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. IPR2018-00120
U.S. Patent No. 7,964,580

_____

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 obvious in light of the prior art. Specifically, the '580 claims a specific prodrug form of a specific nucleoside compound, but 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	103(a)	Clark ‘147, Clark 2005 and Perrone
2	1-14	103(a)	Clark ‘147, Clark 2005 and McGuigan ‘327

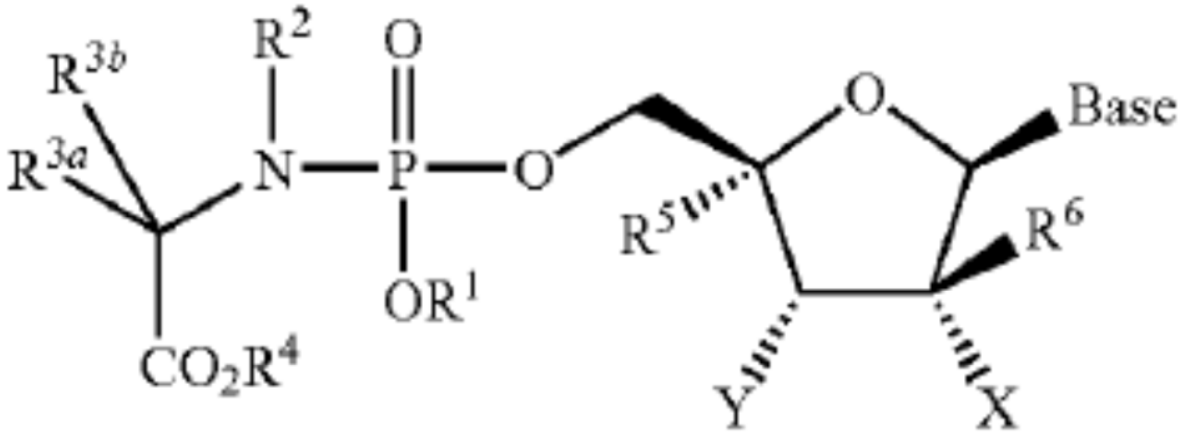
This Petition is supported by the declaration of Joseph M. Fortunak, Ph.D. (EX1002). Dr. Fortunak is well qualified as an expert, possessing the necessary scientific, technical, and other specialized knowledge and training to assist in an understanding of the evidence presented herein, as well as possessing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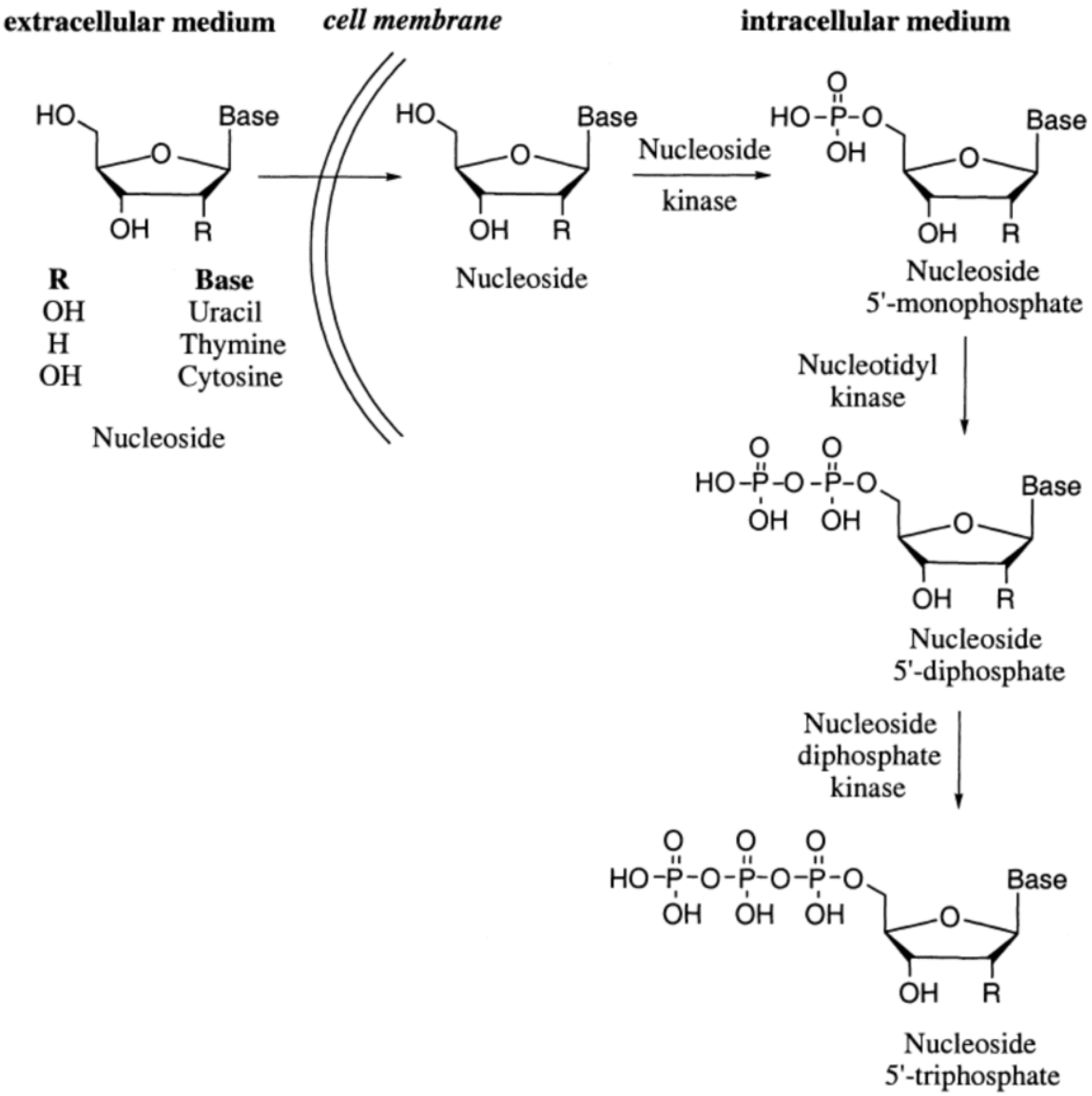


Id.

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'-CMethylcytidine (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).

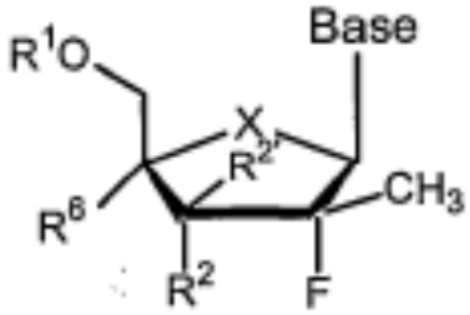
IX. SCOPE AND CONTENT OF THE PRIOR ART

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

A. WO 2005/003147 to Clark ("Clark '147"; EX1006)

Clark '147 is prior art under 35 U.S.C. § 102(b) to the '580 patent because it was published on January 13, 2005, more than a year before even the May 30, 2007, filing date of the earliest application to which the '580 patent claims priority.

Clark ‘147 taught (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleosides or prodrugs thereof having the natural β-D configuration and their use for treating hepatitis C virus (HCV). EX1006 at 18. Specifically, Clark ‘147 taught nucleosides of the following formula:



Id. Clark ‘147 taught the base could be a purine or pyrimidine and defined pyrimidine to include uracil. *Id*.

Clark ‘147 also taught that its nucleosides could be administered as a nucleotide prodrug to increase activity, bioavailability, stability or otherwise alter the properties of the nucleoside. *Id*.at 45:24-47:20.

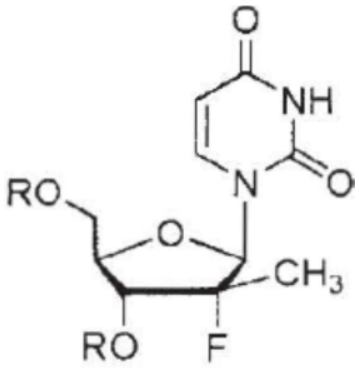
Clark ‘147 taught that a number of nucleotide prodrug ligands were known and that, in general, alkylation, acylation or other lipophilic modification of the mono, di or triphosphate of the nucleoside will increase the stability of the nucleotide. *Id*.at 45:24-47:20.

B. Clark, J., "Design, Synthesis, and Antiviral Activity of 2′-Deoxy-2′-fluoro-2′-C-methylcytidine, a Potent Inhibitor of Hepatitis C Virus Replication," Journal of Medicinal Chemistry, vol. 48, No. 17, pp. 5504-5508 (2005). ("Clark 2005"; EX1007)

Clark 2005 is prior art under 35 U.S.C. § 102(b) to the '580 patent because it was published on July26, 2005, more than a year before even the May 30, 2007, filing date of the earliest application to which the '580 patent claims priority.

Clark 2005 taught 2'-C-methyl nucleosides were potent for HCV inhibition. Clark 2005 further taught that, "[t]he degradation enzymes cytidine deaminase (CDA) and deoxycytidine monophosphate deaminase (dCMPDA) are responsible for the in vivo metabolic conversion of cytidine or cytidine monophosphate to uridine." EX1007 at 3.

Clark 2005 then prepared and tested the 2'-deoxy-2'-fluoro-2'-C-methyluridine, the structure of which is below, for anti-HCV activity.



EX1007 at 3 (Scheme 3).

Table 2 of Clark 2005, copied below, showed that the cytidine and uridine forms of the nucleoside (compounds 1 and 9, respectively) had an identical lack of

toxicity, but that the uridine form also demonstrated no activity as compared to the cytidine. *Id*.

Table 2. Anti-HCV Activity and Cellular Toxicity of Compounds **1**, **9**, 2′-*C*-Methylcytidine (2′-*C*-MeCyd), and 2′-Deoxy-2′-fluorocytidine (2′-FdCyd)

	cpBVDV[a] (MDBK cells)		HCV replicon[b]	
compound	EC_{90} (μM)[b]	CC_{50} (μM)	EC_{90} (μM)	CC_{50}[c] (μM)
1	>100	>100	5.40 ± 2.6	>100
9	>100	>100	>100	>100
2-*C*-MeCyd	2.30 ± 0.1	>100	19.0 ± 5.7	>100
2-FdCyd	>100	>100	6.50 ± 1.6	>100

[a] cpBVDV = cytopathic BVDV. [b] 96 h, average of at least four experiments. [c] MTS CC_{50} was determined in a 4-day assay using the Celltiter 96 nonradioactive cell proliferation assay from Promega (Madison, WI).

EX1007 at 3.

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.

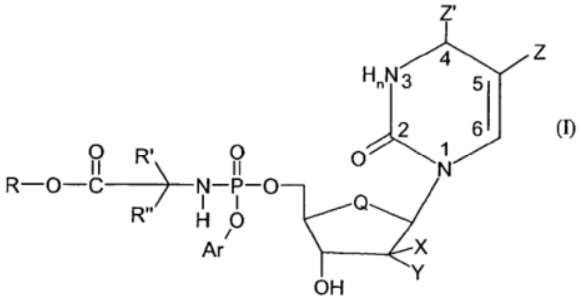
Perrone also taught that a potent HCV inhibitor nucleoside did not show inhibitory activity in the HCV replicon assay because of the extremely slow intracellular 5'-monophosphorylation of the nucleoside. *Id*. at 2-4. In addition, Perrone taught that the triphosphate nucleoside analogue showed potent 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.

D. WO 2005/012327 to McGuigan ("McGuigan '327"; EX1009)

McGuigan '327 is prior art under 35 U.S.C. § 102(b) to the '580 patent because it was published on February 10, 2005, more than a year before even the May 30, 2007, filing date of the earliest application to which the '580 patent claims priority.

McGuigan ‘327 taught phosphoramidate nucleosides and methods of preparation thereof. EX1009. McGuigan ‘327 specifically taught compounds of formula (I) and pharmaceutically acceptable derivatives or metabolites thereof:



Id. at 5.

McGuigan ‘327 taught a synthesis method in which a phosphate-based prodrug of nucleoside analogs is synthesized from an aryloxy phosphoramidate with a leaving group C-l and a uridine nucleoside analog.

McGuigan ‘327 taught that, in its formula (I), “X and Y are independently selected from the group comprising H, F, Cl, Br, I, OH and methyl (-CH3).” *Id.* at 5:22-23.

X. CLAIMS 1-14 ARE UNPATENTABLE

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 4: Claims 1-14 Were Obvious Over Clark '147, Clark 2005 and Perrone

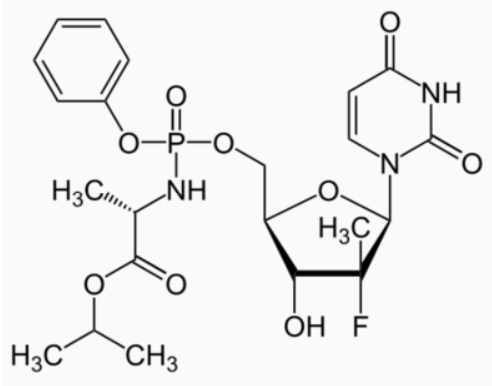
The combination of Clark '147, Clark 2005 and Perrone rendered the claims of the '580 patent obvious. EX1002 at ¶164. One of ordinary skill in the art would have been motivated to combine their teachings because they each related to phosphoramidates of anti-viral nucleosides, and in particular anti-HCV. *Id*. The '580 patent also cites each as references. EX1001 at 3 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.

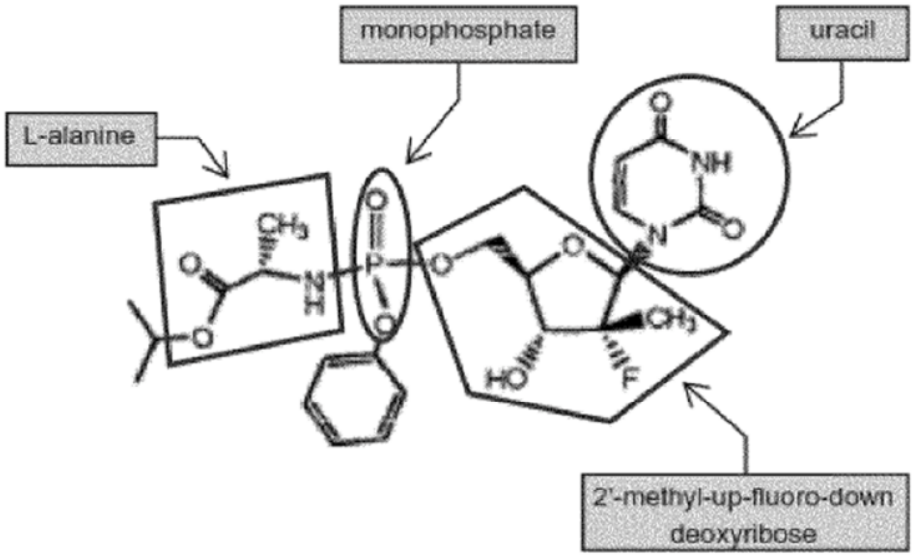
The compound claimed in claim 1 is a 5'-phosphate (phosphoramidate) prodrug of the uridine analog "(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyluridine", wherein the 5'-phosphate group is the "*(phenyl)(isopropyl-L-alaninyl)phosphate*" group. Included within claim 1 is the specific compound of claim 8, which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

formula:



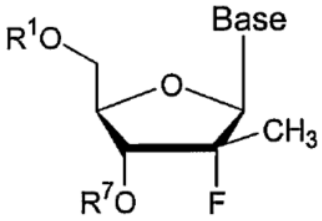
EX1002 at ¶166.

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 ¶167. 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*.



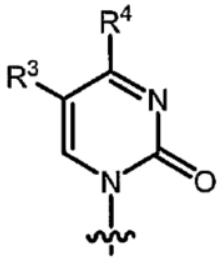
Clark ‘147 taught a set of nucleoside analogs or their prodrugs as HCV inhibitors with the core structure being 2’-deoxy-2’-fluoro-2’-C-methyl nucleoside and its 5’-modified prodrugs. EX1006 at 2. Specifically, Clark ‘147 taught an HCV RNA polymerase inhibitor and its use in treating HCV. See, for example, claim 40, which recited:

> Use of an anti-virally effective amount of a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) of the following formula or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of hepatitis C infection in a host:



wherein

Base is



R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate..., acyl..., alkyl..., sulfonate ester..., a lipid..., an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically-acceptable leaving group which when administered in vivo is capable of providing a compound wherein R1 or R^7 is independently H or phosphate; R1 and R^7 can also be linked with cyclic phosphate group;

R3 and R4 are independently H, halogen..., OH, OR', SH, SR', NH_2, ..."

EX1006 at 137-138.

A POSA would immediately contemplate R^3 as H and R^4 as OH because those are two of the first three substituents listed for those positions. EX1002 at ¶169. In doing so, a POSA would also recognize that this would result in the base being uridine. *Id*. Further, a POSA would select R^1 to be phosphate and R^7 to be H, again because those are the first two substituents listed, and this would result in the 5'-phosphate of "(2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine," which is the same nucleotide moiety as the compound of claim 1 of the '580 patent. *Id*.

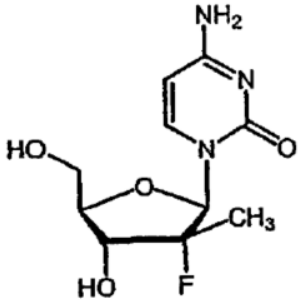
A POSA would readily recognize that these substituents are essentially obligatory for R^1 and R^7 in terms of resulting in a nucleoside which is capable of being activated (i.e., phosphorylated) at the C-5' position and which also results in the natural C-3' substitution of -OH. EX1002 at ¶170.

In terms of R^4, a POSA would naturally pick this group = OH or NH_2 as these would result in cytidine or uridine base substitution on the sugar rings. EX1002 at ¶171. The R^3 substitution would naturally first be chosen as an -H (hydrogen atom) because this results in incorporation of the natural cytosine and uracil rings into the nucleoside. *Id*.

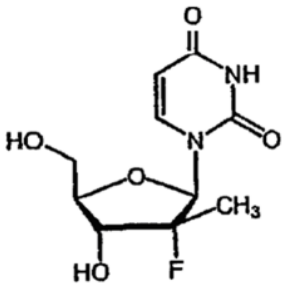
These would not necessarily be the only substitutions that a POSA would infer from Clark '147, but they are the simplest, and they would be considered as obligatory from the perspective of a medicinal chemist. EX1002 at ¶172. Incorporating the natural cytidine and uridine rings into the structure would be a

necessary first step in establishing a natural understanding of the structure-activity relationships of a C2'-substituted nucleoside. EX1002 at ¶172. Thus, Clark '147 taught that a 5'-phosphate of "(2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine" is an HCV inhibitor. *Id*.

Furthermore, Example 5 of Clark '147 experimentally validated the HCV inhibition effect of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (formula below), which proved that the 5'-triphosphate of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl cytidine (i.e. C'TP) (an example compound of Claim 40, where R^1=triphosphate, R^7=H, R^3=H, and R^4=NH_2) was an active and potent HCV inhibitor. EX1006 at 88.



(2'R)-2'-deoxy-2'-F-2'-*C*-Me cytidine



(2'R)-2'-deoxy-2'-F-2'-*C*-Me uridine

Because Clark '147 taught that its Base was preferably a purine or pyrimidine and also defined that pyrimidine includes uracil, EX1006 at 137 (claim 40), and because it was common knowledge that uracil is one of the four bases in RNA, a POSA would have been motivated to replace the cytidine in the active (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine 5'-triphosphate with a uridine (R^4=OH) and had an expectation that this would produce a likewise active and

potent HCV inhibitor. EX1002 at ¶174.

Therefore, Clark '147 not only taught that 5'-phosphates of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine are HCV inhibitors, it also motivated a POSA to choose it as an active agent. EX1002 at ¶175. In other words, based on the experimental results of Example 5 of Clark '147 and the common knowledge in the art, a POSA would have been be fully motivated to specifically choose, from the various compounds encompassed by Claim 40, the 5'-phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug) of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine as a practicable HCV inhibitor. *Id*.

Moreover, Claim 40 of Clark '147 also taught that the 5'-phosphate can be a "stabilized phosphate prodrug," EX1006 at 137, which when administered *in vivo* is capable of providing a compound wherein R^1 or R^7 is independently H or phosphate. EX1002 at ¶176. This taught that the 5'-phosphate can be further modified to stabilize the prodrug, and the stabilized phosphate prodrug will turn into the 5'-monophosphate form (R^1=phosphate, and R^7=H) to be activated. *Id*.

Specifically, Clark '147 taught:

> Any of the nucleosides described herein can be administered <u>as a nucleotide prodrug to increase the activity, bioavailability, stability</u> or otherwise alter the properties of the nucleoside. A number of nucleotide prodrug ligands are known. In general, <u>alkylation,</u>

acylation or other lipophilic modification of the mono, di or triphosphate of the nucleoside will increase the stability of the nucleotide. Examples of substituent groups that can replace one or more hydrogens on the phosphate moiety are alkyl, aryl, steroids, carbohydrates, including sugars, 1, 2-diacylglycerol and alcohols. Many are described in R. Jones and N. Bischofberger, Antiviral Research, 27 (1995) 1-17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect.

EX1006 at 47:16-25 (emphasis added).

Further, Clark '147 taught:

The nucleosides described herein can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside. A number of nucleotide prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono-, di-or triphosphate of the nucleoside reduces polarity and allows passage into cells. Examples of substituent groups that can replace one or more hydrogens on the phosphate moiety are ailcyl, (sic) aryl, steroids, carbohydrates, including sugars, 1,2- diacylglycerol and alcohols. Many are described in R. Jones and N. Bisehoferger, Antiviral Research, 1995,

27: 1-17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect."

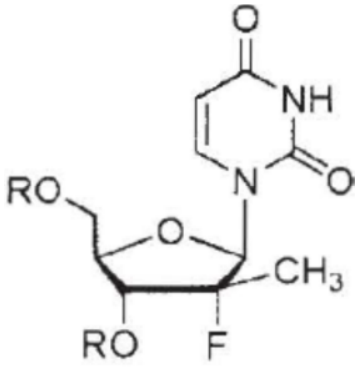
EX1006 at 15-24 (emphasis added).

Therefore, Clark '147 explicitly taught that alkylation, acylation, arylation, or other lipophilic modification can be made to the phosphate group in the 5'-phosphate of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine to increase its activity, bioavailability and stability, and that the modified prodrug will convert into the 5'-monophosphate form (U'MP) after its entry into the cell. EX1002 at ¶179.

Therefore, claims 1 and 8 of the '580 patent are different from Clark '147 only in that the stable 5'-phosphate group on the nucleoside analog in claims 1 and 8 of the '580 patent is the "(phenyl)(isopropyl-L-alaninyl)phosphate" group. EX1002 at ¶180.

Clark 2005 taught, "The degradation enzymes cytidine deaminase (CDA) and deoxycytidine monophosphate deaminase (dCMPDA) are responsible for the in vivo metabolic conversion of cytidine or cytidine monophosphate to uridine." EX1007 at 3. Thus, Clark 2005 taught that the cytidine form of the Clark '147 nucleoside could metabolically convert *in vivo* to the uridine form. *Id*.

Clark 2005 tested both 2'-deoxy-2'-fluoro-2'-C-methylcytidine and 2'-deoxy-2'-fluoro- 2'-C-methyluridine, the structure of which is below, for anti-HCV activity.



EX1007 at 3 (Scheme 3).

Clark 2005 showed in Table 2 that the cytidine and uridine forms of the nucleoside had an identical lack of toxicity. *Id*. Clark 2005 also showed in Table 2 that the uridine form demonstrated no activity as compared to the cytidine. *Id*.

The Clark 2005 results would have motivated a POSA to understand the lack of activity of the uridine form and to pursue methods to activate the uridine if the lack of activity were due to inefficient phosphorylation. EX1002 at ¶184.

General knowledge in the art as described above would have motivated a person skilled in the art to use the well-known strategy to select a suitable stable 5'-phosphate group for (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine of the Clark '147 and Clark 2005, in order to increase its activity.

One would have been specifically motivated to refer to Perrone, which taught a phosphoramidate "ProTide" approach to confer potency against hepatitis C virus by activating otherwise inactive nucleosides. EX1008. Specifically, Perrone taught use of an aryloxy phosphoramidate group as the 5'-group of a

uridine analog can significantly boost the inhibitory activity against the HCV RNA polymerase. *Id*. at 1. Perrone also taught that a potent HCV inhibitor nucleoside did not show inhibitory activity in the inhibition assay against RNA replication of HCV because of the extremely slow intracellular 5'-monophosphorylation of the nucleoside. *Id*.

To address this issue, Perrone employed the well-known conventional ProTide strategy and prepared about 20 stable phosphate-based prodrugs of the nucleoside, wherein the aryl group on the phosphate group renders the prodrugs strongly lipophilic so that the prodrugs can readily permeate the cell membrane. *Id*. at 4. These prodrugs are hydrolyzed into 5'-monophosphate derivatives of the nucleoside in the cell to bypass the 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 nucleosides of Clark '147 and had a reasonable expectation of success in doing so because of the general knowledge that nucleosides needed to be phosphorylated to active in HCV replication and the fact that Perrone provided several examples of comparable nucleosides being triphosphorylated by its ProTide approach. EX1002 at ¶188. Applying Perrone's

ProTide approach to Clark '147 and Clark 2005's promising nucleoside would result in the compound claimed in claims 1 and 8 of the '580 patent. *Id*. Thus, Clark '147, Clark 2005 and Perrone render claims 1 and 8 obvious. *Id*.

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 Clark '147 and Clark 2005, 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. EX1002 at ¶189. Such stable modified 5'-phosphate group could also activate the inactive uridine nucleoside of Clark '147 and Clark 2005, which a POSA would be motivated to achieve. *Id*.

A POSA reading Clark '147, Clark 2005 and Perrone would have been 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 Clark '147 and Clark 2005. EX1002 at ¶190.

The nucleosides taught in Perrone and the (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine taught in Clark '147 and Clark 2005 are both uridine analogs used to inhibit HCV through the same mechanism. EX1002 at ¶191. 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 Clark '147 and Clark 2005'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. A POSA would have been motivated to try to attach each to the 5'-position of Clark '147 and Clark 2005's (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine resulting in the compounds of claims 1 and 8. EX1002 at ¶192.

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. Thus, Perrone described exactly the same problem as Clark '147 and Clark 2005 and suggested the same solution to the problem. EX1002 at ¶193. As both Clark '147 and Clark 2005 and Perrone lie in precisely the same technical filed, and each describe exactly the same problem and propose the same general solution, a POSA would have been motivated to combine their teachings. *Id*.

Specifically, a POSA would have been motivated to prepare the corresponding L-alanine derivatives 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. EX1002 at ¶194; EX1008 at 4. A POSA would in particular prepare the derivatives of PSI-6206 that correspond to compounds 14, 15 and 17 in Perrone because they are described as having "exceptional" antiviral activity. EX1002 at ¶194; EX1008 at 3-4.

In considering the similarity of Clark '147, Clark 2005 and Perrone, a POSA would not focus on the structural differences between the parent nucleosides, 2'-deoxy-2'-fluoro-2'-C-methyluridine and 4'-aziduridne. EX1002 at ¶195. A POSA would investigate the 2'-deoxy-2'-fluoro-2'-C-methyluridine nucleoside in Clark 2005 as a lead compound and incorporate the specific phosphoramidate substituents from Perrone because they were taught to provide an optimal solution for delivering an active HCV nucleoside to target cells. *Id*.

Thus, the compound of claims 1 and 8 would have been obvious to a POSA based on the teachings of Clark '147, Clark 2005 and Perrone. *Id*.

The compounds of claims 1 and 8 of the '580 patent did not produce any unexpected results. EX1002 at ¶197. 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 4. 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 ¶197.

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 ¶198; 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 ¶198.

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 ¶199; EX1012 (McGuigan 2006) 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).

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.

Clark '147 and Clark 2005 taught that their compounds were potent and safe inhibitors of HCV replication. EX1006 at 2; EX1007 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 ¶202.

Further, Perrone also taught that applying its phosphoramidate ProTide approach to nucleosides could activate them as HCV inhibitors for use in treating people. EX1008 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 ¶203. Thus, Clark '147, Clark 2005 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

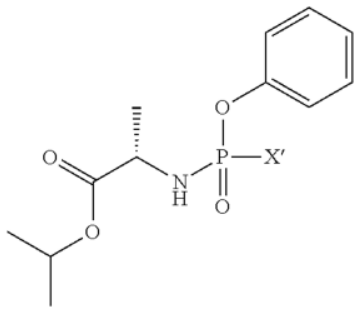
of the compound or a stereoisomer thereof as claimed in claim 1." Claims 11 and 12 are identical to claims 4 and 5 except that they depend from claim 8 instead of claim 1.

Clark '147 and Clark 2005 taught that their compounds were potent and safe inhibitors of HCV replication. EX1006 at 2; EX1007 at1. 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, Clark '147, Clark 2005 and Perrone rendered claims 4, 5, 11 and 12 obvious.

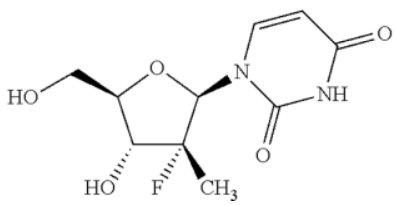
4. Claims 6, 7, 13 and 14 (process of preparing and product)

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 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 ¶207. Thus, Clark '147, Clark 2005 and Perrone rendered claims 6, 7, 13 and 14 obvious. *Id*.

B. Ground 5: Claims 1-14 Were Obvious Over Clark '147, Clark 2005 and McGuigan '327

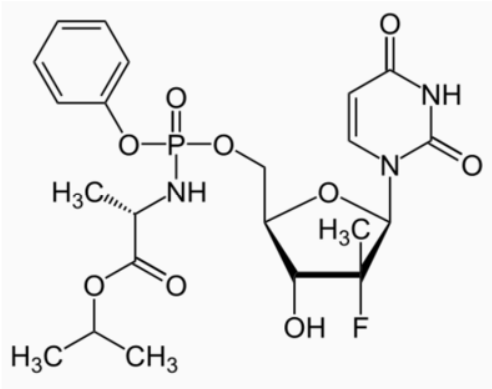
The combination of Clark '147, Clark 2005 and McGuigan '327 rendered the claims of the '580 patent obvious. EX1002 at ¶208. One of ordinary skill in the art would have been motivated to combine their teachings because they each related to phosphoramidates of anti-viral nucleosides. *Id*. The '580 patent also cites each as references. EX1001 at 3 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.

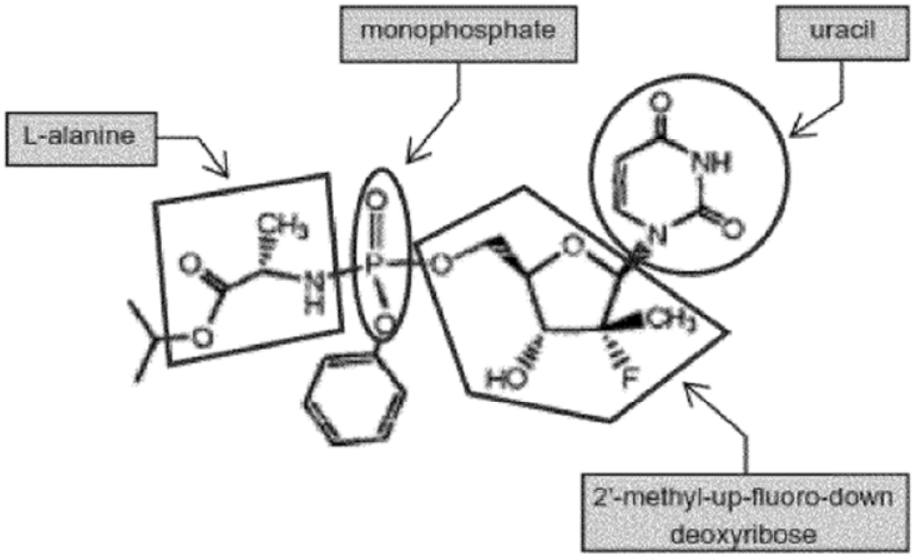
The compound claimed in claim 1 is a 5'-phosphate (phosphoramidate) prodrug of the uridine analog "(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyluridine", wherein the 5'-phosphate group is the "*(phenyl)(isopropyl-L-alaninyl)phosphate*" group. Included within claim 1 is the specific compound of claim 8, which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



EX1002 at ¶210.

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 ¶211. 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"

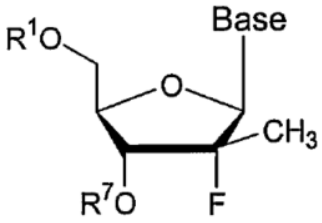
position. *Id*. The deoxyribose sugar is substituted with a base at the conventional position via a glycosidic bond. *Id*. The base is uracil. *Id*.



Clark '147 taught a set of nucleoside analogs or their prodrugs as HCV inhibitors with the core structure being 2'-deoxy-2'-fluoro-2'-C-methyl nucleoside and its 5'-modified prodrugs. EX1006 at 2. Specifically, Clark '147 taught an HCV RNA polymerase inhibitor and its use in treating HCV. See, for example, claim 40, which recited:

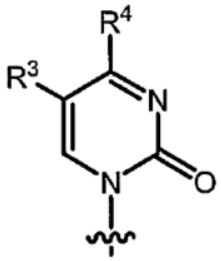
> Use of an anti-virally effective amount of a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) of the following formula or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis

of hepatitis C infection in a host:



wherein

Base is



R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate..., acyl..., alkyl..., sulfonate ester..., a lipid..., an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically-acceptable leaving group which when administered in vivo is capable of providing a compound wherein R1 or R^7 is independently H or phosphate; R1 and R^7 can also be linked with cyclic phosphate group;

R3 and R4 are independently H, halogen..., OH, OR', SH, SR', NH_2, ...”

EX1006 at 137-138.

A POSA would immediately contemplate R^3 as H and R^4 as OH because those are two of the first three substituents listed for those positions. EX1002 at ¶213. In doing so, a POSA would also recognize that this would result in the base being uridine. *Id*. Further, a POSA would select R^1 to be phosphate and R^7 to be H, again because those are the first two substituents listed, and this would result in the 5'-phosphate of "(2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine," which is the same nucleotide moiety as the compound of claim 1 of the '580 patent. *Id*.

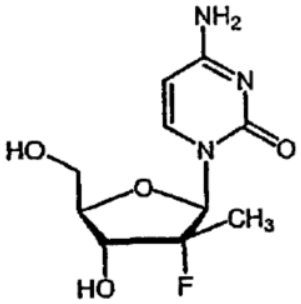
A POSA would readily recognize that these substituents are essentially obligatory for R^1 and R^7 in terms of resulting in a nucleoside which is capable of being activated (i.e., phosphorylated) at the C5' position and which also results in the natural C3' substitution of -OH. EX1002 at ¶214.

In terms of R^4, a POSA would naturally pick this group = OH or NH_2 as these would result in cytidine or uridine base substitution on the sugar rings. EX1002 at ¶215. The R^3 substitution would naturally first be chosen as an -H (hydrogen atom) because this results in incorporation of the natural cytosine and uracil rings into the nucleoside. *Id*.

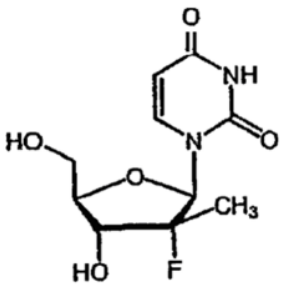
These would not necessarily be the only substitutions that a POSA would infer from Clark '147, but they are the simplest, and they would be considered as obligatory from the perspective of a medicinal chemist. EX1002 at ¶216.

Incorporating the natural cytidine and uridine rings into the structure would be a necessary first step in establishing a natural understanding of the structure-activity relationships of a C2'-substituted nucleoside. *Id*. Thus, Clark '147 taught that a 5'-phosphate of "(2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine" is an HCV inhibitor.

Furthermore, Example 5 of Clark '147 experimentally validated the HCV inhibition effect of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (formula below), which proved that the 5'-triphosphate of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl cytidine (i.e. C'TP) (an example compound of Claim 40, where R^1=triphosphate, R^7=H, R^3=H, and R^4=NH_2) was an active and potent HCV inhibitor. EX1006 at 137.



(2'R)-2'-deoxy-2'-F-2'-*C*-Me cytidine



(2'R)-2'-deoxy-2'-F-2'-*C*-Me uridine

Because Clark '147 taught that its Base was preferably a purine or pyrimidine and also defined that pyrimidine includes uracil, EX1006 at 137 (claim 40), and because it was common knowledge that uracil is one of the four bases in RNA, a POSA would have been motivated to replace the cytidine in the active (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine 5'-triphosphate with a uridine

(R^4=OH) and had an expectation that this would produce a likewise active and potent HCV inhibitor. EX1002 at ¶218.

Therefore, Clark '147 not only taught that 5'-phosphates of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine are HCV inhibitors, it also motivated a POSA to choose it as an active agent. EX1002 at ¶219. In other words, based on the experimental results of Example 5 of Clark '147 and the common knowledge in the art, a POSA would have been be fully motivated to specifically choose, from the various compounds encompassed by Claim 40, the 5'-phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug) of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl uridine as a practicable HCV inhibitor. *Id*.

Moreover, Claim 40 of Clark '147 also taught that the 5'-phosphate can be a "stabilized phosphate prodrug," EX1006 at 137:16, which when administered *in vivo* is capable of providing a compound wherein R^1 or R^7 is independently H or phosphate. EX1002 at ¶220. This taught that the 5'-phosphate can be further modified to stabilize the prodrug, and the stabilized phosphate prodrug will turn into the 5'-monophosphate form (R^1=phosphate, and R^7=H) to be activated. *Id*.

Specifically, Clark '147 taught:

> Any of the nucleosides described herein can be administered <u>as a nucleotide prodrug to increase the activity, bioavailability, stability</u> or otherwise alter the properties of the nucleoside. A number of

nucleotide prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono, di or triphosphate of the nucleoside will increase the stability of the nucleotide. Examples of substituent groups that can replace one or more hydrogens on the phosphate moiety are alkyl, aryl, steroids, carbohydrates, including sugars, 1, 2-diacylglycerol and alcohols. Many are described in R. Jones and N. Bischofberger, Antiviral Research, 27 (1995) 1-17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect.

EX1006 at 47:16-25 (emphasis added).

Further, Clark '147 taught:

The nucleosides described herein can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside. A number of nucleotide prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono-, di-or triphosphate of the nucleoside reduces polarity and allows passage into cells. Examples of substituent groups that can replace one or more hydrogens on the phosphate moiety are ailcyl, (sic) aryl, steroids, carbohydrates, including sugars, 1,2- diacylglycerol and alcohols. Many are

described in R. Jones and N. Bisehoferger, Antiviral Research, 1995, 27: 1-17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect."

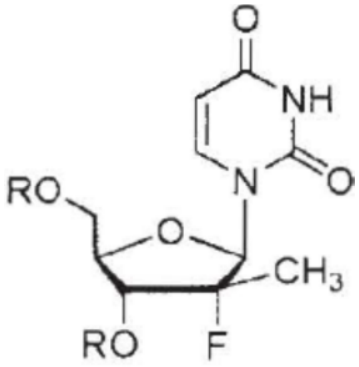
EX1006 at 15-24 (emphasis added).

Therefore, Clark '147 explicitly taught that alkylation, acylation, arylation, or other lipophilic modification can be made to the phosphate group in the 5'-phosphate of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine to increase its activity, bioavailability and stability, and that the modified prodrug will convert into the 5'-monophosphate form (U'MP) after its entry into the cell. EX1002 at ¶223.

Therefore, claims 1 and 8 patent are different from Clark '147 only in that the stable 5'-phosphate group on the nucleoside analog in claims 1 and 8 is the "(phenyl)(isopropyl-L-alaninyl)phosphate" group. EX1002 at ¶224.

Clark 2005 taught, "The degradation enzymes cytidine deaminase (CDA) and deoxycytidine monophosphate deaminase (dCMPDA) are responsible for the in vivo metabolic conversion of cytidine or cytidine monophosphate to uridine." Thus, Clark 2005 taught that the cytidine form of the Clark '147 nucleoside could metabolically convert *in vivo* to the uridine form. EX1007 at 3.

Clark 2005 tested both 2'-deoxy-2'-fluoro-2'-C-methylcytidine and 2'-deoxy-2'-fluoro- 2'-C-methyluridine, the structure of which is below, for anti-HCV activity.

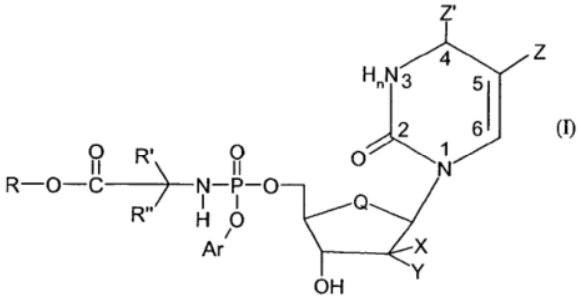


EX1007 at 3 (Scheme 3).

Clark 2005 showed in Table 2 that the cytidine and uridine forms of the nucleoside had an identical lack of toxicity. *Id*. Clark 2005 also showed in Table 2 that the uridine form demonstrated no activity as compared to the cytidine. *Id*.

The Clark 2005 results would have motivated a POSA to understand the lack of activity of the uridine form and to pursue methods to activate the uridine if the lack of activity were due to inefficient phosphorylation. EX1002 at ¶228. General knowledge in the art as described above would have motivated a person skilled in the art to use the well-known strategy to select a suitable stable 5'-phosphate group for (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine of the Clark '147 and Clark 2005, in order to increase its activity. *Id*.

One would have been specifically motivated to refer to McGuigan '327's teaching of compounds of formula (I):



(I)

wherein:

R is selected from the group comprising alkyl, aryl and alkylaryl;

R' and R" are, independently, selected from the group comprising H, alkyl and alkylaryl, or R' and R" together form an alkylene chain so as to provide, together with the C atom to which they are attached, a cyclic system;

Q is selected from the group comprising -O- and-CH_2-;

X and Y are independently selected from the group comprising H, F, Cl, Br, I, OH and methyl (-CH_3);

Ar is a monocyclic aromatic ring moiety or a fused bicyclic aromatic ring moiety, either of which ring moieties is carbocyclic or heterocyclic and is optionally substituted;

Z is selected from the group comprising H, alkyl and halogen; and

n is 0 or 1, wherein when n is 0, Z' is -NH_2 and a double bond exists

between position 3 and position 4, and when n is 1, Z' is =O;

with the proviso that when n is 1, X and Y are both H, R is methyl (-CH_3), one of R' and R" is H and one of R' and R" is methyl (-CH_3), then Ar is not phenyl (-C_6H_5).

EX1009 at 5-6.

McGuigan '327 taught that, in its formula (I), "X and Y are independently selected from the group comprising H, F, Cl, Br, I, OH and methyl (-CH3)," and specifically highlighted that, "[p]referably, R is methyl, ethyl, *n*- or *i*- propyl," *Id*. at 9:20, "preferred compounds include those where R' and R" are both methyl, one of R' and R" is H and one of R' and R" is methyl," *Id*. at 10:5-6, "preferably Q is O," *Id*. at 11:14, and "More preferably, Ar is selected from the group comprising: Ph-." *Id*. at 13:1-2.

Therefore, a POSA would have been encouraged by McGuigan '327 to select Q=O, n=1, Z'=O, Z=H, X=-CH_3, Y=F, Ar=phenyl, R=isopropyl, R'=H, and R"=-CH_3, in the compound of formula (I) of McGuigan '327 which would be identical to the compound of claims 1 and 8. EX1002 at ¶231. A POSA would have been motivated to select these substituents because they were indicated by McGuigan '327 to be preferred and Clark '147 and Clark 2005 taught the same exact sugar ring and base structure. *Id*.

Thus, it would have been obvious to a person skilled in the art to obtain the

compound of claims 1 and 8 based on Clark '147 and Clark 2005 and McGuigan '327 in combination with the general knowledge in the art at the time. *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.

Clark '147 and Clark 2005 taught that its compounds were potent and safe inhibitors of HCV replication. EX1006 at 2; EX1007 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 ¶234. Thus, Clark '147, Clark 2005 and McGuigan '327 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

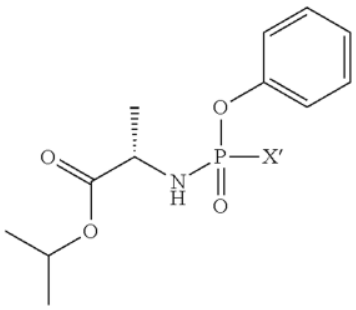
selected from among hepatitis C virus … .” EX1001 at 493:54-63. Claim 5 of the ‘580 patent recites, “A method of treating a hepatitis C virus infection in a subject in need thereof, which comprises: administering to the subject an effective amount of the compound or a stereoisomer thereof as claimed 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.

Clark ‘147 and Clark 2005 taught that its compounds were potent and safe inhibitors of HCV replication. EX1006 at 2; EX1007 at 1. Further, McGuigan ‘327 also taught that applying its phosphoramidate ProTide approach to nucleosides could activate them as antivirals for use in treating people. EX1009 at 3. Thus, Clark ‘147, Clark 2005 and McGuigan ‘327 rendered claims 4, 5, 11 and 12 obvious. EX1002 at ¶236.

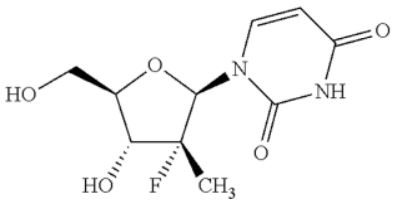
4. Claims 6, 7, 13 and 14 (process of preparing and product)

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″

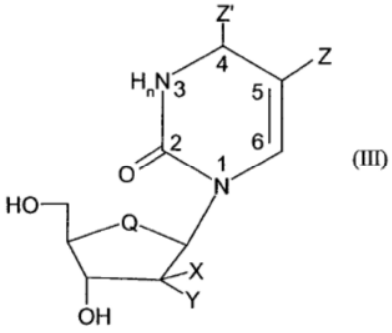


5′

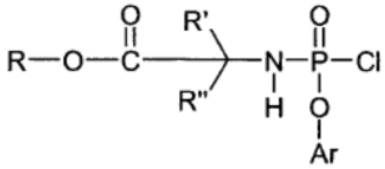


wherein X′ is a leaving group. Claim 7 recites, "A product comprising the compound or a stereoisomer thereof as claimed in claim 1 obtained by a process comprising: reacting a compound 4″ with a nucleoside analog 5′," wherein 4' and 5' are the same as in claim 6. Claims 13 and 14 are identical to claims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

McGuigan '327 taught a process for the preparation of its compounds comprising reacting of a compound of formula (III) with a compound of formula (IV):



(III)



(IV)

wherein, Ar, n, Q, R, R', R", X, Y, Z and Z' have the meanings described above with respect to formula (I). EX1009 at 18:28 – 19:5.

Therefore, as discussed above, a POSA would have been encouraged by McGuigan '327 to select Q=O, n=1, Z'=O, Z=H, X=-CH_3, Y=F, Ar=phenyl, R=isopropyl, R'=H, and R"=-CH_3 in the compound of formula (I) of McGuigan '327 which would be identical to the compound of claim 1. EX1002 at ¶239.

In the process taught by McGuigan '327, the compound of formula (III) is identical to the nucleoside analog 5' of the '580 patent and the compound of formula (IV) is identical to the compound 4" of the '580 patent except the Cl bonded to the phosphorous atom. EX1009 at 18:28 – 19:5. But a POSA would know that Cl is an example of a leaving group (X'). EX1002 at ¶240.

Therefore, McGuigan '327 discloses a synthesis method within the methods of claims 6, 7, 13 and 14, in which a phosphate-based prodrug of nucleoside analogs is synthesized from (i) an aryloxy phosphoramidate with a leaving group Cl and (ii) a uridine analog. EX1002 at ¶241.

When facing the technical problem of how to synthesize the compound of

the ‘580 patent, a person skilled in the art under the teaching of McGuigan ‘327 would have readily envisaged using a generally known phosphate moiety of (i.e. the *(*phenyl)(isopropyl-L-alaninyl)phosphate) having a leaving group (e.g. Cl) to react with the nucleoside analog moiety of Clark ‘147 and Clark 2005 (*i.e.* (2’R)-2’-deoxy-2’-fluoro-2’-C-methyluridine) to obtain the claimed compound. EX1002 at ¶242.

The process of claims 6, 7, 13 and 14 would have been obvious to a person skilled in the art in light of McGuigan ‘327. EX1002 at ¶243. In addition, the process of claims 6, 7, 13 and 14 does not produce any unexpected technical effects. EX1002 at ¶243.

Thus, Clark ‘147, Clark 2005 and McGuigan ‘327 rendered claims 6, 7, 13 and 14 obvious. EX1002 at ¶244.

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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Email: dan@ravicher.com

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 10,841 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