UNITED STATES PATENT AND TRADEMARK OFFICE

_____

BEFORE THE PATENT TRIAL AND APPEAL BOARD

_____

INITIATIVE FOR MEDICINES, ACCESS & KNOWLEDGE (I-MAK), INC.
Petitioner

v.

GILEAD PHARMASSET LLC
Patent Owner

_____

Case No. IPR2018-00103
U.S. Patent No. 7,429,572

_____

PETITION FOR *INTER PARTES* REVIEW

TABLE OF CONTENTS

I. INTRODUCTION

Initiative for Medicines, Access & Knowledge (I-MAK), Inc. ("Petitioner") requests *inter partes* review ("IPR") of all 19 claims of United States Patent No. 7,429,572 to Clark ("the '572 patent," EX1001) under the provisions of 35 U.S.C. § 311, § 6 of the Leahy-Smith America Invents Act ("AIA"), and 37 C.F.R. § 42.100 et seq. The '572 patent issued on September 30, 2008, and is currently assigned to Gilead Pharmasset LLC ("Patent Owner"). This petition demonstrates that all 19 claims of the '572 patent are unpatentable.

In particular, the '572 patent claims pharmaceutical compounds that were already published by the United States Government years before Patent Owner applied for the '572 patent. Since American taxpayers had already paid for research that identified the compounds claimed in the '572 patent, its claims are invalid. Other scientists also publicly identified the pharmaceutical compounds claimed by the '572 before Patent Owner applied for the '572 patent. Thus, its claims are invalid based on that prior art as well.

In short, the '572 patent claims pharmaceutical compounds that were already known because of the work of others, including the United States government. Thus, the '572 patent's claims are unpatentable and should be cancelled.

II. MANDATORY NOTICES

A. Real Parties-in-Interest (37 C.F.R. § 42.8(b)(1))

The real parties-in-interest for this petition are Initiative for Medicines, Access & Knowledge (I-MAK), Inc., and the Laura and John Arnold Foundation.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

Petitioner is not aware of any other matter that would affect, or be affected by, a decision in this proceeding.

C. Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3))

Petitioner designates Daniel B. Ravicher (Reg. No. 47,015) as lead counsel. Petitioner is a not-for-profit public charity of limited resources and has been unable to retain back-up counsel. Petitioner respectfully requests that the Board exercise its authority under 37 C.F.R. § 42.5(b) to waive or suspend the requirement under 37 C.F.R. § 42.10 that Petitioner designate at least one back-up counsel.

D. Service Information (37 C.F.R. § 42.8(b)(4))

Papers concerning this matter should be served on the following:

Address:	Daniel B. Ravicher Ravicher Law Firm PLLC 2000 Ponce De Leon Blvd Ste 600 Coral Gables, FL 33134
Email:	dan@ravicher.com
Telephone:	786-505-1205

Petitioner consents to service by email to dan@ravicher.com.

III. REQUIREMENTS FOR REVIEW

A. Grounds for Standing

Petitioner certifies that the ’572 patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting the *inter partes* review sought herein. The required fee is being paid through the Patent Trial and Appeal Board End to End System. The Office is authorized to charge fee deficiencies and credit overpayments to Deposit Account No. 601986.

B. Identification of challenge

Petitioner respectfully requests cancellation of claims 1-19 of the ’572 patent based on the following grounds:

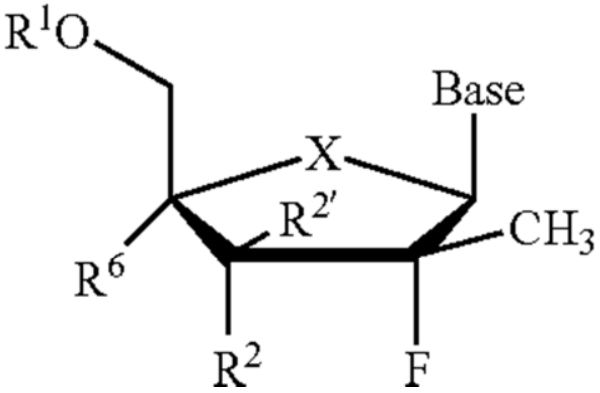
#	Claims	35 U.S.C. §	Prior Art
1	1-16	102(b)	Klecker (EX1005)
2	1-19	102(b)	Sommadossi (EX1006)
3	1-19	103(a)	Sommadossi (EX1006) and Klecker (EX1005)

This Petition is supported by the declaration of Joseph M. Fortunak, Ph.D. (EX1002). Dr. Fortunak is well qualified as an expert, possessing the necessary scientific, technical, and other specialized knowledge and training to assist in an understanding of the evidence presented herein, as well as possessing the expertise necessary to determine and explain the level of ordinary skill in the art as of the relevant timeframe.

The Petition and its supporting materials, which are listed in the Appendix, establish a reasonable likelihood that Petitioner will prevail with respect to cancellation of the challenged claims. See 35 U.S.C. § 314(a).

IV. OVERVIEW OF THE '572 PATENT

The '572 patent generally relates to compositions and methods for treating a *Flaviviradae* infection, including hepatitis C virus. EX1001. The '572 patent specifically relates to nucleoside compounds of the following general formula:



EX1001 at 11:27-40.

In defining the structure's various components, the '572 states that the base can be "a naturally occurring or modified purine or pyrimidine base." EX1001 at 11:43-44. The '572 patent further provides a long list of substituents for each of X and R1, R2, R2' and R6. EX1001 at 11:45 – 12:26.

The following chart describes the '572 patent's 19 claims:

Claim(s)	Recite
1-5	Genera of compounds within the general formula.
6	A specific compound within the general formula.
7-12	Pharmaceutical compositions comprising the compounds of claims 1-6.
13-14	Methods of synthesizing the compound of claim 1.
15	A specific compound within the general formula.
16	A pharmaceutical composition comprising the compound of claim 15.
17-19	Liposomal compositions comprising liposomes comprising the compounds of claims 1, 6 and 15.

V. FILE HISTORY OF THE '572 PATENT

U.S. Patent Application No. 10/828,753 ("the '753 application"), filed on April 21, 2004, issued as the '572 patent on September 30, 2008. The '753 application claimed the benefit of Provisional Application No. 60/474,368 ("the '368 provisional application"), which was filed on May 30, 2003.

During prosecution of the '753 application, Patent Owner addressed two different references that disclosed genera of compounds that included the compounds Patent Owner sought to claim. Those two references were U.S. Patent App. Pub. No. US 2007/0042939 to LaColla ("LaColla") and U.S. Patent No. 7.105,499 to Carroll ("Carroll").

The Examiner cited LaColla as the basis for a 102(e) rejection because it claimed priority to three provisional applications, including one filed on June 28,

2002, roughly a year before the ‘368 provisional application was filed. EX1004 at 13. The Examiner did not cite Carroll as the basis for a rejection. Rather, Patent Owner brought Carrol to the Examiner’s attention in June 2007. *Id*. at 55.

Patent Owner overcame the Examiner’s 102(e) rejection based on LaColla by arguing it did not qualify as prior art because the relevant portion of LaColla cited against the pending claims was not included within any of the three provisional applications to which LaColla claimed priority. *Id*. at 40-42. Instead, Patent Owner argued, the relevant portion of LaColla cited against the pending claims first appeared in its parent utility application filed on June 27, 2003, which was roughly a month after the ‘368 provisional application’s May 30, 2003, filing date. *Id*.

Patent Owner further argued that the LaColla provisional applications did not anticipate the pending claims because their disclosures would not allow one to “at once envisage” the claimed compounds. *Id*. at 42-43. Patent Owner then proceeded to argue the claimed compounds were not obvious over LaColla because data presented in the ‘753 application showed that the specific cytidine compound claimed in original claim 11 (final claim 6) showed “exceptional anti-flavivirus activity.” *Id*. at 47.

Patent Owner submitted additional evidence on this point in the form of a declaration by two of Patent Owner’s employees, Drs. Phillip Furman and Michael

Sofia, who concluded that the cytidine compound claimed in original claim 11 (final claim 6) unexpectedly had more activity and less cytotoxicity than structurally similar compounds. *Id*. at 52.

Regarding Carroll, Patent Owner made virtually the same arguments as it did regarding LaColla. First, Patent Owner argued Carroll did not qualify as prior art because its disclosure of a comparable genus of compounds did not appear in its priority applications until after the '753 application was filed. *Id*. at 56-57. Second, Patent Owner argued that one of ordinary skill in the art would not have "at once envisaged" the claimed genus of compounds from the "vast number" of compounds disclosed in Carroll. *Id*. at 57. Third, Patent Owner argued that the evidence cited above with respect to LaColla also showed that the claimed compounds were not obvious over Carroll. *Id*.

The Examiner subsequently allowed the claims without making any substantive response to Patent Owner's arguments regarding LaColla or Carroll. *Id*. at 71. The Examiner concluded instead that LaColla was not prior art. *Id*.

As discussed further below, the data provided by Patent Owner did not show that the claimed compounds had unexpectedly high anti-viral activity and low cytotoxicity. EX1002 ¶35. First, none of the data referenced by Patent Owner, either in the '753 application or the declaration submitted by Drs. Furman and Sofia, related to the uridine compound specifically claimed in original claim 130

(final claim 15) or generally claimed in original claim 6 (final claim 1). *Id*. Second, the data provided in the ‘753 application actually showed that the cytidine compound performed comparably to prior art compounds. *Id*. Third, the declaration submitted by Drs. Furman and Sofia contained inadequate parameters and other scientific flaws rendering it unreliable. *Id*. Fourth, the declaration submitted by Drs. Furman and Sofia compared the single cytidine example of the application to only two of the many possible compounds of LaColla without providing any justification for such a limited and selective comparison. *Id*.

VI. PERSON OF ORDINARY SKILL IN THE ART

Because the ’572 patent pertains to nucleoside compounds, a person of skill in the art at the time of the alleged invention (“POSA”) would have either (1) a Ph.D. in chemistry or a closely related field with some experience in an academic or industrial laboratory focusing on drug discovery or development, and would also have some familiarity with antiviral drugs and their design and mechanism of action, or (2) a Bachelor’s or Master’s degree in chemistry or a closely related field with significant experience in an academic or industrial laboratory focusing on drug discovery and/or development for the treatment of viral diseases. EX1002 ¶42.

VII. CLAIM CONSTRUCTION

In an *inter partes* review, a claim in an unexpired patent is given its broadest

reasonable construction in light of the specification. 37 C.F.R. § 42.100(b). Claim terms are also "generally given their ordinary and customary meaning," which is the meaning that the term would have to a person of ordinary skill in the art at the time of the invention in view of the specification. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Under either standard, there is a reasonable likelihood that Petitioner will prevail with respect to the challenged claims.

The '572 patent provides definitions for certain claim terms, but these definitions are conventional. EX1002 ¶43. Thus, there is no reason to give any of the terms of the claims of the '572 a meaning other than their ordinary and accustomed meaning. *Id*. While the specification of the '572 patent relates to treatment for hepatitis C virus ("HCV"), none of the claims contain any limitations relating thereto. EX1002 ¶44. Thus, the broadest reasonable interpretation of the claims is that none of them are limited to HCV treatment. *Id*.

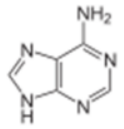
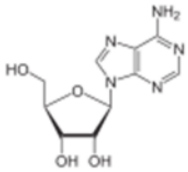
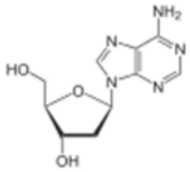
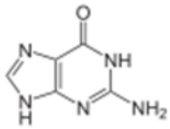
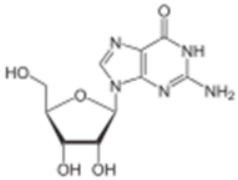
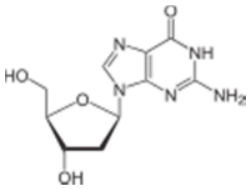
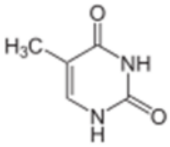
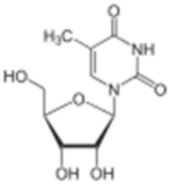
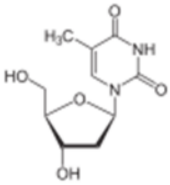
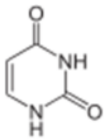
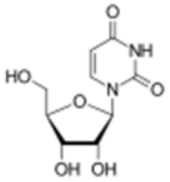
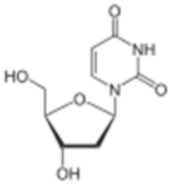
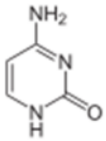
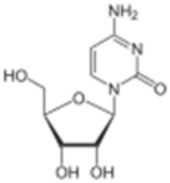
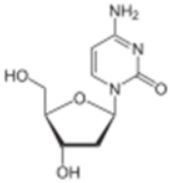
VIII. BACKGROUND KNOWLEDGE IN THE ART

The background discussed below reflect knowledge skilled artisans would bring to bear in reading the prior art at the time of the invention and thereby assists in understanding how one would have inherently understood the references and why one would have been motivated to combine the references as asserted in this Petition. *Ariosa Diagnostics v. Verinata Health, Inc.*, No. 15-1215, slip op. 1, 11-12 (Fed. Cir. 2015). This knowledge of a skilled artisan is part of the store of

public knowledge that must be consulted when considering whether a claimed invention would have been obvious. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007); *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362-63 (Fed. Cir. 2013).

A. Nucleoside Analog Drugs Inhibited Viral Diseases

Nucleosides were well-known to be found as structural components in deoxy-ribonucleic acids (DNA) or ribonucleic acids (RNA). EX1002 ¶46. Nucleosides are glycosylamines composed of a five-carbon sugar linked to what is known as a nitrogenous base. *Id*. Adenine, cytosine, guanine, thymine, and uracil are naturally-occurring nitrogenous bases. Naturally-occurring, five-carbon sugar rings include ribose and deoxyribose. *Id.* The following table shows structures for these nitrogenous bases as well as the respective products of linking these bases to ribose and deoxyribose sugar rings. *Id*.

Nitrogenous Base	Ribose Derivative	Deoxyribose Derivative
 Adenine	 Adenosine (A)	 Deoxyadenosine (dA)
 Guanine	 Guanosine (G)	 Deoxyguanosine (dG)
 Thymine	 5-Methyluridine (m^5U)	 Thymidine (dT)
 Uracil	 Uridine (U)	 Deoxyuridine (dU)
 Cytosine	 Cytidine (C)	 Deoxycytidine (dC)

It was also well known that analogs of naturally-occurring nucleosides were attractive targets for drug discovery and that such analogs were routinely used to

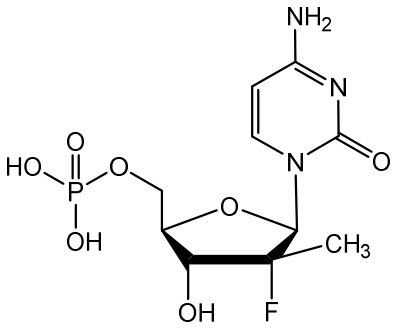
treat diseases including viral infections and cancers. EX1002 ¶47. Examples of such drugs included idoxuridine and gemcitabine for the treatment of cancers. *Id*. Additional examples of nucleoside drugs for the treatment of viral diseases included azidothymidine (AZT), stavudine (d4T), and lamivudine (3TC) for the treatment of HIV viral infections. *Id*. Ribavirin is another nucleoside analog used for the treatment of viral diseases including hepatitis C viral infections. *Id*. Acyclic nucleoside analogs were also known for the treatment of viral diseases. *Id*. Such drugs included tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide fumarate (TAF) for the treatment of HIV and hepatitis B viral infections. *Id*.

B. Nucleoside Drugs Required Phosphorylation to be Active

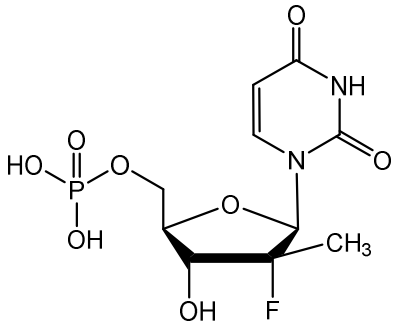
Nucleosides, however, were also well-known to be useful only after intracellular, enzymatic conversion into their corresponding phosphate analogs – usually the triphosphate being the active form. EX1002 ¶48. McGuigan -C. et al. "Nucleoside Analogues Previously Found to be Active Against HIV May be Activated by Simple Chemical Phosphorylation", FEBS Letters, vol. 322, pp. 249-252 (1993) ("McGuigan 1993"; EX1007); McGuigan, C. et al. "Certain Phosphoramidate Derivatives of dideoxy uridine (ddU) are Active Against HIV and Successfully By-pass Thymidine Kinase", FEBS Letters vol. 351, pp. 11-14 (1994) ("McGuigan 1994"; EX1008)). This conversion was known to happen in a stepwise fashion, with the first step being conversion to the corresponding

monophosphate. *Id*. Such phosphorylations are mediated by enzymes. *Id*.

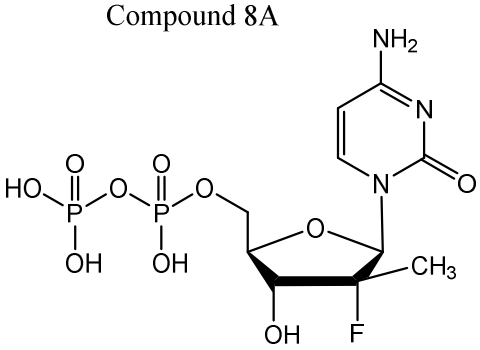
Shown below are the mono-, di-, and triphosphate analogs of compounds falling within the genera of nucleoside compounds of claim 1 of the ‘572 patent. EX1002 ¶49. These are the mono-, di-, and tri-phosphate forms of C-2’-deoxy-C-2’-methyl(up)-C-2’-fluoro(down) pyrimidine nucleosides. *Id*. The nucleosides from which these nucleotides are derived are the subject of claims 6 and 15 of the '572 patent. *Id.*



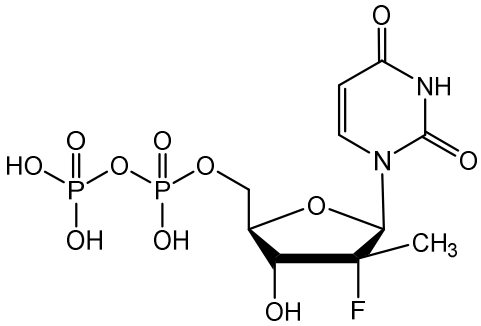
Compound 8A



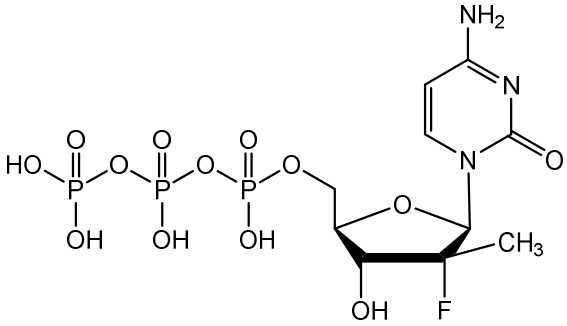
Compound 8B



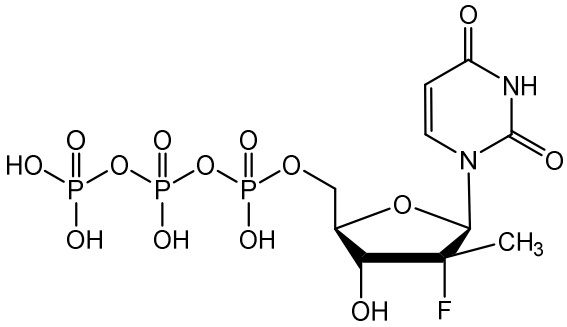
Compound 8C



Compound 8D



Compound 8E



Compound 8F

These phosphorylated forms of the nucleoside (in particular compounds 8E and 8F) claimed in the '572 patent would have been expected to be active therapeutic agents as compared to the nucleoside alone. EX1002 ¶50.

C. Some Nucleoside Drugs Were Poor Substrates for Intracellular Phosphorylation

A problem presented itself, however, in the identification of phosphorylated

compounds 8A through 8F, and in particular, 8E and 8F as promising antiviral drugs. EX1002 ¶51. Many nucleoside drugs – in particular uridines – were also known to be poor substrates for conversion into their monophosphate forms. *Id*. (*citing* McGuigan 1993 (EX1007); McGuigan 1994 (EX1008)). This was very important because drugs that would otherwise be very potent for disease treatment would be inactive if they did not undergo phosphorylation inside a target cell. *Id*.

It was known that the means existed to assess whether failure to undergo efficient mono-phosphorylation affected the biological activity of potential nucleoside drugs. EX1002 ¶52 (*citing* WO 01/90121 to Sommadossi ("Sommadossi"; EX1006 187:11, 188:2)). In addition, it was also known that nucleosides could be converted into nucleotide prodrugs of their monophosphate forms. *Id*. (*citing* McGuigan 1993 (EX1007); McGuigan 1994 (EX1008)).

D. Use of Fluorine in Nucleoside Drugs Could Produce Potent Activity

There was a substantial body of common knowledge about the use of fluorine as a substituent in nucleoside drugs. EX1002 ¶53. For example, it was common knowledge that fluorine was very useful as a halogen in many approved drugs, and that fluorine was (i) substitutable to provide advantages versus other atoms and functional groups as well as for any of the other halogens; (ii) successful in the 2' down position when methyl was in the 2' up position; and (iii) preferred over hydroxy at the 2' position of antiviral nucleosides. *Id*.

Indeed, as one article stated in 1998, "The controlled introduction of fluorine into organic molecules, especially biomolecules and analogues of natural products, has received much attention from synthetic organic chemists in recent years." EX1002 ¶54 (*quoting* McAtee et al., *A Completely Diastereoselective Electrophilic Fluorination of a Chiral, Noncarbohydrate Sugar Ring Precursor: Application to the Synthesis of Several Novel 2'-Fluoronucleosides*, J. Org. Chem, 1998, 63, 2161 ("McAtee"; EX1009)).

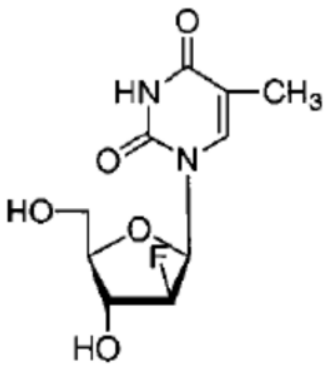
E. Fluorine Was Substitutable For Other Halogens In Nucleosides

It was known in the art of medicinal chemistry generally and the art of nucleoside compounds specifically that the halogens chloro, bromo, iodo, and fluoro, often collectively referred to as just "halos" or "halogens," were substitutable for one another. EX1002 ¶55. For example, as discussed in more detail below, WO 99/23104 to Klecker ("Klecker"; EX1005 at 17:3-5) taught that any halogen could be used at each of the 2' up, 2' down, 3' up and 3' down positions (identified as W, X, Y and Z), and Sommadossi taught, "The term halo, as used herein, includes chloro, bromo, iodo, and fluoro," *Id*. (*quoting* EX1006 at 52:31). Thus, one of ordinary skill would have understood a teaching of any halo to be a teaching of all halos unless there was an express discussion why a particular halo was to be excluded from the teaching. *Id*.

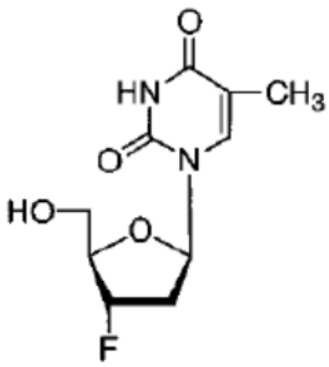
F. Fluorine in Nucleosides Could Impart Biological Activity

It was commonly known that fluorine incorporated into nucleosides could result in dramatically improved biological activity. EX1002 ¶56. For instance, Pankiewicz, *Review: Fluorinated Nucleosides*, Carbohydrate Research, 327, 87-105 (2000) ("Pankiewicz"; EX1010), taught that, "Introduction of fluorine atoms into components of nucleic acids in general and nucleosides in particular frequently leads to a dramatic change in their biological activity." *Id*.

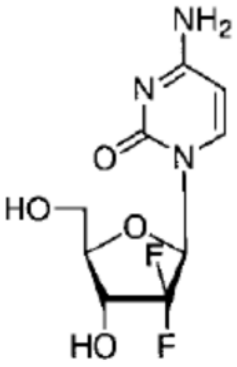
Pankiewicz illustrated this with three well-known examples of existing art (FMAU, FLT, and Gemcitabine), the formulas of which are provided below. EX1002 ¶57 (*citing* EX1010 at 2).



FMAU



FLT



Gemcitabine

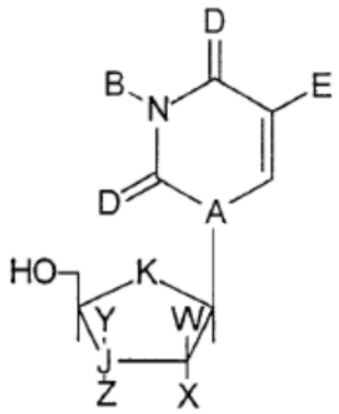
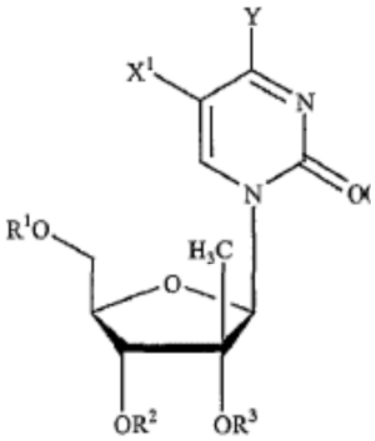
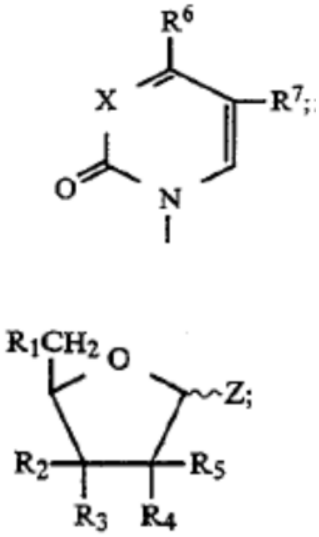
These compounds showed respectively potent antiviral (FMAU, FLT) and anticancer (Gemcitabine) activity while the analogous compounds without fluorine (-H or –OH rather than -F) lacked therapeutic activity. *Id*.

Pankiewicz also taught, "Fluorine is a mimic of a proton (small size) or

hydroxyl group (similar polarity) and is able to form hydrogen bonding (as an acceptor)." EX1002 ¶58 (*citing* EX1010 at 2). Pankiewicz further summarized knowledge in the prior art that electronic effects in C-2'-fluorinated nucleosides stabilize the glycosyl bond towards hydrolysis and affect (i.e., reduce) the susceptibility of cytosine and adenosine analogs for enzymatic deamination. *Id*. This meant that – in addition to benefits in physicochemical effects and drug activity derived from the introduction of a fluoro group – C-2'-fluorinated nucleosides would be more stable and have a longer duration of action in the body. *Id*.

G. Fluorine Was Successful in the 2' Down Position When Methyl Was in the 2' Up Position

U.S. Patent No. 5,420,266 to Britton *et al*. ("Britton"; EX1011) taught a process for improving nucleosides having a formula substantially similar to those in Sommadossi and Klecker discussed in more detail below. EX1002 ¶59. The following table shows these compounds.

Klecker	Sommadossi	Britton
	 (V)	

Id.

Britton recognized the common knowledge that fluoro was an acceptable substituent at the R^4 position (e.g. the 2' down position) and that a lower alkyl, i.e. methyl, was an acceptable substituent at the R^5 position (e.g. the 2' up position). EX1002 ¶60 (citing EX1011 at 2 (2:48-52)). Britton is merely one example of literature expressing the common knowledge that nucleoside drugs were known to successfully have fluoro in the 2' down position when methyl was in the 2' up position. *Id.*

H. Fluorine Was Preferred Over Hydroxy at the 2' Position in Nucleoside Compounds

It was also common knowledge that fluorine was a preferred substituent to be used in nucleosides at the 2' position as compared with hydroxyl groups.

EX1002 ¶61. These nucleosides were known for the treatment of *Flaviviradae* viruses, including Yellow Fever, West Nile virus, Zika virus, Dengue fever, and hepatitis A, B, and C. *Id*.

McAtee represented what was generally known about fluoronucleosides in general and 2'-fluoronucleosides in particular:

> Fluorine may also serve as an isopolar and isosteric mimic of a hydroxyl group since the C-F bond length (1.35 Å) is so similar to the C-O bond length (1.43 Å) and because fluorine is a hydrogen-bond acceptor. **The ability of fluorine to mimic a hydroxyl group makes this atom uniquely suited to nucleoside analogues as a replacement of OH in the sugar portion of a nucleoside.** In addition to our long standing interest in the synthesis of novel nucleoside analogues, we were interested in incorporating an α-fluorine substituent at the 2' position of the sugar ring for several reasons. First, the electronegativity of fluorine should stabilize the anomeric bond and suppress a significant pathway of in vivo decomposition, thereby improving the acid stability of the nucleoside (Scheme 1).
>
> Second, hydroxyl groups often serve as "handles" for the first step in oxidative degradation of biomolecules in vivo. By replacing OH with F, it is possible to create a ribo-like sugar that has a substituent at the 2' position sterically and electronically similar to a hydroxyl group, but which cannot undergo oxidative catabolism. Thus, the in vivo half-life of the compound may be improved."

EX1002 ¶62 (citing EX1009 at 2161 (emphasis added)). McAtee therefore

discloses why fluorine in the 2' position of nucleosides may be preferred over –OH to improve duration of action; namely the additional stability towards metabolism. *Id*.

McAtee also explicitly taught that F and OH are isosteres, and the 2'-α-OH in nucleosides can not only be replaced with F to obtain several 2'-fluoronucleosides, but that such a replacement would improve the stability and *in vivo* half-life of the nucleoside. EX1002 ¶63.

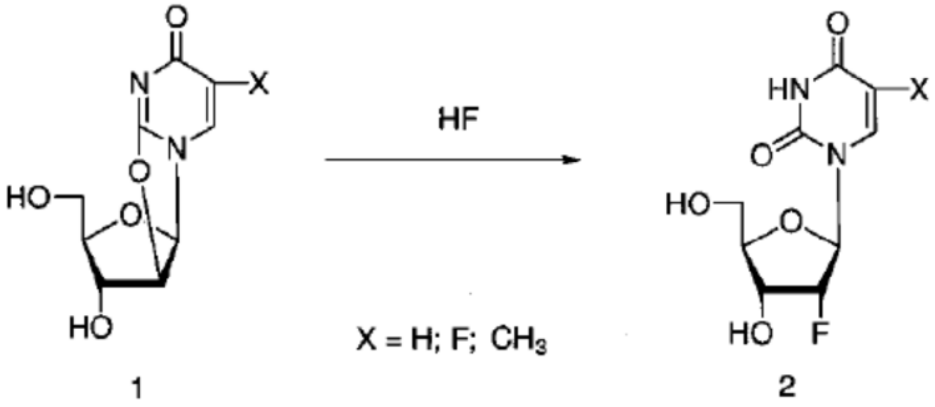
Thus, it was well known by at least the mid-1990s in the field of medicinal chemistry that isosteres were interchangeable and expected to have the same or similar biological effects. EX1002 ¶64. Biological isosteres (bioisosteres) were used in nearly all drug discovery programs in order to improve the properties of drug candidate molecules with respect to (e.g.,) stability, binding potency, metabolism, or pharmacokinetic properties. *Id*. It was common knowledge that replacing isosteres was routine and conventional in drug design and development. *Id*.

I. Fluorine Could be Incorporated Into Nucleoside Sugar Rings by a Number of Synthetic Methods

It was well known that there were a number of different methods for incorporating fluorine into the sugar ring of nucleosides. EX1002 ¶65. In the 1960s, Codington *et. al*., J. Amer. Chem. Soc., 83, 5030-5031 (1961) ("Codington"; EX1012), disclosed the first introduction of fluorine into the C-2'

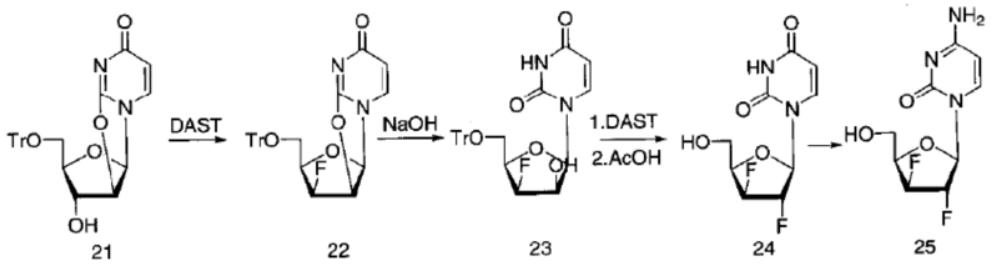
position of a nucleoside by reaction of 2,2'-anhydrocytidine with hydrofluoric acid. *Id*.

Pankiewicz taught that Codington's introduction of fluorine into the C-2' down position could be shown as Scheme I below:

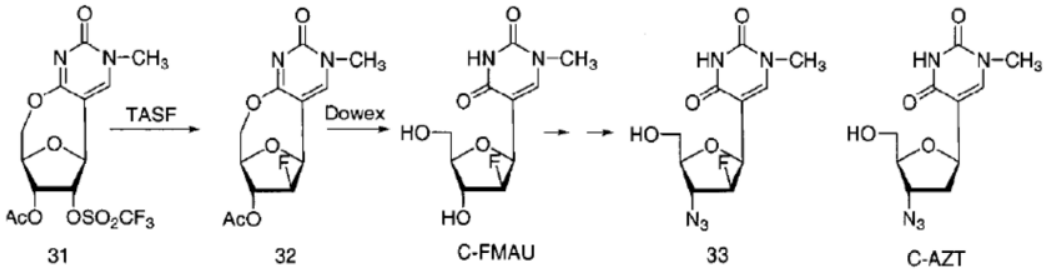


EX1002 ¶66 (citing EX1010 at 2).

The introduction of fluorine into nucleosides could also be accomplished by a second broad strategy. EX1002 ¶67. Pankiewicz summarized the general knowledge by showing that various reagents (e.g., DAST, TASF, KHF_2, tetrabutylammonium fluoride, LiF) could be used to directly replace hydroxyl or related leaving group derivatives on nucleosides. *Id*. Pankiewicz provided representations of these generally known replacements in Schemes 5 and 6, reproduced below.



Scheme 5.

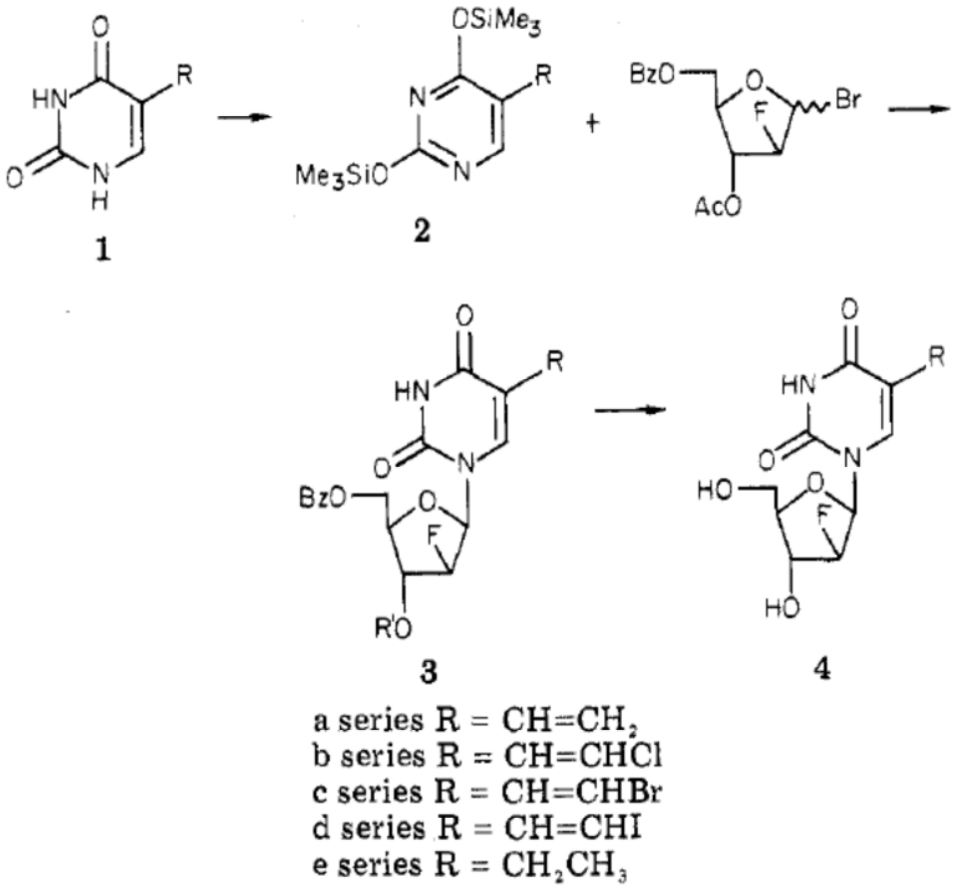


Scheme 6.

Id. (citing EX1010 at 91).

It was also generally known that fluorine could be readily introduced into a sugar ring before the incorporation of a nucleobase, thereby providing a third, very different and versatile approach to the introduction of fluorine into nucleoside drugs. EX1002 ¶68. This is illustrated below in Scheme 1 from Watanabe et. al., *Nucleosides 129. Synthesis of Antiviral Nucleosides: 5-Alkenyl-1-(2-deoxy-2-fluoro-β-D-(arabinofuranosyl)uracils,* J. Med. Chem., 27, 91-94 (1984) ("Watanabe"; EX1013).

Scheme I



Id.

These are some representative examples of references that taught successful fluorination of nucleosides through various methods. EX1002 ¶69. There were many other references that taught the same. *Id*.

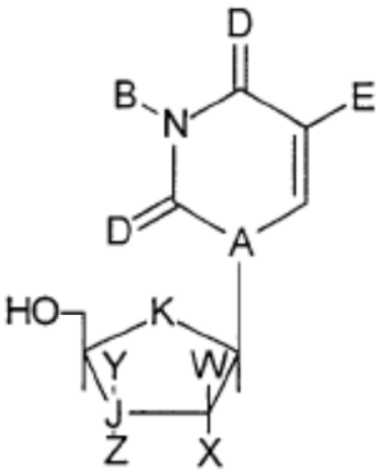
IX. SCOPE AND CONTENT OF THE PRIOR ART

Two specific references teach or suggest the compounds and methods recited in claims 1-19 of the ’572 patent. EX1002 ¶70.

A. WO 99/23104 to Klecker ("Klecker", EX1005)

Klecker is prior art under 35 U.S.C. § 102(b) to the '572 patent because it was published on May 14, 1999, more than a year before the May 30, 2003, filing date of the earliest application to which the '572 patent claims priority. Klecker is a patent application filed by the United States government as represented by the Secretary of Health and Human Services and the National Institutes of Health.

Klecker taught nucleosides having the following formula:



wherein: A = N, C;

B = H, hydroxy, halogen, acyl (C1 -C6), alkyl (C1 –C6,), alkoxy (C1 -C6);

D = O, S, NH2;

E = H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, halogen, or any substituent which is readily cleaved in the body to generate one of the before listed groups;

W, X, Y, Z = H, hydroxy, halogen, alkyl (C1-C6), alkoxy (C1 -C6), a label containing moiety or a label;

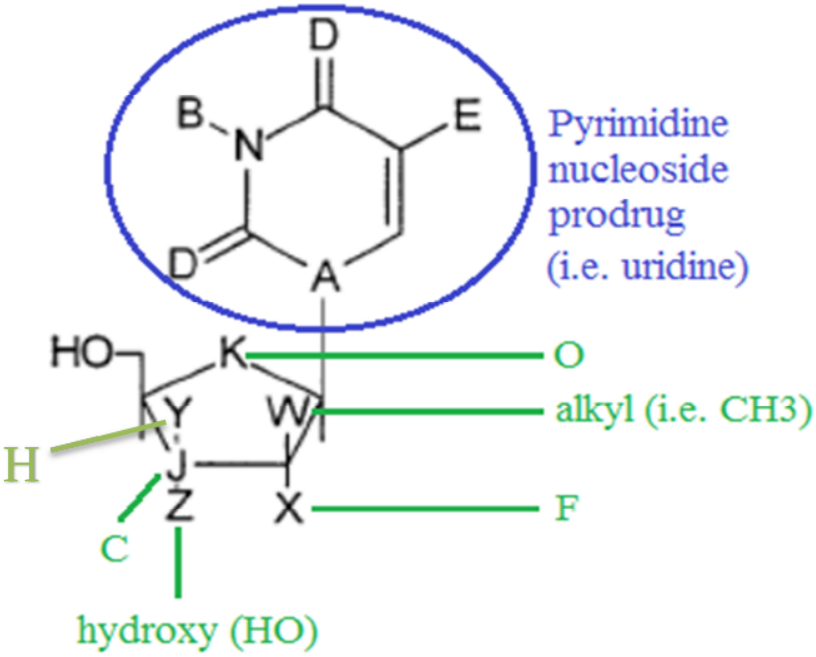
J = C, S; and

K = O, C.

EX1002 ¶71; EX1005 at 3:7-9, 16:17 – 17:7, 46:1-16 (claim 20).

Klecker further specifically taught nucleoside analogues that were pyrimidine nucleosides, and in particular uridine analogues. EX1002 ¶72; EX1005 at 20:24-26. Klecker further specifically taught that, "F can also be placed below the ring at the 2'-position, (i.e., X=F.") which may be described as possessing a stereochemistry of "down" EX1002 ¶72; EX1005 at 21:25-26.

Taking just these disclosures together results in the following sub-genus of compounds:



EX1002 ¶73.

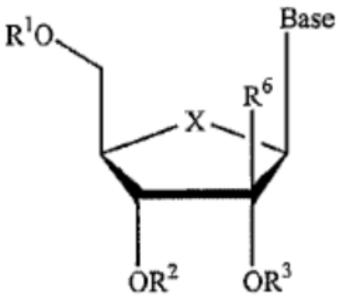
Klecker also taught that a phosphate group could be added at the 5'-position, EX1002 ¶74; EX1005 at 19:7-20, and that pharmaceutical compositions could be made of its compounds. EX1002 ¶74; EX1005 at 20:15-23.

Klecker also taught how to synthesize its nucleosides. EX1002 ¶75; EX1005 at 28:33-33:18. Klecker taught that its compounds could exist as enantiomers and be included in pharmaceutical compositions or formulations. EX1002 ¶75; EX1005 at 17:15-20, 20:10. Klecker also taught a Fluorination Procedure by displacing a C2' leaving group derived from an –OH by KHF_2. EX1002 ¶75; EX1005 at 31:1 – 32:5. Klecker also taught DAST as an alternative fluorination agent. *Id.*

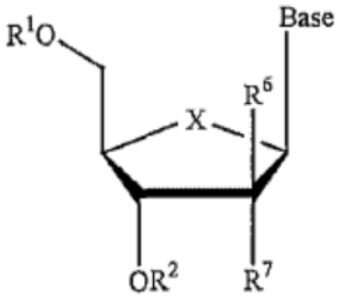
B. WO 01/90121 to Sommadossi ("Sommadossi", EX1006)

Sommadossi is prior art to the '572 patent under 35 U.S.C. § 102(b) because it was published on November 29, 2001, more than a year before the May 30, 2003, filing date of the earliest application to which the '572 patent claims priority.

Sommadossi taught compounds, compositions and methods for the treatment of hepatitis C virus of various formulas, including the following:



(X)

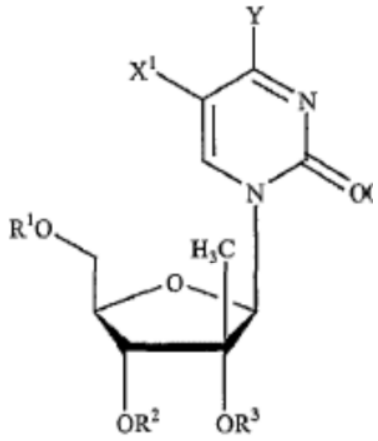


(XI)

EX1002 ¶76; EX1006 at 14:6-27. The only difference between Formula X and Formula XI is the change from OR^3 in Formula X to R^7 in Formula XI. *Id.*

With respect to Formula XI, Sommadossi expressly taught that R^7 could be, "chlorine, bromine, iodine." EX1002 ¶77; EX1006 at 14:6-27. Thus, Sommadossi taught that, for nucleoside prodrugs with this sugar ring structure, OR^3 and R^7 were interchangeable, and that R^7 could be a halogen. *Id*.

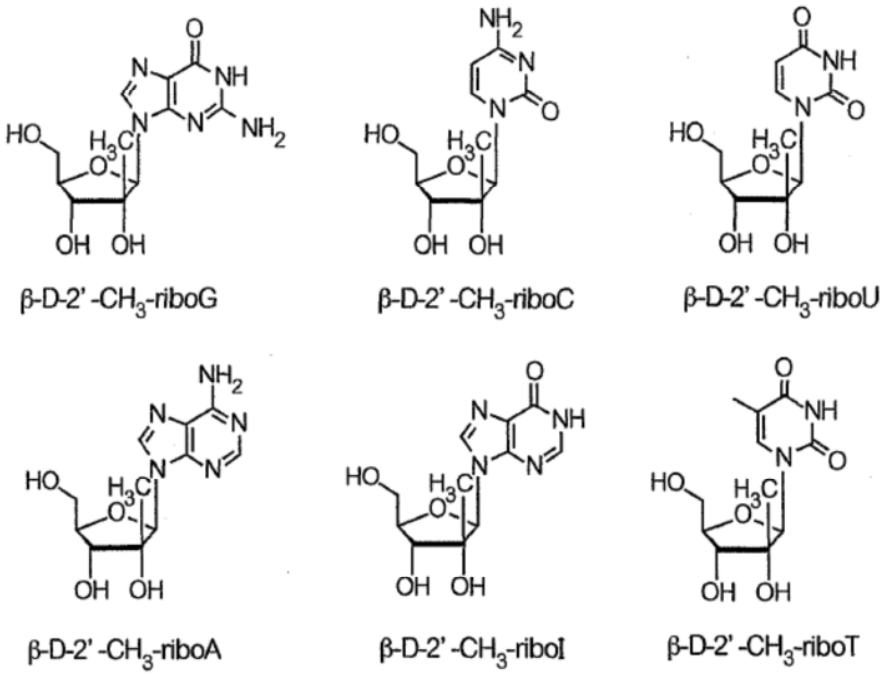
Sommadossi further taught sub-genus of the Formula X nucleoside prodrugs where R^6 was methyl and Base was a pyrimidine or purine base, as shown in the following formula:



(V)

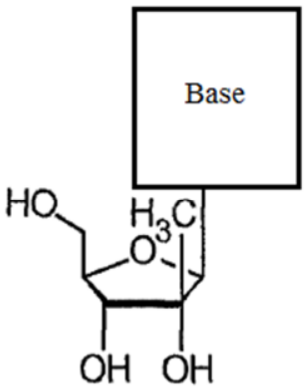
EX1002 ¶78; EX1006 at 12:1-16, 129:1 – 133:1. Sommadossi taught that in this Formula V, R^1 could be H, monophosphate, diphosphate or triphosphate, and R2 could be H. *Id*.

Narrowing down even further to specific compounds, in Figure 1 Sommadossi provided eight illustrative compounds, the first six of which not only all adopted Formula V, but had the exact same sugar ring as shown below:



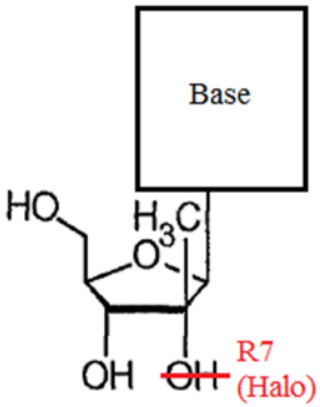
EX1002 ¶79; EX1006 at 294 (FIG. 1 "Chemical Structure of Illustrative Nucleosides") and 203-205 (claims 19-24).

Thus, while Sommadossi taught broad genera of compounds, it also specifically highlighted nucleoside compounds of the following structure as being particularly "Illustrative":



EX1002 ¶80.

Combining this highlighted structure with Sommadossi's express teaching that its nucleosides could substitute R^7 at the 2' down position for OH, and that R^7 could be a halo, a person of skill in the art would have immediately envisaged the following compound being taught by Sommadossi:



EX1002 ¶81.

While Sommadossi only expressly identified chlorine, bromine, and iodine as halogens that could be substituted at the R^7 position, *see*, *e.g.*, EX1006 at 14:24-27, one of ordinary skill in the art would have interpreted the exclusion of fluorine to have been a typographical mistake because there is no explanation in Sommadossi why fluorine was not included in the list of substituents for the 2' down position. EX1002 ¶82. Further, Sommadossi repeatedly includes fluorine when referencing other halogens. *Id*. at 14:20-23 (regarding R^6). A POSA would have interpreted Sommadossi to teach the inclusion of fluorine when discussing chlorine, bromine and iodine, including specifically at R^7. EX1002 ¶82.

Regardless of the reason for the failure to expressly include fluorine (-F)

from the listed halogen substituents at R^7, as discussed above, it was generally known that fluorine was a common bioisosteric replacement for an -OH group in medicinal chemistry and that the use of fluorine at the C2' position of nucleoside drugs was useful and indeed preferred when methyl was in the 2' up position. EX1002 ¶83.

Sommadossi's teaching that R^7 could be chlorine, bromine and iodine would thus inherently teach one of skill in the art that R^7 could also be fluorine. EX1002 ¶84.

Sommadossi also taught that a phosphate group could be added at the 5'-postiion, EX1002 ¶85; EX1006 at 8:22, and that pharmaceutical compositions could be made of its compounds, EX1002 ¶85; EX1006 at 8:15.

Sommadossi also taught how to synthesize its nucleosides. EX1002 ¶86; EX1006 at 64-65 ("Scheme 1"). Sommadossi further taught liposomal compositions comprising liposomes in combination with its compounds as a pharmaceutical delivery form. EX1002 ¶86; EX1006 at 62:10-21.

X. CLAIMS 1-19 ARE UNPATENTABLE

Each and every feature of claims 1-19 of the '572 patent can be found in the prior art references identified below in Grounds 1 and 2. EX1002 ¶87. In addition, a POSA would have been motivated to combine the references set forth in Ground 3 below and had a reasonable expectation of success of arriving at the subject

matter of each of the claims of the ’572 patent. EX1002 ¶87.

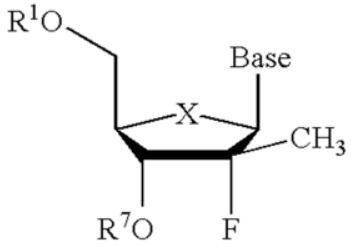
Each of claims 1-19 is presented below followed by an analysis of the claims. The analysis below identifies exemplary disclosure of the cited references with respective to the corresponding claim elements, and is not meant to be exhaustive. EX1002 ¶88.

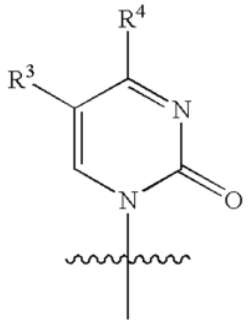
A. Ground 1: Claims 1-16 Were Anticipated by Klecker

Klecker (EX1005) taught every element of claims 1-16 of the ‘572 patent. EX1002 ¶89.

1. Claims 1-5 (genera of compounds)

Claim 1 of the ‘572 patent recites:

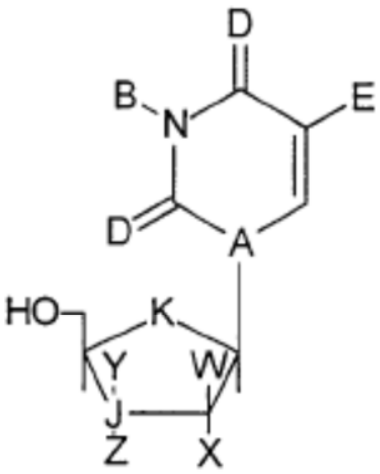
> 1. A (2′R)-2′-deoxy-2′-fluoro-2′-C-methyl nucleoside (β-D or β-L) or its pharmaceutically acceptable salt of the structure:
>
> 
>
>
> wherein Base is a pyrimidine base represented by the following formula:



X is O; R^1 and R^7 are independently H, a monophosphate, a diphosphate, a triphosphate, a H-phosphonate, alkyl, an alkyl sulfonyl, or an arylalkyl sulfonyl; and

R^3 is H and R^4 is NH_2 or OH.

EX1001 at 40:27-57. As discussed above, Klecker taught the following formulas:



wherein: A = N, C;

B = H, hydroxy, halogen, acyl (C1 -C6), alkyl (C1 –C6,), alkoxy (C1 -C6);

D = O, S, NH2;

E = H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, halogen, or any substituent which is readily cleaved in the body to generate one of the before listed groups;

W, X, Y, Z = H, hydroxy, halogen, alkyl (C1-C6), alkoxy (C1 -C6), a label containing moiety or a label;

J = C, S; and

K = O, C.

See, e.g., EX1005 at 46:1-17 (claim 20).

For the substituents A, B, D, and E, Klecker taught they would be selected from typical pyrimidine bases, EX1005 at 32:19-22, which would then lead one of skill to immediately envisage the generally known cytidine and uridine bases, wherein A would be N, B would be H, D would be O or NH_2 and E would be H. EX1002 ¶91.

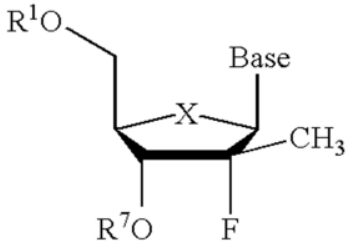
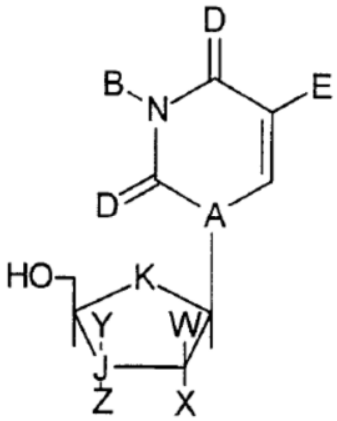
Klecker also taught fluorine was a preferred substituent at the X position, EX1005 at 21:21-26, and one of skill in the art would generally know that methyl would be a correspondingly preferred selection at the W position. EX1002 ¶92. Klecker taught W can be an alkyl (C1 – C6). *Id.* at 46:11-15 (claim 20). A POSA would know from general knowledge and common sense that methyl is a preferred lower alkyl in that group. EX1002 ¶92.

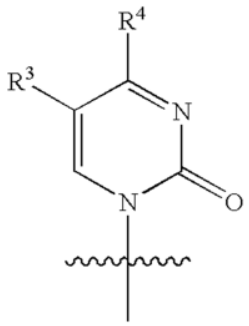
One of ordinary skill in the art would envisage K as being either O or C, since those were the only two substituents identified by Klecker for that position. EX1002 ¶93; EX1005 at 46:16 (claim 20). A POSA would also know from general knowledge and common sense that K being O creates a natural sugar ring commonly found in nucleosides. EX1002 ¶93.

At the 3' position, while Klecker identified a number of potential substituents, C is the first substituent identified for J, and H and OH are the first

two substituents identified for Y and Z. EX1005 at 46:11-15. Thus, one of ordinary skill in the art would envisage their implementations, i.e. J as C, Y as H and Z as OH. EX1002 ¶94.

Thus, one of ordinary skill in the art reading Klecker would immediately envisage compounds that fall squarely within the compounds of claim 1 of the '572 patent. EX1002 ¶95. This is shown in the chart below:

'572 Patent, Claim 1	Klecker
1. A (2′R)-2′-deoxy-2′-fluoro-2′-C-methyl nucleoside (β-D or β-L) or its pharmaceutically acceptable salt of the structure:  	 Given the teachings of Klecker and the general knowledge in the art, one would envisage Klecker to specifically teach W as CH_3, X as F, Y as H, J as C, and Z as OH. EX1005 at 44:1-17.

wherein Base is a pyrimidine base represented by the following formula: 	Klecker taught the base of its nucleosides could be pyrimidine bases, which would therefore have A as N, B as H, D as O and E as H. EX1005 at 32:19-22.
X is O;	Klecker taught K can only be O or C and one of skill would immediately envisage both alternatives. EX1005 at 44:16.
R^1 and R^7 are independently H, a monophosphate, a diphosphate, a triphosphate, a H-phosphonate, alkyl, an alkyl sulfonyl, or an arylalkyl sulfonyl; and	See formula above showing H in the same position as R^1 and R^7. Klecker teaches that –OH in the above structure may be phosphorylated to nucleotides and incorporated into DNA. EX1005 at 25:5-32.
R^3 is H	The first substituent taught by Klecker for this position is H, and thus one of skill would immediately envisage that selection. EX1005 at 46:3.
R^4 is NH_2 or OH.	Only three substituents are taught by Klecker for this position, D, and they include NH_2. One of skill would immediately envisage each of the three alternatives. EX1005 at 46:5.

EX1002 ¶95.

As shown in the chart, a POSA reading Klecker would immediately envisage compounds that fall within claim 1 of the ‘572 patent for the reasons

explained above. EX1002 ¶96. Klecker thus anticipated claim 1.

Claim 2 depends from claim 1 and merely adds, "wherein R^7 is H and R^1 is a monophosphate, or diphosphate, or a triphosphate." EX1001 at 40:58-61. Claim 3 depends from claim 1 and merely adds, "R^7 is H and R^1 is diphosphate or a triphosphate." *Id*. at 40:62-64. Claim 4 depends from claim 1 and merely adds, "wherein R^7 is H and R^1 is triphosphate." *Id*. at 40:65-67. Claim 5 depends from claim 1 and merely adds, "wherein R^1 and R^7 are H." *Id*. at 41:1-3.

Klecker expressly taught Z in the same position as R^7O in the '572 patent, and the second substituent identified by Klecker for Z is OH. EX1002 ¶98; EX1005 at 46:1-17. A POSA would immediately envisage the selection of OH for Z, not only because it was listed second by Klecker, but also because it was generally known to be a natural selection for the sugar of nucleosides. EX1002 ¶98. Therefore, Klecker taught R^7 is H. *Id*.

While Klecker does not expressly teach a monophosphate, diphosphate, or triphosphate at the same position identified in claim 1 of the '572 patent as R^1, Klecker did teach that its compounds are converted into nucleotides, including by phosphorylation. EX1002 ¶99; EX1005 at 25:5-32. Such phosphorylation would inherently include the mono-, di- and tri- phosphate forms of Klecker's compounds. EX1002 ¶99.

Specifically, a POSA would also have known that the monophosphate,

diphosphate, and triphosphate at R^1 in claim 1 of the '572 patent described intermediates in the obligatory pathway for intracellular bioactivation of nucleoside drugs. EX1002 ¶100.

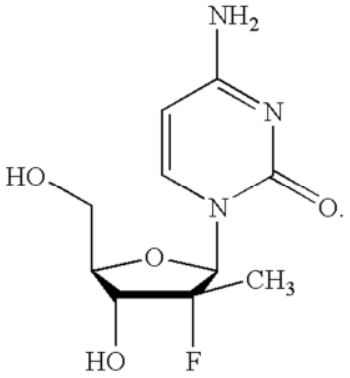
Nucleoside drugs act by inhibiting processes that involve DNA or RNA. *Id*. Such nucleoside drugs are not delivered to a patient as these phosphate forms. *Id*. Rather, they are converted into these mono-, di-, and triphosphates *in vivo* as part of the process by which the body activates them for use. *Id*. Such mono-, di, and triphosphate derivatives of nucleosides were well known. *Id*. For this reason, Klecker inherently taught R^1 is triphosphate, as recited in claims 2, 3 and 4 of the '572 patent. EX1002 ¶101.

Klecker also expressly taught its compounds had OH at the 5' position. EX1002 ¶102; EX1005 at 46:1-2. Thus, the substituent identified as R^1 in claim 1 of the '572 patent is taught to be H by Klecker. EX1002 ¶102.

Klecker thus anticipated claims 2, 3 and 4.

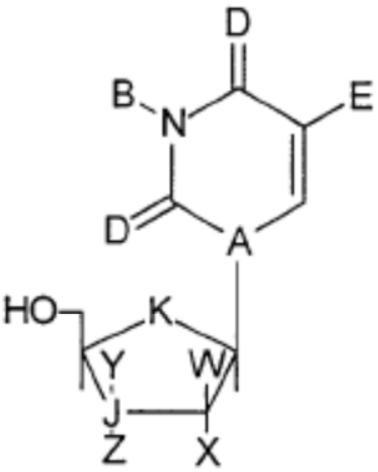
2. <u>Claim 6 (specific compound)</u>

Claim 6 claims, "A (2′R)-2′-deoxy-2′-fluoro-2′-C-methyl nucleoside (β-D) or its pharmaceutically acceptable salt thereof of the formula:



EX1001 at 65:4-19.

Klecker in Figure 1 and claim 20 taught:



wherein: A = N, C;

B = H, hydroxy, halogen, acyl (C1 -C6), alkyl (C1 –C6,), alkoxy (C1 -C6);

D = O, S, NH2;

E = H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, halogen, or any substituent which is readily cleaved in the body to generate one of the before listed groups;

W, X, Y, Z = H, hydroxy, halogen, alkyl (C1-C6), alkoxy (C1 -C6), a label containing moiety or a label;

J = C, S; and

K = O, C.

EX1005 at 46:1-17.

As discussed above with respect to claim 1, Klecker expressly taught the specific selection of substituents as claimed in claim 6. EX1002 ¶105.

First, for the substituents A, B, D, and E, Klecker taught they would be selected from typical pyrimidine bases, EX1005 at 32:19-22, which would lead one of skill to immediately envisage a cytidine base, wherein A would be N, B would be H, D would be NH, D would be O and E would be H. EX1002 ¶106.

Klecker also taught fluorine was a preferred substituent at the X position, EX1005 at 21:21-26, and one of skill in the art would generally know that methyl would be a correspondingly preferred selection at the W position. EX1002 ¶107. Klecker taught W can be an alkyl (C-1 – C-6). *Id*. at 46:11-15 (claim 20). A POSA would know from general knowledge and common sense that methyl is a preferred lower alkyl in that group. EX1002 ¶107.

One of ordinary skill in the art would envisage K as being either O or C, since those were the only two substituents identified by Klecker for that position. EX1002 ¶108; EX1005 at 46:16 (claim 20). A POSA would also know from general knowledge and common sense that K being O creates a natural sugar ring commonly found in nucleosides. EX1002 ¶108.

At the 3’ position, while Klecker identified a number of potential substituents, C is the first substituent identified for J, and H and OH are the first two substituents identified for Y and Z. EX1005 at 46:11-15. Thus, one of ordinary

skill in the art would envisage their implementations, i.e. J as C, Y as H and Z as OH. EX1002 ¶109.

One of skill in the art reading Klecker would immediately envisage the specific compound of claim 6 of the ‘572 patent. EX1002 ¶110. Klecker thus anticipated claim 6.

3. Claims 7-12 (pharmaceutical compositions)

Claims 7-12 claim pharmaceutical compositions comprising the nucleosides of claims 1-6 or their pharmaceutically acceptable salts and a pharmaceutically acceptable carrier. EX1001 at 65:20-37.

Klecker taught the following respecting pharmaceutical compositions of the compounds of claim 20,

> The formulation may be presented in a unit dosage form and may be prepared by conventional pharmaceutical techniques. Such techniques include the step of bringing into association the active ingredient and the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into association, the active ingredient with liquid carriers or finely divided solid carriers or both, optionally with one or more accessory ingredients, and then, if necessary, shaping the product.

EX1005 at 19:37–20:9.

In addition, Klecker taught:

> It should also be understood that the compounds or pharmaceutical

compositions of the present invention may also be administered by topical, transdermal, oral, rectal or parenteral (for example, intravenous, subcutaneous or intramuscular) route or may be incorporated into biodegradable polymers allowing for the sustained release of the compound, the polymers being implanted in the vicinity of the tumor or where the drug delivery is desired."

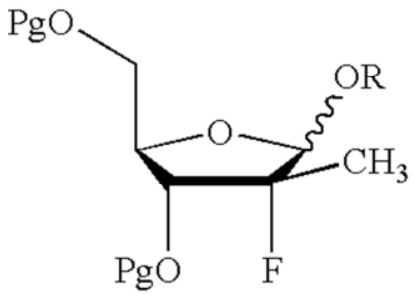
EX10 and 20:13-23. Thus, Klecker taught all of the additional limitations of claims 7-12. EX1002 ¶113. For these reasons, Klecker anticipated claims 7-12.

4. <u>Claims 13 and 14 (method of synthesizing)</u>

Claim 13 of '572 recites the following method of synthesis:

A method of synthesizing a nucleoside of claim 1, which comprises glycosylating the pyrimidine with a compound having the following structure;

1-4

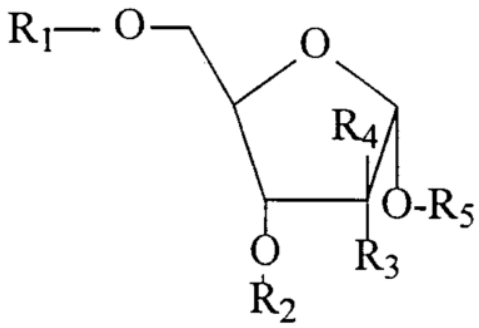


wherein R is lower alkyl, acyl, benzoyl, or mesyl; and Pg is selected from among C(O)-alkyl, C(O)Ph, C(O)aryl, CH_3, CH_2-alkyl, CH_2-alkenyl, CH_2Ph, CH_2-aryl, CH_2O-alkyl, CH_2O-aryl, SO_2-alkyl, SO_2-aryl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or both Pg's may come together to for a 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene).

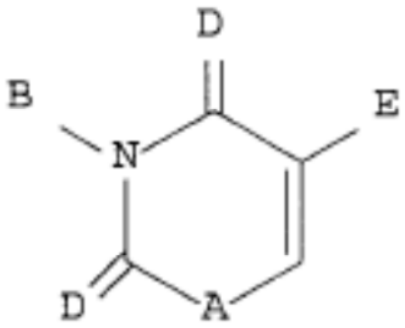
EX1001, 65:38 – 66:4.

Klecker teaches a method of synthesis its compounds comprising the steps of:

contacting a first molecule of the formula



wherein R_1, R_2 and R_5 may be the same or different and are blocking groups, R_3 is a leaving group and R_4 is H, with a second molecule containing a label under conditions causing the transfer of the label to the position occupied by R_4 ; and contacting the resultant labeled first molecule with a molecule having the structure

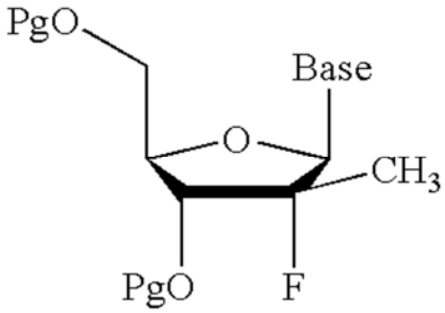


wherein the molecule of such formula contains the substituents discussed above with respect to claims 1 and 6. EX1005, 47:1 – 48:2 (claim 23).

Thus, Klecker taught a nucleoside forming reaction identical to that in claim 13 of the ‘572 patent, because the only difference between them is that Clark claims protecting groups, which Klecker referred to as blocking groups. EX1002 ¶116. There is no difference between Clark’s “protecting groups” and Klecker’s “blocking groups, with the exception that Klecker does not further define these groups while Clark gives many examples of protecting groups..” EX1002 ¶116.

Claim 14 of the ‘572 patent recites:

> 14. A method of synthesizing the nucleoside of claim 1, which comprises selectively deprotecting a 3′-OPg or a 5′-OPg of a compound having the following structure:



> wherein each Pg is independently a protecting group selected from among C(O)-alkyl, C(O)Ph, C(O)aryl, CH_3, CH_2-alkyl, CH_2-alkenyl, CH_2Ph, CH_2-aryl, CH_2O-alkyl, CH_2O-aryl, SO_2-alkyl, SO_2-aryl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or both Pg's may come together to for a 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene).

EX1001, 66:5-23.

Klecker taught:

> To remove the blocking groups from the 3'- and 5'- positions of the sugar, and the 2- and 4-positions of the base, 0.3 mL of 2M ammonia in methanol is added. The mixture is heated at 130 °C for 30 minutes.

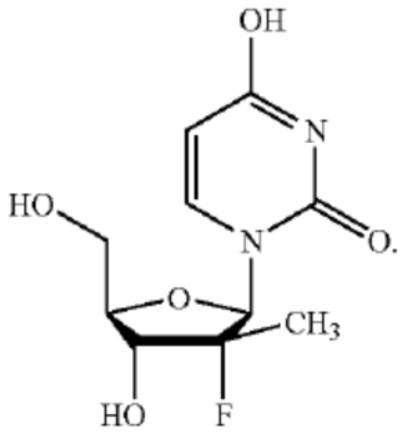
EX1005, 33:4-9.

Thus, Klecker taught a nucleoside forming reaction identical to that in claim 14 of the ‘572 patent, because the only difference between them is that Clark claims protecting groups, which Klecker referred to as blocking groups. EX1002 ¶119. There is no difference between Clark’s “protecting groups” and Klecker’s “blocking groups”, with the exception that Klecker does not further define these groups while Clark gives many examples of protecting groups.EX1002 ¶119.

For these reasons, Klecker anticipated claims 13 and 14.

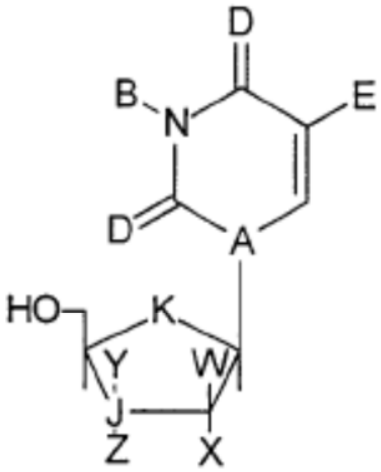
5. <u>Claim 15 (specific compound)</u>

Claim 15 recites, “A (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl nucleoside (β-D) or its pharmaceutically acceptable salt thereof of the formula:



EX1001 at 66:23-39. This is the same compound as in claim 6 except that it has a uridine base as opposed to a cytidine base. EX1002 ¶120.

Klecker in Figure 1 and claim 20 taught:



wherein: A = N, C;

B = H, hydroxy, halogen, acyl (C1 -C6), alkyl (C1 –C6,), alkoxy (C1 -C6);

D = O, S, NH2;

E = H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, halogen, or any substituent which is readily cleaved in the body to generate one of the before listed groups;

W, X, Y, Z = H, hydroxy, halogen, alkyl (C1-C6), alkoxy (C1 -C6), a label containing moiety or a label;

J = C, S; and

K = O, C.

EX1005 at 46:1-17.

As discussed above with respect to claim 1, Klecker expressly taught the specific selection of substituents as claimed in claim 15 of the ‘572 patent. EX1002 ¶122.

First, for the substituents A, B, D, and E, Klecker taught they would be

selected from typical pyrimidine bases, EX1005 at 32:19-22, which would lead one of skill to immediately envisage a uridine base, wherein A would be N, B would be H, D would be O, and E would be H. EX1002 ¶123. The combination of double bond to O at the top position of the base combined with a single bond to NH is equivalent to (a tautomer of) the compound in '572 patent claim 15 with a single bond to OH at the top combined with a double bond to N. EX1002 ¶123.

Klecker also taught fluorine was a preferred substituent at the X position, EX1005 at 21:21-26, and one of skill in the art would generally know that methyl would be a correspondingly preferred selection at the W position. EX1002 ¶124. Klecker taught W can be an alkyl (C1 – C6). *Id*. at 46:11-15 (claim 20). A POSA would know from general knowledge and common sense that methyl is a preferred lower alkyl in that group. EX1002 ¶124.

One of ordinary skill in the art would envisage K as being either O or C, since those were the only two substituents identified by Klecker for that position. EX1002 ¶125; EX1005 at 46:16 (claim 20). A POSA would also know from general knowledge and common sense that K being O creates a natural sugar ring commonly found in nucleosides. EX1002 ¶125.

At the 3' position, while Klecker identified a number of potential substituents, C is the first substituent identified for J, and H and OH are the first two substituents identified for Y and Z. EX1005 at 46:11-15. Thus, one of ordinary

skill in the art would envisage their implementations, i.e. J as C, Y as H and Z as OH. EX1002 ¶126.

For these reasons, one of skill in the art reading Klecker would immediately envisage the specific compound of claim 15 of the ‘572 patent. EX1002 ¶127. Klecker thus anticipated claim 15.

6. Claim 16 (pharmaceutical composition)

Claim 16 of ’572 recites, “A pharmaceutical composition comprising the nucleoside of claim 15 or its pharmaceutically acceptable salt and optionally a pharmaceutically acceptable carrier.” EX1001 at 66:40-41.

Klecker taught the following respecting pharmaceutical compositions of the compounds of claim 20,

> The formulation may be presented in a unit dosage form and may be prepared by conventional pharmaceutical techniques. Such techniques include the step of bringing into association the active ingredient and the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into association, the active ingredient with liquid carriers or finely divided solid carriers or both, optionally with one or more accessory ingredients, and then, if necessary, shaping the product.

EX1005 at 19:37–20:9.

In addition, Klecker taught:

> It should also be understood that the compounds or pharmaceutical

compositions of the present invention may also be administered by topical, transdermal, oral, rectal or parenteral (for example, intravenous, subcutaneous or intramuscular) route or may be incorporated into biodegradable polymers allowing for the sustained release of the compound, the polymers being implanted in the vicinity of the tumor or where the drug delivery is desired."

EX10 and 20:13-23. Thus, Klecker taught all of the additional limitations of claim 16. EX1002 ¶131. Therefore, Klecker anticipated claim 16.

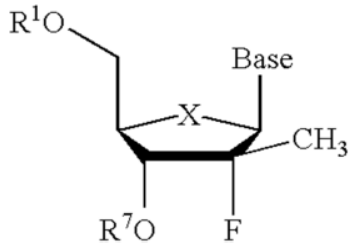
B. Ground 2: Claims 1-19 were Anticipated by Sommadossi

Sommadossi (EX1006) taught every element of claims 1-19 of the '572 patent.

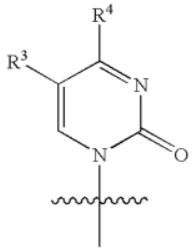
1. Claims 1-5 (genera of compounds)

Claim 1 of the '572 patent recites:

1. A (2′R)-2′-deoxy-2′-fluoro-2′-C-methyl nucleoside (β-D or β-L) or its pharmaceutically acceptable salt of the structure:



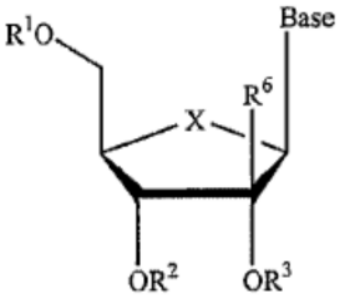
wherein Base is a pyrimidine base represented by the following formula:



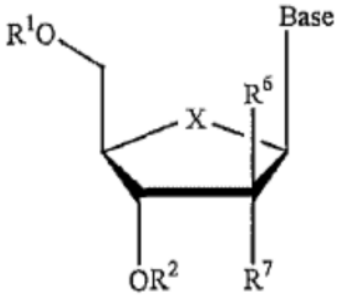
X is O; R^1 and R^7 are independently H, a monophosphate, a diphosphate, a triphosphate, a H-phosphonate, alkyl, an alkyl sulfonyl, or an arylalkyl sulfonyl; and

R^3 is H and R^4 is NH_2 or OH.

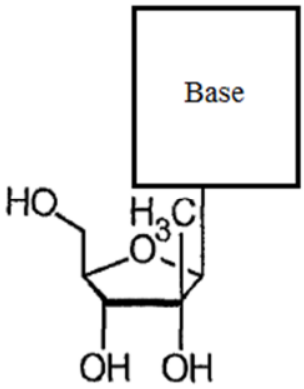
EX1001 at 40:27-57. As discussed above, Sommadossi taught the following formulas:



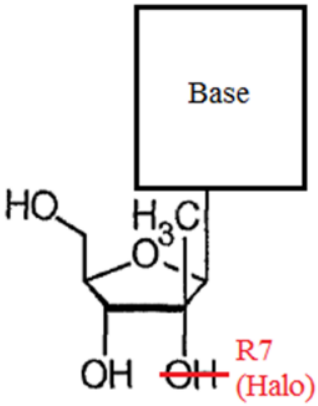
(X)



(XI)



(Fig. 1)



(Fig. 1 with 2' down substitution)

EX1002 ¶132; EX1006 at 14:6-27; 294 (FIG. 1 "Illustrative Nucleosides").

The first two formulas on the top are genera of compounds taught by Sommadossi that are identical to each other except for the 2' down position, where Formula X has OR^3 and Formula XI has R^7. EX1002 ¶133; EX1006 at 14:24-27. Thus, Sommadossi expressly taught making such a substitution. EX1002 ¶133.

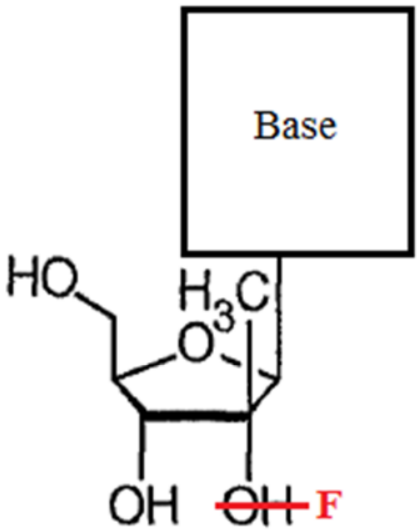
The bottom left formula represents the six illustrative nucleoside species provided by Sommadossi in Figure 1. EX1002 ¶134; EX1006 at 294. The formula on the bottom right is identical to the formula on the bottom left except for making the same substitution of R^7 at the 2' down position that Formula XI made of Formula X. EX1002 ¶134. The formula on the bottom right then notes Sommadossi's teaching that R^7 could be a halo. EX1002 ¶134.

While it is true that Sommadossi only expressly taught that R^7 could be "chlorine, bromine, iodine," EX1006 at 14:26, as discussed above, a POSA would have known that in the field of nucleoside drugs, halogens are substitutable for

each other and, thus, Sommadossi's express teaching of "chloro, bromo and iodo," also inherently taught fluoro. EX1002 ¶135. Further, there is no discussion in Sommadossi of why R^7 could not be fluoro to contradict this common knowledge, and Sommadossi taught that R^6 could be "chloro, bromo, fluoro, iodo." EX1002 ¶135; EX1006 at 14:23.

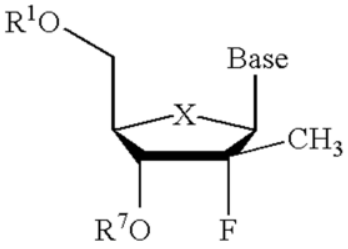
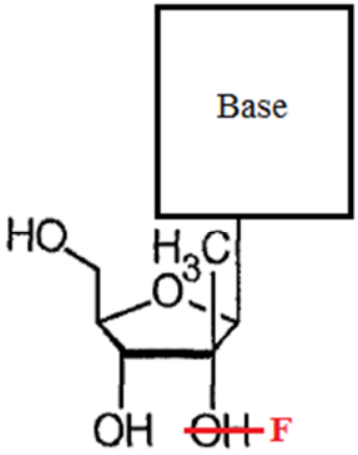
Further, as discussed above, it was also common knowledge, as shown by McAtee, that fluorine was not only a possible substitute for hydroxy at the 2' position, but a preferred one. EX1002 ¶136; EX1009. It was also common knowledge, as shown by Britton, that fluorine was successful in the 2' down position when methyl was in the 2' up position. EX1002 ¶136; EX1011. This common knowledge would have led one, when viewing the disclosure of Sommadossi, to at once envisage F in the 2' down position because CH^3 was in the 2' up position. EX1002 ¶136.

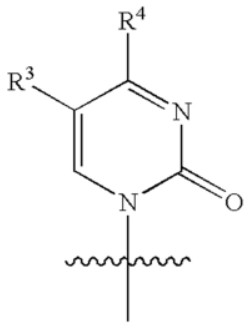
Thus, one of ordinary skill in the art reading Sommadossi would at once envisage the following nucleoside formula:



EX1002 ¶137.

The chart below compares this nucleoside taught by Sommadossi with claim 1 of the ‘572 patent.

‘572 Patent, Claim 1	Sommadossi
1. A (2′R)-2′-deoxy-2′-fluoro-2′-C-methyl nucleoside (β-D or β-L) or its pharmaceutically acceptable salt of the structure:  	 EX 1006 at 14:5-27; 294 (FIG. 1).

wherein Base is a pyrimidine base represented by the following formula: 	"Base is a purine or pyrimidine base as defined herein." EX 1006 at 14:11. Figure 1 of Sommadossi shows 2 "Illustrative" examples of its compounds that have pyrimidine bases represented by this same formula. EX1006 at 294 (FIG. 1).
X is O;	Figure 1 of Sommadossi shows O in the same position as X. EX 1006 at 294 (FIG. 1).
R^1 and R^7 are independently H, a monophosphate, a diphosphate, a triphosphate, a H-phosphonate, alkyl, an alkyl sulfonyl, or an arylalkyl sulfonyl; and	Figure 1 of Sommadossi shows H in the same position as R^1 and R^7. EX 1006 at 294 (FIG. 1).
R^3 is H and	Figure 1 of Sommadossi shows 8 illustrative nucleosides, at least the second and third of which (the cytidine and uridine bases) have H at the R^3 position. EX 1006 at 294 (FIG. 1).
R^4 is NH_2 or OH.	Figure 1 of Sommadossi shows 8 illustrative nucleosides, at least the second and third of which (the cytidine and uridine bases) have R^4 is NH_2 or OH. EX 1006 at 294 (FIG. 1).

EX1002 ¶138.

As shown in the chart, a POSA reading Sommadossi would immediately envisage compounds that fall within claim 1 of the '572 patent for the reasons

explained above. EX1002 ¶139. Sommadossi thus anticipated claim 1.

Claim 2 depends from claim 1 and merely adds, "wherein R^7 is H and R^1 is a monophosphate, or diphosphate, or a triphosphate." EX1001 at 40:58-61. Claim 3 depends from claim 1 and merely adds, "R^7 is H and R^1 is diphosphate or a triphosphate." *Id*. at 40:62-64. Claim 4 depends from claim 1 and merely adds, "wherein R^7 is H and R^1 is triphosphate." *Id*. at 40:65-67. Claim 5 depends from claim 1 and merely adds, "wherein R^1 and R^7 are H." *Id*. at 41:1-3.

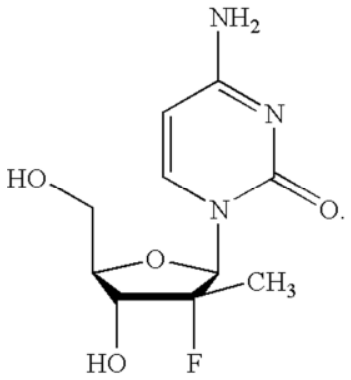
As shown in the first row of the chart above, Sommadossi expressly taught H in the same position as R^7 and in fact highlighted that selection in its Figure 1 "Illustrative Nucleosides." EX1002 ¶141; EX1006 at 294. Sommadossi also taught that it could have a monophosphate, diphosphate, or triphosphate at the same position identified in claim 1 as R^1. *See*, for example, Sommadossi's Formula V, position R^1, which can be, "phosphate (including monophosphate, disphosphate, triphosphate)." EX1006 at 12:1-5. Thus, Sommadossi taught all of the additional limitations of claims 2-5. EX1002 ¶141. Therefore, Sommadossi anticipated claims 2-5.

A POSA would also have known that the monophosphate, diphosphate, and triphosphate at R^1 as identified in claim 1 describes intermediates in the obligatory pathway for intracellular bioactivation of nucleoside drugs. EX1002 ¶142. Nucleoside drugs act by inhibiting processes that involve DNA or RNA. The

phosphate derivatives of such nucleoside drugs are not inventive nor are they delivered as these phosphate derivatives. *Id*. Rather, they are converted into these mono-, di-, and triphosphates *in vivo* as part of the process by which the body activates them for use. *Id.* Such mono-, di, and triphosphate derivatives of nucleosides were well known before the ‘572 patent. *Id*.

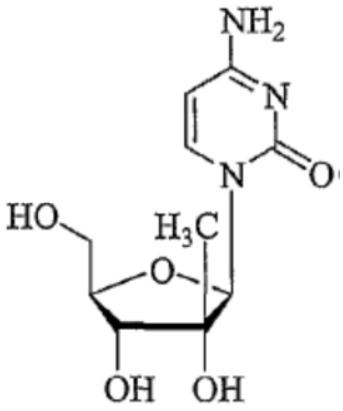
2. <u>Claim 6 (specific compound)</u>

Claim 6 claims, “A (2′R)-2′-deoxy-2′-fluoro-2′-C-methyl nucleoside (β-D) or its pharmaceutically acceptable salt thereof of the formula:



EX1001 at 65:4-19.

Sommadossi in Figure 1 and claim 175 taught a compound of the structure:



EX1006 at 292, 294.

As discussed above with respect to claim 1, Sommadossi also taught substituting F for OH at the 2' position, which renders its compound identical to the one claimed in claim 6. EX1002 ¶145. Sommadossi thus anticipated claim 6.

3. Claims 7-12 (pharmaceutical compositions)

Claims 7-12 claim pharmaceutical compositions comprising the nucleosides of claims 1-6 or their pharmaceutically acceptable salts and a pharmaceutically acceptable carrier. EX1001 at 65:20-37.

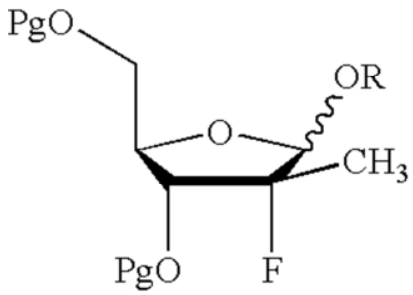
Sommadossi taught, "The invention as disclosed herein is a … composition … or a pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier." EX1006 at 21:22-26. Thus, Sommadossi taught all of the additional limitations of claims 7-12. EX1002 ¶147. Therefore, Sommadossi anticipated claims 7-12.

4. Claims 13 and 14 (method of synthesizing)

Claim 13 of '572 recites the following method of synthesis:

> A method of synthesizing a nucleoside of claim 1, which comprises glycosylating the pyrimidine with a compound having the following structure;

1-4

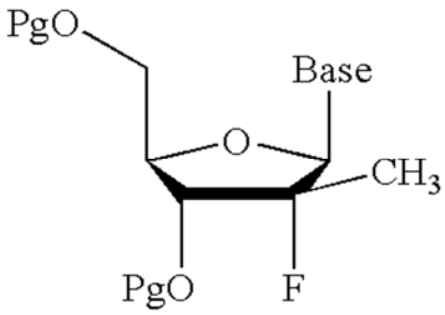


wherein R is lower alkyl, acyl, benzoyl, or mesyl; and Pg is selected from among C(O)-alkyl, C(O)Ph, C(O)aryl, CH_3, CH_2-alkyl, CH_2-alkenyl, CH_2Ph, CH_2-aryl, CH_2O-alkyl, CH_2O-aryl, SO_2-alkyl, SO_2-aryl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or both Pg's may come together to for a 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene).

EX1001, 65:38 – 66:4.

Claim 14 of the ‘572 patent recites:

14. A method of synthesizing the nucleoside of claim 1, which comprises selectively deprotecting a 3′-OPg or a 5′-OPg of a compound having the following structure:



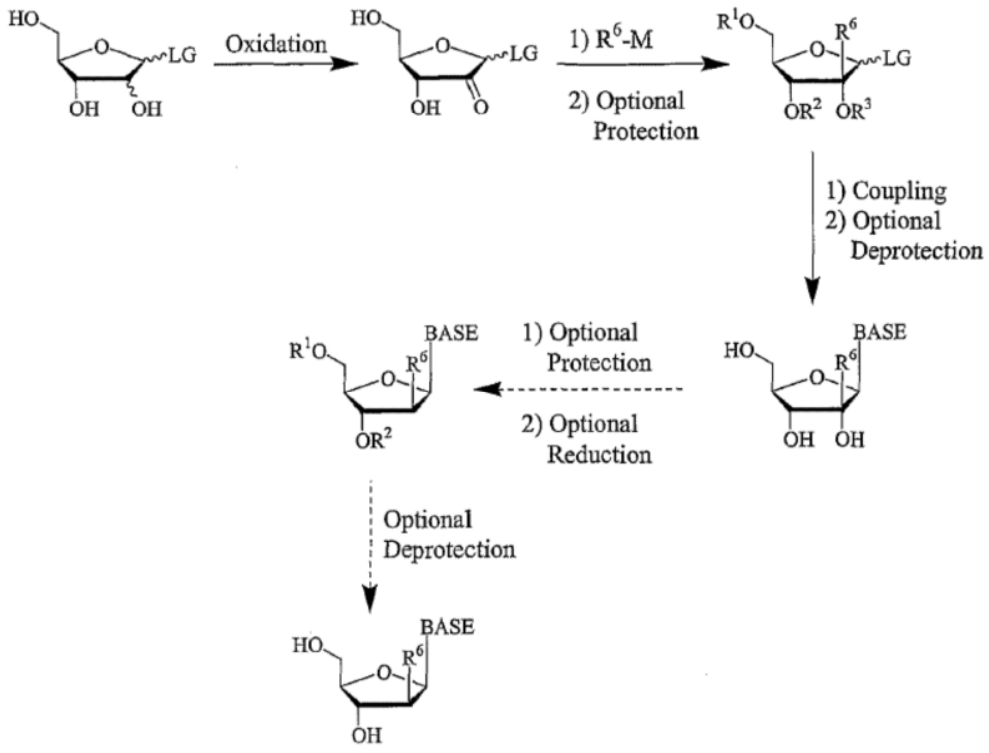
wherein each Pg is independently a protecting group selected from among C(O)-alkyl, C(O)Ph, C(O)aryl, CH_3, CH_2-alkyl, CH_2-alkenyl, CH_2Ph, CH_2-aryl, CH_2O-alkyl, CH_2O-aryl, SO_2-alkyl, SO_2-aryl, tert-

butyldimethylsilyl, tert-butyldiphenylsilyl, or both Pg's may come together to for a 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene).

EX1001, 66:5-23.

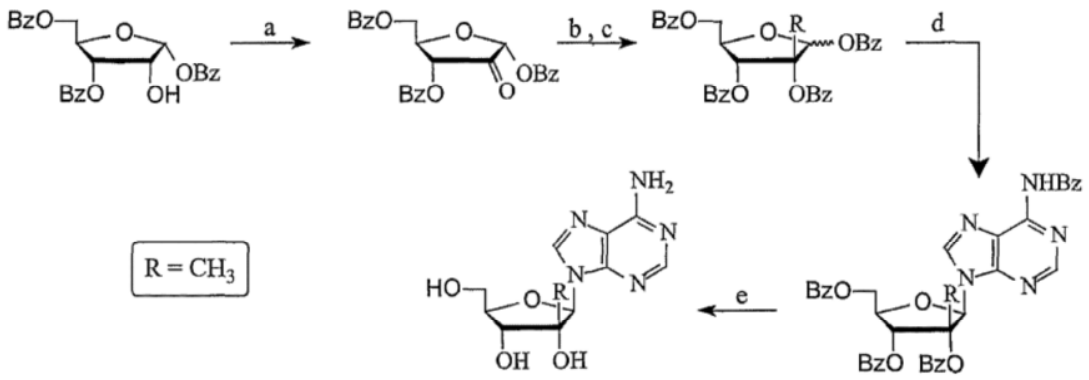
Sommadossi taught in Schemes 3 and 8, copied below, the synthesis of nucleosides by (e.g.,) coupling of a nucleobase or appropriate derivative with a sugar ring, followed by deprotection by removal of benzoyl protecting groups with (e.g.,) ammonia/methanol.

Scheme 3



EX1006 at 69:3-4.

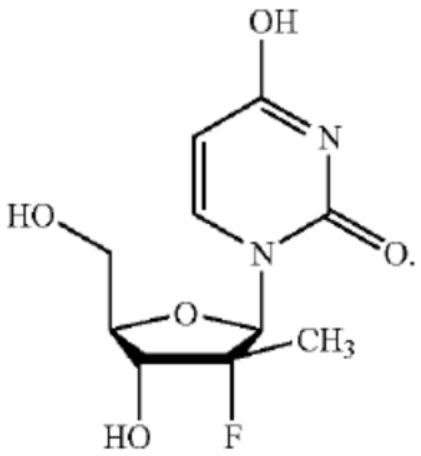
Scheme 8



EX1006 at 115:1-116:2. Sommadossi's Schemes 3 and 8 are identical to the process of claims 13 and 14. EX1002 ¶150. Sommadossi thus anticipated claims 13 and 14.

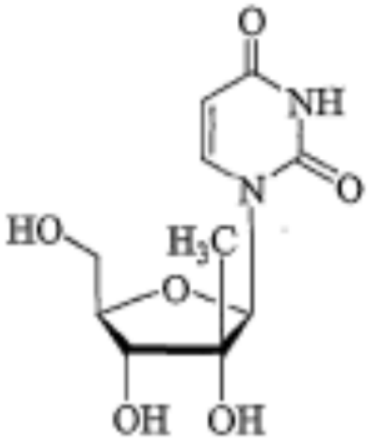
5. Claim 15 (specific compound)

Claim 15 recites: "A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (b-D) or its pharmaceutically acceptable salt thereof of the formula:



EX1001 at 66:24-39.

Sommadossi in Figure 1 and claim 177 taught, "A use of a compound of the structure:



EX1006 at 293, 294.

As discussed above with respect to claim 1, Sommadossi also taught substituting a halo (which a POSA would understand to include F) for OH at the 2' position, which renders its compound identical to the one claimed in claim 15. EX1002 ¶152. The combination of double bond to O at the top position of the base combined with a single bond to NH is equivalent to (a tautomer of) the compound in claim 15 with a single bond to OH at the top combined with a double bond to N. EX1002 ¶152. Sommadossi thus anticipated claim 15.

6. Claim 16 (pharmaceutical composition)

Claim 16 of '572 recites, "A pharmaceutical composition comprising the nucleoside of claim 15 or its pharmaceutically acceptable salt and optionally a pharmaceutically acceptable carrier." EX1001 at 66:40-41.

Sommadossi taught, "The invention as disclosed herein is a … composition … or a pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier." EX1006 at 21:22-26. Thus, Sommadossi taught all of the additional limitations of claim 16. EX1002 ¶154. Therefore, Sommadossi anticipated claim 16.

7. Claims 17-19 (liposomal compositions)

Claims 17-19 claim liposomal compositions comprising liposomes comprising the compounds of claims 1, 6 and 15 and optionally a pharmaceutically acceptable carrier. EX1001 at 66:43-52.

Sommadossi taught, "Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) are also preferred as pharmaceutically acceptable carriers." EX1006 at 62:10-21. Thus, Sommadossi taught all of the additional limitations of claims 17-19. EX1002 ¶156. Therefore, Sommadossi anticipated claims 17-19.

C. Ground 3: Claims 1-19 were Obvious Over Sommadossi and Klecker

The combination of Sommadossi and Klecker render claims 1-19 of the '572 patent obvious. EX1002 ¶157.

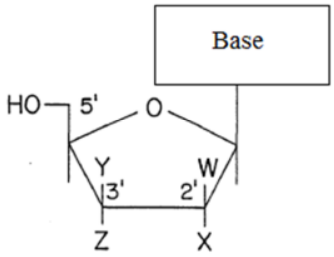
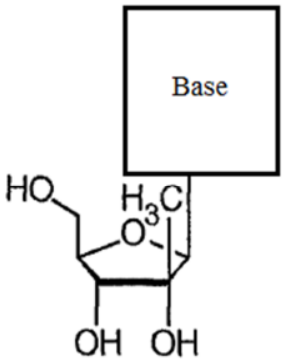
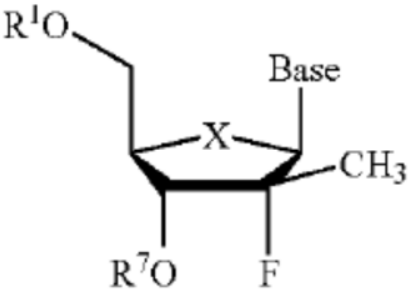
One of ordinary skill in the art would have been motivated to combine the teachings of Sommadossi and Klecker because they both relate to nucleoside compounds with pyrimidine bases and in fact teach virtually identical structures.

EX1002 ¶158. Sommadossi and the related U.S. patent to Klecker (U.S. Patent No. 6,753,309) are also both cited by the ‘572 patent as references, further supporting the conclusion that a POSA would have been motivated to combine their teachings. EX1001 at 2-3; EX1002 ¶158.

1. Claims 1-5 (genera of compounds)

The only possible difference between Sommadossi and claim 1 of the ‘572 patent is the presence of fluorine at the 2’ down position instead of hydroxyl. EX1002 ¶159. Such would have been an obvious modification given the general knowledge in the art and the teaching of Klecker. *Id*.

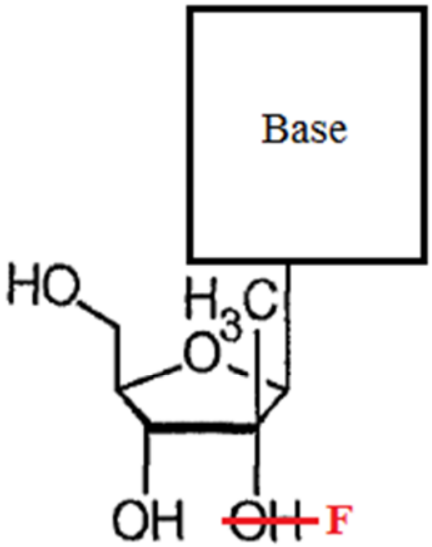
The following table compares the compounds taught by Klecker and Sommadossi with the compounds claimed by the ‘572 patent in claim 1. EX1002 ¶160. One of skill in the art would select the Sommadossi compound as a lead compound to modify because, while Sommadossi disclosed many compounds, it highlighted only eight in Figure 1 as being “Illustrative Nucleosides” and 6 of those 8 had the structure identified in the chart below. *Id*. A POSA reading Sommadossi would choose the general structure of the 6 Illustrative Nucleosides above all others to pursue for further modification to improve upon its pharmacological properties. *Id*.

Klecker	Sommadossi	'572 Patent, Claim 1
 "wherein W, X, Y, Z = H, hydroxy, halogen, alkyl (C1-C6), …"		 "wherein X is O; R1 and R7 are … H, …"

Klecker taught virtually the same nucleoside structure as Sommadossi and further expressly taught, "F can also be placed below the ring at the 2'-position." EX1005 at 21:25-26. A POSA would have been motivated to apply the teaching of Klecker of F at the 2' down position to Sommadossi's lead compound because common knowledge at the time, as represented by at least McAtee and Britton, was that F was not only substitutable for OH at the 2' down position in anti-viral nucleosides, it was actually preferred, especially when methyl is in the 2' up position. EX1002 ¶161; EX1009; EX1011. This general knowledge combined with the express teaching of Klecker would have motivated one of ordinary skill in the art to replace the OH at the 2' down position in Sommadossi with F. EX1002 ¶161.

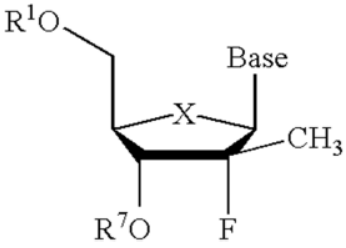
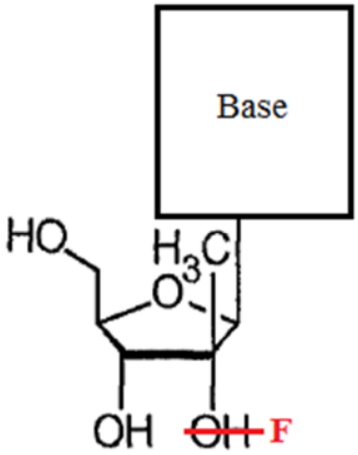
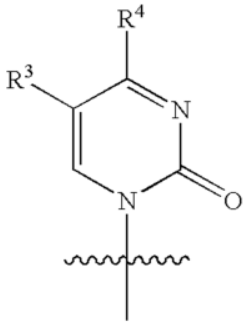
A POSA would have also had a reasonable expectation of success in being able to make this substitution because, as discussed above, many methods were known to successfully fluorinate nucleosides, as shown by. Codington (EX1012), Pankiewicz (EX1010), McAtee (EX1009) and Watanabe (EX1113)

Thus, a POSA combining Sommadossi and Klecker along with common knowledge would have found the following nucleoside obvious:



EX1002 ¶163.

The chart below compares this nucleoside with claim 1.

‘572 Patent, Claim 1	Sommadossi + Klecker
1. A (2′R)-2′-deoxy-2′-fluoro-2′-C-methyl nucleoside (β-D or β-L) or its pharmaceutically acceptable salt of the structure:  	 Sommadossi provided this structure as its “Illustrative Nucleosides.” EX 1006 at 14:1-27; 294 (FIG. 1) Klecker taught, “F can also be placed below the ring at the 2’- position, X=F.” EX1005 at 21:25-26.
wherein Base is a pyrimidine base represented by the following formula:  	“Base is a purine or pyrimidine base as defined herein.” EX 1006 at 14:11. Figure 1 of Sommadossi shows 2 “Illustrative” examples of its compounds that have pyrimidine bases represented by this same formula. EX1006 at 294 (FIG. 1).
X is O;	Figure 1 of Sommadossi shows O in the same position as X. EX 1006 at 294 (FIG. 1).

R^1 and R^7 are independently H, a monophosphate, a diphosphate, a triphosphate, a H-phosphonate, alkyl, an alkyl sulfonyl, or an arylalkyl sulfonyl; and	Figure 1 of Sommadossi shows H in the same position as R^1 and R^7. EX 1006 at 294 (FIG. 1).
R^3 is H and	Figure 1 of Sommadossi shows 8 illustrative nucleosides, at least the second and third of which (the cytidine and uridine bases) have H at the R^3 position. EX 1006 at 294 (FIG. 1).

EX1002 ¶164. As shown in the chart, Sommadossi and Klecker combined with common knowledge in the art would lead one to the genus of compounds of claim 1. *Id*. Thus, Sommadossi and Klecker render claim 1 obvious.

During prosecution of the ’572 application, Patent Owner argued that its claims were not obvious because supposedly unexpected results supported patentability. EX1004 at 47. However, the data relied on by Patent Owner to support its argument of unexpected results was not only incomplete; it actually showed that the claimed compound was what a POSA would have expected. EX1002 ¶165. Thus, the data provided by Patent Owner did not show that the claimed compounds had unexpectedly high anti-viral activity and low cytotoxicity. *Id*. If it showed anything at all, it showed quite the opposite. *Id*.

First, the only data provided by Patent Owner related to just the cytidine nucleoside that is specifically claimed in original claim 11 (final claim 6). EX1004 at 47. None of the data relied on by Patent Owner related to the uridine compound

specifically claimed in original claim 130 (final claim 15) or the full scope of the genera of compounds claimed in original claim 6 (final claim 1), which includes the uridine form. EX1002 ¶166. Thus, the only claims of the ‘572 patent to which the data provided by Patent Owner during the prosecution history is relevant are claims 6 and the claims that depend from it, i.e. claims 12 and 18. *Id*. None of the other claims of the ‘572 patent (i.e. claims 1-11, 13-17 and 19) are limited to just the cytidine compound, and some do not cover the cytidine compound at all (i.e. claims 15, 16 and 19). *Id*.; EX1001 at 64:27 – 66:51.

Second, the data provided in the ‘572 application actually showed that the cytidine compound performed similarly to – not different from – the selected prior art compounds used as comparables. EX1002 ¶167. For example, in Table 1, copied below, the claimed cytidine compound was assayed against two compounds that are indicated in Figure 1 of Sommadossi. EX1004 at 49.

TABLE 1

Summary of the Anti-HCV Replicon Activity of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine*

Replicon	(2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine	2'-C-methylcytidine	2'-C-methyladenosine
HCV-WT 1b	4.6 ± 2.0	21.9 ± 4.3	2.1 ± 0.27
S282T mut. 1b	30.7 ± 11.7	37.4 ± 12.1	>100
9-13 (subgenomic)	4.6 ± 2.3	13.0	0.7
21-5 (full-length)	1.6 ± 0.7	6.6	0.6

*Values represent EC_{90} (μM)

Looking across the results of the four different types of assays, the cytidine compound of '572 claim 6 ("(2'R)-2'-deoxy-2'-fluoro-2'-C'methylcytidine") is more active (3-5x potency) than the compound where –OH is present rather than fluorine ("2'-C'methylcytidine"). EX1002 ¶168. The compound of claim 6, however, is actually less active than the compound where –OH is present rather than fluorine at C2', but the cytidine is replaced by adenosine ("2'-C-methyladenosine."). *Id*. Table 1 shows that this adenosine analogue is 2.2-6.5x more potent in these assays. *Id*.

None of these three compounds had substantial activity against the S282T (1b) mutation of the wild-type virus. EX1002 ¶169. To a POSA this does not

justify a conclusion that the compound of claim 6 has unexpected superior results. *Id*. Thus, the C2'-fluoro compound demonstrates activity within the range of the two Sommadossi compounds. *Id*.

Specifically, the claimed cytidine had activity of (i) 4.6 in HCV-WT 1b where the two prior art compounds had an IC90 (all results in μM concentration) of 2.1 and 21.9; (ii) 4.6 in the subgenomic (9-13) assay where the two prior art compounds had activity of 0.7 and 13.0, and (iii) 1.6 in the 21-5 (full-length) assay where the Sommadossi compounds had activity of 0.6 and 6.6. EX1002 ¶170.

Each of these results shows that the activity of the claim 6 compound was within the activities of the two Sommadossi compounds. EX1002 ¶171. The only assay for which the cytidine had greater potency than both compounds was S282T mut. 1b, where the claimed cytidine had activity of 30.7 while the Sommadossi compounds had activity of 37.4 and >100. *Id*. While the claimed cytidine had greater activity than both Sommadossi compounds in this one assay, all 3 compounds were essentially inactive in this assay (>30 μM IC90). *Id*. Even if these compounds were strongly active against the 282T mutation, this minimal difference would not be a surprising or unexpected, given that the Sommadossi compounds had activity ranges that were order of magnitudes different from one another. *Id*.

In Table 3, copied below, the potency of the claimed cytidine as its

triphosphate form in the HCV 1b NS5B Polymerase assay has a range of 1.7 to 7.7μM, while the Sommadossi cytidine compound had potency within that range (6.0μM). EX1004 at 49.

TABLE 3

	HCV 1b NS5B Polymerase Assay (IC_{50}, μM)		
	(2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine TP	2'-C-methylcytidine TP	2'-C-methyladenosine TP
Wild-Type	1.7 ± 0.4[a]	6.0 ± 0.5	20.6 ± 5.2
NS5B S282T	7.7 ± 1.2[b] 2.0[a] 8.3 ± 2.4[c]	26.9 ± 5.5	>100

[a]Values determined using batch 1;
[b]Value determined using batch 2 and 3; and
[c]Value determined using batch 2.

These results show no difference as compared to the triphosphate form of the Sommadossi 2'-C-methylcytidine – which is the direct analogue for which –OH has is present rather than F at C2'. EX1002 ¶173. The triphosphate form of the adenosine analogue was less active in this assay, which indicates a lack of reliability in comparing the enzymatic assay for NS5B activity versus the results of the cellular replicon assay. *Id*. Moreover, the results from this assay were not reproducible between different batches of the claim 6 compound, which renders the data unreliable. *Id*.

Patent Owner argued that Table 5, copied below, showed a lack of activity in

BVDV, which is typically used as a surrogate model for HCV testing. EX1004 at 50. It was well-known to a POSA that this assay was no longer a standard surrogate for measuring activity of compounds against HCV. EX1002 ¶174. The only conclusion that can be drawn from this result, therefore, is that the claimed cytidine compound is inactive against BVDV while the two Sommadossi compounds are very active. *Id.* Again, this does not support a claim of unexpectedly superior activity for the claimed cytidine compound. *Id.*

TABLE 5

Summary of Antiviral Activity of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine

Virus	(2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (EC_{90}, μM)	2'-C-methylcytidine (EC_{90}, μM)	2'-C-methyladenosine (EC_{90}, μM)
BVDVncp	>22	0.5	1.2
BVDVcp	>100	2	1.5
RSV	>100	>100	>100
HIV[a]	>100	ND	ND
HBV	>10	>10	ND
Coronavirus 229E	>100	ND	ND

ND = Not determined.

Table 5 also shows that the claimed cytidine compound was not better than the Sommadossi compounds for the other listed viruses either, i.e. RSV, HIV, HBV and Coronavirus 229E. EX1002 ¶175. So, again, Table 5 does not provide

any basis to conclude the C2'-fluorinated cytidine nucleoside had any unexpected results. *Id*.

Finally, Table 6, copied below, merely showed that the claimed cytidine compound was not less toxic than the Sommadossi methylcytidine. EX1004 at 51. The claimed compound was slightly less toxic than the 2'-C- methyladenosine. However, the 2'-C- methyladenosine was also more potent, resulting in almost identical therapeutic indices (ratio of activity to cytotoxicity) between these two compounds.

TABLE 6

Cytotoxicity Studies[a]

Cell Line	(2'R)-2'-deoxy-2'-fluoro-2'-C methylcytidine CC_{50}, µM	2'-C-methylcytidine CC_{50}, µM	2'-C-methyladenosine CC_{50}, µM
CloneA	>100	>100	37
Huh7	>100	>100	30
HepG2	75	>100	58
MDBK	>100	>100	
PBM	>100		
CEM	>100		
Vero	>100		
MRC-5	>100		

[a]Results determined using MTS assay.

The table actually shows that the claimed cytidine compound was not less cytotoxic than the Sommadossi cytidine compound, which provides no basis to

conclude the claimed cytidine had unexpected results. EX1002 ¶177. Several of the assays run on the claimed compound were not run on the two comparator compounds, thereby providing a less than complete analysis for such cytotoxcities in the respective assays.

In summary, the data presented in the patent application supports a conclusion that the claimed cytidine compound is roughly equal in HCV activity and not superior in cytotoxicity to the two Sommadossi compounds to which it is compared. EX1002 ¶178. As such, the limited comparison indicates that C-2' methyl (up) C-2' fluoro (down) nucleosides do not show unexpected results over C-2' methyl (up) C-2' OH (down) compounds. *Id.*

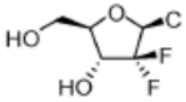
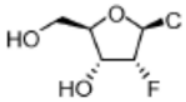
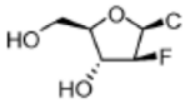
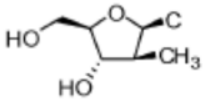
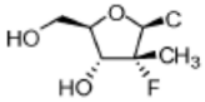
Third, the additional data provided in the Declaration by Drs. Furman and Sofia was again limited to only the cytidine compound. EX1004 at 52. They did not assay the uridine compound of claim 15 of the '572 patent or any other compounds within the genus claimed by claim 1 of the '572 patent. *Id.*

Drs. Furman and Sofia also only compared the cytidine compound to four specific prior art compounds, which were not representative of the breadth of the prior art. EX1004 at 52. Of particular relevance, the new data provided by Drs. Furman and Sofia specifically did not compare the claimed cytidine compound to either the Klecker or Sommadossi compounds discussed above. EX1002 ¶180. Thus, the declaration did not provide data relevant to the

obviousness of the ‘572 patent here. *Id*.

The table provided by Drs. Furman and Sofia in their declaration, copied below, compared the HCV activity and cytotoxicity of compound No. 5, the compound sought to be claimed, to 4 other compounds. EX1004 at 65.

Activity and Cytotoxicity Comparison of 2' Substituted Cytidine Analogs

№	Compound	HCV Activity EC_{90} (μM)	Cytotoxicity			
			Clone A CC_{50} (μM)	Hep G2 CC_{50} (μM)	BxPC3 CC_{50} (μM)	CEM CC_{50} (μM)
1		<1	<0.1	<1	<1	<1
2		5.66	>100	400	10	6
3		Can not determine: Toxic to cells	<50	200	5	5
4		9.73	10.47	40	<1	<1
5		4.5	>100	>1000	>1000	>1000

C represents cytosine.

The data in the table shows that the HCV activity of compound 5 was not meaningfully better than that of compounds 2 and 4, two known anticancer agents. EX1002 ¶182. Compound 5 was less active against HCV than compound 1, gemcitabine, another known nucleoside anticancer drug. *Id.* Specifically, the

claimed cytidine compound 5 had HCV activity of 4.5, while compounds 2 and 4 had activity of 5.66 and 9.73, and compound 1 had HCV activity of <1. *Id*. Thus, the claimed cytidine compound did not have superior activity over the prior art compounds. *Id*.

Regarding cytotoxicity, the HepG2, BxPC3, and CEM cell lines are all assays for anticancer activity. EX1002 ¶183. Each of the four prior art compounds to which Drs. Furman and Sofia compared the claimed cytidine compound were known anticancer agents. *Id*. Thus, the fact that they showed cytotoxity would have been expected. *Id*.

Further, the data provided in the declaration of Drs. Furman and Sofia directly contradicts the data in Table 6 that was included with the application. EX1002 ¶184. Specifically, as shown below, Table 6 stated that the claimed cytidine compound had a cytotoxicity of CC_{50} of 75µM in HepG2, but the declaration stated that the same compound in the same assay had a cytotoxicity of CC_{50} of >1000µM. *Id*.; EX1004 at 51 and 53.

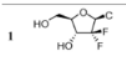
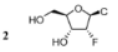
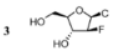
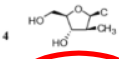
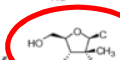
TABLE 6

Cytotoxicity Studies[a]

Cell Line	(2'R)-2'-deoxy-2'-fluoro-2'-C methylcytidine CC_{50}, μM	2'-C-methylcytidine CC_{50}, μM	2'-C-methyladenosine CC_{50}, μM
CloneA	>100	>100	37
Huh7	>100	>100	30
HepG2	75	>100	58
MDBK	>100	>100	
PBM	>100		
CEM	>100		
Vero	>100		
MRC-5	>100		

[a]Results determined using MTS assay.

Activity and Cytotoxicity Comparison of 2' Substituted Cytidine Analogs

№	Compound	HCV Activity EC_{50} (μM)	Cytotoxicity Clone A CC_{50} (μM)	Hep G2 CC_{50} (μM)	BxPC3 CC_{50} (μM)	CEM CC_{50} (μM)
1		<1	<0.1	<1	<1	<1
2		5.66	>100	400	10	6
3		Can not determine: Toxic to cells	<50	200	5	5
4		9.73	10.47	40	<1	<1
5		4.5	>100	>1000	>1000	>1000

C represents cytosine.

These directly contradictory results render the declaration by Drs. Furman and Sofia highly suspect on this point. *Id.*

Patent Owner argued that, "one would expect that a compound that has β-methyl and an α-fluoro would have properties akin to the combined properties of compounds 2 and 4." EX1004 at 54. That is not correct. EX1002 ¶185. A POSA would not make such a hasty conclusion as there is ample evidence in medicinal chemistry both for and against such a conclusion. *Id.* Thus, the properties shown in the table for compound 5, as compared to compounds 2 and 4, was not unexpected. *Id.*

In sum, there is no evidence in the record that shows any of the claimed compounds have unexpected properties. EX1002 ¶186. Even if the data did arguably show unexpected results, since it only relates to the cytidine form, it is only relevant to claim 6 and its dependent claims, which are limited to just that form on such a comparative basis. *Id.*

Further, while it is true that, to determine whether claims would have been obvious, one must consider "all evidence of obviousness and nonobviousness before reaching a determination," *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1365, fn. 5 (Fed. Cir. 2012), a strong case of *prima facie* obviousness may outweigh any objective indicia of nonobviousness. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010). Thus, even if there may have been a showing of unexpected results, that does not overcome Petitioner's showing of obviousness, especially since Petitioner has not had the opportunity at this stage to conduct discovery on the issue.

Claim 2 depends from claim 1 and merely adds, "wherein R^7 is H and R^1 is a monophosphate, or diphosphate, or a triphosphate." EX1001 at 40:58-61. Claim 3 depends from claim 1 and merely adds, "R^7 is H and R^1 is diphosphate or a triphosphate." *Id*. at 40:62-64. Claim 4 depends from claim 1 and merely adds, "wherein R^7 is H and R^1 is triphosphate." *Id*. at 40:65-67. Claim 5 depends from claim 1 and merely adds, "wherein R^1 and R^7 are H." *Id*. at 41:1-3.

Insofar as such phosphate derivatives of the nucleosides of claim 1 exist, they are not only obvious but they are inherent to intracellular processes for the incorporation of nucleosides into the synthesis of RNA and DNA. EX1002 ¶188. (EX1007). Such processes were not only well-known to one of ordinary skill in the art, but were also known to be the operable mechanism by which all nucleosides

are incorporated into living systems. *Id.*

Further, as shown in the first row of the chart above, Sommadossi expressly taught H in the same position as R^7 and in fact highlighted that selection in its Figure 1 "Illustrative Nucleosides." EX1006 at 294. Sommadossi also taught that it could have a monophosphate, diphosphate, or triphosphate at the same position identified in claim 1 as R^1. *See*, for example, Sommadossi's Formula V, position R^1, which can be, "phosphate (including monophosphate, disphosphate, triphosphate)." EX1006 at 12:1-5. Thus, Sommadossi taught all of the additional limitations of claims 2-5. EX1002 ¶189. Sommadossi and Klecker therefore render claims 2-5 obvious.

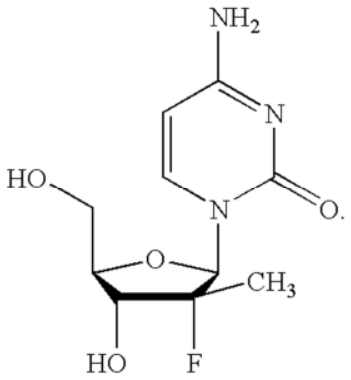
In addition, while Klecker does not expressly teach a monophosphate, diphosphate, or triphosphate at the same position identified in claim 1 of the '572 patent as R^1, Klecker did teach that its compounds are converted into nucleotides, including by phosphorylation. EX1005 at 25:5-32. Such phosphorylation would inherently include the mono-, di- and tri- phosphate forms of Klecker's compounds. EX1002 ¶190.

A POSA would also have known that the monophosphate, diphosphate, and triphosphate at R^1 as identified in claim 1 describes intermediates in the obligatory pathway for intracellular bioactivation of nucleoside drugs. EX1002 ¶191. Nucleoside drugs act by inhibiting processes that involve DNA or RNA. *Id*. The

phosphate derivatives of such nucleoside drugs are not inventive nor are they delivered as these phosphate derivatives. *Id*. Rather, they are converted into these mono-, di-, and triphosphates *in vivo* as part of the process by which the body activates them for use. *Id.* Such mono-, di, and triphosphate derivatives of nucleosides were well known before the '572 patent. *Id*.

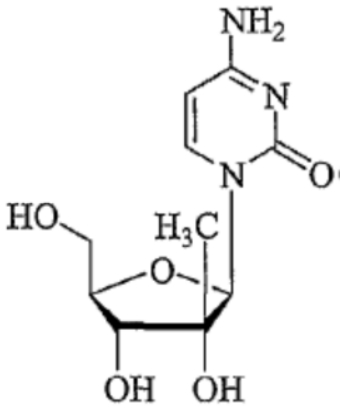
2. <u>Claim 6 (specific compound)</u>

Claim 6 claims, "A (2′R)-2′-deoxy-2′-fluoro-2′-C-methyl nucleoside (β-D) or its pharmaceutically acceptable salt thereof of the formula:



EX1001 at 65:4-19.

Sommadossi in Figure 1 and claim 175 taught a compound of the structure:



EX1006 at 292, 294.

As discussed above with respect to claim 1, Sommadossi and Klecker combined with common knowledge not only taught, but motivated, substituting F for OH at the 2' down position, which renders its compound identical to the one claimed in claim 6. EX1002 ¶194. Thus, Sommadossi and Klecker render claim 6 obvious.

3. Claims 7-12 (pharmaceutical compositions)

Claims 7-12 claim pharmaceutical compositions comprising the nucleosides of claims 1-6 or their pharmaceutically acceptable salts and a pharmaceutically acceptable carrier. EX1001 at 65:20-37.

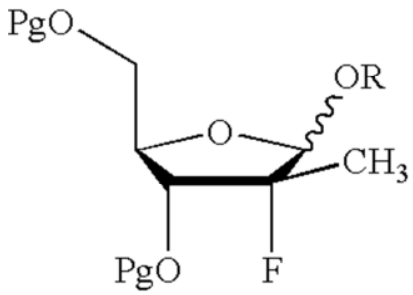
Sommadossi taught, "The invention as disclosed herein is a … composition … or a pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier." EX1006 at 21:22-26. Thus, Sommadossi taught all of the additional limitations of claims 7-12. EX1002 ¶196. Therefore, Sommadossi and Klecker render claims 7-12 obvious.

4. Claims 13 and 14 (method of synthesizing)

Claim 13 of '572 recites the following method of synthesis:

> A method of synthesizing a nucleoside of claim 1, which comprises glycosylating the pyrimidine with a compound having the following structure;

1-4

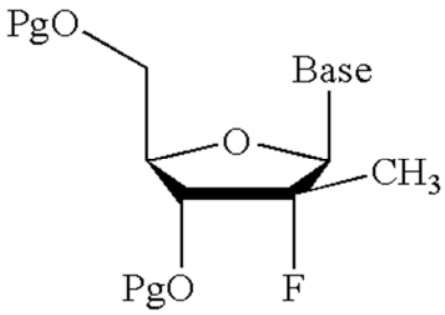


wherein R is lower alkyl, acyl, benzoyl, or mesyl; and Pg is selected from among C(O)-alkyl, C(O)Ph, C(O)aryl, CH_3, CH_2-alkyl, CH_2-alkenyl, CH_2Ph, CH_2-aryl, CH_2O-alkyl, CH_2O-aryl, SO_2-alkyl, SO_2-aryl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or both Pg's may come together to for a 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene).

EX1001, 65:38 – 66:4.

Claim 14 of the ‘572 patent recites:

14. A method of synthesizing the nucleoside of claim 1, which comprises selectively deprotecting a 3′-OPg or a 5′-OPg of a compound having the following structure:



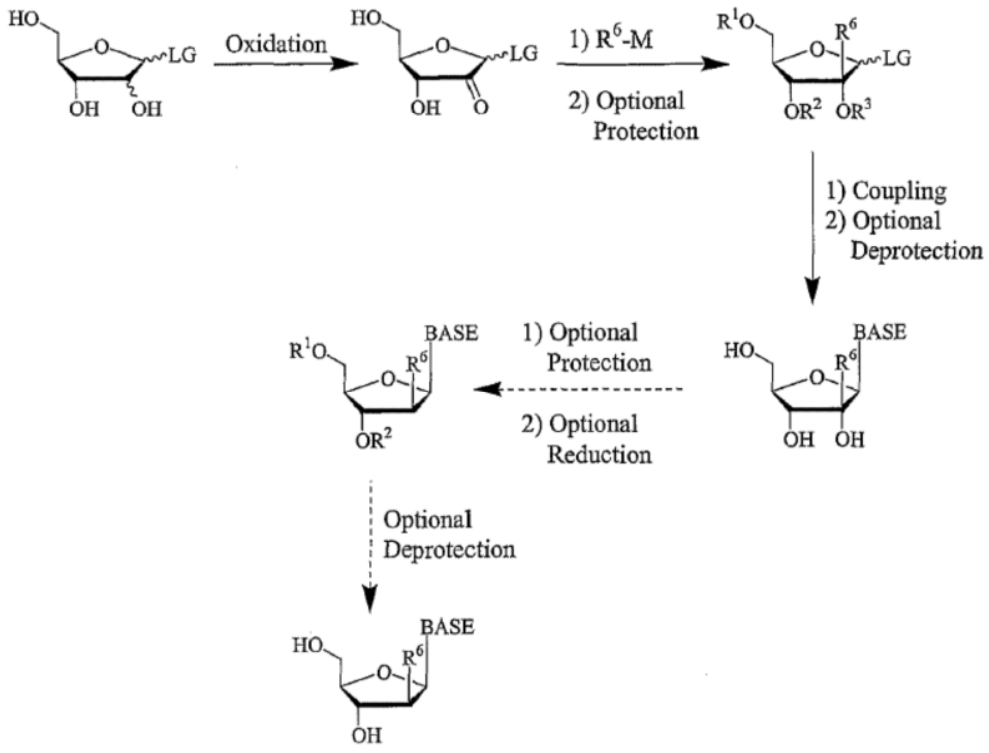
wherein each Pg is independently a protecting group selected from among C(O)-alkyl, C(O)Ph, C(O)aryl, CH_3, CH_2-alkyl, CH_2-alkenyl, CH_2Ph, CH_2-aryl, CH_2O-alkyl, CH_2O-aryl, SO_2-alkyl, SO_2-aryl, tert-

butyldimethylsilyl, tert-butyldiphenylsilyl, or both Pg's may come together to for a 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene).

EX1001, 66:5-23.

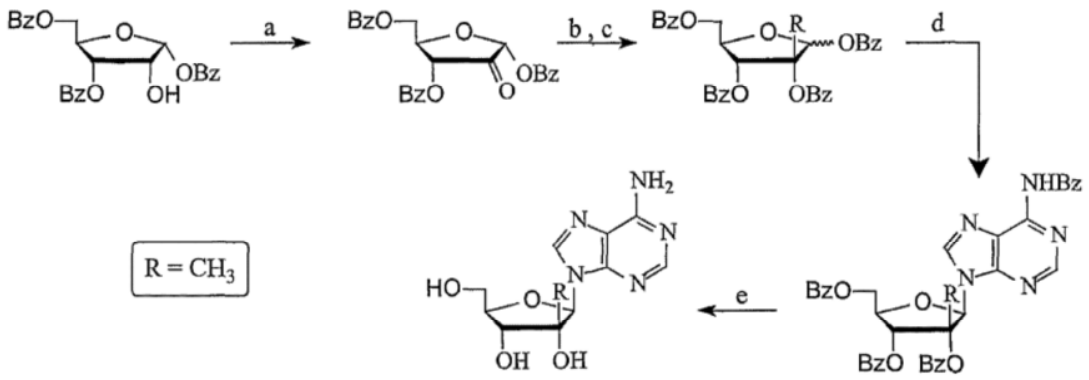
Sommadossi taught in Schemes 3 and 8, copied below, the synthesis of nucleosides by (e.g.,) coupling of a nucleobase or appropriate derivative with a sugar ring, followed by deprotection by removal of benzoyl protecting groups with (e.g.,) ammonia/methanol.

Scheme 3



EX1006 at 69:3-4.

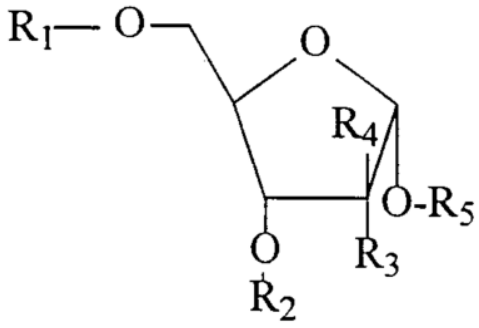
Scheme 8



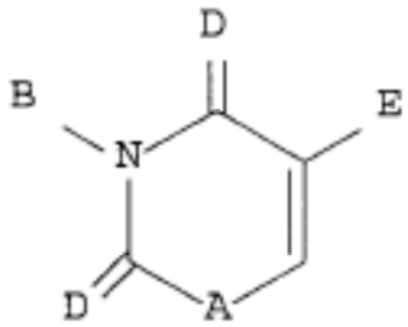
EX1006 at 115:1-116:2. Sommadossi's Schemes 3 and 8 are identical to the process of claims 13 and 14. EX1002 ¶199.

Further, Klecker taught a method of synthesis its compounds comprising the steps of:

contacting a first molecule of the formula



wherein R_1, R_2 and R_5 may be the same or different and are blocking groups, R_3 is a leaving group and R_4 is H, with a second molecule containing a label under conditions causing the transfer of the label to the position occupied by R_4 ; and contacting the resultant labeled first molecule with a molecule having the structure



wherein the molecule of such formula contains the substituents discussed above with respect to claims 1 and 6. EX1005, 47:1 – 48:2 (claim 23).

Thus, Klecker taught a nucleoside forming reaction identical to that in claim 13 of the ‘572 patent, because the only difference between them is that Clark claims protecting groups, which Klecker referred to as blocking groups. EX1002 ¶201. There is no difference between Clark’s “protecting groups” and Klecker’s “blocking groups”, with the exception that Klecker does not further define these groups while Clark gives many examples of protecting groups. *Id*.

Klecker also taught:

> To remove the blocking groups from the 3'- and 5'- positions of the sugar, and the 2- and 4-positions of the base, 0.3 mL of 2M ammonia in methanol is added. The mixture is heated at 130 °C for 30 minutes.

EX1005, 33:4-9.

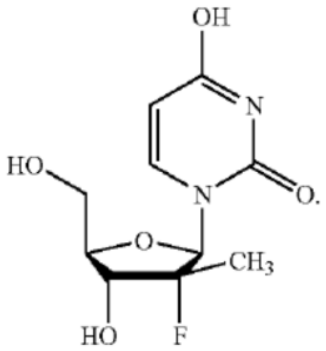
Thus, Klecker taught a nucleoside forming reaction identical to that in claim 14 of the ‘572 patent, because the only difference between them is that Clark

claims protecting groups, which Klecker referred to as blocking groups. EX1002 ¶203. There is no difference between Clark's "protecting groups" and Klecker's "blocking groups", with the exception that Klecker does not further define these groups while Clark gives many examples of protecting groups. *Id*.

For these reasons, Sommadossi and Klecker render claims 13 and 14 obvious.

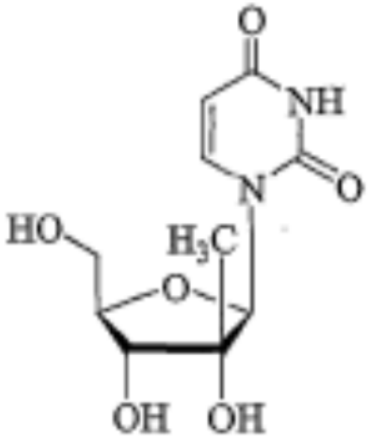
5. Claim 15 (specific compound)

Claim 15 recites: "A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (b-D) or its pharmaceutically acceptable salt thereof of the formula:



EX1001 at 66:24-39.

Sommadossi in Figure 1 and claim 177 taught, "A use of a compound of the structure:



EX1006 at 293, 294.

As discussed above with respect to claim 1, one of ordinary skill in the art combining the teachings of Sommadossi and Klecker along with common knowledge would have found it obvious to substitute F for OH at the 2' position, which renders its compound identical to the one claimed in claim 15. EX1002 ¶206. The combination of double bond to O at the top position of the base combined with a single bond to NH is equivalent to (a tautomer of) the compound in '572 patent claim 15 with a single bond to OH at the top combined with a double bond to N. *Id.*

Because Klecker taught virtually the same nucleoside structure as Sommadossi and further expressly taught, "F can also be placed below the ring at the 2'-position," EX1005 at 21:25-26, one of ordinary skill in the art would have been motivated to combine the teaching of Klecker of F at the 2' down position with Sommadossi because common knowledge at the time, as represented by at

least Codington (EX1012), Pankiewicz (EX1010), McAtee (EX1009) and Watanabe (EX1113) was that F was not only substitutable for OH at the 2' down position in anti-viral nucleosides, it was actually preferred, especially when methyl is in the 2' up position. EX1002 ¶207. This general knowledge combined with the express teaching of Klecker would have motivated one of ordinary skill in the art to replace the OH at the 2' down position in Sommadossi with F. *Id*.

One or ordinary skill in the art would have also had a reasonable expectation of success in being able to make this substitution because, as discussed above, many methods were known to successfully fluorinate nucleosides. EX1002 ¶208. Thus, Sommadossi and Klecker render claim 15 obvious.

6. <u>Claim 16 (pharmaceutical composition)</u>

Claim 16 of '572 recites, "A pharmaceutical composition comprising the nucleoside of claim 15 or its pharmaceutically acceptable salt and optionally a pharmaceutically acceptable carrier." EX1001 at 66:40-41.

Sommadossi taught, "The invention as disclosed herein is a … composition … or a pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier." EX1006 at 21:22-26. Thus, Sommadossi taught all of the additional limitations of claim 16. EX1002 ¶210.

Further, Klecker taught the following respecting pharmaceutical compositions of the compounds of its claim 20,

> The formulation may be presented in a unit dosage form and may be prepared by conventional pharmaceutical techniques. Such techniques include the step of bringing into association the active ingredient and the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into association, the active ingredient with liquid carriers or finely divided solid carriers or both, optionally with one or more accessory ingredients, and then, if necessary, shaping the product.

EX1005 at 19:37–20:9.

In addition, Klecker taught:

> It should also be understood that the compounds or pharmaceutical compositions of the present invention may also be administered by topical, transdermal, oral, rectal or parenteral (for example, intravenous, subcutaneous or intramuscular) route or may be incorporated into biodegradable polymers allowing for the sustained release of the compound, the polymers being implanted in the vicinity of the tumor or where the drug delivery is desired.

EX10 and 20:13-23. Thus, Klecker taught all of the additional limitations of claim 16. EX1002 ¶212. Sommadossi and Klecker therefore render claim 16 obvious.

7. Claims 17-19 (liposomal compositions)

Claims 17-19 claim liposomal compositions comprising liposomes comprising the compounds of claims 1, 6 and 15 and optionally a pharmaceutically acceptable carrier. EX1001 at 66:43-52.

Sommadossi taught, “Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) are also preferred as pharmaceutically acceptable carriers.” EX1006 at 62:10-21. Thus, Sommadossi taught all of the additional limitations of claims 17-19. EX1002 ¶215. Sommadossi and Klecker therefore render claim 17-19 obvious.

XI. CONCLUSION

For these reasons, claims 1-19 of the ’572 patent are unpatentable over the asserted prior art. Petitioner therefore respectfully requests that an *inter partes* review be instituted and that they be found unpatentable and canceled.

Respectfully submitted,

Dated: October 25, 2017

/Daniel B. Ravicher/

Daniel B. Ravicher, Lead Counsel
Reg. No. 47,015
Ravicher Law Firm, PLLC
2000 Ponce De Leon Blvd Ste 600
Coral Gables, FL 33134
Tel: (786) 505-1205
Email: dan@ravicher.com

Counsel for Petitioner

XII. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 7,429,572
1002	Declaration of Joseph M. Fortunak, Ph.D.
1003	*Curriculum Vitae* of Joseph M. Fortunak, Ph.D.
1004	File History Excerpts
1005	Klecker
1006	Sommadossi
1007	McGuigan 1993
1008	McGuigan 1994
1009	McAtee
1010	Pankiewicz
1011	Britton
1012	Codington
1013	Watanabe

XIII. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 13,797 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully,

Dated: October 25, 2017

/Daniel B. Ravicher/
Daniel B. Ravicher, Lead Counsel
Reg. No. 47,015

XIV. CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), I certify that I caused to be served a true and correct copy of the foregoing PETITION FOR *INTER PARTES* REVIEW and supporting materials (Exhibits 1001-1013 and Power of Attorney) by overnight courier (Federal Express or UPS), on this 25th day of October, 2017, on the Patent Owner at the correspondence address of the Patent Owner as follows:

GILEAD PHARMASSET LLC
303A COLLEGE ROAD EAST
PRINCETON, NEW JERSEY 08540

Respectfully,

Dated: October 25, 2017

/Daniel B. Ravicher/
Daniel B. Ravicher, Lead Counsel
Reg. No. 47,015