UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

GILEAD PHARMASSET LLC
Patent Owner

_____

Case No. IPR2018-00119
U.S. Patent No. 7,964,580

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PETITION FOR *INTER PARTES* REVIEW

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I. INTRODUCTION

Initiative for Medicines, Access & Knowledge (I-MAK), Inc. ("Petitioner") requests *inter partes* review ("IPR") of all 14 claims of United States Patent No. 7,964,580 to Sofia et al. ("the '580 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 '580 patent issued on June 21, 201, and is currently assigned to Gilead Pharmasset LLC ("Patent Owner"). This petition demonstrates that all 14 claims of the '580 patent are unpatentable.

The '580 patent claims pharmaceutical compounds, compositions and methods that were already known and obvious in light of the prior art. Specifically, the '580 claims a specific prodrug form of a specific nucleoside compound, but that prodrug form of the nucleoside was already known as a result of being previously published at a scientific conference. In addition, the prodrug technique used was by Patent Owner was entirely conventional and the nucleoside compound to which Patent Owner applied the prodrug technique had been previously disclosed (and patented) by Patent Owner years before. Taking a known prodrug approach and applying it to a known nucleoside is not an invention. It's obvious.

Thus, the '580 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 filing concurrently herewith another petition for *Inter Partes* Review of the '580 patent in order to comply with the word count limit for a single petition. 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 ’580 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 1-14 of the ’580 patent based on the following grounds:

#	Claims	35 U.S.C. §	Prior Art
1	1-14	102(a)	Sofia
2	1-14	103(a)	Sofia and Perrone
3	1-14	103(a)	Ma and Perrone

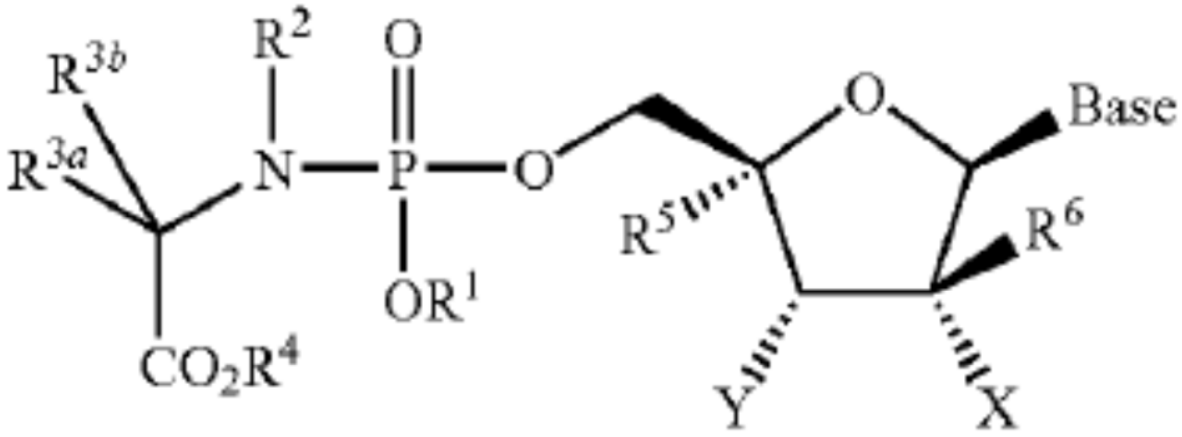
This Petition is supported by the declaration of Joseph M. Fortunak, Ph.D. (EX1002). Dr. Fortunak is well qualified as an expert, possessing the necessary scientific, technical, and other specialized knowledge and training to assist in an understanding of the evidence presented herein, as well as possessing 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 '580 PATENT

The '580 patent relates to phosphoramidate prodrugs of nucleoside derivatives of the following general formula:



EX1001 at 4:40 – 7:10. In defining the structure's various components, the '580 patent states that the Base is "a naturally occurring or modified purine or pyrimidine base." EX1001 at 6:5-6. The '580 patent further provides a long list of substituents for each of R^1, R^2, R^{3a}, R^{3b}, R^4, R^5, R^6, X and Y. EX1001 at 4:59 – 6:4.

The following chart describes the '580 patent's 14 claims:

Claim(s)	Recite
1, 8	Specific compounds within the general formula and its stereoisomers.

2, 9	Compositions having the compound of claim 1 or 8.
3, 10	Compositions for treating hepatitis C virus having an effective amount of the compound of claim 1 or 8.
4, 11	Methods of treating a subject infected by one of several viruses by administering an effective amount of the compound of claim 1 or 8.
5, 12	Methods of treating a subject infected by hepatitis C virus by administering an effective amount of the compound of claim 1 or 8.
6, 13	Processes for preparing the compound of claim 1 or 8.
7, 14	Products having the compound of claim 1 or 8 made by the process of claim 6 or 13.

V. FILE HISTORY OF THE '580 PATENT

U.S. Patent Application No. 12/053,015 ("the '015 application"), filed on March 21, 2008, issued as the '580 patent on June 21, 2011. The '580 patent claims the benefit of two provisional applications, Provisional Application No. 60/909,315 filed on March 30, 2007 ("the '315 provisional application"), and Provisional Application No. 60/982,309 filed on October 24, 2007 ("the '309 provisional application").

During prosecution of the '015 application, the Examiner allowed the claims without making any substantive prior-art based rejections.

VI. PERSON OF ORDINARY SKILL IN THE ART

Because the '580 patent pertains to nucleoside compounds, a 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 at ¶35.

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 '580 patent provides definitions for certain claim terms, but these definitions are conventional. Thus, there is no reason to give any of the terms of the claims of the '580 a meaning other than their ordinary and accustomed meaning.

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).

Below is a description of some of the relevant aspects of what was generally known in the art as of March 30, 2007.

A. The Use of Nucleoside Analogs As Antiviral Agents And Their Mechanism of Action Were Known

It was generally known to persons skilled in the art that viruses replicate their genetic materials in their host cell through one of two mechanisms. EX1002 at ¶39. RNA viruses and reverse-transcribing (RT) viruses rely on their special DNA/RNA polymerase to synthesize viral DNA/RNA chains in the host cell, while DNA viruses use host-cell DNA polymerases to synthesize their viral DNA chains. *Id*.

The basic building blocks that DNA/RNA polymerases recognize and use to synthesize viral DNA/RNA are 5'-triphosphate nucleosides (NTP, where N=A, U/T, G, C). EX1002 at ¶40. Nucleoside (N), after entering the cell, is converted

into its 5'-monophosphate (NMP) by the intracellular host or viral nucleoside kinase. *Id*. NMP is then further converted into the 5'-triphosphate form (NTP), and finally NTP is recognized by host or viral RNA/DNA polymerases and added to the tail of the viral DNA/RNA chain being synthesized. *Id*. The below figure exemplifies the known mechanism for phosphorylation of nucleosides for incorporation into RNA. *Id*.

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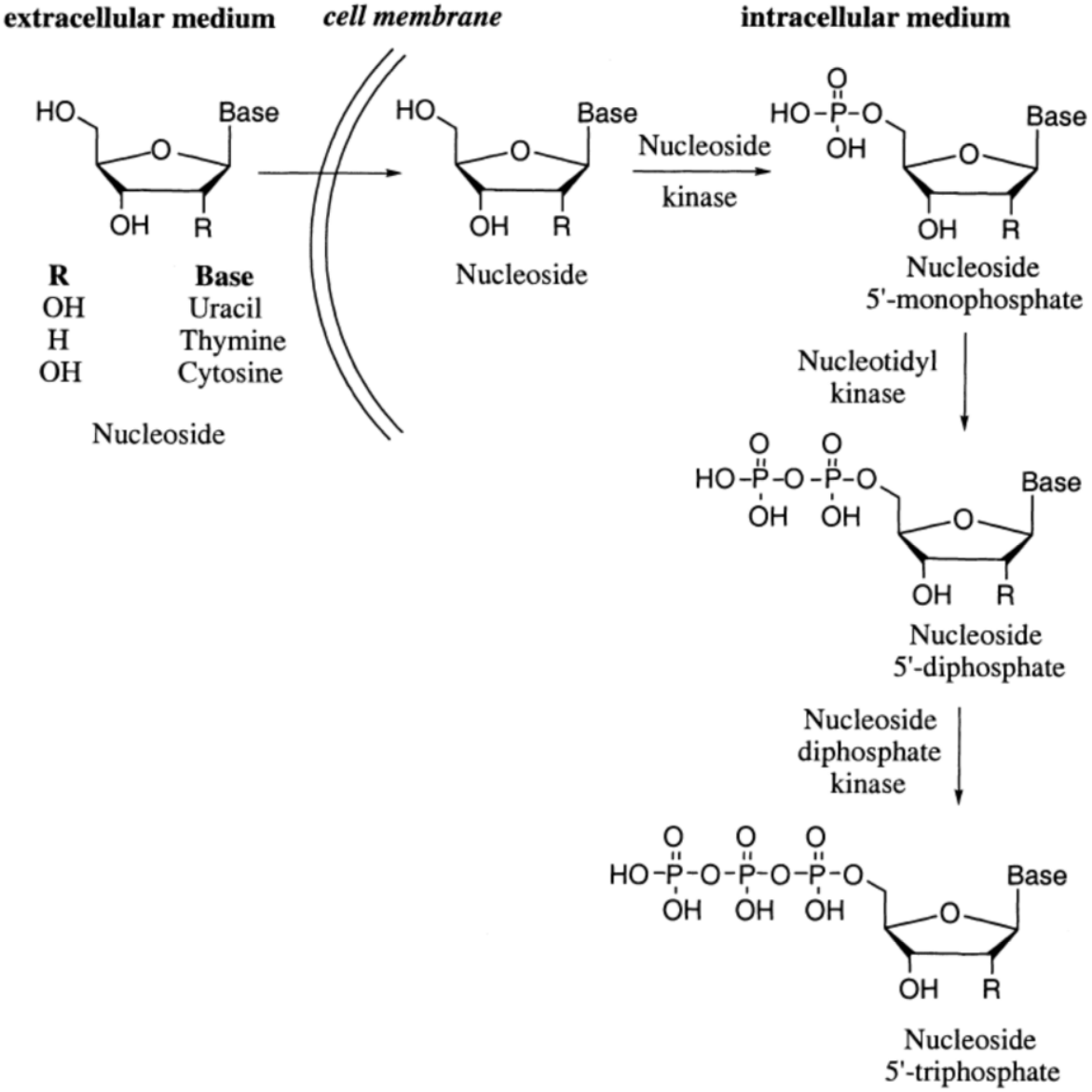


Id.

The incorporation of modified nucleosides, however, into lengthening RNA chains can result in viral inhibition, when the modified nucleoside will inhibit further incorporation of subsequent nucleoside units. EX1002 at ¶41. This inhibition is known as "chain termination." *Id.* Based on this mechanism, people in

the art have long used nucleoside analogs (N') that are recognizable by viral DNA/RNA polymerases or viral nucleoside kinases to subsequently inhibit the chain extension of viral DNA/RNA. *Id*.

Specifically, such nucleoside analogs (N') are recognized by host or viral nucleoside kinases and converted sequentially into their 5'-triphosphate (NTP), which is then recognized by a corresponding host or viral DNA/RNA polymerase in the cell so as to compete with natural 5'-triphosphate nucleosides (NTP) and finally added to the tail of the viral DNA/RNA chain being synthesized. EX1002 at ¶42. The extension of the viral DNA/RNA chain is terminated because of the difference between the analog and natural nucleosides, which results in suppression of viral replication. *Id*.

Several references recognized this general knowledge. EX1002 at ¶43. First, Wagner et al. "Pronucleotides: Toward the *In Vivo* Delivery of Antiviral and Anticancer Nucleotides" Medical Research Reviews, 2000, 20(6), 417-451 ("Wagner"; EX1010), described the use of nucleoside analogs for inhibition of various viruses. *Id*. Second, WO 2005/003147 to Clark ("Clark '147"; EX1006) described research and results about use of various nucleoside analogs for treatment of *Flaviviridae* infections from 1994 to 2004. *Id*.; EX1006 at 12:11 – 13:4.

The first commercially available antiviral nucleoside was the anti-herpes

virus uridine analog Iododeoxuridine, which was synthesized in the 1950s. EX1002 at ¶44; Prusoff et al. "Synthesis and biological activities of iododeoxyuridine, an analog of thymidine" Biochim Biophys Acta., 1959, 32(1), 295-6 ("Prusoff"; EX1011).

Since then many nucleoside analogs have been discovered and used as inhibitors of viral enzymes involved in viral DNA/RNA synthesis, including those listed in the table below. EX1002 at ¶45.

Anti-viral nucleoside analog	**Target for inhibition**	**Analogous to**	**Publication time**
9-β-D-arabinofuranosyladenine (Vidarabine)	DNA polymerase of multiple viruses	adenosine	1964
Acycloguanosine (ACV, Aciclovir)	herpes simplex virus thymidine kinase; varicella herpes zoster virus thymidine kinase	guanosine	1970s
Ribavirin	Hepatitis C virus (HCV) RNA polymerase	guanosine /adenosine	1972
2′,3′-dideoxy-3′-thiacytidine (3TC, Lamivudine)	Hepatitis B virus (HBV) reverse transcriptase; HIV reverse transcriptase	cytidine	1980s
Stavudine (d4T)	HIV reverse transcriptase	thymidine	1980s
Azidothymidine (AZT, Zidovudine)	HTLV-III/LAV reverse transcriptase	thymidine	1985
	HIV reverse transcriptase	thymidine	1986

2′,3′-dideoxyinosine (ddI, Didanosine)	HIV reverse transcriptase	adenosine	1988
2′,3′-dideoxycytidine (ddC, Zalcitabine)	HIV reverse transcriptase	cytidine	1988
dideoxy uridine (ddU) 5'-phosphates	HIV reverse transcriptase	uridine	1994
Emtricitabine (FTC)	HIV reverse transcriptase	cytidine	1996
Abacavir (ABC)	HIV reverse transcriptase	guanosine	Before 1998
DHPG (Ganciclovir)	Cytomegalovirus guanosine kinase	guanosine	1998
Entecavir (ETV)	HBV reverse transcriptase	guanosine	1990s
(2'R)-2'-dO-2'-F-2'-*C*-methyluridine 5'-phosphate	HCV RNA polymerase	uridine	2005
Telbivudine	HBV reverse transcriptase	thymidine	2005
4'-azido-uridine 5'-phosphoramidate	HCV RNA polymerase	uridine	Feb 2007

Thus, as of March 2007, it was generally known that nucleoside analogs suppress viral replication by incorporation into viral DNA/RNA chains. EX1002 at ¶46.

B. Anti-Viral Nucleosides Must Be Converted Into Their Triphosphates To Be Active, Monophosphorylation Was The Rate-Limiting Step In Such Conversion, and 5'-Phosphate Prodrugs Enabled Nucleosides To Overcome This Limitation

It was well known that, to interact with HCV NS5B polymerase, anti-viral

nucleosides must first be converted into their triphosphate form. EX1002 at ¶47. This was described, for example, in Ma et al. "Characterization of the Metabolic Activation of Hepatitis C Virus Nucleoside Inhibitor β-D-2'-Deoxy-2-Fluro-2'-C-Methylcytidine (PSI-6130) and Identification of a Novel Active 5'-Triphosphate Species" J. Biol. Chem., 2007, 282(41), 29812-29820 ("Ma"; EX1005), which recognized this general knowledge, saying, "[c]onversion to the active 5'-triphosphate form by cellular kinases is an important part of the mechanism of action for nucleoside analogs." *Id.*; EX1005 at 2.

Perrone et al. "Application of the Phosphoramidate ProTide Approach to 4'-Azidouridine Confers Sub-micromolar Potency versus Hepatitis C Virus on an Inactive Nucleoside" J. Med. Chem. 2007, 50(8), 1840-1849 ("Perrone"; EX1008) also recognized this general knowledge, saying, "[a]ll antiviral agents acting via a nucleoside analogue mode of action need to be phosphorylated, most of them to their corresponding 5'-triphosphates." EX1002 at ¶48; EX1008 at 1.

It was also well known that, for incorporation of a nucleoside analog into the viral DNA/RNA chain, kinase-mediated 5'-monophosphorylation of the nucleoside analog (N'→N'MP) is generally the rate-limiting step in the course of its triphosphorylation. EX1002 at ¶49. Several references recognized this general knowledge. *Id*.

First, Perrone recognized that, "the first phosphorylation step to produce the

5’-monophosphate has often been found to be the rate-limiting step in the pathway to intracellular nucleotide triphosphate formation.” EX1002 at ¶50; EX1008 at 1 (“The first phosphorylation step to produce the 5'-monophosphate has often been found to be the rate-limiting step in the pathway to intracellular nucleotide triphosphate formation”). Second, Wagner recited that ddNs’ activation is hindered at the first phosphorylation step. EX1002 at ¶50; EX1010 at 2. Third, McGuigan, et al. “Application of Phosphoramidate ProTide Technology Significantly Improves Antiviral Potency of Carbocyclic Adenosine Derivatives” J. Med. Chem., 2006, 49, 7215-7726 (“McGuigan 2006”; EX1012), recognized that, “in most cases the first phosphorylation to the 5’-monophosphate is the rate-limiting step.” EX1002 at ¶50; EX1012 at 1.

Perrone (EX1008), Wagner (EX1010), and McGuigan 2006 (EX1012) also evinced the general knowledge that, although 5’-triphosphates of some nucleoside analogs (NTP) are potent viral inhibitors, these nucleoside analogs (N’) themselves showed little or no activity in inhibition assays, generally because of the host cell’s lack of corresponding kinase activity which renders the 5’-monophosphorylation of these analogs extremely slow. EX1002 at ¶51.

Several other references recognized this general knowledge. EX1002 at ¶52. First, McGuigan et al. “Certain phosphoramidate derivatives of dideoxy uridine (ddU) are active against HIV and successfully by-pass thymidine kinase” FEBS

Letters, 1994, 351, 11-14 ("McGuigan 1994"; EX1013), recognized that nucleoside analogs have limitations because they depend on kinase-mediated activation to generate the bioactive (tri)phosphate forms. EX1002 at ¶52; EX1013 at 1. McGuigan 1994 also recognized that dideoxythymidine and 3'-O-methylthymidine are nucleoside analogs which are inactive against HIV, while their triphosphates are exceptionally potent inhibitors of HIV reverse transcriptase, and the inactivity of these nucleoside analogs is attributed to poor phosphorylation by host cells. *Id*.

McGuigan 2006 also recognized that poor phosphorylation can be a major cause of poor activity, with several examples now known where nucleoside analogs are inactive but the corresponding triphosphates are inhibitors at their enzyme target. EX1002 at ¶53; EX1012 at 1.

To address this widely known issue, it was contemplated in the art to use the 5'-phosphate of nucleoside analogs as a prodrug to "bypass" the kinase-mediated monophosphorylation so that it can be quickly converted into the active triphosphate form. EX1002 at ¶54. Since 1990 or earlier, stable 5'-phosphate-based prodrugs of nucleoside analogs have been designed and employed to improve the intracellular delivery and activation of the nucleoside analogs, and such prodrugs could readily be hydrolyzed into 5'-monophosphates of the nucleoside analogs (NMP) by enzymes inside the cell. EX1002 at ¶54; EX1013 (McGuigan 1994).

The 5'-monophosphate is then rapidly converted into the triphosphate form to be fully activated. EX1002 at ¶54. Such a technique has been called "Pronucleotide" or simply "ProTide". *Id*.

First, Wagner, recognized that various prodrug or "pronucleotide" approaches have been devised and investigated, with the general goal of promoting passive diffusion through cell membranes and increasing the bio-availability of nucleosides or phosphorylated nucleosides. EX1002 at ¶55; EX1010 at 3 and n8. This approach of derivatization had been applied using various protecting groups for the phosphate moiety. *Id*.

Second, Cahard et al. "Aryloxy phosphoramidate triesters as pro-tides" 2004, 4(4), 371-81 ("Cahard"; EX1014) recognized that aryloxy phosphoramidate triesters are an effective pro-tide motif for the intracellular delivery of charged antiviral nucleoside monophosphates and that the phenyl alanyl phosphoramidate approach was successful on a range of nucleosides by many research groups. EX1002 at ¶56; EX1014 at 1, 4.

Third, Perrone recognized that unmodified nucleoside monophosphates are unstable in biological media and also show poor membrane permeation because of the associated negative charges at physiological pH. EX1002 at ¶57; EX1008 at 1. Perrone also recognized that the known aryloxy phosphoramidate ProTide approach allows bypass of the initial kinase dependence by intracellular delivery of

the mono-phosphorylated nucleoside analog as a membrane-permeable ProTide form. *Id*. The technology greatly increased the lipophilicity of the nucleoside monophosphate analog with a consequent increase of membrane permeation and intracellular availability. *Id*.

The "ProTide" technology was known to show great success in the intracellular delivery and activation of many nucleoside analogs. EX1002 at ¶58. A large number of thus-modified nucleosides showed a boost in the inhibition activity on virus replication by tens, hundreds, or even thousands of times, in comparison with the parent nucleoside analogs. *Id*.

McGuigan 1994 recognized that the aryloxy phosphoramidate (3c) of a ddU increases its potency by approximately 50 times. EX1002 at ¶59; EX1013 at 3 (Fig. 1).

Cahard recognized that the aryloxy phosphoramidate prodrug (21) for d4A boosts the activity of the parent nucleoside analog d4A by 1000 – 4000 fold and the aryloxy phosphoramidate prodrug (22) for ddA boosts the activity of the parent nucleoside analog ddA by >100 fold. EX1002 at ¶60; EX1014 at 2 (Fig. 1) and 3.

McGuigan 2006 recognized that the ProTide approach was highly successful when applied to L-Cd4A with potency improvements in vitro as high as 9000-fold against HIV. EX1002 at ¶61; EX1012 at 1. McGuigan 2006 also recognized that several aryloxy phosphoramidate prodrugs achieve an anti-HIV activity at the level

of about 10 nM. EX1002 at ¶61; EX1012 at 4 (Table 1).

Therefore, the "Pronucleotide" or "ProTide" strategy had been a conventional technical means in the art. EX1002 at ¶62.

In summary, it was generally known that, for antiviral 5'-phosphate prodrugs, the antiviral activity lies in the nucleoside itself. EX1002 at ¶63. It was also generally known that the intracellular delivery (cell membrane permeation) relies on the lipophilicity rendered by the modified phosphate group and that their intracellular hydrolysis into the monophosphate form is mainly attributed to the structural nature of the modified phosphate group and the corresponding enzymes in the host cell. *Id*.

C. The Means Were Available to Determine Which Nucleosides Were Kinase Dependent

The general knowledge that many nucleosides were kinase-dependent in activation to their triphosphates was reflected in an early reference in the field by McGuigan 1994. EX1002 at ¶64; EX 1013 at 1-3. The means existed to assess the cellular uptake and subsequent phosphorylation of nucleosides. EX1002 at ¶64; Ma EX1005 at 4-8. Thus, it was generally known that the identification of nucleoside analogs whose activity was kinase-dependent was readily available. EX1002 at ¶64.

D. Narrowing The Selection Of Options For The Phosphoramidate Prodrug

Phosphoramidate prodrugs have optional substation to be selected at the: 1) amino acid moiety; 2) ester group on the amino acid; 3) ester group on phosphorous; and 4) optional substitution on nitrogen of the amino acid. EX1002 at ¶65. Of these possibilities, the range of realistic options is reasonably limited. *Id*. Perrone demonstrates how the amino acid moiety is most often glycine, alanine or valine, and how the ester group on the amino acid is most often methyl, isopropyl, or benzyl. *Id*.; EX1008. The useful ester groups on phosphorous are aryl (typically phenyl). EX1002 at ¶65.

It would be readily known to a POSA that designing an appropriate ProTide involves a selection process that is limited in scope and adaptable to a nucleoside that is the promising drug candidate. EX1002 at ¶66. As such, the selection of a phosphoramidate prodrug moiety would require labor, but with a limited selection of options and a high degree of probable success. *Id*.

E. Phosphoramidates Improved Nucleosides

It was well-known in the art, *e.g.* McGuigan 1994, that the biological activity of nucleosides could be hampered due to poor phosphorylation by one or more of the kinases needed for conversion to the active triphosphate form. EX1002 at ¶67; EX1013. This limitation was known to be overcome by the incorporation of phosphoramidate ProTide technology. EX1002 at ¶67; EX1012 (McGuigan 2006).

Such phosphoramidates were known to be precursors of active triphosphates and to inhibit viral replication in infected whole cells. EX1002 at ¶67.

Phosphoramidates were also known to improve physicochemical properties of nucleosides, resulting in dramatic increases in intracellular concentrations of nucleoside analogs. EX1002 at ¶68; EX1013 (McGuigan 1994). Enzyme-mediated hydrolysis of the phosphoramidates resulted in the nucleoside monophosphate being released, thus bypassing the need for the slow, first-step monophosphorylation. EX1002 at ¶68.

F. The '580 Patent Acknowledges This Common Knowledge

The '580 patent acknowledged that the antiviral principle of nucleoside analogs and the use of 5'-phosphate-based prodrugs of nucleoside analogs to bypass the rate-limiting mono-phosphorylation and promote intracellular delivery was generally known. EX1002 at ¶69. In particular, the '580 patent uses the term "pronucleotides" to refer to exactly the conventional knowledge described above that had been repeatedly published for more than a decade. EX1001 at 4:30.

The '580 patent acknowledges that its purported invention is merely selecting a specific nucleoside analog and modified 5'-phosphate groups based on the well-known "ProTide" approach. EX1002 at ¶70.

For example, the '580 patent states in its Background that:

> Nucleoside inhibitors of NS5B polymerase can act either as a

non-natural substrate that results in chain termination or as a competitive inhibitor which competes with nucleotide binding to the polymerase. To function as a chain terminator the nucleoside analog must be taken up by the cell and converted in vivo to a triphosphate to compete for the polymerase nucleotide binding site. This conversion to the triphosphate is commonly mediated by cellular kinases which imparts additional structural requirements on a potential nucleoside polymerase inhibitor. Unfortunately, this limits the direct evaluation of nucleosides as inhibitors of HCV replication to cell-based assays capable of in situ phosphorylation.

In some cases, the biological activity of a nucleoside is hampered by its poor substrate characteristics for one or more of the kinases needed to convert it to the active triphosphate form. Formation of the monophosphate by a nucleoside kinase is generally viewed as the rate limiting step of the three phosphorylation events. To circumvent the need for the initial phosphorylation step in the metabolism of a nucleoside to the active triphosphate analog, the preparation of stable phosphate prodrugs has been reported. Nucleoside phosphoramidate prodrugs have been shown to be precursors of the active nucleoside triphosphate and to inhibit viral replication when administered to viral infected whole cells (McGuigan, C, et al., *J. Med. Chem.*, 1996, 39, 1748- 1753; Valette, G., et al., *J. Med. Chem.*, 1996, 39, 1981-1990; Balzarini, J., et al., *Proc. National Acad Sci USA*, 1996, 93, 7295-7299; Siddiqui, A. Q., et al., *J. Med. Chem.*, 1999, 42, 4122-4128; Eisenberg, E. J., et al., *Nucleosides, Nucleotides and Nucleic Acids*, 2001, 20, 1091-1098; Lee, W.A., et al., *Antimicrobial Agents and Chemotherapy*, 2005, 49,

1898); US 2006/0241064; and WO 2007/095269.

Also limiting the utility of nucleosides as viable therapeutic agents is their sometimes poor physicochemical and pharmacokinetic properties. These poor properties can limit the intestinal absorption of an agent and limit uptake into the target tissue or cell. To improve on their properties prodrugs of nucleosides have been employed. It has been demonstrated that preparation of nucleoside phosphoramidates improves the systemic absorption of a nucleoside and furthermore, the phosphoramidate moiety of these "pronucleotides" is masked with neutral lipophilic groups to obtain a suitable partition coefficient to optimize uptake and transport into the cell dramatically enhancing the intracellular concentration of the nucleoside monophosphate analog relative to administering the parent nucleoside alone. Enzyme-mediated hydrolysis of the phosphate ester moiety produces a nucleoside monophosphate wherein the rate limiting initial phosphorylation is unnecessary."

EX1001 at 3:56 – 4:39 (emphasis added).

IX. SCOPE AND CONTENT OF THE PRIOR ART

The following references, alone or in combination with each other, taught or suggested the compounds, compositions and methods recited in claims 1-14 of the '580 patent. EX1002 at ¶72.

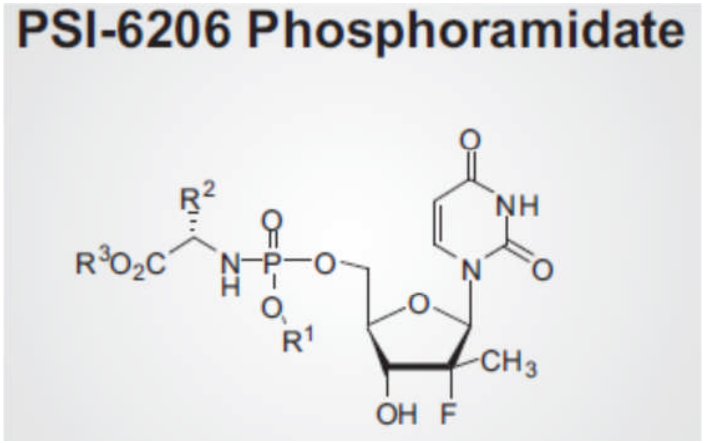
A. Sofia et al., "β-D2′-Deoxy-2′-C-methyluridine Phosphoramidates: Potent and Selective Inhibitors of HCV RNA Replication", Poster #P-259, presented at the 14th International Symposium on Hepatitis C Virus and Related Viruses, Glasgow, Scotland, UK, Sep. 9-13, 2007. ("Sofia"; EX1004)

Sofia is prior art under 35 U.S.C. § 102(a) to the '580 patent because it was published by September 13, 2007, before the October 24, 2007, filing date of the '309 provisional application to which the '580 patent claims priority. While the '580 patent also claims priority to the '315 provisional application filed on May 30, 2007, that application did not include a description of the specific compounds claimed by the '580 patent. EX1002 at ¶73. While it discusses broad genera of compounds, it does not discuss the specific compounds and stereochemistry around the phosphorous atom claimed in the '580 patent. *Id*. Thus, the claims of the '580 patent are only entitled to the October 24, 2007, priority date, not the May 30, 2007, priority date. As such, the September 2007 publication of Sofia makes it prior art under 102(a).

Sofia taught a prodrug of β-D-2'-deoxy-2'-fluoro-2'-C-methylcytidine (PSI-6130) for the treatment of chronic hepatitis C. EX1004 at 1. In particular, Sofia taught that the triphosphate of PSI-6130 was a potent inhibitor of the HCV NS5B polymerase. *Id*.

Sofia also taught that PSI-6130 was converted to its uridine metabolite (PSI-6206) via cytidine deaminase and that, "phosphoramidates of PSI-6206 [were] as

much as 100X more potent than the cytidine analog PSI-6130." *Id*. at n. 2. The structure of PSI-6206 phosphoramidate taught by Sofia is presented below. *Id*. at 1.



Sofia additionally taught that while PSI-6206 was not an inhibitor of HCV in the replicon assay and was not metabolized to its monophosphate derivative, its triphosphate was a potent inhibitor of the HCV NS5B polymerase. *Id*. at 1. Sofia further taught that metabolism studies showed the monophosphate of PSI-6130 was partially metabolized to the uridine monophosphate (PSI-6206), which could be converted to the triphosphate derivative. *Id*.

Sofia taught that investigating the potential for utilizing PSI-6206 as an inhibitor of HCV replication required bypassing the first phosphorylation step, which could be accomplished by the preparation of phosphoramidate derivatives at the 5'-position. *Id*. Sofia taught that such a strategy produced potent and safe inhibitors of HCV. *Id*. In Table 4, Sofia expressly taught that the uracil base compound (PSI-7672) had significantly more antiviral activity than the cytosine

base compound, by an order of 15 times more. *Id*.

B. Ma, Characterization of the Metabolic Activation of Hepatitis C Virus Nucleoside Inhibitor β-D-2'-Deoxy-2-Fluro-2'-CMethylcytidine (PSI-6130) and Identification of a Novel Active 5'-Triphosphate Species," The Journal of Biological Chemistry, vol. 282, No. 41, 29812-29820, Oct. 12, 2007 ("Ma"; EX1005)

Ma is prior art under 35 U.S.C. § 102(a) to the '580 patent because it was published on October 12, 2007, before the October 24, 2007, filing date of the '309 provisional application to which the '580 patent claims priority. While the '580 patent also claims priority to the '315 provisional application filed on May 30, 2007, that application did not include a description of the specific compounds claimed by the '580 patent. EX1002 at ¶73. While it discusses broad genera of compounds, it does not discuss the specific compounds and stereochemistry around the phosphorous atom claimed in the '580 patent. *Id*. Thus, the claims of the '580 patent are only entitled to the October 24, 2007, priority date, not the May 30, 2007, priority date. As such, the October 12, 2007, publication of Ma makes it prior art under 102(a).

Ma taught β-D-2'-deoxy-2'-fluoro-2'-C-methyluridine (RO2433, PSI-6026), a deaminated derivative of β-D-2'-deoxy-2'-fluoro-2'-C-methylcytidine (PSI-6130). EX1005 at 1. Ma taught that the uridine analog RO2433 was inactive in the replicon assay, but explained that the inactivity was most likely due to it being a poor substrate for the kinase responsible for its monophosphorylation. *Id*. at 8.

Without first being monophosphorylated, Ma taught RO2433 could not go on to form its active triphosphate RO2433-TP. *Id*. at 8. Ma thus taught the corresponding phosphorylated metabolites of RO2433 and that the 5'-triphosphate (TP) of RO2433 (RO2433-TP) inhibited HCV RNA synthesis in HCV replicon cells and also inhibited the action of recombinant HCV polymerase NS5B with potencies comparable with those of the 5'-triphosphate of PSI-6130 (PSI-6130-TP). *Id*. at 4-8. Ma also taught that the uridine analog RO2433-TP had superior intracellular stability compared to the cytidine analog PSI-6103. *Id*. at 8.

C. Perrone et al. "Application of the Phosphoramidate ProTide Approach to 4'-Azidouridine Confers Sub-micromolar Potency versus Hepatitis C Virus on an Inactive Nucleoside" J. Med. Chem. 2007, 50(8), 1840-1849 ("Perrone"; EX1008)

Perrone is prior art under 35 U.S.C. § 102(a) to the '580 patent because it was published on March 17, 2007, before even the May 30, 2007, filing date of the earliest application to which the '580 patent claims priority.

Perrone taught a phosphoramidate "ProTide" approach to confer potency against hepatitis C virus by activating otherwise inactive nucleosides. Specifically, Perrone taught that the addition of an aryloxy phosphoramidate group at the 5'-position of a uridine nucleoside can confer antiviral activity inhibitory activity in the HCV replicon assay for a compound that was otherwise inactive against hepatitis C virus. EX1008 at 2.

Perrone also taught that a potent HCV inhibitor nucleoside did not show

inhibitory activity in the HCV replicon assay because of the extremely slow intracellular 5'-monophosphorylation of the nucleoside. *Id*. at 2-4. In addition, Perrone taught that the triphosphate nucleoside analogue showed potent inhibition of HCV in the NS5B Polymerase assay as a means of identifying nucleosides which were inefficiently phosphorylated. *Id*. at 1.

Perrone employed the well-known ProTide strategy to prepare about 20 stable phosphate-based prodrugs of the nucleoside. *Id*. at 4 (Table 1). These prodrugs were hydrolyzed into 5'-monophosphorylated derivatives of the nucleoside inside the cell, thereby bypassing the need for kinase-mediated monophosphorylation. *Id*. at 1-2. Among these aryloxy phosphoramidate prodrugs, Perrone particularly taught that, "the isopropyl ester (15) showed high potency and represented one of the most active phosphoramidates prepared." *Id*. at 3.

X. CLAIMS 1-14 ARE UNPATENTABLE

Each and every feature of claims 1-14 of the '580 patent can be found in the prior art reference identified below. EX1002 at ¶92. In addition, a POSA would have been motivated to combine the references as discussed below and had a reasonable expectation of success of arriving at the subject matter of each of the claims of the '580 patent. EX1002 at ¶92.

Each of claims 1-14 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 at ¶93.

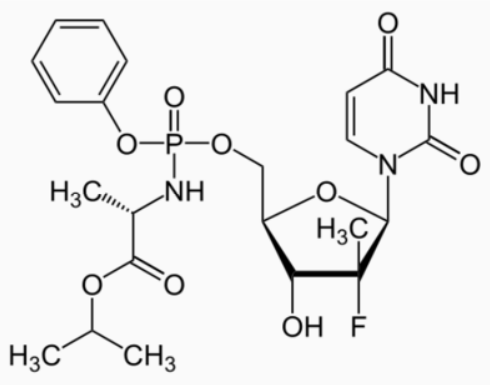
A. Ground 1: Claims 1-14 Were Anticipated By Sofia

All of the claims of the '580 patent were anticipated by Sofia. EX1002 at ¶94.

1. Claims 1 and 8 (compound)

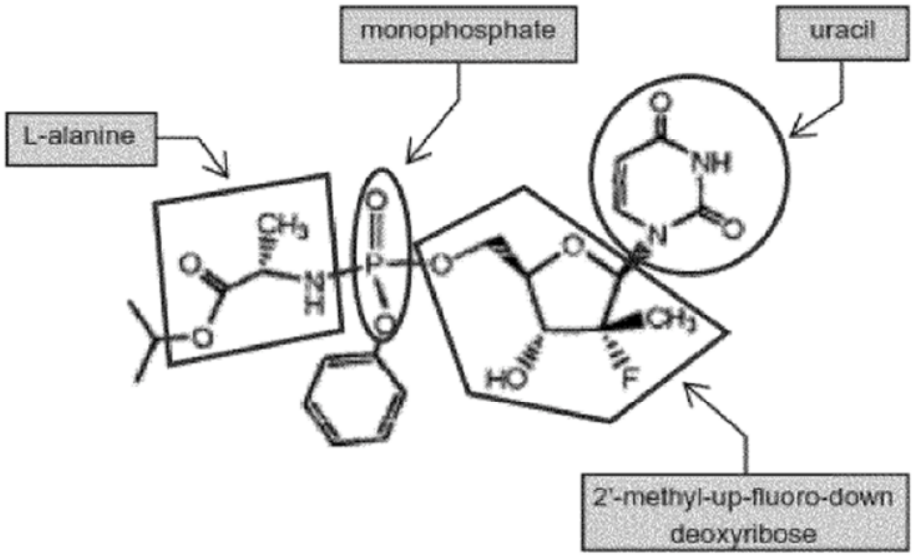
Claim 1 of the '580 patent recites, "(S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid isopropyl ester or a stereoisomer thereof." EX1001 at 493:42-46. Claim 8 recites, "(S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino) propanoate." EX1001 at 495:27-31.

The compound claimed in claim 1 is a 5'-phosphate (phosphoramidate) prodrug of the uridine analog "(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyluridine", wherein the 5'-phosphate group is the "*(phenyl)(isopropyl-L-alaninyl)phosphate*" group. EX1001 at 493:42-46. Included within claim 1 is the specific compound of claim 8, which has the formula:

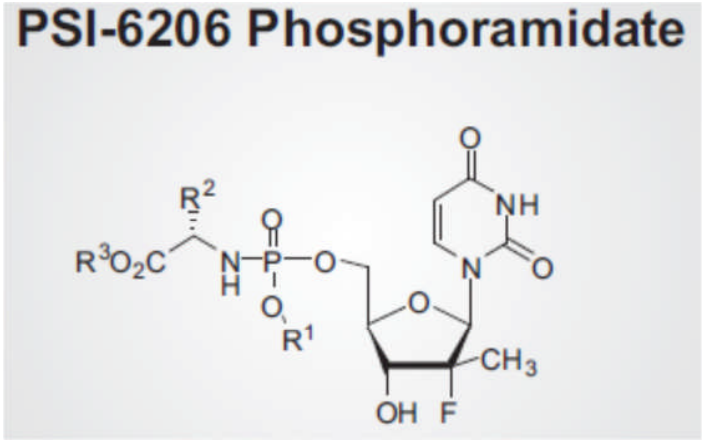


Id.; EX1002 at ¶96.

As can be seen from the formula, the compound of claim 1 is composed of a deoxyribose sugar, a base, and a masked phosphate group. EX1002 at ¶97. An annotated version of this compound is set out in the following diagram that shows the compound has a deoxyribose sugar ring, which is substituted at the 2'-position with a methyl group in the "up" configuration and a fluoro radical in the "down" position. *Id*. The deoxyribose sugar is substituted with a base at the conventional position via a glycosidic bond. *Id*. The base is uracil. *Id*.



Sofia taught a prodrug of β-D-2'-deoxy-2'-fluoro-2'-C-methylcytidine (PSI-6130) for the treatment of chronic hepatitis C. EX1004 at 1. In particular, Sofia taught that the triphosphate of PSI-6130 was a potent inhibitor of the HCV NS5B polymerase. *Id*. Sofia also taught that PSI-6130 was converted to its uridine metabolite (PSI-6206) via cytidine deaminase and that, "phosphoramidates of PSI-6206 [were] as much as 100X more potent than the cytidine analog PSI-6130." *Id*. at n. 2. The structure of PSI-6206 phosphoramidate taught by Sofia is presented below. *Id*. at 1.



Sofia additionally taught that while PSI-6206 was not an inhibitor of HCV in the replicon assay and was not metabolized inside the cell to its monophosphate derivative, its triphosphate was a potent inhibitor of the HCV NS5B polymerase. *Id.* at 1. Sofia further taught that the monophosphate of PSI-6130 was partially metabolized to the uridine monophosphate PSI-6206, which could be converted to its triphosphate derivative. *Id.*

Sofia taught that investigating the potential for utilizing PSI-6206 as an inhibitor of HCV replication required bypassing the first phosphorylation step, which could be accomplished by the preparation of phosphoramidate derivatives at the 5'-position. *Id.* Sofia taught that such a strategy produced potent and safe inhibitors of HCV. *Id.* In Table 4, Sofia expressly taught that the uracil base compound (PSI-7672) had significantly more antiviral activity (15x) than the cytosine base compound. *Id.*

Sofia thus taught a 5'-triphosphate of the uridine nucleoside (2'R)-2'-deoxy-

2'-fluoro-2'-*C*-methyluridine as claimed in claims 1 and 8 patent. *Id*. Therefore, Sofia anticipated claims 1 and 8. EX1002 at ¶101.

2. Claims 2, 3, 9 and 10 (compositions comprising compound)

Claim 2 of the '580 patent recites, "A composition comprising the compound or a stereoisomer thereof as claimed in claim 1 and a pharmaceutically acceptable medium." EX1001 at 493:47-49. Claim 3 of the '580 patent recites, "A composition for treating a hepatitis C virus, which comprises an effective amount of the compound or a stereoisomer thereof as claimed in claim 1 and a pharmaceutically acceptable medium." *Id*. at 493:50-53. Claims 9 and 10 are identical to claims 2 and 3 except that they depend from claim 8 instead of claim 1.

Sofia taught that its compounds were potent and safe inhibitors of HCV replication. EX1004. Inherent in this teaching are compositions comprising such compounds and a pharmaceutically acceptable medium and that such compositions are for treating hepatitis C. EX1002 at ¶123. Thus, Sofia anticipated claims 2, 3, 9 and 10. *Id*.

3. Claims 4, 5, 11 and 12 (methods of treating viral infections)

Claim 4 of the '580 patent recites, "A method of treating a subject infected by a virus, which comprises: administering to the subject an effective amount of the compound or a stereoisomer thereof as claimed in claim 1; wherein the virus is selected from among hepatitis C virus … ." EX1001 at 493:54-63. Claim 5 of the

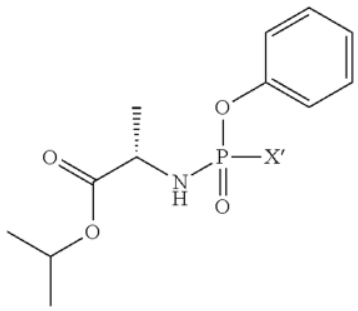
‘580 patent recites, “A method of treating a hepatitis C virus infection in a subject in need thereof, which comprises: administering to the subject an effective amount of the compound or a stereoisomer thereof as claimed in claim 1.” Claims 11 and 12 are identical to claims 4 and 5 except that they depend from claim 8 instead of claim 1.

Sofia taught that its compounds were potent and safe inhibitors of HCV replication. EX1004. Thus, Sofia anticipated claims 4, 5, 11 and 12 of the ’580 patent. EX1002 at ¶126.

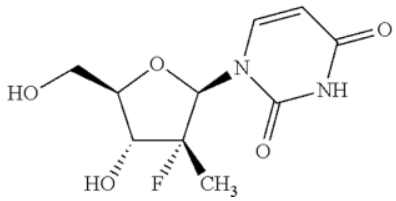
4. Claims 6, 7, 13 and 14 (process of preparing and product)

Claim 6 recites, “A process for preparing the compound or a stereoisomer thereof as claimed in claim 1, said process comprising: reacting a compound 4″ with a nucleoside analog 5′

4″



5′



wherein X′ is a leaving group. Claim 7 recites, "A product comprising the compound or a stereoisomer thereof as claimed in claim 1 obtained by a process comprising: reacting a compound 4″ with a nucleoside analog 5′," wherein 4' and 5' are the same as in claim 6. Claims 13 and 14 are identical to claims 6 and 7 except that they depend from claim 8 instead of claim 1.

Sofia taught the same reaction as claimed in claims 6 and 7 in its Scheme 1. EX1004. Inherent in that teaching is that the reaction would be part of a process to prepare a compound that would become a pharmaceutical product. EX1002 at ¶129. Thus, Sofia anticipated claims 6, 7, 13 and 14. *Id.*

B. Ground 2: Claims 1-14 Were Obvious Over Sofia and Perrone

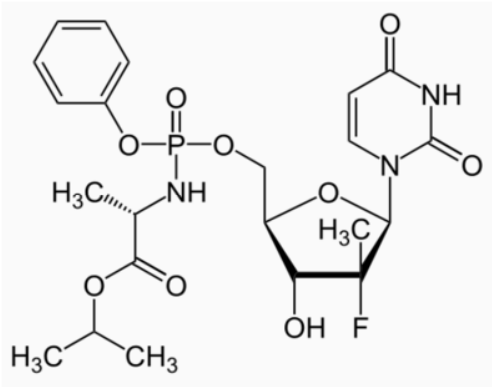
All of the claims of the '580 patent were obvious over Sofia and Perrone. *Id.* A POSA would have been motivated to combine their teachings because they both related to phosphoramidates of anti-viral nucleosides, and in particular anti-HCV. *Id.* The '580 patent also cites both as references. EX1001 at 4 and 5.

1. Claims 1 and 8 (compound)

Claim 1 of the '580 patent recites, "(S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid isopropyl ester or a stereoisomer thereof." EX1001 at 493:42-46. Claim 8 recites, "(S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-

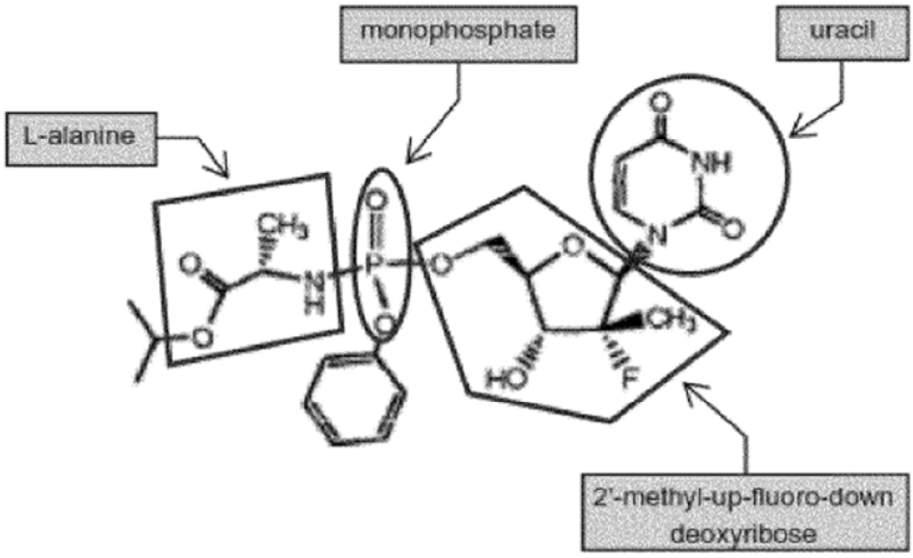
hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino) propanoate." EX1001 at 495:27-31.

The compound claimed in claim 1 is a 5'-phosphate (phosphoramidate) prodrug of the uridine analog "(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyluridine", wherein the 5'-phosphate group is the "*(phenyl)(isopropyl-L-alaninyl)phosphate*" group. EX1001 at 493:42-46. Included within claim 1 is the specific compound of claim 8, which has the formula:

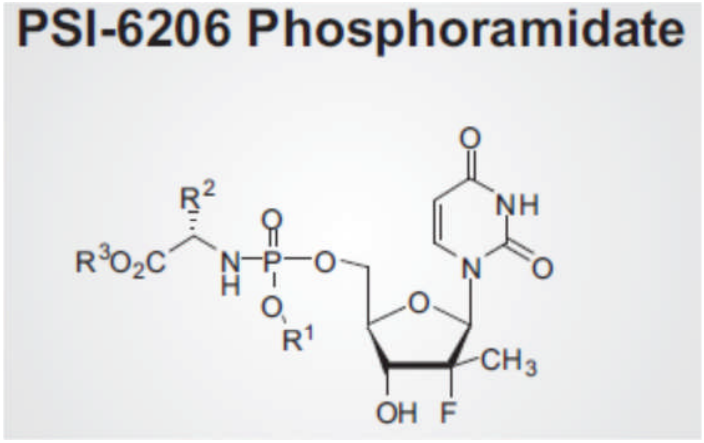


Id.; EX1002 at ¶96.

As can be seen from the formula, the compound of claim 1 is composed of a deoxyribose sugar, a base, and a masked phosphate group. EX1002 at ¶97. An annotated version of this compound is set out in the following diagram that shows the compound has a deoxyribose sugar ring, which is substituted at the 2'-position with a methyl group in the "up" configuration and a fluoro radical in the "down" position. *Id*. The deoxyribose sugar is substituted with a base at the conventional position via a glycosidic bond. *Id*. The base is uracil. *Id*.



Sofia taught a prodrug of β-D-2'-deoxy-2'-fluoro-2'-C-methylcytidine (PSI-6130) for the treatment of chronic hepatitis C. EX1004 at 1. In particular, Sofia taught that the triphosphate of PSI-6130 was a potent inhibitor of the HCV NS5B polymerase. *Id*. Sofia also taught that PSI-6130 was converted to its uridine metabolite (PSI-6206) via cytidine deaminase and that, "phosphoramidates of PSI-6206 [were] as much as 100X more potent than the cytidine analog PSI-6130." *Id*. at n. 2. The structure of PSI-6206 phosphoramidate taught by Sofia is presented below. *Id*. at 1.



Sofia additionally taught that while PSI-6206 was not an inhibitor of HCV in the replicon assay and was not metabolized inside the cell to its monophosphate derivative, its triphosphate was a potent inhibitor of the HCV NS5B polymerase. *Id.* at 1. Sofia further taught that the monophosphate of PSI-6130 was partially metabolized to the uridine monophosphate PSI-6206, which could be converted to its triphosphate derivative. *Id.*

Sofia taught that investigating the potential for utilizing PSI-6206 as an inhibitor of HCV replication required bypassing the first phosphorylation step, which could be accomplished by the preparation of phosphoramidate derivatives at the 5'-position. *Id.* Sofia taught that such a strategy produced potent and safe inhibitors of HCV. *Id.* In Table 4, Sofia expressly taught that the uracil base compound (PSI-7672) had significantly more antiviral activity (15x) than the cytosine base compound. *Id.*

Sofia thus taught a 5'-triphosphate of the uridine nucleoside (2'R)-2'-deoxy-

2'-fluoro-2'-*C*-methyluridine as claimed in claims 1 and 8 patent. *Id*.

A POSA, reading Sofia, would immediately envisage the selection of these specific substituents for R^1, R^2 and R^3 because of the general knowledge that phosphoramidate derivatives were useful for kinase by-pass. EX1002 at ¶102. Typically, R^1 is aryl, the substituent R^2 merely dictates the structure of the naturally occurring amino acid and R^3 is a simple alkyl group. *Id*. Indeed, the variability of R^2 in the prior art was much narrower than the full range of naturally-occurring amino acids, largely being restricted to glycine, alanine, valine, and phenylalanine (i.e., R^2 = H, CH_3, isopropyl, and benzyl). *Id*. Thus, the variability at R^1, R^2 and R^3, when viewed through the eyes of the skilled person familiar with nucleoside prodrug technology, would have been very limited. *Id*.

Moreover, a POSA would have known that certain specific combinations of R^1, R^2 and R^3 do actually exist that provide potent and safe inhibitors of HCV replication. EX1002 at ¶103. While synthesizing and testing the range of compounds discussed in Sofia may take some labor, it would require only a routine amount of effort given the technology and resources available to a POSA. *Id*.

A POSA would know that the purpose of the phosphoramidate prodrug was to confer adequate stability and lipophilicity to deliver the nucleoside prodrug safely into the cell. EX1002 at ¶104. After this delivery, the prodrug moieties were removed by known intracellular enzymes to yield the monophosphate. *Id*. Given

this knowledge, the range of possible combinations for R^1, R^2, and R^3 would be further limited. *Id*.

Perrone taught a phosphoramidate "ProTide" approach to confer potency against hepatitis C virus by activating otherwise inactive nucleosides. EX1008. Specifically, Perrone taught that the addition of an aryloxy phosphoramidate group at the 5'-position of a uridine nucleoside can confer antiviral activity inhibitory activity in the HCV replicon assay for a compound that was otherwise inactive against hepatitis C virus. EX1008 at 1-3.

Perrone also taught that a potent HCV inhibitor nucleoside did not show inhibitory activity in the HCV replicon assay because of the extremely slow intracellular 5'-monophosphorylation of the nucleoside. *Id*. at 3. In addition, Perrone taught that the triphosphate nucleoside analogue showed potent inhibition of HCV in the NS5B Polymerase assay as a means of identifying nucleosides which were inefficiently phosphorylated. *Id*. at 1.

Perrone employed the well-known ProTide strategy to prepare about 20 stable phosphate-based prodrugs of the nucleoside. *Id*. at 4 (Table 1). These prodrugs were hydrolyzed into 5'-monophosphorylated derivatives of the nucleoside inside the cell, thereby bypassing the need for kinase-mediated monophosphorylation. *Id*. at 1-2. Among these aryloxy phosphoramidate prodrugs, Perrone particularly taught that, "the isopropyl ester (15) showed high potency and

represented one of the most active phosphoramidates prepared." *Id*. at 3.

A POSA would have been motivated to apply the phosphoramidate ProTide approach of Perrone to the known HCV nucleoside PSI-6206 and had a reasonable expectation of success in doing so because of both the general knowledge that nucleosides needed to be phosphorylated to be active in inhibiting HCV replication and the fact that Perrone provided several examples of comparable nucleosides being triphosphorylated by its ProTide approach. EX1002 at ¶108; EX1008 at 4.

More specifically, Perrone taught that a stable modified 5'-phosphate group suitable for nucleoside analog 5'-phosphates is the "*(phenyl)(isopropyl-L-alaninyl)phosphate*" group, which has the same function in Perrone as in Sofia, i.e., a function of increasing the activity, bioavailability and stability of an anti-HCV uridine analog, with the same mechanism and purpose of promoting intracellular delivery of a uridine analog and bypassing the kinase-mediated 5'-monophosphorylation. EX1008 at 4.

A POSA reading Sofia and Perrone would be motivated to develop an active prodrug and would have envisaged applying the aryloxy phosphoramidate group identified to be highly active in Perrone to the (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine taught in Sofia. EX1002 at ¶110; EX1004 at 1; EX1008 at 1.

The nucleosides taught in Perrone and the (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine taught in Sofia are both uridine analogs used to inhibit HCV

through the same mechanism. EX1002 at ¶111. The structural difference between these two uridine analogs themselves would not have dissuaded a POSA who wanted to obtain a more active and potent prodrug by applying Perrone's phosphoramidate group to the 5'-position of Sofia's (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine. *Id*.

In addition, there are only 6 highly active phosphoramidate groups particularly identified in Perrone (*i.e.* No.14, 15, 17, and 33-35). EX1008 at 4 (Tables 1 and 3). A POSA would have been motivated to try to attach each to the 5'-position of Sofia's (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine resulting in the compounds of claims 1 and 8. EX1002 at ¶112.

Perrone describes a uridine analog (4'-aziduridne) which, like PSI-6206, is inactive in the HCV replicon assay although its triphosphate form (4'-azidouridine-TP) is a potent inhibitor of HCV NS5B polymerase. EX1008 at 1, 2-3, 5. Thus, Perrone described exactly the same problem as Sofia and suggested the same solution to the problem. EX1002 at ¶113. As both Sofia and Perrone lie in precisely the same technical filed, and both documents describe exactly the same problem, and both documents propose the same general solution, the skilled person would not hesitate to combine their teaching. *Id*.

A POSA would have been motivated to prepare the corresponding L-alanine derivatives which are all shown in Table 1 of Perrone to exhibit low or sub-

micromolar activity and had a reasonable expectation of success in achieving the same outcome as Perrone. EX1008 at 4. Specifically, a POSA would prepare the derivatives of PSI-6206 that correspond to compounds (14), (15) and (17) in Perrone because they are described in Perrone as having "exceptional" antiviral activity. EX1002 at ¶114; EX1008.

In considering the similarity of Perrone and Sofia, a POSA would not focus on the structural differences between the parent nucleosides, PSI-6206 and 4'-aziduridne. EX1002 at ¶115. A POSA select the nucleoside in Sofia as a lead compound due to its superior properties and then seek to modify its structure by incorporating the specific phosphoramidate substituents from Perrone that were taught to provide an optimal solution for delivering an active HCV nucleoside to target cells. EX1002 at ¶115; EX1008 at 4.

The compounds of claims 1 and 8 did not produce any unexpected results. EX1002 at ¶116. First, Perrone provided the technical teaching that use of the "*(phenyl)(isopropyl-L-alaninyl)phosphate*" group (No.15) significantly boosts the activity of anti-HCV nucleoside analogs. EX1008 at 3. Therefore, because Perrone and the '580 patent employed the same mechanism and theory, any activity improvement achieved by the claimed compound using the same modified 5'-phosphate group would have been expected. . EX1002 at ¶116.

Second, the "*(phenyl)(isopropyl-L-alaninyl)phosphate*" group (No.15)

disclosed in Perrone boosts the inactive parent nucleoside to an activity of EC_{50} = 0.77 μM, while the target application uses the same phosphoramidate group to boost the inactive parent nucleoside (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine to an activity of the same magnitude of that achieved in Perrone. . EX1002 at ¶117; compare EX1001 at 249 to EX1008 at 4.

Therefore, even if (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine is inactive, the '580 patent's claimed prodrug form does not produce unexpected results. EX1002 at ¶118.

Third, in the prior art, use of phosphoramidate prodrugs (ProTide) achieved increases in antiviral activity of as high as thousands of times the activity of the unmodified parent nucleoside, even to an activity/potency of several nM. *See*, ***e.g.***, McGuigan 2006, EX1012 at 1, 4 (Abstract and Table 1).

With regards to HCV phosphoramidate prodrugs (ProTide) achieved an increase in anti-HCV activity of more than 450-fold, to an activity of EC_{50}=0.22 μM. EX1008 at 4 (Table 3).

Applying Perrone's ProTide approach to Sofia's promising nucleoside would result in the compound claimed in claims 1 and 8 of the '580 patent. EX1002 at ¶121. Thus, Sofia and Perrone render claims 1 and 8 of the '580 patent obvious. *Id*.

2. Claims 2, 3, 9 and 10 (compositions comprising compound)

Claim 2 of the '580 patent recites, "A composition comprising the compound or a stereoisomer thereof as claimed in claim 1 and a pharmaceutically acceptable medium." EX1001 at 493:47-49. Claim 3 of the '580 patent recites, "A composition for treating a hepatitis C virus, which comprises an effective amount of the compound or a stereoisomer thereof as claimed in claim 1 and a pharmaceutically acceptable medium." *Id*. at 493:50-53. Claims 9 and 10 are identical to claims 2 and 3 except that they depend from claim 8 instead of claim 1.

Sofia taught that its compounds were potent and safe inhibitors of HCV replication. EX1004. Inherent in this teaching are compositions comprising such compounds and a pharmaceutically acceptable medium and that such compositions are for treating hepatitis C. EX1002 at ¶123.

Further, Perrone also taught that applying its phosphoramidate ProTide approach to nucleosides could activate them as HCV inhibitors for use in treating humans. EX1008 at 1, 2-3, 5. Inherent in this teaching are compositions comprising such compounds and a pharmaceutically acceptable medium and that such compositions are for treating hepatitis C. EX1002 at ¶124. Thus, Sofia and Perrone rendered claims 2, 3, 9, and 10 obvious. *Id*.

3. Claims 4, 5, 11 and 12 (methods of treating viral infections)

Claim 4 of the '580 patent recites, "A method of treating a subject infected

by a virus, which comprises: administering to the subject an effective amount of the compound or a stereoisomer thereof as claimed in claim 1; wherein the virus is selected from among hepatitis C virus … .” EX1001 at 493:54-63. Claim 5 of the ‘580 patent recites, “A method of treating a hepatitis C virus infection in a subject in need thereof, which comprises: administering to the subject an effective amount of the compound or a stereoisomer thereof as claimed in claim 1.” Claims 11 and 12 are identical to claims 4 and 5 except that they depend from claim 8 instead of claim 1.

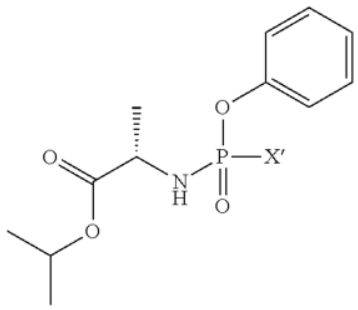
Sofia taught that its compounds were potent and safe inhibitors of HCV replication. EX1004.

Further, Perrone also taught that applying its phosphoramidate ProTide approach to nucleosides could activate them as HCV inhibitors for use in treating people. EX1008 at 1. Thus, Sofia and Perrone rendered claims 4, 5, 11 and 12 of the ’580 patent obvious. EX1002 at ¶127.

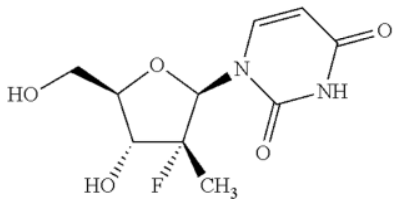
4. Claims 6, 7, 13 and 14 (process of preparing and product)

Claim 6 recites, “A process for preparing the compound or a stereoisomer thereof as claimed in claim 1, said process comprising: reacting a compound 4″ with a nucleoside analog 5′

4″



5′



wherein X′ is a leaving group. Claim 7 recites, "A product comprising the compound or a stereoisomer thereof as claimed in claim 1 obtained by a process comprising: reacting a compound 4″ with a nucleoside analog 5′," wherein 4' and 5' are the same as in claim 6. Claims 13 and 14 are identical to claims 6 and 7 except that they depend from claim 8 instead of claim 1.

Sofia taught the same reaction as claimed in claims 6 and 7 in its Scheme 1. EX1004. Inherent in that teaching is that the reaction would be part of a process to prepare a compound that would become a pharmaceutical product. EX1002 at ¶129.

Further, Perrone also taught as part of its phosphoramidate ProTide approach the reaction as claimed in claims 6 and 7 in its Scheme 1. EX1008 at 3 (1842). Inherent in that teaching is that the reaction would be part of a process to prepare a

compound that would become a pharmaceutical product. EX1002 at ¶130. Thus, Sofia and Perrone rendered claims 6, 7, 13 and 14 obvious. *Id*.

C. Ground 3: Claims 1-14 Were Obvious Over Ma and Perrone

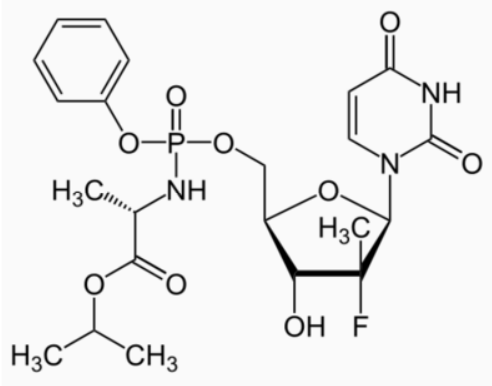
All of the claims of the '580 patent were obvious over Ma and Perrone. EX1002 at ¶131. One of ordinary skill in the art would have been motivated to combine their teachings because they both related to phosphoramidates of anti-viral nucleosides, and in particular anti-HCV. *Id*. The '580 patent also cites both as references. EX1001 at 5 and 6.

1. Claims 1 and 8 (compound)

Claim 1 of the '580 patent recites, "(S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid isopropyl ester or a stereoisomer thereof." EX1001 at 493:42-46. Claim 8 recites, "(S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino) propanoate." EX1001 at 495:27-31.

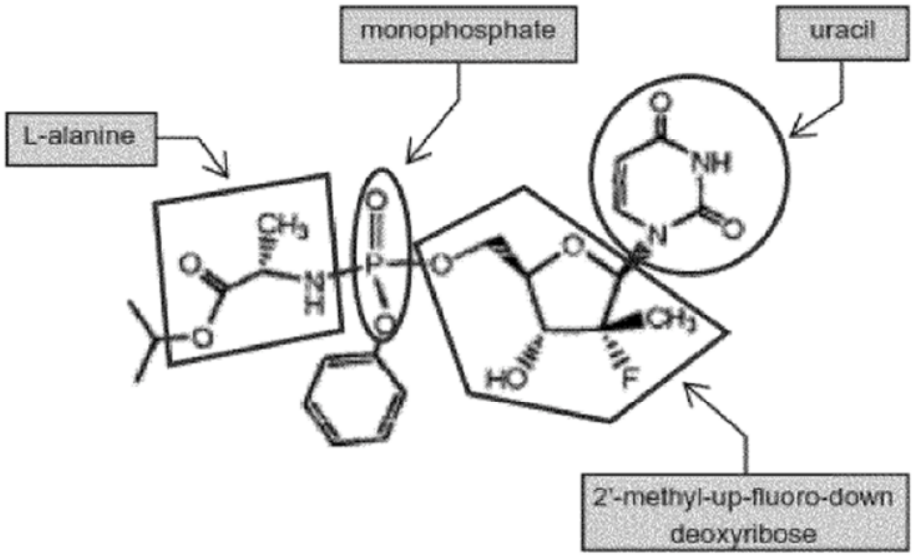
The compound claimed in claim 1 is a 5'-phosphate (phosphoramidate) prodrug of the uridine analog "(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyluridine", wherein the 5'-phosphate group is the "*(phenyl)(isopropyl-L-alaninyl)phosphate*" group. Included within claim 1 is the specific compound of claim 8, which has the

formula:



EX1002 at ¶133.

As can be seen from the formula, the compound of claim 1 is composed of a deoxyribose sugar, a base and a masked phosphate group. EX1002 at ¶134. An annotated version of this compound is set out in the following diagram that shows the compound has a deoxyribose sugar ring, which is substituted at the 2'-position with a methyl group in the "up" configuration and a fluoro radical in the "down" position. *Id*. The deoxyribose sugar is substituted with a base at the conventional position via a glycosidic bond. *Id*. The base is uracil. *Id*.



Ma taught β-D-2'-deoxy-2'-fluoro-2'-C-methyluridine (RO2433, PSI-6026), a deaminated derivative of β-D-2'-deoxy-2'-fluoro-2'-C-methylcytidine (PSI-6130). EX1005 at 1. Ma taught that the uridine analog RO2433 was inactive in the replicon assay, but explained that the inactivity was most likely due to it being a poor substrate for the kinase responsible for its monophosphorylation. *Id*. at 8.

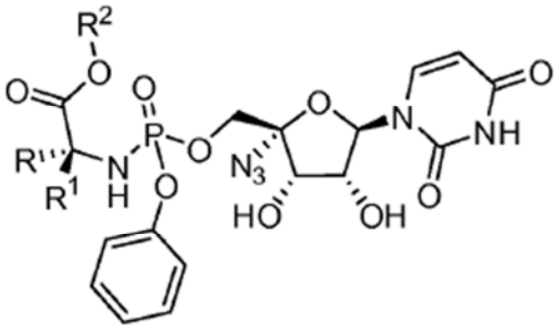
Although Ma taught that RO2433-TP was highly potent in both the native HCV replicon and HCV NS5B polymerase assays, with good intracellular stability, it was not itself considered a good drug candidate because it was well-known that 5'-phosphates (nucleotides) are unstable in biological media and show poor membrane penetration due to associated negative charges at physiological pH. EX1002 at ¶136.

Ma taught that similar problems to those described for RO2433 had been

previously reported in the art. EX1005. Specifically, Ma cites to Perrone, which described another uridine analog (4'-azidouridne) which, like RO2433, was inactive in the HCV replicon assay but which was shown to be highly potent when delivered as a monophosphate prodrug. EX1002 at ¶137.

Perrone taught that 4'-azidocytidine (R1479) is a potent inhibitor of HCV replication in cell culture and that R1479-TP is a potent inhibitor of HCV NS5B polymerase. EX1008 at 5. In contrast, the corresponding uridine analog (4'-azidouridine, shown below, was inactive in the cell based replicon system although its triphosphate form (4'-azidouridine-TP) is a potent inhibitor of HCV NS5B polymerase. EX1002 at ¶138. This is the same situation reported in Ma for the cytidine analog PSI-6130 and the uridine analog RO2433. EX1002 at ¶138; EX1005 at 8

Perrone describes the preparation of twenty-two aryloxy phosphoramidate derivatives of 4'-azidouridine. EX1008 at 2. The generic structure of the aryloxy phosphoramidates is shown below:



The aryloxy phosphoramidates were designated compounds 11-32 and the activity of the compounds in the HCV replicon assay was determined. The results are presented in Table 1 on page 1843 of Perrone. EX1008 at 4.

Compared to the inactive parent nucleoside 4'-azidouridine (1) a number of the aryloxy phosphoramidate derivatives showed potent activity. EX1002 at ¶140. In particular, all the L-alanine derivatives (compounds 11-17) exhibited low or sub-micromolar activity. EX1008 at 4. The activity of three ester derivatives, compounds (14), (15) and (17), is described as exceptional and noted as providing strong support for the ProTide kinase by pass approach. *Id*. at 3-4. These compounds also were not toxic, displaying CC50 values of >100 μM. EX1008 at 4 (Table 1).

Starting from Ma with a view to solving the above mentioned technical problem it would have been obvious to adopt the teaching of Perrone. EX1002 at ¶141. Both are in precisely the same technical field (uridine inhibitors of HCV NS5B polymerase) and both documents describe exactly the same problem (inactive uridine analog that is highly potent in its triphosphate form that is a poor substrate for monophosphorylation). *Id*.

However, in the present situation, the case that a POSA would have combined the teaching of Ma and Perrone is even more pressing because Ma provides a specific cross reference to Perrone. EX1005 at n21. In considering the

teaching of Perrone the skilled person would be motivated to prepare aryloxy phosphoramidates of RO2433 in the reasonable expectation of solving the technical problem in the same way as Perrone. EX1002 at ¶142. The skilled person would prepare the corresponding derivatives of RO2433 which are shown in Table 1 of Perrone, especially the compounds (14), (15) and (17) which are described in 07 as having "exceptional" antiviral activity. EX1008 at 4.

The aryloxy phosphoramidate of RO2433 which corresponds to compound (15) of Perrone is the claimed compound. EX1002 at ¶143. As such, one of ordinary skill in the art would have found the claimed compounds obvious because of the simple combination of the teaching of Ma and Perrone. *Id*.

Any argument that Ma would lead one of skill in the art to pursue the cytidine analog instead of the uridine should be rejected because, although both 1) activity against the target, and 2) intracellular stability are important criteria highlighted in Ma, there is no information in Ma about many aspects of the behavior of these compounds that would need to be determined if they are to progress in clinical studies. EX1002 at ¶144.

Therefore, at the stage of development reported in Ma, a POSA would not select one of these promising candidates for further testing and ignore the other. EX1002 at ¶145. A POSA would choose to investigate both compounds further. *Id*. Further inspection would, however, in at least one important aspect indicate that

the uridine nucleoside would be preferred over the cytidine as a drug candidate. *Id*.

Indeed, insofar as one of skill in the art would be motivated to choose between a cytidine or a uridine nucleoside, Ma would lead one to select the uridine. EX1002 at ¶146. The intracellular half-life of a drug is an important measure of the duration of its activity. *Id*. Ma taught that there was a very substantial difference between the intracellular half-life of RO2433-TP and PSI-6130-TP. EX1005 at 1 and 9. In fact, the intracellular half-life of RO2433-TP was approximately eight times as long as the intracellular half-life of PSI-6130-TP (38 hours versus 4.7 hours). EX1002 at ¶146. Therefore, a POSA would recognize that this difference might indeed be an important factor. *Id*.

A POSA would not pursue only a single compound, but rather be motivated to prepare a number of compounds in accordance with the structure activity relationship described in Perrone. EX1002 at ¶147. This was standard practice in the relevant technical field of pharmaceutical drug discovery and would certainly not have been an undue burden given the information contained in Perrone and the common general knowledge concerning the preparation of phosphoramidates. *Id*. Importantly the list of compounds to be prepared and tested would certainly include the claimed compound corresponding to the "exceptionally" active compound (15) in Perrone. *Id*.

While there are structural differences in the nucleoside structures in Ma and

Perrone, i.e. between RO2433 and 4'-azidouridine, a POSA would have been motivated to take the phosphoramidate moiety shown to be effective with the uridine analog in Perrone and apply it to the uridine analog of Ma in order to enhance the activity of RO2433 taught by Ma as a promising anti HCV compound. EX1002 at ¶148. Incorporating a prodrug moiety onto the nucleoside, importantly, would be known not to alter the inherent antiviral activity of the nucleoside triphosphate. *Id*.

In the same way that changes to part of a drug molecule, such as ribose substitution, can alter its interaction with the target enzymes, preserving the molecular structure of the relevant part of a drug molecule can maintain the interaction with a target enzyme. EX1002 at ¶149. A POSA would therefore have had a reasonable expectation that a phosphoramidate moiety that is an effective substrate for the esterase and phosphoramidase in one nucleoside analog would also be an effective substrate for exactly the same enzymes as part of a similar nucleoside analog against the same target organ and the same targeted disease. *Id*.

In other words, a POSA would have a reasonable expectation that the phosphoramidate SAR developed in the HCV replicon assay for the uridine analog 4'-azidouridine in Perrone would be comparable when transferred to the uridine analog RO2433 described in Ma and tested in the same HCV replicon assay. EX1002 at ¶150.

The compounds of claims 1 and 8 patent did not produce any unexpected results. EX1002 at ¶151. First, Perrone provided the technical teaching that use of the "*(phenyl)(isopropyl-L-alaninyl)phosphate*" group (No.15) significantly boosts the activity of anti-HCV nucleoside analogs. EX1008. Therefore, because Perrone and the '580 patent employed the same mechanism and theory, any activity improvement achieved by the claimed compound using the same modified 5'-phosphate group would have been expected. EX1002 at ¶151.

Second, the "*(phenyl)(isopropyl-L-alaninyl)phosphate*" group (No.15) disclosed in Perrone boosts the inactive parent nucleoside to an activity of EC_{50} = 0.77 μM, while the target application uses the same phosphoramidate group to boost the inactive parent nucleoside (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine to an activity of the same magnitude of that achieved in Perrone. EX1002 at ¶152; Compare EX1001 at 249 to EX1008 at Table 1, 4. Therefore, even if (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine is inactive, the '580 patent's claimed prodrug form does not produce unexpected results. EX1002 at ¶152.

Third, in the prior art, use of phosphoramidate prodrugs (ProTide) achieved increases in antiviral activity of as high as thousands of times the activity of the unmodified parent nucleoside, even to an activity/potency of several nM. EX1002 at ¶153; EX1012 (McGuigan 2006) at 1 and 4. For example, with regards to HCV phosphoramidate prodrugs (ProTide) achieved an increase in anti-HCV activity of

more than 450-fold, to an activity of EC_{50}=0.22 μM. EX1008 at 4 (Table 3).

2. Claims 2, 3, 9 and 10 (compositions comprising compound)

Claim 2 of the '580 patent recites, "A composition comprising the compound or a stereoisomer thereof as claimed in claim 1 and a pharmaceutically acceptable medium." EX1001 at 493:47-49. Claim 3 of the '580 patent recites, "A composition for treating a hepatitis C virus, which comprises an effective amount of the compound or a stereoisomer thereof as claimed in claim 1 and a pharmaceutically acceptable medium." *Id*. at 493:50-53. Claims 9 and 10 are identical to claims 2 and 3 except that they depend from claim 8 instead of claim 1.

Ma taught that its compounds were potent and safe inhibitors of HCV replication. EX1005 at 1. Inherent in this teaching are compositions comprising such compounds and a pharmaceutically acceptable medium and that such compositions are for treating hepatitis C. EX1002 at ¶156.

Further, Perrone also taught that applying its phosphoramidate ProTide approach to nucleosides could activate them as HCV inhibitors for use in treating humans. EX1008 at 1. Inherent in this teaching are compositions comprising such compounds and a pharmaceutically acceptable medium and that such compositions are for treating hepatitis C. EX1002 at ¶157. Perrone also demonstrated that such activated nucleosides were non-toxic in a cellular assay. EX1008 at 4. Thus, Ma and Perrone rendered claims 2, 3, 9, and 10 obvious. EX1002 at ¶157.

3. Claims 4, 5, 11 and 12 (methods of treating viral infections)

Claim 4 of the '580 patent recites, "A method of treating a subject infected by a virus, which comprises: administering to the subject an effective amount of the compound or a stereoisomer thereof as claimed in claim 1; wherein the virus is selected from among hepatitis C virus … ." EX1001 at 493:54-63. Claim 5 of the '580 patent recites, "A method of treating a hepatitis C virus infection in a subject in need thereof, which comprises: administering to the subject an effective amount of the compound or a stereoisomer thereof as claimed in claim 1." Claims 11 and 12 are identical to claims 4 and 5 except that they depend from claim 8 instead of claim 1.

Ma taught that its compounds were potent and safe inhibitors of HCV replication. EX1005 at 1. Ma also taught that its compounds could be used "as part of optimized combination regimens," *Id*., which inherently taught co-administering with other antivirals. EX1002 at ¶159.

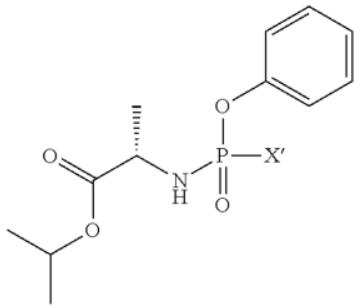
Further, Perrone also taught that applying its phosphoramidate ProTide approach to nucleosides could activate them as HCV inhibitors for use in treating people. EX1008 at 1. Thus, Ma and Perrone rendered claims 4, 5, 11 and 12 of the '580 patent obvious. EX1002 at ¶160.

4. Claims 6, 7, 13 and 14 (process of preparing and product)

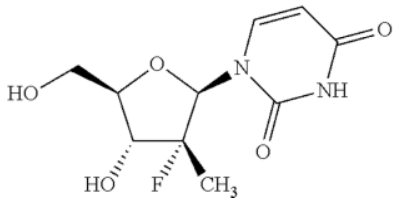
Claim 6 recites, "A process for preparing the compound or a stereoisomer

thereof as claimed in claim 1, said process comprising: reacting a compound 4″ with a nucleoside analog 5′

4″



5′



wherein X′ is a leaving group. Claim 7 recites, "A product comprising the compound or a stereoisomer thereof as claimed in claim 1 obtained by a process comprising: reacting a compound 4″ with a nucleoside analog 5′," wherein 4' and 5' are the same as in claim 6. Claims 13 and 14 are identical to claims 6 and 7 except that they depend from claim 8 instead of claim 1.

Perrone taught the same reaction as claimed in claims 6 and 7 in its Scheme 1. EX1008 at 3. Inherent in that teaching is that the reaction would be part of a process to prepare a compound that would become a pharmaceutical product. EX1002 at ¶162.

Further, Perrone also taught as part of its phosphoramidate ProTide approach

the reaction as claimed in claims 6 and 7 in its Scheme 1. EX1008 at 3. Inherent in that teaching is that the reaction would be part of a process to prepare a compound that would become a pharmaceutical product. EX1002 at ¶163. Thus, Ma and Perrone rendered claims 6, 7, 13 and 14 obvious. *Id*.

XI. CONCLUSION

For these reasons, claims 1-14 of the ’580 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/

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Counsel for Petitioner

XII. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 7,964,580
1002	Declaration of Joseph M. Fortunak, Ph.D.
1003	*Curriculum Vitae* of Joseph M. Fortunak, Ph.D.
1004	Sofia
1005	Ma
1006	Clark ‘147
1007	Clark 2005
1008	Perrone
1009	McGuigan ‘327
1010	Wagner
1011	Prusoff
1012	McGuigan 2006
1013	McGuigan 1994
1014	Cahard

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 10,812 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 1001-1014 and Power of Attorney) by overnight courier (Federal Express or UPS), on the date below on the Patent Owner at the correspondence address of the Patent Owner as follows:

GILEAD PHARMASSET LLC
C/O GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CALIFORNIA 94404

Respectfully,

Dated: October 25, 2017

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