and So324 on HIV-induced cytopathicity in MT-4 and CEM cells, on MSV-induced transformation of murine C3H/3T3 cells, and on virus production in M/M

	EC_{50}, μM*							CC_{50}, μM
	MT-4 cells		CEM/0		CEM/TK⁻	M/M	C3H/3T3 cells	MT-4
Compound	HIV-1 (III_B)	HIV-2 (ROD)	HIV-1 (III_B)	HIV-2 (ROD)	HIV-2 (ROD)	HIV-1 (Ba-L)	MSV	
d4T	0.65	0.77	0.80	0.78	25	0.25	2.6	4.0
So324	0.066	0.067	0.18	0.20	0.075	0.02	15	>100

*Compound concentration required to inhibit HIV-induced destruction of MT-4 or giant cell formation in CEM cell cultures or MSV-induced transformation of C3H/3T3 cells by 50%. CEM/TK⁻ cells are TK-deficient CEM cells.

87. Table 1 shows the testing in cell culture for antiviral activity (determination of EC_{50} values) for the d4T prodrug (called So324) compared to d4T. The data shows that the EC_{50} values are lower (i.e., better antiviral activity) for the prodrug than for d4T in the various cell lines relevant to HIV-1 and HIV-2. On the right side of the table the cytotoxicity (CC_{50}) values are shown; the prodrug significantly reduces the cytotoxicity (higher CC_{50}) as compared to d4T. As I said previously, the goal for a virologist is to find a drug with a good selectivity index – high efficacy (low EC_{50}) together with no or very low cytotoxicity (high CC_{50}). The Balzarini group has demonstrated this with this prodrug approach in these HIV model systems.

88. The Patent at paragraph [0008] then states that the Balzarini paper gives "*an optimal description of phenyl methoxyalaninyl phosphoramidate as the prototype promoiety for the intracellular delivery of bioactive nucleotides*".

89. The Patent appears to extrapolate from the antiviral results shown in the Balzarini paper and claims that the same phosphoramidate approach is applicable to cancer therapy. The skilled virologist would not be sufficiently qualified to comment on this aspect of the Patent. However, the skilled virologist would know that a virologist and an oncologist would have opposing views on the potential usefulness of cytotoxic compounds. The skilled virologist is aware that anti-cancer compounds are cytotoxic whereas compounds

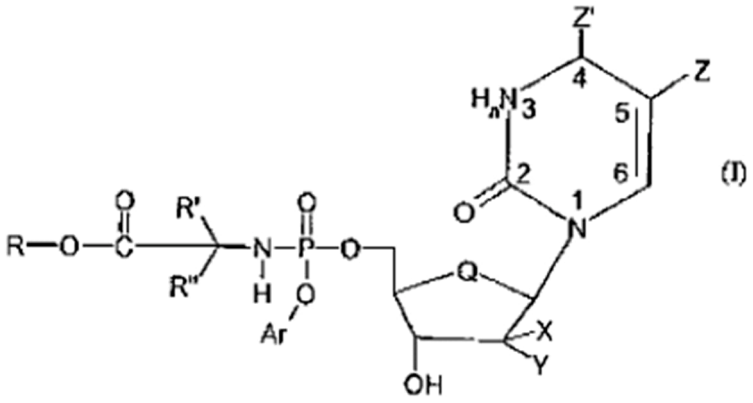
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with good properties as potential antiviral agents will have as low a cytotoxic activity as possible. Therefore, to the skilled virologist there would be no basis upon which an extrapolation can be made that a compound which is useful as an antiviral will be useful as an anti-cancer agent. That makes no sense at all.

90. I have reviewed the remainder of the Patent for material relevant to the skilled virologist and I note that there is very little. In particular the experimental procedures from paragraphs [0075] through to [0296] all relate to synthetic organic chemistry and would be of little if any interest to the skilled virologist. Likewise, the Table of data at the end of the Patent presents what appears to be activity data for a range of phosphoramidate prodrugs of BVdU and gemcitabine in three cancer cell lines. The skilled virologist would not be sufficiently qualified to comment on this data. Finally, the Patent sets out some mouse, *in vivo* cancer model data which again would be beyond the expertise of the skilled virologist to interpret.

Technical Contribution of the Patent and the Divisional

91. The Patent and the Divisional relate to a class of nucleoside phosphoramidate compounds set out as Formula I (although the definitions of some of the substituents at X, R, R', R", Ar and Z vary somewhat between the claims of the two documents).



92. The skilled virologist will recognize this structure as having a phosphoramidate portion on the left side of the structure and a nucleoside portion on the right side. The skilled virologist considering antiviral compounds will not pay too much attention to the phosphoramidate prodrug portion of the molecule – as stated above, they are aware that this portion has at best only a "pharmacological effect". The skilled virologist would focus

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instead on the nucleoside portion and see that the base moieties are single-membered rings reminiscent of pyrimidines such as cytidine and uridine.

93. The key part of the nucleoside structure of Formula I for the skilled virologist would be the proposed modification at the 2' position on the sugar ring. There is always a fluorine atom at the 2'-alpha (down) position whereas there is a list of possible modifications at the 2'-beta (up) position.

94. The skilled virologist considering a possible antiviral effect of Formula I compounds would be curious as to why the authors of the Patent have limited the 2'-down position to a fluorine atom only and not permitted a hydrogen atom or a hydroxyl group to be present at the same position. They would see no obvious scientific rationale for this limitation.

95. The list of potential substitutions at the 2'-up position includes halogens and CH_3. The skilled virologist in July 2003 would have no idea, without testing them in standard assays first, whether any of these, together with fluorine in the 2'-down position, would produce a nucleoside with antiviral effect. At that time (and to a great extent still today) this was an empirical field. It was not possible to make nucleoside modifications with the expectation that antiviral efficacy would result. It would have been a process done in hope rather than expectation. As I have said, only when a nucleoside analogue resulted in good antiviral efficacy would prodrug approaches be considered.

96. The suggestion that the claimed classes of compounds would be therapeutically useful is made even less credible by the fact that Formula I encompasses an enormous number of individual compounds,[14] with no defined structure activity relationship.

97. A key point is that the Patent aims at a prodrug approach for nucleosides for the treatment of cancer and presents results in cell-based and animal-based model systems for cancer. However, even if effects useful for cancer were shown (and I am not sufficiently qualified to comment on that) this does not mean that useful effects will also be seen in model systems for the study of antivirals.

98. Antiviral model systems will be different: the cells are often different and therefore the animal models are different; and the prodrugs may not be metabolized in the same way

[14] According to Prof Micklefield, the number of compounds covered by the Patent/Amendments is vast, likely being in excess of 10^{20} compounds and even the Divisional will still likely cover many thousands of compounds.

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as in cells or model systems that are relevant to cancer. Furthermore, even different viral infections must be considered differently, given that different viruses can infect different cells.

99. The only data provided in the Patent is from antiproliferation assays for phosphoramidate prodrugs of BVdU and gemcitabine.

100. From the skilled virologist's perspective several of the compounds presented in the Table of data in the Patent show EC_{50} values which are extremely high – with concentrations in the region of hundreds of micromolar. EC50 in this context refers to the anti-proliferative effect of the compounds which, in the skilled virologist's eyes would be like the CC50 value in the assessment of an antiviral drug. From the skilled virologist's point of view, such compounds would have been viewed as non-cytotoxic. The remaining compounds on the Table show widely varying EC_{50} values. To the skilled virologist, the data appears to have no pattern – there does not appear to be an effect which applies to all of the compounds. The apparent variability for this set of compounds would not permit the skilled virologist to make any prediction as to the cytotoxic activity of the other numerous compounds claimed in the Patent and in the Divisional. The skilled virologist would consider it to be speculation to assert that the entire class of compounds would or would not have cytotoxic activity. It would be necessary to approach it on a compound-by-compound basis. The skilled virologist would be primarily interested in compounds that are not cytotoxic.

101. There is no antiviral data provided in the Patent at all. No reference is made to the authors having carried out even basic antiviral experimental investigations to see if any of the compounds have potential for the treatment of viral infections. The skilled virologist would not know without testing them first, if any given compound would be efficacious against any viral infections.

102. Even if the Patent had contained some actual antiviral data in relation to BVdU or gemcitabine or their phosphoramidate prodrugs, the skilled virologist would still not be able to extrapolate such data to all of the different nucleosides and nucleoside analogues claimed, nor to all possible DNA and RNA viruses. The skilled virologist would not have any reason to believe such notional antiviral data would be predictive of the activity of such a wide range of compounds with such different structures. Nor would the availability of any such antiviral data give the skilled virologist any more expectation that such a wide range of compounds would be likely to be useful as antiviral therapies. Given the complete

absence of antiviral data in the Patent, the skilled virologist could not accept the proposition that the Patent had made any sort of contribution in the field of antiviral therapy.

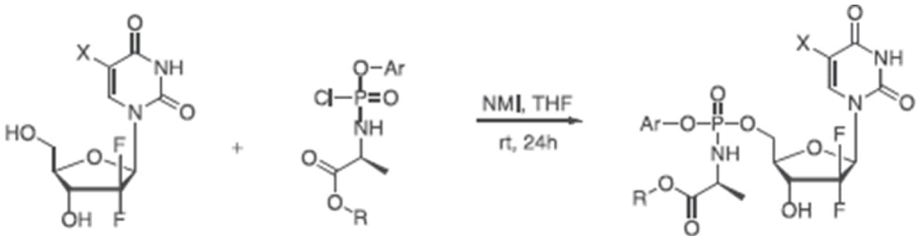
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103. B&B asked me to comment on what the skilled virologist's view would be of the results reported for in Quintiliani for the compounds designated 16 to 21.

104. This paper presents compounds that according to the abstract show "*selective activity against the feline herpes virus replication in cell culture*" which is said to be "*due to a specific recognition (activation) by the virus encoded thymidine kinase*".

105. As shown by Scheme 2 on page 4339 of the paper, Compounds 16 to 21 are phosphoramidate prodrugs of core nucleosides 8, 9, 10 and 11.



8 X= I
9 X= Br
10 X= Cl

12 Ar= Ph, R= Bn
13 Ar= Ph, R= CH_3
14 Ar= Naph, R= Bn
15 Ar= Naph, R= CH_3

16 X= I, Ar= Ph, R= Bn, 3%
17 X= I, Ar= Ph, R= CH_3, 5%
18 X= I, Ar= Naph, R= Bn, 6%
19 X= I, Ar= Naph, R= CH_3, 1%
20 X= Br, Ar= Ph, R= Bn, 7%
21 X= Cl, Ar= Ph, R= Bn, 4%

Scheme 2.

106. Tables 1 & 2 of Quintiliani present antiviral data for various compounds assayed in a number of cell-based viral models for Herpes simplex virus-1, Feline herpes virus, Herpes simplex virus-2, Vaccinia virus, Varicella-zoster virus and cytomegalovirus.

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Table 1
Cytotoxicity and anti-herpes virus activity of compounds in HEL and CRFK cell cultures

Compound	EC_{50}[a] (μM)					Minimum cytotoxic concentration[b] (MCC)(μM)	CC_{50}[c] (μM)
	Herpes simplex virus-1 (KOS) (HEL)	Herpes simplex virus-1 TK⁻ KOS ACV[r] (HEL)	Feline herpes virus (CRFK)	Herpes simplex virus-2 (G) (HEL)	Vaccinia virus (HEL)	(HEL)	(CRFK)
8	16 ± 6.9	20	1.2 ± 0.4	64 ± 33.4	>100	>100	>100
9	15 ± 7.8	73 ± 38.9	2.4 ± 1.1	>100	>100	>100	>100
10	33 ± 17.7	78 ± 29.7	13 ± 10	⩾100	>100	>100	>100
11	12 ± 0	20	>100	39 ± 7.8	⩾100	>100	>100
16	27 ± 9.9	⩾100	4.4 ± 3.6	50 ± 0	58 ± 0	>100	⩾70
17	>100	>100	28 ± 4.5	>100	>100	>100	>100
18	>20	>20	>20	>20	>20	>100	36
19	>100	>100	>20	>100	>100	>100	92
20	>100	>100	11.6 ± 0.7	>100	>100	>100	>100
21	>100	>100	>100	>100	>100	>100	>100
Brivudin	0.08	250	30	250	10	>250	>100
Cidofovir	2	2	1.3	2	10	>250	>100
Acyclovir	0.4	50	1.0	0.4	>250	>250	>100
Ganciclovir	0.03	0.8	–	0.03	>100	>100	–

CRFK cells: Crandell-Rees Feline Kidney cells.
HEL cells: human embryonic lung fibroblast cells.
[a] Compound concentration affording 50% inhibition of the virus-induced cytopathic effect.
[b] Minimum cytotoxic concentration required to cause a microscopically detectable alteration of normal cell morphology.
[c] 50% Cytotoxic concentration, or compound concentration required to reduce cell viability as determined with the colorimetric formazan-based MTS assay.

Table 2
Activity of compounds against varicella-zoster virus (VZV) and cytomegalovirus (HCMV) in human embryonic lung (HEL) cells

Compound	EC_{50}[a] (μM)						Minimum cytotoxic concentration[b] (μM)	CC_{50}[c] (μM)
	TK^+ VZV strains		TK^- VZV strains		HCMV strains			
	YS	OKA	07-1	YS/R	AD-169	Davis	(HEL)	(HEL)
8	13 ± 1	9.1 ± 0.8	>50	>50	>50	>50	>50	>100
9	23	11 ± 4	>50	>50	>50	>50	>50	>100
10	>50	⩾50	>50	>50	>50	>50	>50	>100
11	10	5.8 ± 3.4	>50	>50	>50	>50	>50	100
17	–	>50	>50	–	>50	>50	>50	51
18	–	8.5 ± 3.5	37 ± 7	–	>50	>50	>50	49
19	29 ± 3	25 ± 9	>50	>50	>50	>50	>50	⩾100
20	–	39	>50	–	>50	>50	>50	⩾50
21	–	>50	>50	–	>50	>50	>50	⩾100
Acyclovir	4.9	1.4	43	111	–	–	>400	>400
Brivudin	0.011	0.030	⩾60	>150	–	–	⩾300	512

[a] Effective concentration required to reduce virus plaque formation by 50%. Virus input was 20 plaque forming units (PFU) for VZV or 100 PFU for HCMV.
[b] Minimum cytotoxic concentration that causes a microscopically detectable alteration of cell morphology.
[c] 50% Cytostatic concentration or compound concentration required to reduce cell growth by 50%.

107. The data in Tables 1 & 2 show that several compounds do not show significant antiviral activity, e.g., EC_{50} >50μM or >100μM across a number of viral models. In any event they would have no value as potential antiviral agents because their assay results indicate the same value for EC_{50} as for CC_{50}. The compound essentially behaves as expected for a negative control. One compound (compound 21) was not only inactive in all viral models tested but was also non-cytotoxic.

108. On page 4340 of the paper, at the start of the conclusions section, it is stated: *"A series of 2'-deoxy-2',2'-difluoro-5-halouridines and their corresponding phosphoramidates were synthesized and investigated for antiviral activity and for cytotoxicity. 2'-Deoxy-2',2'-difluoro-5-iodo- and 5-bromo-uridines showed significant activity against feline herpes*

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virus, while none of the ProTides were endowed with antiviral activity."

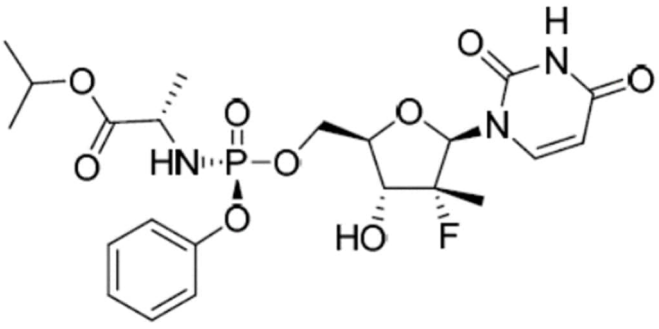
109. Also on page 4340, (left column) the paper also states: *"No antiviral activity was found for the corresponding ProTides. The observation that the phosphoramidate prodrugs of 8, 9 and 10 were devoid of marked antiviral activity is suggestive of a very limited release of the 5'-monophosphate and/or the parent derivative from the prodrugs in cell culture (Tables 1 and 2). Kinetic experiments of drug release in the intact virus-infected cells should reveal this issue."*

110. The reference to limited release of the 5'-monophosphate is an interesting observation. The authors are seeking an explanation for why the ProTides show results which are no better or even significantly worse than the underlying nucleoside analogues. For example the EC_{50} results for compound 8 v compound 19 show either no difference (>50μM or >100μM for both) or the ProTide shows a higher EC_{50} by a factor of up to 15-fold. The authors note that that the 5'-monophosphate form of the nucleoside analogue is not being released inside the cell and hypothesize that kinetic experiments may reveal the underlying reason for this apparent failure in the unmasking of the monophosphate. Without 5'-monophosphate delivered inside the cells, the nucleoside cannot be converted into its active triphosphate form.

GILEAD'S SOFOSBUVIR PRODUCTS

111. B&B have informed me that Gilead's sofosbuvir products (Sovaldi®, Harvoni®, Epclusa® and Vosevi®) are asserted to infringe the Patent and the Divisional.

112. Sofosbuvir is a prodrug of 2'-deoxy-2'-fluoro-2'-C-methyl uridine monophosphate and has the following structure.



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113. Prior to Gilead's launch of sofosbuvir products, the standard treatment for HCV infection involved the administration of α-interferon or pegylated α-interferon (IFN) and ribavirin (RBV). This combination treatment typically lasted 24 or 48 weeks and in almost all cases produced severe side effects including anaemia, fatigue, flu-like symptoms, as well as neurological disorders and mental disorders such as anxiety and depression. In addition, with 24 weeks of therapy with peg-IFN and ribavirin, the so-called sustained virological response (i.e., no virus is detectable 12 weeks after the end of therapy) ("SVR") was only about 67% for HCV Genotypes 2 or 3. SVR rates were even less than 50% in patients infected with HCV Genotype 1.

114. When it was first approved, Gilead's sofosbuvir product Sovaldi® provided the first potent, all-oral, interferon-free, curative regime for HCV infection. Sofosbuvir is a backbone in combination with other antiviral drugs in Harvoni®, Epclusa® and Vosevi®). Some of these products were approved for the treatment of HCV genotypes 1 to 6.

115. Sofosbuvir (in the Gilead products) provides a number of important benefits:

a) It is associated with significantly higher cure rates compared to what was previously achieved;

b) has a simple dosage regime being an oral treatment, one pill administered once a day. This means that patients are more likely to adhere to the treatment as prescribed;

c) It is not cytotoxic and clinical trials revealed very few side effects. It has an excellent selectivity index;

d) It has few drug reactions meaning that people on other medications previously unable to take IFN/RBV can take sofosbuvir;

e) It has a significantly shorter duration of treatment: 8 to 24 weeks, compared to 24 or 48 weeks for IFN/RBV; and

f) It can be taken by patients previously not eligible for treatment including those with advanced liver disease and after liver transplantation.

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STATEMENT OF TRUTH

I confirm that I have made clear which facts and matters referred to in this report are within my own knowledge and which are not. Those that are within my own knowledge, I confirm to be true. The opinions I have expressed represent my true and complete professional opinions on the matters to which they refer.

I understand that proceedings for contempt of court may be brought against anyone who makes, or causes to be made, a false statement in a document verified by a statement of truth without an honest belief in its truth.

Signed: 

Professor Matthias Götte

Dated: Edmonton, Alberta, Canada this 1st day of November 2022